CLINICAL MANAGEMENT OF THE HIV-INFECTED ADULT

A MANUAL FOR MIDLEVEL CLINICIANS

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Use of the Manual

This manual is intended for use in collaborative practice models. Geographic variations in health care practice conventions and frequent changes in standards of HIV care require that the treatment guidelines be carefully reviewed by the medical, nursing, and physician assistant team in your facility to make sure they conform to acceptable local and current approaches. Medical treatment updates are posted frequently to several websites, including the http://www.aidsinfo.nih.gov site, and it is recommended that every provider be familiar with all relevant guidelines.

 Please note that these treatment recommendations are not intended to replace clinical research literature or current USPHS guidelines, and may not include the full range of treatment options for all HIV-infected patients. Independent verification of all information is necessary before undertaking care of HIV-infected clients, particularly in the face of rapidly-changing HIV treatment standards. Some recommendations are not in accord with FDA-approved usage for certain drugs, but are based on findings from clinical trials and recommendations from expert providers. For more information or to offer comments, please contact Patricia Yeargin, listed below.

How to Obtain Copies of the Manual

This manual is available in both print and compact disk formats from the Southeast AIDS Training and Education Center (SEATEC) and from the Midwest AIDS Training and Education Center (MATEC), through the communication channels below. In addition, the manual is downloadable from the Internet site of the AIDS Education and Training Center National Resource Center at http://www.aids-etc.org, in the Education and Training Resources section.

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Emory University School of Medicine
735 Gatewood Road, NE
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404-727-2929, fax 404-727-4562
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SEATEC Web Page: http://www.seatec.emory.edu

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808 S. Wood St. (M/C 779)
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Internet e-mail: matec@uic.edu
MATEC Web Page: http://www.matec.info

HIV/AIDS Resources for Clinicians

Telephone Consultation and Information for Health Care Providers

National HIV/AIDS Clinicians' Consultation Center
(800) 933-3413, staffed from 7:30 a.m. to 5:00 p.m. Pacific Time, Monday-Friday. This warmline number is for use by ***health care providers only***, to obtain phone consultation regarding individual patient management and care from San Francisco General Hospital and University of California at San Francisco's HIV-expert clinicians.

HIV/AIDS Treatment Information Service and HIV Clinical Trials Information
(800) HIV-0440, Monday-Friday, 12 noon to 5 p.m. Eastern Time, NIH will supply clinical HIV information and treatment guidelines, by phone or mail (see website URL next page).

National Prevention Information Service and HIV/AIDS Statistics
(800) 458-5231, Monday-Friday 9 a.m. to 6 p.m. Eastern Time, the CDC National Prevention Information Service will supply statistics and other HIV information (see website URL next page).

Registry: Infants Exposed to Antiretroviral Drugs *in utero*
(800) 258-4263, to put antiretroviral-exposed newborns on observational study for data on long-term toxicity. Monday-Friday, 8:30 a.m. to 5:30 p.m. Eastern time.

Registry for HIV Non-Occupational Post-Exposure Prophylaxis
1-877-448-1737 for information on enrolling HIV-exposed persons in an observational study of post-exposure prophylaxis in non-occupational exposure situations, sponsored by the CDC (see website URL next page)

TB Expert Consultation
(800) 4TB-DOCS, available 9 a.m. to 5 p.m. Eastern time for *health care provider consultation only,* by University of Medicine and Dentistry of New Jersey and the University Hospital clinicians

Occupational Exposures to HIV/Blood-Borne Pathogens
(888) HIV-4911, a 24-hour hotline for consultation on post-exposure management from San Francisco General and University of California at San Francisco.

Complementary HIV Therapies
(888) 644-6226, open 8:30 a.m. to 5 p.m. Eastern, Monday-Friday, the NIH Office of Alternative Medicine serves as a clearinghouse for both HIV and non-HIV related therapies.

AIDS Updates: NIH Documents and Other HIV Information
If you have no Internet access, **(800) 458-5231**, CDC National Prevention Information Network (formerly CDC National AIDS Clearinghouse) will mail single copies of US Public Health Service and Infectious Disease Society guidelines for prevention of opportunistic infections and HIV treatment in adults, children, and pregnant women. If you have Internet access, see websites below.

HIV/AIDS Websites for Health Care Providers

http://www.medscape.com – HIV/AIDS page contains treatment and review articles, recommendations, conference updates, CME offerings, and HIV medication and antiretroviral drug interaction information

http://www.ama-assn.org/aids – includes updates from news, treatment information, links to medical and AIDS search engines

http://www.aidsinfo.nih.gov – contains updated treatment guidelines, clinical trials and other HIV information

continued on next page

HIV/AIDS Websites for Health Care Providers, continued

http://hivinsite.ucsf.edu – contains treatment information, with excellent pages on occupational HIV exposure management

http://www.hivguidelines.org/public_html/CENTER/clinical-guidelines – includes mental health, oral health, comprehensive adult and pediatric guidelines from the New York AIDS Institute

http://www.HIVdent.org – contains oral manifestations of HIV, with pictures, and general HIV information

http://www.cdcnpin.org – contains HIV prevention and treatment information, as well as archived copies of the *AIDS Daily Summary;* **http://www.cdc.gov/hiv/graphics.htm** contains HIV epidemiology slide sets

http://www.aids-etc.org – AIDS Education and Training Centers National Resource Center, contains HIV/AIDS slides, references, HIV clinical news and many teaching resources for health care providers. For a roster of all the AIDS Education and Training Centers, see next page.

http://www.hivpepregistry.org – for registry of non-occupationally HIV-exposed patients who are placed on post-exposure prophylaxis, in a CDC observational study of practices and effectiveness

http://www.seatec.emory.edu – contains handouts for teaching health care providers, local/regional conference offerings, and other treatment and referral information

E-mail Updates

http://www.cdcnpin.org/db/public/dnmain.htm to subscribe to HIV/AIDS/STD/TB Prevention News Daily Update, with HIV-related news abstracts and HIV conference information

http://aidsinfo.nih.gov/other/subscribe.asp to subscribe to email notification when HIV Treatment Guidelines are updated

Patient Education Materials and Handouts

http:www.aidsinfonet.org – has excellent 1-page handouts on HIV medications and opportunistic infections by National AIDS Treatment Information Project and New Mexico AIDS InfoNet

http://www.thebody.com – exhaustive resources from AIDS information services, including the AIDS Treatment Information Service

http://www.aidsinfonyc.org – the AIDS Treatment Data Network produces very accurate and fairly simple fact sheets on opportunistic diseases, treatments and medications

Additional Resources from AIDS Education and Training Centers

A system of AIDS Education and Training Centers (AETCs) has been established through a cooperative agreement program of the Health Resources and Services Administration, within the US Public Health Service, Department of Health and Human Services. The goal of the AIDS ETC program is to increase the number of health care providers who are effectively educated and motivated to counsel, diagnose, treat, and manage individuals with HIV infection, and to assist in the prevention of high risk behaviors which may lead to infection.

The AETCs are a national network of centers responsible for designated geographic areas in which they conduct targeted, HIV education programs for health care workers. **The AETCs also provide information about HIV resources, drug trials, referrals, and treatment guidelines.** ***Please contact your regional AETC to learn about training services available in your area. See roster next page for listing of AETCs.***

Current Roster of AIDS Education and Training Centers

Serving **New York and New Jersey**
New York/New Jersey AETC
Columbia University, School of Public Health
600 W. 168th St., Suite 1040
New York, NY 10032
212-305-8291 or 342-0276
http://nyviaetc.org

Serving **Arizona, California, Hawaii, Nevada**
Pacific AIDS ETC
Dept. of Family & Community Med.
University of California, San Francisco
74 New Montgomery St., Suite 600
San Francisco, CA 94105-3444
415-597-8198
http://www.ucsf.edu/paetc

Serving **Ohio, Michigan, Kentucky, Tennessee**
Great Lakes to Tennessee Valley AETC
Wayne State University
AIDS Research and Education Program
2727 Second Ave., Suite 138
Detroit, MI 48201-2671
313-962-2000
http://www.science.wayne.edu/~arep/Main.htm

Serving **Alabama, Georgia, North Carolina, South Carolina**
Southeast AIDS Training and Education Center
Emory University School of Medicine
735 Gatewood Road, NE
Atlanta, GA 30322-4950
404-727-2929
http://www.seatec.emory.edu

Serving **Pennsylvania, Delaware, Maryland, West Virginia, Virginia, Washington DC**
Pennsylvania/Mid-Atlantic AETC
University of Pittsburgh
Graduate School of Public Health
Dept. of Infectious Disease and Microbiology
130 DeSoto St., G-15 Parran Hall
Pittsburgh, PA 15261
412-624-1895
http://www.pamaaetc.org/

Serving **Arkansas, Louisiana, Mississippi**
Delta Region AIDS ETC
LSU Health Sciences Center
136 South Roman St., 3rd Floor
New Orleans, LA 70112
504-903-9788
http://www.deltaaetc.org

Serving **North Dakota, South Dakota, Utah, Colorado, Kansas, New Mexico, Nebraska, Wyoming**
Mountain Plains AIDS ETC
University of Colorado Health Sciences Center
4200 E. 9th Avenue, Box A-089
Denver, CO 80262
303-315-2516
http://www.uchsc.edu/sm/aids

Serving **Florida, Puerto Rico, Virgin Islands**
Florida/Caribbean AIDS ETC
University of South Florida
USF Center for HIV Education and Research
13301 Bruce B. Downs Blvd,
MHC-1336
Tampa, FL 33612
813-974-4430
http://www.faetc.org

Serving **Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont**
New England AIDS ETC
University of Massachusetts Medical School
23 Miner St.
Boston, MA 02215-3318
617-262-5657
http://www.neaetc.org

Serving **Illinois, Indiana, Iowa, Minnesota, Missouri, Wisconsin**
Midwest AIDS Training and Education Center
University of Illinois at Chicago
808 S. Wood St. (M/C 779), #173
Chicago, IL 60612-7303
312-996-1373
http://www.matec.info

Serving **Texas and Oklahoma**
Texas and Oklahoma AIDS ETC
Parkland Health and Hospital System
1936 Amelia Court
Dallas, TX 75235
214-590-2181

Serving **Alaska, Idaho, Montana, Oregon and Washington**
Northwest AIDS ETC
University of Washington
901 Boren Ave., Suite 1100
Seattle, WA 98104-3508
206-685-6844
http://www.northwestaetc.org

National Minority AIDS ETC
Howard University
2041 Georgia Avenue, NW,
Suite 2300
Washington, DC 20060
202-865-3300
http://www.nmaetc.org

National HIV/AIDS Clinicians Consultation Center (NCCC)
San Francisco General Hospital
995 Potrero Ave., Bldg 80-83
San Francisco, CA 94110
415-206-3978
http://www.ucsf.edu/hivcntr

AETC National Resource Center
University of Medicine & Dentistry of New Jersey
30 Bergen St., ADMC #4
Newark, NJ 07103
973-972-0410, ex 226
http://www.aids-etc.org

International Training and Education Center on HIV
University of Washington
901 Boren Ave., Suite 1100
Seattle, WA 98104
206-685-6841

for more information:
HRSA, HIV Education Branch
HIV/AIDS Bureau
5600 Fishers Lane, Room 4C-03
Rockville, MD 20857
301-443-6364
http://www.hrsa.gov/hab/educating.htm

Table of Contents

CHAPTER 1: Assessment
Initial History

Purpose:
To provide a comprehensive standardized database for the assessment and treatment of HIV-related problems, including acute intervention and ongoing supportive care, this is a sample format to cover most HIV-related and general health problems that may require follow-up.

History of Present Illness
An opening inquiry about testing and exposure is followed by an assessment of past and current HIV manifestations and treatment:

Testing

1. When did you take the HIV antibody test?
   a. Where was your first positive HIV test performed?
   b. Did you bring a copy of your HIV test results (EIA and Western Blot) today?
   c. Why did you take the HIV antibody test?
   d. Have you ever had a negative HIV test? When was the last negative test?

2. **How do you think you were exposed to HIV?**
   If the patient is able to answer this question satisfactorily, questions 3-7 may not be needed.

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Sexual

3. Have any of your sex partners informed you that they were HIV positive or have AIDS? Have you ever had unprotected vaginal, oral, or anal intercourse, even one time, particularly as the receptive partner? Has any previous partner been in jail or prison? Have you or your partner(s) had any sexually transmitted disease? Have you received donor sperm during artificial insemination?

Substance Use

4. Have you ever used injection drugs (including steroids or vitamins) and shared needles or works, even one time? Have any of your current or past sex partners done so?

Transfusion

5. Did you receive any blood or blood products between 1977 and 1985? Have you ever had surgery during which you were likely to have received blood? Do you or any of your current or previous sexual partners have hemophilia? Have any of your current or previous sexual partners had surgery or blood transfusions between 1977 and 1985?

Occupational

6. Do you work in health care? If so, have you been exposed to blood or infectious body fluids on the job? Have you ever had a needlestick with a contaminated needle or sharp? Did you report to employee health, did you have follow-up testing? Was the exposure source ever tested for HIV or other blood borne pathogens?

Tattoos

7. Do you have any tattoos? Where and when did you get them? Did the tattoo artist use a sterile needle and clean ink?

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Treatment Status

8. Where do you usually go for health care?
9. Have you ever sought care for your HIV?
10. Are you currently under care for your HIV infection?
    If yes, do you know your most recent CD4 count? What is the lowest it's been, and when?
    Do you know your most recent viral load results? What is the highest it has been, and when?
11. Are you currently on medications for HIV, either antiretroviral or to prevent opportunistic infection?
12. Have you previously been on medications for HIV or AIDS? When, what, and how long?
13. Have you participated in any research protocols? Would you be interested in participating?

HIV-Related Illnesses

14. Have you ever had an opportunistic infection? If yes, what and when?
15. Have you had any other HIV-related problems, including cancers and infections?

LTBI Status

16. When was your most recent TB skin test and result? If positive, where were you treated, with what, and for how long? Have you been exposed to or lived with anyone who had tuberculosis (TB)? Have you ever been in homeless shelters or incarcerated (including volunteer work in those sites)?
17. What brought you to this clinic for care now?

Medications

1. What medications for HIV are you taking? Doses, frequencies, and adherence?
2. What HIV medications have you taken previously? What and for how long?
3. For each medication, why was it stopped?
4. What other medications do you take?
5. Any vitamins, supplements, or herbal preparations?

Immunizations

1. When was your last tetanus shot? Have you had a Pneumovax (pneumococcal vaccine), and when?
2. Have you had the Hepatitis A vaccination series? How many and when? Hepatitis B vaccine? How many and when? Which childhood immunizations did you have?

Allergies

1. Are you allergic to any medications, foods, or substances?
2. For each: What type of reaction did you have?

Past Medical and Surgical History

Chronic Diseases

1. Do you receive medical care for any chronic conditions, such as diabetes, high blood pressure, heart disease, asthma, emphysema, sickle cell, ulcers, reflux, irritable bowel, thyroid or kidney problems?

Previous Illnesses

2. Have you ever been hospitalized? When, for what, how long, and where? Any surgeries or major illnesses, injuries? What kind, when, and any effects afterward?

STD's

3. Have you ever been treated for syphilis, gonorrhea, proctitis, vaginitis, genital herpes, chlamydia, NGU (non-gonococcal urethritis), pelvic inflammatory disease, or genital warts (HPV)? Note site, date, treatment, compliance. Ever had an abnormal pap smear?

Hepatitis

4. Have you ever had Hepatitis? Type (A, B, C)? What's your hepatitis serostatus?

TB History

6. Have you ever had active tuberculosis? Are you taking, or have you previously taken, anti-TB medications (type, dose, duration)?

Gynecologic

7. Have you ever been pregnant? If yes, how many full term, premature, miscarriages or abortions, living children? Have you had children after the time you think you were infected? Did you take HIV medications during those pregnancies?

Family History

Family Hx

In your immediate family (parents, siblings, aunts, uncles, grandparents) have there been any chronic diseases such as diabetes, heart disease, kidney or lung problems, cancer, AIDS/HIV, addictions, schizophrenia, depression, dementia, anxieties, phobias, addictions, family violence, abuse? Are they still living? If not, causes of death and ages at death.

Social History

Living Situation

1. Where do you live? Type of residence? Finances; heat/plumbing; refrigeration? Are you married? Do you have children? With whom do you live, i.e., significant others, roommates, children? Are they aware of your HIV status? Partner's or children's HIV status?

Support System 2. Significant other, friends nearby; relationship with sibs/parents/children.
Do your friends, family, partner know about your HIV status? Are they supportive? What community resources have you used for support groups, social services, or assistance?

Occupation 3. Are you currently employed? What kind of work do you do? What hours do you work? Other sources of income? Do you have health insurance? Do you or will you have to pay out of pocket for prescription medications? Have you applied for Medicare, AIDS drug assistance, or other?

Travel 4. Have you ever lived or traveled to other parts of the US? Where, when, how long? Do you travel often? Have you been outside the US, to Mexico, or the Caribbean within the past few years?

Diet 5. Tell me what you eat during a typical day. Do you consume raw (unpasteurized) milk, raw eggs, raw or rare meat, deli meats, soft cheeses, or raw fish? Do you grow your own vegetables? What is your source of water (city, well, etc.)?

Pets 6. Do you have or have you had any pets have you had in the past year? What kind of pets, and who cleans up after them?

Exercise 7. What kind of physical exercise and recreational activity do you participate in? How often? Any swimming, rafting, boating?

Before the next six questions, it is helpful to begin with a statement such as: "Since sex is an important part of overall health, we ask everyone the following questions. You do not have to answer any questions that you are uncomfortable with. Tell me only what you want me to know."

Sexual Orientation/ Identity 8. Do you have sex with men, women, or both? Do you consider yourself heterosexual, homosexual, or bisexual, other? If applicable: Do you consider yourself male or female? Have you ever had hormone therapy? Have you had or considered having a sex change? Any sex-change surgery?

Sexual Practices 9. Do you have oral sex? Anal sex? Vaginal sex? Other activities? How do you protect yourself from sexually transmitted infections? With what kinds of sex do you use condoms or other barrier methods? (If MSM: are you more often the receptive or insertive partner, and what protection do you use for each?) When was the last time you had unprotected sex? Do you use alcohol or drugs before or during sex? Do you think alcohol or drugs make it more difficult for you to follow a safer sex plan?

Prevention 10. Have you made any changes in your sexual behavior because of STDs or HIV? How do you protect your sex partner(s) from HIV? What percentage of the time do you and your partner(s) use condoms (or other barriers, as appropriate)?

Sex trading 11. Have you ever exchanged sex for food, shelter, drugs, or money?

Contraception 12. For heterosexual/bisexual patients: method of birth control, duration of use; use of additional barriers. Are you interested in becoming pregnant? If yes, any plans for when? Are you interested in birth control?

Substance Use 13. How often do you drink alcohol? How many drinks per week average? Tobacco? How many cigarettes per day/how much smokeless tobacco? For how long? Recreational or illicit drugs (What drugs do you use off the street?) What drugs, how much, how long? Are you ever worried about your drug/alcohol use? Have you ever drunk so much or taken so much that the next day you didn't remember what you did ("blackouts")? Have you ever experienced withdrawal symptoms (cravings, "the shakes," DTs, etc.?) Are you on any medicine to help you sleep or to relax? Any pain relievers?

Mental Health

Therapy 1. Are you seeing a therapist or mental health professional? Any previous counseling or mental health problems? Have you thought about seeing a mental health provider? Have you ever been hospitalized for psychiatric illness? Ever been diagnosed with depression, anxiety, panic or bipolar disorder, etc.? Have you or are you taking any medications for these conditions?

Ever thought about hurting yourself? (If yes, probe for previous suicide attempts; Are you feeling that way now? If yes, see *Suicidal Ideation* in Neuropsychiatric section and prepare for immediate referral if necessary.)

Coping 2. How have you been coping with being HIV positive? How do you handle your problems/stresses? Do you have someone you can talk to? What do you do to relax?

Violence 3. Have you ever been sexually abused, assaulted, or raped? In your adult life, have you lived in any situation with physical violence or intimidation? When have these occurred? Are you afraid for your safety now?

Childhood Trauma 4. Thinking back to your childhood, did you experience or observe violence, abuse, or neglect? Did you grow up with both parents? Any alcoholism or drug use in your household when you were a child?

Review of systems

For each positive answer, location, characteristics, duration of symptoms, exacerbating and alleviating factors

General

Fatigue 1. Do you wake up feeling tired? Do you tire easily after normal activities?

Fever 2. Do you have a fever? How high, and how often?

Night Sweats 3. Do you ever sweat so much at night that it soaks your sheets and nightclothes?

Chills 4. Do you experience shaking or teeth-chattering when you feel cold?

Anorexia 8. How is your appetite?

Weight/ 9. How often do you check your weight? How is it compared to one year ago? What is a normal weight for you? Have you lost weight? How much and over what time interval?

Body changes 10. Have you noticed changes in your face or body? Any increase in waist, collar, or breast size? Increased visibility of veins in arms and legs? Any problems with shrinking buttocks?

Eyes

Vision 11. Have you noticed any changes in your vision, especially blurred vision or vision loss, double vision, new "floaters" or flashes of light? Have you noticed this problem in one or both eyes?

Mouth, Ears, Nose, Throat

Thrush 12. Have you noticed any white spots in your mouth or a white coating on your tongue? Do you ever get sores in your mouth or the back of your throat?

Other 13. Any nosebleeds, throat pain, mouth lesions, gum problems?

Cardiovascular

Cardiac 14. Do you have chest pain? Any shortness of breath during the night? How far can you walk or run before you get short of breath? Any heart murmurs, palpitations? Any swelling in feet, hands?

Pulmonary

Cough 15. Do you have a cough? Can you describe it? (dry or productive; amount, color, odor, presence of blood in sputum)? When do you cough more, morning or night?

Dyspnea 16. Do you ever feel short of breath? Does that happen when you are sitting still, lying down, or moving around? How severe is your shortness of breath? Does it prevent you from doing anything? Do you ever wheeze?

Gastrointestinal

Dysphagia 17. Do you have any problems with food sticking in your throat or being difficult to swallow? Do you notice it's easier to swallow liquids? Solids? Do you gag or get nauseated when trying to eat?

Odynophagia 18. Do you have pain in your throat, esophagus, or behind your breastbone when you swallow?

N/V 19. Do you have problems with nausea or vomiting?

Bloating Pain 20. Do you feel uncomfortably full after eating, even if you have only eaten a little food? Problems with abdominal pain?

Reflux 21 Do you ever have heartburn? When does it happen—after eating, lying down, empty stomach?

Gas 22. Do you have problems with belching or flatulence after eating? Is this new or unusual for you?

Diarrhea 23. Do you have diarrhea, or more than 3-5 unformed stools a day? For how long? (If yes, see *Diarrhea* protocol). Can you describe it? Note color change, odor, presence of blood, pus, mucus, or tenesmus (rectal pain on defecation). Do you have pain or cramping with diarrhea?

Bowel habits 24. What are your usual bowel habits? Do you have problems with constipation, blood in the stools, or other?

Genito-urinary

Genital 25. Any lesions or sores on your genital area, now or in the past? Have you ever had genital herpes; if yes, how often do you have outbreaks? When was the most recent outbreak?

Women 26. Last menstrual period? Any changes in your menstrual cycle? Lower abdominal pain? Any vaginal discharge or odor? Have you had yeast infections? If yes, how many in the past year?

Men 27. Any swelling or testicular pain? Any difficulty starting your stream of urine? Are you getting up at night to urinate? Any discharge from your penis?

Urinary 28. Any burning or pain on urination? Ever had a bladder or kidney infection? Ever had kidney stones? Ever have to go to the bathroom and not make it in time?

Musculoskeletal

Myalgia/Pain 29. Do you have any muscle aches or pains? Any other pain going on right now? Back pain, joint pain and/or swelling? Ever broken any bones?

Skin

Herpes Zoster 30. Have you ever had chickenpox (varicella)? Have you had "shingles"? Where were they on your body? How long did it take for the pain to resolve?

Tinea 31. Do you have fungal infections on your skin, especially groin, fingernails, toenails, or feet?

Folliculitis 32. Do you have any new "acne" on your face, back or chest?

Seborrheic 33. Do you have new flaking or itching on your skin or scalp? Dermatitis

Skin Lesions 34. Have you noticed any new moles, bruises, or bumps on your skin? Any new rashes or skin problems? Any moles that changed shape, size, or color?

Neurologic

Headache 35. Do you get headaches? How often? Where? Can you describe the headache? Any new problem with headaches? Are they associated with fever? With nausea? With vomiting? With sensitivity to light? How long do they last? Do you have any other symptoms along with your headaches? What makes them worse or better?

Memory 36. Do you ever feel confused? Do you have difficulty remembering things? Have you had any difficulty concentrating?

Gait 37. Have you noticed any changes in the way you walk? Has anyone told you that you walk differently?

Neuropathy 38. Do you have any numbness, tingling, or pain in hands or feet?

Seizures 39. Have you ever had a seizure or “fit”?

Weakness 40. Do you have or have you had any weakness in your arms or legs?

Endocrine

Diabetic 41. Any increase in thirst, hunger, or urination?

Thyroid 42. Low energy? Hair loss? Heat or cold intolerance? Have your eyes changed in appearance?

Hematologic/lymphatic

Adenopathy 43. Do you have swollen glands? Have they grown larger or more tender?

Bruising or Bleeding 44. Any difficulty with easy bruising or prolonged bleeding after injury? Nosebleeds or bleeding gums?

Psychiatric

Mood 45. Do you feel more angry, sad, depressed, numb, irritable, or anxious than usual?

Sleep 46. How are you sleeping? How many hours do you sleep each night? More or less than you used to? Do you take naps?

Plan:

1. Conduct physical assessment, focusing on subjective findings elicited in the history.

2. If physical exam is not done at this point, initiate a temporary problem list, flow sheet, and 1-2 paragraph summary. Consult with clinic physician.

3. Refer to Social Services for other clinic services, to Mental Health or community/other resources as needed.

4. PPD testing if not done in the last year, and previously PPD-negative.

5. Review need for pneumonia, influenza and other immunizations (See *Recommended Immunizations* in Health Maintenance section), and give as needed.

6. Review lab results (see *Initial Labs* in Assessment section); refer for antiretroviral adherence counseling and education if a candidate for highly active antiretroviral therapy (HAART)

7. Plan for patient education regarding preventing opportunistic infections and HIV prevention (see *Preventing Exposure to Opportunistic Infections* and *Preventngf HIV Transmission* in Health Maintenance section)

Initial Physical Exam

Purpose:

Essential points to be covered in an initial clinic intake visit. It is important to conduct a thorough initial history and physical assessment, even if previous medical records are available, because this is the best opportunity to get a complete picture of the patient's physical and emotional status, and of their place in the spectrum of HIV disease. In addition, many of the conditions that put immune-compromised patients at risk for disease can be detected early during a thorough physical assessment.

S: Patient states s/he has HIV infection.

O/A: General appearance: Note the overall appearance, demeanor, and affect of your patient in a few sentences of "global impression." This impression can be very important to you later when you assess disease progression.

V/S:
- *WT:* Record at each visit. **Weight is the single most important long-term, objective measure of disease progression.**
- *HGT:* Should be measured once.
- *BP:* Hypertension is common and should be evaluated.
- *TEMP:* Measure at each visit. High or sustained fever is an indication of opportunistic infection.
- *PULSE*: Provides baseline rate for later evaluation of anemia, dehydration, and other.
- *Waist*: Waist and hip circumference should be measured for comparison if patient is later placed on HAART
- *BMI:* Calculate body mass index (BMI), which is helpful in assessing for obesity, wasting, and HAART related weight gain. Divide weight in pounds by height in inches, then divide result by height in inches. Multiply the result by 703. Formula: **[(wt in lbs. ÷ ht. in inches) ÷ ht in inches] x 703 = BMI**
  Based on NIH guidelines, a BMI between 25 and 29.9 is considered overweight, and 30 or more is considered obese.

EYES:
Assess visual acuity and visual fields by confrontation. On funduscopic exam, ideally with mydriatics, look especially carefully for retinal lesions. Note presence/absence of **white or yellowish retinal discoloration, infiltrates, or hemorrhages** which might suggest cytomegalovirus retinitis, retinal necrosis, or ocular toxoplasmosis**.** Tests of extraocular movements and pupillary size and reaction should be done to detect possible intracranial lesions. Referral to ophthalmologist q 6 months once CD4 <100/mm^3 for dilated slit-lamp exam. Refer immediately if patient has retinal lesions or new visual disturbances.

EARS / NOSE:
Both ears and nose are common sites for Kaposi's Sarcoma lesions or HSV, and sinusitis is a frequent problem in HIV-infected individuals. Visualize nasal turbinates and palpate frontal and maxillary facial sinuses.

ORAL CAVITY:
The exam is conducted under strong light, the clinician should be gloved, and s/he should use gauze to draw out the tongue for complete examination. Assess gingiva and teeth. Note the presence and location of warts (HPV disease), ulcers on the mucosa or mouth corners, white plaques, or violaceous macules or papules that would indicate HSV, aphthous ulcers, KS or hairy leukoplakia

ENDOCRINE: Check thyroid for enlargement, tenderness, nodules, asymmetry.

LYMPH NODES:
The palpation and measurement of nodes is critical to proper disease staging. Spend time assuring that this part of the examination is well done. Fine-needle aspiration or excision biopsy should be considered if the patient reports rapid new enlargement of lymph nodes or if physical exam is suspicious (see *Lymphadenopathy* in Complaint-Specific section). Note and document sites and characteristics of each palpable node:

Node Sites

- posterior cervical chain
- anterior cervical chain
- submandibular
- submental
- supraclavicular
- axillary
- intracostal
- epitrochlear
- inguinal
- femoral

Characteristics

- size (2 dimensions, in mm.)
- consistency (hard, fluctuant, soft)
- tenderness
- mobility
- definition (discrete, matted)
- symmetry

SKIN:
Patients should disrobe completely so that all skin areas can be visualized and assessed. Include scalp, axillae, palms, pubic and perianal areas, soles. Describe all lesions: size, borders, color, symmetry/asymmetry, distribution, raised/flat, induration, encrustation. Look for evidence of folliculitis, seborrheic dermatitis, psoriasis, Kaposi's, fungal infections, prurigo nodularis, etc.

LUNGS:
Auscultate and percuss. Findings of crackles or wheezes, particularly when coupled with involuntary cough on deep inspiration, suggest a bacterial process, PCP, or asthma.

HEART:
Auscultate rate rhythm, listen for extra heart sounds, murmurs, and palpate for point of maximal impulse. Injection drug users may have murmurs indicative of endocarditis; heart failure or cardiomyopathy may be evidenced by S3 or laterally displaced PMI.

BREASTS:
Palpate for breast masses in both men and women. Check for symmetry, discharge dimpling, and masses.

ABDOMEN:
Auscultate, percuss, and palpate abdomen. Findings of hepatomegaly or hepatic tenderness or splenomegaly may suggest mycobacterial infection; fungal infection; viral infection including Hepatitis B or C; or lymphoma. Percuss and record liver size at mid-clavicular line and percuss area of splenic dullness.

EXTREMITIES/ MUSCULATURE:
Assess muscle bulk (normal, decreased), muscle tenderness (r/o myositis), and muscle weakness for the major muscle groups. Look for evidence of peripheral fat atrophy, and consider measuring baseline arm thigh, and chest circumferences for later comparison. Nail changes (clubbing, cyanosis, fungal infections) should also be noted. Assess for pedal edema.

GENITALS/ RECTUM:
Inspect the external genitalia and perirectal area. Ulcerative lesions, vesicles and crusted lesions should be cultured for HSV, syphilis, and chancroid if a previous diagnosis does not exist (see *Herpes* and *Syphilis* in Disease Specific section). Men who have sex with men and HIV-infected women are at increased risk for anal HSIL and some evidence supports anal Pap smears in these populations. Further studies on screening and treatment programs for anal HSIL need to be completed before a general recommendation can be made. Interimly, some clinicians screen high-risk patients (for example, any patient with peri-anal warts) with annual anal pap smears.

Female patients must have a pelvic examination which includes a bimanual and speculum exam. A Pap smear to detect cervical abnormalities, an endocervical swab for GC and chlamydia, (or a nucleic acid amplification test) and a posterior pool swab for wet mount to detect trichomoniasis, candida, and bacterial vaginosis should be performed. Abnormal or inconclusive Pap smears require colposcopic follow-up, as invasive cervical CA progresses rapidly in women with HIV (see *Cervical Pathology/Atypia* in Disease-Specific section)

In **male patients**, digital rectal with prostate exam to evaluate for tenderness and enlargement. In **all patients with a history of anal intercourse**, rectal tone, discharge and tenderness should be noted. Testicular exam to detect tenderness, enlargement, masses.

NEUROLOGIC:
Perform a brief but thorough baseline neurologic exam. Assess mental status, eliciting orientation, judgment, recent and remote memory, and ability to calculate (serial subtraction). Cranial nerves should be individually tested. Test deep tendon and plantar reflexes. Assess extremity strength & gait to discern neuropathies and cerebellar disease. Peripheral sensory exam should include light touch and vibratory stimuli. Assess fine motor skills such as rapid alternating movements (often abnormal in dementia).

PSYCHIATRIC:
There is no brief testing which allows for rapid psychiatric diagnosis. Note the patient's general mood (depressed, anxious, hypertalkative, etc); the verbal content, i.e., discussion of suicide; and inappropriate or unusual behavior, such as extremes of denial, hostility, or compulsiveness. See Neuropsychiatric section for more complete information on common pathologies. Refer emergency situations, such as potential suicide or violence to Crisis Mental Health for immediate evaluation. Refer to mental health or substance abuse counselor for suspected addiction, adjustment disorder, depression, PTSD, childhood sex abuse or other abuse history.

P: If the entire exam cannot be completed at initial visit, a note should be made on the patient database on what portions of the exam are to be completed at the next clinic visit. Begin patient education, if not already in progress.

1. Complete patient database.
2. Complete follow-up studies or labs suggested by history and exam (See Initial Screening Labs protocol).
3. Prescribe OI prophylaxes as appropriate (see Health Maintenance section); and refer for antiretroviral adherence counseling if appropriate.
4. Document problem list, assessment, and plan for patient care.
5. Present patient to one of the staff physicians, emphasizing problem areas needing further resolution.

Patient Education:

1. HIV is a chronic, life-threatening illness. Close medical monitoring and constant vigilance are extremely important for staying well as long as possible. Review physical exam and lab findings when available and share with patient to introduce treatment options and recommendations (see *Initial Lab*s in Assessment section). Discuss patients' health goals, adherence to appointments and to medications. Review what symptoms need to be reported, such as fevers, rashes and other health events, and how to go about getting needed care.

2. Reinforce a holistic approach to wellness. Stress reduction, rest, and mental health are possible self-care issues to discuss. Physical, emotional, and spiritual health are all connected and must be given attention.

3. Teach women how to perform breast self-examination and males how to perform self-testicular exams.

4. Discuss with the patient which people actually need to know about their HIV infection. Generally, this will be health care providers and sexual partners. Beyond that, patients need to consider who among their friends/family are likely to offer support and empathy, versus who is likely to stigmatize the patient or inappropriately disclose the patient's HIV status to others. See *HIV Prevention* in the Health Maintenance section for recommendations on reducing risk of intimates, and partner notification.

5. Discuss living arrangements, financial and insurance status, personal safety, child care. Refer to case manager as needed for assistance with social services if this has not already been done.

6. Other instructions as needed dependent on patient situation and plan of care. See Health Maintenance section and any relevant treatment recommendations based on diagnoses and problems identified in visit.

7. Other general patient education is specified in the Health Maintenance section under HIV Prevention and OI Prevention. Education about HIV and about their personal health is ongoing, and vital to the success of any treatment. Review and relevant questions should be revisited at each appointment.

Initial and Interim Labs

Purpose: To provide a guideline for monitoring patients with HIV infection which identifies other co-infections and assists in tracking disease progression. Note that documentation of HIV status (+EIA and WB) should be on the chart; if not, it should be performed at first opportunity.

TEST	RATIONALE	RESULT	RECOMMENDED ACTION
T-cell subset: CD4 and CD8 count, % and ratio	Staging; treatment; prognosis	CD4 > 500/mm^3	Repeat q 6 months; evaluate risk of clinical progression. Antiretrovirals (HAART) indicated if high viral load (see *HAART*)
		≤ 500/mm^3	Start antiretroviral therapy if symptomatic, if CD4 count < 350, or if VL >55,000; retest q 3 months. See *HAART*
		≤ 200/mm^3 or ≤ 14%	PCP prophylaxis; repeat CD4 q 3 months; start ARVs if at all possible
		≤ 100/mm^3	Toxo prophylaxis if toxo IgG+ (see *Toxoplasmosis prophylaxis)*
		≤ 50/mm^3	DMAC prophylaxis (see protocol)
Plasma HIV-1 RNA	Estimate risk of disease progression; determine if ARVs indicated	undetectable	maintain current regimen
		measurable virus	Follow *Antiretroviral Therapy* guide; if pregnant, see *Pregnancy* in Health Maintenance section (see also Viral load)
Antiretroviral Drug Resistance Testing	Determine to which antiretroviral medications the patient's HIV is susceptible when viral suppression is poor on HAART regimen. Only helpful if patient is currently taking the drugs in question and VL is > 1000	No resistance to current regimen detected	Look for other causes of regimen failure, e.g., poor adherence or absorption (see A*ntiretroviral* section)
		Resistance to all or part of current regimen	Change HAART regimen if possible; obtain expert consultation
CBC with differential & platelets	Detect anemia, thrombocytopenia, leukopenia	normal	Repeat q 6 - 12 months
		abnormal	Work up & follow as indicated; monitor hematologic toxicity of medications (see Medications section)
Biochemical profile	Detect hepatic enzyme elevations, electrolyte abnormalities, hyperglycemia, renal insufficiency, useful to monitor drug toxicity	normal	Repeat annually, and as needed to monitor antiretroviral therapy
		abnormal	Work up & follow as indicated
Lipid Profile	Baseline information prior to HAART therapy	normal	Repeat q 3-4 mos. after starting HAART
		abnormal	Interventions as in *Hyperlipidemia* section. Repeat q 4-6 wks until LDL goal reached, then q 4-6 months

TEST	RATIONALE	RESULT	RECOMMENDED ACTION
PSA	Prostate cancer screen (**males over 50 with > 10 year life expectancy only**)	normal	Repeat, along with digital rectal exam, annually
		abnormal	Refer to GU for follow-up
Hepatitis A serology	Screen for previous immunity in those > 40 y.o.	normal (neg)	Offer Hepatitis A vaccine if HCV+ or high risk group (See *Immunizations*)
		abnormal (pos)	No vaccine necessary
Hepatitis B serology (if un-vaccinated)	Hepatitis B surface antigen and core antibody	(-) core ab	Consider vaccine
		(+) surf ag	Work up & treat as appropriate Infants born to HBsAg+ mothers should receive HBIG and HBV vaccine at separate sites within 12 hours of birth
Hepatitis C EIA (antibody)	Hepatitis C screening	normal	Teach patient to avoid infection (false negatives occur in 20%)
		abnormal (positive)	HCV RNA PCR (or RIBA) to confirm HCV infection. (Negative result does not completely R/O infection; see protocol)
VDRL or RPR	Syphilis screening	negative	Repeat annually
		positive	See syphilis protocol
Anti-Toxoplasma IgG	Detect exposure; if positive, increased risk of developing CNS toxoplasmosis	Normal/negative	Teach patient to avoid exposure. Repeat if patient becomes symptomatic or when CD4 count drops to 100 (See *Prevention of Exposure to OIs* in Health Maintenance)
		abnormal/positive	Note as baseline information Start toxoplasmosis prophylaxis when CD4 drops to 100 or less (see protocol)
G6PD level	Prevent hemolytic reactions by screening susceptible males, of African, Mediterranean, Asian, Sephardic Jewish descent	Normal	No intervention necessary beyond documentation
		Abnormal	Avoid oxidant drugs such as dapsone, primaquine, sulfonamides
CMV antibody (only those with no hx of IDU or contact with male homosexuals)	Detect exposure, may reveal future disease risk	normal	Teach patient how to avoid exposure; if transfusion required, use CMV-negative or leukocyte-reduced blood (See *Prevention of exposure to OIs*)
		abnormal	Be aware of disease risk later in HIV infection, when CD4 count <50
UA	Detect proteinuria or pyuria	normal	Repeat annually
		abnormal	Rule out HIVAN* and other causes of nephropathy

TEST	RATIONALE	RESULT	RECOMMENDED ACTION
PPD	Detect latent TB infection	normal	Repeat q 6 mos or annually based on risk
		abnormal (induration ≥ 5 mm)	Evaluate for active TB; see *Latent TB Infection* in Health Maintenance section
CXR	Detect latent or active diseases	normal	Repeat as indicated for pulm. sx or +PPD
		abnormal	Evaluate for TB, PCP, other pathology
Pap smear	Detect cell changes	normal	Repeat in 6 months, then annually
		abnormal	Work up, treat (see Cervical Atypia) and follow up more frequently as indicated by condition
GC and chlamydia testing	With initial pap on all women; and any symptomatic men. To detect STDs.	Negative	Counsel re avoiding STDs; repeat if needed
		Positive	Treat patient; refer partner(s) of previous 60 days for evaluation and treatment
GC and chlamydia testing, urethral	Sexually active men who have sex with men (MSMs)	Negative	Re-test annually
		Positive	Treat; refer partners from 60 days as above
GC and chlamydia testing, pharynx	Sexually active (MSMs) who have oral-genital contact	Negative	Re-test annually
		Positive	Treat; refer partners from 60 days as above
GC and chlamydia testing, rectal	Sexually active (MSMs) who have receptive anal sex	Negative	Re-test annually
		Positive	Treat; refer partners from 60 days as above
Dilated retinal Exam	Detect CMV or toxo or HIV retinopathy	normal	Dilated exam q year with CD4-cells >100; q 6 months if CD4-cells <100
		abnormal	Follow up immediately with ophthalmologist

NOTE: When starting antiretrovirals or other medications with potential systemic toxicities, refer to protocol and prescribing information to determine which additional labs may be needed for follow-up.

Patient Education:

1. Safer sex (review specifics appropriate to patient's sexual practices and infections; see *HIV Prevention* and *Prevention of Exposures to OIs* in Health Maintenance section) for prevention of patient exposure to Herpes, Hepatitis B, Hepatitis C, other STDs, and to prevent patient exposing others to HIV or other pathogens.

2. If Toxoplasma IgG-negative, see *Prevention of Exposure to Opportunistic Infections* section in Health Maintenance section.

3. If CMV (-): CMV is shed in semen, vaginal, and cervical secretions, saliva and urine of infected people. Latex condoms will help reduce risk. From women considering childbearing, CMV should be assiduously avoided to prevent severe disease and even death of the neonate. See *Prevention of Exposure to Opportunistic Infections* in Health Maintenance section.

4. For people who are Hepatitis C negative and still use injection drugs, offer referral to drug treatment program. See *Prevention of Exposure to Opportunistic Infections* and *Preventing HIV Transmission* sections in Health Maintenance section.

References:

CDC. USPHS/IDSA Guidelines for Preventing Opportunistic Infections Among HIV-Infected Persons. *MMWR* 2002; 51 (No. RR-8).

CDC. Guidelines for Using Antiretroviral Agents Among HIV-Infected Adults and Adolescents: Recommendations of the Panel on Clinical Practices for Treatment of HIV. *MMWR* 2002; 51 (No. RR-7)

CDC. Sexually Transmitted Disease Treatment Guidelines 2002. *MMWR* 2002; 51 (No. RR-6).

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Interim Physical Exam

Purpose:

To gather and document a standard written record of clinically important data over many visits, to enable the clinician to track disease progression and formulate a plan for intervention. Note the patient's general appearance and demeanor at each visit. It is also important to document new or ongoing symptoms and functional limitations at each visit. This is particularly useful when outside agencies must determine the client's disability status (See *Karnofsky Performance Scale* at the end of Assessment section.)

The following table lists the suggested frequency of examination and follow-up for monitoring HIV-infected patients. Note that individual medications and abnormalities may call for additional directed examinations. (See *Initial and Interim Labs* for suggested frequencies of lab tests.)

SYSTEM	SUGGESTED MINIMUM FREQUENCY
Vital Signs (Temp, BP, Pulse, Respiration) Weight Oral exam Psychiatric--mood, affect Neuro evaluation Skin	Every visit
Visual & funduscopic exam Lymph nodes Ears/nose Abdominal exam Heart & lungs	Every 3 Months
Pap smear, pelvic exam	Every 6 months x 2, and if both are normal, annually thereafter (see *Cervical Atypia* in Disease Specific section)
Breast and testicular exam Genito-rectal, prostate exam	Annually

References:

CDC. USPHS/IDSA Guidelines for Preventing Opportunistic Infections among HIV-Infected Persons. *MMWR* 2002; 51 (No. RR-8).

Bartlett JG, Gallant JE. *2001-2002 Medical Management of HIV Infection.* 2001, Baltimore, Johns Hopkins University Division of Infectious Diseases.

Hecht F and Soloway B. The Physical Exam in HIV Infection. AIDS Clinical Care. 3(1) p. 4-5.

Hollander H. Initiating Routine Care for the HIV-Infected Adult. In Sande MA, Volberding PA (Eds) The Medical Management of AIDS, Fifth Ed. Philadelphia, WB Saunders. 1997, pp.107-112.

Disease Staging & Classification

Purpose:

The US Centers for Disease Control and Prevention revised the HIV/AIDS classification system in 1993, "to emphasize the clinical importance of the $CD4^+$ lymphocyte count in the categorization of HIV-related clinical conditions."[1] This system expanded the definition of AIDS to include all HIV-infected people with $CD4^+$ counts of <200 mm^3, plus patients diagnosed with three additional opportunistic infections: pulmonary tuberculosis, invasive cervical cancer, and recurrent bacterial pneumonia. Even if clinicians are not involved in AIDS reporting activities, they should be proficient in the use of this staging classification**. To be classified as an AIDS case, patients must demonstrate laboratory evidence of HIV infection PLUS one or more of the following: CD_4 cell count below 200/mm^3, CD_4 percentage below 14%, presence/history of an AIDS-indicator condition** (see next page).

S: The patient states s/he is HIV seropositive.
Take a careful history to elicit and document any HIV-related symptomatology; see *Initial History* in Assessment section.

O: Perform initial or interim physical exam and appropriate laboratory studies according to *Initial Physical* and *Initial and Interim Labs* in Assessment section.

A: Rule out other causes of immune system suppression.

P:
1. Obtain CD4+ lymphocyte absolute count and percent (and other labs as indicated).
2. Document HIV seropositivity, by repeating HIV test or obtaining written result from test site.
3. Evaluate laboratory results and symptoms, and make staging classification according to the following system (note patient's CDC classification in chart on Problem List). [1]

CLINICAL CATEGORIES

CD4+ CELL CATEGORIES	(A) Asymptomatic, acute HIV* or PGL**	(B) Symptomatic, not (A) or (C) conditions	(C) AIDS-indicator conditions***
(1) > 500/mm3	A1	B1	C1
(2) 200-499/mm3	A2	B2	C2
(3) <200/mm3	A3	B3	C3

PATIENTS IN CATEGORIES A3, B3, C1, C2,& C3 ARE REPORTABLE AS AIDS CASES IN THE UNITED STATES, EFFECTIVE JANUARY 1, 1993.

* Acute HIV is primary HIV infection, characterized by flu- or mononucleosis-like illness, or meningitis, generally occurring within 6 weeks of a documented exposure to HIV. See *Appendix C*.

** PGL = persistent generalized lymphadenopathy.

*** AIDS-indicator conditions are the list of 26 clinical conditions listed on the following page.

Patient Education:

1. Although the definition of a case of AIDS has changed, patients will not be automatically eligible for disability; inability to function will still require documentation.

2. Refer the patient who seems stunned by the news of their diagnosis for a one-month follow-up appointment (although sooner is better) for mental health evaluation.

3. Risk of progression is mainly determined by the HIV-1 RNA level (viral load), along with the CD4 count; see pages 19 and 22. Illness may be delayed significantly by appropriate medical care. See *Antiretroviral Therapy, Health Maintenance, and Viral load* sections

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AIDS-Indicator Conditions

- Bacterial pneumonia, recurrent (≥ 2 episodes in 12 months)
- Cervical carcinoma, invasive, confirmed by biopsy
- Candidiasis of the bronchi, trachea, or lungs
- Esophageal candidiasis
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month duration)
- Cytomegalovirus disease (other than liver, spleen or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- HIV encephalopathy
- Herpes simplex: chronic ulcers (>1 month duration), or bronchitis, pneumonitis or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary in brain
- Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary
- Mycobacterium tuberculosis, pulmonary, disseminated or extrapulmonary
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis pneumonia
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome (weight loss >10% of baseline body weight, associated with either chronic diarrhea or fever)

Category B conditions are defined as symptomatic conditions occurring in an HIV-infected adolescent or adult which meet at least one of the following criteria:

a) They are attributed to HIV infection and/or indicate a defect in cell-mediated immunity:
b) They are considered by physicians to have a clinical course/management that is complicated by HIV infection.

Examples (NOT all-inclusive)

- Listeriosis
- Pelvic inflammatory disease
- Idiopathic thrombocytopenic purpura
- Recurrent bacterial endocarditis, meningitis, or sepsis
- Persistent or resistant vulvovaginal candidiasis
- Constitutional symptoms, such as fever (>38.5 C) or diarrhea lasting >1 month
- Nocardiosis
- Peripheral neuropathy
- Oropharyngeal candidiasis (thrush)
- Herpes zoster (shingles), involving at least 2 episodes or more than 1 dermatome

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Surveillance Case Definition of HIV Infection

Surveillance Case Definition of HIV Infection (including AIDS), is included for public health surveillance purposes only. HIV is not reportable in all states, but legal requirements may change from year to year. This is the definition of HIV infection for reporting in states where it is required.

In adults, adolescents, children ≥ 18 months of age, **a reportable case of HIV Infection meets any of the following criteria:**

Laboratory Criteria

Positive result on a screening test for HIV antibody (e.g., repeatedly reactive enzyme immunoassay) followed by a positive result on a confirmatory (sensitive and more specific) test for HIV antibody (e.g., Western blot or immunofluorescence antibody test), **OR**

Positive result on any of the following HIV virologic tests:

HIV nucleic acid (DNA or RNA) detection test, such as DNA PCR or plasma HIV-1 RNA (viral load)

HIV p24 antigen test, including the neutralization assay

HIV isolation in viral culture, **OR**

Clinical Criteria (if the above criteria are not met):

Diagnosis of HIV infection based on the laboratory criteria above that is documented in a medical record by a physician, **OR**

Any conditions that meet the criteria included in the case definition for AIDS.

References

Centers for Disease Control. December 18, 1992. *1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS among Adolescents and Adults.*

Centers for Disease Control and Prevention. Guidelines for national Human Immunodeficiency Virus case surveillance, including monitoring for Human Immunodeficiency Virus Infection and Acquired Immunodeficiency Syndrome. *MMWR* 1999; 48(RR-13)

CD4 Staging & Prognosis

Definition: T-lymphocytes (or CD4 cells) are primary attack cells for HIV. Three measurements of T-lymphocytes have clinical implications in the management of HIV-infected patients: absolute CD4 count, CD4 percent (the percent of T-lymphocytes with the CD4 surface receptor), and the CD4: CD8 ratio (T-helper: T-suppressor ratio). As HIV infection progresses, all three of these indices decline. The CD4 panel is used for staging and definition purposes, and to determine when to start a particular OI prophylaxis. It is less useful than virus load in predicting risk of disease progression. (See *Initial and Interim Labs*, in Assessment section.)

STAGING BASED ON CD4 COUNT: Dr. Paul Volberding, of the University of California at San Francisco and VA Medical Center, developed the following disease staging classification for HIV based on CD4 counts:

STAGE	TYPICAL CD4 COUNT	TYPICAL DURATION
Acute/Primary HIV	1000 - 500	1 - 4 weeks
Asymptomatic	750 - 200	2 - 15 years
Early symptomatic	500 - 100	<1 - 5 years
Late symptomatic	200 - 50	<1 - 3+ years
Advanced disease	50 - 0	<1 - 2+ years

Risk of Developing AIDS* Based on Initial CD4 COUNT and HIV-1 VIRAL LOAD among Homosexual Men not on HAART, in MACS Cohort

Patients with CD4 ≤ 200 % developing AIDS-defining complication* within:

Viral load: by RT-PCR	3 years	6 years	9 years
≤ 1500	§	§	§
1,501 - 7,000	§	§	§
7,001 - 20,000	14.3%	28.6%	64.3%
20,001 - 55,000	50.0%	75.0%	90.0%
>55,000	85.5%	97.9%	100%

Patients with CD4 201-350 % developing AIDS-defining complication* within:

Viral load by RT-PCR:	3 years	6 years	9 years
≤ 1500	--	--	--
1,501 - 7,000	--	20.0%	32.2%
7,001 - 20,000	6.9%	44.4%	66.2%
20,001 - 55,000	36.4%	72.2%	84.5%
>55,000	64.4%	89.3%	92.9%

Patients with CD4 >350 % developing AIDS-defining complication* within:

Viral load by RT-PCR:	3 years	6 years	9 years
≤ 1500	1.7%	5.5%	12.7%
1,501 - 7,000	2.2%	16.4%	30.0%
7,001 - 20,000	6.8%	30.1%	53.5%
20,001 - 55,000	14.8%	51.2%	73.5%
>55,000	39.6%	71.8%	85.0%

* In this group, AIDS was defined using the 1987 definition, which did not include asymptomatic people with CD4 counts <200
§ Too few subjects were in the category to provide a reliable estimate of AIDS risk.

References:

CDC. Guidelines for Using Antiretroviral Agents among HIV-Infected Adults and Adolescents: Recommendations of the Panel on Clinical Practices for Treatment of HIV. *MMWR* 2002; 51 (No. RR-7)

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CD4 Monitoring

Introduction:

Three measurements of CD4 cells (also called T-cells) have clinical implications in the management of HIV-infected patients: absolute CD4 count, CD4 percent (the percent of T-lymphocytes with the CD4 surface receptor), and the CD4 (T-helper) : CD8 (T-suppressor) ratio. As HIV infection progresses, all three of these indices decline. Because these measurements rely on calculations of multiple variables, they can be imprecise. Many factors affect CD4 counts, including illness, vaccination, diurnal variation, lab error, and inter-lab differences (See PATIENT EDUCATION section below). Since CD4 counts tend to fall gradually, a marked inconsistency in levels and results from previous testing should prompt the clinician to repeat the test(s) before changing the way the patient is managed. The Centers for Disease Control and Prevention recommend that anti-retroviral therapy be instituted based in part on CD4 count. Anti-PCP prophylaxis is recommended when the patient's CD4 count reaches 200/mm^3, DMAC prophylaxis when the count is at or below 50/mm^3, and toxoplasmosis prophylaxis when CD4 count is 100/mm^3 or less in patients whose toxoplasmosis IgG is positive.

S: Patient states that s/he has HIV infection.
O: Complete the initial or interim physical exam as per protocol.
A: Rule out other causes of immune suppression.
P: LABS

1. Obtain CD4 and viral load testing. Consider resistance testing if the patient is failing antiretroviral regimen he or she is currently taking. See *Initial and Interim Labs* in Assessment section for other lab work that should be done for each patient.
2. Monitor results and manage per the following schematic:

See *HAART* in Antiretroviral Therapy section for more specific information.

Clinical Category	CD4 Count	Plasma HIV 1 RNA	Antiretroviral Therapy Recommendations	REPEAT TEST
Asymptomatic	> 350/mm^3	< 55,000	Many experts would defer therapy and observe, recognizing that the 3-year risk of developing AIDS in untreated patients is < 15%	Every 3-4 months if not on HAART (see below if HAART started)
Asymptomatic	> 350/mm^3	> 55,000	Some experts would recommend initiating therapy, since the 3-year risk of AIDS in untreated patients is 30%. Others would defer therapy and monitor CD4 counts more often.	Every 3-4 months until HAART is started, then check for VL response at 2-8 weeks; monitor CD4 and VL every 3-4 months if satisfactory response
Asymptomatic	201-349/mm^3	Any value	Treatment would generally be offered, although controversy still exists	As above
Asymptomatic, AIDS	<200/mm^3	Any value	Treat with ARVs (see Health Maintenance section for prophylaxis recommendations)	As above
Symptomatic (AIDS, severe symptoms)	Any value	Any value	Treat	As above

* Before beginning antiretrovirals, a full assessment of readiness, most appropriate regimen, and other factors must take place. Antiretroviral therapies that are started before the client is ready to adhere to the regimen may severely restrict future treatment possibilities.

Adapted from Guidelines for Using Antiretroviral Agents Among HIV-Infected Adults and Adolescents, 2002, http://www.aidsinfo.nih.gov

Patient Education:

1. T-cell levels are variable. Don't pin your emotions and hopes to a single lab result.

2. Get T-cells tested at roughly the same time of day each visit.

3. T-cells often increase with highly effective antiretroviral therapy. However, we may need to leave you on some of the same prophylaxis medications as you were when the count was lower. If your T-cell count goes up and stays up, we may be able to discontinue some of the prophylaxis medications in a few months. If your count goes down later, we will need to re-start them.

References:

CDC. USPHS/IDSA Guidelines for Preventing Opportunistic Infections among HIV-Infected Persons. *MMWR* 2002; 51 (No. RR-8).

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Viral Load Testing

Background:
The amount of HIV (virus burden) in the body is highest shortly after HIV infection, during the time just prior to seroconversion on the HIV antibody test. Some weeks after infection, the plasma virus level (HIV RNA) decreases and tends to reach a fairly stable level during the asymptomatic period. The virus remains active during this period; the host's immune system is killing millions of viruses per day, sacrificing a similar number of CD4 cells in the process. Although the body replaces the CD4 cells quite rapidly, it tends to lose ground over time and CD4 counts decline if HIV is untreated.

Numerous studies have shown that patients who have a higher plasma virus level progress to symptomatic disease and death much more rapidly than patients with low or undetectable levels. Plasma HIV RNA quantitation is now accepted as a necessary monitoring tool in HIV prognosis and treatment.

Viral load testing in conjunction with CD4 cell counts, is used to assess prognosis and monitor progress and as a determinate to initiating or changing HAART. The viral load assays are HIV RNA PCR (Amplicor HIV-1 Monitor, Roche Laboratories), the branched chain DNA or bDNA (Bayer Versant HIV-1 RNA assay), and the nucleic acid sequence-based amplification of NASBA (NucliSens HIV RNA test from bioMerieux). Thresholds for detection are 20-50 copies/mL for the ultrasensitive assay and 200-400 copies/mL for the standard assay. The difference in cost between the standard and ultrasensitive assays may be up to $200 and therefore the standard assay should be ordered in the initial evaluation of an untreated HIV positive patient.

Patients undergoing seroconversion and those with advanced disease may have viral loads as high as 10,000,000 while those who are asymptomatic will demonstrate viral loads considerably lower. As with the T-cells, viral loads are also affected by illness and recent vaccinations. Assessing any significant change in the viral load should take this into consideration and measurement should be deferred for 4 weeks following illness or vaccination.

If funding permits**, baseline** (standard) viral RNA should be checked at least twice before starting an antiretroviral regimen, because of test variability and because many factors can cause temporary increases of HIV RNA. In situations where the viral load is extremely high, and there is no reason to believe it is in error, some clinicians would start HAART before seeing a second result. **Follow-up** viral load measurement should be performed at regular intervals depending on the patient's response to therapy. In the stable patient, viral load monitoring should take place every 3-4 months. In patients who require a change in therapy, viral load measurements should be repeated within 4 weeks after making a change. See section on *Antiretrovirals* for further discussion.

Follow-up: Use the same type of lab test used for baseline to check plasma HIV RNA 3-4 weeks after starting any new antiretroviral regimen. See Antiretroviral Guidelines for further information on expected decreases. Virus load tests should subsequently be monitored along with the CD4 counts to detect signs of regimen failure.

Note that patients with very high baseline viral loads may take longer to show the full effect from an effective regimen. Some studies have suggested that patients with very high virus loads may take up to 6 months to see maximal reduction in virus loads. Patients with extremely high viral loads are also less likely to achieve undetectable viral loads than patients with low baseline virus levels.

TABLE: Likelihood of Developing AIDS within 3 Years, without HAART Therapy

	Viral Load >55,000	Viral Load 20,000-55,000	Viral Load 7,000-20,000	Viral Load 1500-7,000	Viral Load <1500
CD4 >750	**32.6%**	**9.5%**	**3.2%**	**2.0%**	**n/a**
CD4 501-750	**32.6%**	**16.1%**	**8.1%**	**2.0%**	**3.7%**
351-500 CD4	**42.9%**	**16.1%**	**8.1%**	**2.0%**	**n/a**
201-350 CD4	**64.4%**	**40.1%**	**8.1%**	**n/a**	**n/a**
<200 CD4	**85.5%**	**40.1%**	**n/a**	**n/a**	**n/a**

Viral load (VL) values are the equivalents converted to RT-PCR values, from the MACS cohort.
From: Mellors et al, 1997.

Test results may be affected by patient factors
The viral load may be higher during the 6 to 8 weeks following immunizations, although there are conflicting opinions on whether this occurs in every patient. Viral load is expected to be higher during acute illnesses or intercurrent infections, including TB, PCP, bacterial pneumonia, and herpetic outbreaks, and immunizations can raise HIV-1 RNA levels for 2-4 weeks. **Viral load testing for the purpose of making antiretroviral therapy decisions should not be done during these times.**

If a patient has missed one or more doses of antiretroviral medications, the viral load will immediately begin to climb. When drawing follow-up viral load, assess recent adherence to the full regimen as well as the patient's overall adherence since the last appointment.

Margin of error
Differences of ½ log (or about 5-fold) may be due to assay variability, and should not be considered significant unless part of a trend. There may be more or less variability as testing is implemented in different laboratories. If in doubt, call the performing laboratory and to find out about margin of error.

Indications for Plasma HIV-1 RNA Testing*

Clinical Indication	Information	Use
Syndrome consistent with acute or primary HIV infection	Establishes diagnosis when HIV antibody test is negative or indeterminate	Diagnosis (should be confirmed by standard HIV antibody test in 2-4 months after initial test)
Initial evaluation of newly diagnosed HIV infection	Baseline viral load, or "set point"	Decision to start or defer therapy
Every 3-4 months in patients not on therapy	Changes in viral load	Decision to start therapy
2-8 weeks after starting antiretroviral therapy	Initial assessment of drug regimen efficacy	Decision to continue or change therapy
3-4 months after starting antiretroviral therapy	Maximal effect of therapy	Decision to continue or change therapy
Every 3-4 months in patients on antiretroviral therapy	Durability of antiretroviral suppression	Decision to continue or change therapy
Clinical event or significant decline in CD4 cells	Association with changing or stable viral load	Decision to initiate, continue, or change therapy

*Plasma HIV-1 RNA results should generally be verified with a second test before starting or changing therapy.

Table adapted from 2002 DHHS Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents.

Patient Education:

1. Viral load is the best indicator of how active HIV is in your body.

2. Higher viral loads mean that you are likely to progress to AIDS more quickly (see table on previous page).

3. Several different antiretroviral drugs may be used in combination to reduce the amount of virus in your body. All these regimens require that you take each dose on time, every time, so you must spend some time working out a plan before starting. (See *Adherence* information and *Antiretroviral* section if patient is getting ready to start HAART.)

References:

CDC. Guidelines for Using Antiretroviral Agents among HIV-Infected Adults and Adolescents: Recommendations of the Panel on Clinical Practices for Treatment of HIV. *MMWR* 2002; 51 (No. RR-7)

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O'Brien WA, Grovit-Ferbas K, Namazi A, et al. Human Immunodeficiency Virus-Type 1 replication can be increased in peripheral blood of seropositive patients after influenza vaccination. Blood, 1995;86(3)1082-1089.

Karnofsky Performance Scale

Definition:

This assessment tool is used to assist clinicians and caretakers to measure the patient's ability to carry out activities of daily living, and should be noted at each patient visit. Documentation of Karnofsky score is usually very helpful if patient applies for disability benefits, and may be helpful for some research applications.

DESCRIPTION	PERCENT (%)
Normal; no complaints; no evidence of disease	100
Able to carry on normal activity; minor signs and symptoms of disease	90
Normal activity with effort; some signs and symptoms of disease	80
Cares for self; unable to carry on normal activity or do work	70
Requires occasional assistance, but is able to care for most personal needs	60
Requires considerable assistance and frequent medical care	50
Disabled; requires special care and assistance	40
Severely disabled; hospitalization indicated although death not imminent	30
Very sick; hospitalization necessary; requires active support treatment	20
Moribund; fatal processes progressing rapidly	10
Dead	0

CHAPTER 2: Health Maintenance
Recommended Immunizations

Purpose:

Although little specific research has been completed on effectiveness of immunizations in HIV-infected people, immunocompromised people are at higher risk for many types of infections. Both pneumococcal and influenza vaccine are thought to be helpful in adults with HIV infection. For adults who have not completed routine childhood immunizations, guidance is listed in the table below. Hepatitis B vaccine should be considered for all sexually active adults who do not have serologic evidence of prior exposure. The efficacy of vaccines in HIV patients is better when CD4 counts are greater than 200.

Immunizations for HIV+ Adults and Adolescents

Vaccine Type	Asymptomatic HIV Disease	Symptomatic HIV Disease
Pneumococcal	yes (q 5 years), if CD4 count ≥ 200 *	yes (q 5 years), if CD4 count ≥ 200*
Influenza	yes (yearly)	yes (yearly)
Tetanus-diphtheria	yes, if indicated (q 10 yrs; or if injured, after 5 years)	yes, if indicated
Hepatitis B**	yes, if seronegative	yes, if seronegative
Hepatitis A	yes, if HCV+, IDU, MSM, international travelers, hemophiliacs or with no serologic evidence of prior disease	yes, if HCV+, IDU, MSM, international travelers, hemophiliacs or with no serologic evidence of prior disease
Varicella zoster***	**NO** (avoid exposure if possible; use VZIG a.s.a.p., at least within 96 hours, if exposure occurs)	**NO** (avoid exposure if possible; use VZIG a.s.a.p., at least within 96 hours, if exposure occurs)
Measles/MMR	yes (if otherwise indicated)	yes (if otherwise indicated, although not recommended if severely immunocompromised)
Rotavirus	**NO**	**NO**
Smallpox****	**NO**	**NO**

* In patients who received pneumococcal vaccine when their CD4 count was <200, but have subsequently risen above 200 in response to HAART, repeat vaccination should be considered.

** Infants born to HBsAg+ mothers should receive HBIG and HBV vaccine at separate sites within 12 hours of birth. Infants born to mothers of unknown HBsAg status should receive HBV vaccine within 12 hours of birth and have maternal HbsAg drawn simultaneously; if mother is HbsAg+, infant should receive HBIG before 1 week of age. For further information on immunizing HIV infected children, see CDC, USPHS/IDSA Guidelines for Preventing Opportunistic Infections Among HIV-Infected Persons, *MMWR* 2002; 51 (No. RR-8).

*** HIV-negative susceptible household contacts (especially children) of HIV infected susceptible patients should be vaccinated with VZV, so that they will not transmit VZV to the HIV+ patient.

**** Neither individuals with HIV nor people who live with HIV+ individuals should not receive smallpox vaccine, unless they have been exposed to smallpox. See CDC website for more complete information (http://www.bt.cdc.gov)

Additional Recommended Immunizations for HIV+ Patients Traveling to Developing Countries

Immune globulin (omit if patient has serologic evidence of Hepatitis A)
Hepatitis A vaccine, if travels often and no serologic evidence of Hepatitis A
Measles or MMR (omit if patient has evidence of immunity). Severely immunocompromised patients should not receive measles vaccine; immune globulin should be given to measles-susceptible, severely immunocompromised persons traveling to measles-endemic countries.
Typhoid, inactivated parenteral
Polio, enhanced inactivated

Destination-dependent: **Meningococcus, plague, rabies, Japanese encephalitis, yellow fever;** see *Prevention of Exposure to Opportunistic Infections* in Health Maintenance section for more detail. Note that yellow fever vaccine is a live virus vaccine,

with uncertain safety and efficacy for HIV infected persons, which should be avoided if possible. Asymptomatic persons who cannot avoid exposure to yellow fever should be offered the choice of vaccination. If no vaccine is given, advise patients of risk, instruct on avoidance of vector mosquito bites, and provide vaccination waiver letter.

Routine vaccinations should be reviewed and updated before travel. All patients traveling to other countries should be evaluated for both routine and destination-specific immunizations and prophylaxes based on their destinations. Call (888) 232-3299, and CDC will fax a directory on how to request travel information. Those with internet access can check the CDC web page at: **http://www.cdc.gov/travel/index.htm** . The Special Needs Traveler section contains a link to HIV. Select the "travelers health" option for regional travel documents and outbreak information. For those without internet access, call toll free, 1-877-FYI-TRIP.

See also *Preventing Exposure to OIs* guideline, section on **travel-related exposures**.

References:

CDC. USPHS/IDSA Guidelines for Preventing Opportunistic Infections among HIV-Infected Persons. *MMWR* 2002; 51 (No. RR-8).

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Hecht FM, Soloway B. *HIV Infection: A Primary Care Approach*. Revised Edition. Waltham: Massachusetts Medical Society. 1993; 39-40.

Wilson, M. Traveling with HIV. *AIDS Clinical Care.* 1991; 3:49-51.

CDC. Measles pneumonitis following MMR vaccination of a patient with HIV infection, 1993. *MMWR* 1996;45(28)603-606.

Sande MA, Gilbert DN, Moellering RC Jr. *The Sanford Guide to HIV/AIDS Therapy, 10th edition*. 2001; Hyde Park, VT, Antimicrobial Therapy, Inc.

Preventing HIV Transmission

Purpose: Patients with HIV infection, with few exceptions, want to protect loved ones from becoming infected. It is important to be sure your patient understands how HIV is not transmitted, as well as how to protect intimate partners and others who may inject drugs. This section offers HIV prevention recommendations for the HIV-infected person.

Information alone, especially on subjects like sexual activity and drug use, cannot be expected to change patient behavior. For areas where the patient experiences difficulty in protecting others, mental health or other professional resources may be required. Patient education needs are variable and individual as well. Assess current level of knowledge and perceived deficits before proceeding.

Additionally, all of the information that any one patient needs can not be covered at one visit. If the patient can read well, written literature can be given to reinforce education in key areas, but the patients' understanding must be verified. Written materials cannot replace a direct conversation with the patient.

All of these items will need to be revisited at follow-up visits, to check understanding, level of adherence, mitigating factors, and answer questions that will arise. Patient educators, nurses, peer counselors, social workers and mental health providers may also be employed to discuss these situations with patients.

General Information on HIV Transmission and Prevention

Learn what patient and immediate family (if family is aware of patient's HIV status) believe about HIV transmission. Be sure patient understands how the virus is not transmitted, such as sharing plates and eating utensils, using the same bathrooms, etc., and allay unnecessary fears.

Advise patient not to share toothbrushes, razors, douche equipment, or sex toys, to avoid the potential for transmitting HIV via blood or sexual secretions. These also have the ability to transmit other bloodborne infections, such as Hepatitis C, to the patient. Also, the patient should not donate blood, plasma, tissue, organs or semen, since these can all transmit HIV to the recipient.

Sexual Transmission

From information in sexual history, discuss sexual practices that might put others at risk, and ways to reduce risk, such as limiting numbers of sexual partners, condom use, and abstaining from sex (especially in drug or alcohol using situations, when judgment may be impaired). Educate patient about relative risks of sexual practices. Talk about disclosing HIV status to new sex partners, as well as current and previous ones. Refer to local support groups services which educate and promote patient's sharing this information with intimate partners.

Partner Notification Discuss with patient whether s/he has discussed HIV status with current sexual partner(s) and anyone who has shared needles with the patient. If not, determine if the patient has plans to do so. Offer to assist, if needed, by having the patient bring in the partner(s) to discuss and offer HIV testing to the partner(s). Social workers or counselors may be needed to handle repercussions and referrals. Past sexual partners can be dealt with after current partner(s) are notified. Local health departments can often help with partner elicitation and referral while protecting the patients' confidentiality.

Prevention of Sexual Transmission Use of latex or polyurethane condoms during every act of sexual intercourse, from start to finish, greatly reduces risk of HIV transmission A great deal of public information has recently been focused on discrediting condoms' ability to reduce STD risk. Although condoms are not as effective in reducing transmission of organisms such as HPV and HSV, which may result from viral shedding from skin, condoms have been proven to be very effective at greatly reducing HIV risk and the risk of STDs that are transmitted via discharge. In the event of allergy to latex, or other difficulty with latex condoms, polyurethane male or female condoms may be substituted. Although these barriers have not been tested as thoroughly as latex condoms, they can greatly reduce risk if properly used. Use of latex condoms and other effective barriers (such as latex dental dams or flexible plastic film during oral sex on females) will also prevent the transmission of HIV to others. In the event of latex allergy in either partner, be sure that patient knows acceptable substitutes that are available in the area, e.g., polyurethane, and to avoid "natural skin" or "lambskin" condoms, which are not recommended for HIV prevention.

Male condom use: Condoms must be used correctly and with every sexual act in order to be highly effective in preventing HIV transmission. Be sure that the patient knows exactly how to use a condom.

1. Use a new latex or polyurethane condom with each act of sex (oral, anal, or vaginal), being sure that the condom is undamaged, and within its expiration date.

2. Carefully handle the condom to avoid damage from fingernails, teeth, etc.
3. Being sure that the condom roll faces out, roll the condom on the erect penis before any genital contact with partner
4. Use only water-based lubricants with latex condoms. Oil-based lubricants (such as mineral oil, cooking oils, massage oils, body lotion, petroleum jelly) can weaken latex or cause it to break.
5. Adequate lubrication during intercourse, both inside and outside the condom, helps reduce the risk of condom breakage.

Avoid use of nonoxynol-9 (N-9) spermicides. Recent data suggests that N-9 may actually increase risk of HIV transmission during vaginal intercourse, and can damage rectal lining. N-9 should never be used for anal intercourse.

Female condom use: The female condom (Reality®), made of thin, flexible polyurethane, may be an option for women whose male partners will not use male condoms or for couples who do not like them. Female condoms are more expensive than male condoms, but may be procured at a lower cost at some health departments or Planned Parenthood clinics. They are also generally less well-known to patients, and may be unacceptable to some women whose culture or religion prohibits or discourages touching one's own genitals. **The female condom cannot be used at the same time as a male condom.**

Be sure the woman knows how to use the female condom before she needs it; after teaching, encourage practice when alone at home and unhurried. Women who have used the diaphragm, cervical cap, or contraceptive sponge may find it easier to master using the female condom. Directions for use of the condom are included in each box, but are reproduced briefly here for teaching purposes.

The female condom is a thin polyurethane pouch with a flexible ring at the opening, and another unattached flexible ring that sits inside the pouch to keep it in position in the vagina. Each device is pre-lubricated but each box includes extra lubricant. Illustrated instructions are in each package.

1. Open pouch by tearing at notched edge of packet, and take out the female condom. Be sure that the lubricant is evenly distributed on the inside by rubbing the outsides together.
2. Find a comfortable position, such as standing with one foot up a chair, or sitting with knees apart, or squatting down. Be sure the inner ring is inside, at the closed end of the pouch.
3. Hold the pouch with the open end hanging down. While holding the outside of the pouch, squeeze the inner ring with your thumb and middle finger. Still squeezing, spread the labia with your other hand, and insert the closed end of the pouch into the vagina.
4. Now, put your fingers into the pouch itself, which should be inside the vagina, and push the inner ring and the pouch the rest of the way up into the vagina with your index finger. Check to see that the front side of the inner ring is just past the pubic bone. The back part of the inner ring should be up behind the cervix. The outer ring and about an inch of the pouch will still be hanging outside the vagina.
5. Until you and your partner become comfortable using the female condom, use your hand to guide the penis into the vagina, keeping it inside the pouch. If, during intercourse, the outer ring is getting pushed up inside the vagina, stop, remove the old female condom and start over with a new one. Extra lubricant on the penis or the inside of the female condom may help keep this from happening.
6. After intercourse, take out the condom by squeezing and twisting the outer ring to keep the semen inside the pouch. Throw away in a trash can; do not flush. Do not re-use.

If there are problems, you can call 1-800-274-6601.
More information is available on the manufacturer's website, at **www.femalehealth.com**

Oral sex: For oral sex on men, a male condom should be used from start to finish. Unlubricated and flavored varieties are available. For oral sex on women, flexible plastic kitchen wrap can be used. Dental dams are also available, and some specialty shops carry larger, thinner squares of latex that are more suited to this purpose. Male condoms can also be cut lengthwise along one side prior to unrolling, and used like a dental dam. Some people use lubricants on the genital side of the plastic wrap or dental dam. If a latex dental dam is being used, or a latex condom is to be used later, use only water-based lubricants for this purpose.

Injection Drug Use

Discuss substance use, including steroids, reinforcing the adverse effects that these drugs can have on the body and the immune system. Assess whether referral for treatment is appropriate, and be aware of referral resources and mechanisms. If the patient is using injection drugs, discuss how readily HIV is spread through needle-sharing, and how re-used or shared needles and syringes can cause additional infections (septicemia, endocarditis, Hepatitis C). If the client shares needles or syringes, refer to needle exchange or harm reduction programs if they are available.

Assess each patient's readiness to change his/her drug injection practices, and refer to drug treatment programs as appropriate. Refer to addiction counselor for motivational interviewing, if available. After completion of substance abuse treatment, relapse prevention programs and ongoing support will be needed.

If the patient is continuing to use needles, discuss ways to avoid needle-sharing, and refer to a needle exchange program so that syringes and needles are not re-used. A partial listing of needle exchange sites may be found at www.nasen.org, although many states either do not have or cannot list their facilities. Local harm reduction activists may be aware of specific programs for obtaining clean needles and syringes.

If the patient continues to inject drugs, do careful prevention counseling:

1. Never reuse or share needles, syringes, water, or drug preparation equipment. If injection equipment is ever reused, teach how to take syringe barrel, plunger, and needle apart before cleaning with bleach and water.
2. Use only sterile syringes obtained from a reliable source (pharmacies, needle exchange programs).
3. Use sterile or boiled water to prepare drugs. If not available, use clean water from a reliable source such as fresh tap water.
4. Use a new or disinfected container (cooker) and a new filter (cotton) to prepare drugs.
5. Clean the skin around the injection site with a new alcohol swab before injecting.
6. Safely dispose of syringes after one use.

Maternal-Infant HIV Transmission: Risk of maternal-infant transmission varies from 20-30% without specific HIV treatment to reduce the risk; however, with specialized interventions during and after the pregnancy, including use of triple-drug antiretroviral regimens, infant risk can usually be reduced to <2%. **Be sure that the woman is aware that she will need specialized preconceptional, prenatal, intrapartum and postpartum care, and refer appropriately. She will also need to consider that bottle-feeding the baby is recommended, since breastfeeding confers an additional 12-15% risk of HIV transmission to the baby.** See *Reducing Maternal-Infant HIV Transmission* in this section for more complete discussion of these interventions and patient education.

Other activities that may pose HIV transmission risk:

Non-injection drug use can also pose a risk of blood exposures; for example, the sharing of cocaine straws or sniffers through which cocaine is inhaled. These straws may easily penetrate fragile nasal mucosa and become contaminated with blood before being used by the next individual, who may then experience mucous membrane exposure or even a cut or break in the mucous membrane from the bloody object.

Patients should be aware of risk of contamination of **tattoo equipment and inks**, and avoid situations where they might either share HIV or pick up other bloodborne pathogens.

Acupuncturists generally use sterile needles, but clients should verify this before using their services.

Post-Exposure Prophylaxis for Non-Occupational HIV Exposure (NPEP): Post-exposure prophylaxis for accidental sexual exposures, sexual assaults, and other non-occupational exposures may be considered for high-risk situations. As with occupational PEP, a risk assessment must be completed; and antiretroviral therapy, if indicated, must be started in a timely manner. The risks and toxicities of antiretroviral drugs must be weighed against potential benefits, and the client's informed consent obtained. Guidelines were recently published by Brown University AIDS Program and Rhode Island Department of Publich Health, and are available online at http://www.brown.edu/Departments/BRUNAP/backnpep.htm

References:

CDC. USPHS/IDSA Guidelines for Preventing Opportunistic Infections among HIV-Infected Persons. *MMWR* 2002; 51 (No. RR-8).

CDC. Sexually Transmitted Disease Treatment Guidelines 2002. *MMWR* 2002; 51 (No. RR-6).

US Public Health Service Task Force recommendations for the use of antiretroviral drugs in pregnant women infected with HIV-1 for maternal health and for reducing perinatal HIV-1 transmission in the United States, updated 2002. Downloaded from http://www.aidsinfo.nih.gov/

Manufacturers' product information.

Preventing Exposure to Opportunistic Infections

Purpose:

Patients with HIV infection are more susceptible to certain infections. Exposure to some of the opportunistic pathogens may be minimized or avoided if the patient is made aware of the possible dangers associated with them.

Sexual exposures

Patients should use latex or polyurethane condoms during every act of sexual intercourse, in order to reduce the risk of exposure to cytomegalovirus, herpes simplex virus, hepatitis C, and human papillomavirus as well as to other sexually transmitted pathogens. Although polyurethane male and female condoms have not been tested as thoroughly as latex condoms, they can greatly reduce risk if properly used. Correct use of condoms and other effective barriers (such as latex dental dams or flexible plastic film during oral sex on females) will also prevent the transmission of HIV to others. Avoidance of sexual contact in the presence of herpetic lesions (on the mouth or genitals) may also help reduce herpes simplex transmission, although herpes can be transmitted in non-outbreak conditions as well.

Patients should avoid sexual practices that may result in oral exposure to feces (e.g., oral-anal contact) to reduce the risk of intestinal infections such as cryptosporidiosis, shigellosis, campylobacteriosis, amebiasis, and hepatitis A and B. Latex or polyurethane condom use alone may not reduce the risk of acquiring these fecal-orally transmitted pathogens, especially those which have low infectious doses. Persons wishing to reduce their risk of exposure might consider using dental dams or other barrier methods (e.g., plastic food wrap) for oral-anal and oral-genital contact; changing condoms after anal intercourse; and wearing latex, nitrile, or other intact waterproof gloves during digital-anal contact. Frequently washing hands and genitals with warm soapy water during and after activities which may bring them in contact with feces may further reduce the risk of illness.

See *HIV Prevention* in this section for specific information on how to use male and female condoms. Consistent and correct use of condoms greatly reduces the risk of STDs.

Injection Drug Use Exposures

Injection drug use puts HIV-infected persons at risk for Hepatitis C infection, additional strains of HIV (some of which may be drug-resistant), and other blood-borne pathogens. Assess each patient's readiness to change his/her practices, and refer to drug treatment programs as appropriate. If the patient is continuing to use needles, discuss ways to avoid sharing needles and other drug equipment, and refer to a needle exchange program so that syringes and needles are not re-used. Specific recommendations on injection and other drug use can be found in *HIV Prevention*, in this section. **All susceptible injection drug users should be immunized against HBV and HAV.**

Environmental and occupational exposures

Certain activities or types of employment may increase the risk of exposure to tuberculosis. These include volunteer work or employment in health care facilities, correctional institutions, and shelters for the homeless as well as in other settings identified as high risk by local health authorities. Decisions about whether or not to continue with such activities should be made in conjunction with the health care provider and should take into account such factors as the patient's specific duties in the workplace, the prevalence of tuberculosis in the community, and the degree to which precautions designed to prevent the transmission of tuberculosis are taken in the workplace. These decisions will affect the frequency with which the patient should be screened for tuberculosis.

Child-care providers and parents of children in **child-care facilities** are at increased risk of acquiring CMV infection, cryptosporidiosis, and other infections (e.g., Hepatitis A and giardiasis) from children. Any HIV-infected child-care provider, who has a low risk of CMV (i.e., no history of injecting drug use or contact with male homosexuals) should be tested for CMV antibody. If found to be negative, the risk of acquiring infection can be diminished by good hygienic practices, such as handwashing after fecal contact (e.g., during diaper changing), and after contact with urine and saliva. Any CMV-negative person with HIV who needs a transfusion should receive blood that is CMV-negative or leukocyte-reduced.

HIV-infected children and adults who are **susceptible to varicella-zoster virus** (those with no history of chickenpox or shingles) should avoid exposure to persons with chickenpox or shingles. Household contacts, especially children, should be vaccinated against VZV if they are HIV-negative and have no history of chickenpox, so that they will not transmit ZVZ to their HIV-infected contact. In the event a susceptible HIV-infected person is exposed to a close contact with chickenpox or shingles, varicella zoster immune globulin (VZIG) should be administered as soon as possible (ideally within 48 hours, but at least within 96 hours) of the exposure. Anti-varicella titers can be performed after exposure if uncertain as to susceptibility. Some clinicians substitute

acyclovir 800 mg po 5 times a day for three weeks instead of the VZIG, although data on its efficacy for this indication are lacking.

Contact with animals: Occupations involving contact with animals (e.g., veterinary work and employment in pet stores, farms, slaughterhouses) may pose a risk of cryptosporidiosis, toxoplasmosis, salmonellosis, campylobacteriosis, or Bartonella infection. However, the available data are insufficient to justify a recommendation against work in such settings.

Contact with young farm animals, especially animals with diarrhea, should be avoided to reduce the risk of cryptosporidiosis.

Soil exposure: Glove use and handwashing after gardening or other contact with soil may reduce the risk of cryptosporidiosis and toxoplasmosis.

In histoplasmosis-endemic areas, patients should avoid activities known to be associated with increased risk (e.g., stirring up dust when working with surface soil; cleaning chicken coops; disturbing soil beneath bird-roosting sites; cleaning, remodeling, or demolishing old buildings; and exploring caves.)

In coccidioidomycosis-endemic areas, when possible, patients should consider avoiding activities associated with increased risk, including those involving extensive exposure to disturbed native soil (e.g., at excavation sites, on farms, or during dust storms).

Pet-related exposures

Health care providers should advise HIV-infected persons of the potential risk posed by pet ownership. However, they should be sensitive to the possible benefits of pet ownership and should not routinely advise persons with HIV to part with their pets. They should also advise their patients of the following.

General

Veterinary care should be sought when a pet develops a diarrheal illness. If possible, HIV-infected persons should avoid contact with animals that have diarrhea. A fecal sample should be obtained from animals with diarrhea and examined for Cryptosporidium, Salmonella, and Campylobacter.

When obtaining a new pet, HIV-infected persons should avoid animals <1 year old, especially those with diarrhea. Because the hygienic and sanitary conditions in pet breeding facilities, pet stores, and animal shelters are highly variable, the patient should exercise caution when obtaining a pet from these sources. Stray animals should be avoided. Animals < 6 months of age, especially those with diarrhea, should be examined by a veterinarian for Cryptosporidium, Salmonella, and Campylobacter before the patient has contact with the animal.

Patients should wash their hands after handling pets (especially before eating) and avoid contact with pets' feces to reduce the risk of cryptosporidiosis, salmonellosis, and campylobacteriosis.

Cats

Patients should consider the potential risks of cat ownership such as the risk of toxoplasmosis and bartonella infection, as well as enteric infections. Those who elect to obtain a cat should adopt or purchase an animal that is > 1 year of age and in good health to reduce the risk of cryptosporidiosis, bartonella infection, salmonellosis, and campylobacteriosis.

Litter boxes should be cleaned daily, preferably by an HIV-negative, nonpregnant person; if the HIV-infected patient performs this task, he or she should wash hands thoroughly afterward to reduce the risk of toxoplasmosis.

Also to reduce the risk of toxoplasmosis, cats should be kept indoors, should not be allowed to hunt, and should not be fed raw or undercooked meat. Flea control will help reduce risk of Bartonella infections.

Although declawing is not generally advised, patients should avoid activities that may result in cat scratches or bites to reduce the risk of bartonella infection. Patients should also wash sites of cat scratches or bites promptly and should not allow cats to lick open cuts or wounds.

Testing of cats for toxoplasmosis or bartonella infection is not recommended.

Birds

Screening of healthy birds for Cryptococcus neoformans, Mycobacterium avium, or Histoplasma capsulatum is not recommended. Areas contaminated with bird droppings should be avoided if possible, and soil beneath bird-roosting sites should not be disturbed. Chicks and ducklings have been associated with salmonellosis.

Other

Contact with reptiles (such as snakes, lizards, iguanas, and turtles) should be avoided to reduce the risk of salmonellosis.

Gloves should be used during the cleaning of aquariums to reduce the risk of infection with *Mycobacterium marinum.*

Contact with exotic pets, such as nonhuman primates, should be avoided.

Food and Water-Related Exposures

Raw or undercooked eggs (including foods that may contain raw eggs, such as some preparations of hollandaise sauce, Caesar and certain other salad dressings, some mayonnaises, eggnog, uncooked cake and cookie batter); raw or undercooked poultry, meat, or seafood, especially raw shellfish; unpasteurized dairy products; unpasteurized fruit juice; and raw seed sprouts (alfalfa, mung bean sprouts) may contain enteric pathogens. Poultry and meat are safest if internal temperature is verified with a meat thermometer to 165 F for red meats and 180 F for poultry. If a thermometer is not available, meats should be cooked until no traces of pink remain, to prevent gastrointestinal infections and toxoplasmosis. However, color changes do not always correlate with internal temperature. Produce should be washed thoroughly before being eaten.

Cross-contamination of foods should be avoided. Uncooked meats should not be allowed to come into contact with other foods; hands, cutting boards, counters, and knives and other utensils should be washed thoroughly after contact with uncooked foods.

Although incidence of listeriosis is low, it is a serious disease that occurs unusually frequently among HIV-infected persons with severely immunosuppression. An immunosuppressed person with HIV who wishes to reduce the risk of listeriosis may elect to:

- Avoid soft cheeses (feta, brie, camembert, blue-veined, and Mexican style cheeses such as queso fresco). Hard cheeses, processed cheeses, cream cheese, cottage cheese, and yogurt are generally safe from listeriosis.
- Cook leftover foods or ready-to-eat foods, such as hot dogs, until they are steaming hot before eating.
- Avoid foods from delicatessen counters, such as prepared meats, salads, cheeses, or heat these foods until steaming if eaten. Canned or shelf-stable pate and meat spreads need not be avoided.
- Avoid raw or unpasteurized milk or milk products, including goat's milk, or foods containing unpasteurized milk or milk products.

Patients should not drink water directly from lakes or rivers because of the risk of cryptosporidiosis and giardiasis. Even accidental ingestion of lake, river, or ocean water while swimming, rafting, boating, skiing, or engaging in other types of recreational activities carries this risk.

During outbreaks or in other situations in which a community "boil water" advisory is issued, boiling water for 1 minute will eliminate the risk of cryptosporidiosis. Use of submicron personal-use water filters (home/office types) and/or bottled water may reduce the risk. Not all bottled water can be considered free of oocysts, however. Water that has been distilled, filtered with an "absolute" 1 micron or submicron filter, or by reverse osmosis, is considered safe. Current data are inadequate to recommend that all HIV-infected persons boil or otherwise avoid drinking tap water in non outbreak settings.

However, persons who wish to take independent action to reduce the risk of waterborne cryptoporidiosis may choose to take precautions similar to those recommended during outbreaks. Such decisions are best made in conjunction with the health care provider. Persons who opt for personal-use filter or bottled water should be aware of complexities involved in selecting the appropriate products, the lack of enforceable standards for the destruction or removal of oocysts, the cost of the products, and the difficulty of using these products consistently, e.g., toothbrushing, eating out, and travel.

Patients taking precautions to avoid cryptosporidiosis in drinking water should be advised that ice made from tap water can be a source of infection. Also, fountain beverages served in restaurants, bars, theaters, and other public places may pose a risk, because these beverages, as well as the ice they contain, are made from tap water. Nationally distributed brands of bottled or canned carbonated soft drinks are safe to drink. Commercially packaged noncarbonated soft drinks and fruit juices that do not

require refrigeration until after they are opened (e.g., those that can be stored unrefrigerated on grocery shelves) also are safe. Nationally distributed brands of frozen fruit juice concentrate are safe if they are reconstituted with water from a safe source. Fruit juices that must be kept refrigerated from the time they are processed to the time of consumption may be either fresh (unpasteurized) or heat treated (pasteurized); only those labeled pasteurized should be considered safe. Other pasteurized beverages and beers are also considered safe to drink. No data are available concerning survival of Cryptosporidium oocysts in wine.

Travel-Related Exposures

Travel, particularly to developing countries, may carry significant risks for the exposure of HIV-infected persons to opportunistic pathogens, especially for patients who are severely immunosuppressed. Consultation with health care providers and/or with experts in travel medicine will help patients plan itineraries.

During travel to developing countries, HIV-infected persons are at much higher risk for food-borne and waterborne infections than they are in the United States. Foods and beverages--in particular, raw fruits and vegetables, raw or undercooked seafood or meat, tap water, ice made with tap water, unpasteurized milk and dairy products, and items purchased from street vendors --may be contaminated. Items that are generally safe include steaming-hot foods, fruits that are peeled by the traveler, bottled (especially carbonated) beverages, hot coffee or tea, beer, wine, and water brought to a rolling boil for 1 minute. Treatment of water with iodine or chorine may not be as effective as boiling but can be used, perhaps in conjunction with filtration, when boiling water is not practical.

Waterborne infections may result from the swallowing of water during recreational activities. To reduce the risk of cryptosporidiosis and giardiasis, patients should avoid swallowing water during swimming and recreational activities, and should not swim in water that may be contaminated (e.g., with sewage, animal or human wastes).

Antimicrobial prophylaxis for traveler's diarrhea is not recommended routinely for HIV-infected persons traveling to developing countries. Such preventative therapy can have adverse effects and can promote the emergence of drug-resistant organisms. Nonetheless, several studies (none involving an HIV-infected population) have shown that prophylaxis can reduce the risk of diarrhea among travelers. Under selected circumstances (e.g., those in which the risk of infection is very high and the period of travel brief), the provider and patient may weigh the potential risks and benefits and decide that antibiotic prophylaxis is warranted.

For those individuals to whom prophylaxis is offered, fluoroquinolones, such as ciprofloxacin (500 mg q.d.) can be considered, although fluoroquinolones should not be used for pregnant women or children. Trimethoprim-sulfamethoxazole (TMP-SMZ, one double-strength tablet daily) has been shown to be effective, but resistance to this drug is now common in tropical areas. Persons already taking TMP-SMZ for prophylaxis against carinii pneumonia (PCP) may gain some protection against traveler's diarrhea. For HIV-infected persons who are not already taking TMP-SMZ, the provider should use caution when prescribing this agent for prophylaxis of diarrhea because of the high rate of adverse reactions and the possible need for the agent for other purposes (e.g., PCP prophylaxis) in the future.

All HIV-infected travelers to developing countries should carry with them a sufficient supply of an antimicrobial agent to be taken empirically *should diarrhea develop*. One appropriate regimen is 500 mg of ciprofloxacin b.i.d for 3-7 days. Alternative antibiotics (e.g., TMP-SMZ) should be considered as empirical therapy for use by pregnant women. Travelers should consult a physician if their diarrhea is severe and does not respond to empirical therapy, if their stools contain blood, if fever is accompanied by shaking chills, or if dehydration develops. Antiperistaltic agents such as diphenoxylate and loperamide are used for the treatment of diarrhea; however, they should not be used by patients with high fever or with blood in the stool, and their use should be discontinued if symptoms persist beyond 48 hours.

Travelers should be advised about other preventive measures appropriate for anticipated exposures, such as chemoprophylaxis for malaria, protection against arthropod vectors, treatment with immune globulin, and vaccination. They should avoid direct contact of the skin with soil and sand (e.g., by wearing shoes and protective clothing and using towels on beaches) in areas where fecal contamination of soil is likely.

In general, live virus **vaccines** should be avoided. An exception is measles vaccine, which is recommended for nonimmune persons, although not recommended for those who are severely immunocompromised. Immune globulin should be considered for measles-susceptible, severely immunocompromised persons traveling to measles-endemic regions. Inactivated (killed) poliovirus vaccine should be used instead of oral (live) poliovirus vaccine. Persons at risk for exposure to typhoid fever should be given inactivated parenteral typhoid vaccine instead of the live attenuated oral preparation. Yellow fever vaccine is a live virus

vaccine with uncertain safety and efficacy in HIV-infected persons. Travelers with HIV infection who are unvaccinated and for whom travel is necessary should be advised of the risk, instructed in methods for avoiding the bites of vector mosquitoes, and provided with a vaccination waiver letter. Travelers with asymptomatic HIV who cannot avoid potential exposure to yellow fever should be offered the choice of vaccination after disclosure of its limitations.

In general, killed and recombinant vaccines (e.g., diphtheria-tetanus, rabies, HBV, HAV, Japanese encephalitis) should be used for HIV-infected persons as they would be for non-HIV-infected persons anticipating travel. Preparation for travel should include a review and updating of routine vaccinations, including diphtheria-tetanus. The currently available cholera vaccine is not recommended for persons following the usual tourist itinerary, even if travel includes countries reporting cases of cholera.

Routine vaccinations should be reviewed and updated before travel. All patients traveling to other countries should be evaluated for both routine and destination-specific immunizations and prophylaxes based on their destinations.

Travelers should be told about other **area-specific risks** and instructed in ways to reduce those risks. Geographically focal infections that pose a high risk to HIV-infected persons include visceral leishmaniasis (a protozoan infection transmitted by the sandfly) and several fungal infections (e.g., Penicillium marneffei infection, coccidioidomycosis, and histoplasmosis). Many tropical and developing areas have high rates of tuberculosis, which is a particular risk for HIV-infected persons. Call (888) 232-3299, and CDC will fax a directory on how to request travel information. Those with internet access can check the CDC web page at: **http://www.cdc.gov/travel/index.htm** . **The Special Needs Traveler section contains a link to HIV**. Select the "travelers health" option for regional travel documents and outbreak information. For those without internet access, call toll free, 1-877-FYI-TRIP.

Adapted from:

CDC. USPHS/IDSA Guidelines for Preventing Opportunistic Infections among HIV-Infected Persons. *MMWR* 2002; 51 (No. RR-8).

CDC. Sexually Transmitted Disease Treatment Guidelines 2002. *MMWR* 2002; 51 (No. RR-6).

PCP Prophylaxis

Definition:

Pneumocystis pneumonia (PCP) prophylaxis is treatment given to HIV-infected individuals to **prevent either a primary episode of PCP**, or the **recurrence of infection**. Pneumocystis remains the most common life-threatening infection among U.S. residents with advanced HIV disease. PCP prophylaxis should be administered to all HIV positive patients with either a CD4 count of <200/mm^3 or with a history of thrush. Information from the Multicenter AIDS Cohort Study (MACS) suggests that as patient CD4 counts begin falling toward 200, they should be measured more frequently. PCP prophylaxis may be indicated in patients with CD4 counts >200/mm^3 in the presence of oral thrush or of fever >100 degrees which persists for longer than 2 weeks.

S: HX: **HIV seropositive** **Previous PCP episode**
TB history **Allergy to sulfa drugs**
Fever (duration)

O: CD4+ cell count <200/mm^3 or CD4+ percent <14; or oral candidiasis, fever >100 degrees persisting >2 weeks.

A: Assess for history of TB infection or exposure, drug allergies.

P:

1. Trimethoprim-Sulfa (TMP-SMX, Bactrim, Septra) double strength, 1 tablet daily. An alternate dosage is one TMP-SMX single strength tab qd, although the lower dose may not be as effective as the DS tabs in preventing other bacterial infections. Another regimen which may be preferable to the client is one DS tablet PO 3 times per week (example: Monday, Wednesday, Friday).
   WARNING: Many patients become intolerant of sulfa medications. Severe reactions may include: persistent neutropenia, severe erythroderma and Stevens-Johnson syndrome (bullae & desquamation of the skin). Some patients with milder reactions can be desensitized, but this must be done cautiously and requires diligence on the part of the patient, and careful management by provider (see protocol: *Sulfa Desensitization*). These sulfa-containing regimens are also active against toxoplasmosis.

2. **Alternative prophylaxis regimen**: Dapsone 100mg po QD, or 50 mg po BID (note: these regimens do not prevent activation of toxoplasmosis.)
   Second alternative: Dapsone 200mg po + pyrimethamine 50 mg. + leukovorin 25 mg., all once per week. Or, Dapsone 50 mg po qd, and pyrimethamine 50 mg + leukovorin 25 mg each week. These regimens are also effective at reducing risk of toxoplasmosis activation.
   WARNING: Observe for pallor, bluish or ashen skin coloration. Methemoglobinemia is a side effect of dapsone therapy. Screen **for G6PD deficiency before starting dapsone**. (Approx. 10% of African-American males, and 1-2% of Mediterranean, Indian, and Asians deficient.)

3. Aerosolized pentamidine (AP) 300mg once a month, via Respirgard II nebulizer.
   WARNING: May increase the risk of extrapulmonary pneumocystosis, pneumothorax and bronchospasm. Increases risk of TB transmission to others if patient has active pulmonary tubercular disease, unless ventilation (negative pressurized facility with outside venting) is adequate. Do not use in patients in whom TB is suspected. Provides no protection against toxoplasmosis.

4. Atovaquone suspension 1500 mg qd or 750 mg po bid with meals (very expensive and should not be used if other alternatives are available.) Should be taken with high-fat meals for best absorption.

Discontinuing prophylaxis:

If the patient was started on PCP prophylaxis because of a low CD4 count, and the CD4 count has risen back above 200 in response to highly effective antiretroviral therapy, data now suggests that PCP prophylaxis can be safely discontinued in patients responsive to HAART who have a sustained increase (> 3 months) in CD4 cells, with the following cautions.

If the patient is on secondary prophylaxis, that is, has had PCP in the past, and the episode of PCP occurred at a CD4 count >200, it is prudent to continue PCP prophylaxis for life regardless of how high the CD4 count rises as a consequence of HAART.

If the provider chooses to discontinue PCP prophylaxis, clinical status and lab indices must be closely observed to determine when to resume prophylaxis.

Patient Education:

1. Report adverse drug reactions to your care provider (rash, high fever) immediately. Do not take any more of the PCP prophylaxis medication until you clear it with your provider.

2. PCP prophylaxis is generally lifelong. Taking all your medication, or keeping your appointments for pentamidine treatments is very important to prevent this life-threatening form of pneumonia.

3. If PCP prophylaxis is discontinued due to sustained rise in CD4 count while on HAART, you may need to re-start it in the event you stop HAART, your CD4 count drops or if your condition worsens.

4. PCP can recur in spite of prophylaxis. Call your care provider if you notice increasing cough, fever, and shortness of breath on exertion.

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Sulfa Desensitization

Background:

During the past 10 years, numerous papers have been published on the efficacy of desensitizing HIV-infected patients who have had reactions to Trimethoprim-sulfamethoxazole (TMP-SMX). TMP-SMX is reportedly the most effective prophylaxis in current use for Pneumocystis Pneumonia. In addition, it is effective in preventing toxoplasmosis encephalitis in those with severe immune compromise who have evidence of previous infection. TMP-SMX is also quite inexpensive, which is a rarity in the world of AIDS treatment. Because of its effectiveness as a prophylaxis and usefulness in treating OIs, several methods of desensitizing AIDS patients with previous reactions to TMP-SMX have been tried. The starting dosage and length of dose escalation vary from 6 hours to 21 days, and dosage intervals vary from 15 minutes to 24 hours. Success rates hover around 80% in most cases, and may be higher in those patients with <200 CD4 cells/ml[3].

S: Patient reports previous reaction to Sulfa, Bactrim, or Septra, such as erythema, pruritis, or rash. Denies anaphylaxis, Stevens-Johnson or erythema multiforme reactions; no reaction in which vesiculation, desquamation, ulceration, exfoliative dermatitis, etc., occurred.

O: CD4 count <200, or other important indication for TMP-SMX

A: Reaction to Sulfa, possibly reversible with desensitization protocol

P: Begin 10-day desensitization protocol starting with pediatric oral suspension, which contains 40 mg of TMP and 200 mg of SMX per 5 ml (1 teaspoon). If there is any question about the severity of previous reaction, have the patient take the initial morning dose in the clinic so that she/he may be monitored for 3-4 hours before going home. (This assumes that emergency treatment, including IV access materials and IV fluids, antihistamines and steroids, are readily available.) Patients experiencing mild adverse effects may take longer to complete the regimen, as noted below the schedule information.

Ten-Day desensitization regimen.

Patient takes commercially-available pediatric suspension (containing TMP 8 mg and SMX 40 mg per mL), followed by DS tablets, as follows:

Days	Dose (TMP/SMX)	Volume or Tablet
1-3	8/40	1 mL
4-6	16/80	2 mL
7-9	40/200	5 mL
10-12	80/400	½ DS tab (or 1 SS tab)
13 and thereafter	160/800	1 DS tab

In the event of mild reaction: If patient experiences mild reaction or itching, the same dose can be given for an additional day. Antihistamines or antipyretics may be used to treat symptoms of mild reactions.

In-Clinic 4-hour desensitization regimen.

A more rapid desensitization process may be completed in-clinic, and again assumes that treatment for adverse reactions is readily available there. It involves serial dilutions of the pediatric suspension, 1 to 10, diluted out to 1:10,000. The solution is given each hour as the patient is observed. This assumes that emergency treatment, including IV access materials and IV fluids, antihistamines and steroids, as well as an experienced observer and treater, are readily available. If patient begins to notice symptoms, observe B/P, pulse, check for skin rashes, flushing, and mucous membranes for redness. Such reactions demand discontinuation of sulfa and administration of antihistamines, steroids, fluids and other supportive care until stable.

Time (hour)	Dose (TMP/SMX)	Dilution
0	0.004 / 0.002 mg.	1:10,000 (5 mL)
1	0.04 / 0.2 mg.	1:1,000 (5 mL)
2	0.4 / 2.0 mg.	1:100 (5 mL)
3	4 / 20 mg	1:10 (5 mL)
4	20 / 200 mg	Undiluted (5 mL)
5	160 / 800 mg	1 DS tablet

Patient education for home desensitization regimen:

1. Explain the benefits of being able to use TMP-SMX. Be sure she/he understands and is able to follow instructions.

2. Measure your dose carefully and take it each morning, followed by a glass (6-8 oz) of water. Ask patient to do a return demonstration, if possible, using the syringe that s/he will use to do the actual measuring at home.

3. This drug can make you very ill unless you pay attention to any problems you have. It is extremely important that you check your temperature each afternoon. If your temperature is more than 100.5 by mouth, stop the Bactrim and contact your clinician. Note: if you have shaking chills, check your temperature as soon as the shaking stops, and contact the clinic. If you continue the Bactrim despite a red rash and/or fever, serious illness or life-threatening reaction may occur. Report any adverse event immediately.

4. Stop the regimen and return to the clinic or to the Emergency Room immediately if you develop a red rash, blisters on your skin or in your mouth, or vomiting. Check your skin each evening, and any time you notice itching.

5. In the event you have mild itching or faint rash, you can take diphenhydramine (Benadryl) 25-50 mg. every 4 hours as needed. If this persists, stay with the same dose for an additional day; and call or come into the clinic if you have questions or concerns.

6. Call or come in for alternate dosage instructions in the event of persistent itching without rash.

Patient education for all desensitized patients:

7. After desensitization is complete, continue to take the daily dosage. If the drug is stopped, the entire regimen may have to be repeated.

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Latent TB Infection

Screening:

The USPHS/IDSA recommends that all patients with HIV be screened for TB by the Mantoux method (5-TU PPD). Routine evaluation for anergy is not recommended, since anergy may wax and wane over the course of HIV infection.

If the TB skin test (TST) is negative, testing should be repeated at least annually, even though the likelihood of a false-negative test increases as CD_4 count decreases. A second, "booster" tuberculin test may be placed 7-28 days after an initial negative test; this is called *two-step testing*. A positive "booster" TST is considered evidence of infection with TB (either latent infection or active disease). Clinicians should consider repeating the TST if the patient's CD4 count rises to >200 in response to HAART. All HIV-positive patients with 5 mm induration in response to the TST and no history of treatment for TB should be evaluated carefully to rule out active TB, including CXR, sputum for AFB stain and culture x 3 if cough present, and careful history and physical examination.

If no evidence of disease, several regimens are available to treat latent TB infection (LTBI). If available, offer **directly observed preventive therapy** (DOPT), which is now considered optimal. If the client is on protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs), rifamycin-protease inhibitor interactions should be taken into consideration if non-INH therapy is being considered for LTBI:

1. Isoniazid 300 mg qd, + pyridoxine 50 mg qd, x 9 months
2. Isoniazid 900 mg po + pyridoxine 100 mg po twice a week x 9 months (directly observed therapy)

Alternative preventive regimens:

3. Rifampin* 600 mg qd x 4 months or Rifabutin* 300 mg po qd x 4 months
4. Rifampin* 600 mg po qd + PZA 15-20 mg/kg po x 2 months
5. Rifabutin* 300 mg qd + pyrazinamide 15-20 mg/kg qd x 2 months *(Note that the rifabutin-pyrazinamide regimen has been associated with severe liver injury and death, and should be used with caution.* See follow-up section and pregnancy notes)

*if on ARVs, see drug interactions/dosage adjustments table, in *Mycobacterium Tuberculosis* in Disease Specific section.

Close contacts of patients with pulmonary TB: Any HIV-infected patients who are close contacts of patients with infectious TB (smear-positive pulmonary disease) **should receive preventive therapy regardless of PPD results or previous courses of chemoprophylaxis**, after active TB has been excluded. Such contacts should be tested with 5 U PPD if previously negative, and started on preventive therapy. If the TST result is initially negative, the individual should be evaluated again three months after discontinuation of contact with the infectious source, and the information obtained should be considered in the decision about whether chemoprophylaxis should continue.

For patients whose contact has a **high probability of Isoniazid resistance**, use one of the non-INH containing regimens above.

Any patient with a **history of prior untreated or inadequately treated TB** that healed, who has still not received adequate treatment, **should receive appropriate treatment regardless of age or results of TST. Immediate consultation with a TB expert is recommended.**

If contact has **known MDR-TB** (TB that is resistant to INH, Rifampin, and possibly other TB drugs), or patient has a high probability of exposure to MDR-TB, treat LTBI with drugs to which the source patient is susceptible. This will require consultation with local public health authorities and possibly with outside experts, and will depend on susceptibility isolates from the source patient. Additional resources may include CDC's TB Division, at (404) 639-8140 or 1-800-4TB DOCS, New Jersey Medical School's National TB Center Information Line.

Pregnancy: HIV-infected pregnant women with positive TST and no evidence of active TB should receive standard prophylaxis as soon as possible. In HIV-infected pregnant women, chest X-Ray is performed with lead shielding and prophylaxis should not be deferred, even during the first trimester. The preferred prophylaxis in pregnancy is a 9-month isoniazid regimen. Alternative regimens, such as rifampin or rifabutin, should be used with caution because of limited experience, although anecdotal evidence has shown no problems with rifampin thus far. Pyrazinamide is generally avoided during pregnancy, especially the first trimester, because of lack of information concerning fetal effects. Pyridoxine should be administered with INH to avoid peripheral neuropathy.

BCG is contraindicated in HIV-infected patients because of its potential to cause disseminated disease.

Follow-up: Monthly evaluation is required, except for patients on RIF-PZA regimens, who should be assessed every two weeks during the regimen (including AT), and should be given only a 2-week supply of medication at each visit. An AT > 5 times the upper limit of normal in an asymptomatic person and any AT> normal if accompanied by symptoms of hepatitis, or serum bilirubin above normal generally requires stopping the medication. Monitor liver function monthly on patients whose pretreatment LFTs were abnormal, those with HCV or who abuse alcohol, pregnant women, postpartum women, and those who need LFTs because of other hepatotoxic medications. Review all medications and assess for drug interactions at each visit. Review signs of hepatic toxicity and remind patient to return to clinic immediately for any such symptoms.

Updates: Refer to http://www.cdc.gov/nchstp/tb for any updates in guidelines for management of TB infection.

Patient education:

1. Even though you have the TB germ in your body (latent TB infection), you cannot pass the germ to others at this time. However, because you have HIV infection, the TB germ will have an easier time making you sick.

2. The medicine you are starting will help kill the TB germ and reduce your chances of getting sick with active TB later.

3. It is important that you take all of your medicine, every day, to avoid allowing the TB germ to start growing and making you sick.

4. If you have side effects, such as rash or itching, contact us immediately. Occasionally, INH can cause tingling or numbness in the hands or feet. The pyridoxine (B6) that you take should help prevent that, but let us know if it occurs.

5. Avoid alcohol while on these medications. The medicines for TB are processed by your liver, and, when combined with alcohol, can easily overload the liver. Also, be aware that acetaminophen (Tylenol) is also processed by the liver; keep your intake to a minimum. (If you have Hepatitis C, this is even more important.)

6. We will be taking blood at intervals to be sure your liver is working well, so be sure to come in for all your follow-up appointments. Bring all medications, vitamins, and supplements that you are taking so that we can check for drug interactions.

7. If you experience nausea, vomiting, poor appetite, abdominal pain, notice your urine darkening or becoming cola-colored, return to the clinic immediately. Likewise, if you notice your eyes or skin yellowing, return to the clinic immediately. These can be signals that your liver is being overwhelmed, and it is important to find out before permanent damage is done.

8. Rifampin will turn sweat, tears, urine, and plastic contact lens orange, and will make birth control pills ineffective. A backup method of contraception must be used until treatment is complete.

9. Patients on RIF-PZA should be advised to stop the drugs immediately and return to clinic if they experience abdominal pain, vomiting, yellow skin or eyes, or other symptoms.

References:

CDC. USPHS/IDSA Guidelines for Preventing Opportunistic Infections among HIV-Infected Persons. *MMWR* 2002; 51 (No. RR-8).

US DHHS Panel. Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents. 2/4/02; downloaded from http://www.aidsinfo.nih.gov/

CDC. *Core Curriculum on TB: What the clinician should know, 4th ed*. 2000, Atlanta, USDHHS.

American Thoracic Society/CDC. 2001 Update: Fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions. American Thoracic Society/CDC Recommendations, 2001, (34) 733-736.

Centers for Disease Control and Prevention. Updated guidelines for the use of rifabutin or rifampin for the treatment and prevention of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. *MMWR 2000*; 49 (9).

Centers for Disease Control and Prevention. Prevention and treatment of tuberculosis among patients infected with human immunodeficiency virus: Principles of therapy and revised recommendations. *MMWR*, 1998; 47 (No. RR-20).

Toxoplasmosis, Primary Prophylaxis

Definition & Background: The USPHS/IDSA Guidelines recommends that all HIV-infected patients be tested for toxoplasmosis IgG antibody soon after diagnosis of HIV infection. Toxoplasmosis-IgG-negative patients should be counseled to avoid sources of infection (see section of Prevention of Opportunistic Diseases), and should be re-tested for toxoplasmosis IgG when CD_4 counts fall below 100 to determine whether they have seroconverted and are therefore at risk for toxoplasmosis encephalitis (TE). (**See toxoplasmosis protocol for more information on active disease and secondary prophylaxis**.)

S: HIV positive, no toxoplasmosis history or symptomatology
allergies to sulfa, dapsone, pyrimethamine?

O: HIV-infected
Toxoplasma IgG positive (for toxo-negative patients, see patient education note #1 below)
CD_4 count less than 100
For sulfa-allergic patients of African-American, Mediterranean, or Asian descent, G6PD level prior to Dapsone

A: Increased susceptibility to activation of latent toxoplasmosis infection

P: Use of TMP-SMZ in doses recommended for PCP prophylaxis appears effective against toxoplasmosis as well. If the patient is allergic to sulfa, pyrimethamine 75 mg + dapsone 200 mg + leukovorin 25 mg po q week; or dapsone 50-100 mg qd plus weekly pyrimethamine 50 mg po and leukovorin 25 mg po to make a regimen that will reduce TE in sulfa-allergic persons. Atovaquone 1500 mg po qd is another alternative, though quite expensive. **Neither aerosolized pentamidine nor dapsone alone provides protection against TE.**

WARNING: With Dapsone, observe for pallor, bluish or ashen skin coloration. Methemoglobinemia is a side effect of dapsone therapy. Dapsone can also cause hemolytic anemia in G6PD deficiency; check G6PD before starting dapsone. (Approx. 10% of African-American males, and 1-2% of Mediterranean, Indian, and Asians deficient.)

Discontinuation of prophylaxis: Primary prophylaxis for TE can be discontinued in patients who have responded to HAART with sustained CD4 counts >200 for at least 3 months. CD4 counts should be carefully monitored and prophylaxis resumed in patients whose CD4 counts drop back below 200.

In pregnancy: TMP-SMZ may be used as primary prophylaxis during pregnancy. Rarely, women with evidence of remote toxoplasmosis have transmitted the infection to their newborns. Because of the low incidence of TE during pregnancy, and the possible risk associated with pyrimethamine therapy, prophylaxis that includes pyrimethamine should generally be deferred until after pregnancy, although pyrimethamine may be used with caution to treat active toxoplasmosis during pregnancy in sulfa-allergic patients. Pregnant HIV-infected women who have evidence of primary toxoplasmic infection or active toxoplasmosis should be evaluated and managed during pregnancy in consultation with specialists (see Toxoplasmosis protocol). Infants born to women with serologic evidence of toxoplasmosis and HIV should be evaluated for congenital toxoplasmosis.

Note: for secondary toxoplasmosis prophylaxis, see Toxoplasmosis protocol.

Patient Education:

1. **For patients who are toxoplasmosis IgG-negative**, counsel to avoid eating raw or undercooked meat, especially pork, lamb, game and venison. Wash hands after handling raw meat and after gardening or contact with soil. Encourage patients not to adopt or handle stray cats; and if they own cats, to wash hands thoroughly after cleaning litter boxes. Daily cleaning of litter boxes reduces formation of the infectious cysts of toxoplasmosis. Cats should be kept indoors and fed dry or commercially-prepared cat food to avoid ingesting live prey which may carry the organism. (See *Prevention of Exposure to OIs*, in this section.)

2. For patients who are starting toxo prophylaxis, explain that the medication is to help prevent activation of an organism already present in their bodies. Discuss side effects of drug(s) with patient, including what action to take in the event of allergic response.

Reference:

CDC. USPHS/IDSA Guidelines for Preventing Opportunistic Infections among HIV-Infected Persons. *MMWR* 2002; 51 (No. RR-8).

DMAC Prophylaxis, Primary

Purpose:

To prevent or reduce the occurrence of Disseminated Mycobacterium Avium Complex. DMAC is an infection which is common in late HIV infection, and usually occurs in people with CD4 counts <50. Once a patient has DMAC disease, the organism cannot be eradicated, and lifelong suppressive treatment with multiple drugs is necessary -see Mycobacterium Avium treatment information.

S: Hx: HIV infected
Any fevers, chills, night sweats, weight loss?
Drug allergies?

O: CD4 count ≤ 50
R/O current DMAC infection with clinical assessment which may include AFB blood cultures, if warranted (see DMAC treatment protocol for complete information)
Review current drug regimen for meds which may interact with DMAC prophylaxes.

A: Increased risk of DMAC due to immunosuppression
No current DMAC symptoms or suspicion of infection

P: Start Azithromycin 1200 mg/week p.o. q week; or 1 gram Azithromycin sachet may be substituted (not FDA-approved for this indication). Or, may use: Clarithromycin 500 mg po bid. However, clarithromycin is not recommended during pregnancy. Some protease inhibitors interact with clarithromycin (see drug interaction info). Dose adjustment is required in renal insufficiency. Note that if breakthrough DMAC occurs, there is a chance it may be macrolide resistant.

Alternative: Rifabutin 300 mg po qd may be used. Many antiretroviral drugs cannot be used concomitantly with rifabutin, and others require dose adjustments for the antiretroviral and/or rifabutin. See drug interaction tables in the antiretroviral section, with special attention to NNRTIs and PIs; refer to complete prescribing information. **Active MTB must be ruled out before starting rifabutin, as tuberculosis can develop resistance to rifabutin which will extend to rifampin as well.** Resistance can greatly complicate the treatment of TB infection, and should be carefully avoided. Additionally, rifabutin should not be used with clarithromycin; it can be used with Azithromycin in standard doses, but this combination is not recommended as standard of care.

Pregnancy: Azithromycin is the drug of choice during pregnancy, although some treaters withhold it during the first trimester. Clarithromycin has shown teratogenicity in animal studies.

Note: for secondary prophylaxis, see DMAC Treatment protocol.

Discontinuation of primary prophylaxis: In persons responding to HAART with sustained increases in CD4 counts to ≥ 100 for ≥ 3 months, should discontinue DMAC primary prophylaxis to reduce pill burden, drug toxicity, drug interactions, and expense. Careful observation and monitoring are required; and prophylaxis should be re-instituted if the patient's CD4 count decreases to < 50-100.

Patient Education:

1. Discuss side effects of the selected medication and how the client should respond in event of rashes, diarrhea, etc.
2. Explain purpose of medication, and be sure that the client understands dose and frequency.
3. Reinforce the need to continue the medication indefinitely in order to reduce the risk of DMAC.
4. For women of child-bearing potential who are on clarithromycin, stress the need for effective contraception to avoid potential teratogenic effects.

References:

CDC. USPHS/IDSA Guidelines for Preventing Opportunistic Infections among HIV-Infected Persons. *MMWR* 2002; 51 (No. RR-8).

Sande MA, Gilbert DN, Moellering RC Jr. *The Sanford Guide to HIV/AIDS Therapy, 10th edition.* 2001; Hyde Park, VT, Antimicrobial Therapy, Inc.

Reducing Maternal-Infant HIV Transmission

Purpose:

1) To offer women who are HIV-infected, pregnant, and wish to carry their pregnancy to term, the option of using medication to reduce the risk of transmitting HIV to their infants; and
2) To discuss this option with HIV-infected women who are considering pregnancy.

Background Note on Prenatal HIV testing: As of 2002, the USPHS recommends voluntary HIV testing for all pregnant women, regardless of perceived HIV risk factors. This policy is due to the rising rate of heterosexual transmission of HIV, which is now the predominant route of transmission for adult and adolescent women in the U.S, accounting for ~64% of all cases in women. Unfortunately, many women are unaware of their sex partner's HIV risk, which complicates HIV reporting by adding many women to the "No Identified Risk" category. In addition, there are still substantial numbers of women who are infected as a result of current or past injection drug use. All pregnant women should receive non-coercive HIV information to ensure informed, voluntary consent or informed refusal for HIV testing.

HIV testing should be offered early in pregnancy. It is helpful for infected women to be counseled about their infant's HIV risk early in pregnancy, so that they may decide whether to continue the pregnancy, as well as to consider which vertical transmission reduction methods might be appropriate for them. The primary concern of the clinician, however, must be the health of the pregnant woman. All counseling must be non-coercive, and care for the woman must not be threatened or terminated if she refuses testing or declines antiretroviral treatment. Risk reduction counseling should be offered to all women, even those who refuse testing.

Women who present in labor, with no history of prenatal testing, may be offered a rapid response HIV test; though a positive result from a single test would be conditional, the woman can be counseled that it is very likely that she is infected. Even this late in the pregnancy, action may be taken to reduce the infant's HIV risk. Confirmatory testing must be done as soon as possible to curtail unnecessary treatment of the infant.

S: Reports learning she was infected during prenatal HIV testing; or woman with known HIV-infection becomes pregnant.

HX: Have other children been tested? HIV status of partner
Current medications, including over the counter, vitamins, supplements, herbal preparations
Antiretroviral history, with attention to ARV intolerances or failures
Symptoms or difficulty with pregnancy
Under obstetrician's care or need referral
Social situation
Recreational drugs, alcohol, tobacco use, hx and current

O: HIV test on chart for documentation
Review viral load and CD4 history
Review results of any resistance testing previously done
Review other labs if available
Document weight, B/P, vital signs
See *Initial Physical* and *Initial/interim Labs* in Assessment section, if not already completed

A: HIV+ pregnant woman
Fetus at risk of HIV infection, with ~20-25% chance of becoming infected if mother untreated
Fetus potentially at risk for other OIs affecting mother (contingent on maternal immunologic status)

P: Labs (see Initial labs, complete if not already done)

Antiretrovirals as indicated, if detectable HIV viral load to reduce maternal viral load and fetal risk. Note that the woman must be counseled about risks and benefits of ARV regimens, and **the final decision regarding use of ARVs is the responsibility of the woman.** A decision to not accept treatment should not result in punitive action or denial of care. Women who wish to receive only ZDV should have the benefits of a full ARV regimen explained to them, e.g., the further reduction of risk down to ~2%, but ZDV alone should not be denied if she wishes not to take other ARVs. ZDV is generally to be included in ARV regimen unless the woman is intolerant or refuses.

If not already on ARVs, counsel re beginning ARVs at the beginning of the second trimester or as soon as possible thereafter

Co-manage prenatally with obstetrician

Prepare woman for bottle-feeding the baby, since breastfeeding confers an additional 12-15% HIV risk to the infant

Plan consult with HIV-expert pediatrician at birth

Prognosis

Maternal: Pregnancy has been associated with a transient reduction in the CD4 count, especially in the third trimester. Initial concern that pregnancy could greatly accelerate HIV disease has not been borne out in subsequent clinical observations, although a minor influence on HIV progression has not been ruled out. Otherwise, the same laboratory and clinical indicators are used to estimate stage of disease and risk of progression. Optimal antiretroviral therapy (highly active antiretroviral therapy, or HAART) should be discussed with the woman in detail, including the purpose of HAART and its potential to reduce HIV risk to baby as well as benefit the woman, potential side effects, what is and is not known about effects on the fetus, relationship of viral load to transmission, and the possibility of enrolling the baby in a follow-up study to observe for any adverse effects of in utero exposure to antiretrovirals. Most women opt for antiretroviral therapy; for those who do not wish to go on HAART, or for those for whom antiretrovirals are not indicated, ZDV may be used alone to help reduce the HIV transmission risk. Despite concern that ZDV alone during pregnancy may contribute to the risk of ZDV-resistant virus, studies suggest that this is rare. However**, use of ARV drugs in suboptimal combinations (such as dual therapy using ZDV with lamivudine or NNRTI), even over a limited time, often results in maternal drug resistance and limited treatment options in the future.**

Fetal: Infants born to HIV-infected women have a 70-80% chance of being spared HIV infection even without treatment. Vertical transmission of HIV in the U.S. has averaged about 15-30% if no antiretroviral therapy is used. Transmission may occur during antepartum, during delivery, or during breastfeeding. Increased likelihood of transmission is associated with high maternal viremia, common in very early (seroconversion) or very late (AIDS) HIV disease; low maternal CD4; premature rupture of membranes, especially with duration >4 hours before delivery; illicit drug use during pregnancy, and chorioamnionitis at delivery. HIV disease in infants often has a more rapid progression than in adults, and illness commonly occurs in the first year of life. High viral load is associated with more rapid disease progression in pediatric as well as adult patients.

Other adverse outcomes such as preterm birth, low birth weight, and pregnancy complications have not differed significantly from matched HIV-negative controls.

Diagnosis of neonatal HIV infection is confounded by the fact that all infants born to HIV-infected women carry maternal HIV antibody until age 12-18 months. In infants younger than 12 months (and possibly up to 18 months), the standard HIV antibody test will detect maternal, not infant, HIV antibody. Viral culture, qualitative PCR, or even viral load testing may be used to determine true infection status as early as 2-3 months of age. Most clinics perform qualitative PCR tests between birth and 48 hours (if done at birth, cord blood is not used due to possibility of contamination by maternal blood), two weeks, one month, and two months.

If the child is positive on the two-week HIV PCR test, many clinicians presumptively discontinue ZDV monotherapy in favor of a pediatric HAART regimen. When a positive PCR is found, a viral load test is performed, along with a repeat PCR. If these are positive, the child is presumed to be infected and no further PCRs are performed. If the initial tests are negative, repeat testing is done at age 3-6 months. For infants who are presumed uninfected, HIV antibody testing is watched every six months until it becomes undetectable (negative); antibody testing is used at 18 months to confirm positive HIV status.

Viral load testing or quantitative PCR (HIV-1 RNA) might be a reliable way to detect infection, since it is sensitive and specific. However, it is more expensive than the qualitative PCR, and has been associated with occasional false positives in adults, especially when viral load results are low. It has not been tested sufficiently in this setting to substitute completely for qualitative PCR in diagnosing infection in exposed newborns.

Infants born to infected women are routinely placed on PCP prophylaxis starting at 4-6 weeks of age, since PCP may occur within the first few months of life if the infant is HIV-infected. If testing confirms that the infant is uninfected, prophylaxis is discontinued. (See www.aidsinfo.nih.gov for more pediatric treatment guidelines and information.)

Background: Infant HIV Risk Reduction

Interim results of a randomized, multicenter study (PACTG 076) were reported in early 1994. Final estimates showed that transmission of HIV from infected women to their infants was reduced from 22.6% among controls to 7.6% among infants of women who received zidovudine (ZDV) during the second and third trimester of pregnancy, as well as intravenous zidovudine during delivery. Infants of the women in the ZDV group were also given ZDV syrup for the first 6 weeks of life. Of 184 children born in the placebo group, 40 were infected, and of 180 in the ZDV group, 13 were infected. Occurrences of major and minor congenital abnormalities were approximately equal between the two groups.

The ACTG 076 regimen consisted of:

1. 100 mg ZDV po five times a day, starting at 14-34 weeks of gestation and continuing throughout the pregnancy [Note: 300 mg bid is now standard dosing, even in pregnancy];
2. administration of I.V. ZDV to the woman during labor, with a 1-hour loading dose of 2 mg/kg, followed by continuous infusion of 1 mg/kg/hour until delivery; and
3. ZDV syrup given to the newborn at 2 mg/kg of body weight per dose q 6 hours, starting 8-12 hours after birth, for the first 6 weeks of life.

Toxicities from zidovudine were minimal among the women, and three women in each group (ZDV and placebo) discontinued the study because of toxicity attributed to the study drug. Some infants on ZDV had a transient decrease in hemoglobin, which returned to the levels of the control infants by 12 weeks of age without treatment. Rate of congenital abnormalities were similar between the ZDV and placebo groups.

Subsequent studies have demonstrated that ZDV reduces HIV transmission even in women with lower CD4 counts, women who have been previously treated with ZDV, and those with more advanced disease than women in the study. Data from countries with limited resources indicate that shorter courses of ZDV reduce transmission risk somewhat less than the course currently recommended in developed countries.

During the PACTG 076 study, women were not given ZDV until after 14 weeks' gestation to avoid drug exposure during fetal organogenesis, so fetal risk during the first trimester could not be assessed. Follow-up studies on uninfected children exposed to ZDV in utero have indicated no significant differences in growth, development, or immunologic status compared to placebo group. Long-term effects of ZDV during the second and third trimester for the infant are not known, although ACTG 219 is under way to observe children exposed in utero to antiretroviral agents until they reach age 21.

Recent findings: As of early 2003, studies have shown that adding 2 or more antiretrovirals to the ZDV regimen further reduces infant risk, in most cases to ≤2%, if the medications are started early enough in pregnancy and result in significant viral load reduction. In select cases, the risk can be further reduced by pre-labor C-section.

Recommendations for use of Antiretroviral Drugs to reduce Perinatal HIV-1 Transmission by Clinical Situation

I. Pregnant HIV-infected women without prior antiretroviral therapy.

Recommendation:
HIV-1-infected pregnant women must receive standard clinical, immunologic and virologic evaluation. Recommendations for initiation and choice of antiretroviral therapy should be based on the same parameters used in non-pregnant individuals (see Antiretroviral Therapy section), with consideration and discussion of the known and unknown risks and benefits of such therapy during pregnancy. See Table 1, this section.

The three-part ZDV regimen* should be recommended for all HIV-infected pregnant women, regardless of HIV-RNA or CD4 levels, to reduce the risk of perinatal transmission. The combination of **ZDV chemoprophylaxis with additional antiretroviral drugs for treatment of HIV infection should be discussed and recommended for infected women whose clinical, immunologic, and virologic status indicates the need for antiretroviral treatment, or whose HIV-1 RNA is > 1000 copies/ml regardless of clinical or immunologic status**.

Women who are in the first trimester of pregnancy may consider delaying treatment until after 10 to 12 weeks gestation.

II. HIV-infected women receiving antiretroviral therapy during the current pregnancy.

Recommendation:
HIV-1 infected pregnant women receiving antiretroviral therapy in whom pregnancy is identified after the first trimester should continue therapy. If the current therapeutic regimen does not contain ZDV, the addition of ZDV or substitution of ZDV for another nucleoside analog antiretroviral is recommended after 14 weeks gestation, if possible

Women receiving antiretroviral therapy whose pregnancy is recognized during the first trimester should be counseled regarding the benefits and potential risks of antiretroviral administration during this period, and continuation of therapy should be considered. Women whose ARV regimen includes efavirenz should be offered a substitute ARV.

If antiretroviral therapy is discontinued during the first trimester, all antiretroviral drugs should be stopped and reintroduced simultaneously to avoid the development of resistance.

Intrapartum and newborn ZDV administration* is recommended regardless of the antepartum antiretroviral regimen.

III. HIV-infected women in labor who have had no prior therapy.

Several possible regimens can be offered:

1. single dose nevirapine (200 mg po) at the onset of labor followed by a single dose of nevirapine for the newborn at 48 hours of age (2 mg/kg po); (note that some studies have suggested up to 20% of women who get the single dose nevirapine regimen later show NNRTI resistance, which may limit the woman's future treatment options.)
2. oral ZDV (600 mg) and 3TC (150 mg) at onset of labor, then 300 mg ZDV q3 hr and lamivudine 150 mg q12 hours until delivery; followed by oral ZDV 4 mg/kg q 12 hr and 3TC 2 mg/kg q 12 hours x 7 days for the newborn;
3. intrapartum intravenous ZDV* (2 mg/kg loading dose, then continuous infusion of 1 mg/kg/hr until delivery), followed by 6 weeks of ZDV (2 mg/kg q 6 hours) for the newborn; or
4. the 2-dose nevirapine regimen along with intrapartum ZDV and 6 weeks of ZDV for the newborn* (see dosing in #1 and #3). This combination has not been tested for efficacy of reducing transmission, but offers the theoretical benefit of synergy, and would be advantageous if maternal virus happened to be resistant to either drug.

In the immediate postpartum period, the woman should have appropriate assessments (e.g., CD4 count, HIV-1 RNA) to determine whether antiretroviral therapy is recommended for her own health.

IV. Infants born to HIV-infected women who have received no antiretroviral therapy during pregnancy or intrapartum.

Recommendation:
The 6-week neonatal component of the ZDV chemoprophylactic regimen should be discussed with the mother and offered for the newborn. ZDV should be initiated as soon as possible after birth, preferably within 6-12 hours after birth.

Some clinicians may choose to use ZDV in combination with other antiretroviral drugs, particularly if the woman has known or suspected ZDV-resistant virus. However, the efficacy of this approach is unknown for prevention of transmission is unknown and appropriate dosing regimens for neonates are incompletely defined.

In the immediate postpartum period, the woman should undergo appropriate assessments (e.g., CD4 count, HIV-1 RNA) to determine if antiretroviral therapy is required for her own health. The infant should undergo early diagnostic testing so that if he or she is HIV-infected, treatment can be initiated as soon as possible.

***Availability of drugs:** If the pregnant woman will need the intrapartum and/or postpartum pediatric ZDV regimen, prior arrangements will need to be made with the pharmacy that will be supplying the ZDV in intravenous and syrup form, to verify that these medications will be in stock and available on short notice when needed. The Labor and Delivery area may also need special pre-admission instructions about initiating and administering the ZDV infusion.

Intrapartum Care

Women who are on HAART should bring their antiretrovirals with them to the hospital, and, except for ZDV, they should be administered by mouth throughout labor and delivery. ZDV should be given intravenously though a separate IV line, due to drug incompatibility with oxytocin.

Intrapartum management is not substantially altered by maternal HIV status, beyond intravenous ZDV, although it should be less obstetrically invasive. Fetal scalp electrodes, clips, or piercing of the scalp for blood sampling may pose an increased risk, by allowing fetal inoculation with infectious secretions from the uterus and vagina. However, if monitoring cannot be accomplished in any other way, scalp electrodes may be needed.

Some clinicians advocate bathing the infant immediately after birth to remove any infectious maternal secretions from the neonate's skin, rationalizing that the cold stress would be less hazardous than exposure to possible infection through small skin breaks. Cleanse the skin thoroughly with alcohol and povidone-iodine if any injections are given to the newborn prior to a complete bath. Afterwards, the injection site should be covered with an adhesive bandage to prevent contamination with secretions remaining on the skin. Gloves and other standard precautions should be used to prevent health care worker exposure to maternal secretions when working with women in labor, and for handling the newborn before and during the bath.

A 1996 study suggests risk of HIV transmission nearly doubles in association with rupture of membranes (ROM) greater than four hours before delivery (14% vs 25% in Landesman, et al.) Pregnant women with HIV should never be sent home with ruptured or leaking membranes, and in fact, need to be informed of the need to come in earlier in the course of labor than women without HIV. Other studies have pointed to prolonged labor, complicated delivery, episiotomy, laceration greater than second degree, scalp electrode or fetal scalp sampling, forceps or vacuum delivery, or chorioamnionitis.

The US Public Health Service does not recommend C-section unless it is otherwise indicated, or if the viral load is >1000 at the time of delivery, in part because the complication rate from C-section tends to be higher in HIV-infected women.

Monitoring

Women, their children, and other family members ideally should receive care together in a family-centered setting. Gynecologic, pediatric, infectious disease, and other specialties should coordinate services to ensure appropriate follow-up for all HIV-affected family members.

Women

HIV-infected pregnant women on ZDV should be assessed monthly for hematologic and liver chemistry abnormalities, as recommended for non-pregnant patients, in addition to routine pregnancy labwork. She will need other labs needed for other antiretrovirals that she is taking. Consider stopping the ZDV for severe anemia, an absolute granulocyte count less than 750, or SGOT/SGPT greater than five times the upper limit of normal. CD4 lymphocyte count should be monitored as well, to determine whether prophylaxes for OIs should be initiated (see *Treatment during Pregnancy*). Other antiretrovirals may require additional monitoring of blood chemistries.

Infants

A baseline CBC and differential should be performed at birth. Repeat hemoglobin is recommended at 6 and 12 weeks of age. ZDV should be administered with caution to infants with severe anemia (Hb < 8), ensuring treatment of the anemia and intensive monitoring if the drug is used. ZDV is usually replaced by HAART (which may or may not include ZDV) if the infant has positive PCR results at 2 week follow-up. Newborns exposed to antiretroviral agents in utero can be placed in this confidential follow-up study by calling 1-800-258-4263, 8:30 to 5:30 p.m. Eastern time.

Pediatric treatment information is beyond the scope of this guideline. Refer to http://www.aidsinfo.nih.gov/ for updated pediatric antiretroviral therapy guidelines, as well as immunizations and opportunistic infection prevention guideline for pediatric-specific information. The National Pediatric and Family HIV Resource Center (NPHRC) at 1-800-362-0071 is open 9 a.m. to 5 p.m. Eastern, and also has pediatric and family information. See also *HIV/AIDS Resources*, after the Acknowledgments section in this manual, for additional recommendations.

Patient Education:

1. Studies have shown that ZDV reduces risk of transmission of HIV from pregnant women to their infants from about 23% to around 8%, but does not completely eliminate risk of transmission. Use of other antiretroviral drugs in combination with ZDV may lower the baby's risk to about 2%.

2. Risk of transmitting HIV to the baby is also dependent on your viral load. More aggressive antiretroviral therapy, using 3 or more drugs, may reduce the viral load to much lower levels, and this possibility should be discussed.

3. As with all patients who are on antiretrovirals or pregnant, medical monitoring and follow-up for both conditions are essential. You must stay as healthy as possible in order to increase your chances of having a healthy baby.

4. Short-term risks of ZDV to women and infants are usually minimal and manageable. Common maternal ZDV side effects are nausea, which may be managed by taking with meals or saltines; headache, for which acetaminophen may be used; and malaise. (Discuss also effects of other prescribed ARVs.)

5. Long-term risks of ZDV and antiretroviral therapy to patients and their children are not as well defined as we would like, although studies 10 to 12 years later have shown no increased risk of birth defects. Any possible risk must be weighed against the benefit of reducing HIV transmission risk.

6. ZDV and other antiretrovirals must be taken consistently until delivery to maximize benefit in reducing risk of infecting the infant.

7. Report to the Labor and Delivery area immediately in the event of membrane rupture. (Be sure that L&D staff know not to send this patient home with ruptured membranes.)

8. You will need IV ZDV during labor and delivery. Review how this will be handled once she arrives in the labor and delivery area. Although this should be pre-arranged with the hospital she plans to use, unforeseen events could delay recognition of need for a ZDV drip. She will need to know the back-up plan.

9. Discuss with the woman in advance what kind of HIV testing will be available for her infant, and how soon the child's actual HIV infection status can be known. Remind her that she is responsible for consenting to or refusing these tests for her child.

10. The newborn must be dosed consistently and monitored regularly during the first six weeks of life. Verify mother's understanding of ZDV syrup dosage measurement, and give written instructions based on infant's weight.

11. Infant should be bottle fed, since breastfeeding increases the infant's risk of becoming infected by 12-15%.

12. Discuss any future plans for childbearing, and arrange appropriate contraception as needed.

13. After delivery, woman and infant will need frequent medical follow-up, with gynecologic care and of the mother's HIV infection, neonatal health maintenance, and determination of the infant's infection status. Help her find a pediatric provider qualified to care for HIV-exposed or HIV-infected children.

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Treatment During Pregnancy

Purpose:

To provide optimal care to any woman with known HIV infection who is pregnant, or who is found to be HIV-infected during the course of a pregnancy.

The first task in caring for a pregnant woman with HIV is to provide counseling that will allow an **informed reproductive choice**. Whatever choice she makes should be supported. If she chooses to continue her pregnancy, antepartum care must be tailored to her needs. Most important to remember is that a pregnant woman must have all treatments indicated by her HIV infection unless there is compelling evidence that treatment presents an unacceptable risk to the fetus. She must be counseled about risks and benefits of treatments and alternatives, and she must be included in treatment decision-making.

Antepartum Care

Initial HIV physical exam and labwork, including Pap smear, (see *Initial PE* and *Initial and Interim Labs* in Assessment section) must be performed if not already done, especially screening for syphilis, gonorrhea, chlamydia, bacterial vaginosis (BV), Hepatitis B, Hepatitis C, toxoplasmosis, rubella, and tuberculosis. Appropriate therapy must be undertaken for abnormal findings and existing disease. In addition, all routine prenatal labs and screening should be performed as on HIV uninfected women

CD4 count and viral load (HIV-1 RNA) must be performed, initially and every three months during pregnancy. Pap smears should be followed every six months, with colposcopy referrals for abnormal results. Monitor for outbreaks of genital herpes and other conditions related to HIV.

Note that women at high risk for syphilis should have serologic testing twice in the last trimester, at 28 weeks and at delivery. Additionally, any woman who has a stillborn infant after 20 weeks' gestation should be tested. Any positive syphilis titer should be considered an infection in a pregnant woman, unless adequate treatment history is clearly documented in the medical records and subsequent antibody titers have declined. Women at high risk of STDs (new or >1 sex partner, for example) should have repeat Hepatitis B, chlamydia, gonorrhea, and BV screening late in pregnancy. BV should be treated with clindamycin or oral metronidazole, since topical agents did not reduce risk of preterm delivery. Note that patients on ritonavir may experience symptoms due to the small amount of alcohol in the capsules.

Liver enzymes and electrolytes should be evaluated more frequently during the last trimester of pregnancy for women on nucleoside analogue drugs, to detect rare but life-threatening disorders of liver metabolism.

Immunizations during pregnancy:*

MMR (Measles/Mumps/Rubella)	**Contraindicated**
Influenza	May be given after first trimester
Hepatitis B	May be given as needed
Pneumococcal	May be given as needed
Tetanus-Diphtheria	May be given as needed
Hepatitis A	May be given if at high risk of infection, if HCV-infected, or other indication (see *Immunizations* in Health Maintenance section)
Varicella Zoster	**Contraindicated in all HIV-infected adults**

*Note: some caregivers try to avoid giving immunizations during the third trimester of pregnancy because of the potential for transient viral load increase post-immunization. This is still a theoretical risk, based on the information that most HIV transmission to the fetus occurs late in pregnancy or during delivery, and that transmission risk tends to increase along with maternal viral load. The increase in viral load may be prevented with HAART, and some clinicians defer immunizations until HAART is underway.

Women with <200 CD4 cells should be started on PCP prophylaxis, such as TMP-SMX, aerosolized pentamidine, or dapsone, none of which have been shown to be teratogenic. Women with CD4 counts ≤50 should be started on DMAC prophylaxis with azithromycin (see *DMAC Prophylaxis* in Health Maintenance section); if toxo IgG+, and sulfa-allergic, toxo prophylaxis may be deferred until after delivery (see *Toxoplasmosis Prophylaxis* in Health Maintenance section).

Tuberculosis prophylaxis for any woman with either a positive PPD (≥ 5 mm induration) **or a history of exposure to active TB** should be started promptly once active disease is ruled out. Isoniazid should be given with pyridoxine to prevent peripheral neuropathy, and both continued for 9 months (see *Latent TB Infection* in Health Maintenance section for more complete information). Pregnant HIV-infected women with active TB should generally be treated as any HIV-infected adult without regard to stage of pregnancy (see *Mycobacterium Tuberculosis* in Disease-specific section). **Streptomycin is not usually given in pregnancy because of a dose-related risk of eighth cranial nerve damage with irreversible deafness**. **Consult with an infectious disease specialist or TB expert on any patient who has multi-drug-resistant TB.**

Women should be carefully monitored for **opportunistic infections** during pregnancy, with special note given to nonspecific symptoms such as fatigue, back pain, and weight loss, which may be due to HIV rather than pregnancy. Respiratory symptoms in particular merit rapid, aggressive investigation.

HIV-infected women can have all the complications seen in uninfected women, such as hypertensive disorders, ectopic pregnancies, psychiatric illnesses, multiple gestation, pre-term delivery, and STDs. It is important that these problems be recognized quickly and treated appropriately to avoid life-threatening complications. Most HIV treaters co-manage HIV-infected pregnant women with an experienced OB-GYN who can observe for any problems of pregnancy. Communication between the two of them about medications, expectations, and complications are vital for the health and well-being of both mother and baby.

Choosing an Antiretroviral Regimen

A highly active regimen of antiretroviral drugs which includes zidovudine (ZDV) should be offered to all HIV-infected pregnant women to reduce transmission to the infant (see *Reducing Maternal Infant Transmission*, in Health Maintenance section) when antiretrovirals are indicated. These drugs must be offered and discussed in terms of what is and is not known about teratogenicity and long-term effects on the infant, and weighed against the reduction in perinatal transmission afforded by antiretroviral therapy. Because most of the antiretroviral drugs are relatively new, such information is limited. All antiretroviral drugs approved as of 12/02 by the US FDA are classified as Category B or C for use during pregnancy, although efavirenz is contraindicated during pregnancy, as is the liquid formula of amprenavir. It is recommended that the combination of stavudine and didanosine be avoided in pregnancy due to increased risk of lactic acidosis (See **Table 1: Antiretrovirals in Pregnancy** for brief on each approved drug, this section; see first page of **Common HIV Medications** section for explanation of pregnancy categories.)

Further discussion of specific drugs can be found in the US Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States (*Morbidity and Mortality Weekly Report* , vol 51, RR. #18, 2002) and the frequent updates which appear on the HIV AIDS Treatment Information Service website (http://www.aidsinfo.nih.gov/).

Because new antiretrovirals continue to be approved, individual drug companies must be consulted to learn the FDA pregnancy categories and results of animal gestational testing of new drugs.

The fetal HIV risk also relates to maternal viral load, although recent data indicate that antenatal use of HAART to reduce plasma viral load to very low or undetectable levels may lower the infant's HIV risk to 2% or less. It is important to note that transmission has occasionally occurred at low maternal viral loads (see *Reducing Maternal Infant Transmission*, in Health Maintenance section). If viremia persists in the pregnant woman despite adherence to HAART, the International AIDS Society-USA recommends resistance testing (see Resistance Testing, at end of antiretroviral section), particularly if there has been prior antiretroviral exposure or if there is a high prevalence of resistant virus in the community.

Antiretroviral Pregnancy Registry. In order to improve tracking of fetal effects, several pharmaceutical manufacturers have been compiling a database of infants exposed to antiretroviral drugs in utero to determine whether patterns of fetal/neonatal abnormalities occur. Several pharmaceutical companies now sponsor a registry to collect this data. **Newborns exposed to antiretroviral agents can be placed in this confidential follow-up study by calling 1-800-258-4263, 8:30 a.m. to 5:30 p.m. Eastern time;** fax is 800-800-1052. Providers are encouraged to add to the available information on fetal risk by using this registry at first contact with a pregnant woman on ARVs. More information can be obtained at www.apregistry.com.

Additionally, although current US Public Health Service guidelines recommend treating HIV infection in pregnant women using the same principles and modalities as for non-pregnant individuals, some clients and HIV providers elect to withhold antiretroviral therapies during the first trimester, since that is known to be a period of rapid organogenesis with potential for increased risk of birth defects if teratogen exposure occurs. If this option is selected, the woman must understand that she must stop all antiretroviral therapies at once, then resume them concurrently later, in order to reduce the risk of developing antiretroviral-resistant HIV. The woman should be made aware of the risk of viral rebound during the HAART interruption.

Table 1: Antiretrovirals in Pregnancy

Antiretroviral Drug	FDA Pregnancy Category	Placental Passage [Newborn:Maternal Drug Ratio]	Long-Term Animal Carcinogenicity Studies	Animal Teratogenicity Testing*
zidovudine**	C	Yes (human) [0.85]	Positive (rodent, non-invasive vaginal tumors)	Positive: rodents, near lethal dose
zalcitabine	C	Yes (rhesus) [0.3 - 0.5]	Positive (rodent, thymic lymphomas)	Positive: Rodents: hydrocephalus at high dose)
didanosine	B	Yes (human) [0.5]	Negative (no tumors, lifetime rodent study)	Negative
stavudine	C	Yes (rhesus monkey) [0.76]	Not completed	Negative (rodents: sternal bone calcium decreases)
lamiduvine	C	Yes (human) [~1.0]	Negative (no tumors, lifetime rodent study)	Negative
abacavir	C	Yes (rats)	Not completed	Positive (anasarca and skeletal malformations at 1000mg/kg [35Xhuman exposure] during organogenesis; these defects occurred in rats but not rabbits)
tenofovir	B	Yes (rat and monkey)	Not completed	Negative (osteomalacia when high doses given to juvenile animals)
saquinavir	B	Minimal (human)	Not completed	Negative
indinavir	C	Minimal (human)	Not completed	Negative (but extra ribs in rodents)
ritonavir	B	Minimal (human)	Positive (rodent, liver adenomas and carcinomas in male mice)	Negative (but cryptorchidism in rats)
nelfinavir	B	Unknown	Not completed	Negative
amprenavir	C	Unknown	Not completed	Negative (but thymic elongation; incomplete ossification of bones; in rats and rabbits)
lopinavir-ritonavir	C	Unknown	Not completed	Negative (but delayed skeletal ossification and increased skeletal variations in rats at maternally toxic doses)
nevirapine	C	Yes (human) [~1.0]	Not completed	Negative
delavirdine	C	Unknown	Not completed	Positive: Ventricular septal defect in rodents
efavirenz	C	Yes (cynomolgus monkeys, rats rabbits) [~1.0]	Not completed	Positive: Anencephaly, anophthalmia; microphthalmia in cynomologus monkeys

*Animal studies generally overestimate human teratogenicity: Out of 1,200 known animal teratogens, only about 30 are known to be teratogenic in humans.

**Despite some animal data showing potential teratogenicity of ZDV when near-lethal doses are given to pregnant rodents, considerable human data available to date show that risk to the fetus, if any, is extremely small when given to the pregnant mother beyond 14 weeks gestation. Follow up to 6 years of age for 734 infants born to HIV-infected women with in utero exposure to ZDV has not demonstrated tumor development. However, no data is available on longer follow up for later effects.

Table adapted from USPHS Task Force recommendations for the use of antiretroviral drugs in pregnant women infected with HIV-l for maternal health and for reducing perinatal HIV-1 transmission in the United States updated 11/22/02. Downloaded from http://www.aidsinfo.nih.gov/.

Discussion of treatment options and recommendations should be non-coercive, and the final decision regarding the use of antiretroviral drugs is the responsibility of the woman. A decision to decline treatment with ZDV and/or other drugs should not result in punitive action or denial of care, nor should use of ZDV be denied to any woman who wishes to minimize exposure of the fetus to other antiretroviral drugs and therefore chooses to receive only ZDV during pregnancy to reduce the risk of perinatal transmission. The woman should be informed that ZDV alone does not reduce the baby's HIV risk as much as a potent triple-drug regimen, and also that monotherapy of any antiretroviral drug confers a risk of drug resistance.

Assure referral to appropriate social services for food, housing, child care, and parenting skills. Counseling and psychological support for patient and/or partner may be needed, as well as substance abuse and detox programs for self or partner. Family planning, legal or domestic violence services may be needed for some patients during and after pregnancy.

Co-management and communication with the obstetrician or nurse-midwife is imperative throughout the pregnancy and early postpartum period.

Nutrition and weight must be assessed and observed throughout the antepartum period. Pre-pregnancy weight must be compared to height, to determine if the patient is underweight, normal or overweight. A food diary may be a useful tool in assessing intake, and nutritional counseling is recommended. Set a weight goal at first prenatal visit, based on pre-pregnancy weight and height:

1. Women with normal pre-pregnancy weight should gain about one pound per week in the second and third trimester, for a total of 25-35 lbs (11.5-16 kg)
2. Underweight women should gain a little more than a pound per week (0.5 kg), for a total of 28-40 lbs during pregnancy (12.5-18 kg)
3. Overweight women should gain somewhat less than one pound per week (0.3 kg), for a total of 15-25 lbs.

Nausea and vomiting. Women who are not on antiretroviral therapies at the beginning of their pregnancy are usually assessed and placed on HAART at the end of the first trimester, when nausea and vomiting of early pregnancy have improved. Women with signs of dehydration should be assessed and appropriately treated in collaboration with the obstetrician or nurse-midwife. Any medications used for N/V must be assessed for drug-drug interactions with any HIV-related medications the woman is already taking.

Hyperglycemia. Women on protease inhibitors may be at higher risk of glucose intolerance and must be carefully monitored. Some clinicians check glucose tolerance at 20-24 weeks and again at 30-34 weeks if the woman is taking PIs. The baby is checked for neonatal hypoglycemia at 1 and 4 hours.

Mitochondrial toxicity is a rare but life-threatening complication which can result in lactic acidosis when using nucleoside analogue drugs. Careful monitoring for this and other liver toxicity is necessary.

Hyperbilirubinemia. Women who are on indinavir may be at higher risk of neonatal hyperbilirubinemia, so additional testing is performed. The woman's bilirubin is checked during labor and the baby has an additional test on the 2nd or 3rd day of life.

Recurrent Genital Herpes. Women with HIV are more likely to experience outbreaks due to their immunosuppression, and neonatal infection can be severe even if it is detected and treated early. Additionally, HSV lesions may increase the risk of exposing the infant to HIV. If a woman has an active outbreak of genital HSV or experience prodromal symptoms at the time of labor or membrane rupture, C-section is indicated. Some experts recommend giving prophylactic acyclovir (400 mg po tid; see *Herpes Simplex* in Disease-Specific section for complete dosing options) from 36 weeks to delivery to women who have even one episode of HSV-2 during their pregnancy. This is generally well-tolerated in patients, and may prevent the need for C-section, but an additional medication complicates their antiretroviral regimen and may make adherence more challenging.

Pain Management during labor and delivery may be complicated by drug interactions with antiretrovirals and by the higher medication tolerance in women who have addictions. Additional pain medication may be needed for women with histories of drug use.

Balance the risk of fetal inoculation and HIV infection during **invasive procedures** (amniocentesis, chorionic villus sampling, percutaneous umbilical cord blood sampling) against the benefits of these procedures. These procedures are relatively contraindicated, and should be undertaken only after discussion and consent from the pregnant woman. (See Intrapartum Care, in Reducing Maternal-Infant Transmission.)

Patient Education:

1. Use of a prenatal vitamin supplement is helpful, but cannot replace healthy food intake. Develop a plan with the patient for attaining the desired weight gain during pregnancy, while maintaining a healthy nutritional intake.

2. Cigarette, alcohol and drug use contribute to poor maternal nutrition and can harm the developing fetus. Illicit drug use also increases the risk of transmitting HIV to the infant. Injection drugs can transmit HBV, HCV, and CMV to the mother as well as to the baby.

3. Be sure all procedures are understood with regard to their risks and benefits both to the pregnant woman and the fetus.

4. Discuss risks and benefits (to woman and fetus) of each medication to be taken during pregnancy, including those about which there is little data on teratogenicity.

5. For women with negative toxoplasmosis titers, explain the need to avoid undercooked meats, soil, and animal feces.

6. Careful use of safer sex during pregnancy is important to prevent STDs and CMV, which can cause more complications when HIV is present. STDs could also harm the fetal development and possibly increase HIV transmission risk to the baby as well. New infections of genital herpes during pregnancy can cause severe complications and even death in neonates.

7. Discuss the option of using zidovudine as part of the strategy to reduce the risk of perinatal HIV transmission to her newborn, allowing her to choose whether to add zidovudine to her regular antiretroviral regimen (if applicable), or take it alone. The risk of zidovudine-resistant HIV should also be discussed if ZDV is used alone.

8. Reinforce regularly and clearly the notion that when the mother cares for herself, she is caring for her infant. Talk with the patient about stress, the importance of adequate mild-to-moderate exercise, and sufficient rest.

9. Teach her how to obtain medical attention quickly when the first signs of opportunistic infection or other complications occur. Discuss with her what to watch for, and how to get help when emergencies arise in the evenings and on weekends and holidays.

10. Regular prenatal care is extremely important to prevent complications of pregnancy.

10. Help the patient clarify her child care options, and to begin putting in place long-term child care and guardianship plans should she become too sick to care for her child/children.

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CHAPTER 3: Complaint-Specific Workups
Anemia

Definition:

Hemoglobin <13.8 for men, < 11.7 for women. Anemia of chronic disease is very common in the HIV-infected population, with increasing prevalence at lower CD4 counts and higher viral loads. Other causes of anemia are amenable to treatment and can result in improved quality of life. Patients who have gradual declines in hemoglobin may compensate and be asymptomatic even at very low hemoglobin levels.

S: Patient may c/o weakness, palpitations, dyspnea on exertion, dizziness, headache, malaise.
Check for hx of fever, wt loss, pain, other symptoms suggestive of infectious or neoplastic etiology.
Verify current medications, and find out which supplements including OTC and herbal preparations the patient takes.

O: Postural pulses and B/P to R/O dehydration. Check for tachycardia, pallor. After CBC has confirmed anemia, check retics, MCV and peripheral blood smear to start the workup. Review recent chemistries and CD4 count. PE to look for new lymphadenopathy or masses or other localizing symptoms.

A/P:

Low retics (<2), low MCV	Low retics, normal MCV	Low retics, high MCV	High retics
The cause is more likely to be iron deficiency, usually due to chronic blood loss from neoplasm, gastrointestinal infection such as CMV, or menorrhagia	Likely culprits are drugs (atovaquone, dapsone, primaquine, pyrimethamine, ganciclovir, interferon alpha, amphotericin, flucytosine, and others), bone marrow neoplasm; infectious bone marrow infiltration with DMAC, MTB, fungal organisms; neoplasm; renal failure; or anemia of chronic disease. With B-19 parvovirus infection, the patient is likely have a reticulocyte count of <0.2%, and to show a profound isolated anemia, compared to fungal, parasitic, or mycobacterial infections, in which the patient usually has pancytopenia	May be due to B_{12} or folic acid deficiency, possibly due to malabsorption; liver disease, antiretroviral drugs (such as AZT or hydroxyurea) or other medications. May also be due to autoimmune process	Consider hemolysis. An elevated LDH, low haptoglobin, or increased indirect bilirubin would support this dx. Check for hemolysis due to oxidant drugs, such as ribavirin or primaquin, G6PD deficiency (dapsone, sulfa). If the RBCs are fragmented and thrombocytopenia is present, DIC or TTP may be causing the problem
May need: 1. Stool guaiac X3; if +, may need endoscopy to determine cause of bleeding. Refer to GI service. 2. Iron studies, including ferritin, transferrin, TIBC. Ferritin often elevated in anemia of chronic disease, but low level will confirm Fe deficiency. 3. Hemoglobin electrophoresis (for patients with normal iron studies)	May need: 1. AFB and fungal blood cultures (if constitutional symptoms consistent with OI, see fever work-up) 2. FNA or bx as indicated for unexpected lymphadenopathy to R/O neoplasm, mycobacteria 3. Refer for bone marrow test for suspected lymphoma, neoplasm, B-19 parvo	May need: 1. B_{12} level 2. RBC folate	May need**:** Peripheral blood smear, platelet count (if not already done)

Additionally, for symptomatic patients, or those with declining hemoglobin levels < 7, arrange for urgent transfusion.
Discontinue offending drugs, if appropriate substitutes available, and follow CBC.

Treat appropriately if infectious pathogen identified (see applicable treatment guidelines), or if neoplasm detected.

Patients with HIV-related anemia usually respond to control of viral replication using HAART. Ritonavir appears to stimulate growth of hematopoeitic progenitors and may have a direct effect on improving hematopoiesis.

Refer for treatment of neoplasm or bleeding.

For B-19 parvovirus, some clinicians place on HAART immediately. Others use Immunoglobulin G 0.4 gm/kg IV qd x 5-10 days, with follow-up detect signs of relapse; tx may need to be repeated.

If no treatable pathology identified:
With normocytic, isolated anemia, Hb > 10 g/dl, and patient who is fairly late in disease (CD4 ct <200), with no unexplained constitutional symptoms, most likely dx is anemia of chronic disease. Close follow-up and avoidance of hematotoxic medications is indicated.

Note: Patients with symptomatic anemia and erythropoeitin levels less than or equal to 500 IU/L may benefit from erythropoeitin 100-200 U/kg of body weight, 3X/week until RBC count normalizes. RBC must be checked weekly, as polycythemia can occur. Injections are then being dropped back to weekly. Patients who do not respond to epo may have occult iron, folate, or B_{12} deficiency, which must be corrected for response to occur.

Follow up:

Check H&H at least monthly if HB <10 or declining, or if otherwise indicated. If on epo, RBC count must be checked weekly, as noted above.

Patient Education:

1. Return to clinic for increasing weakness, dizziness, or rapid heart rate.
2. Report fevers, night sweats, unusual bleeding, new pains, or visual disturbances immediately.
3. If starting HAART: discuss treatment schedule and adherence (see *Antiretroviral Therapy*)

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Diarrhea

Definition:

More than 4 loose stools or watery stools/day for >3 days. May also appear in a recurring or intermittent pattern.

S: **Patient complains of diarrhea.**

HX:
- Volume of stools, frequency, consistency, compared to usual pattern
- Duration of diarrhea
- Fever (see *Fever* in Complaint section)
- Nausea / vomiting (see protocol)
- Tenesmus
- Abdominal pain (location) / cramping
- Bloody stools or rectal bleeding
- Exposure to unsafely prepared food or contaminated water
- Fecal-oral contact
- Exposure to ill people with similar symptoms: (diapered) babies, pets, farm animals, reptiles
- Receptive anal intercourse
- Recent travel
- Weight loss: how much over what period
- KS or CMV at other sites
- Medications and when each started
- Supplements and herbals
- Recreational drugs/withdrawal
- Previous similar episodes

O: **Physical exam / check lab history**

- Temperature
- comparative weight
- funduscopic exam for CMV
- hydration status: skin turgor; orthostatic pulse & B/P
- abdomen: organomegaly, tenderness
- oral exam for mucosal KS, candidiasis, ulcerations
- most recent CD4 count (<200 may allow agents that usually cause acute diarrhea to become chronic or systemic)

A: **Assess for dehydration.**
Partial differential diagnosis:

Usually associated with acute:	*Often associated with chronic:*	*Other/rarer causes:*
Shigella flexneri	Microsporidiosis	Medication effect
Salmonellosis	Giardiasis	Pancreatitis
Campylobactor jejuni or other sp.	Cryptosporidiosis	Herpes enteritis
Clostridium difficile	Isospora belli	Lactose intolerance
Enteric viruses (adeno, rota, corona, astro, picobirna, calvirus)	M. avium complex	Small bowel overgrowth
Staphylococcal enteritis	Cytomegalovirus enteritis	Histoplasmosis (rare)
	Entamoeba histolytica	Pneumocystosis (rare)
	Cyclospora	Idiopathic

P:

- During workup, keep hydrated (orally if possible, intravenously if necessary, with glucose/electrolyte solution). Medicate for nausea as needed. Use combinations of Lomotil, Immodium and Questran or psyllium to help symptoms by slowing peristalsis and giving bulk to stools (one regimen for high-volume diarrhea includes Immodium 2mg TID; Lomotil 2mg after each loose stool, up to 6 per day; and psyllium BID). Note: do not use lomotil or immodium to slow peristalsis if *C. difficile* or Enterotoxigenic E. Coli is suspected.

- If diarrhea concomitant with starting of new antiretroviral regimen, consider drug most likely to be the culprit, esp. nelfinavir, buffered ddI, tenofovir, or PI. If nelfinavir, consider adding calcium 500 mg po bid; otherwise lomotil 2 mg po after each loose stool until diarrhea controlled. If ineffective, substitute for drugs most likely to be the culprit.

- Helpful lab tests: CD4 count; electrolytes; stool studies (C&S*, WBC smear, cryptosporidium and giardia antigen [if available; if not, O&P* microscopy; cryptosporidium may also be detected with modified Giemsa stain], microsporidium stain, C. difficile toxin); complete fever workup if febrile, including AFB blood cultures. Contact laboratory to determine recommendations for detecting more elusive organisms.
  *(If negative, repeat x 2).

- Treat pathogens as appropriate once diagnosed. If stool studies are negative x 3, refer for flexible sigmoidoscopy and biopsy. If all studies are negative and diarrhea persists, repeat in 6-8 weeks. Pathogens are identified in 50-85% of cases, although not always on the first diagnostic search.

- If the patient has **salmonella** in stool, perform blood cultures at the time and after treatment; dissemination of this organism is 100-fold more common in AIDS patients than the immunocompetent. Salmonella bacteremia may also present independent of diarrhea. Salmonella can also be chronic. May need antibiotic for suppression therapy, such as Cipro 500 mg. po bid x 14 days; Bactrim DS 1 - 2 tabs bid x 14 days.

- No curative therapy is available for **cryptosporidiosis**, although some clinicians have seen improvement on HAART. See *Cryptosporidiosis* in Disease-Specific section for other modalities.

- If foreign birth or travel, suspect microsporidia.

- New agents are under study for treating **microsporidiosis**, specifically Albendazole 400 mg po bid, followed by chronic suppressive therapy, has shown some efficacy in treating the Encephalitozoon (Septata) intestinalis and Enterocytozoon bieneusi varieties of microsporidia. Atovaquone (Mepron) is an alternative to try, at 750 mg po tid, then chronic suppressive therapy.

- Use nutritional supplements as needed or as recommended by dietician. Lactose-free lowfat diets are sometimes useful in slowing diarrhea; depending on response, other regimens include low-residue foods. Refer to dietician for further recommendations.

References:

Guerrant RL, Van Gilder T, Steiner TS et al. Practice guidelines for the management of infectious diarrhea. *CID.* 2001 (32) 331-351.

CDC. Diagnosis and Management of Foodborne Illnesses. *MMWR* 2001 (50) RR 2.

Thielman NM, Guerrant RL. An algorithmic approach to the workup and management of HIV-related diarrhea. *Journal of Clinical Outcomes Management.* 1997, (4) 2.

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Bollinger RC, Quinn TC. Tropical diseases in the HIV-infected traveler. In Broder S, Merigan TC Jr, Bolognesi D (Eds). *Textbook of AIDS Medicine.* Baltimore: Williams & Wilkins. 1994; 311-322.

Bolognesi D (Eds). Textbook of AIDS Medicine. Baltimore: Williams & Wilkins. 1994; 541-554.

Wanke CA. Intestinal microsporidial infection in HIV patients. *AIDS Clinical Care.* 1994; 6: 45-49.

Manufacturers' product labeling.

Ear, Nose, Sinus, Mouth

Ears: HIV-infected patients have no increase in ear-related complaints when they are compared with immunocompetent patients.

S: Patient complains of ear pain, decreased hearing or hearing loss, feeling of fullness in the ear, and popping or snapping sensation in the ear.

HX: Current or recent sinus infection
Head or ear trauma
Drainage or blood from the ear?

O/A/P: Proceed as you would with any immunocompetent patient.

Nose & Sinuses:

Nose-related complaints are infrequent in this patient population unless there are herpetic or KS lesions present on the nasal mucosa. Epistaxis can occur in patients with idiopathic thrombocytopenic purpura (ITP). Sinus complaints are very frequent in these patients.

S: Patient complains of epistaxis, or nasal pain. Patient complains of painful frontal or maxillary headaches (worse at night or in early morning), persistent postnasal drip or mucopurulent nasal discharge. Also, general malaise, aching or pressure behind the eyes, and toothache-like pain.

HX: Previous sinus infections or respiratory allergies
Recent or current URI
Nasal bleeding or discharge
Facial trauma
Pain worse when patient bends forward
Medications/effects

O: Examine the nose and sinuses, visualizing the nasal mucosa with light and speculum looking for areas of bleeding, purulent drainage, ulcerated lesions or discolored areas. Palpate or percuss the sinuses for areas of tenderness, look for areas of swelling over the sinuses & visualize the posterior pharynx for mucopurulent drainage. Transillumination may be helpful. Examine teeth and gums for caries and inflammation of gingivae, and check maxillary teeth with tongue blade (5-10% of maxillary sinusitis is due to dental root infection). Refer to oral health for tooth sensitivity, gingival inflammation, or caries.

A: **Epistaxis:** ITP, tumor, herpetic lesions, or Kaposi's sarcoma. Suspect ITP if platelet count is low, and bleeding is difficult to control. HSV appears as painful, ulcerated vesicles of the nasal mucosa. Tumors may be caused by KS, squamous papilloma, or lymphoma; biopsy is necessary to determine etiology.

Acute sinusitis: Infection of one or more of the paranasal sinuses is a common ENT complaint in HIV infection, generally caused by Streptococcus pneumoniae, H. influenzae, or Moraxella catarrhalis, although other gram positives occur. Fungi are also possible causative agents; parasites such as microsporidia are rare. (See sinusitis protocol.)

Chronic sinusitis may benefit from intranasal steroid sprays, such as Flonase (tm). Patients with exacerbations should be treated as acute sinusitis. (See *Sinusitis,* in Disease-specific section.)

Postnasal drip: This is another frequently encountered problem for the HIV-infected patient who may be secondary to either sinusitis or allergy.

P: Epistaxis is managed as in the immunocompetent patient with coagulopathies or tumors. Cauterization of an identified bleeding point or packing may be necessary.

Postnasal drip can usually be controlled with the use of a nasal decongestant spray. A non-steroidal inhaler such as phenylephrine should be the first inhaler of choice. Do not use oxymetazolone > 3 days, to prevent occurrence of

rebound congestion. Intranasal steroids may be used, but may carry a minimally increased risk of additional immunosuppression.

Mouth &Throat:

The oral cavity is the most common area of head and neck complaints in patients with HIV infection.

S: Patient complains of white patches, red areas on the dorsal surface of the tongue and/or hard/soft palate, decreased taste sensation, painful mouth, ulcerated lesions, sore gums, loose teeth, dysphagia or odynophagia.

HX: Usual oral hygiene routine
Date of last dental examination
Involuntary weight loss
Patient actions to relieve symptoms, and their utility
Medications (note that ddC, dapsone, and other drugs may cause apthous ulcers)

O: Thorough examination of the mouth and throat with a tongue depressor and a good light is mandatory. Observe for white patches and plaques on the mucous membranes and note whether they can be partially removed with scraping. Examine the dorsal surface of the tongue and hard and soft palates for red, flat, subtle lesions (erythematous candidiasis). Check for ulcerations, inflamed gums, loose teeth, any discolorations or nodular lesions on the hard palate. Look for ribbed, whitish appearing lesions particularly on the lateral aspects of the tongue. Check the pharynx for tonsillar enlargement and all of the above-mentioned abnormalities; rule out non-HIV-related pharyngitis, including strep, or other URI.

A: **Oral Candidiasis or Thrush:** see protocol

Oral Hairy Leukoplakia: appears as raised, ribbed, "hairy" white lesions usually located on the lateral margins of the tongue but OHL can occur anywhere in the mouth. Lesions are usually asymptomatic, but may be a cosmetic problem.

Kaposi's Sarcoma (KS): lesions appear as red, blue or purplish lesions, flat or nodular in appearance, solitary or multiple, most commonly appearing on the hard palate. They may also occur on gingival surfaces or anywhere else in the mouth. Diagnosis may be made by biopsy and histologic examination.

Gingivitis: See Linear gingival erythema or Acute necrotizing periodontitis protocol.

Herpes simplex: lesions appear as single or clustered vesicles developing into ulcerated, crusted lesions on the keratinized tissues within the oral cavity such as the hard palate and gingival tissues. Patients will complain of pain, and many times will have difficulty eating and drinking if oral lesions are extensive. Cultures are diagnostic if positive, but negative results are common if lesions are > 72 hours old or resolving (see *Herpes* in Disease-Specific section).

Aphthous Ulcers: lesions are eroded, marginated areas surrounded by erythema. They range in size from 1mm to 1cm. They are painful and appear on non-keratinized tissues such as the soft palate, floor of the mouth, or buccal mucosa (see *Oral Ulceration* in Complaint-specific section).

Oral Warts: Single or multiple papillomatous warts with multiple white, spikelike projections. See *Oral Warts* in Disease-Specific section.

Note: Most of these complications can also occur in the esophagus (see also: Esophageal Problems, Esophageal Candidiasis, and CMV protocol.)

P:
1. KOH preparations of white lesions can differentiate fungal infections from hairy leukoplakia. Biopsy of oral lesions can determine if KS is present.
2. See Disease-Specific Treatment for treatment parameters.
3. Refer to Oral Health or HIV-expert dentist as needed.
4. If patient is having mouth pain, anorexia, or problems with taste, refer to dietician.

References:

Uphold CR, Graham MV. *Clinical Guidelines in Family Practice, 3rd edition*. Barmarrae Books, Inc. Gainesville, FL 1998.

Sande MA, Gilbert DN, Moellering RC Jr. *The Sanford Guide to HIV/AIDS Therapy, 8th edition.* 1999; Hyde Park, VT, Antimicrobial Therapy, Inc.

Greenspan JS, Greenspan D. Oral complications of HIV infection. In Sande MA and Volberding PA (eds) 1999. *Medical Management of AIDS, 6 ed.* Philadelphia, WB Saunders, 157-169.

Reznik DR. Director of Oral Health, Grady Infectious Disease Program, Personal communication, 1999.

Kuntz S. University of Washington Virology Research Lab, Personal communication, 4/18/00

Esophageal Problems

Definition: Difficulty eating or taking pills, rarely with drinking liquids (dysphagia), and/or midline retrosternal pain after swallowing (odynophagia). Pain may be diffuse along the esophagus or very localized in one or more places. If untreated, may result in undernutrition, dehydration and/or weight loss.

Etiology of dysphagia in AIDS patients may be mechanical due to candida, up to 79% of the time; other fungi or bacteria appear less often. Less commonly, neoplasm, such as KS or lymphoma, or other cause of stricture may produce symptoms. Esophageal ulcerations are usually associated with pain (odynophagia); and in one case series, 50% were due to CMV, 40% were idiopathic or HIV-related, and 5% were due to HSV. In up to 25% of symptomatic patients, ulcerative disease may co-exist with candida esophagitis.

Neuromuscular or neurologic causes of dysphagia may result in difficulty initiating swallowing, and usually includes difficulty drinking liquids. It is more commonly associated with regurgitation, and seen in very elderly patients, usually those with stroke or neurodegenerative disease.

S: Patient complains of difficulty swallowing solid foods, and/or odynophagia. . Patient may complain of food "sticking," or may complain of midline retrosternal pain when eating. The symptom of "hiccups" may also be associated with esophageal disease, with or without other symptoms. Check for history of oral thrush, aphthous ulcers, CMV, candida esophagitis, or GERD ("acid indigestion" or reflux), other concurrent GI symptoms such as abdominal pain or diarrhea. Determine location of pain, and whether it is diffuse or focal. Take recent dietary history to assure intake is adequate; check medications, including OTC, supplements, herbals.

O: Oral and physical examination for signs of candida, ulcerations, neoplasms
Weight comparison
Funduscopy for CMV retinitis
Abdominal exam for tenderness and organomegaly
Vital signs, esp. temp
Recent CD4 count
Check for thyromegaly or cervical lymphadenopathy

A: partial differential diagnosis:
esophageal candidiasis, especially with CD4 counts <200 (common)
HSV ulceration (odynophagia common, usually with CD4 count <200)
CMV and idiopathic ulcers mostly with CD4 counts <100, usually with focal odynophagia. (Fever often accompanies CMV, but not HSV, candida or idiopathic ulcers)
GERD, with or without esophageal irritation or erosion
Lymphoma
Kaposi's sarcoma

P: Ascertain that the patient can swallow pills before sending home with a prescription.

Fluconazole 200 mg p.o. today then 100 mg po qd for 2-3 weeks (see *Esophageal Candidiasis* in Disease-specific section for more options); if symptoms resolve within a few days, no further testing is required. Complete the course of fluconazole. If symptoms persist, request endoscopy with biopsy of suspicious lesions; note that fluconazole-resistant candida may require IV therapy. Note drug interactions with HAART and whether or not patient is pregnant, since this may modify choice of drugs.

Idiopathic ulcers may respond to oral corticosteroids (prednisone 40 mg/day, tapered 10 mg per week for 4 weeks; a shorter course may be effective for smaller ulcers) or combination of H2 antagonists and sucralfate. In some circumstances, thalidomide 200 mg/day is used, but women of child-bearing potential are not generally candidates for this therapy. Up to 40 or 50% of these patients relapse, and may require re-treatment.

CMV can be treated with valganciclovir; see *Cytomegalovirus* in Disease-specific section. HSV can be treated with acyclovir (see *Herpes Simplex* in Disease-specific section). Neoplastic disease requires referral to oncologist for treatment.

Patients whose primary symptoms are more typical of "heartburn" or reflux, especially with GERD history, may receive a trial of H2 blockers or PPIs as appropriate.

Patient Education:

Take liquid food supplements and soft, bland, high-protein foods until symptoms resolve.
Return to clinic if symptoms persist beyond 5 or 6 days.

References:

Wilcox CM, Monkemuller KE. Gastrointestinal Disease. In AIDS Therapy 1999 (Dolin R, Maur H, Saag MS eds)752-756.

Sande MA, Gilbert DN, Moellering RC Jr. 2001. The Sanford Guide to HIV/AIDS Therapy, 10th ed.

Uphold CR, Graham, MV. 1999. Clinical Guidelines in Adult Health, 2nd edition. Barmarrae Books, Gainesville FL

Dieterich DT, Poles MA, Cappell MS, Lew EA. Gastrointestinal manifestations of HIV disease, including the peritoneum and mesentery. 537-566. Textbook of AIDS Medicine, second ed.

Eye Problems

S: **Patient complains of blurred vision, peripheral vision loss, visual field defects, ("I can only see half a page in a book"), floaters.**

HX: Use of corrective lenses
Unilateral or bilateral symptoms
Specifics of visual defect: scotomata,
Narrowed visual field or decreased peripheral vision
Intercurrent or recent shingles or VZV
Headache
Fevers
Pain
Reading, distance, or both
Age
Other associated symptoms

O: Recent CD4 and viral load. Visual acuity exam, using Snellen chart, and test ability to read small print, such as classified ads. An Amsler grid may be useful in locating areas of retinal pathology. Test cranial nerves 2, 3, 4, & 6. Perform funduscopic exam with pupillary dilatation if available, and note retinal appearance, lesions, condition of disc, vessels and macula.

A: **Differential diagnoses include:**

Refraction problems: measured as abnormal Snellen or inability to read fine print; may be due to presbyopia or other causes.

Keratitis: except for VZV keratitis, corneal infections are probably no more common than in general population. When disease does occur, it may be more severe. Requires slit-lamp exam by ophthalmologist; may be due to ZVZ, HSV, CMV, bacteria, fungi, or microsporidia.

Iridocyclitis: anterior chamber inflammation, fairly common in HIV, may present with pain, photophobia, blurred or decreased vision, and red eyes. May be due to infectious agents, medications (rifabutin), or endogenous uveitis (Reiter's syndrome). Slit-lamp exam is needed to confirm diagnosis; requires ophthalmology consult. Treatment of pathogen or discontinuation/dose reduction of offending drug is indicated; topical steroids may be adjunctive measure.

HIV retinitis: cotton wool spots on retina appear as small fluffy white lesions with indistinct borders, and are not associated with exudates or hemorrhages. These lesions are seen in many patients with HIV, and are usually benign and non-progressive.

CMV retinitis: appears as creamy to yellowish lesions, white granular areas with perivascular exudates and hemorrhages. The abnormalities initially appear in the periphery, but progress if untreated to involve the macula and optic disc. Usually a complication of advanced HIV infection with CD4 <50. See *Cytomegalovirus* in Disease-Specific section.

Retinal necrosis: appears as granular, yellowish, non-hemorrhagic lesions that rapidly extend and coalesce, with punctuate lesions. May be acute or rapidly progressive; rapidly progressing peripheral necrosis frequently causes blindness, thought to be VZV-associated, although some retinal necrosis can be due to other herpes viruses. Treatment is urgent.

Toxoplasmosis retinitis: yellow-white infiltrates without hemorrhage; frequently accompanied by active vitreous inflammation.

s

Neurologic complications: may manifest in papilledema, optic neuritis, cranial nerve palsies, visual field defects and other ways; may signify encephalopathies, increased intracranial pressure, meningitis, or CNS lymphomas. Thorough neurologic exam is required to determine if MRI, LP, or other diagnostics needed.

P:

1. Refer to ophthalmologist for dilated retinal or slit-lamp exam and definitive diagnosis. **If symptoms arouse suspicion of CMV retinitis or retinal necrosis, this should be set up within 24-72 hours.**
2. Patients with suspected CMV retinitis or retinal necrosis may require hospitalization for IV therapy, although with CMV retinitis, may be treated with p.o. valganciclovir. See *Cytomegalovirus* in Disease-Specific section for therapeutic regimens and patient education.

References:

Cunningham Jr ET. Ocular complications of HIV infection. In Sande MA and Volberding PA (eds) 1999. Medical Management of AIDS, 6 ed. Philadelphia, WB Saunders, pp 171-184.

Gnann JW Jr. Varicella-Zoster Virus Infections. 1999. In Dolin R, Masur H, Saag MS (Eds) *AIDS Therapy*. 1999. New York: Churchill Livingstone.

Fever

Definition:

While fever may accompany HIV infection at many stages in the spectrum of infection, fever in the HIV-infected patient with a low CD4 count (<300/mm^3) should prompt the clinician to search diligently for opportunistic infection.

S: **Patient complains of persistent fever, or new-onset fever of >101^o F.**

HX: Duration of fever

- Unprotected sexual contacts
- Travel within past 6-12 months
- IV line or venous access device
- Recent injection drug use
- Other medications (as a cause of fever)
- Visual disturbances (see *Eye problems*)
- Diarrhea, tenesmus (see *Diarrhea*)
- Pain (or H/A: see *Headache*)
- Hepatitis history
- Neurologic symptoms (see *Neurologic symptoms*)
- Cough or shortness or breath (see *Pulmonary symptoms*)
- Nasal or sinus symptoms
- Rash, lesions, soft tissue inflammation
- Asymmetric, tender, or new lymphadenopathy
- Vaginal/urethral discharge
- Other localizing symptoms

Use of anti-pyretic agents (ASA, NSAIDS, Acetaminophen), when was most recent dose?

O: Document evidence of fever, weight loss. Search for evidence of infectious focus. Check orthostatic vital signs. Attend to adenopathy, neuro, mouth, eyes (including fundus) sinuses, lungs, GI tract, joints, ears, GU tract, uterus, and rectum. Recent CD4, viral load, granulocyte count, H&H.

A: **Partial differential diagnosis:**

More often with low CD4 count

- PCP
- DMAC
- Cryptococcosis
- CMV
- Lymphoma, other neoplasm
- Sinusitis
- TB (atypical and/or extra-pulmonary)
- STD
- Endocarditis
- Disseminated histoplasmosis

May occur at any CD4 count

- Severe anemia
- Hepatitis
- TB (pulmonary)
- PID
- UTI
- Otitis
- Bacterial bronchitis or pneumonia
- Abcess
- Bacteremia or sepsis
- VZV
- TTP
- Autoimmune process
- Drug induced fever *

*common culprits include sulfonamides, dapsone, amphotericin, pentamidine, thalidomide, penicillin, clindamycin, carbamazepine, phenytoin, barbiturates, bleomycin,

P:

1. Establish CD4 count and viral load
2. Blood cultures (bacterial, mycobacterial, fungal)
3. Urinalysis, urine culture if UTI symptoms
4. CBC with differential
5. Liver enzymes
6. Gram stain and AFB smear of sputum
7. Culture of sputum for bacterial pathogens, AFB if productive cough present
8. CXR; sinus films if indicated by symptoms and PE
9. Serum cryptococcal antigen (if CD4 count <300 and not done in past 2-3 months).

10. New lymphadenopathy—aspirate with culture, including AFB and fungal, cytology
11. Cytopenias—bone marrow aspirate and biopsy may be needed. See applicable treatment guidelines.
12. Fever of unknown origin (FUO), defined as persistent fever >101° F, for >3 weeks without findings on initial workup may require more intensive workup, such as LP, other scans or biopsies. Consult with ID physician or HIV expert clinician to determine if hospitalization or other specific labs are needed.
13. Refer to dietician to avoid weight loss during hypermetabolic state
14. See **Disease-Specific Section** if HIV-related cause is identified.

References:

Cross KJ, Hines, JM, Gluckman SJ. Fever of Unknown Origin. In Buckly RM, Gluckman SJ (Eds) *HIV Infection in Primary Care* 2002. Philadelphia: WB Saunders.

Bartlett JG, Gallant JE. *2001-2002 Medical Management of HIV Infection.* 2001; Baltimore, Johns Hopkins University Division of Infectious Diseases.

NC SPNS Integration Project: Fever of Unknown Origin. From website www.ncsip.duke.edu/ downloaded 6/14/02.

Headache

S: Patient complains of new type of headache.

HX: History of headaches/migraines
H/O head trauma
New rashes or ulcerations
Allergies, hx of sinusitis
Dizziness, vertigo, nausea
Unprotected sex, new sex partner
Fevers
Neurologic symptoms (see *Neurologic symptoms*)
New medications (ddI, ZDV, ABC)
Usual vs. recent caffeine intake
Relieved by any medication?

O: Check vital signs. Look for fever, orthostasis, hypertension. Examine head and neck for nodes, trauma, mobility, sinus tenderness. Eye exam/funduscopic exam for lesions, papilledema, mental status and neurologic exam. Oral exam for lesions, dental abscess, thrush, pharyngeal drainage. Lung exam for abnormal sounds. Check genitals and skin for rashes, including palms and soles.

A: **Partial differential diagnosis:**

- cryptococcal meningitis
- neurosyphilis
- tuberculous meningitis
- PML
- toxoplasmic encephalitis
- CMV meningoencephalitis or retinitis
- encephalitis, other
- CNS lymphoma
- systemic infection
- Sinusitis
- anemia
- Fever
- depression
- anxiety disorder
- stress/tension headache
- migraine or cluster h/a
- caffeine withdrawal
- hypertension

Other causes of non-HIV related headache should be considered.

P: **Labs/Procedures:**

1. CBC with differential (if fever or suspected anemia. See *Anemia* and *Fever*.)
2. Biochemical Profile
3. Serum cryptococcal antigen (if fever and CD4 count < 200)
4. Toxoplasma IgG (if previously negative and CD 4 count < 200)
5. RPR/FTA

When indicated:

6. Sinus films
7. Head CT scan with contrast or MRI (see *Neurologic Symptoms* protocol)
8. LP CSF studies to include India Ink stain, cryptococcal antigen, VDRL, AFB cultures, fungi & routine cultures, cell count, and chemistries.

TX:

1. Treat symptomatically until diagnosis is established with NSAIDS, Acetaminophen, or narcotics (if indicated to control pain).
2. Refer to Disease-Specific Treatment, or primary care management guidelines as appropriate for specific therapy.

References:

Bartlett JG, Gallant JE. *2001-2002 Medical Management of HIV Infection.* 2001; Baltimore, Johns Hopkins University Division of Infectious Diseases..

Lymphadenopathy

Definition:

Lymphadenopathy in HIV infection may have a multitude of origins, including infectious and neoplastic causes. Persistent Generalized Lymphadenopathy is very common in HIV, and involves ≥ 2 non-contiguous nodes, which are generally symmetrical, firm, mobile, non-tender, and discrete from surrounding tissue. As long as these nodes are stable and ≤ 2 cm in size, no further action is needed. Rapid involution of such previously enlarged nodes is a poor prognostic sign. If nodes are ≥ 2 cm, tender, fluctuant, asymmetrical, and/or adherent to surrounding tissue, they are more likely to indicate neoplasm or infection other than HIV, and require workup.

S: **Patient complains of new or persistent glandular swellings in neck, armpit or groin.**

HX: Injecting drug use
Recent injuries or infection in area of node drainage
Medications such as Phenytoin
Other systemic or local symptoms

O: **PE:** Patient presents with 2 or more non-contiguous enlarged lymph nodes in inguinal, neck, axillary or abdominal regions. Note size, location, degree of tenderness, mobility and consistency of all palpable nodes.

A: Partial differential diagnosis:

Infectious Causes	**Neoplastic Causes**	**Other Causes**
Secondary syphilis	Lymphoma	Serum sickness
Tuberculosis	Acute and chronic	Sarcoidosis
EBV mononucleosis	lymphocytic leukemias	Phenytoin Systemic lupus
Hepatitis B	Kaposi's sarcoma	Rheumatoid arthritis
HIV infection	Breast cancer	
DMAC		
CMV		
Toxoplasmosis		
Histoplasmosis		
Rubella or measles		
Oral/dental infections		
LGV		
Chancroid		
Bartonella		

P: **LABS/PROCEDURES:**

1. Perform symptom-directed laboratory examination to pinpoint or rule out infectious causes.
2. In the presence of non-specific symptoms, order CBC, differential, liver function tests, RPR, urinalysis, CXR, PPD.
3. Obtain blood cultures if patient is febrile.
4. Biopsy nodes (or fine needle aspirate) if they do not resolve spontaneously within 4 weeks after start of observation, if they become larger/bulkier, if >3 cm in size and asymmetrical, or if patient has unexplained systemic symptoms.
5. Antiretroviral therapy may be helpful.

Patient Education:

1. If nodes increase in size or tenderness, call your clinician.
2. Lymphadenopathy may come and go throughout the course of your illness.

References:

Kocurek K, Hollander H. Primary and preventive care of the HIV-infected adult. In Sande MA and Volberding PA (eds) 1999. Medical Management of AIDS, 6 ed. Philadelphia, WB Saunders, 125-126.

Libman H. Generalized lymphadenopathy. In: Libman H, Witzburg RA. Clinical manual for the care of the adult patient with HIV infection. Boston: Boston City Hospital.1990; 61-69.

Nausea and Vomiting

Definition: Nausea with or without vomiting, and occasionally vomiting without nausea, can occur at any stage of HIV infection. It may be a manifestation of a life-threatening complication of antiretroviral therapy, to an early sign of serious infectious or neoplastic complication in late stage AIDS and/or an early toxicity to any number of medications a patient may be on.

S: Patient complains of nausea with or without vomiting, or vomiting without nausea.

Hx:
- Medications, new and ongoing
- Supplements and non-prescription substances
- Duration of symptoms
- Jaundice
- Dysphagia or Odynophagia
- Hematemesis
- Fever
- Stiff neck
- Changes in vision
- Polyuria
- Polydipsia
- Headache
- Hepatitis history
- Toxoplasmosis encephalitis history
- Cryptococcal or (other chronic meningitis) history
- CNS lymphoma history
- Pruritis
- Lightheadedness, dizziness, vertigo or orthostatic sx
- Abdominal pain
- Pancreatitis history
- CMV history
- Diarrhea or other GI symptoms
- Renal failure history
- Unprotected sex or missed menses in female

O: Document:
- Fever
- Orthostatic changes in pulse and B/P
- Oral lesions (especially thrush and/or ulcerations)
- Dryness of oral mucosa
- Skin turgor
- Focal neurologic changes
- Check recent CD4 count
- Retinal findings (esp. papilledema)
- Abdominal findings (tenderness, distension, masses, organomegaly
- Pelvic tenderness
- Mental Status changes
- Neck stiffness or other signs of meningeal irritation

A: Partial Differential:
- Medication effect or reaction
- Drug-drug interactions
- Pancreatitis
- Meningitis from TB, cryptococcus, or other fungus
- Pelvic Inflammatory Disease
- Sepsis
- Toxoplasmosis encephalitis
- Uremia
- Diabetic ketoacidosis
- Lactic acidosis due to NRTI (see *Lactic Acidosis*)
- Esophagitis (see *Esophageal Problems*)
- Hepatitis, infectious or drug-related
- Peritonitis
- Myocardial infarction
- Adrenal insufficiency
- CNS lymphoma
- Pregnancy
- Foodborne illness

P:
1. Hydration if needed
2. CBC with differential
3. BUN creatinine, electrolytes
4. Glucose; if elevated, arterial pH
5. Cortisol and cortrysin stimulation test if indicated (fatigue, weakness, unexplained abdominal pain, weight loss, orthostasis, usually in late stage AIDS)
6. Amylase, lipase if symptoms of pancreatitis
7. Blood cultures and other fever workup as needed (see *fever* protocol)
8. Brain CT if neuro symptoms (see *Neurologic Symptoms* in Complaint-specific section)
9. If odynophagia or dysphagia, see *Esophageal Symptoms* in Complaint-specific section
10. EKG if chest pain or suspicious symptoms
11. Lactate levels, electrolytes, aminotransferases, CPK, LDH, lipase and amylase if lactic acidosis is suspected (see *lactic acidosis* in Antiretroviral Therapy section)
12. Pregnancy test if indicated
13. Consult with HIV-expert clinician to determine if hospitalization or other labs may be needed

See Disease-Specific Treatment or other relevant guidelines once cause is identified. **It is very important to identify the etiology of N&V, unless the patient has reached end-stage and comfort is the only goal of therapy**. Symptomatic treatment can be considered after workup and exclusion of life-threatening illness. Alternatively, if N&V is due to medications which are vital to the patient, and complications are not life-threatening, then chronic anti-emetic therapy may be the most feasible choice.

Symptomatic Treatment:
Promethazine HCl 25 mg tabs or 12.5 mg. suppositories q 8-12 hours as needed.
Metaclopramide and other anti-nausea medications may be considered.
Dietary consult to maintain nutrition if the patient is expected to experience chronic nausea

References:

Hasler WL. Approach to the patient with nausea and vomiting (chapter 35). In: Yamada T, Alpers DH, Lane L, et al (Eds). *Textbook of Gastroenterology*, Vol 1, 3rd ed. Lippincott Williams and Wilkins, Philadelphia 1999; 775-794

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Hofstede HJ, de Marie S, Foudraine NA, et al. Clinical features and risk factors of lactic acidosis following long-term antiretroviral therapy: 4 fatal cases. *Int J STD AIDS* 2000; 11:611-616.

Neurologic Symptoms

Definition:

In the setting of HIV, especially with advanced disease, there are numerous etiologies of masses, meningitis, and other neurologic abnormalities. With new-onset neurologic symptoms, it is important to rule out mass lesions or CNS infections, both treatable causes that can rapidly progress.

S: Patient reports new onset of ataxia, seizures, speech impairment, photophobia, stiff neck; vision, concentration or memory deficits. Family may report forgetfulness, lethargy, disorientation, personality change, altered mental status.

HX:

Fever	Date of onset
Duration, type, number of seizures	Headaches, type, duration, onset
N/V	History of previous seizures or seizure medication
Careful history of drug and alcohol use	Trauma (within past few weeks)
Date/time of last use of drug/alcohol use	Weakness, paresis
Malaise, somnolence	Description from observer, if available

O: **PE:** Carefully note orthostatic vital signs. Perform complete mental status and neurologic exam. Ophthalmologic exam for papilledema. Check recent CD4 (note that opportunistic causes, except TB, tend to occur at CD4 counts <100.)

A: Partial differential diagnosis:

- Toxoplasmosis
- Lymphoma or other malignancy
- Cryptococcosis
- CMV encephalitis
- Tuberculosis / meningitis
- Neurosyphilis
- CMV polyradiculopathy
- Myopathy
- Medication toxicity
- West Nile Virus
- Progressive multifocal leukoencephalopathy
- Alcohol/other CNS depressant withdrawal seizures
- Drug-induced seizures (cocaine, speed)
- Hypoglycemic seizure/diabetes
- Idiopathic seizure disorder
- Neuropathy
- Bacterial meningitis
- HIV dementia*
- Delirium due to infection, anemia, dehydration, electrolyte imbalance
- Histo or coccidioidomycosis (endemic areas: recent travel, occasionally bird exposure)

*Differentiate delirium from dementia. Delirium presents as acute onset of clouded sensorium, disturbed and fluctuating level of consciousness, disorientation, cognitive deficits, and reduced attention, sometimes with hallucinations. Delirium is often due to medication toxicities, infections, hypoxia, hypoglycemia, electrolyte imbalances, or mass lesions, and is frequently correctable. Dementia emerges more gradually with cognitive impairment, behavioral, motor and affective changes (see dementia protocol.)

P:

1. Evaluate for inpatient workup, especially if febrile
2. RPR
3. Schedule CT scan with IV contrast, or MRI
4. Serum cryptococcal antigen if recent CD4 count < 100
5. LP if no mass lesion detected on CT scan, or if deemed safe by neurologist. Check opening pressure, and obtain these labs on CSF: India Ink stain, ABF smear & culture, RPR/VDRL, cell count & differential, protein/glucose, C & S, cryptococcal antigen, CMV qPCR
6. Toxoplasmosis titer if not previously positive (if recent CD4 count <100)
7. Drug and alcohol screen (although alcohol is usually metabolized by the time withdrawal symptoms set in, generally 7-48 hours after last alcohol intake)
8. Consult Neurology service
9. Schedule EEG for new-onset seizures
10. Once cause identified, treat as indicated; see Disease-Specific section if appropriate.

Patient Education:

1. Don't drive or operate machinery due to risk of seizure and loss of consciousness.
2. Avoid intoxicating substances.
3. Educate other members of household regarding medication regimen if patient is forgetful, and help devise a plan for medication and appointment adherence.

References:

Cantor CR, McCluskey L. CNS Complications. In Buckley RM, Gluckman SJ (Eds) HIV Infection in Primary Care. 2002; New York, WB Saunders

Bartlett JG, Gallant JE. *2001-2002 Medical Management of HIV Infection.* 2001; Baltimore, Johns Hopkins University Division of Infectious Diseases.

Sande MA, Gilbert DN, Moellering RC Jr. *The Sanford Guide to HIV/AIDS Therapy, 10th edition.* 2001; Hyde Park, VT, Antimicrobial Therapy, Inc.

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Oral Ulceration

Definition:

Necrotic or eroded oral mucosa, including tongue. Most such lesions are idiopathic (apthous) or of viral etiology, although they also may be due to fungal, parasitic, or bacteriologic pathogens. **Herpetic ulcerations** tend to appear on keratinized tissues such as the hard palate or gingiva. **Aphthous ulcerations** tend to manifest on non-keratinized tissues such as the floor of the mouth, soft palate and lingual (bottom) surface of the tongue.

S: Patient complains of painful ulcerative areas in mouth. May have difficulty eating, drinking, swallowing, or opening mouth. May also complain of sore throat.

Hx: Inquire about other ulcerative gastrointestinal diseases, including HSV, CMV or histoplasmosis; r/o trauma, burn. Note current drugs, particularly zalcitabine (ddC) and dapsone; inquire about ETOH and smoking history.

O: Red or white-bordered erosions or ulcerations varying in size from 1 mm to 2 cm on buccal mucosa, oropharynx, tongue, lips, gingiva, hard or soft palate.

A: R/O recurrence of previous gastrointestinal/oral lesions, such as HSV, CMV, idiopathic lesions, histoplasmosis, or drug-induced ulceration. HSV lesions may appear as clusters of vesicles that may coalesce into ulcerations with scalloped borders

Lab: May perform HSV cultures on oral ulcerations which appear on keratinized tissues or the dorsal and lateral surfaces of the tongue, scraping near margin of lesion; or open fresh vesicle if available. Negative HSV cultures increase when collections are taken from older, resolving herpetic areas; usually herpetic lesions >72 hours old will not yield a positive culture.

P: If HSV culture is positive, or if HSV is strongly suspected due to appearance, hx, or recurrence, treat with acyclovir while awaiting results of culture. Do not use topical steroids without concomitant acyclovir if lesion is of possible herpetic etiology.

If patient is on ddC or dapsone, try to substitute other agents and check for improvement in lesions.

Recalcitrant aphthous ulcerations should be treated with topical corticosteroids. For multiple small lesions, use Decadron (dexamethasone) elixir, 5 cc qid--rinse and hold as long as possible, 1-2 minutes, then spit. Continue treatment for one week, observing until lesions resolve. If no resolution or improvement in one week, oral corticosteroids may be needed: Prednisone 40 mg po qd for one week. If this is ineffective, request biopsy to rule out CMV, HSV, or neoplastic disease.

Assess nutritional status and consider adding Avera, Ensure, Boost, Sustacal, or other liquid food supplement if food intake has decreased or weight loss occurs. Refer to dietician.

Pain control is important in this case to maintain food intake and prevent weight loss:

1) Topicals: For small accessible ulcerations, apply Orabase Soothe-N-Seal (2-octyl cyanoacrylate) directly to the lesion q 4-6 hours. (This is an over the counter product.)
2) For larger ulcerations or those which present in the posterior oropharynx, prescribe Gelclair Dose packs (disp 4) Rinse for 1-2 minutes then expectorate TID. As with all oral topicals, inform patients not to eat or drink for at least 30 minutes after the application.
3) Hurricaine spray (xylocaine viscous) prn; swish and expectorate.
4) **Systemic:** see *pain management protocol.*

Refer to Oral Health or HIV-expert dentist as needed.

Refer to registered dietician if client is having pain, problems eating, or weight loss.

Note: Thalidomide 200 mg qd x 2 weeks is available for oral apthous ulcers. It should not be used in women of child-bearing potential due to its teratogenicity. If no other alternative, it must be used very carefully with thorough patient education, pregnancy testing, and 2 concomitant methods of birth control.

Pulmonary Symptoms

Definition:

Shortness of breath (SOB) and/or cough, should be evaluated immediately in a patient with HIV infection, due to high probability of pulmonary infection. Anemia, pulmonary, and cardiovascular disease are also possibilities.

S: Patient complains of dyspnea or cough.

HX: Duration
TB exposure/PPD history
Productive or non-productive cough
If productive, color/clarity/blood
Chest pain, pleuritic?
Night sweats
Lower extremity/dependent edema
Medications, especially ACE inhibitors
Asthma
With exertion/at rest
Orthopnea, PND
Fever
PCP Prophylaxis
Weight loss
Weight gain
N/V
Smoking history
Other pulmonary history

O: Perform history and physical exam, paying special attention to lungs and CXR, although lungs may sound clear even with PCP. Check vital signs, especially temperature and respiratory rate; check weight.
LABS: CD4+ <300/mm^3 is more common in OIs and lactic acidosis.

NOTE: With the threat of TB, insist that patients who are coughing wear a surgical mask in the clinic/office until TB is ruled out; both nose and mouth must remain covered at all times. This should protect against discharge of large infectious droplets into the environment.

A: Partial differential diagnosis:

- bacterial pneumonia
- PCP (common, may occur despite prophy and at higher CD4 s)
- pulmonary KS
- coccidioidomycosis
- profound anemia
- congestive heart failure
- reactive airway disease
- bronchitis, bronchiectasis
- influenza
- ACE inhibitor-induced cough
- tuberculosis (can occur at any CD4 count)
- CMV pneumonia
- histoplasmosis
- legionellosis
- primary atypical pneumonia (mycoplasma)
- lymphoid interstitial pneumonitis
- lung CA/neoplasm
- pulmonary cryptococcosis
- lactic acidosis
- GERD

Most cases of pneumonia should be hospitalized for evaluation and therapy. **Common diagnostics:**

1. CXR for suspected pneumonia, KS, or TB (see *MTB* in Disease-Specific section if TB is suspected); gallium scan when CXR normal and PCP suspected
2. Induced sputum (outside, or in negative pressure room or area which is safely vented to the outside, to prevent possible TB aerosolization) for special stains to rule out PCP cytology; also request:
   Gram stain of sputum
   Sputum smear for AFB
   Culture sputum for bacteria, mycobacteria and fungi
3. If febrile, blood cultures for bacteria, mycobacteria (and fungi if CD4 count < 100)
4. If PCP suspected, ABG's on room air w/exercise; calculate A:a gradient; LDH may also be elevated
5. CBC (leukocytosis)
6. Bronchoscopy with bronchoalveolar lavage and biopsy if indicated and possible
7. Pulmonary function tests may be indicated if no infectious etiology (no fever, CXR and sputum WNL)
8. Refer to dietician to help prevent weight loss

9. If Lactic Acidosis suspected (nausea, SOB with tachypnea, abdominal pain, fatigue, etc in presence of long-term NRTI therapy) see *Lactic Acidosis* in Antiretroviral Therapy section.
10. Once use determined, follow Disease-Specific guidelines; if AFB stain (smear) is positive, admit into negative-pressure room and start TB treatment with 4 drugs while awaiting identification (see *MTB* in Disease-Specific section)

References:

Braffman MN. Pneumonia. In Buckly RM, Gluckman SJ (Eds) *HIV Infection in Primary Care* 2002. Philadelphia; WB Saunders: 205-215.

Bartlett JG, Gallant JE. *2001-2002 Medical Management of HIV Infection.* 2001; Baltimore, Johns Hopkins University Division of Infectious Diseases.

Fischbach F. *A Manual of Laboratory and Diagnostic Tests, 6th ed*. 2000; New York, Lippincott.

Vaginitis/vaginosis

Definitions:

Vaginitis: Inflammation of the vagina, usually characterized by a vaginal discharge containing many WBCs; may be accompanied by vulvar itching and irritation.
Vaginosis: characterized by increased vaginal discharge, without WBCs or inflammation.

S: Patient c/o discharge, with or without odor, itching, burning, pelvic pain, vulvar pain, or pain on intercourse.

Hx:
- Duration of symptoms
- Sexual history, esp, recent partner change, unprotected sex
- Relationship of symptoms to sexual contact
- Contraceptive use, especially:
  - Vaginal Contraceptive Film
  - Other Nonoxynol-9 products
  - Condoms, type
- Feminine hygiene products, e.g., sprays, deodorants
- Perfumed toiletries, e.g., bath salts, scented toilet tissue or sanitary napkins
- Douching
- Post-coital bleeding
- Vulvodynia
- Pain or burning on urination
- Dyspareunia
- Recent antibiotic use
- History of STD, PID
- Medications, including supplements

O: Examine external genitalia, including perineum and anal area, for:
- Inflammation
- Edema
- Excoriation
- Lesions

Speculum exam for:
- Discharge color/quality
- Erythema, edema, erosions, lesions
- Cervical friability
- Foreign body
- Cervical sample if indicated for STD testing

Obtain smears for wet mounts and pH paper from vaginal wall
Bimanual exam for masses or tenderness, if indicated

A: Partial differential diagnosis:
- Bacterial vaginosis
- Candidiasis
- Trichomonas
- PID
- Chlamydia
- UTI
- Normal vaginal discharge
- Gonorrhea
- Condyloma
- Herpes
- Contact dermatitis from irritants/perfumes
- Latex/condom allergy
- Tinea or other fungus

P: Wet mounts with Saline and potassium hydroxide (KOH), for:
- Clue cells, whiff test of KOH prep. If positive, check pH; if >4.5, treat for BV:
  - See STD guidelines (first reference). Treatment is same as for HIV-negative women, e.g., Metronidazole 500 mg po bid x 7 days; (Note that patients on ritonavir may experience symptoms due to the small amount of alcohol in the capsules) **or**
  - Metronidazole gel 0.75%, 1 applicatorful intravaginally qd x 5 days.
  - Alternatively, clindamycin 2% cream, 1 applicatorful intravaginally q hs x 7 days
  - (The guidelines also offer other regimens that are less effective for BV, which may be helpful for patients who have adherence problems and other issues.)
- Motile trichomonads (see STD guidelines (first reference), same as for HIV-negative women, with Metronidazole 2 gms single dose or 500 mg BID x 7 days; topicals not as effective)
- Spores and hyphae suggesting candida, see *Vulvovaginal Candidiasis* in Disease-Specific section.
- WBCs suggestive of infection such as STD
- **Note that multiple conditions or pathogens may present concurrently**

Herpes culture if indicated by lesions (see HSV protocol)
Chlamydia and gonorrhea testing if indicated; see STD guidelines (first reference)
U/A (with or without C&S) if primarily urinary symptoms
If suspected irritant or allergen, including N-9, D/C use of product
If related to latex condom use, switch to polyurethane male or female condoms
For tenderness on cervical motion, or other suspicions of PID, see *PID* in Disease-Specific section.
Workup or refer as needed for other abnormalities on bimanual exam

Patient education:
1. If starting metronidazole: Wait 24 hours after the last drink of alcohol before starting metronidazole. Avoid any form of alcohol during the course, and for 24-48 hours thereafter for the drug to get out of your system. Alcohol and metronidazole together can cause severe nausea and vomiting, and other immobilizing symptoms. Also, patients on ritonavir may experience symptoms due to the small amount of alcohol in the capsules; call if nausea and vomiting occur.

2. Clindamycin cream and ovules are oil-based and will weaken latex condoms, diaphragms, and cervical caps

3. BV recurrence is very common. Report for re-treatment if symptoms recur.

4. Avoid douching.

5. For any STD or trich: Bring in your sexual partner for evaluation and treatment to avoid being re-infected.

6. If female condom is to be used: Teach how to use, and recommend that the woman try it before she needs it, in an unrushed, quiet, private environment. See *Prevention of HIV Transmission* in Health Maintenance section.

References:
Centers for Disease Control and Prevention, 2002. Sexually transmitted diseases treatment guidelines. *MMWR*;51(No. RR-6)

Hawkins JW, Roberto-Nichols DM, Stanley-Haney JL, 2000. Protocols for Nurse Practitioners in Gynecologic Settings, 7th ed. Tiresias Press, Inc.

Abularach S, Anderson J. Gynecologic Problems, 2001. In *A Guide to the Clinical Management of Women with HIV*. Anderson JR (ed). HIV/AIDS Bureau, HRSA

CHAPTER 4: Neuropsychiatric Disorders

Anxiety Disorders

Definition:

Anxiety symptoms are a universal accompaniment of HIV. The patient may have mild symptoms to full-blown panic attacks, based on uncertainty about the disease and treatment. Symptoms of anxiety can mimic symptoms of physical illness. It is important to differentiate anxiety with and without panic attacks. The criteria for diagnosis include unrealistic or excessive worry about two or more life circumstances for greater than six months, and at least six of the subjective complaints listed below.

S: Patient complains of:

Trembling, twitching or feeling shaky
Restlessness
Shortness of breath or smothering sensations
Sweating or cold, clammy hands
Skin rashes
Nausea, diarrhea or other abdominal distress
Frequent urination
Feeling keyed up or on edge
Difficulty concentrating
Irritability
Muscle tension, aches or soreness
Easy fatigability
Palpitations or accelerated heart rate
Dry mouth
Dizziness or lightheadedness
Flushes or chills
trouble swallowing or "lump in the throat"
Exaggerated startle response
Erouble falling or staying asleep

HX:

Family history of similar problems
Anxiety patterns—constant, intermittent, timing
New, sudden onset vs. recurrence of previous episodes
Sleep disturbances
Recent stressors
Medications, supplements, herbals
Caffeine intake
Recreational drugs/alcohol (current or recent past)
Concomitant illnesses
Other physical symptoms

O: Physical examination, with neuro and mental status. Note skin rashes, heart rate, respiratory rate (shortness of breath, hyperventilation), tremor.

A: Partial differential/rule out:

- Thyroid disease
- Hypoglycemia
- Lung disease
- Substance withdrawal (e.g., alcohol, benzodiazepines)
- Electrolyte imbalances
- Allergic reactions
- Medications such as efavirenz, INH, steroids, theophylline
- Heart disease, arrhythmias
- Caffeine intoxication
- Substance use (amphetamines, cocaine)
- Anemia
- CNS OIs or malignancies
- B_{12} deficiency
- Immune disorders
- Sleep disturbances/deprivation
- Infection

LABS:

1. EKG
2. Thyroid studies
3. Blood glucose
4. Arterial blood gases
5. Other labs as indicated based on symptoms and physical examination

P: **TX**

1. **Behavioral interventions:** stress management group, relaxation therapy, visualization and guided imagery (refer to available community-based support).

2. **Psychotherapy** may be indicated where HIV-experienced professionals are available and the patient is capable of forming an ongoing relationship.
3. **Pharmacotherapy** - Doses are generally lowered as the patient becomes more symptomatic or as liver function declines. Interactions between SSRIs, benzodiazepines and HIV medications are fairly common. Consult with an HIV expert or pharmacist before prescribing.
   a. SSRI (selective serotonin re-uptake inhibitors) type antidepressants, including fluoxetine (Prozac), paroxetine (Paxil), and sertraline (Zoloft) may be effective. Antidepressants used for anxiety symptoms are generally lower than required to manage depressive symptoms. Venlafaxine time release (Effexor XR), at doses of 75-225 mg/day, has recently been approved for treatment of generalized anxiety disorder. Note: monitor B/P at higher doses of venlafaxine.
   b. Treatment may include intermediate half-life benzodiazepines such as oxazepam (Serax) 10mg Q6H, lorazepam (Ativan) 0.5mg Q8H; or alprazolam (Xanax) 0.25mg Q6-8H if buspirone (Buspar) is not tolerated or to help anxiety symptoms while buspirone is taking effect. Longer-acting benzodiazepines such as clonazepam (Klonipin) may also be useful at dosing of 0.5 mg bid. **Benzodiazepines are used for acute, short-term management only because of tolerance and physiologic dependence.** This is more problematic in patients with previous history of addiction. Note that **ritonavir and lopinavir-ritonavir (Kaletra) are contraindicated with triazolam** (Halcion) and raise blood levels of many benzodiazepines; use with caution if necessary; use low doses, and avoid other CNS depressants while on therapy. Consult with clinical pharmacist. **Midazolam (Versed) and triazolam (Halcion) are contraindicated with all protease inhibitors, delavirdine, and efavirenz, as is St. John's Wort (an herbal).**
   c. Buspirone (Buspar) is a non-addictive anxiolytic. Dose begins at 5mg po TID; increase by 5mg per dose each week until patient reaches 10-15mg po TID (for a total daily dose of 30-45mg). It will take several weeks for patients to notice a decrease in anxiety, during which time low-dose benzodiazepines may be used. Major side effects are dizziness and lightheadedness.
   d. Some sedating antidepressants are effective, non-addictive anxiolytic agents, such as trazodone (Desyrel) 25-100mg at hs, or imipramine (Tofranil) 25-100mg at hs.

Patient Education:

1. Behavioral interventions can really help to reduce anxiety, but may take practice; seek help from a therapist, an experienced source or friend.

2. Some patients develop problems with sexual function on fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), or venlafaxine (Effexor). Report problems to prescriber.

References:

CDC. Guidelines for Using Antiretroviral Agents Among HIV-Infected Adults and Adolescents: Recommendations of the Panel on Clinical Practices for Treatment of HIV. *MMWR* 2002; 51 (No. RR-7)

New York State Department of Health AIDS Institute, 2001. Mental health care for people with HIV infection: HIV clinical guidelines for the primary care practitioner. Downloaded 6/19/02 from website:
http://www.hivguidelines.org/public_html/CENTER/clinical-guidelines

Manufacturers' product information, 2002

McDaniel, S. Personal communication, 6/00

Depression

Definition:

Major depression is a cause of significant morbidity among people with HIV disease. Management of this condition may be complicated by its multi-factorial etiology. Not only does a diagnosis of HIV cause psychological crisis, it may complicate underlying psychological/psychiatric problems (e.g., substance abuse, homophobia, stigma). Further, direct viral infection of the CNS causes a number of neuropsychiatric syndromes. Finally, both constitutional disease and medication can impair neurologic function and/or mood. The clinician's task is four-fold: to maintain a high index of suspicion of depression and screen frequently for mood disorders; to elicit any history of prior psychiatric diagnoses or treatment; to rule out organic causes of mood/function alterations; to refer for appropriate psychiatric evaluation and psychosocial support, including substance abuse counselors and domestic violence service providers. Patients with untreated depression are at continuing risk for unsafe behaviors which may lead to HIV transmission. They may also become self-destructive or suicidal.

Background: Importance of treating depression in HIV-infected patients

1. Major depression associated with co-morbid medical illness, including HIV infection, has been associated with numerous adverse events such as:
   a) Decreased survival
   b) Increased hospital stays
   c) Impaired quality of life
   d) Decreased treatment adherence, which is a primary concern in light of complicated dosing regimens of new antiretroviral therapies
   e) Increased risk behaviors

2. While independent of physical symptoms, recent research has concluded that depressive affect is associated with higher mortality rates in HIV-infected gay men (Mayne et al., 1996). Stress and depressive symptoms, especially when they occur jointly, are associated with diminished immune parameters in HIV-infected gay men (Lesserman et al., 1997)

S: **Patient complains of:**

- Depressed mood, sadness, hopelessness
- Insomnia or hypersomnia
- Fatigue or loss of energy
- Decreased ability to concentrate
- Recurrent thoughts of death or suicide
- Diminished interest or pleasure in activities
- Appetite changes with weight changes (up or down)
- Feelings of worthlessness or guilt
- Psychomotor agitation or retardation

HX: Any five of these symptoms occurring more days than not for at least two weeks is clinically significant for a major affective disorder, requiring intervention.

Take a careful history of timing of symptoms, their relationship to life events (HIV testing, loss of friend, etc.) and any other physical changes noted along with mood changes. Elicit personal and family history of depression or suicidal behavior. Probe for suicidal thoughts, plans, materials to execute the plan; inquire about hallucinations, paranoia. Medication and substance use histories are important also

O: Mental status exam, including affect, mood, orientation, appearance, agitation or psychomotor slowing; neurologic exam if appropriate.

A: Rule out:

- Bereavement
- Psychotic depression
- Med effects (steroids, efavirenz, INH, alpha interferon, TMP-SMX etc.)
- OIs affecting the CNS (toxo, crypto, CNS CMV, PML, etc.)
- HIV encephalopathy
- Hypo or hyperthyroid
- B_{12}, folate (B_6), zinc, or vitamin A deficiency
- Adjustment disorder (acute reaction to a life crisis, such as HIV diagnosis, bereavement, job loss, etc)
- Neurosyphilis
- Dysthymia (depressed mood of longstanding duration with less intense symptoms)
- Substance-induced mood disorder (intoxication or withdrawal)
- Dementia
- Endocrine disorders such as Addison's disease or hypotestosteronism

LABS: Check thyroid functions (TFT's), B_{12} and folate levels.

P: **ASSURE** that patient has been admitted to available community organization support structure.

REFER for psychiatric evaluation/treatment if patient is:

- Suicidal (see Suicidal Ideation protocol)
- Unresponsive to treatment
- Displaying psychotic symptoms
- Debilitated or functionally impaired by severe symptoms

Pharmacotherapy - Use medications with least possible anti-cholinergic side effects.*

1. Possible antidepressant regimens, with therapeutic dosages and positive and negative effects:
   Fluoxetine (Prozac): 10-40 mg/day (refer to psych service for treatment.)
   Positive effects: rarely sedating, often energizing, no cardiovascular side effects, no anti-cholinergic effects, non-fatal in overdose.
   Negative effects: insomnia, agitation, nausea, headache, sexual dysfunction in men and women; long half-life.
   Paroxetine (Paxil): 10-40 mg/day
   Positive effects: may be sedating (use at hs; can be useful with depression-associated insomnia)
   Negative effects: (see fluoxetine)
   Sertraline (Zoloft): 50-100 mg/day
   Positive effects: decreased incidence of drug-drug interactions vs. fluoxetine and paroxetine.
   Negative effects: (see fluoxetine)
   Venlafaxine XR: (Effexor XR): 75-375 mg/day
   Positive effects: minimal drug-drug interactions.
   Negative effects: nausea, headache, nervousness, sexual dysfunction. Note: monitor B/P at higher doses of venlafaxine.
   Citalopram (Celexa) 30-60 mg/day
   Positive effects: minimal drug-drug interactions
   Negative effects: mild nausea, possible sedation

2. A therapeutic trial is 4-6 weeks at therapeutic dose; if considering a trial, refer for psychiatric consultation. Continue medications for 1 year following resolution of symptoms, because of significant risk of recurrence. After this time, treatment may be gradually tapered if so desired by the patient, with careful monitoring for recurrence of symptoms. Recurrence risk increases if the first depressive episode is inadequately treated, or if patient has had multiple depressive episodes.

3. Other newer antidepressants, such as mirtazapine (Remeron) may be particularly useful when insomnia is a significant symptom and/or sexual dysfunction has been caused by other antidepressant agents such as fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor). Mirtazapine should be dosed at bedtime because of its sedating side effects. Individuals may also experience an increase in appetite and weight gain, in addition t dry mouth. Mirtazapine has minimal drug-drug interactions. Therapeutic dose range is 15-45 mg/day.

4. Bupropion sustained release (Wellbutrin SR) may also be used in individuals with depression who are experiencing sexual dysfunction caused by other antidepressant agents. Bupropion SR dosing should not exceed 400 mg/day (in bid divided doses) due to increased risk of seizures, particularly in individuals who have other risk factors for seizures). Bupropion (Wellbutrin SR) has minimal drug-drug interactions. It may have an "activating effect" which can be experienced as agitation and/or insomnia in some and may also have an appetite suppressant effect as well.

5. Nefazodone (Serzone) is not recommended as an antidepressant within the HIV/AIDS patient population, because pre-existing liver abnormalities complicate monitoring. This medication has recently been found to cause liver dysfunction and life-threatening liver failure in rare case, as has received a Black Box warning from the FDA. If the patient has ever had liver toxicity from the drug, restarting is completely contraindicated.

6. Treatment may involve anti-depressant combinations, including psycho-stimulants. Patients with prominent insomnia may benefit from the addition of trazodone 25-50 mg, given 1-2 hours before bedtime.

   *Because of the potent inhibition of the microsomal cytochrome P450 isoenzymes by protease inhibitors (especially Norvir), antidepressants used concomitantly with protease inhibitors should be used in lower doses to prevent antidepressant side effects/toxicity. Interactions between SSRIs and HIV medications are fairly common. Consult with an HIV expert or pharmacist before prescribing.

Refer for Psychotherapy

1. Individual psychotherapy with skilled, HIV-experienced mental health professional.

2. Patient should have the capacity and motivation to maintain an ongoing relationship.

Patient Education:

1. Illness (physical or emotional) is not a character flaw, moral or spiritual weakness. It's a normal characteristic of HIV infection. Sadness is always normal but a major depression is always abnormal and can be greatly helped with medication. Antidepressants are given for a long time, usually over a year, to help you with the chemical imbalances associated with depression.

2. If you are starting on antidepressant medications, expect to take it 2-4 weeks before noticing any improvement. Your symptoms should continue to improve after that, up to 6 weeks. It is important to continue taking your medications so that these symptoms don't start back up.

3. Some patients develop problems with sexual function on Paxil, Prozac, Zoloft, or Effexor. Report problems to prescriber.

4. Notice your major symptoms of depression, and be aware of what factors got you to seek treatment. You will need to monitor yourself for recurrences, and get help if your symptoms come back. By the time you notice that your sleep, appetite, mood, activity level, concentration, fatigue, isolation, are beginning to change because you feel sad or helpless or stuck, it's time to get help.

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Panic Disorder

Definition:

Panic disorder is persistent fear that interferes with the ability to conduct the affairs of daily living. A patient is diagnosed as having panic disorder when they have experienced four panic attacks within a 4-week period, or at least one panic attack followed by a month of persistent fear. There is a significant incidence of suicide in panic disorder patients. Panic disorder may also interfere with activities of daily living, including medical appointments, because patients may associate panic attacks with leaving home, driving, health care providers, etc. Usual onset is late adolescence to mid-thirties, often concomitant with major depressive disorder, social phobia, and general anxiety disorder.

S: **Patient complains of panic attacks, or describes episodes of:**

- trembling or shaking
- sweating
- feeling of choking
- nausea or abdominal distress
- hot flushes or chills
- chest pain or discomfort
- fear of dying
- shortness of breath or smothering sensations
- dizziness, unsteady feelings, lightheadedness, or faintness
- palpitations or accelerated heart rate
- depersonalization or derealization
- numbness or tingling sensations
- fear of going crazy or losing control

Any four or more of the above symptoms accompanying multiple panic attacks is diagnostic of panic disorder, in the absence of physical causes. Panic attacks, by definition, are self-limited and peak quickly, usually within 10 minutes or less. Symptoms that persist continuously for longer periods suggest other etiologies.

Hx: New onset vs. previous history, frequency, duration of each panic attack, and onset of panic episodes; usual setting. Identify if there are triggers such as being outside (agoraphobia) vs. random episodes. Relationship to food or hunger. Caffeine, stimulants/recreational drugs, and alcohol intake, usual and recent. Sleep disturbances, concomitant illnesses. Current medications, herbals, supplements. Any associated symptoms, such as rash, cough, fever, concomitant with onset. Family history of mood and psychiatric illnesses, particularly anxiety and panic.

O: Complete physical exam, including thyroid, cardiac, pulmonary, neuro. During actual panic attacks, increased heart rate or respiratory rate.

A: Partial differential/rule out:

- hypoglycemia
- hyperthyroidism
- pheochromocytoma
- major depression with superimposed panic attack
- cardiac insufficiency, CHF
- medication effect
- withdrawal from or intoxication with psychoactive substances: caffeine, amphetamines, cocaine, or other
- phobia: a specific response to a specific stimulus. A patient with panic attacks is unsure of when they will recur and what will trigger them.
- respiratory infection
- allergic reactions

P: **LABS:**

1. Thyroid studies, if symptoms indicate
2. Blood glucose, GGT, if symptoms related to hunger or consistent with rebound hypoglycemia
3. Arterial blood gases for ongoing SOB
4. EKG if chest pain

TX:

1. Behavioral Interventions: Stress management group, relaxation therapy, visualization and guided-imagery, cognitive-behavioral therapy (refer to community-based support). Emergency referrals may be needed.

2. Low dose tricyclic or selective serotonin reuptake inhibitor (fluoxetine [Prozac], sertraline [Zoloft], paroxetine [Paxil]) gradually titrated to therapeutic antidepressant dose; consult psychiatry. Venlafaxine extended release (Effexor XR), 75-225 mg qd may also be helpful in treating panic symptoms. Note:

Monitor B/P at higher doses of venlafaxine. Tricyclics such as amitriptyline and imipramine may reach higher blood levels when co-administered with amprenavir; SSRIs and benzodiazepines may interact with antiretrovirals. Consult with HIV expert or pharmacist. Treat at least 6 months beyond resolution of symptoms.

3. Many patients will require initial short term treatment with benzodiazepines, which are titrated downward as the antidepressant is titrated upward. **Benzodiazepines are used for acute, short-term management only because of tolerance and physiologic dependence.** This is more problematic in patients with previous history of addiction. Note that **ritonavir and lopinavir-ritonavir (Kaletra) are contraindicated with triazolam** (Halcion) and raise blood levels of many benzodiazepines; use with caution if necessary; use low doses, and avoid other CNS depressants while on therapy. Consult with clinical pharmacist. **Midazolam (Versed) and triazolam (Halcion) are contraindicated with all protease inhibitors, delavirdine, and efavirenz, as is St. John's Wort (an herbal).**

Insomnia

Definition:

Insomnia is a common accompaniment to HIV infection, especially as the disease progresses, and is usually chronic rather than the transient disturbances of sleep that are a normal part of life. Most insomnia related to HIV can be characterized by the amount, quality, or timing of sleep. Insomnia is a frequent subjective complaint and may be a part of progressive fatigue and diminished functioning.

S: **Patient may complain of:**

- Difficulty initiating sleep
- Early morning waking
- Mind racing, "can't shut thoughts off"
- Difficulty maintaining sleep
- Nonrestorative sleep (although adequate in amount, leaves patient feeling non-rested)
- Nighttime restlessness

HX: Bedtime sleep habits and collaborative history with sleep partner if possible; try to quantify how long they actually sleep each night. Query about snoring, shift work, exercise, nighttime reflux/heartburn; screen for depression and anxiety (see *Depression* and *Anxiety*, in this section). Ask about anxiety, nightmares, life stressors, and any over the counter medications or supplements used to promote sleep. Pay close attention to alcohol and recreational drug use, caffeine intake, and concurrent medications that may have insomnia as a side effect (ZDV, corticosteroids, pseudoephedrine, antihistamines with decongestant component). Ask about collar size; > 16 or 16 ½ is more often associated with sleep apnea.

O: General symptom-directed physical exam, body habitus, neuro exam, and mental status.
Polysomnography may be indicated when physiologic cause suspected, or for severe cases, and may show a characteristic sleep disorder attributed to HIV:
Increased total slow-wave sleep, percentage of slow-wave sleep, stage 1 shifts, REM periods, arousals.
Decreased sleep latency, total percentage stage 2 sleep, average REM durations

A: Partial differential/rule out:

- Mmedication side effects
- Recreational drug use
- Anxiety disorder (see *Anxiety*, this section)
- Caffeine
- Disturbance of sleep/wake cycle due to too much time in bed
- Cognitive impairment (*Dementia*, this section)
- Transient insomnia related to acute stress
- Major depression (insomnia is a primary symptom, see *Depression*, this section)
- Other identifiable sleep disorders (sleep apnea, periodic leg movements)
- Pain
- Alcohol intake (interferes with sleep ~2-4 hours after ingestion)

P: **TX:**

1 **Behavioral Strategies** - correct sleep habits: establish a bedtime routine, stimulus control, avoid vigorous exercise within 3-4 hours of bedtime, reduce/eliminate daytime napping, no eating/reading/TV/working in bed, get up at same time each day regardless of total hours of sleep. Be sure client has a dark, quiet, comfortable environment conducive to sleep. If unable to get to sleep after 15-20 minutes, get up, go into another room for non-stimulating activity in dim light (such as reading), and do not go back to bed until sleepy. Teach or refer for relaxation techniques.

2. Discontinue caffeine, CNS stimulants, alcohol, tobacco, tapering if necessary to avoid withdrawal symptoms.

3. **Pharmacotherapy:**

a. Antihistamines, such as diphenhydramine or hydroxyzine 25-50mg QHS (remember anticholinergic side effects)

b. Sedating antidepressants, such as trazodone 25-50mg, or amitriptyline 10-50mg QHS. Check for drug interactions with antiretrovirals and other medications. Mirtazapine (Remeron) is a newer antidepressant with fewer drug interactions, which may be used in low doses (7.5-15 mg) for insomnia.

c. Sedative-hypnotics, such as triazolam 0.125-0.25mg QHS prn; temazepam 15mg QHS; newer agents such as Doral, Prosom, Ambien. Because of addictive potential, and problems with amnesia, confusion, etc, these should be used for only short-term management (5-7 days). **Midazolam (Versed) and triazolam (Halcion) are contraindicated with all protease inhibitors, delavirdine, and efavirenz, as is St. John's Wort (an herbal).**

4. Mental health consult if problems persist or depression is suspected.

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Suicidal Ideation

Introduction:

Transient suicidal thoughts occur throughout the course of HIV disease. Risk of suicide is especially high for depressed patients and at pivotal points in the illness: learning of HIV status; disclosure to family and friends, start of HAART or other HIV medication, loss of job, appearance of first symptom(s); major changes in lifestyle, decreasing CD4 counts; major illness or hospitalization; AIDS diagnosis; at evaluation for dementia; and at the loss of a significant relationship. A suicide assessment must always be included in a psychiatric evaluation. Risk factors for suicide attempts include:

- social isolation (single, widowed, divorced, alone)
- financial difficulty
- substance abuse, especially alcohol
- relapse into drug use after significant recovery
- severe anxiety, depression, or other mental health disorder
- multiple losses or recent stressors
- prior suicide attempts
- abandonment by family, friends or significant others
- stigmatization due to illness, sexual orientation, substance use history
- prevalence of HIV-related problems at work
- any acute change in health status
- fear of HIV associated dementia
- organic disease
- teen years or age > 45
- hopelessness
- perception of poor social support

S: **Patient exhibits or personal caregiver discloses:**

- Active suicidal ideation with intent and plan (giving away significant personal belongings, saying goodbye, gathering the means - gun, pills, writing a note).
- Passive withdrawal from therapy, decreased adherence: stopping medications, not keeping appointments.
- Patient may express desire for disease to progress more rapidly.

HX: Past history of suicide attempts
Friend or family member who has committed suicide
Query about risk factors, above

O: Self-inflicted injuries may be present: wrist lacerations, neck burns. Perform mental status exam and suicide assessment. Probe for other depressive symptoms and immediacy of potential suicidal intent
Sample questions:
It sounds as if you're in great pain. Have you ever thought life is not worth living?
Do you often think of death?
Do you think about hurting yourself?
How might you do that?
Is this something you feel you might do?

A: Evaluate for depression, risk factors and contributing psychiatric illness or situational stressors. Determine immediacy of potential suicidal intent. (If mental health professional is available on-site, or can be obtained, an urgent consultation is often helpful in making these determinations.)

P:

1. If patient exhibits active suicidal ideation with a plan, **hospitalize** immediately, preferably in a psychiatric facility.
2. If suicidal behavior is passive, refer for psychotherapy with HIV-experienced mental health provider.
3. Contact the patient between appointments. Enlist the help of significant others, inviting them to accompany the patient to the next visit, and see all of them together. Consider a support group or peer referral if available.
4. Consider dispensing medications on a weekly basis for the purposes of:
   a. Monitoring emotional status and treatment adherence
   b. Preventing availability of lethal dose of medications.
5. Contract with patient not to harm self and to contact clinician and/or to go to hospital if suicidal ideations become active.

Follow-up: in consultation with mental health, be sure that appropriate treatment for underlying or persisting psychiatric illness is ongoing. Assess at each follow-up visit for adherence to mental health care and for re-occurrence of symptoms.

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HIV Associated Dementia

Definition:

HIV is neurotropic, directly invading brain tissue shortly after infection. HIV-Associated Dementia, also called AIDS Dementia Complex (ADC) was the most frequent single neurologic complication of AIDS, affecting 40-60% of all AIDS patients, but has greatly diminished in the HAART era. The American Psychiatric Association's (APA) definition of dementia is "an organic mental disorder defined as a loss of intellectual abilities of sufficient severity to interfere with social or occupational functioning."

Patients may present with ambulation/gait problems, mania, panic, psychosis, withdrawal or anxiety. Dementia is progressive, with a variable course; some patients have a rapid progression and decline, others a slow decline. Patients with HIV-related neurocognitive impairments are often acutely aware of their deterioration, which may lead to an adjustment disorder with profound fear, anxiety, or depression.

S: Patient complains of (or caregiver reports) impairment in memory (short-term and long-term), abstract thinking, judgment, and higher cortical functioning. The patient's personality may have changed, interfering with relationships, and s/he can no longer carry on normal social or occupational functions. Some patients experience only minor forgetfulness and diminished visual/motor skills.

Hx:	Medications	Approximate onset of symptoms
	Drug withdrawal	OI symptoms
	Pain	Query about common manifestations, below

O:

Early Manifestations		Late Manifestations	
• Impaired concentration	• Memory loss	• Global cognitive dysfunction	• Mutism
• Depressed mood	• Apathy	• Amnesiac features	• Aphasia
• Psychotic features, paranoia	• Agitation	• Frontal lobe disturbance	• Weakness
• Unsteady gait	• Clumsiness	• Organic hallucinations	• Spasticity
• Motor weakness	• Personality change	• Parkinsonism	• Dyskinesia
• Irritability	• Tremor, poor handwriting	• Vegetative state	• Ataxia

Screening Exam:

1. Ask patient to write name, date and location; to spell "world" backwards; to perform memory-object recall of three objects after five minutes; to make change from a dollar.
2. Perform funduscopic exam, check symmetry of brow wrinkling, eyelid closure, pupil size, Romberg and other tests to R/O focal neurologic deficits.
3. Check gait by asking patient to walk rapidly, turn and stop. Ask patient to walk on heels and tiptoes. Test steadiness of gait with eyes open and closed. Ask patient to stand from a squat without assistance.
4. Check temp and perform thorough PE to determine potential reversible causes such as OIs

A:

1. Always rule out treatable/reversible CNS condition: toxoplasmosis, cryptococcoma, MAI, lymphoma, CMV ventriculitis or encephalitis, normal pressure hydrocephalus, or meningitis associated with syphilis, TB, or Cryptococcus neoformans.
2. Rule out delirium: an acute manifestation of cognitive impairment with the inability to pay attention. Can be related to metabolic disturbance, but medication side effects often lead the list as causes of delirium, such as those with anticholinergic side effects (Elavil, Phenergan, Compazine, and Benadryl, among others). An anticholinergic delirium is characterized by visual and/or tactile hallucinations, confusion, and, at times, agitation. Other offenders include Demerol, lithium (at toxic levels, which may happen in a stable patient with a serious OI or dehydration), agonist-antagonist analgesics such as Talwin, and short-acting benzodiazepines such as Versed and Halcion.
3. Rule out depression, which can present as cognitive impairment.

ADC Stage	Characteristics
Stage 0 (normal)	Normal mental and motor function
Stage 0.5 (subclinical)	Equivocal symptoms of cognitive or motor dysfunction. No impairment of work or capacity for activities of daily living (ADL)
Stage 1 (mild)	Evidence of intellectual or motor impairment but able to perform most ADL
Stage 2 (moderate)	Unable to work but can do self-care
Stage 3 (severe)	Major intellectual incapacity or motor disability
Stage 4 (endstage)	Nearly vegetative

Adapted from Bartlett, 2001, p 138 (first reference)

P: **LABS:**

1. Check thyroid function, B_{12}, folate, RPR, chemistries and electrolytes, LFTs, CBC.
2. Order CT scan or MRI, looking for cortical atrophy, ventricular enlargement, masses.
3. A lumbar puncture will show increased protein, mononuclear pleocytosis.
4. EEG (mild, non-specific slowing).
5. Refer to psychiatrist for further evaluation and neuropsychological testing, if needed.

TX:

Pharmacotherapy

1. HAART may be helpful with treatment of ADC; for patients who are potentially candidates for HAART, a regimen should be recommended. Even though the ability of the drugs to penetrate the blood-brain barrier would appear to be crucial, it may be more effective to use the most potent regimen available, and in particular, one that the patient is likely to adhere to. Studies from the 1980s showed that zidovudine monotherapy was effective with ADC, so some clinicians always include it in the HAART regimen for anyone with ADC. Others suggest that two drugs that cross the blood-brain barrier should be used: zidovudine, stavudine, abacavir, lamivudine, nevirapine, nelfinavir, and indinavir. Efavirenz, didanosine, lamivudine, and amprenavir cross to a lesser degree.

2. Treat depressive symptoms with low dose SSRI medications other than Prozac (see *Depression*, this section, for specifics). Prozac has a long half-life and may be problematic.

3. Antipsychotics may be useful in treating agitation and hallucinations, but these patients are often extremely sensitive to anticholinergic side effects and extrapyramidal symptoms. Newer neuroleptic/antipsychotic agents such as olanzapine and risperidone have lower incidence of significant side effects than older drugs. Starting doses: olanzapine 2.5 mg hs; risperidone 0.5-1 mg po hs. Note that these drugs may interact with antiretrovirals, especially Ritonavir. Consult psychiatry.

4. Psychostimulants such as Ritalin and Dexedrine have been used to improve attention, concentration, and psychomotor function. Doses of Ritalin start at 5mg for a test dose, then 2.5-5.0mg bid is given, increasing by doses of 5mg QOD. Usual doses are in the range of 20-30mg/day. Monitor BP, P, restlessness, agitation, nausea, and psychosis.

Psychosocial intervention

1. For a patient knowledgeable about HIV, a dementia workup or diagnosis will often precipitate a crisis, with increased risk of suicide.

2. Behavioral management strategies may assist the patient with early manifestations of dementia to continue living with some degree of independence, yet be safe in the home environment. Memory aids such as posted notes, calendars, alarmed pill boxes, and other environmental cues may help.

3. It is critical to enlist the support of significant others/family at this stage of the illness. Because the disease is frightening and may be progressive, the patient and support system needs assistance anticipating and planning for the future. Planning for assisted living or other in-home custodial care should begin early. Severe or late dementia causes fear, misunderstanding and frustration for both patient and caregivers. All involved will require help from visiting nurses, social workers, hospice workers, physicians. Respite care is likely to be

needed, as well as attention to medication. Home care may cease to be appropriate when a patient's dementia-related problems become overwhelming to care takers.

4. Avoid benzodiazepines, which tend to increase confusion and decrease concentration.

5. Advanced directives are a major consideration for the patient with early manifestations of dementia.

Patient Education:

1. Maintain your support system as much as possible. Around the clock supervision may become necessary.

2. (For patients who are candidates for HAART): Find someone to help with your antiretroviral medications if at all possible. Antiretroviral therapy, if taken on schedule and as prescribed, seems to have helped some people with ADC. Enlist family members or roommates to support antiretroviral regimen, including teaching them schedule, side effects, and whom to call with problems and questions.

3. Use cues in the environment (notes, calendars, alarms) to help yourself remember medicines, appointments, social events, and other things that are important to you. Have a friend stay with you overnight and assist you to make your house safer, post your reminders, etc.

4. Get a referral to a support group or an HIV-experienced counselor who can respond to your fears and concerns.

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Pain Syndrome

Definition:

Pain is a significant symptom commonly experienced by people with HIV infection, and its prevalence increases as the disease progresses. Because many conditions may be refractory to specific therapy, and the duration of diagnostic workups may be lengthy, symptomatic treatment should not be delayed. Pain is significantly undertreated, especially in women HIV patients due to factors ranging from providers' lack of knowledge to patients' fear of addiction.

S: Patient reports pain. Site varies with underlying cause including: headache; abdominal, back, or throat pain; arthralgias; myalgias; pain in feet/hands; various other sites; patients often feel pain from two or more sources at once.

Hx: Obtain history of location, quality, severity, onset, timing, exacerbating or alleviating factors, setting in which it occurs, associated manifestations. Have patient rank the pain on a scale of 1-10. Note that pain ratings >3 interfere markedly with patient activities. This scale should be used consistently for repeat assessments.

O: Complete symptom-directed PE, neuro exam. Look for masses, lesions, localizing signs. If peripheral symptoms, check sensation and vibratory sense. Signs of discomfort, elevated heart rate and blood pressure may be present. Ha

A: Pain may be secondary to:

- Herpes simplex*
- Peripheral neuropathy*
- Pancreatitis
- Kaposi's sarcoma*
- Lymphoma
- Unidentifiable causes
- Herpes zoster (active or post-herpetic neuralgia)*
- Mycobacterium Avium Complex*
- ZDV-induced headaches
- Medications
- HIV-related headaches (encephalopathy, toxoplasmosis, cryptococcal meningitis, etc.) see *Neurologic* workup in Complaint-Specific section

*see specific topic in Disease-Specific section for treatment of underlying causes

P: Diagnostic workup; eliminate or treat underlying cause, if possible. During workup, begin pharmacologic management. Using a consistent rating scale, determine level of pain at which the patient believes he will be able to perform essential activities. Frequent follow-up will be needed, especially after regimen changes, with continued monitoring after the patient achieves functionality.

Step 1. Acetaminophen and/or NSAIDs should be tried first for mild to moderate pain. If patient continues to report pain, add (do not substitute, unless intolerant of the NSAID or cannot take acetaminophen) Step 2 medications

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Step 2. Opiate analgesics, which remain the mainstay for moderate or severe pain.

a. Meperidine should be avoided (its active metabolite, normeperidine, has activating properties and may cause delirium)
b. Dosage adjustment frequently necessary
c. Oral:parenteral ratios need attention when changing route
d. Side effects need to be anticipated (constipation, drowsiness, nausea, itching, urinary retention)
e. If pain control is not achieved with prn schedules, set up dosages around the clock, increasing the dosage as needed to achieve consistent pain control. For breakthrough pain, use a prn in addition to the scheduled dosage.

Step 3. Adjuvant and non-pharmacologic analgesics; check drug interactions with antiretrovirals:

a. Tricyclic antidepressants (amitriptyline 10-50mg/day; nortriptyline 10-50mg/day)
b. Psychostimulants (Ritalin 5-30mg/day)
c. If pain is localized, TNS units, nerve blocks, or epidurals may be useful in controlling pain or reducing its level

d. Anticonvulsants (gabapentin, dosed at 300-600 mg po tid to qid. Decrease dose for impaired renal function.)
e. Relaxation imagery, acupuncture, biofeedback, peer support group, and counseling may also help in pain management.

4. Substance abuse, methadone maintenance, pain and HIV
   a. Patients with a history of addiction who are in drug-free recovery may be concerned about relapse if opiates are used. Try to help these patients achieve adequate pain relief with non-addictive medications and alternative therapies (see adjuvant analgesics). Referral to pain management specialists with a clear statement of the problem may be required.

   b. Methadone-maintained patients: note that nevirapine is an inducer of the opioid receptor system and concomitant use with methadone may result in opioid withdrawal. Higher doses of methadone and other opioids may be needed. Ritonavir may also decrease methadone levels. See *HAART* in Antiretroviral Therapy section and dose interaction charts for further information.
   - This subgroup still requires active analgesia for pain
   - Do not decrease methadone dose; select a different analgesic for pain
   - Be aware of judgmental attitudes of some medical staff

   c. Active substance-abusing patients:
   - May elicit fears of manipulation from providers
   - May be extremely difficult to treat
   - Need clearly stated limits, with direct discussion about drug misuse; state consequences ahead of time
   - May require higher opiate doses secondary to tolerance
   - Knowledge of specific pain syndromes will help clinician
   - Need consistency of treatment plan among clinicians
   - Should have only one clinician responsible for managing pain medication regimen
   - Should not have opioids withdrawn during an acute pain event

Note: Referral to psychiatry or pain clinic may be necessary for patients with persistent problems.

Patients with endstage AIDS may have different considerations for pain management. A full guideline for palliative care, including pain management, is available at: http://hab.hrsa.gov/tools/palliative/

Patient Education:

1. Pain management is part of your treatment and we will need your feedback to make the best treatment decisions. If your pain persists >24 hours, at a level that interferes with daily life, please call back so that we can change the plan and try additional measures if needed.

2. We do not expect full pain relief in most cases, but to relieve it enough that you can perform your daily activities.

3. Explain that "mild" pain meds (NSAIDs, ASA, acetaminophen) are continued even when "stronger" medications are started because their mechanism of action is different than opiates. This combination of pain medication has additive effects so that pain may be controllable with a lower narcotic dose.

4. If patient is put on "round the clock" medications, explain that they are to be taken on schedule, with the designated prn medication between doses for breakthrough pain.

5. Opiates are noted for causing severe constipation; discuss with patient the necessity to remain hydrated; offer stool softeners, laxatives, or other measures to begin quickly if constipation occurs.

6. Explain potential for opiates' interactions with recreational drugs or alcohol, which can result in CNS depression, coma, or death.

7. Patients on opiates need to make alternative arrangements about driving and operating machinery.

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Peripheral Neuropathy

Definition:

Persistent pain syndrome resulting from damage to the axonal parts of nerves, generally in late disease. Usually characterized by sensory symptoms which generally far exceed actual sensory or motor dysfunction. The sensory symptoms (see below) generally produce significant discomfort in terms of pain and may not cause sensory ataxia or motor weakness. The most common neuropathy seen in AIDS patients is usually distal sensory neuropathy. Etiology can vary, as can its management (see *Pain Syndromes*, this section).

S: May complain of numbness or burning in feet, pins-and-needles sensation, shooting or lancinating pain, feeling that their shoes are too tight and their feet swollen; for some, walking is difficult or impossible due to the discomfort. This may progress up above the ankle before the hands or fingers are affected.

Take a careful history including:

A. Symptom onset and progression, if any
B. Symptom distribution (to determine single vs. multiple nerve involvement)
C. Symmetry of symptoms
D. Nature/quality of pain
E. Past medical history (to include illnesses such as AIDS or diabetes mellitus)
F. Alcohol intake - amount and extent of use.
G. Current and recent medications, particularly ddC, ddI, INH, and d4t; rarely dapsone. Include when the drug was started.
H. Any other neurologic symptoms

O: Physical exam - Neurological exam often reveals sensory deficits which can be focal, symmetric, or asymmetric. May present with "stocking-glove" distribution of sensory symptoms. Diminished reflexes and muscular weakness, either symmetric or asymmetric, may or may not be present. Patients with significant motor weakness or paralysis, especially if progressive over a few days or a few weeks time, should be evaluated emergently to rule out neurologic CMV.

A: **Partial differential/rule out:**

Metabolic etiologies
Infections (such as herpes zoster, meningitis)
CMV polyradiculopathy or mononeuritis (rare, but progressive, ascending, with autonomic and/or motor impairment; consult with expert clinician. Hospitalization and immediate treatment is required. CMV is more common in AIDS and severe immune suppression)
Toxicity (ARV nucleosides such as ddC, ddI, and d4t; INH)
Alcohol
Diabetes Mellitus
Hypothyroidism
Vitamin B_{12} deficiency
Immune-mediated and auto-immune (subacute Guillain-Barre, demyelinating polyneuropathy, and MS-like presentations--more common early in HIV; SLE and others are possible)
Compression (secondary to tumor/metastatic disease)
Trauma
Genetic/hereditary
Nerve damage secondary to ischemia (such as diabetes mellitus)

P: **Labs:** Blood glucose, thyroid function, electrolytes, B_{12} level; others may be indicated for atypical or acute presentations

Treatment/management:
Peripheral neuropathy due to ARV nucleosides, such as D4T,ddI, ddC, may be reversible if recognized early and the offending agent discontinued. Usually this starts within weeks or a few months after starting the drug, and may take several weeks after drug is discontinued for improvement to begin. Occasionally, an acute, treatable infection (zoster, CMV) is responsible. Otherwise, peripheral neuropathy is a chronic condition, and management is aimed controlling symptoms and helping the patient cope with the pain.

Usual management is empiric, initially employing non-steroidals along with adjuvant medications below, such as the tricyclic antidepressants and selective serotonin re-uptake inhibitor (SSRI) antidepressants. Some experts recommend lidocaine 20-30% ointment.

Patients with neuropathic pain are treated with the general approach of the WHO ladder of pain management, described more completely in *Pain Syndromes,* this section. If the initial meds are ineffective, then go to the anticonvulsants, particularly gabapentin in the doses noted below. In the event that NSAIDs provide some pain relief, they should be continued as the anticonvulsants are added. In some patients, opiates may also need to be added; however, it is important to note that ritonavir may interfere with their action, and opiate doses may need to be increased.

1. **Tricyclic antidepressants**
   a. Nortriptyline - starting dose: 10-25 mg qhs; usual maintenance dose 20-150 mg qhs
   b. Amitriptyline - starting dose: 10 mg qhs - usual maintenance dose: 20-150 mg qhs.
   Side effects: may include sedation, anticholinergic effects (such as dry mouth and urinary retention), orthostatic hypotension.

2. **Anticonvulsants**
   a Gabapentin (Neurontin) - starting dose: 100mg tid or 300 mg at hs; usual maintenance dose: 300-600 mg tid-qid. Dose may be increased to a maximum of 1200 mg. tid. Decrease dose in patients with impaired renal function.
   b. Divalproex sodium (Depakote) - starting dose: 500 mg bid; usual maintenance dose: 500-750mg bid-tid. Side effects: weight gain, sedation, temporary hair loss, nausea, diarrhea. Monitor blood level (50-100 range) and liver function tests.
   c. Lamotrigine (Lamictal) 25 mg. bid, increasing to 300 mg/day over 6 weeks has shown effectiveness in clinical trials.

3. **SSRI-type antidepressants**
   a. Paroxetine (Paxil) - starting dose: 20 mg qd; usual maintenance dose: 20-40 mg qd.
   Side effects may include: sedation, weight gain, sexual dysfunction, nausea
   b. Venlafaxine (Effexor) - starting dose: 37.5 mg qd; usual maintenance dose, 75-300 mg per day, in divided doses (or use Effexor XR once a day).
   Side effects: hypertension may be problem at higher doses; headache, nausea, sexual dysfunction.
   Note: Analgesic effects of antidepressants are independent of antidepressant effects and generally occur at lower doses

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CHAPTER 5: Disease-Specific Treatment

Bacillary Angiomatosis

Definition:

Bacillary angiomatosis or peliosis: *Bartonella henselae* and *B. quintana*, which can cause cat scratch fever and trench fever, respectively, can also cause vascular proliferative lesions that can form in many different organs:

lymph nodes	skin	GI tract
lungs	bone	blood
heart	spleen	bone marrow
liver	brain	

Most of these problems are due to *B. henselae.* Liver lesions, or bacillary peliosis (BP) may be concomitant with other systemic manifestations or skin lesions. Dermatologic presentations are variable, from red, vascular lesions with smooth or friable surfaces, to cellulitic plaques, KS-like lesions, dry scaly plaques on erythematous bases, or subcutaneous nodules. Lesions of bacillary angiomatosis (BA) may be chronic, present for up to a year. They can be differentiated from KS, since a collar of scale is usually present around the border of the BA lesion.

S: c/o skin lesion(s), usually tender. May also note fever, weight loss, abdominal pain. Patient is likely to own or have had exposure to cats; may or may not recall flea bites.

O: hepatosplenomegaly or anemia may be present, in addition to or in absence of the skin lesions described above. BA or BP usually occur with CD4 counts <50, although cat-scratch fever may manifest in immunocompetent individuals. Heart murmur may indicate endocarditis.

A: Partial differential diagnosis:

- Kaposi's sarcoma
- Angiosarcoma
- Pyogenic granuloma
- Septicemia of other etiology

Diagnostic tests: Biopsy may be needed to establish etiology, although up to half of febrile patients may be diagnosed by a specific type of blood culture. The organism requires special culture conditions: lysis centrifugation must be followed by culture on chocolate agar and incubated with 5% CO2 for up to 15 days. Stain with Warthin Stary stain.

If heart murmur noted, obtain echocardiogram.

P: Treatment must be prolonged to reduce the risk of relapse, generally 12 weeks or more for skin manifestations alone. For systemic manifestations, evaluate for hospitalization and consider longer course of treatment

Clarithromycin 500 bid, or
Azithromycin 250 po qd or
Ciprofloxacin 500-750 po bid

Alt: Erythromycin 500 mg. po qid, or
Doxycycline 100 mg po bid

For seriously ill patients, hospitalize and start antibiotics intravenously. Rifampin 300 mg po BID is usually added to their treatment regimen, although this may necessitate interruption of the antiretroviral regimen due to drug interactions.

Relapsed patients are re-treated for 16 weeks or more.

Patient Education:

1. Medications must be taken for the full 12 (or more) weeks, and on schedule, in order to control the infection.

2. After course of medication is complete, return for any recurrent symptoms such as fever or new lesion growth.
3. Antiretroviral therapy may be added (if patient is not already on it, and is ready to try it) after you have been on the antibiotics for 4 or 5 weeks. (See *HAART* in Antiretroviral Therapy section and Adherence information in Appendix B.)
4. Women of childbearing age should be counseled to avoid pregnancy if on TCN or clarithromycin.
5. Careful flea control for pets will help prevent exposure to these infections. Consult your vet for appropriate measures.

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Cervical Pathology/Atypia

Definition:

About 30-60% of Pap smears in HIV+ women have cytological abnormalities, and 15-40% have evidence of dysplasia, about 10 fold higher than those of HIV-negative women. The prevalence of cervical neoplasia is about 5 times higher in women infected with HIV, possibly because immunosuppression associated with HIV infection may allow activation of human papillomavirus. One recent study showed that 20% of women with HIV developed squamous epithelial lesions (SIL) within a 3-year period. Frequent Pap monitoring and careful follow-up are essential to prevent progression to invasive cervical cancer, which has been an AIDS-indicator condition since 1/1/93.

S: Most often, the patient with early neoplasia is asymptomatic. The classic symptom of early invasive cervical neoplasia is intermittent, painless metrorrhagia (intermenstrual bleeding), which may initially present as post-coital spotting. Late symptoms of invasive cervical carcinoma include flank and leg pain, dysuria, hematuria, rectal bleeding and obstipation.

HX:

- Sexual activity before age 20
- Genital warts, previous or current HPV
- Cigarette smoker
- Previous abnormal Pap
- LMP
- Multiple sexual partners
- Oral contraceptive use
- Inadequate Pap screening history
- Cervical cancer-when and how treated
- Pregnancy

O: A speculum exam is usually unremarkable for women with SIL only. However, cervical inflammation and discharge due to infection may accompany SIL. In contrast, an exophytic or ulcerative cervical lesion that can bleed profusely may be visible in invasive neoplasia.

A: HIV+, with higher risk of progression to invasive cancer

P: LABS/PROCEDURES:

1. Perform screening Pap smear on all HIV-infected patients every 6 months x 2, and if these are normal, annually thereafter. Note that "reflex testing" is now available, in which a second sample is sent at the initial screening (or the original sample is stored in liquid media and can be re-used), and is tested for HPV only if the Pap is reported as ASC-US. If HPV test is negative, the woman can be spared a second visit and colposcopy, which is the usual follow up for ASC-US.

   <u>Results of atypical/abnormal Pap may show:</u>
   ASC-US: Atypical Squamous Cells of Undetermined Significance
   ASC-H: Atypical Squamous Cells—cannot exclude HSIL
   Atypical Cells, NOS (Not otherwise specified)
   - Endocervical
   - Endometrial
   - Glandular

   Atypical (favor neoplastic)
   - Endocervical
   - Glandular

   AG-US: Atypical Glandular Cells of Undetermined Significance
   Endocervical adenocarcinoma in situ (AIS)
   Adenocarcinoma
   - Endocervical
   - Endometrial
   - Extrauterine
   - NOS

   LSIL: Low-grade Squamous Intraepithelial Lesion (previously CIN I, koilocytosis, or HPV lesion)
   HSIL: High-grade Squamous Intraepithelial Lesion (previously CIN II or III)
   Squamous Cell Carcinoma
   Other malignant neoplasms may be listed

2. Abnormal/atypical Pap follow-up:

   ASC-US: Referral for colposcopy is recommended for all immunosuppressed patients with ASC-US, regardless of CD4 count, viral load or HAART. If ASC-US persists, colposcopy with directed biopsy. If normal, follow up as usual with Paps at 6 and 12 months. HPV testing at 1 year is recommended, if available, and repeat colposcopy if positive.

   ASC-H: Refer for colposcopy and directed biopsy.

   AG-US: Because of the high rate of significant lesions in patients with AG-US, recommend colposcopy and endocervical curettage, with endometrial sampling if abnormal bleeding or age >35. Women with AG-US and more specific cell origin should be managed accordingly—for example, women with atypical endometrial cells of undetermined significance should have endometrial sampling. Refer to appropriate specialist for management of abnormal findings. If colposcopy normal, follow up at 4-6 months x 4 screenings; if normal, back to usual screening intervals.

   LSIL: Colposcopy and directed biopsy are indicated. If no CIN or neoplasms found, Pap at 6 and 12 months, or do HPV DNA at 12 months. If positive, refer to specialist for management.

   HSIL or squamous cell carcinoma: should undergo colposcopy with endocervical assessment and directed biopsy as soon as possible. Refer to Oncology.

   Adenocarcinoma in Situ (AIS)—Refer for colposcopy

   Note: pregnancy may contraindicate such procedures as endocervical curettage.

Patient Education:

All patients

1. If you smoke, quit. Cigarette smoking appears to heighten the risk of cervical cancer, and makes HPV more difficult to treat. Discuss options for smoking cessation, and refer to American Lung Association if programs available in your area.

2. Use latex or polyurethane male or female condoms (or plastic barriers for oral sex on women) during every act of sexual intercourse to reduce the risk of transmitting Human Papillomavirus (the usual cause of cervical cancer) to partners, and to reduce your risk of exposure to other sexually transmitted pathogens.

3. It is important to keep your follow-up appointments for Pap (or colposcopy) so that we can be sure that if anything is developing, we can detect it and take care of it early, before it spreads or requires major surgery.

ASC-US, ASC-H

1. ASC-US does not mean that you have cancer or that you will get cancer. Further testing is required to find out. It does mean that you have some unusual cells that we must monitor to be sure that nothing malignant is developing.

LSIL/HSIL

1. Keep your appointments! Early treatment is essential to prevent keep the disease limited; if it invades, it can spread to other organs and cause death. After treatment: you are at higher risk of recurrence and should be careful to have Pap smears every six months.

Invasive cervical cancer:

1. A diagnosis of invasive cervical cancer in an HIV-infected woman often indicates rapidly-progressive, terminal illness, although aggressive treatment may offer some hope. If the care provider and patient have not discussed plans for home care, adoption of children, and preparation for disability and death, this diagnosis should prompt them to begin this dialogue.

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Cryptococcal Disease

Definition:

A systemic or CNS fungal infection caused by the organism Cryptococcus neoformans. In immunocompetent patients, it is usually asymptomatic, self-limited and confined to the lungs. The organism is ubiquitous, but particularly plentiful in soils enriched with bird droppings; may be present in fruit skins or juices, as well as unpasteurized milk.

S: **Patient complains of fever, headaches, malaise, nausea and/or vomiting, and occasionally photophobia. Some patients will complain of cough or shortness of breath if the disease involves the lungs. Cryptococcal meningitis may also cause confusion, personality or behavior changes, blindness, deafness, and if left untreated, coma and death.**

O: Document fever; funduscopic, neuro, pulmonary, skin exams need particular attention. Check for dehydration, visual acuity, and nuchal rigidity (uncommon). Symptoms depend upon locus of infection. The organism can infect almost all organs in the body, but most commonly causes disease of the meninges, skin, or lungs, and in AIDS patients often becomes disseminated, with fungemia.

Meningitis: Fever, vomiting; occasionally stiff neck, altered mental status, but rarely seizures. Papilledema with loss of visual acuity may be noted, and cranial nerves III and VI may show deficits. Positive cryptococcal antigen in peripheral blood and CSF, positive fungal cultures of peripheral blood and CSF, possibly positive CSF India Ink stain. High opening pressure on LP may be noted.

Fungemia: As many as 70% of patients with Cryptococcus have fever, with positive blood cryptococcal antigen and positive fungal cultures of peripheral blood or lymph nodes will have negative CSF cryptococcal antigen and CSF fungal cultures.

Skin involvement: is common, with lesions—papules, nodule, or ulcers, but most commonly described as resembling molluscum lesions. Usually occur with disseminated disease.

Pulmonary cryptococcosis: Cough, dyspnea, fever, pleuritic chest pain, occasionally tachypnea or fine rales; positive cryptococcal antigen and fungal culture of peripheral blood. Chest film may show diffuse or focal infiltrates (which sometimes appear nodular or miliary) and intrathoracic adenopathy are most common. Tuberculosis should always be ruled out.

A: Determine whether or not CNS symptoms, whether or not the patient is dehydrated

P: Fever workup should include blood cultures, including AFB and fungal, cryptococcal antigen of peripheral blood, sputum cultures including AFB stain and culture, urinalysis, urine cultures, chest X-Ray. If any neuro symptoms, obtain CT to rule out mass/threat of herniation prior to obtaining **lumbar puncture, which is always indicated when cryptococcal antigen is found peripherally**.

LP testing: Always measure opening pressure; a high pressure contributes to mortality. Obtain CSF labs: India Ink stain, fungal cultures, cryptococcal antigen, chemistries, cell counts, VDRL. Other poor prognostic indicators include low CSF glucose levels, <20 leukocytes/mm3, altered mental status, and cryptococci isolated from extraneous sites.

TX:
CNS disease: Admit for 2-wk induction with Amphotericin B intravenously, 0.7-0.8 mg/kg/day. Repeat LP; if culture positive, continue amphotericin B for one more week. Because Amphotericin-B is highly irritating, it is recommended that a central line be inserted for these infusions. Amphotericin B has many side effects, including fever, rigors, hypotension, N/V, and nephrotoxicity as well as anemia, leukopenia, hypokalemia, hypomagnesemia, and hypocalcemia. Labs must be monitored closely during course of treatment. Note that Liposomal Amphotericin or Amphotericin B Lipid Complex reportedly reduces rigors and other immediate effects of amphotericin infusion, and may be used for patients having difficulty with infusion effects. CBC and platelet counts are monitored throughout therapy.

Some studies suggest that the addition of flucytosine (25 mg/kg po q 6 hours) for the first two weeks of treatment, especially in patients with two or more poor prognostic indicators, showed an additive if not synergistic effect in combination with amphotericin-B. Flucytosine levels should be monitored (peak 70-80 mg/L; trough 30-40 mg/L). Higher levels are associated with bone marrow toxicity. Note that dosage must be adjusted in renal insufficiency.

Prolonged elevation of CSF pressure has been found to contribute to morbidity and mortality. Steroids do not seem to alter this. If initial opening pressure >250 mm/water, repeat LP at 1-3 day intervals as needed for pressure reduction; removing 20-40cc of fluid may be required. Check closing pressure. Occasionally, ventriculostomy or ventricular-peritoneal shunt may be indicated.

After symptoms resolve, switch to fluconazole po, 400 mg/day for 8-10 week course. After completion, decrease fluconazole to 200 mg/day for lifelong maintenance. Many authorities recommend re-checking LP to be sure CSF is sterile before dropping to maintenance dose. Recurrence is not unusual, but is greatly reduced by maintenance therapy. Itraconazole 200 mg po bid is sometimes used as an alternative for patients who cannot take fluconazole, but may be less efficacious. Itraconazole does not penetrate the CSF. Note also drug interactions with INH, ddI, rifamycins and other common drugs.

Lung or cryptococcal fungemia, with negative CSF cryptococcal antigen and cultures: Start fluconazole 400 mg/day for 6-10 weeks, then drop to maintenance dose of 200/day. Re-check fungal blood cultures and cryptococcal antigen to verify effectiveness of therapy. Peripheral antigen titers may be monitored to observe for resistance to fluconazole. In this event, Amphotericin may be used for maintenance therapy; dosage being 1mg/kg IV once or twice per week.

Pregnancy Note: Fluconazole and other azole drugs are not recommended during pregnancy; especially in the first trimester, women would continue on Amphotericin rather than switching to Fluconazole.

Suppressive therapy should be lifelong unless immune reconstitution occurs due to HAART. After initial therapy is completed, if patient remains asymptomatic, and has a sustained increase (>6 months) in CD4 cells >100-200, it is reasonable to consider discontinuation of suppressive therapy (also called "secondary prophylaxis") with close observation for recurrence and/or a drop in DC4 cells. Re-institute suppressive therapy if CD4 count <100-200.

Patient Education:

1. Cryptococcosis is not curable in AIDS, but requires lifelong treatment. If you have a good response to HAART, with long-term improvement in your CD4 counts, we may be able to stop the medication, but even then, you must be closely monitored. Relapse is common if lifelong therapy is not used. (Patient must understand importance of careful adherence to treatment.)
2. Even with therapy, disease may recur. Report fevers or recurrence of symptoms immediately.
3. Avoid pregnancy while on any azole drug. Fetal craniofacial and skeletal abnormalities have been reported.

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Cryptosporidiosis

Definition:

An intestinal infection caused by a protozoan parasite, usually self-limited in immunocompetent patients. It produces profuse, watery diarrhea with abdominal cramping in immunocompromised patients. Inability to clear cryptosporidia is a marker of severe immune suppression and is an AIDS-indicator disease if an HIV-infected patient's diarrhea caused by this organism has persisted for four weeks or longer. Cryptosporidium may also cause cholangitis, and, rarely, infection in other sites outside the GI tract.

S: Patient complains of some combination of diarrhea, RUQ abdominal pain and cramping, flatulence, nausea, vomiting, fever, anorexia, weight loss, and/or malaise (see *diarrhea* workup protocol).

HX: Anal-oral contact
Ingestion of contaminated or unsafe water, including swimming/boating/rafting incidents
Duration of symptoms (>2 weeks)
Stool frequency (6-26 bowel movements daily)
Stool volume (mean 3.6 liters)
Diarrhea consistency/bloody? (usually watery and without gross blood)
Recent travel, especially out of the country

O: **PE:** Document weight loss
Abdominal tenderness, often diffuse
Recent labs: CD4+ count (likely to be <150/mm^3)

A: Rule out bacterial, viral and other parasitic causes of diarrhea (see *Diarrhea* workup, in Complaint-Specific section).

P: LABS/PROCEDURES:

1. Stool testing for ova and parasites
2. Fecal leukocytes negative
3. To differentiate cryptosporidium from yeast:
   - Use an iodine stained wet mount; cryptosporidium will be colorless and yeast will be brown;
   - Use a modified Kenyoun acid-fast stain - oocysts stain red and yeast stains green; or
   - Test stool for cryptosporidium using IFA
4. If stool for O&P is negative x 3, refer for upper and lower endoscopy.
5. If cholangitis suspected, consider abdominal ultrasound of RUQ to detect biliary ductal dilatation, and/or endoscopic retrograde cholangiopancreatography (ERCP)

TX:

1. Most patients experience symptom improvement or remission on HAART. Evaluate for appropriateness of HAART therapy and begin ASAP. Control of viral replication often results in clearing the pathogen. There is no proven efficacious therapy as of 2002 that will treat only the parasite.

2. Provide supportive care and symptomatic relief through:
   - Fluid and electrolyte replacement
   - Antidiarrheals: lomotil, loperamide
   - Tincture of opium (paregoric), alone or in combination with other antidiarrheal agents
   - Antispasmodics
   - Antiemetics

   Humatin (paromomycin sulfate) 1 gm po BID + azithromycin 600 mg po qd with food for 4 weeks has helped some patients; after four weeks give paromomycin alone, 500 mg po bid. This regimen has not been curative.

3. Other drugs with anecdotal support:
   a. Clinical trial of Nitazoxamide (Cryptaz) 2 gm/day available with AIDS Clinical Trials Unit; call Romark Labs at 813-282-8544 to obtain drug on investigational basis.
   b. Octreotide (sandostatin) 50 mcg (micrograms) SQ q 8 hours X 48 hours. Increase dose stepwise, if no response, to a maximum of 500 mcg q 8 hours.

4. Consult and/or refer to clinic nutritionist or registered dietician.

5. Evaluate usefulness of elemental diet.

Patient Education:

1. Educate patient to increase oral fluids (not alcohol), avoid foods that aggravate diarrhea, and increase calories.
2. Provide supportive counseling to patient, discussing how to manage symptoms and isolation that may accompany diarrhea.
3. Explain that HAART (if appropriate) may decrease symptoms or help the body eradicate the parasite.
4. Recommend that patients with active cryptosporidiosis not work as foodhandlers, nor share a room with other severely immunocompromised patients because of potential for inadvertent transmission of oocysts.

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CDC. USPHS/IDSA Guidelines for Preventing Opportunistic Infections Among HIV-Infected Persons. *MMWR* 2002; 51 (No. RR-8)

Cytomegalovirus Disease

Definition:

Cytomegalovirus (CMV) is a member of the human herpes virus family, and is common among sexually active adults. It can be spread by sexual or other close personal contact, blood-to-blood contact (transfusion or needle-sharing), through organ transplantation, or perinatally. Estimates of the prevalence of CMV infection in the developed countries include 40-60% of the adult population; in less-developed countries, seroprevalence ranges up to 80-100%. While most infected are asymptomatic, CMV is a major cause of morbidity and mortality in the AIDS patient with CD4 counts <50. Disease represents either primary infection or reactivation of latent infection. Patients on successful HAART regimens have greatly reduced risk of symptomatic CMV disease. The virus can result in several clinical illnesses in patients with HIV infection, including: chorioretinitis, pneumonia, esophagitis, colitis, encephalitis, polyradiculopathy, adrenalitis and hepatitis.

S: Patient with documented HIV infection may complain of:

- Floaters, scotomata (blind spots), loss of peripheral or field vision (chorioretinitis)
- Headache, difficulty concentrating, sleepiness, personality changes (encephalitis)
- Mouth ulcerations
- Dysphagia or odynophagia (esophagitis)
- Abdominal pain and bloody diarrhea, weight loss, rectal ulcers, and fever (colitis)
- Persistent fever, fatigue, weight loss (adrenalitis)
- Shortness of breath, dyspnea on exertion, dry cough (pneumonia—rare in AIDS patients)
- Bilateral lower extremity weakness, urinary retention, incontinence/spasticity (polyradiculopathy)
- Low back pain, especially radiating to perianal area (polyradiculopathy, myelitis)
- Family may report confusion, apathy, lethargy, somnolence, withdrawal, personality change (CMV encephalitis)

HX: Duration of symptoms
Sexual orientation
(higher prevalence in homosexual males)
Injection drug use
Transfusion or transplantation
Query about symptoms above

O: **PE:** Document significant weight loss, fever
Document presence/absence of rectal ulcers
Neurologic exam with cranial nerve function
Hypo or hyper-reflexia of lower extremities
Sensory deficits (usually with preserved vibratory and proprioception)
Mini-mental status exam: document confusion if present
Document delirium: changing level of consciousness, disorientation, clouded sensorium, etc. (see *Neurologic symptoms* in Complaint-Specific section)
Funduscopic exam will show "cottage cheese in ketchup", yellow-white granular lesions with hemorrhage and vascular exudates in patients with retinitis, usually following vasculature
Nystagmus
Karnofsky scale score

LABS: CD4+ count variable, usually <50/mm^3
Presence of CMV in urine, semen, cervical secretions or BAL fluid is not diagnostic of active disease, and not all patients with positive blood, urine or tissue cultures have clinical illness.
CXR: Normal or diffuse interstitial infiltrates.
If suspect CMV and no diagnostic retinal exam, obtain PCR. If CMV PCR is negative it argues against CMV. In the presence of neuro symptoms, CSF PCR for CMV may be helpful; if positive it is more likely to be CMV disease than if PCR is negative for CMV

A: Rule out cotton-wool spots and progressive outer or acute retinal necrosis if CMV retinitis suspected. (Dilated retinal exam should be done by ophthalmologist emergently to prevent permanent vision loss.)
Rule out other gastrointestinal pathogens where GI disease is suspected
Rule out Pneumocystis pneumonia, in pulmonary disease
Rule out other causes of neurologic deterioration if CMV encephalitis suspected

P: LABS/PROCEDURES:

1. Ophthalmic exam with dilatation is diagnostic for CMV chorioretinitis
2. CMV in other sites must be documented by BAL, visualization with endoscopy, or tissue biopsy. Look for the presence of viral inclusions ("owl's eye cells") in biopsy material.
3. GI disease is diagnosed by endoscopy and biopsy. Patient will still need ophthalmology exam to R/O concomitant eye disease. Those with GI disease should also see dietician to prevent weight loss.
4. Consider LP with CMV PCR if polyradiculopathy/myelitis is suspected. CSF findings: pleocytosis with prominent polymorphonuclear leukocytosis and low to normal glucose are common
5. Since brain biopsy is the only confirmatory procedure for diagnosis of CMV encephalitis, diagnosis is made by exclusion. Brain biopsy is indicated in the patient with an encephalitis-like picture.
6. CMV serology is not helpful, since most adults have antibodies to CMV.

TX: Ganciclovir is useful in treating patients with CMV-related chorioretinitis, and may be useful in treating GI disease & pneumonia. Its use in other CMV-related disease is less well documented. Consider starting HAART only after 4 weeks of therapy for CMV, since symptom exacerbation (such as uveitis) due to immune inflammatory response may occur with HAART. After that time, however, if the client is willing to take HAART and a suitable regimen can be found, it should be started. If the client responds to HAART, the survival rate and decrease in disease recurrence confers a much more favorable prognosis.

Ganciclovir or valganciclovir dosage in patients with normal renal function:

1. **Induction:** Valganciclovir (Valcyte) 900 mg po bid with food x 21 days (this formulation quickly converts to ganciclovir in the body, and has good bioavailability). This regimen can only be used if patient is thought to be capable of adhering to it. Frequent follow-up is advised. Or, patient can be placed on IV drug, below.
   IV ganciclovir (Cytovene) 5mg/kg IV q 12 hrs. x 14-21 days. Place an indwelling longterm venous access.
2. **Maintenance:** Valganciclovir (Valcyte) 900 mg po qd; or
   IV ganciclovir 6-7mg/kg IV QD, for CMV retinitis

   Alternative: Oral Ganciclovir, 1000mg TID with food, after induction is completed and retinitis is stable. Generally not recommended due to poor bioavailability, and should not be used in patients with more sight-threatening disease (Zone 1--includes fovea, optic disc and areas nearby). It may be used in others, mainly as an adjunct to local therapy such as implants or intravitreal injections, but more rapid disease progression occurs.

Follow-up while on ganciclovir/valganciclovir:

The most serious adverse reaction to the ganciclovir family is bone marrow suppression, with neutropenia, leucopenia, anemia, and thrombocytopenia. Monitor CBC with WBC, differential, and platelet count every 2 weeks x 2 months on therapy. **An absolute granulocyte count of < 750 warrants discontinuation of the drug.** If this is necessary, appropriate alternative therapy is started to prevent progression until the granulocyte count is corrected. Colony-stimulating factors may be started (see below).

Neutropenia may be treated with G-CSF or GM-CSF (Neupogen) to allow for continued treatment with Ganciclovir. Patients whose neutropenia may be potentiated by sulfa may respond to leukovorin (folinic acid) 10 mg po qd.

Repeat dilated retinal exam q 6 weeks to assess response, re-induce or change therapy prn.

Note: Intraocular ganciclovir implants deliver 1.4 mcg/h for up to 8 months, and are effective against CMV retinitis. This modality is preferred for those patients with sight-threatening (Zone 1) disease. Unfortunately, disease in the other eye occurs in half the patients by the end of 6 months and nearly 1/3 experience visceral CMV disease. Patients with implants should be considered for systemic ganciclovir (IV using standard doses; or PO at 1 gm tid) as well. Other local therapies under investigation include intravitreal injection of ganciclovir or foscarnet, which would also require adjunctive systemic therapy.

Foscarnet (Foscavir) is generally reserved for breakthrough infection (clinical changes suggesting progression or reactivation of disease), or intolerance to ganciclovir, although some authorities consider it an acceptable alternative for initial treatment.

1. Foscarnet induction dosage: 60mg/kg IV q 8 hrs., or 90 mg/kg IV q 12 hrs., x 14-21 days
2. Maintenance: 90-120mg/kg IV QD (requires placement of indwelling IV access device) Hydration of at least 500 ml of fluid before each dose or concomitant with foscarnet infusion.
3. Adverse reactions: renal insufficiency, tetany due to calcium shifts, seizures or neutropenia common.

4. Monitor creatinine clearance at baseline to adjust dosage according to nomogram, and repeat if serum creatinine becomes elevated. Biochem profile, magnesium, CBC weekly x 1 month, then q 2 weeks if stable.

Alternative: Cidofovir (Vistide) may be used, at 5 mg/kg q week for 2 weeks, along with probenecid on infusion days, 2 gm po 3 hours before, 1 gm po 2 hours after, and 1 gm po 8 hours after the cidofovir infusion. Also, 1 liter of normal saline is given over 1 to 2 hours immediately before the cidofovir infusion to minimize renal toxicity. Maintenance is 5 mg/kg every two weeks along with probenecid and saline. Side effects from the probenecid are problematic, along with renal toxicity. Cidofovir is contraindicated in patients with baseline urinary protein 2+, serum creatinine 1.5, or creatinine clearance 55 ml/min. U/A must be checked prior to each dose (see Medications section and prescribing information). Additionally, intraocular pressure must be rechecked every 6 months, due to risk of ocular hypotony.

For patients who fail monotherapy with ganciclovir or foscarnet, combination therapy is sometimes used for re-induction:

Ganciclovir 5 mg/kg q 12 hours IV + Foscarnet 60 mg/kg q8h or 90 mg/kg q12h

Note: Watch for **retinal detachment** in any patient with CMV retinitis, which 50-60% of patients experience in the first year after diagnosis. Patients must report any vision loss immediately, and regular follow up with an ophthalmologist is required.

CMV maintenance therapy may be discontinued in some clients receiving HAART whose CD4 counts have been >100-150 for more than 6 months in response to HAART, but the decision must be made in conjunction with the ophthalmologist, considering:

a) Location of the retinal lesion;
b) Vision in the unaffected eye;
c) Feasibility of regular ophthalmologic exams (i.e., adherence to follow-up appts.)

Patients must be monitored for disease progression as well as immune reconstitution uveitis, and CD4 counts measured regularly**. Resumption of maintenance therapy would be needed if CD4 counts drop <100-150, or other signs of HAART failure.**

Note: **CMV encephalitis** is an endstage diagnosis. If a durable medical power of attorney, a will, plans for home care and terminal care have not been discussed, this diagnosis should prompt the clinician to initiate these conversations with the patient and caregiver. Refer to social worker, chaplain, or mental health clinician with experience in counseling on these issues if appropriate.

Patient Education:

1. People with CMV retinitis must expect to remain on suppressive therapy for life to prevent blindness, although patients with CMV esophagitis or enteritis usually improve with 2-4 weeks on induction therapy.

2. With GI disease, follow-up endoscopy is needed to verify regression of lesions before discontinuing therapy. Recurrence of symptoms warrants repeat of endoscopy, so let us know immediately if symptoms recur. We would need to biopsy and start back on induction therapy if CMV again shows up.

3. Adverse reactions to current therapies are common. (Offer assistance to cope with the possibility of therapeutic failure, and, in the case of CMV retinitis, with the threat of permanent loss of sight.)

4. Treatment of CMV retinitis only halts progression, and does not reverse the damage already done to the retina. Vision will not return to pre-CMV status.

5. Report any vision deterioration to provider immediately. Retinal detachment or progression of CMV must be treated immediately to avoid further vision loss.

6. Teach maintenance of indwelling venous access lines, if used; have patient return demonstration before discharge.

7 If you have not been on highly active antiretroviral therapy, it is usually best to wait a few weeks after starting treatment for CMV to avoid inflammatory problems due to resurgence of the immune system. Some patients who go on HAART have had good responses, with very low viral loads and rising CD4 cells. This helps the body fight CMV, and allows some patients to discontinue maintenance therapy.

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Drug manufacturers information, 2002

Dermatologic Staph Infections

Definition:

Staphylococcus aureus is the most common cause of bacterial skin infections in patients with HIV. Staph infection may present as bullous impetigo, cellulitis, folliculitis, hidradenitis suppurativa-like plaques, abscesses or ecthyma. Presentation and treatment are determined by the depth of the infection. Note also that staph infections can occur as complications of other skin pathology. Patients with HIV are at risk from superinfection and bacteremia from infections that, in other patients, might be thought to be trivial. Hospital admission for IV antibiotic therapy is indicated when systemic toxicity accompanies a staphylococcal skin infection.

S: Patient complains of itchy rash; inflammation of the skin and subcutaneous tissue; pustules or abscess. Query regarding constitutional symptoms, such as fever, which may suggest systemic spread. Review medications, supplements, and herbal preparations.

O: **PE: NOTE: THESE CONDITIONS MAY BE HIGHLY CONTAGIOUS. DURING EXAM &/OR CULTURE OF ANY SKIN LESIONS, THE HEALTH CARE WORKER IS ADVISED TO WEAR GLOVES, AND WASH HANDS THOROUGHLY AFTER REMOVAL.**

Bullous impetigo: facial, groin or axillary superficial blisters or erosions, often with yellow crusts.

Ecthyma: a superficially ulcerated "punched out" or eroded lesion with an extremely adherent crust. A purulent layer of material can usually be found under the crust.

Folliculitis: follicular pustules (pruritic, often very painful lesions) are visible on the face, trunk, in the axillae or groin. A tiny central pustule may be visible when the skin is stretched, although sometimes lesions are almost urticarial. These may extend below the skin surface, forming abscesses, or in rare cases, large, violaceous hidradenitis-like plaques with pustules. Note that excoriations may obscure primary lesions.

Cellulitis: findings include swelling, tenderness, erythema and warmth of localized tissue, most commonly on the face and extremities. May be associated with other types of lesions.

A: Rule out other causes of skin ulcerations/eruptions:

- candida albicans
- cutaneous hypersensitivity reactions to drug therapy
- streptococcal infection
- rule out DVT in lower extremity cellulitis
- KS
- pyogenic granuloma
- angiosarcoma
- drug reaction

P: **LABS:** Culture lesions if staph suspected. Perform microscopic examination of purulent material. In BA, stain biopsy specimen with silver stain to differentiate from KS. Blood cultures if bacteremia is suspected. Note that MRSA is common in some urban areas among HIV-infected patients.

TX:

1. Impetigo: Dicloxacillin (500mg PO QID x 7-14 days); cephalexin 500 mg po qid x 10-14 days; or Erythromycin 500 mg QID X 7-14 days. If patient has been on azithromycin for DMAC prophylaxis, staph infections are likely to be resistant to erythromycin and other macrolides.
2. Deeper or refractory/recurrent lesions: Add Rifampin, 600mg PO QD to above. Drain loculated abscesses and remove crusts on ecthymatous areas. Apply adjunctive topical therapy (clindamycin 1% solution or erythromycin 2% solution). Recurrent lesions may indicate nasal carriage, which can be treated with topical mupirocin or bacitracin ointment to anterior nares tid x 7 days.
3. If methicillin-resistant staph, use linezolid (Zyvox®) 600 mg po bid x 10-14 days for complicated skin infections; for uncomplicated MRSA infections use 400 mg po q 12 hours for 10-14 days.
3. If extensive cellulitis suspected, admit for inpatient IV antibiotic therapy (consult ID specialist).

Patient Education:

1. Wash area with antibacterial soaps (such as Hibiclens, Betadine or benzoyl peroxide wash).

2. Impetigo is highly contagious. Avoid hand contact with lesions, and do not allow other people to touch the areas.

3. If not improved in 3-5 days, return to clinic.

4. Instruct on safe performance of warm soaks in Domboro's solution if needed for discomfort/irritation.

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Manufacturer's product information, 2002

Esophageal Candidiasis

Definition:

A fungal infection of the esophagus caused by *Candida albicans*, or other species, such as *C. (Torulopsis) glabrata*, *tropicalis*, or *krusei*. Responsible for most cases of esophageal disease in AIDS. An AIDS-indicator condition.

S: **Patient complains of difficult (dysphagia) or painful (odynophagia) swallowing, "sticking" of food, or midline retrosternal pain, fullness, or burning. Odynophagia is often indicative of ulcerative esophageal disease, such as CMV, HSV, or idiopathic ulceration.**

HX: CD4 count < 200

Oral thrush (may or may not accompany this episode).

Weight loss secondary to eating difficulties.

O: **PE:** Document presence or absence of oral thrush, angular stomatitis, and any other oral cavity lesions. Note patient's weight. Check for fever, which argues against candidiasis, unless it is a comorbid condition with another OI.

A: Partial differential includes cytomegalovirus, herpes virus ulcerations, aphthous ulcers, lymphoma or KS. Other fungal entities *(Candida kruseii or Candida glabrata)* may not respond to fluconazole.

P: **PROCEDURES:**
Presumptive diagnosis can be made on the basis of a history of recent onset of retrosternal "food sticking" or pain in the presence of oral candidiasis. If systemic therapy is ineffective and symptoms persist, obtain endoscopy with biopsy, gram stain of tissue or exudate, and culture to rule out other causes of esophagitis.

TX:

1. If patient is able to swallow pills, Fluconazole 200mg po on day 1, then 100 mg po qd for three weeks, or two weeks after symptoms resolve. If fluconazole fails, endoscopy is indicated to R/O other causes of symptoms.
2. If able to swallow pills, Ketoconazole 200mg tablets PO BID until symptoms resolve (usually within 7-10 days). Note that ketaconazole interacts with many drugs, and generally should not be used with HAART regimens.
3. In the presence of endoscopic evidence of candidiasis and symptoms refractory to above oral therapies, IV amphotericin 0.5 mg/kg qd, fluconazole 400-800 mg qd or bid, itraconazole 100 bid, or itraconazole 200mg oral solution po qd x 14 days is indicated. Alternatively, caspofungin (Cancidas®), although approved for aspergillosis, appears effective for esophageal candidiasis, 70 mg loading dose followed by 50 mg IV qd.
4. Fluconazole suppressive therapy at 100-200 mg po qd may be considered for patients with multiple episodes of esophageal candidiasis, but azole resistance may occur with long-term use. Azole-resistant infections are treated with IV Amphotericin or Ampho lipid complex. Voriconazole and posiconazole, if available, may have some activity against fluconazole-resistant isolates; drug interactions may be problematic.
5. Refer to dietician.

Patient Education:

1. Take all prescribed medication, and notify care provider if symptoms worsen or side effects of therapy occur.
2. Plan meals that are soft, moist, easy to swallow and non-irritating.
3. Report recurrence of symptoms immediately.
4. Women on azole drugs should avoid pregnancy.

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Hepatitis C Infection

Background

HCV is a single-stranded RNA virus which is transmitted primarily through blood exposures, but can also be transmitted through sexual contact. In some populations of HIV-infected IDUs and hemophiliacs, up to 90% may also have HCV. In HIV+ men who have sex with men, around 15% have HCV; around 2 - 3% of monogamous heterosexual partners of HCV-infected people have HCV. Females have a 3-fold higher risk of HCV from unprotected heterosexual contact with an infected partner. Individuals with multiple partners and other STD risks have 4 – 6% risk of infection.

Course of disease: About 60 - 85% of people who become infected with HCV are unable to clear the virus and become chronically infected. Major manifestations are usually not seen in immunocompetent people for 15-20 years, although transiently elevated ALTs may occur during earlier stages. The virus can cause gradual hepatic fibrosis and eventual cirrhosis, endstage liver disease, and hepatocellular cancer (HCC). Death can occur from portal hypertension and esophageal varices coupled with thrombocytopenia and decreased coagulation proteins; decompensated liver disease; hepatocellular carcinoma, or some combination of these conditions. Patients with HIV tend to have more rapid disease progression.

Testing: HCV EIA tests are sometimes falsely negative in HIV+ patients, although the third version of the test is much more sensitive and specific; it is the least expensive and most helpful screening test currently available. The US PHS recommends that HIV+ people who test positive on the EIA should next be tested using HCV RNA technology. Falsely negative HCV viral loads are less common. Though the RIBA test is used for confirmatory testing in HIV-negative patients, it is less useful in HIV+ populations due to a high rate of indeterminate results**. Patients with a negative EIA who are suspected of having HCV should have HCV viral load testing.**

***Genotyping* for those with HCV** is also helpful in assessing likelihood of response to therapy, as well as determining duration of treatment for HCV. Genotype 1 patients have a 28% sustained virologic response to interferon alfa plus ribavirin for 48 weeks, whereas other genotypes have ~66% sustained virologic response. Pegylated interferon in combination with ribavirin produces better responses, although research in HIV+HCV co-infected patients is still underway.

Impact of co-infection on vertical HIV and HCV transmission: Women coinfected with HIV and HCV have a higher rate of transmitting HIV to their infants, in some studies showing a 10% (or greater) risk above that of women infected with HIV alone. Due to the HIV, they are also more likely to pass on the HCV to their infants. Approximately 20% of babies born to HIV+ HCV+ mothers may have HCV, versus 5-6% to infants of HCV+ women without HIV. Breastfeeding is not known to transmit HCV, although HIV-infected women are advised against breastfeeding due to risk of transmitting HIV.

Treatment for HCV: The NIH recommendations from June 2002 suggest that patients who are actively using alcohol, pregnant women, patients with untreated depression, renal disease, and those with advanced cirrhosis are not candidates for treatment. Trials of patients on methadone treatment have been satisfactory, and the NIH suggests that even patients who are using illicit drugs may be able to benefit from treatment and should be evaluated on a case-by-case basis.

Patients with higher risk of progression to cirrhosis should be higher priority for treatment. Although patients with HIV may have less of a response to therapy than those without HIV, people with higher CD4 counts tend to have better responses than those with lower counts. Risk is indicated by portal or bridging cirrhosis, with moderate inflammation and necrosis, measurable HCV RNA levels, and / or persistently elevated ALT levels. However, because ALT levels do not correlate with liver damage, and some patients with normal ALTs will have abnormal liver biopsies, many experts will treat those with normal ALTs. Liver biopsy is very useful for staging the patient prior to making decisions about HCV treatment. Before scheduling a biopsy, however, it is helpful to educate the patient about the success rates with their genotype, side effects, duration and logistics of treatment, so that the patient can decide whether he or she is willing to undertake the treatment program if it is indicated.

The most effective treatment for HCV in the presence of HIV, thus far, appears to be combination therapy with pegylated interferon alfa and Ribavirin. In HIV-negative patients, some 50% achieve HCV viral clearance on this combination. Clinical trials are ongoing in HIV-infected patients but preliminary results suggest similar response rates. Data suggests that early virologic response (minimum of 2 log decrease in HCV viral load 12 weeks into treatment) is predictive of sustained virologic response to treatment.

Interferon reduces CD4 counts without affecting HIV RNA. Neutropenia may be a significant adverse reaction to pegylated interferon among HIV-infected patients. Ribavirin interacts with several of the HAART drugs and is a known teratogen.

The decision of whether or not, and when, to undertake HCV treatment for people infected with HIV must be individually determined. Some experts begin with HAART with the idea that by improving CD4 counts they may improve response to HCV therapy. Others choose to treat HCV before initiating HAART in those with high CD4 counts and low HIV viral loads in order to simplify treatment and improve tolerability of HAART. It is best to consult with an HCV treatment expert to determine appropriateness and timing of HCV treatment.

Impact of HCV Infection on HAART: Some patients with HCV will experience worsening of their hepatic picture with HAART, although most experts still recommend starting HAART in these patients. This effect has been noted more often with ritonavir, although it has been a problem with regimens that do not contain ritonavir as well. It is worth noting that some HCV+ patients tolerate ritonavir, and even hydroxyurea, without significant LFT increase. Some other medications that are known to be hepatotoxic which can pose problems for people with impaired liver function include nevirapine, fluconazole, isoniazid, and azithromycin.

Patient Education:

1. Although Hepatitis C shows few symptoms for the first years, it can cause gradual damage to the liver and eventual liver failure. You can slow the damage by avoiding alcohol and any medications (including over-the-counter drugs and recreational drugs) that may tax the liver. Check with your pharmacist or health care provider if you have questions about a specific medication or supplement.

2. If you are considering child-bearing, you run a higher risk of infecting your baby with HIV and/or Hepatitis C, because each makes it easier to transmit the other. Preventive medicines to reduce the baby's HIV risk may not work the same in women with HCV. Also, if you take ribavirin and interferon, men and women will need to avoid pregnancy during and after the therapy is completed because of their potential to cause birth defects or abnormalities.

3. If you have children who were born after you were HCV-infected, consider having them tested as well. Even though their risk is low, they should be monitored.

4. Antiretroviral drugs are more likely to cause problems with your liver because of your HCV. If you start to take an antiretroviral regimen (HAART), your liver function tests will be watched carefully to be sure that your body is able to process the medicines.

5. Use safer sex to avoid exposure to Hepatitis B, which can greatly worsen your liver function if it is acquired in addition to HCV. Even if you have had the vaccine series for Hepatitis B, this can still be a risk.

6. Consider discussion HCV with your sex partner(s), and suggest testing for HCV.

7. You will need to receive two shots for Hepatitis A vaccination six months apart (if you haven't already had them), since Hepatitis A can cause more damage or death in the presence of HCV.

8. If you use injection drugs, consider going into a detox program to get off them. This will reduce the strain on your liver, protect you from bloodborne illnesses that can affect your liver, as well as help keep you from sharing HCV with others. If you are not ready to go off injection drugs, please let us know so that we can try to help you find a source for clean, single-use needles.

9. Hepatitis C is not spread by coughing, sneezing, hugging, sharing food and water, or other casual contact.

10. As with HIV, to avoid passing HCV on to others, do not share toothbrushes, dental appliances, razors, sex toys, tattoo equipment, injection equipment or personal care items that may have blood on them. Use safer sex to protect yourself and your partner(s).

11. The HCV treatment interferon alfa can cause flu-like symptoms, body aches, fevers, and depression. Most of these symptoms are treatable with medications. It is particularly important that you let us know right away if you are

experiencing depression. There are antidepressant medications that can help relieve this, but the medications take a couple of weeks to "kick in."

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Herpes Simplex, Mucocutaneous

Definition:

Herpes simplex (types 1 and 2) cause both primary and recurrent oral and genital disease. Most often a vesicular eruption of the oral or perioral area, vulva, mucous membranes, perianal skin, and occasionally inguinal or buttock areas, which develops into tender or painful ulcerated lesions frequently covered with a clear yellow crust. The typical painful vesicular or ulcerative lesions are absent in many patients. Many patients with HSV are unaware of their diagnosis, but an estimated 60% of patients with HIV have serologic evidence of HSV-2. (See current STD guidelines, first reference, for more complete discussion of diagnosis and management of HSV.) Persistent HSV eruption (> 1 month) is an AIDS-indicator diagnosis.

S: **Patient complains of eruption of red, painful sores on mouth ("fever blister"), genital or anal area.** May c/o burning, tingling, or itching prior to eruption of lesions.

HX: Blisters will rupture, ulcerate, generally crusting over and healing in approximately 7-14 days. They may be pruritic and are often painful. As immunosuppression progresses the lesions may recur more often, become larger or coalesce, and take longer to heal.

O: Punctate, grouped vesicular or ulcerative lesions on an erythematous base are present on the mouth, anus, or external genitals, or are visible on speculum or anoscopic exam. Lesions may coalesce and present as large painful ulcerations in the presence of severe immunosuppression, sometimes spreading to skin of thighs, lips, or face. Recurrent lesions may start atypically, first appearing as a fissure, pustule, or abrasion. Lesions within the oral cavity will usually appear on keratinized tissues such as the hard palate or gingiva.

A: Partial differential: CMV, aphthous ulcers, candida, syphilis, chancroid., drug-related eruption

P: **LABS:**

1. Obtain herpes virus culture from a freshly opened vesicle or the edge of the lesion for confirmation. Note that lesions that are >72 hours old or that are beginning to resolve do not show HSV in culture. (If in doubt of HSV status, serologic tests capable of distinguishing between HSV 1 and 2 have been available since 1999 to identify patients between outbreaks. Older tests that do not accurately distinguish HIV-1 from HSV-2 antibody, despite claims to the contrary, are still on the market. Serologic type-specific glycoprotein-based tests must be specifically requested, and are expensive. Newly-infected patients take several weeks to become seropositive.)
2. If culture is not available, perform a Tzanck smear from the edge of the ulcer, stain with Giemsa or methylene blue to reveal multinucleated giant cells. Note that this is fairly insensitive.
3. If cultures are negative and there is a high suspicion of HSV infection, skin biopsy may be taken from the edge of the ulcer, although this is also fairly insensitive at detecting HSV. Biopsy material may also be cultured.
4. Strongly consider an RPR for syphilis when presented with any genital, anal, or oral ulceration.

Treatment for episodic outbreak:

Acyclovir (Zovirax) 400 mg PO 3 to 5 times a day until ulcers heal, usually 5 to 10 days. Some treaters use acyclovir 200 mg po 5 times a day. This helps the healing of lesions but does not prevent recurrences.

Alternative therapy for episodic outbreak:

1. Famciclovir 500 mg po tid x 5-10 days. Acyclovir-resistant herpes viruses are generally famciclovir resistant as well. Dose reductions are required for renally-impaired patients.
2. Valacyclovir 1 gm po bid x 5-10 days. Not useful with acyclovir-resistant strains.
3. If herpes resistant to acyclovir, ganciclovir resistance is usually present as well. Foscarnet (40 mg/kg/q8h, IV) can be used until clinical resolution of severe/debilitating outbreaks unresponsive to the acyclovir family.

Chronic Suppressive Therapy:

Suppressive therapy with acyclovir if indicated by frequent/severe recurrences: 400 to 800mg po bid or tid, indefinitely. Famciclovir 500 mg po bid may also be used, as may valacyclovir 500 mg po bid. Note that one small study has shown patients infected with HSV-2 who are on suppressive therapy have 48% lower HIV viral loads. More studies are needed to determine limitations and other potential benefits of such therapy.

Patient Education:

1. HSV has no cure, and outbreaks may occur at intervals for the rest of your life.

2. HSV is easily spread through kissing (if mouth or lips infected) or sexual contact (oral, anal, vaginal). HSV is often transmitted when no lesions are present, so it is important to inform any sex partner of your infection prior to sex. Avoid all sexual contact while lesions are visible, because a lot of virus is present at those times. Safer sex practices may reduce transmission, depending on the location of infectious site. If transmitted, however, your partner will also have it for life.

3. Avoid use of occlusive dressing or ointments, which can prevent healing.

4. Acyclovir is most effective when taken early in the outbreak, so (for patients not on suppressive therapy) it is important to keep medication on hand and start treatment at first signs of eruption.

5. Explain the risk of neonatal HSV to all clients, including men: HSV in a pregnant woman can cause severe illness in newborns. Obstetricians and pediatricians should be informed of maternal infection or of maternal exposure to infected sex partner during pregnancy. HSV-infected individuals should avoid sexual contact with pregnant women who do not have HSV, since new HSV infection in pregnancy is much riskier to the baby than herpes infection acquired before the pregnancy.

6. For additional information and support for people with HSV, refer to helpline (404) 292-6364 (Atlanta area) or to national herpes hotline at 919-361-8488.

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Herpes Zoster/Shingles

Definition:

Shingles is a skin or mucosal infection occurring along a dermatome caused by the herpes zoster/varicella virus (HZV/VZV), representing reactivation of chickenpox. Zoster is frequently seen during the course of HIV infection and is particularly common in healthy appearing individuals before the onset of other HIV-related symptoms. It may be particularly painful, necrotic and hemorrhagic in the HIV-infected population. Disseminated infection usually involves the skin and the visceral organs. Outbreaks involving >2 dermatomes are considered disseminated.

S: Patient complains of painful skin blisters or ulcerations along one side of the face or body. Patient complains of loss of vision secondary to the appearance of facial lesions. Pain in a dermatomal distribution may precede the appearance of lesions by many days (prodrome).

HX: Duration of pain or blisters (avg. 2-3 weeks if untreated)
History of chickenpox (usually in childhood)

O: **PE:** Vesicular lesions with erythematous bases following dermatomes, may be bullous and/or hemorrhagic. Necrotic lesions may persist as long as 6 weeks. Neuralgias: excruciating/disabling pain. Dermatomal scarring (particularly in dark-skinned individuals). Particularly note lesions in the eye area, or tip of nose, along the trigeminal nerve. These represent a therapeutic emergency.

A: Rule out other causes of vesicular skin eruptions, (i.e., herpes simplex).
Assess contact exposure (see #3 below)

P: **LABS:** Herpes cultures from freshly opened vesicle, or biopsy from border of lesions

TX:

1. Treatment should begin within 72 hours of outbreak. Acyclovir (Zovirax) PO 800mg 5 times/day x 10 days may attenuate an HZV/VZV attack if started early. If new blisters are still appearing at the end of treatment, repeat course of oral therapy or consider intravenous tx.
2. **Consult an ophthalmologist STAT if lesions appear in the eye area or on tip of nose, or if patient c/o visual disturbances**, since VZV-related retinal necrosis can cause blindness.
3. HZV/VZV is contagious, and contact or airborne spread from vesicle fluid may cause chickenpox in non-immune people. If a child in the patient's household has HIV, consult the Pediatric HIV specialist a.s.a.p. (See post-contact chickenpox prevention note below)
4. Analgesics for pain; narcotics may be required.
5. The risk of post-herpetic neuralgia may be reduced by antiviral therapy, but if it occurs, will require special pain control techniques:
   a) Nortriptyline 10-20 mg q hs and increased to a level that controls pain or produces intolerable side effects. Other TCAs may be used (see *Pain Syndromes*, in Neuropsychiatric section.)
   b) Lidocaine 5% patches provide good local relief with minimal systemic absorption. Up to 3 patches may be applied simultaneously to the affected area, up to 12 hours in each 24 hour period.
   c) Gabapentin 100-300 mg po tid, up to 3600 mg daily total dose.
   d) Sustained release opiates may be required, up to 30 mg bid.
   See *Pain Syndromes* in Neuropsychiatric section for more options and specific recommendations

ALTERNATIVE TX:

1. Famciclovir 500 mg po q8h x 7 days may be used for milder (non-disseminated) cases. Acyclovir-resistant herpes viruses are generally famciclovir resistant as well. Dose reductions are required for patients with renal impairment.
2. Valacyclovir 1 gm po q8h x 7 days, starting within 72 hours of lesion eruption. Dose reductions are required for patients with renal disease. Viruses resistant to acyclovir are also resistant to valacyclovir.

SEVERE or NON-RESPONSIVE CASES:

1. IV acyclovir (10 -12 mg/kg q8h x 7-14 days; older adults require dosage reduction to 7.5 mg/kg; patients with renal impairment require further dosage modification) may be indicated in the severely immunocompromised, if the ophthalmic branch of the trigeminal nerve is affected, if dissemination has occurred, if patient does not respond to oral therapy, or if pain is intractable. Refer to infectious disease physician.

2. Acyclovir resistance may occur in patients previously treated with acyclovir, and foscarnet may be required for effective treatment.

Post-contact Chickenpox Prevention Note: Patients, including pregnant women, who have no history of chickenpox or shingles or who have no detectable antibody against VZV should be administered varicella zoster immune globulin (VZIG) as soon as possible but at least within 96 hours after close contact with a patient who has chickenpox or shingles. Even immunocompetent adults with primary VZV (chickenpox) develop viral dissemination to visceral organs. HIV-infected patients may develop encephalitis, pneumonia, or polyradiculopathy during primary (chickenpox) or reactivated (shingles) zoster.

Patient Education:

1. Bathe skin lesions in mild soap and water. In necrotic cases, warm moist compresses should be used 2-3 times a day to remove debris.

2. Antibiotic ointments may aid in the prevention of secondary infection, and may help keep dressings from sticking.

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Histoplasmosis

Definition:

An infection caused by *Histoplasma capsulatum*, a fungus that thrives in soil contaminated by certain bird and bat droppings. In the US, found most often along the Ohio and Mississippi River valleys, as well as in central, mid-Atlantic and south central states, Alabama to southwest Texas. It is also found in Quebec and Ontario, Canada; Mexico; Central and South America, Africa, Eastern Asia, and Australia. In highly prevalent areas, such as Indianapolis and Kansas City, ≥80% of the population has been exposed to infection through inhalation of airborne spores. The initial infection may be asymptomatic and a healthy person usually will not develop subsequent disease. However, immunosuppressed individuals may develop pneumonitis, skin, and/or CNS involvement. It is often a reactivation of latent infection, presenting late in the course of HIV disease (CD4+ <100/mm^3), and often disseminated. Progressive disseminated histoplasmosis (PDH) is an AIDS-defining illness. Within endemic areas, PDH represents 5% of OIs among AIDS patients; in hyperendemic areas, incidence is as high as 25%, but it can be difficult to diagnose because symptoms are non-specific. Also, clinicians may not suspect it, particularly when patients are seen in low-incidence areas.

S: **Patient complains of fever, weight loss, fatigue, cough, shortness of breath, skin lesions, adenopathy, CNS changes, or abdominal pain.**

HX: Duration of symptoms. Usually symptoms occur 1-2 months prior to presentation.
Significant risk of exposure (note that absence of reported exposure does not rule out histoplasmosis):

- Residence or travel in **endemic areas** (or coastal AIDS centers of NY, LA, SF, Miami);
- **Occupational hx:** farming, construction/remodeling;
- **Hobbies** that increase contact with caves, bird roosts/nests, or farm areas.
- **Soil** with high organic content and undisturbed bird droppings, such as that around old chicken houses and bird roosts.

O: *Histoplasmosis* presents with a variety of clinical features/syndromes, many of which may be non-specific:

CLINICAL MANIFESTATIONS

Respiratory (50-60%)

- Pneumonia
- Pneumonitis

Neurologic (18-20%)

- Meningitis, cerebritis
- Encephalopathy
- Focal parenchymal lesions

Dermatologic (10%)

- Follicular, pustular,
- maculopapular, or
- erythematous lesions

Constitutional (95%)

- Weight loss
- FUO

Septicemia Syndrome (10-20%)

- Hypotension
- Respiratory insufficiency
- Renal / hepatic failure
- Disseminated intravascular coagulopathy
- High fever

Unusual manifestations

- Pancreatitis
- Pericarditis
- Colonic ulcers / masses
- Thrombocytopenia
- Chorioretinitis
- Mesenteric / omental nodules

PE: Document fever. Common findings include enlargement of liver, spleen, and lymph nodes. Characterize skin and mouth lesions. Neurologic and respiratory exam if symptoms.

A: Partial differential includes other deep-seated fungal infections, such as blastomycosis and coccidioidomycosis; also mycobacterial disease (Mycobacterium avium or MTB); lymphoma

P: **LABS/PROCEDURES:**

1. Culture blood and bone marrow for histoplasmosis; Wright stain of buffy coat of blood to look for intracellular organisms.
2. Complement fixation or radioimmunoassay to detect histo antibody in 75% of cases with PDH (may not be useful in endemic areas, cannot distinguish old infection from active disease).

3. Wheat's *Histoplasma capsulatum* polysaccharide urine antigen test is sensitive and specific; available from Histoplasmosis Reference lab, 1-800-HISTO-DG
4. Biopsies of lymph nodes, liver, lesions, and lungs can be diagnostic in up to 50% of cases; bone marrow can be stained with methenamine silver to show the organism within macrophages
5. Observe blood studies for abnormal creatinine, pancytopenia (neutropenia <500/mm^3; thrombocytopenia <50,000/mm^3)
6. Check LDH and ferritin, as both may be elevated in disseminated disease. In particular, a ferritin level higher than 10,000 usually indicates DMAC, disseminated TB, or histoplasmosis.

Induction Therapy:

1. For **mild-moderate histoplasmosis without CNS involvement**, may start with itraconazole 200 mg po tid or 300 mg po bid x 3 days, then to maintenance dosing below. (Check pregnancy status in women of child-bearing potential before starting itraconazole, and assure appropriate birth control is being used. Note potential drug interactions with Itraconazole, especially rifamycins.) Histoplasma meningitis is treated with Amphotericin B only, due to poor itraconazole penetration into the CNS.

2. For **severe infection or CNS involvement**, admit for inpatient induction therapy: Obtain central venous access. Amphotericin B 50mg IV qd (or 0.5-1 mg/kg/day); after 7-14 days induction, patient may complete IV therapy as an outpatient. Patients should receive a total dose of 10-15mg/kg (up to 1.5gm), at 0.8mg/kg three times a week. Prehydrate patient. Creatinine clearance should be done if high BUN/creatinine. Follow urine histo antigen while on therapy.

Maintenance/suppressive therapy:

Weekly (or bi-weekly) infusions of amphotericin B, 1 mg/kg; or itraconazole, 200mg po bid. (Check pregnancy status in women of child-bearing potential before starting itraconazole, and assure appropriate birth control is being used.) Note potential drug interactions with itraconazole, especially rifamycins. **Patients who complete initial therapy should remain on chronic suppressive therapy.** There is insufficient evidence to warrant a recommendation to discontinue therapy when CD4 counts rise in response to HAART. If relapse is proven, re-induce with Amphotericin-B.

Patient Education:

1. This is an endstage disease, with a high mortality rate due to relapse. The patient must be counseled about the need for lifetime suppressive therapy and the prognosis. If a durable medical power of attorney, a will, plans for home care and terminal care have not been discussed, the care provider should initiate these conversations with the patient and/or caregivers. Refer to social worker, chaplain, or mental health clinician if needed.

2. Histoplasmosis is not transmitted from person to person, so no isolation is necessary.

3. Even with maintenance therapy, relapses can occur. Report symptoms immediately.

4. Avoid pregnancy while on itraconazole due to possibility of craniofacial and skeletal defects.

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HIV-Associated Nephropathy

Definition:

HIV infection can complicate existing renal disease and cause two types of pathologically distinct diseases, named HIV-associated nephropathy (HIVAN), and HIV-associated immune-mediated renal disease. One type of HIV-associated immune-mediated renal disease is thought to be caused by immune complexes with HIV itself; another is precipitated by Hepatitis C, which is very common in injection drug users and others with HIV. The HCV-related variety can present more like HIVAN, with nephrotic syndrome, hypertension, and rapid progressive renal insufficiency.

HIV-associated immune-mediated renal disease presents with low-grade proteinuria, hematuria, and mild or no renal insufficiency, and rarely progresses to endstage renal disease. Immune complexes are deposited in the glomeruli, leading to proliferative glomerulonephritis and renal insufficiency. In contrast, HCV-related immune-mediated disease can produce cryoglobulinemic glomerulonephritis and progress to endstage quickly.

HIV-associated nephropathy (HIVAN) has a poor prognosis, usually progressing from a focal glomerulonecrosis to endstage renal disease over the course of weeks or months. It produces a high-grade proteinuria and normal or large kidneys with increased echodensity on ultrasound, and occurs more often in males of African descent. Once thought related to drug use, now thought to be a direct effect of HIV gene expression in the kidneys. Fewer than half of HIVAN cases have a history of IDU; some cases have occurred in children with neonatal HIV. Treatment can be beneficial if instituted early.

S: Patient complains of easy fatigue, swelling of limbs and face, or generalized swelling.

O: PE may reveal peripheral edema. Blood pressure is usually normal. Check HCV EIA for positivity; and any trend toward renal insufficiency in previous labwork, such as protein in U/A or low albumin levels.

A: Partial differential diagnosis:

Prerenal	**Renal**	**Postrenal/Obstruction**
Dehydration	Acute tubular necrosis	Drugs
Sepsis	Amphotericin B	Sulfadiazine
NSAIDs	Aminoglycoside therapy	Indinavir
	Pentamidine	Acyclovir
	Foscarnet	Malignancy
	Acyclovir	
	Cidofovir	
	Radiocontrast	
	Hypotension	
	Acute interstitial nephritis	
	Sulfamethoxazole	
	Dapsone	
	NSAIDs	
	Rifampin	
	Glomerular diseases	
	HIVAN	
	HCV-related renal disease	
	Microangiopathic hemolytic anemia	

Rule out diabetes; obstruction (stones, neoplasia); hypertension; drug toxicity (IV pentamidine, NSAIDs, indinavir, foscarnet, amphotericin B, or aminoglycoside therapy); syphilis; extrapulmonary/renal TB, hypotension due to dehydration.

P: **LABS/PROCEDURES:**

1. Document renal insufficiency with BUN/ creatinine.
2. Order kidney ultrasound--increased echodensity is a common finding in HIVAN. Large-stone obstructions will also be visible, facilitating emergency referral.

3. Check U/A for urine sediment, microscopic hematuria (common with indinavir or sulfadiazine crystals). Obstruction may be in tubules, not visible on ultrasound; in these cases, vigorous re-hydration usually restores renal function.
4. U/A showing brown or granular casts suggests acute tubular necrosis. Nephritis most often shows WBCs, WBC casts, possibly slight proteinuria or hematuria.
5. If tuberculosis suspected, urine for AFB stain and culture each morning for 3 days. Pyuria or hematuria may also be present, though routine cultures will be negative. Renal TB may be concurrent with pulmonary disease.
6. Measure qualitative urine protein (dipstick); if protein >1+, order 24 hr. urine, test for protein and creatinine clearance; measure serum protein/albumin. In nephrotic syndrome, serum albumin is decreased, with increased serum cholesterol and peripheral edema; 24 hour urine will show >3 g protein.
7. Consider ANA and complement levels.
8. Renal biopsy may show focal segmental glomerular sclerosis, the most common pathologic lesion of HIVAN.

TX:

1. If renal tuberculosis or untreated syphilis is discovered, begin appropriate treatment for the underlying condition immediately.
2. Discontinue nephrotoxic medications.
3. Refer to nephrology early in the course of disease so plans may be made for dialysis if needed.
4. Institute fluid/volume status management and appropriate dietary restrictions (Na, K, Mg, Phosphorus); consult dietician for teaching of patient and family.
4. Use of steroids in patients with HIVAN can be beneficial; using prednisone 60 mg/day for 2-11 weeks decreased protein excretion and serum creatinine. ACE inhibitors, if used before significant decline in renal function, can decrease protein losses by decreasing glomerular filtration rate. Most patients progress rapidly to end-stage renal disease within 6-8 months, although earlier diagnosis of renal disease, more aggressive treatment, and continuous ambulatory peritoneal dialysis are changing this picture.
5. Highly active antiretroviral therapy may improve prognosis for HIV-associated nephropathy.

Patient Education:

1. HIVAN is an end-stage condition. It is important to discuss issues of disability and death with the patient at this point. It may be helpful to learn how the patient might feel about peritoneal dialysis, if that is a possibility for the patient.

2. Even though no therapy will cure this condition, special diet and medications can prolong your kidney function and your life.

3. Discuss antiretroviral therapy, if appropriate (see antiretroviral therapy and adherence information).

4. Consult with dietician to learn about renal diet and fluid restrictions. If you do not shop for and prepare your own food, bring along the person (or persons) who does this for you.

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HIV-Related Cardiomyopathy

Definition:

Cardiac disease has been reported in patients with AIDS based on clinical, echocardiographic and autopsy findings. While abnormalities are often clinically silent, patients have developed pericarditis, congestive heart failure, cardiomyopathy, focal myocarditis, abnormal wall motion, pericardial effusions and cardiac tamponade. Cardiac abnormalities may be caused by primary HIV infection of the myocardium, by superinfections or by the sequelae of drug therapy, substance abuse, renal impairment, or pulmonary disease. Pathogens such as CMV, toxoplasmosis, candida, EBV, and coccidiodes have been discovered to affect the myocardium. HIV-related cardiomyopathy is characterized by left ventricular dilatation and hypocontractility, which may result in heart failure and pulmonary congestion. Clinical cardiomyopathy is seen in 1-4% of AIDS patients.

S: **Patient complains of difficulty breathing, swelling, or chest pain at mid-sternum. Frequently patients are asymptomatic.**

HX: Previous cardiovascular disease
Hypertension
History of MI
Medications which cause mitochondrial toxicity, such as NRTIs
Substance abuse, especially cocaine, injecting drug use or alcoholism
Cardiotoxic medications, especially adriamycin chemotherapy or foscarnet
Significant emotional distress

O: PE: Check for pulsus paradoxus. Patient may exhibit signs compatible with congestive heart failure. Poor quality heart sounds, loss or displacement of PMI, tricuspid or mitral valve murmurs (related to valvular insufficiency), are early signs. Late signs include: signs of pulmonary congestion; peripheral edema.

A: Partial differential: pericardial effusion (most common etiology is TB or MAC); pericardial lymphoma or KS; other viral myocarditis; hypertensive cardiomyopathy. Refer immediately for tamponade or suspected lactic acidosis (see antiretroviral section for workup).

P: **LABS/PROCEDURES:**

1. Order PA and lateral CXR; may show globular, enlarged heart. Late signs: pulmonary edema.
3. Order EKG. Changes likely to be non-specific.
4. Echocardiography is important in determining cause and type of CHF (look for pericardial effusion, reduced ejection fraction).
5. If pericardiocentesis for large effusion or tamponade (or for any effusion accompanying clinical pericarditis with pain and fever) is performed, be sure that fluid is stained and cultured for microbiologic entities, including AFB, as well as examined for neoplastic cells.
6. If patient has been on HAART, check lipid profile.

TX:

1. If patient is not on HAART, it may be helpful to the patient's condition.
2. Diuresis with furosemide or other "loop" diuretics.
3. Afterload reduction with ACE inhibitor for clinical CHF with the typical dilated left ventricle and decreased systolic function. Note: if good left ventricular function with diastolic dysfunction, avoid ACE inhibitors and afterload reducers and instead use nitrates, diuretics, beta blockers or calcium channel blockers.
4. Bed rest, TED hose for edema.
5. Low salt diet: schedule with dietician for instruction.
6. Consider discontinuation of all unnecessary drugs, especially nucleosides (ddI, ddC or ZDV) for 4 weeks; repeat echo in 2 weeks. If drugs are the culprit, the condition is usually improved.
7. Consider digitalis and possibly coumadin if ejection fraction is very low (< 25%).

FOLLOW-UP:

1. Monitor electrolytes biweekly for 2 months after starting diuretics (especially potassium); then monthly after stabilization.
2. Appropriate follow up for treatment selected.

Patient Education:

1. Reduce stress, appropriate rest, and maintain adequate nutritional intake.
2. The diuretics prescribed to you will make you urinate more often.
3. Keep legs elevated and wear TED hose to decrease swelling in the legs and feet.
4. Avoid alcohol, cocaine, and other drugs, which can greatly worsen your heart's function.

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Immune Thrombocytopenic Purpura

Definition:

Immune thrombocytopenic purpura (ITP) is a hematologic disorder that occurs in up to 40% of patients with HIV, and tends to occur early in HIV infection. Symptoms such as spontaneous bleeding rarely occur until the count falls below 20,000 (normal range is 150,000 - 400,000), and even then patients with HIV rarely have significant bleeding compared to other groups, such as cancer chemotherapy patients. Thrombocytopenia may result from decreased platelet survival, decreased production or sequestration in liver, spleen, or other sites. Along with lymphadenopathy, ITP is now recognized as a common manifestation of HIV infection.

S: Most patients are asymptomatic. Patients may complain of gingival bleeding, rectal bleeding, epistaxis or the appearance of new bruises or red blotchy rash on the skin or palate.

HX: Alcohol use
Medications, including NSAIDs, TMP-SMX, pyrimethamine, ribavirin, rifabutin, ganciclovir or valganciclovir

O: Review previous platelet counts, since a precipitous drop could indicate an emergency situation such as thrombotic thrombocytopenic purpura or DIC. Check previous CBC for other cytopenias.

PE: Document presence of cutaneous or palatal petechiae, ecchymoses, epistaxis. Neuro exam; check for fever or localizing signs.

A: Partial differential for thrombocytopenia in HIV:

Drug-induced	neoplasia
ITP	infections involving bone marrow (MTB, fungus, parvo B-19, pneumocystis
TTP	although thrombocytopenia is usually concomitant with anemia in these
bone marrow failure	infections (See *Anemia* workup in Complaint-specific section)
aplastic anemia	alcohol-related

P: **LABS:**

1. Perform CBC, including WBC, RBC, HGB, HCT, MCV, MCHC, platelets and differential. Check stool for guaiac.
2. Order bone marrow aspirate; results should be consistent with peripheral destruction, and should show adequate to increased megakarocytes.
3. If febrile or renal/CNS dysfunction noted, consider DIC screen and examine peripheral blood smear for shistocytes which would indicate thrombotic thrombocytopenic purpura (TTP) and require hospital admission.

TX:

1. Discontinue all non-essential medications that may be responsible, especially ASA and other NSAIDs.
2. Institute combination antiretroviral therapy, if patient is not already on it and is an appropriate candidate.
3. No specific therapy if patient is asymptomatic and platelet count >20,000.
4. Consult to Hematology service when ITP is suspected, and for performance of bone marrow aspirate or biopsy. Bone marrow aspirate is particularly helpful in patients with unusual or severe presentations, or pancytopenia.
5. Most drug therapies provide temporary improvement at best. Possible therapies may include:
   a. IVIG 400 mg/kg every day for 4-5 days can be used to raise the platelet count quickly for 2-3 weeks, in cases of acute bleeding or if perioperative control needed.
   b. Rho(D) Immune globulin 25-50 micrograms/kg/day for one week, then 50 micrograms/kg IV q 3 wk prn. Has been effective in non-splenectomized, Rho(D)-positive patients.
   c. Prednisone 1mg/kg/day for a minimum of 21 days; relapse common. May be helpful in acute/emergency situation.
   d. Interferon alfa, 3 million units sq 3 x week has shown effectiveness in several small studies.
   e. Splenectomy rarely indicated, usually reserved for severe, recalcitrant disease; relapse may still occur, and post-surgical sepsis has occurred.
5. Monitor CBC with differential every 3-4 days, if any suspicion of active bleeding or oozing from nose, gums, etc. Follow-up platelet counts regularly to detect further decrease and monitor for improvements with therapy.

Patient Education:

1. Avoid dangerous activities, especially contact sports.
2. Stop all nonessential medications, particularly aspirin and NSAIDs.

3. Immediately report any bleeding to your care provider. Come to the clinic for any symptoms of occult bleeding, which may include weakness, fainting, SOB, DOE, black tarry stools, or tachycardia. Counsel patient and family to seek emergency treatment for neurologic symptoms, such as new H/A, N/V, or loss of consciousness.
4. Come to clinic when any sign of infection occurs (redness, swelling, pain, fever, diarrhea, vomiting, shortness of breath).
5. Use stool softeners to avoid straining. If GI bleeding is suspected, give occult-blood detection kits for home use.
6. Use a soft toothbrush to prevent gums from bleeding.

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Kaposi's Sarcoma

Definition:

An endothelial neoplasm of the skin, mucosal surfaces, and/or internal organs, the most common tumor seen in HIV, now considered to be caused by Human Herpesvirus Type 8 (HHV-8). Non-AIDS-related Kaposi's sarcoma (KS) is an indolent, multicentric tumor found in older Mediterranean or Jewish men. Epidemic, or AIDS-associated KS, is a fulminant, disseminated neoplasm, histopathologically identical to the other forms. Although they share the same cause, they markedly different in clinical presentation and progression. Kaposi's sarcoma is the AIDS-indicator disease of 15% of reported cases to date. Persons co-infected with HIV and HHV-8 are at risk of developing KS; it is most often found in men with a history of same-sex partners. The progression of disease may be rapid or slow, but the overall prognosis is poor. Epidemic KS is often disseminated, involving the skin, lymphatic system, lungs, GI tract, liver, spleen, and/or heart. AIDS treatment centers have reported a decline in new cases of KS since the advent of HAART.

S: Early disease: Patient finds a new asymptomatic, pigmented lesion or lesions on the skin, usually the head or neck, or oral cavity. This cutaneous presentation is most common, occurring in 95% of cases. Extensive oral involvement may cause tooth loss, pain and ulceration. Occasionally, patients may present with constitutional symptoms of weight loss (> 10%), night sweats, or persistent fever (> 2 weeks with no infectious cause).

Late disease: Patients with previously asymptomatic KS lesions may complain of swelling and pain in lower extremities, penis, scrotum or face. Pulmonary KS presents with intractable cough, bronchospasm, hemoptysis, chest pain, and dyspnea.

HX:
- Duration of lesion(s)
- Frequency of new lesion appearance
- Male with same-sex sexual partner(s)
- Injection drug use
- Female with bisexual male partner

O: **PE:** **Cutaneous:** To assist in the early diagnosis of KS, clinicians must examine the patient's entire skin surface. Findings will include subcutaneous nodular lesions on the skin or oral cavity. At first these are small (mm-cm in size), red-brown to violaceous (due to the vascular nature of the tumor), non-blanching, non-pruritic, painless and palpable. Lesions may occur anywhere on the skin; common sites include: face (under the eye and on the tip of the nose), behind the ear, the oral cavity, and on the extremities. Progressive cutaneous KS may present as tumor plaques (on the thighs or soles of feet), or as exophytic tumor masses, which can bleed, necrose or become extremely painful.

GI: Visceral KS may present in the larynx or anywhere in the GI tract (mouth, pharynx, stomach, duodenum). This disease is usually asymptomatic, except when it presents with intestinal obstruction or GI bleeding. It may also cause protein-losing enteropathy. A thorough oral examination (including hard/soft palate, gingiva, muco-buccal folds, oropharynx) is necessary to detect early oral KS. Visceral disease is uncommon in absence of extensive cutaneous disease.

Lymphatic KS: Lymphedema associated with KS usually appears in patients with visible cutaneous lesions, causes edema out of proportion to the extent of visible lesions. Common sites include the face, neck, penis, scrotum and lower extremities, and usually a whole contiguous area is involved. Disease may be striking and rapidly progressive.

Pulmonary KS: A rapidly progressive form, usually presenting with a severe, pneumonia-like picture. Patient will exhibit difficulty breathing, bronchospasm and/or cough and hypoxemia. CXR typically shows diffuse interstitial infiltrates, often accompanied by nodules and pleural effusion.

Review labs: CD4+ count can be relatively high (200-500/mm^3)

In the presence of constitutional symptoms, negative cultures for infectious agents.

A: Partial differential:
Cutaneous symptoms: cat scratch disease, bacillary angiomatosis (see *Bacillary Angiomatosis* protocol), dermatofibromas, granulomas, insect bites, stasis ulcers.
Pulmonary: PCP, CMV pneumonia, pulmonary lymphoma (rare).
GI: lymphoma, other causes of GI bleeding or enteropathy.

AIDS Clinical Trials Group staging for Kaposi's Sarcoma:

	Good Risk (0) ***All* of the following**	**Poor Risk (1)** ***Any* of the following**
Tumor (T)	Confined to skin and/or lymph nodes and/or nonnodular oral disease confined to the palate	Tumor-associated edema or ulceration Extensive oral KS Nonnodal viscera
Immune system (I)	CD4 cells ≥ 150/ mm^3	CD4 cells <150/mm^3
Systemic Illness (S)	No history of OI or thrush No "B" symptoms (unexplained fever, night sweats, >10% involuntary weight loss, or diarrhea) Karnofsky score ≥ 70	History of OI and/or thrush; "B" symptoms present Karnofsky score <70 Other HIV-related opportunistic illness

P: Since most people with KS do not die as a direct result of it, goals of treatment are generally palliation of symptoms and cosmetic improvement.

PROCEDURES:

1. Order punch biopsy of skin or mucous membrane lesions (via Dermatology, Oncology, or Oral Surgery consult) to verify diagnosis and rule out infectious or other neoplastic etiologies.
2. Order bronchoscopy and biopsy for pulmonary lesions if symptoms.
3. Order endoscopy and biopsy for GI lesions if abdominal pain or dysfunction.
4. Fine needle aspirate of lymph node.

TX: Refer to oncologist once biopsy is confirmed by pathology. If patient is not on HAART, evaluate for appropriateness of therapy and begin as soon as possible. Clinicians have noted non-progression of lesions, or even regression of KS, with effective antiretroviral therapy. This can be combined with other treatment modalities, depending on severity and speed of progression.

KS is a systemic illness, but options for local treatment of **limited disease** include:

- Observation: limited, stable cutaneous disease is often not specifically treated)
- Topical treatment with alitretinoin gel (Panretin) 0.1%
- Radiation therapy (limited use, more for localized or facial lesions; may cause mucositis when used for oral or pharyngeal lesions; or fibrosis and reduced skin elasticity as later complications.)
- Intralesional chemotherapy
- Cryotherapy
- Laser therapy

For more **extensive disease** (rapidly-progressing disease, lymphedema, intraoral or pharyngeal disease that interferes with eating, pulmonary KS, painful or bulky lesions):

- Intralesional chemotherapy with bleomycin, vinblastine, daunorubicin, or interferon alfa.
- Systemic antineoplastics: liposomally encapsulated doxorubicin or daunorubicin, vincristine, paclitaxel (Taxol), etoposide (VP16), or bleomycin; these can be used alone, or in combination for visceral or extensive cutaneous disease.
- Interferon alfa works well for patients with higher CD4 counts.
- Currently, studies are underway using antivirals effective against HHV-8, and angiogenesis inhibitors such as IL-2 and thalidomide.
-

Patient Education:

1. Patients with swollen or edematous lesions run the risk of developing cellulitis, when lesions can become infected and progress rapidly. Urge patients to take care not to injure these lesions, to keep them clean, and to call their care provider if lesions appear to be spreading or if swelling worsens.

2. Patients diagnosed with KS should be urged to return to clinic if they develop respiratory or GI symptoms.

3. Recommend cosmetic preparations to cover facial lesions. Suggest support group referral for patients having difficulty coping with their appearance.

4. The course of KS in AIDS is unpredictable, but is rarely a cause of death. Limited, stable disease is often not treated due to the toxicities of therapy.

5. HHV-8, the virus that causes KS, can be spread by deep kissing, unprotected sex, and sharing needles.

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Linear Gingival Erythema

Definition:

Inflammation of the gingiva, characterized by a 2 to 3 mm. band of intense erythema around the necks of the teeth. Also known as Red-Band Gingivitis, these erythematous changes are usually generalized, but may be confined to one or more teeth.

S: Patient complains of bleeding, tender gum tissue.

O: Oral exam reveals inflamed gingival tissues, which bleed easily upon manipulation. There are characteristic red bands of gingival tissue around the necks of one or more teeth.

A: Rule out Rapidly-Advancing Periodontal Disease, Necrotizing Ulcerative Periodontal Disease (NUP--see protocol), or Kaposi's sarcoma lesions.

P: **NOTE: DISEASE MAY PROGRESS RAPIDLY into Necrotizing Ulcerative Periodontitis (NUP). TREAT ORAL SYMPTOMS AGGRESSIVELY; refer to a dentist and carefully educate the patient to improve oral hygiene.**

TX:

1. PerioGard (0.12% chlorhexidine gluconate) rinse BID for two weeks will relieve some of the symptoms. It is important to refer to a dentist for a thorough dental prophylaxis (cleaning). If the combination of cleaning and PerioGard are not successful, it may be appropriate to add an antibiotic (preferably narrow-spectrum, which will leave the gram positive aerobic flora unperturbed) such as:
   Metronidazole 500 mg po BID x 7 - 10 days (Note that patients on ritonavir may experience symptoms due to the small amount of alcohol in the capsules) **or**
   Augmentin 875 mg po BID x 7 - 10 days

2. Factor replacement for hemophiliacs prior to all dental procedures, including cleaning.

Patient Education:

1. Good oral hygiene is CRITICAL to arresting gum and tooth loss. Brush and floss after every meal.
2. Get your teeth cleaned professionally at least every 6 months.
3. **Do not drink alcohol while taking metronidazole, and for at least 24-48 hours after last dose. If on ritonavir, note that some people experience symptoms. Please call if you have nausea or vomiting.**
4. **Do not eat or drink for 20 minutes after rinsing with PerioGard.**

References:

Lamster IB, Grbic JT, Mitchell-Lewis DA, et al. New concepts regarding the pathogenesis of periodontal disease in HIV infection. *Ann Periodontology* 1998 Jul;3 (1):62-75.

Yeung SC. HIV infection and periodontal disease. *Ann R Australas Coll Dent Surg* 2000 Oct;15:331-334

Molluscum Contagiosum

Definition:

A benign viral infection of the skin, caused by a pox virus and transmitted by direct contact. Molluscum presents as flesh-colored, white or yellow hemispherical papules, 2-5 mm in size, sometimes with white cores in their umbilicated centers, often found on head or neck. The infection is more common in symptomatic or advanced HIV disease, and occurs in up to 20% of AIDS patients. In immunocompetent patients, lesions often resolve within 6-12 months, after the host develops immunity to the virus. In persons with HIV, there is a strong correlation between the number of lesions, their resistance to treatment, and the degree of immunocompromise.

S: **Patient complains of new or increased acne-like lesions on the face, upper trunk or genitals.**

HX: No complaints of pain, itching or burning are associated with these lesions. If genital, they are sexually transmitted; patient may recall such lesions on the genitals of a previous partner. Query about fever or other systemic symptoms.

O: **PE:** Clinical examination is generally diagnostic for Molluscum. Note presence, distribution and number of flesh-colored papules. Look for umbilicated lesions with white centers; transverse illumination of papules shows opaque center.

A: Partial differential: Disseminated cryptococcosis or other fungal infection, which may superficially resemble Molluscum. STDs, especially syphilis, if in the genital area.

P: **LABS:** If cryptococcosis is suspected, obtain serum cryptococcal antigen or skin biopsy. In genital infection, evaluate for the presence of other STDs (especially syphilis).

TX: Molluscum is difficult to eradicate in HIV-infected clients, and lesions often recur. Treatment is only indicated in the presence of bothersome or distressing lesions, and may need to be repeated every 2-3 weeks until lesions are resolved. Significant improvement is seen after highly effective antiretroviral therapy is started. Refer to a dermatologist for evaluation and treatment. Therapeutic options include:

a. Highly active antiretroviral therapy, if patient is an appropriate candidate;
b. Cryotherapy with liquid nitrogen;
c. Removal of the molluscum body at the core of each lesion, using a large gauge needle;
d. Electrosurgery or light electrocautery;
e. Cantharidin topical therapy or peeling agents such as salicylic acid.
f. Topical Retin-A applied at HS may help prevent new lesions but does not help established lesions; cannot be used on genitalia or eyelids.

Patient Education:

1. Molluscum infection is benign; if not treated and patient can manage its cosmetic effects without undue anxiety, s/he can be reassured that it doesn't present a risk to other body systems.
2. Avoid shaving in areas with lesions, as they can be spread to other sites.
3. Molluscum infection is sexually and non-sexually transmissible through direct contact with lesions. Review barrier precaution use/negotiation.
4. If the dermatologist prescribes topical therapy with Retin-A or cantharidin, don't use these drugs on the genitals or around the eyes, since they can be very irritating to such sensitive skin.

References:

Chin J. *Control of Communicable Diseases in Man, 17th Ed*. Washington, DC: American Public Health Association, 2000.

Appiah YE, Gross PR. Skin manifestations of HIV infection. In Buckly RM, Gluckman SJ (Eds) *HIV Infection in Primary Care* 2002. Philadelphia: WB Saunders: 120-121.

Berger TG. Dermatologic care of the AIDS patient. In Sande MA and Volberding PA (eds) 1999. *Medical Management of AIDS, 6 ed.* Philadelphia, WB Saunders, 185-194.

Mycobacterium Avium Complex

Definition:

Disseminated Mycobacterium avium complex (DMAC) is an opportunistic infection caused by the Mycobacterium-avium intracellulare (MAI) microorganism. These organisms occur worldwide, and have been isolated from soil, water, animals, birds and foods. The estimated prevalence of disseminated MAC disease is 15-25% of patients with advanced HIV infection; this epidemic has arisen concurrently with the AIDS epidemic. Unlike Mycobacterium tuberculosis, DMAC results from primary infection with the organism, not reactivation. DMAC (disseminated Mycobacterium avium complex) is diagnosed when the organism is isolated from blood, lymph nodes, bone marrow, or liver. While MAC colonization occurs in many patients, disseminated disease occurs late in HIV disease, contributing to general disability, cachexia and death. Prophylaxis for MAC can prolong life and prevent associated morbidity in patients with late-stage AIDS.

S: **Patient complains of one or more of the following symptoms: persistent fever, night sweats, weight loss, anorexia, chronic diarrhea, weakness, fatigue, and/or abdominal pain. Fever may also be cyclical, normal during day.**

HX: Probe for symptoms above, other symptoms of infection
Assess Karnofsky score, whether diminished function in performing ADL

O: **PE:** Document fever, weight loss, presence of enlarged or tender liver or spleen, or abdominal tenderness. Skin pallor and relative tachycardia may suggest anemia; jaundice may suggest extrahepatic obstruction (rare).

LABS: CD4+ lymphocyte count usually < 50/mm^3
Review CBC, chemistries. In the presence of increasing anemia and/or leukopenia, suspect MAC. Alkaline phosphatase is elevated in about one-third of patients.

A: Rule out other infectious or neoplastic causes of constitutional symptoms, anemia or organomegaly. Partial differential would include:

Mycobacterium tuberculosis	Pyogenic abscess
Cytomegalovirus	Lymphoma
Deep seated/disseminated fungal infection	Other septicemia

P: **LABS:** To establish the diagnosis, Mycobacterium avium must be isolated from a normally sterile site. Patients with Mycobacterium avium cultured from sputum, bronchial wash or stool may only be colonized and should have a blood isolator tube drawn for AFB culture to determine if dissemination has occurred.

1. Culture blood in an isolator tube for AFB.
2. Order serum alkaline phosphatase, hematocrit and hemoglobin, if not done recently.
3. CT scan of chest and abdomen may be helpful to look for intra-abdominal and mediastinal lymphadenopathy and verify hepatosplenomegaly.
4. If blood cultures are negative and MAC is suspected, biopsy lymph node, liver or bowel (endoscopy) to establish the presence of DMAC by culture and microscopic visualization. If evidence suggests pulmonary MAC, obtain CXR and BAL. Positive biopsy specimens will show acid-fast organisms and a weak inflammatory response.

TX: **Single-drug regimens for DMAC are contraindicated**. The USPHS recommends clarithromycin 500 mg BID, or azithromycin 500-600 mg QD; **PLUS** ethambutol* 15 mg/kg po qd; some clinicians recommend the addition of a third drug, either rifabutin (300 mg po qd) or a quinolone (such as ciprofloxacin 750 po bid or ofloxacin 400 mg po bid). If rifabutin is used with indinavir, nelfinavir, amprenavir, or lopinavir, the dose of rifabutin should be decreased to 150 mg po qd; the indinavir increased to 1000 mg po q8h, as is nelfinavir. If ritonavir is used with rifabutin, the RFB dose is 150 mg q o d, or three times a week. If rifabutin is used with efavirenz, the rifabutin dose must be increased to 450 - 600 mg/day. Rifabutin also decreases serum clarithromycin levels. **Neither delavirdine nor saquinavir (unless SAQ boosted with ritonavir) should be used with rifabutin.** Boosted saquinavir requires rifabutin adjustment the same as for ritonavir, to 150 mg 2 - 3 times a week. (See drug interaction table in the *Mycobacterium tuberculosis* guideline for more complete information.)

Since the immune enhancement from HAART may cause a paradoxical inflammatory response if started during active DMAC infection, it may be helpful to start treatment for DMAC for about a month before adding HAART, if

patient is a candidate for it (see *HAART* in Antiretroviral section). This also helps distinguish between reactions to DMAC treatments and HAART . Avoid drug interactions between antiretrovirals and some antimycobacterial drugs, as noted above.

If patient is **not responding to treatment after 2-4 weeks of therapy**, assess adherence, and consider adding one or more drugs (ciprofloxacin, ofloxacin, amikacin).

Treatment for DMAC is generally required for the remainder of the patient's life; although if the patient has completed at least 12 months of DMAC treatment, no longer has symptoms, and responds well to HAART (showing a prolonged [$\geq$ 6-month] increase in CD4 counts above 100/mm^3), it may be reasonable to discontinue DMAC therapy. If this is done, the patient must be carefully monitored for any drop in CD4 counts, or symptoms consistent with recurrent disease. Some clinicians verify negative AFB cultures before discontinuation of therapy.

Treatment should be resumed if CD4 count drops below 100/mm^3, or if symptoms recur.

Refer to dietician to maintain weight.

Patient Education:

1. Medications will not eradicate infection, but should decrease symptoms and improve quality of life. Response to treatment may take up to four weeks. If medications are discontinued, the disease almost always recurs, unless your CD4 count has come up in response to HAART.
2. HAART (if patient has not already failed tx) will help your body fight HIV so that it can more effectively control DMAC infection. (See *Antiretroviral therapy* and adherence information.)
3. Contact clinician immediately if you notice abdominal discomfort, or vision changes on these medications
4. DMAC is a late-stage HIV opportunistic infection. Clinician should discuss preparations for disability care and death. (Referral to a social worker, mental health clinician, or chaplain experienced in such issues may be appropriate.)
5. If gastrointestinal symptoms increase on treatment, call the clinic.

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Mycobacterium Tuberculosis

Definition:

An opportunistic infection caused by *Mycobacterium* tuberculosis (MTB), an aerobic, acid-fast bacillus. It is spread almost exclusively by the respiratory route, as a patient with pulmonary TB coughs, sneezes, sings or talks. As aerosolized MTB bacilli enter susceptible lungs, they multiply, and are transported by alveolar macrophages to the regional lymph nodes. Hematogenous dissemination occurs from the lymph nodes. Exposure to MTB can result in latent infection, which can reactivate to clinical disease in individuals whose cell-mediated immunity becomes compromised by aging, malnutrition, chronic disease, or HIV infection. HIV infection is the most potent co-factor for progression from latent infection to active disease. The observed mortality rate for HIV-infected persons with TB is approximately four times greater than in non-HIV-infected persons.

Groups at highest risk of developing TB include people with HIV; injecting drug, alcohol or cocaine users; homeless or incarcerated individuals; recent immigrants from high prevalence areas; children living with adults in these groups; and the corrections, health and human services workers who care for them. In the developing world, TB is the leading cause of AIDS-related death due to opportunistic infection. Tuberculosis is preventable and generally curable, but can be fatal if left untreated. Inadequate treatment produces multi-drug resistant strains (MDR-TB), which can be fatal to both the source patient and those who acquire active disease from them, including their health care providers. Of note: patients from Ivory Coast, Latvia, Estonia, Russia, the Dominican Republic, and Argentina are more likely to have been exposed to MDR-TB.

Patients with HIV infection can develop active TB from either latent infection activated by immune suppression, or from primary exposure to the organism. Primarily a pulmonary disease in the non-HIV-infected, MTB frequently presents as extrapulmonary disease in patients co-infected with HIV. Multiple systems may be involved, including the bone marrow, lymphatic system, CNS, liver, genito-urinary tract and blood, among others. A further caution to providers is that active MTB may cause selective anergy to the TB skin test. **Note that for an HIV-infected patient, an induration response of ≥ 5 mm at the PPD site is considered a positive test.** This opportunistic infection may occur earlier in the course of HIV disease, often arising when CD4+ counts are only slightly below normal. As HIV disease progresses and immune function decreases, TB presents in a more disseminated manner.

Note: GIVEN THE INCREASED SUSCEPTIBILITY OF HIV-INFECTED PATIENTS TO TUBERCULOSIS, PATIENTS WITH COUGH SHOULD BE KEPT IN RESPIRATORY ISOLATION UNTIL TB IS RULED OUT BY ≥ 2 SUCCESSIVE NEGATIVE FLUOROCHROME EXAMINATIONS OF CONCENTRATED SPUTUM.

PATIENTS WITH ACTIVE PULMONARY TB (EVEN THOSE WITH HIV) SHOULD NOT BE IN THE SAME CLINIC AREAS AS (OTHER) HIV-INFECTED PATIENTS!

S: **Symptoms are often non-specific. Patient may complain of persistent fever, night sweats, weight loss, fatigue, anorexia, productive cough, dyspnea. Extrapulmonary TB can be a very elusive diagnosis.**

HX: Previous PPD date and result (note that in some active TB cases, the PPD positivity rate is only 20-30%)
Exposure to known TB-infected partner, contact, or household member
Documented HIV infection
Substance use history (alcohol, heroin, cocaine)
Recent emigration (particularly from the Caribbean, South & Central America, Southeast Asia, and African nations)
Living conditions (homelessness, overcrowding, incarceration)
Occupational risk (health care, corrections or human services worker)
Chronic disease conditions (diabetes, alcoholism, ESRD)

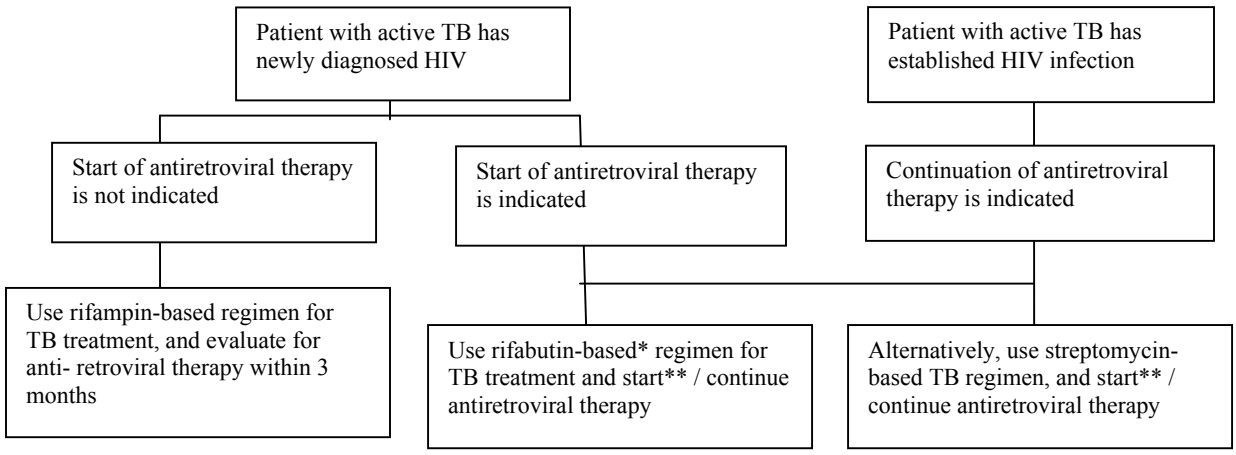
O: **PE:** Document weight loss, lymphadenopathy, respiratory findings.

A: Partial differential:
Other infectious and neoplastic causes of constitutional symptoms, including PCP, MAC, lymphoma.

P: LABS/PROCEDURES: **Culture of sterile sites is diagnostic. Positive AFB sputum smear is presumptive.**

1. Order PPD tuberculin skin test. Only 10-30 percent of HIV-infected patients with TB will have positive PPD tests. Any induration (raised area) should be evaluated further; ignore erythema. False negative PPDs are more common in HIV-infected patients, especially when severely immunocompromised, as well as those with overwhelming TB disease. Generally, an induration of ≥ 5 mm is considered positive in HIV-infected patients, but smaller ones in this setting deserve attention.
2. A "booster" tuberculin test may be placed 7-28 days after an initial negative test. A positive booster test is considered evidence of infection with TB (either latent infection or active disease), as is any positive PPD.
3. Obtain chest X-ray. Chest radiographs in HIV-infected patients with active tuberculosis may not show the classic upper-lobe infiltrates, particularly if CD4 is < 300/mm^3. Rather, they often reveal diffuse, interstitial or lower-lobe infiltrates, or hilar or mediastinal adenopathy.
4. Obtain specimens for AFB smear and cultures depending on symptoms: induced sputum, urine, blood, biopsies of lymph nodes, bone marrow or liver. Culture results take 6-8 weeks**; treat presumptively whenever there is strong epidemiological and clinical evidence of mycobacterial disease is found in a patient with HIV infection. Sputum smears and cultures are positive in 50-70% of HIV-infected patients with pulmonary TB, and negative results can be misleading.**
5. Get LMP date and obtain pregnancy test on females of child-bearing potential.

TX: 1. **Recommendations from CDC for patients with drug-susceptible TB:**



* see Drug Interactions Table for contraindications and dose adjustments.
** When HAART is started concurrent with treatment for active TB, paradoxical reactions are more likely to occur due to enhanced immune response. Some experts recommend postponing HAART until symptoms of TB are well controlled, usually 4-8 weeks.

Adapted from CDC: Prevention and treatment of tuberculosis among patients infected with human immunodeficiency virus: Principles of therapy and revised recommendations. *MMWR*, 1998; 47 (No. RR-20), 25.

2. **NOTIFY THE HEALTH DEPARTMENT OF EVERY NEW CASE OF ACTIVE TUBERCULOSIS. There is an obligation to ensure that household contacts, especially children, are screened for TB. First isolate should have drug-susceptibility testing performed. Results should be reported to the Health Department.**

3. **Directly Observed Therapy (DOT) and other strategies that promote adherence to TB therapy should be used for all patients with HIV-related TB. DOT works!**

4. **Pyridoxine** (vitamin B6) 25-50 mg once daily or 50-100 mg twice weekly should be given to all HIV+ people who receive isoniazid to reduce the potential for peripheral neuropathy.

5. For patients who are receiving therapy with protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors, the initial 2-month phase of a 6-month TB regimen should be isoniazid, rifabutin, pyrazinamide, and ethambutol. These induction drugs are given:
   a) Daily for 8 weeks, or
   b) Daily for at least the first 2 weeks, followed by three-times-a-week dosing for 6 weeks

   The second phase of treatment consists of isoniazid + rifabutin given daily or thrice-weekly for 4 months.

6. **For patients who are not candidates for antiretroviral therapy**, or for those patients not starting HAART along with TB therapy, the preferred treatment continues to be a 6-month regimen consisting of isoniazid, rifampin, pyrazinamide, and ethambutol (or streptomycin.) For the two-month induction phase, these drugs are given:
    a) Daily for 8 weeks, or
    b) Daily for at least the first 2 weeks, then thrice-weekly dosing for 6 weeks

    The second phase consists of isoniazid and rifampin given daily or 3 times a week for 4 months. Alternatively, isoniazid, rifampin, pyrazinamide, and ethambutol (or streptomycin) also can be given 3 times a week for 6 months.

7. **For patients not already on HAART:** Due to the possibility of **paradoxical reactions** from immune enhancement, some experts recommend delaying HAART until symptoms of TB are well controlled, usually 4-8 weeks. If HAART is begun concurrent with treatment for TB and a mild paradoxical reaction occurs, it can usually be managed without changing HAART or TB treatment. However, severe reactions (airway compromise from enlarging lymph nodes, sepsis-like syndromes, and enlarging serosal fluid collections such as pericarditits, pleuritis, peritonitis) may require hospitalization and possibly a short course of steroids (no more than 4-6 weeks).

8. For patients who **cannot use rifamycins**, the initial 2-month phase of a TB regimen consists of isoniazid, streptomycin,* pyrazinamide, and ethambutol** administered:
    a) Daily for 8 weeks, or
    b) Daily for at least the first 2 weeks, followed by thrice-weekly dosing for 6 weeks.

    The second phase consists of isoniazid, streptomycin,* and pyrazinamide administered 3 times a week for 7 months.

9. **Because the most recent recommendations for antiretroviral therapy advise against interruptions of therapy, and because regimens without rifampin are available, previous TB options that allowed stopping PIs in order to use rifampin are no longer recommended.**

* Streptomycin must be administered for the total duration of therapy, or for at least 4 months after culture conversion, usually 6-7 months after the start of treatment. Some experts suggest that when streptomycin is not included in the regimen for the entire 9 months, it should be replaced with ethambutol, and the duration of treatment should be extended from 18 months to 12 months after culture conversion. Alternatives to streptomycin are the injectable drugs amikacin, kanamycin, and capreomycin. Baseline audiometry and renal function tests are required before starting aminoglycosides.

** Prior to starting ethambutol, perform a baseline visual acuity exam and test for red-green color perception.

TB-HIV Treatment Considerations:

1. When possible, patients with HIV and active TB should receive TB treatment from the local or county Health Department. Close consultation between the Health Department and HIV clinician is required to ensure appropriate care, for HIV treatment, medication dosage adjustments, response to therapy, and other factors.

2. **Baseline labs** and testing before starting TB treatment would include recent liver function tests, bilirubin, creatinine or BUN, and CBC with platelet count. If pyrazinamide will be used, a uric acid level should be checked. Ethambutol requires baseline visual acuity and red-green color perception with monthly monitoring.

3. HIV-infected **pregnant women with confirmed or suspected TB disease** should be treated without delay. Regimen should include a rifamycin. Although pyrazinamide is not generally recommended in the US due to inadequate teratogenicity data, the benefits of a TB treatment regimen that includes pyrazinamide outweigh potential PZA-related risks to the fetus of an HIV-infected woman. Aminoglycosides and capreomycin are contraindicated for all pregnant women due to potential adverse fetal effects.

4. **Rifampin-resistant disease:** the nine-month regimen should consist of a 2-month phase of isoniazid, streptomycin, pyrazinamide, and ethambutol. The second phase should consist of isoniazid, streptomycin, and pyrazinamide for seven months. Careful supervision and adherence to therapy are important in this case, since multi-drug resistance can develop for these patients. Consult with TB experts, local health department.

5. **Multi-drug resistant disease** (MDR), that is, resistance to rifampin and isoniazid, should be managed by or in consultation with physicians who are experienced in management of MDR-TB (see #13 below). Early aggressive treatment with appropriate regimens, based on the known or suspected resistance pattern of the MTB isolate, markedly decreases deaths associated with MDR-TB. Recommended duration of treatment for MDR-TB in HIV

infected patients is 24 months after culture conversion, with post-treatment follow-up to detect relapse every 4 months for another 24 months. An aminoglycoside or capreomycin, plus a fluouroquinolone are commonly included in MDR-TB treatment. DOT should always be used for these high-risk patients, along with whatever steps are needed to ensure adherence to therapy. Consult with an HIV-TB treatment expert (see #11 below)

6. Treatment of **extrapulmonary disease**, such as TB meningitis; tuberculous lymphadenitis; pericardial, pleural, or disseminated TB, includes the same basic principles as treatment of pulmonary TB. Consult with an HIV-TB treatment expert (see #11below)

7. Rifampin is contraindicated during treatment with most protease inhibitors. Patients may be placed on rifabutin, as a rifampin substitute, along with indinavir or amprenavir (see table below). Monitor patients on rifabutin for uveitis, leukopenia, and arthralgias. Note that the effect of rifampin as a CYP450 inducer, which lowers serum levels of PIs and NNRTIs, persists for at least 2 weeks after discontinuation of rifampin. **Clinicians who plan to start therapy with PIs or NNRTIs should wait at least 2 weeks after the last dose of rifampin.**

8. **Routine follow-up**: **Repeat sputum smears every 2 weeks until negative.** Repeat AFB culture if persistently positive, and consult infectious disease specialist. After the initial period, see patients every month for clinical evaluation, physical exam, and lab follow-up: LFT's, sputum. Patients on ethambutol need monthly visual acuity; for those on aminoglycosides, monitor renal function. Get expert consultation if treatment failure suspected. Patients with MDR-TB need closer monitoring, expert consultation, and longer follow-up (see #5 and #13.)

9. **Malabsorption of TB drugs** has occurred in some patients with HIV, and has occasionally been associated with TB treatment failures and development of drug resistance to TB drugs. Patients with drug failure or relapse should be evaluated first for adherence and other factors such as drug interactions; but if other causes are ruled out, may benefit from drug level monitoring. Obtain expert consultation.

10. **Interruptions in TB therapy** due to toxicity or other reasons should be taken into consideration when calculating the end-of-therapy date for each individual patient. Completion of therapy is based on total number of medication doses administered and not on duration of therapy alone. Consult with TB expert and/or local Health Department.

11. Refer to http://www.cdc.gov/nchstp/tb for updated guidelines for TB management. **Expert consultation** is recommended when managing difficult cases and MDR-TB. CDC's TB Division, at (404) 639-8140, or 1-800-4TB DOCS, New Jersey Medical School National TB Center Information Line, are possibilities.

Drug Interactions: Dosage Adjustments for Concurrent Treatment with ARVs and Rifamycins

	Rifampin/ARV Doses	Rifabutin/ARV Doses
Saquinavir (softgel, brand Fortovase)	**Contraindicated** unless SQV used with RTV, then no dosage changes	**Not recommended*** unless using SQV with RTV, then use Rifabutin 150 mg 3 times per week/no change*
Nelfinavir	**Contraindicated**	150 mg qd/1000 mg tid or 1250 bid
Indinavir	**Contraindicated**	150 mg qd/1000 mg tid
Amprenavir	**Contraindicated**	150 mg qd (or 300 mg 3 times per week)/no change
Lopinavir/ritonavir	**Contraindicated**	150 mg qod (or 3 times per week)/no change
Ritonavir	No dosage change	150 mg qod (or 3 times per week)/no change
Delavirdine	**Contraindicated**	**Contraindicated**
Nevirapine	**Not recommended**	No dosage changes; insufficient data
Efavirenz	No dosage changes	450 – 600 mg qd or 600 mg po 3 x per week/no change

*Saquinavir (unless boosted with ritonavir) should not be used with rifabutin, because rifabutin decreases saquinavir levels by ~40%. No dose adjustment has been recommended to correct the problem as of early 2003. See Drug Interactions Tables in *HAART,* Antiretroviral Therapy section, for more specific information on type of interaction and rationale for changes

Other rifamycin drug interactions:
Rifabutin decreases serum **clarithromycin** levels. Rifampin speeds the excretion of **dapsone**; individuals may need to have their PCP prophylaxis changed during TB treatment. Rifampin negates the effects of **oral contraceptives.** Women using orals will need to switch contraceptive methods in order to avoid hepatotoxicity and achieve contraceptive efficacy.

Patient Education:

1. All patients with TB+ sputum or bronchoscopy specimens can infect others with TB. All close contacts, especially children, should be screened for TB as soon as possible and given medication to prevent (or treat) active disease.

2. The health department will be notified of your case and will provide required routine follow-up care.

3. IT'S ESSENTIAL TO TAKE ALL YOUR MEDICINE EXACTLY AS PRESCRIBED. If you miss doses, or stop and start the medication, the TB germ can develop resistance to our best medications and become even more dangerous. If you have trouble taking the medication on schedule, contact us immediately.

4. If you become ill, notice your skin or eyes turning yellow, or your urine darkening to the color of coca-cola, SEE YOUR HEALTH CARE PROVIDER IMMEDIATELY.

5. We will be taking blood at intervals to be sure your liver is working well, so be sure to come in for all your follow-up appointments. Bring all medications, vitamins, and supplements that you are taking so that we can check for drug interactions.

6. Rifampin will turn urine, sweat, tears, and plastic contact lens orange.

7. Rifampin will make birth control pills not work. Choose an alternate method of contraception for the period you are under treatment.

8. Discontinue alcohol intake during treatment with TB drugs to avoid increased toxicity or liver damage.

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Necrotizing Ulcerative Gingivitis or Periodontitis

Definition:

The demarcation between necrotizing gingivitis (NUG) and necrotizing ulcerating periodontitis (NUP) was created to define the difference between rapid destruction of soft (gums) and hard (alveolar bone) tissues, respectively. It has not been determined whether or not NUG and NUP are the same or unique entities, and both are classified as Necrotizing Periodontal Diseases. Due to the similarities in the microbial profile and treatment of these two conditions, this discussion will focus on NUP, which is a marker of severe immune suppression.

NUP in HIV+ individuals is characterized by marginal necrosis of the gingiva and rapid destruction of the underlying alveolar bone. It is usually associated with severe pain and spontaneous bleeding. Several case reports have shown extensive destruction leading to exfoliation of teeth within 3 to 6 months from onset, and sequestration of necrotic alveolar bone as well as necrotic involvement of the adjacent mandible and maxilla. The prevalence of NUP in the HIV+ population has been reported as 0 to 5%. It represents the most serious form of periodontal disease associated with HIV.

S: **Patient complains of painful, spontaneously bleeding gums, halitosis, loose teeth (prevalence towards anterior teeth and first molars). "Deep jaw pain" is a common complaint.**

O: Oral exam reveals fiery red, ulcerated gingival tissues. Teeth may either be very loose or already missing and there will be a fetid odor from the mouth. The ulcerated tissues can extend past the attached gingiva to the adjacent mucosa. Necrosis of adjacent bone is also common.

A: Rule out other causes of gingival ulceration: CMV, herpes zoster, HSV, KS.

P: NOTE: Treatment is usually divided into the acute phase and the maintenance phase. **The primary concern in the acute phase is pain control**. For the maintenance phase, treatment is directed towards elimination of causative agents, prevention of further tissue destruction, and promotion of healing.

TX:
1. PerioGard oral rinse (chlorhexidine gluconate) BID after brushing and flossing.
2. Antibiotic therapy (preferably narrow spectrum, which will leave gram positive aerobic flora unperturbed.)
   - A. Metronidazole 250 mg po TID x 10 to 14 days (note that patients on ritonavir may experience symptoms due to the small amount of alcohol in the capsules) **OR**
   - B. Augmentin 875 mg po BID x 10 to 14 days
3. Refer to a dentist for the following:
   - A. Removal of plaque and debris from the site of infection and inflammation
   - B. Debridement of necrotic hard and soft tissues with a 0.12% chlorhexidine lavage

Patient Education:

1. Good oral hygiene is CRITICAL to arresting gum and tooth loss. Brush and floss after every meal. During the acute phase this may be difficult, but it is very important to keep the mouth as clean as possible.

2. Frequent professional cleaning (every 3 months) is recommended during the maintenance phase.

3. DO NOT drink beer, wine, or any other alcohol during treatment with metronidazole, until at least 24-48 hours after last dose. If you do, you can get severe nausea and vomiting, and other very unpleasant problems. If on ritonavir, you may have nausea due to the minute amount of alcohol in the capsule; call if this is a problem for you.

4. DO NOT drink, eat, or rinse your mouth with water for 20 minutes after rinsing with PerioGard.

5. If you have bleeding gums, it may be possible to transmit HIV (or Hepatitis C if you have it) to your partner by "deep kissing" due to blood in the saliva. To avoid exposing your partner to infection, wait until your gums have cleared before resuming activities that may expose your sex partner's mucosa (mouth, urethra, vagina, and other such areas) to saliva that may contain blood.

References:

Lamster IB, Grbic JT, Mitchell-Lewis BA, et al. New concepts regarding the pathogenesis of periodontal disease in HIV infection. *Ann Periodontology* 1998, Jul; 3(1):62-75.

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American Academy of Periodontology, Committee on Research, Science and Therapy. *Periodontal Considerations in the HIV Positive Patient.* Chicago, Ill., 1994

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Winkler JR, Murray PA, Grassi M, Hammerle C. Diagnosis and management of HIV-associated periodontal lesions. *JADA* 1989: 118:25-34s.

Non-Hodgkins Lymphoma

Definition:

Non-Hodgkins lymphomas (NHL) are a heterogeneous group of malignant neoplasms. High-grade B-cell NHL is an AIDS-indicator condition, as is primary CNS lymphoma. While many HIV-infected NHL patients present with a history of generalized lymphadenopathy, AIDS-related NHL is frequently an extranodal disease. Body cavity or primary effusion lymphomas may have no determinable mass lesions. Often disease is advanced at the time of presentation, with involvement of the bone marrow, CNS, GI tract, or liver; although unusual sites may include a wide range: parotid glands, gingiva, rectum, pericardium, subcutaneous tissues and others. As patients with advanced HIV disease live longer, their risk for HIV-related neoplasms may increase. Lymphoma should be suspected in patients with advanced HIV disease who develop new adenopathy.

S: **Non-CNS: Patient complains of node swellings accompanied by persistent fevers, night sweats or weight loss; gastrointestinal bleeding; persistent perirectal pain; bony pain or tenderness; jaundice or light-colored stools; other symptoms depending on site**. May exhibit a wide range of CD4 counts.

CNS (25% of reported cases): Patient complains of confusion, lethargy, memory loss, hemiparesis, aphasia, seizures, headaches, cranial nerve palsies; usually afebrile. Findings may be focal or general. Patients with CNS lymphoma more often have advanced disease with <50 CD4 cells.

HX: New onset adenopathy
Neurologic symptoms
Any new or recent-onset symptoms

O: **PE:** Document presence and size of lymph nodes in the case of asymmetrical lymphadenopathy and/or rapidly enlarging or bulky lymph nodes, although many patients have no node involvement. Document organomegaly. Examine oral cavity for evidence of gingival involvement. Examine perirectal area for evidence of abscess. Document neurologic exam and mental status, changes in Karnofsky performance score.

LABS: Elevated LDH

A: Rule out other infectious causes of constitutional symptoms, jaundice, abscess or cardiopulmonary disease; rule out other neoplastic causes of hepatic or biliary obstruction, GI bleeding, and gingival lesions. In the presence of CNS symptoms, rule out toxoplasmosis, cryptococcosis, or bacterial, mycobacterial or fungal disease.

P: **LABS/PROCEDURES:**

Probable Non-CNS NHL:

1. Biopsy asymmetric or new, rapidly enlarging lymph nodes.
2. If GI symptoms are present, order CT to identify lesions which may be amenable to fine-needle aspiration biopsy.
3. Order serum chemistries. Suspect NHL if LDH levels are elevated.
4. Perform liver biopsy if abdominal studies indicate that it may be a site for fine-needle aspiration, or if abdominal studies are inconclusive.
5. Biopsy perirectal abscess.
6. Biopsy gingival lesions.
7. Order bone scan in the presence of bone pain. Biopsy bone marrow if indicated.
8. If pleural effusion, aspirate for cytology and Human Herpes Virus type 8 (HHV-8) PCR (if available)
9. Patients with documented NHL should have LP checked for lymphoma cells/cytology to determine if leptomeningeal spread has occurred.

Probable Primary CNS lymphoma:

1. Assay serum for cryptococcal and toxoplasma antigens.
2. Promptly order CT or MRI scan. Lymphoma will show solid enhanced lesions, usually multiple and often periventricular, with mass effect. (Toxoplasmosis shows ring-enhanced lesions with mass effect, usually multiple and widely distributed; PML has discrete non-enhanced punctate multifocal lesions with no mass effect.) Note that while NHL may show multiple ring-enhancing lesions, the ring or enhanced area is not uniform in size as with toxoplasmosis lesions, and lesions > 3 cm in size are more consistent with NHL.

3. Perform LP if not contraindicated by the presence of a mass lesion on CT or MRI. Assay spinal fluid for cryptococcal antigen as well as cytology. If Epstein-Barr Virus (EBV) DNA testing is available, a positive result is considered diagnostic for CNS NHL.
4. Brain biopsy is indicated to distinguish CNS toxoplasmosis from CNS lymphoma. If focal lesions are present on imaging, and toxoplasma serology is negative or anti-toxoplasma therapies are failing, order brain biopsy.

TX: Refer to oncology.

Chemotherapy may benefit the NHL patient with a CD4+ count >100/mm^3 and a Karnofsky performance score ≥ 70%, although the immunosuppressive nature of such treatment increases the risk of opportunistic diseases. Treatment may be complicated by poor bone marrow reserve as well as opportunistic infections. Chemotherapy options include low-dose regimens, which may be better for those with low CD4 counts, and standard-dose regimens supplemented by GM-CSF, if needed, in patients with >200 CD4 cells.

In CNS lymphoma, whole brain radiation therapy is the treatment of choice, with clinical response evident in about 75% of treated patients, although survival remains short, at about 2-5 months. Corticosteroids are used concomitantly. Adjunctive chemotherapy may or may not be used.

Patients with high-grade lymphoma, pre-existing AIDS diagnosis, previous OIs, lower CD4 counts, extranodal disease, and elevated LDH (suggesting increased tumor bulk) tend to have poorer survival than those without those factors.

HAART should be continued throughout treatment for best outcome. Patients not on HAART should be started if possible.

Consult/refer to social worker, chaplain, or mental health clinician with expertise in end-of-life issues, as needed.

Patient Education:

1. The prognosis for patients with HIV-related NHL is poor, especially for patients with primary CNS lymphoma. In some cases chemotherapy will not be indicated because it promises no improvement in quality of life.
2. Highly active antiretroviral therapy should be considered if at all possible, to improve treatment outcomes.
2. This diagnosis should prompt the clinician to discuss plans for supportive home care, a durable medical power of attorney, a will, and plans for terminal care with the patient and/or caregiver.

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Kaplan L. HIV-associated lymphoma. In *Clinical Care of the AIDS Patient*. Department of Medicine, University of California at San Francisco 1991: 233-4.

Oral Candidiasis

Definition:

"Oral thrush," a fungal disease of the oral mucosa and tongue, is caused most often by *Candida albicans*, although there have been reports of increased incidence of non-albicans species. In the absence of other known causes of immune suppression, oral thrush in an adult is highly suggestive of HIV infection. Three clinical presentations are common in people with HIV: pseudomembranous, erythematous, and angular cheilitis. As HIV disease progresses, candida infection may invade the esophagus (See *Esophageal Complaints* in Complaint-specific section, and *Esophageal Candidiasis* in Disease-Specific section), causing dysphagia or odynophagia.

S: **Patient complains of white patches on tongue and oral mucosa, smooth red areas on dorsal tongue, burning or painful mouth areas, changes in taste sensation, sensitivity to spicy foods, and decreased appetit**e. Erythematous candidiasis tends to be symptomatic with c/o oral burning, most often while eating salty or spicy foods or drinking acidic beverages.

O: **PE:** Patients presenting with oral candidiasis may be totally asymptomatic, so it is important to inspect the oral cavity thoroughly. Lesions can occur anywhere on the hard and soft palates, under the tongue, on the buccal mucosa or gums, or extending back into the posterior pharynx.

Pseudomembranous candidiasis appears as creamy white curd-like plaques on the buccal mucosa, tongue, and other mucosal surfaces that will wipe away, leaving a red or bleeding underlying surface. Lesions may be as small as 1-2 mm. in size, or extensive plaques covering the entire hard palate.

Erythematous candidiasis presents as a flat red, subtle lesion or lesions either on the dorsal surface of the tongue and/or the hard/soft palates. The tongue may have depapillated red mucosal areas on its dorsal surface.

Angular cheilitis presents with fissuring and redness at either one or both corners of the mouth, and may appear alone or in conjunction with another form of oral candida infection.

A: Partial Differential: For suspected pseudomembranous candidiasis, rule out oral hairy leukoplakia, coated tongue, and other fungal infections. For suspected erythematous candidiasis: R/O burn or trauma.

P: **LABS:** Clinical exam alone is usually diagnostic. Organisms may be detected on smear or culture.

1. Do a KOH preparation of a smear collected by the gentle scraping of the affected area with a wooden tongue depressor. Visible hyphae or blastospheres on KOH mount indicate candida infection.
2. Culture is diagnostic.
3. Refractory cases of oral candidiasis may be caused by *Candida glabrata, C. tropicalis*, or *C. Krusei*, all of which are azole-resistant. Candidiasis which does not respond to therapy should be cultured to check the identity of the fungal species.

TX: **Topical therapies are recommended for mild to moderate cases of intraoral candidiasis.** Treatment with fluconazole can result in selective growth of non-albicans species, and should only be implemented when necessitated by more severe disease.

1. Clotrimazole troches (Mycelex) dissolved in mouth 5 times/day x 2 weeks.
2. Alternative therapy: Nystatin vaginal pastilles dissolved in mouth are very effective, or may use nystatin oral suspension "swish and swallow", 4-6 ml. Swish, retain in mouth as long as possible, then swallow. Recommended therapy with either is QID x two weeks. Note that the oral suspension has a high sugar content, which may precipitate caries or xerostomia.

In moderate to severe cases:

1. Fluconazole 200, then 100 mg po QD X 14 days; note that azole drugs are not recommended during pregnancy.
2. In refractory cases, check to ensure that the causal organism is not azole-resistant. If discovered to be of mycotic etiology, treat with IV Amphotericin B

3. In cases so severe as to interfere with adequate nutrition and hydration, patient may require hospitalization for hydration and nutritional support.

4. In patients who wear partials or dentures, have them soak the prosthesis in chlorhexidine solution (such as PerioGard), then apply a thin coating of Nizoral cream on the acrylic portion of the appliance that will be in contact with the oral mucosa before reinserting into the mouth. This will prevent re-infection by the appliance.

5. Maintenance therapy for future suppression may be necessary, and can range from one Mycelex lozenge per day to one lozenge TID. Fluconazole suppressive therapy is generally not recommended except for those patients with documented esophageal candidiasis due to the possibility of azole resistance with long term use.

Patient Education:

1. Maintain good oral hygiene by brushing teeth after each meal.
2. Rinse mouth of all food before using either lozenges or suspension for treatment. Teach proper use of all medications.
3. Avoid mouth trauma: use a soft toothbrush, don't eat food or drink liquids that are too hot in temperature or too spicy.
4. For patients who have candidiasis under a denture or partial denture: Remove prosthesis before use of topical agents such as Mycelex or Nystatin. At bedtime, place the prosthesis in a chlorhexidine solution, then apply a thin coating of Nizoral cream on the acrylic portion of the appliance before reinserting into the mouth.
5. Women on azole drugs should avoid pregnancy due to possible skeletal and craniofacial abnormalities in infants.

References:

Magaldi S, Mata S, Hartung C, et al. In vitro susceptibility of 137 Candida sp. isolates from HIV positive patients to several antifungal drugs. *Mycopathologia* 2001; 149(2):63-68.

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Oral Hairy Leukoplakia

Definition:

An oral infection caused by the Epstein-Barr virus, appearing as white, corrugated lesions on the lateral surfaces of the tongue. The infection may spread across the tongue's entire dorsal surface, onto the ventral surface, and may occasionally be found on buccal mucosa.

S: **Patient notices new, white lesions on the tongue which cannot be removed with a toothbrush. Pain is not generally associated with oral hairy leukoplakia.**

O: **PE:** Unilateral or bilateral white lesions on the margins, dorsal or ventral surface of the tongue or on buccal mucosa. The lesions may vary in appearance from smooth, flat, small lesions to irregular, "hairy" or "feathery" lesions with prominent folds or projections.

LABS: CD4 count usually < 300

A: Partial differential: oral candidiasis, squamous cell carcinoma, geographic tongue, lichen planus, smoker's leukoplakia, epithelial dysplasia, or white sponge nevus.

P: **LABS/PROCEDURES:**

1. Biopsy lesion only if it is unusual in appearance or ulcerated, to distinguish it from cancer or CMV.
2. Demonstrate Epstein-Barr with electron micropsy or in-situ hybridization.

TX:

1. Since hairy leukoplakia is usually asymptomatic, no treatment is generally necessary.
2. Treat associated candidal infections if present (see *OralCandidiasis*, in this section)
3. If tx becomes necessary due to lack of "taste", Acyclovir 800mg 5 X day for 2-3 weeks will often temporarily relieve symptoms. Relapses are common; maintenance high-dose acyclovir is sometimes used for patients who have recurrent symptomatic OHL.

Patient Education:

1. Instruct patient to comply with regular dental and medical care regimens.
2. If on acyclovir, drink plenty of water to prevent dehydration and potential kidney damage.

References:

Greenspan JS, Greenspan D. Oral Complications of HIV Infection. In Sande MA and Volberding PA (eds) 1999. *Medical Management of AIDS,* 6 ed. Philadelphia, WB Saunders, 157-169.

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Greenspan D. Oral manifestations of AIDS. A*IDS Clinical Care.* 1989; 6: 45-46.

Oral Warts

Definition:

Oral warts are due to infection with human papillomavirus may appear cauliflower-like, spike or raised with a flat surface anywhere within the oral cavity and lips.

S: **Patient notices new, raised lesions in the mouth or on the skin of the lip. Pain is not associated with oral warts unless they have been traumatized**

O: **PE:** The lesions may vary in appearance from smooth, small and slightly raised lesions to cauliflower-like or spiked with prominent folds or projections.
LABS: CD4 count usually < 300

A: Partial differential: squamous cell carcinoma, lichen planus, traumatic hyperkeratinized areas due to cheek biting or tongue thrusting.

P: **LABS/PROCEDURES:**

1. Biopsy lesion only if it is unusual in appearance or ulcerated, to distinguish it from cancer or .
2. Demonstrate HPV with electron micropsy or in-situ hybridization.

TX:

1. Treatment is difficult as these lesions tend to recur. Treatment options include surgical or laser excision, cryosurgery. Extra-oral lesions (lip or corner of mouth) may benefit from use of topical agents to prevent recurrence, such as Imiquimod 5% cream (Aldara), podofilox topical solution (Condylox), or fluorouracil 5% topical (Efudex).

2. Refer to oral health or dentist

Patient Education:

1. Instruct patient to comply with regular dental and medical care regimens.

References:

King MD, Reznik DA, O'Daniels CM, et al. Human Papillomavirus-Associated Oral Warts among HIV-Seropositive Patients in the Era of Highly Active Antiretroviral Therapy: An Emerging Infection. *Clin Infect Dis* 2002;34:641-648.

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Pelvic Inflammatory Disease

Definition:

Pelvic inflammatory disease (PID) is the syndrome resulting from the ascent of microorganisms from the vagina and cervix to the uterine endometrium, fallopian tubes, ovaries or contiguous abdominal structures. Many episodes of PID go unrecognized, due to lack of symptoms or mild, nonspecific symptoms, i.e., dyspareunia, abnormal bleeding, or vaginal discharge. Infecting organisms may include: *Neisseria gonorrheae* and *Chlamydia trachomatis*, which are sexually transmitted; and anaerobic bacteria (*G.vaginalis* or *H. influenzae*), gram-negative rods (*E. coli*), *Streptococcus agalactiae*, gastrointestinal flora, CMV, and mycoplasmas (*M. hominis*), which may not be sexually transmitted. PID is co-epidemic with HIV among some urban populations of reproductive age, and represents a serious infection.

Clinical presentation may include: salpingitis, endometritis, tubal and/or ovarian abscess, and pelvic peritonitis, although PID may present with subtle or mild symptoms even in HIV-infected women. Long-term complications of PID may include infertility, ectopic pregnancy, pelvic adhesions, and chronic pain.

S: **Patient may complain of mild-to-moderate lower abdominal pain and tenderness, dyspareunia, vaginal discharge, fever, chills, menorrhagia or other abnormal vaginal bleeding.**

HX:
- Query about symptoms above, and duration
- Intrauterine device
- Previous diagnosis of gonorrhea or chlamydia
- Previous abdominal or gynecologic surgery
- New sex partner(s), unprotected sex
- LMP
- Vaginal discharge

O: **PE:** Document fever, vital signs. Focus physical on abdominal and pelvic exam: check abdomen for bowel sounds, distension, rebound, guarding, masses, suprapubic and CVA tenderness; complete pelvic exam for abnormal bleeding or discharge; uterine, adnexal, or cervical motion tenderness; pelvic masses or adnexal enlargement.

A: Partial differential:

- Pregnancy, uterine or ectopic
- Ruptured or hemorrhagic ovarian cyst
- Dysmenorrhea
- Appendicitis
- Irritable bowel syndrome
- Cystitis
- Uterine leiomyomas
- Ovarian torsion
- Mittleschmertz
- Diverticulitis
- Kidney stones
- Pyelonephritis

P: **LABS, PROCEDURES, and TREATMENT:**

Empiric treatment of PID should be initiated in sexually active women at risk for STD if the following minimum criteria are met:

- Uterine or adnexal tenderness
- Cervical motion tenderness

Additional criteria which support the diagnosis of PID may include:

- Oral temp > 101 F
- Abnormal cervical or vaginal mucopurulent discharge
- Presence of white blood cells on saline microscopy of vaginal secretions
- Elevated erythrocyte sedimentation rate
- Elevated C-reactive protein
- Lab documentation of cervical infection with N. gonorrheae or C. trachomatis

Definitive criteria:

- Endometrial biopsy with histopathologic evidence of endometritis
- Transvaginal sonogram showing thickened fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex
- Laparoscopic abnormalities consistent with PID

TX: Regimens must provide broad spectrum coverage of likely pathogens. HIV-infected women respond equally well to standard parenteral and oral antibiotic regimens when compared with HIV-negative women. Whether the management of immunodeficient HIV-infected women requires more aggressive interventions (e.g., hospitalization or

parenteral antimicrobial regimens) has not been determined. Decisions about oral vs. parenteral therapy must be individualized.

Indications for hospitalization for patient with PID:

- Uncertain diagnosis; surgical emergency can't be excluded
- Tubo-ovarian abscess
- Severe illness with nausea and vomiting or high fever
- Pregnancy
- Inability to follow outpatient regimen
- Immunosuppression (low CD4 count or significant co-morbidity)

Pregnancy Note: if the woman is pregnant, aggressive treatment is essential to prevent preterm delivery, fetal loss, and maternal morbidity; however, modification of drug regimen may be undertaken to reduce the risk of fetal toxicity; for example, doxycycline is not recommended in pregnant women, and gentamycin may affect the infant's auditory nerve, although usually at higher doses and longer treatments. Hospitalization for parenteral antibiotic therapy is recommended.

Oral/outpatient treatment (see full STD guidelines, first reference):

Regimen 1

Ofloxacin 400 mg orally twice a day for 14 days
OR
Levofloxacin 500 mg orally qd x 14 days,
with or without
Metronidazole 500 mg po bid x 14 days

Regimen 2

Ceftriaxone 250 mg IM in a single dose
OR
Cefoxitin 2 gm IM in a single dose with probenecid 1 gm po administered concurrently
OR
Other parenteral 3rd generation cephalosporin (e.g., ceftizoxime or cefotaxime)
Plus
Doxycycline 100 mg po bid x 14 days
With or without
Metronidazole 500 mg po bid x 14 days

Parenteral/Inpatient treatment:

Regimen 1

Cefotetan 2 gm IV q 12 hours
OR
Cefoxitin 2 gm IV q 6 hours
plus
Doxycycline 100 mg po or IV q12 hours (po form is preferable due to irritant qualities of IV solution)

Regimen 2

Clindamycin 900 mg IV q 8 hours
Plus
Gentamicin loading dose IV or IM (2 mg/kg of body weight) followed by maintenance dose (1.5 mg/kg) q 8 hours. Single daily dosing may be substituted.

Before choosing medications, check **drug interactions.** Nevirapine reduces drug levels of doxycycline as well as metronidazole. Patients on ritonavir and metronidazole may experience symptoms due to the small amount of alcohol in the capsules.

Follow-up:

Patients should demonstrate substantial clinical improvement (e.g., defervescence, reduction in direct or rebound abdominal tenderness and reduction in uterine, adnexal, and cervical motion tenderness) within 3 days after the initiation of therapy. If the patient has not improved, consider hospitalization, additional diagnostic testing, or

surgical intervention. Patients who are initially hospitalized for treatment may be switched to an oral regimen and discharged on oral therapy after they have improved clinically.

Evaluate sexual partners and treat if they had sexual contact with the patient during the 60 days preceding the patients' onset of symptoms.

Some specialists recommend re-screening for *C. trachomatis* and *N. gonorrhoeae* after therapy is completed in women with documented infection with these pathogens.

Patient Education:

1. Take all of your medications. If you are nauseated by your medications, try taking them with food. Do not take antacids with doxycycline. Call or return to clinic right away if you have vomiting or are unable to take your medications.
2. Sexual partners from the previous 60 days need to be examined and tested for sexually transmitted pathogens, and treated as soon as possible with a regimen effective against gonorrhea and chlamydia, even if they have no symptoms. Otherwise you may become infected again.
3. Avoid sexual intercourse until your infection has been cured.
4. Use condoms with every sexual contact to prevent becoming re-infected.
5. DO NOT drink beer, wine, or any other alcohol during treatment with metronidazole, until at least 24-48 hours after last dose. If you do, you can get severe nausea and vomiting, and other very unpleasant problems. (Note that patients on ritonavir may experience symptoms due to the small amount of alcohol in the capsules; warn patients to call if N/V occur)
6. PID can recur; if you have symptoms such as pain or fever again, call or return to the clinic.

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Manufacturers' product information

Pneumocystis Pneumonia

Definition:

Pneumocystis pneumonia (previously called *Pneumocystis carinii* pneumonia, and still called PCP), is caused by an unusual fungus *Pneumocystis jiroveci*. Nearly two-thirds of children develop serum antibodies to pneumocystis by age four. PCP has been associated with various causes of immune system suppression (chemical, neoplastic or congenital) since the 1950's. Cases of PCP in otherwise healthy young homosexual men were among the first reports of AIDS in 1981. The organism can affect many organ sites, the lung being the most common. PCP has declined since the use of prophylaxis and HAART therapy, but it is still a significant cause of morbidity and mortality in HIV-infected patients.

S: **Patient complains of fever, dyspnea on exertion, shortness of breath, dry, non-productive cough, night sweats or fatigue. Pleuritic pain and restrosternal pain or burning may also be present.**

NOTE: GIVEN THE POSSIBILITY OF HIV-ASSOCIATED TUBERCULOSIS, PATIENTS WITH COUGH SHOULD BE KEPT IN RESPIRATORY ISOLATION UNTIL TUBERCULOSIS IS RULED OUT.

HX: Query patient about fever and fatigue, which may be present for weeks, with gradual worsening in shortness of breath. May also present with acute onset symptoms of fevers, chills, sweats, dyspnea and cough. If symptoms have been present for more than a week or two, weight loss is common.

O: **PE:** Patient may appear either well or acutely ill. Tachypnea may be pronounced, and patient may exhibit such a high respiratory rate (>30/min.) that they are unable to speak without stopping frequently to breathe. Chest exam can be normal, with normal breath sounds or minimal rales, although coughing is common on deep inspiration. Increased adventitial sounds suggest an etiology other than PCP. Cyanosis may be present around the mouth, in the nailbeds and on mucous membranes. Cough is either unproductive, or produces a thin, clear or whitish mucus.

LABS: CD4+ usually < 200.
Elevated serum lactate dehydrogenase (LDH) concentration (>350 IU) is common

A: Partial differential:

- asthma
- tuberculosis
- pneumococcal pneumonia
- Mycobacterium avium complex
- lymphocytic interstitial pneumonitis
- bronchitis
- other bacterial pneumonias
- CMV pneumonitis
- fungal pneumonia, esp. cryptococcus
- histoplasmosis
- pulmonary Kaposi's sarcoma

P: **LABS/PROCEDURES:**

1. CXR. Normal or bilateral diffuse interstitial infiltrates. With aerosolized pentamidine prophylaxis, pneumonia may appear as consolidations, cavitations, or upper lobe involvement only; if not on aerosolized pentamidine, such pictures would suggest etiologies other than PCP.
2. ABGs (arterial blood gases). Should be drawn with patient on room air after mild exertion. Findings: Hypoxemia (pO_2<70) with an increased alveolar-arterial oxygen tension (A-a tension) gradient (>9 Torr). Patients with a smoking or COPD history may normally have an A-a gradient greater than 9 Torr. In any case it would be prudent to consider an A-a gradient >18-20 as significant. In respiratory failure gradients >35 Torr are seen. With normal CXR and normal ABGs, Gallium scan may be useful to rule out PCP. [To calculate Aa gradient, obtain PaCO2 and PaO2 from the ABG drawn while patient on room air. Determine the PA02 with the following general equation (for altitudes <10,000 feet): PA02 = 150 - (1.25 x PaCO2). A-a gradient is PAO2-PaO2.]
3. Serum chemistries: LDH level >350 (usually elevated in patients <u>not</u> receiving PCP prophylaxis).
4. Sputum induction: Patient inhales a saline mist and respiratory therapist collects subsequent expectorated sputum, which is stained with giemsa and examined for P. carinii organisms. While sputum induction is a useful tool because of its less invasive approach, it is only diagnostic for PCP in the hands of experienced technicians; check with lab first. Warning: if sputum induction is done in a confined space, it should be done in negative pressure area

or near an exhaust fan vented safely outside; otherwise, if the client has TB, there is a high risk of TB aerosolization.

5. BAL (bronchoalveolar lavage): A surgical procedure wherein a fiberoptic bronchoscope is wedged into the distal bronchus and saline instilled. The aspirate is retrieved and examined for *P. jiroveci*, acid-fast organisms and fungi. This procedure is diagnostic for PCP in most centers. Cultures for mycobacteria and fungi should also be done. If virus isolation is available, inoculate aspirate into cell culture to isolate suspected virus (usually CMV).
6. Transbronchial biopsy or open-lung biopsy is done if lung disease is progressive on treatment; if extrapulmonary PCP is suspected; or if atypical lesions are present.

TX: Treat for 21 days.

1. **Standard therapy:** Trimethoprim-sulfamethoxazole (Bactrim or Septra): 15 mg/kg of TMP component, divided into three or four doses daily; which usually comes out to two DS tabs every 8 hours, oral or IV for 3 weeks (21 days). Note that patients who have had previous mild reactions to sulfa are sometimes successfully desensitized; see Sulfa Desensitization protocol in Health Maintenance section.

   - OR –

   Pentamidine: 4mg/kg/day IV (in a single daily dose) x 3 weeks.

   - OR –

   Dapsone and trimethoprim: Dapsone 100mg PO QD plus
   Trimethoprim 15mg/kg PO QD x 3 weeks.

   Adjunctive corticosteroids: Use of adjunctive corticosteroids is recommended in treatment of PCP in patients with an arterial oxygen pressure <70mm Hg or an Aa gradient >35. Although some recommend starting 40 mg prednisone before the first dose, it must be initiated within 36-72 hours of the start of anti-pneumocystis therapy. Prednisone 40mg BID days 1-5; 40mg QD days 6-10; 20mg QD days 11-21. (Note: histoplasmosis can mimic PCP both in its indolent onset of dyspnea and CXR pattern of reticulonodular infiltrates; however, it will tend to worsen on steroids.)

2. **Alternative therapy:** Clindamycin 600mg IV Q 8 hours (or 300-450 mg po q6h-q8h) and Primaquine base 15-30 mg po qd (be sure patient screened for G6PD deficiency if male of African or Mediterranean descent.)
   - OR –
   Atovaquone 750mg po bid (with fatty meals, mild-moderate PCP only)

3. Patients started on IV therapy can be switched over to PO regimen for the rest of the three-week course when afebrile and improved oxygenation. Note, however, that patients often experience worsening of infiltrates on CXR, and that pneumatoceles may develop despite successful therapy, which increases chances of pneumothorax. Additionally, rashes can develop in patients taking TMP-SMX over 7 - 10 days, which may require change in therapy or desensitization procedure (see *Prophylaxis for PCP* guideline for desensitization schedule).

4. Treatment failures: Trimetrexate is available. Consult infectious disease specialist.

FOLLOW-UP:

1. Hospitalized patients are ready for discharge when ABG's are acceptable on room air with exercise, IV therapy is no longer required, and the patient is tolerating oral medications. **Outpatient follow-up appointment should be 2-3 days post discharge.**

2. Outpatients: Assure that patient has received adequate treatment for PCP. If treatment is interrupted due to intolerance or allergy, resume therapy with new drugs to total 21 days. Obtain post-therapy CBC with differential and Chem 19. If lab tests are back to baseline, order PCP prophylaxis. Restart antiretroviral therapy if it was discontinued during hospitalization.

3. CXR will not clear or appear normal for weeks or months.

4. If patient is not on HAART, assess for appropriateness and feasibility after PCP treatment is completed.

5. Refer to dietician to minimize weight loss and regain weight.

PROPHYLAXIS:
Anti-PCP prophylaxis is indicated in all patients who have survived an episode of PCP, and in any patient whose CD4+ count is < 200/mm^3 or < 14%. See *PCP Prophylaxis* in Health Maintenance Section.

Patient Education:

1. If being treated with sulfa (Bactrim, Septra, TMP-SMX), any rash should be evaluated to rule out medical emergency. Hold sulfa and report to the clinic or emergency room immediately.
2. Do not take dairy products within 2 hours before or one hour after sulfa dose; otherwise your body may not be able to absorb the medicine.
3. Despite a completed course of therapy, patients may still harbor PCP organisms, and PCP may recur. It is important to see your clinician if any of the following symptoms occur: shortness of breath, especially on exercise; fever, chills and sweats; new cough.
4. Regular compliance with anti-PCP prophylaxis is extremely important to prevent repeat episodes. Don't quit taking these medicines without talking with your care provider. Don't let your prescriptions run out.

References:

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Progressive Multifocal Leukoencephalopathy

Definition:

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system to which immunocompromised hosts are vulnerable. PML is caused by the JC virus (JCV), member of the papovavirus family, and is thought to be due to reactivation of latent infection. Though rare, PML occurs more frequently in people whose immunity is compromised by HIV, usually in those with CD4 counts <100, and is rapidly progressive. The interval between first neurologic symptoms and death may be as short as 3-4 months; in rare cases, remission has occurred and patients have survived for several years. To date there is no specific treatment for PML, although in some patients the symptoms improve rapidly on HAART. Paradoxically, HAART undertaken late in disease can exacerbate unrecognized PML, leading to rapid progression and sometimes death.

S: **Patient or caregiver complains of changes/difficulties in speech and/or gait; limb weakness; sudden mono- or hemiparesis; altered mental status; personality changes; seizures; visual changes, including: field deficits, nystagmus, blindness; headache; tremor; cranial nerve palsy; dysphasia or dysarthria**.

O: Patient likely to be alert and afebrile on examination. Note presence or absence of focal neurologic defects (usually multiple deficits ensue in the case of PML); changes in neurologic status since last examination. PML's course is subacute (in contrast to the more rapid courses of toxoplasmosis or CNS lymphoma), though disturbances in speech, vision, or thought may be profound.

A: Partial differential diagnosis:

- Toxoplasmosis
- HIV encephalopathy
- Lymphoma
- CNS Lymphoma
- HIV dementia
- Tuberculosis
- Cerebral vascular disease
- CNS infection with TB, cryptococcosis, or CMV
- Immune reconstitution symptoms from pre-existing disease

P: **LABS/PROCEDURES:**

1. Order CT scan with double contrast or MRI (depending on your institution's ability to give you rapid test results). PML evolves from single to multiple lesions in the subcortical white-matter. On CT, PML typically appears as dense nonenhanced lesions without edema. Typical MRI presentation shows multiple fluffy diffuse hypodense white matter lesions, with poorly defined margins; high signal density on T-2 images with ill-defined margins.
2. Assure that baseline toxoplasmosis serologic titers have been performed.
3. Brain biopsy is gold standard for diagnosis of PML, but unavailable to many clinicians.
4. LP to rule out other causes of dementia, such as chronic meningitis or neurosyphilis. LP is generally normal or shows changes associated with HIV in PML. Send spinal fluid sample for JCV PCR; if positive and CT scan is consistent with PML, presumptive diagnosis is adequate.

TX: There is no accepted treatment regimen for PML, other than highly active antiretroviral therapy. If symptoms are due to immune reconstitution, decadron may help diminish symptoms.

1. Increase intensity of antiretroviral therapy (see *HAART* in Antiretroviral Therapy section), and observe for improvement. Note that, depending on memory and mentation, client may need care provider in the home to assure that medications are taken on schedule.
2. In presence of edema, consider corticosteroids.
3. Arrange to provide supportive care for personal hygiene, nutrition, safety and prevention of further neurologic accident or head injury.

Patient Education:

When a diagnosis of PML has been established or suggested due to a clinical picture of neurologic deterioration, the clinician must initiate a discussion of plans for terminal care (including wills, advanced directives, and supportive care/services) with the patient and family and/or caregiver(s). Supportive treatment will be necessary for an undetermined period of time, and hospice referral should be considered if no clinical improvement in response to a highly effective antiretroviral regimen.

If patient is placed on antiretroviral therapy, be sure that family or friends are taught about the medications and can help patient with adherence.

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Lennox, J Personal communication 1/10/03

Seborrheic Dermatitis

Definition:

A dermatitis characterized by a greasy scale covering a yellow-red base, usually with indistinct margins. In patients with HIV infection, usually the scalp and central face are involved, although it may be present in areas of the ears, chest, upper back, axillae or groin. Some 25-83% of patients with HIV have experienced this disease; it may wax and wane over the course of infection. The etiology of seborrheic dermatitis is thought to be a lipophilic yeast of the Malassezia species (previously known as *Pityrosporum ovale*), which can also cause folliculitis or tinea versicolor.

S: **Patient complains of new rash, sometimes itchy, or of "dry skin" that will not go away in spite of the application of topical moisturizers.**

O: Pruritic or asymptomatic greasy scale rash covering a yellow-red base. Typically found on the scalp, hairline, nasolabial folds, eyebrows, and in or behind ears. May be found under chest hair, in axillary area or groin.

A: Partial differential: Reiter's syndrome, candidiasis, and psoriasis.

P: **LABS:** KOH preparation can rule out candida albicans. Malassezia may show numerous spores with admixed short septate hyphae.

TX:

1. Head and scalp: Wash with a sulfur and salicylic acid (Van Seb, Sebulex), selenium sulfide (Selsun Blue), coal tar, or zinc pyrithione (Head and Shoulders, Danex, Zincon) shampoo daily for several weeks, then once or twice a week, plus a medium potency steroid solution (triamcinolone 0.1%) or ketoconazole shampoo (Nizoral) may be applied.
2. For facial, trunk and groin lesions, possible treatments include topical imidazole cream (Ketoconazole cream 2% or clotrimazole 1%) applied BID, along with 1% to 2.5% hydrocortisone cream to affected area 1-2 times daily. If ineffective, the steroid strength may need to be increased for trunk and groin lesions; after lesions have resolved, decreased concentrations may be used to keep them away.

Patient Education:

1. If using special shampoo, leave it on for 20 minutes before rinsing.
2. Instruct patient that seborrheic dermatitis often recurs. Patients should keep their skin as clean and dry as possible, and watch for recurrences, particularly in winter due to dry heat.
3. At the earliest sign of recurrence, patients should re-start shampoo and/or hydrocortisone therapy to prevent progression to secondary infection.

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Sinusitis

Definition:

Sinusitis is defined as an inflammation involving the membrane lining of any sinus, and is a frequent finding in HIV disease. In general, most acute sinusitis is a secondary bacterial complication of viral respiratory infections, which can cause decreased patency of the nasal ostia, decreased nasal ciliary action and increased mucus production. Most common pathogens of acute sinusitis are: *S. pneumoniae, M. catarrhalis*, and *H. influenzae*. Anaerobic pathogens are more common in chronic sinusitis. *Staph aureus*, Pseudomonas, and Aspergillus may be more common in immunosuppressed people. Most nasal congestion and drainage are due to chronic sinusitis.

S: **Patient complains of facial pain, headache, post-nasal drip, fever.**
HX: Respiratory allergies. Recent onset of URI or "flu."

O: **PE:** Document fever, drainage from sinus ostia; tenderness over sinus cavities; examine nares for signs of inflammation. Check cranial nerves.

A: Partial differential includes sinus blockage by other lesions such as KS, lymphoma, allergic rhinitis or sinusitis. Consider dental abscess, trauma.

P: **LABS/PROCEDURES:**

1. Standard radiologic films (sinus series) can detect cloudiness or air-fluid levels, and are usually all that are required. Note that mucosal thickening is a non-specific finding and may not indicate infection. CT scans can be useful, but should not be done before standard films.
2. Nasal cultures are of little help. Cultures should be reserved for patients undergoing nasal irrigation, antrectomy or sinus biopsy. Fungal cultures are important in chronic sinusitis.

TX:

1. Broad spectrum antibiotics are important. Many of the organisms produce penicillinase, thus drugs like amoxicillin clavulanate 875/125 po bid, cefaclor 500 mg po bid, or Bactrim DS 1 tab po bid may be good choices. In the penicillin-allergic or sulfa-allergic, azithromycin (Z-Pack) or levofloxacin 500 mg po qd x 10 days may be used. Treatment should be coupled with a decongestant/expectorant medication to keep sinuses drained, and antibiotics should be extended for 14 days, since recurrence is common with undertreatment.

2. Refer patients to otolaryngologist for consult and possible surgical drainage/debridement if patient is not responsive to antibiotic therapy; has persistent fever with no other source; or develops altered mental status (rule out brain abscess).

3. Intranasal steroids can be effective with allergic etiologies, as can oral antihistamines.

Patient Education:

1. In acute sinusitis, you need to take your antibiotics on schedule until the entire prescription is gone, in order to prevent recurrence of the infection.
2. During treatment, it is important to keep sinuses drained. Good hydration (lots of water) is helps to keep the mucus thin enough to drain out the sinus passages. If you have do not have high blood pressure, you may also use the over-the-counter decongestant pseudoephedrine, 60 mg every 4-6 hours, to keep sinus passages open and prevent sinus headaches.
3. Return to clinic for swelling of the face or swelling around the eyes, increased facial tenderness, or if symptoms do not improve within 48 hours.

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Syphilis

Definition:

Syphilis is a complex systemic illness caused by the spirochete *Treponema pallidum.* Some reports in the literature suggest that, because of defects in cell-mediated and humoral immunity, co-infection with HIV may alter the natural course of syphilis infection, leaving patients with HIV vulnerable to a rapid clinical course characterized by unusual manifestations, with higher risk of neurologic manifestations and higher rates of treatment failure. Thus both diagnostic and treatment parameters for syphilis may be altered by the presence of HIV disease. Evaluate patients carefully for ocular and neurologic abnormalities.

The natural course of untreated syphilis infection is arbitrarily divided into phases:

1. An *incubation* period lasting about 3 weeks (9-90 days)
2. A *primary* stage characterized by non-painful ulcer (chancre) at the site of sexual exposure, associated with regional lymphadenopathy
3. A *secondary* disseminated stage accompanied by generalized mucocutaneous lesions and lymphadenopathy
4. Periods of subclinical infection (*latent* syphilis) detected only by confirmed serologic tests. This is called *early latent* **if known to be <1 year duration** and *late latent* if known to be >1 year duration, or otherwise as *latent syphilis of unknown duration.*
5. *Late or tertiary* is stage characterized by progressive disease involving the CNS system and/or ascending aorta, but virtually any organ in the body can be involved.
6. CNS disease, or *neurosyphilis*, may occur at any stage of infection. Neurosyphilis can be asymptomatic, and HIV clients with latent or tertiary syphilis should have an LP prior to treatment.

S: **In primary disease, patient complains of new sore (usually perigenital or perirectal, but can be oral or other contact site); in secondary disease, patient complains of a new rash, particularly on trunk or soles and/or palms, and may have fever; malaise; anorexia and weight loss. Other possible secondary symptoms include arthralgias; hair loss; pharyngitis, laryngitis, meningitis, or uveitis. CNS disease may present with problems with vision or hearing, CVA, seizures, hyperactive reflexes, and changes in personality, affect or cognition. Latent syphilis has no symptoms, though patient may recall chancre or rash.**

HX: Previous exposure to syphilis or other STD's
Unprotected sex: specific practices such as oral, anal, or vaginal sexual contact
Multiple sexual partners
Injecting drug or crack use
History of positive serologic tests for syphilis (RPR or VDRL), with or without treatment.

O: **PE:** Thorough physical examination, including neuro; examine all visible mucous membranes and skin, including palms and soles, for lesions or masses. Document presence/absence of heart murmurs or other abnormalities; conjunctival and circumcorneal injection with poor pupil responses suggest iritis.

Primary stage: papule; chancre - a firm, usually painless ulcerated lesion (~10% are painful) with raised borders, clean appearance and no exudate; regional lymphadenopathy.

Secondary stage: multiple, widespread signs. Skin lesions begin on the trunk and proximal extremities, and may be macular, maculopapular, papular or pustular. Rash on the palms and soles is highly suggestive of secondary syphilis. Constitutional symptoms of fever, malaise, anorexia, arthralgia, and pharyngitis/laryngitis are more common at this stage.

Latent stage: no signs beyond lab seropositivity (RPR/VDRL confirmed by a treponemal test). If possible, determine duration of infection, using previous negative lab reports, history of unequivocal symptoms of primary or secondary syphilis, duration of contact with sex partner documented to have syphilis.

Tertiary stage: gumma or cardiovascular complications, such as aortic aneurysm and valvular disease occur late in syphilis. Gumma can grow from skin or mucosal surfaces, destroy bone, and may present in any organ system. Unusual presentations have included: hepatitis, retinitis, posterior uveitis. Note that uveitis and other ocular manifestations are frequently associated with neurologic involvement, and patients with these symptoms should have LPs, and be treated for neurosyphilis.

Neurosyphilis: Can be associated with any stage of syphilis. Changes in personality, affect, sensorium, intellect, insight and judgment; seizures; hyperactive reflexes; abnormal cranial nerve function, with VII & VIII most commonly affected; unilateral facial palsy; hemiplegia; hemiparesis; neurosensory hearing loss; visual changes such as blindness, chorioretinitis, keratoderma; meningitis or encephalitis.

A: Rule out:

- other causes of neurologic disease
- other causes of cardiac murmur
- other causes of ocular disease
- other dermatological conditions causing maculopapular rashes
- constitutional HIV disease

P: **LABS:**

1. **Darkfield** examination of exudate from suspicious chancres or other moist dermatologic lesions; or **direct fluorescent antibody (DFA**) staining of exudate (if available) are considered definitive tests.
2. RPR or VDRL (if not done as part of initial laboratory work-up). These tests may read falsely negative in the presence of HIV infection if the patient has primary syphilis or is incubating syphilis. Treponemal test to confirm positive PRP/VDRL (if not done previously). Specific treponemal tests (Treponemal IgG or FTA-ABS) may become positive earlier in the course of illness.
3. If darkfield and serologies are negative, but clinical suspicion of syphilis is high, rule out the "prozone" phenomenon, which may occur when a nontreponomal serology is read as negative because the specimen was not tested after sufficient dilution. Very high antibody concentrations can prevent formation of detectable antigen-antibody complexes.
4. Clinical evidence of neurologic disease warrants lumbar puncture in all cases. LP is also indicated when treatment for early syphilis fails (if titer does not decrease fourfold/2 dilutions by 12 months), or if a substantial increase in titer occurs. See Treatment section, below, for additional indications. **Examine CSF for:**
   leukocytes >5/mm^3
   protein > 0.4mg/ml
   CSF-VDRL
5. All patients testing positive for syphilis should be tested for other STDs such as gonorrhea and chlamydia.

TX: Note that up to 2/3 of patients with primary, secondary, or even latent syphilis can have a Jarisch-Herxheimer reaction, with headache, chills, fever, arthralgias, malaise, tender lymphadenopathy, and intensification of rash, that starts 2-8 hours after the first treatment dose, and resolves within 24 hours. This self-limited treatment effect is best treated with rest and acetaminophen, and should not be confused with an allergic reaction to penicillin.

Non-neurologic syphilis <1 year's duration, i.e., primary, secondary, and early latent:

1. Benzathine penicillin G - 2.4 million units IM.
2. In penicillin-allergic, non-pregnant patients: Doxycycline 100mg PO BID x 2 weeks, or Tetracycline 500mg PO QID x 2 weeks.
3. Refer penicillin-allergic pregnant women for desensitization to penicillin.

Non-neurologic syphilis >1 year's duration or of unknown duration, i.e., tertiary, late latent, or latent syphilis of unknown duration:

1. CSF examination should be done on all patients with a history of syphilis of greater than one year or of unknown duration.
2. If CSF exam is negative, treat with Benzathine penicillin G, 7.2 million units total (2.4 million units IM weekly x 3 consecutive weeks).
3. In penicillin-allergic clients, refer to infectious disease specialist for desensitization to penicillin.

Neurosyphilis, i.e., syphilis at any stage with neurologic or ocular symptoms:

1. Aqueous crystalline penicillin G: 18-24 million units IV/day (3-4 million units Q 4 hrs x 14 days).
2. *If compliance with therapy can be ensured*, patients may be treated with the following alternative: Procaine penicillin 2.4 million units IM per day, PLUS probenecid 500 mg po qid, both for 10-14 days.
3. Penicillin-allergic patients should be referred for desensitization. These patients require hospitalization and 2 weeks of IV penicillin under close observation.
4. If CSF pleocytosis was initially present, the CSF should be rechecked every 6 months until the cell count normalizes.

Pregnancy: Use penicillin regimen appropriate to stage of infection. Tetracycline and doxycycline should not be used during pregnancy. Erythromycin does not reliably cure an infected fetus. Women treated during the second half of pregnancy are at risk of Jarisch-Herxheimer reaction with resultant contractions, fetal distress, and possible stillbirth. They should be instructed to seek obstetric attention in the event of contractions or decreased fetal movements. This is a rare complication, but concern for this should not delay treatment, given that syphilis can be even more devastating to an infant.

Sex partners: Sexual transmission of syphilis only occurs when mucocutaneous syphilitic lesions are present, which is uncommon after the first year of infection. However, persons exposed sexually to a patient who has syphilis in any stage should be evaluated as follows:

Persons exposed **within the 90 days preceding the diagnosis of primary, secondary or early latent syphilis might be infected even if seronegativ**e; therefore, such persons should be treated presumptively.

Persons exposed **>90 days before the diagnosis of primary, secondary, or early latent syphilis should be treated presumptively** if serologic test results are not available immediately and the opportunity for follow-up is uncertain.

FOLLOW-UP:

All HIV-infected patients treated for syphilis should be clinically and serologically evaluated at 3, 6, 9, 12, and 24 months to rule out treatment failure. Any client with apparent treatment failure should have LP and be re-treated as appropriate.

If, at any time, clinical symptoms develop or non-treponemal titers rise fourfold, a repeat CSF examination should be performed and treatment administered accordingly.

For primary and secondary syphilis: If, between 6 and 12 months, the non-treponemal titer fails to decline fourfold, the CSF exam should be done and treatment administered accordingly.

For latent syphilis: If, between 12 and 24 months, the non-treponemal titer fails to decline fourfold, the CSF exam should be done or repeated, and re-treatment administered accordingly

Patient Education:

1. As per state law, the health department will be notified (or client can be directly referred). A communicable disease specialist will elicit sexual contacts from the previous 3 months (in the case of primary syphilis), 6 months (for those with secondary syphilis) or 12 months (in the case of latent syphilis), and refer them for workup and treatment.
2. Emphasize the need for careful follow-up of syphilis in HIV-infected patients to assure adequate treatment of their infection. Report any recurrent symptoms or rashes.
3. Underline sexual transmissibility of both syphilis and HIV infection. Review patient's sexual practices to assist them with negotiation skills for abstinence, condom use, or alternatives to intercourse.
4. (For patients with primary, secondary, and latent syphilis, at the time of their first treatment dose): You may notice within the next 2-8 hours that you have fever, chills, headache, sore throat, swollen nodes, and worsening of any rashes. This is very common, and seems to be a result of the medicine killing off the syphilis spirochetes. It is not an allergic reaction. You may want to take aspirin or acetaminophen. It goes away within 24 hours; if fever persists, return to clinic.

References:

CDC. Sexually Transmitted Disease Treatment Guidelines 2002. *MMWR* 2002; 51 (No. RR-6).

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Toxoplasmosis

Definition:

Toxoplasma gondii is a common intracellular protozoan that preferentially infects the central nervous system of immunodeficient patients, causing severe neurologic disease in 25-30% of patients with advanced HIV disease. Toxoplasmosis has an infectious reservoir in almost all animals; humans acquire infection either through eating undercooked meat (usually pork or lamb) containing oocysts, or through exposure to cat feces containing oocysts. Acute reactivation of latent toxoplasmosis infection can cause progressive, fatal disease in people with HIV infection. **Chemoprophylaxis against toxoplasmosis now has demonstrable efficacy and should be given to patients with fewer than 100 CD4 cells/mm^3** (see *Toxoplasmosis Prophylaxis* in Health Maintenance section) and positive toxoplasmosis titers.

S: **Complains of new onset dull, constant headache, and/or visual changes. Caregivers may report a subtle alteration in mental status, and patient may report feeling disoriented. New seizures in an HIV-infected patient most often point to the etiology of toxoplasmos**is.

HX: Dull headaches
Altered mental status x 2+ weeks
Disturbances of cognitive function
Fever, confusion, coma

O: **PE:** Focal neurological deficits; findings of aphasia, ataxia, hemiparesis, cranial nerve palsies, changes in gait, changes in mood/affect.

LABS: Evidence of HIV seropositivity
CD4+ count usually < 100/mm^3
Positive serum for Toxoplasma antibodies (95% of patients with toxoplasmosis test positive on IgG)

A: Partial differential:

- cryptococcal meningitis
- primary CNS lymphoma
- primary HIV encephalopathy
- progressive multifocal leukoencephalopathy
- other causes of chorioretinitis such as CMV, HIV, and cryptosporidiosis
- TB meningitis
- brain abscesses of bacterial, fungal, or mycobacterial etiologies
- HSV or CMV encephalitis
- cerebrovascular accident secondary to hemorrhage, hypoxia or emboli from vegetative endocarditis (in IDU's), or neurosyphilis
- AIDS dementia complex

P: **LABS/PROCEDURES:**

1. Toxoplasma serum antibody status: positive (titer changes are uncommon in reactivation disease). Negative toxoplasma titers do not rule out toxoplasmosis.
2. Magnetic resonance imaging (MRI) is the diagnostic scan of choice; detects more subtle lesions than CT.
3. If ordering a CT scan, order a delayed scan after a double dose of contrast medium (DDD scan).
4. Look for any of 3 types of hypodense lesion: ring-enhancing; nodular enhanced with edema; and focal enhancing with edema.

TX:

1. Standard therapy: 100-200 mg loading dose of pyrimethamine, followed by pyrimethamine 50mg to 75mg per day + sulfadiazine 100mg/kg/day (up to 8 gm/day) in 4 divided doses. Supplement with folinic acid (leukovorin) 10mg/day to reduce incidence of pancytopenia. (With higher-dose pyrimethamine, use folinic acid 10-50 mg/day.)

   After at least 6 weeks of initial therapy, dose may be reduced to pyrimethamine 25-50 mg po qd + folinic acid 10 mg po qd + sulfadiazine 0.5 to 1 gm po q6h. Note that some clinicians use higher-end doses of pyrimethamine, while others use the lower-end doses to help minimize the marrow suppressive action of pyrimethamine. See note #4 below.

   Patients at risk should be checked for G6PD deficiency before starting pyrimethamine.

2. Alternative therapy: Clindamycin 600mg Q 6 hr + pyrimethamine 50-75mg/day. After six weeks, dose may be reduced to pyrimethamine 25-50 mg po qd + folinic acid (leukovorin) 10 mg po qd + clindamycin 300 po q6 hours or clindamycin 450 po q 8 hours.

3. Other alternatives include Pyrimethamine (as in #1 above) plus folinic acid (leukovorin) along with one of the following four options. Suppression dose for the following meds is the same as initial dose.
   Clarithromycin 1 gm po q12 h
   Atovaquone 750 mg po q6h
   Azithromycin 1.2-1.5 gm po qd
   Dapsone 100 mg po qd

4. Due to variability in absorption and side effects, definitive dosing recommendations for pyrimethamine are difficult to establish. For most patients, the lower doses are sufficient. It is essential to follow CBC, including platelet counts, while patient is on pyrimethamine. Drug dosage may need to be adjusted, or folinic acid (leukovorin) increased, to control for bone marrow suppression. See *Common HIV Drugs* section and complete prescribing information for other side effects which may limit treatment.

5. Pyrimethamine plus dapsone or sulfadiazine (suppressive therapy doses and above), as well as atovaquone, also serves as adequate prophylaxis for PCP. Pyrimethamine plus clindamycin is not sufficient to prevent PCP.

Follow Up:

If no improvement within 7 – 10 days, brain biopsy may be helpful in showing other treatable etiogy.

Secondary prophylaxis or maintenance therapy is generally lifelong. If patient has completed initial phase of therapy, is asymptomatic of signs of TE, and has had >6 months of CD4 count > 200 in response to HAART, it is reasonable to consider discontinuation of TE maintenance therapy. Some specialists would check MRI before discontinuation of therapy. Patient must be observed for symptoms, and treatment resumed with one of the above regimens if CD4 count goes <200.

PRIMARY PROPHYLAXIS: see *Toxoplasmosis Prophylaxis* in Health Maintenance section.

Patient Education:

1. Return to clinic promptly if rash develops or if symptoms worsen.
2. Help your memory by posting reminder notes, keeping necessary objects (keys, glasses, important phone numbers) in the same, visible place. It will also help to keep a calendar of your appointments posted in a place you look at frequently, across from your kitchen table or favorite chair.
3. Nausea from the pyrimethamine can be reduced by taking it with food.
4. Suppressive therapy must be continued to prevent recurrence.

References:

Liesenfeld O, Wang SY, Remington JS. Toxoplasmosis in the setting of AIDS. In Merigan TC, Bartlett JG, Bolognesi D (Eds), Textbook of AIDS Medicine, 2nd ed. 1999, Baltimore, Williams and Wilkins, 225-259.

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Manufacturer's product information.

Vulvovaginal Candidiasis

Definition:

A vulvovaginal yeast infection caused by several types of Candida. This disease is common in all women, but may occur more frequently and severely in immunocompromised women. Up to 26% of cases are non-*albicans* strains, most commonly *glabrata*, which may not respond to azole therapy. Refractory vaginal candida infections may be the first clinical manifestation of HIV in an infected woman, and can occur early in the course of her disease (at CD4+ counts of >500/mm^3), although rates tend to increase as CD4 counts decrease. This may be in part due to increased antibiotic use. Protease inhibitors appear to decrease incidence of candidiasis.

S: **Patient complains of itching, burning, and or swelling of labia and vulva; a white or yellowish thick vaginal discharge; painful intercourse; external pain and burning on urination.**

HX: Prior diagnosis of vaginal yeast infection
Oral contraceptive use
Recent or ongoing broad spectrum antibiotic therapy

Consider also:
Diabetes history
Cushing's syndrome
Obesity
Hypothyroidism
Pregnancy
Douches, vaginal deodorants, bath additives

O: **PE:** Physical exam of external genitalia may reveal an inflamed vulva with evidence of the discharge on labial folds and vaginal opening. Speculum exam usually reveals a white, thick discharge with plaques adhering to the vaginal walls and cervix. Bimanual exam should be normal, and should not elicit pain or tenderness if this is an uncomplicated yeast infection.

A: Rule out other causes of vaginal discharge and/or pruritus:

- bacterial vaginosis
- pediculosis
- trichomoniasis and other STDs
- atrophic vaginitis
- chemical/mechanical causes
- scabies

P: **LABS:**

1. Perform KOH prep of the discharge, which usually reveals the presence of hyphae and Candida spores (presumptive diagnosis).
2. Definitive diagnosis is made by culture of vaginal secretions.
3. In the presence of urinary tract symptoms beyond external vulvar burning, get clean-catch specimen, perform dipstick and/or culture and sensitivity studies:
4. Testing for gc and chlamydia may be indicated based on history of sexual exposure and other symptoms.

TX:

1. In mild infections, topical vaginal antifungal agents in the form of cream, suppositories or tablets (Monistat, Gyne-Lotrimin, Terazole); 7-day therapy is ideal; offer refills based on the time to next scheduled clinic visit. These creams may also be used on vulva for pruritus. Alternatively, fluconazole 150 mg po x 1, may be used.

2. **NOTE: THE MINERAL OIL BASE IN TOPICAL VAGINAL ANTIFUNGAL PREPARATIONS MAY ERODE LATEX IN CONDOMS, DIAPHRAGMS, AND DENTAL DAMS. ADVISE PATIENT TO DISCONTINUE INTERCOURSE WHILE USING THESE MEDICATIONS.** Non-latex condoms (plastic and polyethylene only) or female condoms (polyurethane) can be used if the patient can get them and knows how to use them. They tend to be much more expensive than latex condoms, and are less often available at health departments and safer sex/HIV prevention sites.

3. For severe or frequently-recurring infections (defined as 4 episodes in a year) prescribe oral antifungal agents: Ketoconazole 200mg BID x 14 days; + 5-day courses each month for 6 months. **Monitor liver function tests.**

This is not an option for clients on **drugs that interact with ketoconazole**, such as delavirdine, indinavir, ritonavir, rifampin, astemizole, triazolam, and many others.

- OR-

Fluconazole (Diflucan) 100-200mg QD x 10-14 days. Note that azole drugs are not recommended during pregnancy, and women on azoles should use effective contraception.

4. Fluconazole, 200mg q week is effective for secondary prophylaxis for severe cases that repeatedly recur, except in pregnant women or women considering pregnancy. Azole resistance is a consideration.

5. Boric acid 600 mg intravaginal gelatin capsules qd x 2 weeks may be an option for refractory cases.

6. Nystatin vaginal pastilles, 100,000 units; insert 1 qd x 14 days.

Patient Education:

1. Maintain good personal hygiene. Wash external genitals daily with either a fresh washcloth or water-soaked cotton balls; wipe vulva & perirectal area from front to back after toileting; do not use baby wipes on inflamed vulval tissue, as they may increase irritation.

2. Avoid the use of perfumed soaps, bubble baths, feminine hygiene or vaginal deodorant products, or bath powders.

3. Don't douche.

4. Wear cotton underwear and avoid tight, constrictive clothing, particularly pantyhose.

5. Finish your medicine even if you're having a period.

6. If you continue to have symptoms, you can purchase Monistat or Gyne-Lotrimin medication over the counter. Start using these as soon as symptoms come back. Call the clinic it your symptoms get worse on these medicines.

7. Avoid pregnancy while on fluconazole or ketaconazole. Some birth defects have been reported.

8. **NOTE: THE MINERAL OIL BASE IN TOPICAL VAGINAL ANTIFUNGAL PREPARATIONS CAN WEAKEN or ERODE LATEX IN CONDOMS, DIAPHRAGMS, AND DENTAL DAMS. ADVISE PATIENT TO DISCONTINUE INTERCOURSE WHILE USING THESE MEDICATIONS.**

9. Sex toys, douche nozzles, diaphragms, cervical caps, etc., can re-infect you if not properly cleaned and thoroughly dried after use.

10. Some studies have suggested that eating yogurt with live cultures (check labels) can reduce occurrence of vaginal yeast infections.

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Hatcher RA, Stewart FH, Trussell J, et al. *Contraceptive Technology*. 15th ed. 1999 New York: Ardent Media. 123-5.

Wasting

Definition:

Loss ≥ 10% of body weight, with low grade fevers (maximum 100.6 °F) for most days of a month's time; and/or diarrhea, ≥ 2 loose stools per day in the absence of concurrent illness. Weight loss can be profound with concurrent infection (or when gastrointestinal pathology prevents adequate caloric intake) and deplete both subcutaneous fat and muscle. Once lost, weight is difficult to regain; therefore, it is important to treat as early as possible. **Loss of ≥5% of body weight is significant in HIV/AIDS patients**; those who have lost down to 70% of ideal body weight are at imminent risk of death.

Weight loss in AIDS:

Weight loss is often a harbinger of secondary infection. In one study, rapid weight loss (>9 lbs in <4 months) was accompanied by secondary infection 82% of the time. Slower weight loss (>9 lbs ≥ 4 months) was more associated with gastrointestinal disease (62% of cases). Therefore, careful workup for treatable OIs and GI disease is a priority when patients present with weight loss. Weight loss in AIDS patients may also directly correlate with decreased food intake, which must be addressed early and often in the course of HIV treatment. Malabsorption may also play a role in weight loss, as does the increase in resting metabolic rate.

AIDS-related energy loss:

Another cause of HIV-related weight loss may be altered lipid metabolism. Free fatty acids released from the periphery are not oxidized and used for energy, but instead are re-synthesized into triglycerides and stored again as fat. Energy is wasted each time fatty acids are re-synthesized, and skeletal muscle protein becomes the primary source of calories. The subsequent loss of lean body mass may or may not be accompanied by weight loss. Unfortunately, adequate caloric intake may not stop this futile cycling and continued skeletal muscle wasting.

Note: For fat redistribution (peripheral fat atrophy with or without central fat accumulation) related to HAART, see *Fat Redistribution* in Antiretroviral section.

S: Patient complains of weight loss, and may report anorexia, early satiety, decreased enjoyment of food.

HX: Question about specifics that may indicate **treatable pathology**, such as:

Pain/discomfort with eating	Association with medication, herbal or supplement use
Diarrhea: frequency, volume, duration	Dietary intake history
Fever: pattern, duration	Lethargy
Abdominal pain or other localizing symptoms	Fatigue
Dizziness	Current vs. past activity level

O: Quantitate weight loss by comparing recorded weights from previous visits. PE may show obvious signs of cachexia, such as temporal wasting and hair loss. Check for signs of infection and/or neoplasia, such as enlarging nodes, new lesions, shortness of breath, fever.

A: **Partial differential for weight loss in AIDS:**

Chronic or indolent infections, especially fungal and mycobacterial (see *Fever* workup in Complaint-specific section.)
treatable causes of diarrhea (see *Diarrhea* protocol)
Oral complications such as ulceration, abscesses, periodontitis (see Oral Ulceration, Necrotizing Ulcerative Periodontitis in Disease-Specific section)
Esophageal pathology with dysphagia or odynophagia (see *Esophageal Symptoms* in Complaint-specific section)
Medication-associated nausea or anorexia
Hypogonadism
Depression (see *Depression* in Neuropsychiatric section)
Adrenal insufficiency
Opportunistic infection

Labs/procedures:

1. Stool workup if diarrhea is present (see *Diarrhea* in Complaint-specific section)
2. AFB and fungal blood cultures (see *Fever* in Complaint-specific section)

3. Consider GI referral for endoscopy if ulcerative esophageal pathology suspected, or for colonoscopy if CMV or other invasive colitis is suspected.
4. Consider CT of chest and abdomen to screen for malignancy
5. Electrolytes
6. Serum testosterone level on men; treat with testosterone if borderline or low.
7. Look at serum albumen, cholesterol, and other indicators of nutritional status.

P: Treat appropriately if infectious pathogen identified.

Initiate dietary referral/consultation for dietary modification and protein/calorie supplements to slow or prevent further weight loss.

If no treatable pathology is identified:

1. Start HAART if patient is a candidate (see antiretroviral therapy section) and willing to commit to regimen.

2. Megestrol (Megace), 80 mg po tid (suspension or tablets), 30 minutes before meals, especially recommended when anorexia is present. Doses of 400-800 mg/day have been tested and shown to be efficacious, with maximum weight gain noted at 800 mg po qd. Much of this weight gain may be fat although some studies have shown increases in lean body mass; body impedance analysis, if available, may help discern effectiveness in muscle gains.

3. Dronabinol (Marinol), 2.5 mg po bid, half an hour to an hour before lunch and dinner, helps improve appetite in some, although weight gained may be more fat than muscle. Most effective in individuals with history of marijuana use. Can be given in escalating doses, up to 10 mg po bid if necessary, though side effects increase. Requires Schedule II Narcotic prescription, with DEA number. Expensive; patient assistance programs may be available.

4. In patients with borderline/low testosterone levels (low levels are <400 ng/dl for men; < 40 ng/dl for women), may supplement with testosterone 200mg IM q 2 weeks for males. Other forms: Nandrolone 100-200 mg IM q 2 weeks; 25-100 mg IM q2 wks in women. Oxandrolone 20 mg po qd can be given in men and women. Alternatives: Oxymetholone 10-15 mg po qd, up to 300 mg./day (males). Halotestin--fluoxymesterone--10 mg po bid. Note that all forms of testosterone are contraindicated in pregnancy. Note also increased risk of liver toxicity with oral preparations.

5. Other preparations of anabolic steroids are available, including patches or gels for application to scrotal skin, but tend to be very expensive.

6. Recombinant human growth hormone (Serostim) has been used for severe weight loss, and may show more lean muscle gain, but is prohibitively expensive for most patients. Call 1-800-714-2437 to see if the patient can qualify for drug assistance program.

Follow up: Continue to track weights to determine effectiveness of any intervention, and monitor for emerging OI symptoms, modifying regimen as needed. Bioelectrical impedance analysis can help determine weight distribution (lean body weight vs. fat), but it may not be available in all sites.

Patient Education:

1. People with HIV tend to consume fewer calories as the infection progresses, and may need to adjust their perception of "healthy" from the popular low-calorie, low-fat regimen to one that will help preserve their muscle mass.

2. Supplement meals with additional calories/protein, such as peanut butter, legumes, cheeses, eggs, instant breakfast drinks, milkshakes, sauces. (Lactose intolerance is more common in AIDS; discuss with client before recommending dairy products.) Talk with the dietician about how you can supplement your food intake, and any specific problems you have had with foods.

3. Progressive strength-building (resistance or weight-lifting type, vs. aerobic type) exercises often help increase muscle mass, and should always be used along with other measures to increase lean body mass and improve energy levels (although this may be somewhat limited in patients who are already having significant fatigue or lethargy.)

4. Report fever, chills, night sweats, cough, diarrhea, or other symptoms of infection as soon as possible, for additional workup.

6. Women on megestrol may have breakthrough bleeding. Women should not take megestrol during pregnancy, especially the first 4 months of gestation, due to increased risk of hypospadias and genital abnormality in the infant.

7. Testosterone preparations can harm a fetus, and pregnancy must be carefully avoided. Use effective birth control consistently and correctly.

8. Testosterone may cause increased hair growth and other masculinizing effects in women. Report menstrual irregularities.

References:

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CHAPTER 6: Antiretroviral Therapy

Antiretroviral Therapy

Background: Combination therapy with 3 or more drugs, commonly known as highly-active antiretroviral therapy (HAART) has generally improved the health and survival of HIV-infected patients. However, concerns about drug interactions, adherence, drug resistance, side effects, and toxicities have modified the way these drugs are used and prompted more caution about concomitant medications and monitoring. As the number of drugs continues to increase, the antiretroviral (ARV) picture is likely to become much more complex. The US Public Health Service keeps a "living document" of frequently-updated recommendations regarding use of ARV medications in adults, including pregnant women. It is available at the website http://www.aidsinfo.nih.gov/, which should be accessed frequently to check for updates and changes in treatment. All clinicians treating HIV-infected patients need to be familiar with the most current version of these guidelines.

S: CD4 count history, including nadir
Viral load history, including pre-therapy if patient currently on ARV regimen
Previous antiretroviral regimens
Current medications, including herbals, supplements, and OTCs
Medication allergies, intolerances, or prominent side effects
Occupation and daily schedule
Self assessment of adherence to previous regimens
Current substance use, including alcohol and recreational drugs
Desire to start or continue ARV regimen
Commitment to adherence
Prediction about adherence to various types of regimens (e.g., bid, tid, q 12 hours, with/without food, etc.), given current life situation
For women of childbearing potential: LMP, current method of birth control, whether/when she wants to have children
History and review of systems (see *Initial History* in Assessment section)

O: Recent/current CD4 and viral load
Liver function, CBC and platelet count, lipids, renal function, chemistries (see *Initial/Interim Labs* in Assessment section)
Drug resistance profiles (if available)
Complete physical exam (see *Initial Physical* in Assessment section)

A:
1. Patient would/would not be likely to benefit from antiretroviral therapy at this time (e.g., do benefits outweigh the risk? See Adult Antiretroviral Therapy Guidelines noted above, which thoroughly address the issue. A brief summary is included in the tables in *CD4 Staging and Prognosis*, and *Viral Load Testing* in Assessment section)
2. Patient is/is not willing to start ARVs at this time (the choice to accept or decline therapy ultimately lies with the patient)
3. Patient is/is not likely to adhere to ARV regimen (an adherence counselor and or mental health clinician may be able to assist with this assessment, and should be called upon if available). No patient should be automatically excluded from consideration for HAART; the likelihood of adherence must be discussed and determined individually.

Review drug interactions between current medications and ARVs under consideration.

P: Initiate, change, or postpone antiretroviral therapy, after patient education about the purpose and logistics of the proposed regimen, and assess potential for adherence. The patient has the right to decline or postpone antiretroviral therapy. This should not affect any other aspect of care; and HAART should be re-offered at each visit. If mental health issues, addiction, or social situation interferes with the patient's intent to adhere, initiate appropriate referrals.

Limitations on antiretroviral therapy: No "average patient" exists. Some patients will do better and some will do worse than what clinical studies would predict. Health care providers must work with each patient to develop a treatment strategy that is both clinically sound and appropriate for that individual's needs, priorities, and circumstances of daily life. Not all patients will be able to tolerate all drugs, and the patient's understanding,

readiness to commit to the regimen, and history of adherence to previous regimens must be considered in choosing them appropriately. See Appendix B: *Adherence*, for further information. Major considerations:

1. Willingness of the individual to begin therapy, coupled with understanding the purpose of and the specific mechanics of the planned regimen-how it will fit into his/her life;
2. Degree of existing immunodeficiency as reflected in the CD4 count;
3. Risk of disease progression, as determined by the HIV RNA level (see Tables in *CD4 Staging and Prognosis*, and *Viral Load Testing* in Assessment section) ;
4. Potential risks and benefits of antiretroviral drugs; and
5. Likelihood of adherence to the prescribed regimen.

Antiretroviral therapy is recommended for patients with any of the following:

- High viral load regardless of CD4 count. The NIH panel recommends that if using RT-PCR viral load assay, treatment should generally be started if patient's viral load is >55,000 copies/ml. The US PHS panel acknowledges that recommendations for therapy cannot be based on any absolute number, with our current limitations on test sensitivity, therapy and data from clinical trials.
- **CD4 count <350** (though some providers might consider deferring tx if stable CD4 count >200, with HIV RNA titers between 5,000-10,000 and no symptoms).
- **Rapidly declining CD4 count** (>300 CD4 loss over a 12 to 18 month period), at any HIV RNA level
- **Symptomatic disease** (oral thrush, hairy leukoplakia, wasting, unexplained fever, or AIDS-defining illness) at any HIV RNA level or CD4 count. Patients with **advanced disease** should be treated with antiretroviral therapy, if they are willing to take the medications and can tolerate the side effects. A maximally suppressive regimen should be used, and should be not be discontinued in the event of opportunistic disease or malignancy, unless there are concerns about toxicity, intolerance or drug interactions
- **Acute or primary HIV infection** if unable to enroll in a clinical trial, and patient is amenable to therapy. Expert consultation, by phone if necessary, is recommended prior to beginning HAART in primary HIV infection. See *HIV/AIDS Resources for Clinicians* at the beginning of this manual, or call the National Clinicians HIV Consultation Service at 1-800-933-3413

For effective starting regimens in patients with no prior therapy, choose one drug or combination from Column A and one pair from Column B (see **Table 1, Recommended Antiretroviral Agents for Initial Treatment of Established HIV Infection** and **Drug Interaction** tables at end of the Antiretroviral section):

Column A	**Column B**
Efavirenz	Didanosine + Lamivudine
Indinavir	Stavudine + Didanosine**
Lopinavir + Ritonavir (co-formulated as Kaletra®)	Stavudine + Lamivudine
Ritonavir + Indinavir	Zidovudine + Didanosine
Nelfinavir	Zidovudine + Lamivudine
Ritonavir + Saquinavir (SGC* or HGC*)	

Recommendations for alternate regimens include possibilities below:

Column A	**Column B**
Abacavir	Zidovudine + Zalcitabine
Amprenavir	
Delavirdine	
Nelfinavir + Saquinavir SGC	
Nevirapine	
Ritonavir	
Saquinavir-SGC*	

*SGC = saquinavir soft gelcaps, e.g., Fortovase. HGC = saquinavir hard gelcaps, e.g., Invirase. Invirase had low bioavailability and is no longer recommended except when taken with medications that raise its blood levels.
** Not recommended during pregnancy due to increased risk of lactic acidosis

Before starting the regimen, it is also necessary to have a **detailed discussion with the patient about his or her readiness to commit** to a difficult, potentially toxic medication regimen, and returning for the required follow-up. The patient must also understand that the first treatment regimen is the best opportunity for effective viral suppression, which is the primary goal of antiretroviral treatment. Numerous strategies are being tested for effectiveness in supporting patient adherence to the regimen. Extensive patient education, telephone contacts of office staff who can answer questions about side effects or difficulties, family meetings and peer support are used in some settings. Rapport and accessibility appear to be important predictors of adherence, and some offices see the patient for two or three appointments prior to starting antiretrovirals. Patients may also be given "test regimens" for a few weeks using inactive pills or mints, to help understand how the medicine schedule may fit into his or her life **before** starting the actual drugs. **The choice to accept or decline antiretroviral therapy ultimately lies with the patient.**

Considerations in Regimen Selection

Patient's schedule and adherence history and projections should be considered in selecting a regimen that the patient will be most likely to adhere to. ARV history and any available resistance profiles should be considered in choosing a regimen that will likely be effective in each patient; note cross-resistance potential in PI and NNRTI classes. In women who are pregnant or seeking pregnancy, consider pregnancy categories and teratogenicity. See Antiretroviral Guidelines (http://www.aidsinfo.nih.gov/) for specific considerations in adults and pregnant women.

Use of multiple classes of drugs: Drug combinations that include only reverse transcriptase inhibitors (RTIs) generally will not reduce virus level as effectively as a combination that includes both RTIs and a protease inhibitor (PI), or RTIs and a non-nucleoside reverse transcriptase inhibitor (NNRTI).

There are many pros and cons to determining the best initial regimen for any patient. Some clinicians advocate use of 2 NRTIs and efavirenz, an NNRTI, to preserve the PI class for later. Others would be more concerned about the toxicities of PIs, and still others would start with a PI-containing regimen because it takes longer than the NNRTI class for resistance to develop. See the discussion of drug resistance as well as the full text of the US Public Health Services-sanctioned treatment recommendations and websites noted in references at the end of this section for more complete discussions.

Avoiding development of drug resistance: *Protease inhibitors, NNRTIs, and lamivudine should never be given alone, intermittently, in dual regimens, suboptimal regimens, or in lower doses than recommended due to potential for rapid development of resistance.* Resistance to NNRTIs and lamivudine develop very quickly in these situations. Patients must take the full dose of all medications on schedule, and not skip doses or take "days off" from their regimens. Careful medication dosing is especially important for protease inhibitors and NNRTIs, since resistance to one drug within the class may transfer to others within the same class. This greatly limits options for future therapy. Resistant viral strains, once developed, may also be transmitted to other people through risky behavior.

Drug Interactions. Many of the antiretroviral drugs interact with each other as well as other common medications, and when starting or changing a regimen, review all the patient's current medications. See full prescribing information and consult tables on in *HAART*, in Antiretroviral Therapy section, which list drugs that should not be used with antiretrovirals, and drugs whose doses must be adjusted when co-administered with antiretrovirals. For further reference, updated interaction information, authored by Charles Flexner, MD, and Stephen C. Piscitelli, Pharm.D., is available from Medscape's HIV internet site at http://www.medscape.com/px/hivscheduler. As of January 2003, this website includes a link to a "Drug-drug interaction calculator" which allows the clinician to enter a regimen of ARVs and other drugs that are planned for a patient, and will search for interactions among the entire set of drugs.

NRTI combinations to avoid due to virologic problems or overlapping toxicities are:

stavudine + zalcitabine (neuropathy)
didanosine + zalcitabine (pancreatitis)
stavudine + zidovudine (antagonism)
zalcitabine + lamivudine

Follow up of Patients Starting HAART

Patients who start new ARV regimen or change to a new regimen must be followed up twice within the first month to assess effectiveness, adherence, tolerability, and side effects of regimen. The goal of therapy is maximal and durable viral suppression, restoration or preservation of immune function, improved quality of life and reduction of HIV-related morbidity and mortality. If the patient is starting on a PI or NNRTI, baseline fasting lipid profile should be obtained before starting therapy.

Viral load should be checked 2-8 weeks after starting a new antiretroviral regimen to verify satisfactory decline**. CD4 count; chemistries, including glucose, liver and renal function tests; CBC with platelet** counts should be performed every 3 - 4 months unless abnormalities or symptomatology indicate more frequent measurements are needed. Patients on NNRTIs or PIs need **lipid profiles** (preferably fasting) at baseline and 3-4 months after starting HAART (if normal), and annually thereafter. If results are abnormal, or the patient has cardiac risk factors, recheck every 3 - 4 months while on the regimen. See *Dyslipidemia* in Antiretroviral section for more information.

Regimen Failure

For patients who appear to be failing therapy—viral load does not decline sufficiently or it resurges after initial suppression, declining CD4 cells, or clinical worsening—refer to the USPHS/IDSA Antiretroviral Therapy Guidelines (www.aidsinfo.nih.org) and consult with HIV-expert clinicians on use of resistance profiles and alternative regimens **before** discontinuing therapy.

Before changing the antiretroviral regimen due to failure, it is essential to carefully assess patient adherence. This may affect the decision to change therapy, and it may impact the new regimen as well. Consider changing antiretroviral regimens in the event of intolerance, non-adherence, or failure.

Failure can be defined as:

- viral load decrease of < 0.5 - 0.75 log by 4 weeks following initiation of therapy, or
- viral load decrease of < 1 log (tenfold) by 8 weeks following initiation of therapy
- viral load does not go below level of detection within 4-6 months of initiating therapy--although, the patient who started with a very high viral load (>100,000) whose viral load stabilizes after six months at <10,000 may not warrant an immediate change in therapy
- repeated detection of virus in plasma after initial suppression to undetectable levels; however, the degree of increase should be considered. The patient should be followed very closely, since most of them subsequently progress to higher levels of viremia in future. Be sure the increase is not due to infection, vaccination, or problem with test methodology.
- any reproducible significant increase in viral load, 3-fold or greater, from the lowest plasma HIV RNA level, that is not due to intercurrent infection, vaccination, or problem with test methodology.
- persistently declining CD4 cell count, measured on at least 2 separate occasions, and
- clinical deterioration; Note that a new opportunistic illness that occurred after antiretroviral therapy was started, in the face of pre-existing severe immunosuppression, may not reflect a failure of antiretroviral therapy unless the effect of therapy on HIV RNA was poor (<10-fold reduction). If the antiretroviral effect was good but the patient was already severely immunocompromised, the appearance of a new opportunistic infection may not reflect failure of ARV, but a persistence of severe immunodepression that did not improve despite adequate viral suppression. Also, paradoxical effects of HAART may occur when patients have pre-existing undetected OIs and the immune response is suddenly enhanced.

A final consideration in deciding whether or when to change therapies is the **limited choice of available agents,** which may further reduce future treatment options for the patient. It is sometimes necessary to balance partial suppression with the likelihood of future resistance. Consultation with an experienced HIV provider is appropriate, as is HIV resistance testing, when considering changes in therapy. In patients with no remaining treatment options among currently approved drugs, refer to an appropriate clinical trial if possible. See also, USPHS guidelines for changing therapy, below.

Susceptibility or resistance testing: It is fairly common for a regimen to fail because of resistance to just one or two drugs. Resistance testing, although expensive and time-consuming, can identify more precisely which drugs may still be used effectively. When drawing blood for resistance testing, it is essential that the patient still be taking the regimen that is failing, so that resistant populations will be present in detectable numbers. (See *Resistance Testing*,

after the drug interaction tables at the end of Antiretroviral section.) Resistance testing is recommended before changing regimens for:

- Virologic failure during HAART
- Suboptimal suppression of viral load

Recent evidence suggests that broad cross-resistance exists among the PIs, and viral strains that are resistant to one of them will have reduced susceptibility to most or all other PIs. Cross-resistance between indinavir and ritonavir is almost complete, and although information about nelfinavir is less available, some degree of cross-resistance between nelfinavir and ritonavir or indinavir may exist. Because of this, when changing from a 2 NRTI/1 PI combination, the likelihood of success is decreased even if the new regimen has 2 new NRTIs and a new PI. Some experts add two new PIs in the subsequent regimen, or switch to a regimen containing 2 NRTIs and an NNRTI. However, the data regarding a 2-NRTI/1-NNRTI regimen as salvage is limited, and risk of NNRTI resistance is increased if NRTI resistance is present. **Note that dosage modification is often required due to drug interactions when setting up any new regimen; see notes under *Drug Interactions* on page 175.** (See drug interaction tables later in this section, as well as antiretroviral therapy guidelines at www.aidsinfo.nih.gov).

Guidelines for changing an antiretroviral regimen for suspected drug failure

1. Criteria for changing therapy include a suboptimal reduction in plasma viremia after initiation of therapy, re-appearance of viremia after suppression to undetectable, significant increases in plasma viremia from the nadir of suppression, and declining CD4 counts.

2. When the decision to change therapy is based on viral load, it is best to confirm with a second viral load.

3. Distinguish between the need to change a regimen due to drug intolerance or inability to comply with the regimen versus failure to achieve the goal of sustained viral suppression; single agents can be changed in the event of intolerance, without resistance testing.

4. In general, do not change a single drug or add a single drug to a failing regimen; it is important to use at least two new drugs and preferably to use and entirely new regimen with at least three new drugs. If susceptibility testing (performed while on the failing regimen) shows resistance to only one agent in a regimen, it may be possible to replace only that drug; however, this approach requires clinical validation.

5. Many patients have limited options for new regimens of desired potency; in some of these cases it is rational to continue the prior regimen if partial viral suppression was achieved.

6. In some cases, regimens identified as sub-optimal for initial therapy are rational due to limitations imposed by toxicity, intolerance or non-adherence, especially in late-stage disease. For patients with no rational alternative options who have virologic failure with return of viral load to baseline (pretreatment levels) and a declining CD4 count, there should be consideration for discontinuing antiretroviral therapy.

7. Experience is limited with combinations of two protease inhibitors or combinations of PIs with NNRTIs; for patients with limited options due to drug intolerance or suspected resistance these regimens provide possible alternative treatment options.

8. There is limited information about the value of restarting a drug that the patient has previously received. Susceptibility testing may be useful in this situation if clinical evidence suggestive of the emergence of resistance is observed. However, testing for phenotypic or genotypic resistance in peripheral blood virus may fail to detect resistant variants which are present in small numbers, and the resistant virus may re-emerge once the drug is started again. Thus, the presence of resistance is more useful information in altering treatment strategies than the absence of detectable resistance.

9. Avoid changing from ritonavir to indinavir or vice versa for drug failure, since high-level cross resistance is likely.

10. Avoid changing among NNRTIs for drug failure, since high-level cross-resistance is likely.

11. The decision to change therapy and the choice of a new regimen requires that the clinician have considerable expertise in the care of people with HIV. Those less experienced in the care of persons with HIV are strongly encouraged to obtain assistance through consultation with or referral to a clinician with considerable expertise in the care of people with HIV. Those clinicians without local experts are invited to see **Resources for HIV/AIDS Clinicians** in front of the table of contents in this book for consultation possibilities.

adapted from USPHS/IDSA guidelines 2002; available from www.aidsinfo.nih.gov

Changing HAART regimen due to toxicity or intolerance: It is important to distinguish whether one is changing a regimen because of drug failure or because of intolerance or drug toxicity. If a regimen is changed due to toxicity or intolerance alone, it is not necessary to change the complete regimen or get resistance testing prior to changing it. If necessary to stop one drug due to intolerance or toxicity, either stop all drugs and resume when the substitute drug is available, or substitute for a new drug from the same class or category as soon as the offending drug is discontinued.

Follow-up of Patients Not Started on HAART

If patient would probably benefit but is not started on ARV therapy: patient should still continue to be seen for monitoring, prophylaxis, and other medical treatment. Changes in lab results and patient condition should be used as opportunities to reassess the patient's wishes for ARVs, and to educate her/him about new medications and research findings. ARVs should be re-discussed and offered at regular intervals to anyone who initially refuses treatment, including a discussion of risk of progression to AIDS or death based on their current CD4 and viral load (see Adult Antiretroviral Guidelines, at http://www.aidsinfo.nih.gov/ or check tables in *CD4 Staging* and *Viral Load Testing* in Health Maintenance section.) If the issue was lack of readiness or probable adherence difficulties, work with adherence counselor (if available) and/or mental health to bolster the patient's support and coping mechanisms, offer trial runs of inactive pills or mints to practice taking "medications" on schedule.

P**atients who don't meet the criteria of the US PHS/IDSA recommendations for starting antiretrovirals** should be monitored regularly with laboratory and physical exams (see Assessment section for physical exam and labs), offered prophylaxis as appropriate, and re-assessed for ARV therapy when they do meet criteria for starting HAART.

Special Situations for Antiretroviral Therapy

Antiretroviral therapy during acute or primary HIV infection

Patients with **acute or primary HIV infection** (PHIV) may experience symptoms within the first few weeks of infection, such as rash, fever, lymphadenopathy, fatigue, weight loss, nausea and headache, but still have a negative or indeterminate result on the HIV antibody test. If a careful HIV risk history reveals the patient to be at significant risk for recent HIV infection, an HIV RNA test can be performed to ascertain whether or not there is viremia. (Note that a low viral load may suggest a false positive.) Although optimal therapy in this group of patients is unknown, combinations of agents that are most likely to maximally suppress viral replication (such as two RTIs and a protease inhibitor) are recommended. The patient must be carefully counseled regarding potential limitations, such as toxicity, pill burden, cost, and the possible development of drug resistance before starting on an antiretroviral regimen. These patients should be maintained with the same kind of follow-up of viral load and CD4 count as patients with established infection. PHIV suspects in whom the initial HIV antibody test was negative, should be re-tested within 3-4 weeks to fully document the diagnosis of HIV infection. See Appendix C: *Primary HIV Infection*.

Pregnant women

Since 1994, ZDV has been recommended to reduce risk of vertical transmission, but is known to be suboptimal therapy for treating the woman. Triple drug HAART regimens are now used during pregnancy in the HIV-infected woman to further reduce risk of transmission to the infant as well as to treat maternal HIV infection. See *Reducing Maternal-Infant HIV Transmission* and *Treatment during Pregnancy* in Health Maintenance section.

Occupational exposure to HIV: See *MMWR* 2001; 50 (No.RR-11) for guidelines on post-exposure prophylaxis (PEP) after bloodborne pathogen exposure. See Appendix D: *Occupational Exposure to HIV Infection*. Each institution must have its own policy, procedures, and antiretroviral drug kit so that PEP can begin without delay

Tables in subsequent pages:

Table 4. Drugs that should not be used with antiretrovirals
Table 5 (2 pages). Drug interactions between protease inhibitors and other drugs: Cautious use/dose modifications
Table 6. Drug interactions between NNRTIs and other drugs: Cautious use/dose modifications
Table 7. Drug interactions between NRTIs and other drugs: Cautious use/dose modifications
See also Appendix A: Recreational Drugs and HAART for more on drug interactions.

Recommended reading:
Complete text of US PHS recommendations and discussion of resistance testing, drug class effects, toxicity and teratogenicity of antiretroviral drugs can be found in adult guidelines at *http://www.aidsinfo.nih.gov/* along with updated USPHS guidelines for antiretroviral treatment during pregnancy and pediatric guidelines. Familiarity with the full text is strongly recommended for all clinicians treating HIV-infected clients. See *HIV/AIDS Resources* in the introductory section of this manual for how to obtain these guidelines without Internet access.

Patient education:

1. Review proposed drug regimen including drug storage, dosage, schedule/interval between drugs, food requirements or restrictions, side effects, toxicities, and type of responses that must be immediately reported.

2. Antiretroviral drugs require a commitment to use. There are limited numbers of such drugs available, and if they are taken incorrectly, your virus can quickly become resistant to the medication. This will mean even fewer choices, and less effective treatment, later on. It might also mean that you could transmit resistant virus to a partner or infant.

3. Review the actual regimen with the client, integrating times for each dose with client's mealtimes--or between them, as appropriate--and be sure it is possible for the client at these times.

4. In the event you are unable to take one of your antiretroviral medications for a day or more (due to illness, severe side effects, hospitalization, and other unexpected circumstances), it is better to stop them all at once rather than keep taking one or two of them. Unless you are having a problem with one of the drugs, you should be able to resume your medications, but it is essential that you re-start them all at one time. Even such carefully-managed interruptions as these can happen too many times, and cause drug resistant mutants. Again, this will limit our options, and should be avoided if at all possible.

5. HIV medications do not prevent infection to others. Safer sex recommendations must be followed, and other high-risk activities (needle sharing, etc.) must be carefully avoided, to keep from spreading the virus to others. See *Preventing HIV Infection* in Health Maintenance section for more information.

6. Experts recommend safer sex and no sharing of needles or drug-using equipment, even with other HIV-infected partners. If the viruses in your body develop resistance to some of these medications, and you pass those viruses on to another person, she/he will not be able to effectively use those medications either. If your partner happens to have a drug-resistant strain of HIV, it is possible for you to become infected with that in addition to the one you have already, which will limit your treatment options. And, of course, Hepatitis C and STDs can be transmitted between partners who both have HIV. See *Avoiding Exposure to Opportunistic Infections* in Health Maintenance section.

References:

CDC. Guidelines for Using Antiretroviral Agents Among HIV-Infected Adults and Adolescents: Recommendations of the Panel on Clinical Practices for Treatment of HIV. *MMWR* 2002; 51 (No. RR-7)

New York AIDS Institute. Clinical Guidelines: Antiretroviral Therapy for Adults, updated February 2002. Downloaded 10/30/02 from http://www.hivguidelines.org/public_html/CENTER/clinical-guidelines

Yeargin PR, Farrington B (eds) *Clinical Management of the HIV-Infected Adult: A manual for mid-level clinicians*. Southeast AIDS Training and Education Center, Midwest AIDS Training and Education Center, Atlanta, 2000.

Donnelly, RJ. Personal Communication. 10/30/02

Table 1

Recommended Antiretroviral Agents for Initial Treatment of Established HIV Infection

Antiretroviral drug regimens are comprised of one choice each from column A and column B. Drugs are listed in alphabetical, not priority, order.

Strongly Recommended	**Column A**	**Column B**
	Efavirenz	Didanosine + Lamivudine
	Indinavir	Stavudine + Lamivudine
	Lopinavir + Ritonavir (co-formulated as Kaletra®)*	Stavudine + Didanosine***
	Nelfinavir	Zidovudine + Lamivudine
	Ritonavir + Indinavir*	Zidovudine + Didanosine
	Ritonavir + Saquinavir (SGC** or HGC**)	
Recommended as an Alternative	Abacavir	Zidovudine + Zalcitabine
	Amprenavir	
	Delavirdine	
	Nelfinavir + Saquinavir - SGC	
	Nevirapine	
	Ritonavir	
	Saquinavir-SGC	
No Recommendation; Insufficient Data to recommend for or against use	Hydroxyurea in combination with other antiretroviral drugs	
	Ritonavir + Amprenavir	
	Ritonavir + Nelfinavir	
Not Recommended; Should Not Be Offered (All monotherapies, whether from column A or B****)	**Column A**	**Column B**
	Saquinavir-HGC**	Stavudine + Zidovudine
		Zalcitabine + Lamivudine
		Zalcitabine + Stavudine
		Zalcitabine + Didanosine

* Ritonavir is used with other protease inhibitors to boost their blood levels in order to maintain higher antiviral activity, and reduce dosage frequency by slowing the metabolism of the PIs that use the cytochrome P-450 pathway. Concomitant use requires dose modification; see drug interaction tables, to follow.

** Saquinavir-SGC, soft-gel capsule (Fortovase®); Saquinavir-HGC, hard gel capsule (Invirase®, the older formulation, with very low bioavailability). Use of Saquinavir-HGC (Invirase) is not recommended, except in combination with ritonavir.

*** Not recommended in pregnancy due to increased risk of lactic acidosis

**** Zidovudine monotherapy may be considered for prophylactic use in pregnant women with undetectable viral load and high CD4 T cells counts to prevent perinatal transmission, as discussed in *Treatment of Pregnant Women* and *Reduction of Vertical HIV Transmission* in Health Maintenance section. If additional antiretrovirals are to be used, a highly active triple drug regimen is required.

-Table adapted from US PHS Panel: Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents. February 4, 2002; downloaded from http://www.aidsinfo.nih.gov/

Table 2

Drug Interactions Between Protease Inhibitors and Non-nucleoside Transcriptase Inhibitors: Cautious Use and Dosage Adjustments

Drug Affected	Nevirapine NVP	Delavirdine DLV	Efavirenz EFV
Indinavir (IDV)	IDV ↓ 28% NVP no effect Dose: IDV 1000 mg q8h NVP standard	IDV↑ >40% DLV no effect Dose: IDV 600 mg q8h DLV standard	IDV ↓31% Dose: IDV 1000 mg q8h EFV standard
Ritonavir (RTV)	RTV ↓ 11% NVP no effect Dose: Standard	RTV ↑ 70% DLV: no effect Dose: DLV: standard RTV: no data	RTV ↑ 18% EFV ↑ 21% Dose: RTV 600 mg bid (500 mg bid for intolerance) EFV standard
Saquinavir (SQV)	SQV ↓ 25% NVP no effect Dose: No data	SQV ↑ 5X˅ DLV no effect Dose: Fortovase 800 mg tid, DLV standard (monitor transaminase levels)	SQV ↓ 62% ˅ EFV ↓ 12% **Co-administration not recommended**
Nelfinavir (NFV)	NFV↑10% NVP no effect Dose: Standard	NFV ↑ 2X DLV ↓ 50% Dose: No data (monitor for neutropenic complications)	NFV ↑ 20% Dose: Standard
Amprenavir (APV)	*No data*	Preliminary information shows 4-fold increase in APV levels and substantial decrease in DLV levels (Cmin ↓ 70%) Dose: Insufficient data	APV AUC ↓ 36% Dose: APV 1200 mg tid as single PI, **or** APV 1200 mg bid + RTV 200 mg bid EFV standard
Lopinavir + Ritonavir (LPV/r)	LPV ↓ Cmin 55% Dose: consider LPV/r 533/133 bid in PI-experienced patients NVP standard	LPV levels expected to ↑ Dose: insufficient data	LPV AUC ↓ 40% EFV no change Dose: consider LPV/r 533/133 mg bid in PI experienced patients EFV standard
Nevirapine (NVP)	_	*No data*	EFV AUC ↓ 22% No effect on NVP
Delavirdine (DLV)	*No data*	_	*No data*

˅ Conducted with Invirase

--Table adapted from : US PHS Panel. *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents.* February 4, 2002; downloaded from http://www.aidsinfo.nih.gov/.

Tran JQ, Peterson C, Garrett M, et al. Pharmacokinetic interaction between amprenavir and Delavirdine: evidence of induced clearance by amprenavir. 2002 *Clin Pharmacol Ther* 72(6) 615-626

Table 3

Protease Inhibitor - Protease Inhibitor Drug Interactions and Dose Adjustments

Drug affected	Ritonavir (RTV)	Saquinavir* (SQV)	Nelfinavir (NLF)	Amprenavir (APV)	Lopinavir + Ritonavir (LPV/r)
Indinavir (IDV)	IDV ↑ 2-5fold. Dose: IDV 400 mg bid + RTV 400 mg bid; **or** IDV 800 mg bid + RTV 100-200 mg bid	IDV-no effect; SQV ↑ 4-7 fold#. Insufficient data for dose recommendation	IDV ↑ 50%; NFV ↑ 80%. Limited data for: IDV 1200 mg bid + NFV 1250 mg bid	APV AUC (area under the curve) ↑ 33% No dosage change	IDV AUC and Cmin ↑ Dose: IDV 600 mg bid
Ritonavir (RTV)	–	RTV-no effect; SQV ↑ 20 fold ˇ#. Dose: Invirase or Fortovase 400 mg bid + RTV 400 mg bid	RTV-no effect; NFV ↑ 1.5 fold. Dose: RTV 400 mg bid + NFV 500-750 mg bid	APV AUC ↑ 2.5 fold. Limited data for APV 600-1200 mg bid + RTV 100-200 mg bid	Lopinavir is co-formulated with RTV as Kaletra®
Saquinavir (SQV)	–	–	SQV ↑ 3-5 fold; NFV ↑ 20%#. Use standard NFV dose + Fortovase 800 mg tid or 1200 mg bid	APV AUC ↓ 32%. Insufficient data for dose recommendation	SQV AUC and Cmin ↑ Dose: SQV 800 mg bid; LPV/r standard
Nelfinavir (NFV)	–	–	–	APV AUC ↑ 1.5 fold Insufficient data for dose recommendation	*No data*
Amprenavir (APV)					APV AUC and Cmin ↑ Dose: APV 600-750 mg bid; LPV/r standard

* Several drug interaction studies have been completed with Saquinavir given as Invirase or Fortovase. Results from studies conducted with Invirase may not be applicable to Fortovase.
ˇ Conducted with Invirase
Conducted with Fortovase

--Table adapted from: US PHS Panel. Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents. February 4, 2002; downloaded from http://www.aidsinfo.nih.gov/

Table 4

Drugs That Should Not Be Used With Antiretrovirals

Drug Category	Indinavir	Ritonavir*	Saquinavir	Nelfinavir	Amprenavir	Nevirapine	Delavirdine	Efavirenz	Lopinavir/r
Ca++ channel blocker	(none)	bepridil	(none)	(none)	bepridil	(none)	(none)	(none)	(none)
Cardiac	(none)	amiodarone, flecainide, propafenone, quinidine	(none)	(none)	(none)	(none)	(none)	(none)	flecainide, propafenone
Lipid Lowering Agents	simvastatin, lovastatin	simvastatin, lovastatin	simvastatin, lovastatin	simvastatin, lovastatin	simvastatin, lovastatin	(none)	simvastatin, lovastatin	(none)	simvastatin, lovastatin
Anti-Mycobacterial	rifampin	(none)	rifampin, rifabutin	rifampin	rifampin	(none)	rifampin, rifabutin	(none)	rifampin
Antihistamine	astemizole, terfenadine	astemizole, terfenadine	astemizole, terfenadine	astemizole, terfenadine	astemizole, terfenadine	(none)	astemizole, terfenadine	astemizole, terfenadine	astemizole, terfenadine
Gastrointestinal Drugs	cisapride	cisapride	cisapride	cisapride	cisapride	(none)	cisapride, H-2 blockers, Proton pump inhibitors	cisapride	cispride
Neuroleptic	(none)	clozapine, pimozide	(none)	(none)	(none)	(none)	(none)	(none)	pimozide
Psychotropic	midazolam, triazolam	midazolam, triazolam	midazolam, triazolam	midazolam, triazolam	midazolam, triazolam	(none)	midazolam, triazolam	midazolam, triazolam	midazolam, triazolam
Ergot Alkaloids (vasoconstrictors)	Dihydro-ergotamine (D.H.E. 45), ergotamine (various forms)	Dihydro-ergotamine (D.H.E. 45), ergotamine (various forms)	Dihydro-ergotamine (D.H.E. 45), ergotamine (various forms)	Dihydro-ergotamine (D.H.E. 45), ergotamine (various forms)	Dihydro-ergotamine (D.H.E. 45), ergotamine (various forms)	(none)	Dihydro-ergotamine (D.H.E. 45), ergotamine (various forms)	Dihydro-ergotamine (D.H.E. 45), ergotamine (various forms)	Dihydro-ergotamine (D.H.E. 45), ergotamine (various forms)
Herbs	St. John's Wort	St. John's Wort	St. John's Wort	St. John's Wort	St. John's Wort	(none)	(none)	(none)	St. John's Wort

* Some of the contraindicated drugs are listed based on theoretical considerations. Thus, drugs with low therapeutic indices yet with suspected major metabolic contribution from cytochrome P450 3A, CYP2D6, or unknown pathways are included in this table. Actual interactions may or may not occur in patients.

Suggested Alternatives:

Simvastatin, lovastatin: atorvastatin, pravastatin, fluvastatin, cerivastatin (alternatives should be used with caution)

Rifabutin: clarithromycin, azithromycin (DMAC prophylaxis), clarithromycin, azithromycin, ethambutol, (DMAC treatment)

Astemizole, terfenadine: loratadine, fexofenadine, cetirizine

Midazolam, triazolam: temazepam, lorazepam

--Table adapted from: US PHS Panel. Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents, 2/4/02; downloaded from http://www.aidsinfo.nih.gov/

Table 5, page 1 of 2

Drug Interactions Between Protease Inhibitors (PIs) and Other Drugs: Cautious Use, Dosage Modifications

Drugs Affected	Indinavir (IDV)	Ritonavir (RTV)	Saquinavir* (SQV)
Ketoconazole	IDV level ↑ 68%; Dose: IDV 600 mg tid	keto level ↑ 3X; Use with caution; max dose 200 mg ketoconazole qd	SQV level ↑ 3X Dose: Standard
Rifampin	IDV level ↓ 89%; **Contraindicated**	RTV level ↓ 35%; ↑ liver toxicity possible Dose: no data	SQV level ↓ 84%; **Contraindicated unless using RTV +SQV,** then use rifampin 600 mg qd or 3x/week
Rifabutin	IDV level ↓ 32% Rifabutin level ↑ 2X Dose: Rifabutin 150 mg qd or 300 mg 3x/week; IDV 1gm tid	Rifabutin level ↑ 4X Dose: rifabutin 150 mg every other day (qod); or dose 3X / week	SQV level ↓ 40%; **Not recommended unless using RTV +SQV,** then use RFB 150 mg 3x/week
Clarithromycin	clari level ↑ 53%; No dose adjustment	clari level ↑ 77%; Adjust dose for renal insufficiency	clari level ↑ 45%; SQV ↑ 177%; no dose adjustment
Oral Contraceptives	norethindrone level ↑ 26%; ethinylestradiol level ↑ 24%; no dose adjustment	ethinylestradiol level ↓ 40% Use alternative or additional method	No data
Simvastatin Lovastatin	Potential for large increase in statin levels. **Avoid concomitant use.**	Potential for large increase in statin levels. **Avoid concomitant use.**	Potential for large increase in statin levels. **Avoid concomitant use.**
Phenobarbitol Phenytoin Carbamazepine	Carbamazepine substantially decreases IDV levels. Consider alternative agent	Unknown; use with caution. Monitor anticonvulsant levels	Uncertain but **may substantially decrease SQV levels.** Monitor anticonvulsant levels
Methadone	No change in methadone levels	Methadone ↓ 37%; may need to ↑ methadone dose	No data
Miscellaneous	Grapefruit juice ↓ IDV levels by 26%; High-fat/high-protein meals ↓ IDV levels by 77-82%. Sildenafil (Viagra) AUC ↑ 2-11 fold; max dose 25 mg per 48 hour period	Desipramine ↑ 145%; reduce desipramine dose. Theophylline ↓ 47%; monitor theophylline levels. Sildenafil (Viagra) AUC ↑ 2-11 fold; max dose 25 mg per 48 hour period. Many other drug interactions possible.	Grapefruit juice increases SQV levels; Dexamethasone decreases SQV levels; Sildenafil (Viagra) AUC ↑ 2-11 fold; max dose 25 mg per 48 hour period

--Table adapted from US PHS Panel: *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents*. February 4, 2002; downloaded from http://www.aidsinfo.nih.gov/ (Also used: manufacturer's product information)

Table 5, page 2 of 2

Drug Interactions Between Protease Inhibitors (PIs) and Other Drugs: Cautious Use, Dosage Modifications

Drugs Affected	Nelfinavir (NFV)	Amprenavir (APV)	Lopinavir/ritonavir (LPV/r)
Ketoconazole	No dose adjustment necessary	APV level ↑ 31%; keto ↑ 44%. Combination under investigation.	LPV AUC ↓ 13%; ketoconazole ↑ 3-fold
Rifampin	Levels ↓ 82% **Contraindicated**	APV AUC levels ↓ 82%; no change in rifampin **Avoid this combination**	LPV AUC ↓ 75%; **Avoid concomitant use**
Rifabutin	NFV level ↓ 32% Rifabutin level ↑ 2X Dose: rifabutin 150 mg qd, or 300 mg 3x/week. NFV 1000 mg tid	APV AUC levels ↓ 15% rifabutin level ↑193% Dose: rifabutin 150 mg qd. or 300 mg 3x/week; standard dose APV	RFB AUC ↑ 3-fold with metabolite ↑ 47.5%. Decrease rifabutin dose to 150 mg every other day. LPV standard
Clarithromycin	No data	APV AUC levels ↑ 18%; no change in clarithromycin levels. No dose adjustment	No data
Oral Contraceptives	norethindrone level ↓ 18% ethinylestradiol level ↓ 47% Use alternative or additional method	Potential for metabolic interactions; use alternative or additional method	ethinylestradiol level ↓ 42% Use alternative or additional method
Simvastatin Lovastatin Atorvastatin Pravastatin	Potential for large increase in statin levels. **Avoid concomitant use. Atorvastatin AUC** ↑ 74%--use with caution. Simvastatin AUC ↑ 505%--not recommended. Potential for large increase in Lovastatin AUC—not recommended.	Potential for large increase in statin levels. **Avoid concomitant use with lovastatin and simvastatin.**	Potential for large increase in statin levels. **Avoid concomitant use.** Atorvastatin ↑ 5.88-fold. Use with caution and monitoring. Pravastatin AUC ↑ 33% No dose adjustment
Phenobarbitol Phenytoin Carbamazepine	Uncertain but **may substantially decrease NFV levels**. Monitor anticonvulsant levels	Uncertain but **may substantially decrease APV levels.** Monitor anticonvulsant levels	Unknown but **may substantially ↓ lopinavir levels**. Monitor anticonvulsant levels
Methadone	NFV may ↓ methadone levels but minimal effect on maintenance dose. Monitor and titrate dose ↑ if needed	No data	Methadone AUC ↓ 53% Monitor and titrate dose ↑ if needed.
Miscellaneous	Sildenafil (Viagra) AUC ↑ 2-11 fold; max dose 25 mg per 48 hour period	Sildenafil (Viagra) AUC ↑ 2-11 fold; max dose 25 mg per 48 hour period	Probable substantial increase in sildenafil ACU. Do not exceed 25 mg in 48 hour period

Table 6

Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) and Other Drugs
Cautious Use and Dose Modifications

Drug Affected	Nevirapine (NVP)	Delavirdine (DLV)	Efavirenz (EFV)
Ketoconazole	ketoconazole level ↓ 63% NVP level ↑ 15 - 30% **Not recommended**	*No data*	*No data*
Rifampin	NVP level ↓ 37% **Not recommended**	DLV level ↓ 96% **Contraindicated**	EFV level ↓ 25% No dose adjustment
Rifabutin	NVP level ↓ 16% No data for rifabutin dose	DLV level ↓ 80% Rifabutin level ↑ 100% **Not recommended**	EFV level unchanged Rifabutin level ↓ 35% Dose: ↑ Rifabutin dose to 450-600 mg qd or 600 mg 3x/week. EFV standard
Clarithromycin	NVP level ↑ 26% clarithromycin ↓ 30% No dose adjustment	clarithromycin level ↑ 100% DLV ↑ 44% Adjust dose for renal failure	clarithromycin level ↓ 39% **Alternative recommended**
Oral Contraceptives	↓ ethinyl estradial levels 20%, use alternative or additional method	*No data*	Ethinylestradiol ↑ 37% No data on other component. Use alternative or additional methods
Simvastatin **Lovastatin**	*No data*	Potential for large increase in statin levels. **Avoid concomitant use**.	No data
Phenobarbitol **Phenytoin** **Carbamazepine**	Unknown; use with caution; Monitor anticonvulsant levels.	Unknown but **may decrease DLV levels substantially**; monitor anticonvulsant levels.	Unknown; use with caution; monitor anticonvulsant levels.
Methadone	NVP level unchanged, methadone↓ significantly. Titrate methadone dose to effect. **When d/c ing NVP, must decrease methadone dose**	*No data*	Methadone ↓ significantly. Titrate methadone dose ↑ to effect
MISCELLANEOUS	*No data*	May increase level of dapsone, warfarin and quinidine. Sildenafil (Viagra): potential for increased concentrations and adverse effects. Max dose 25 mg / 48 hrs	Monitor warfarin when used concomitantly

-- Table adapted from: US PHS Panel. *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents*, 2/4/02; downloaded from http://www.aidsinfo.nih.gov/

Table 7

Drug Interactions Between Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs) and Other Drugs
Cautious Use and Dose Modifications

Drug Affected	Zidovudine (ZDV)	Stavudine (d4T)	Didanosine (ddI)	Tenofovir
Methadone	No data	d4T level ↓ 27%; methadone unchanged. No dose adjustment	ddI level ↓ 41%; methadone level unchanged. Consider ddI dose increase	No data
Ribavirin	Ribavirin inhibits phosphorylation of ZDV; this combination should be avoided if possible	**No data**	No data	No data
Didanosine buffered tablets	No data	**No data**	No data	ddI AUC ↑ by 44%, Cmax ↑ by 28% Monitor for ddI related toxicities
Cidofovir, ganciclovir, valganciclovir	No data	No data	No data	Possibly competes for active tubular secretion with tenofovir, may increase serum concentration of these drugs and/or tenofovir. Monitor for dose-related toxicities

-- Table adapted from: US PHS Panel. *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents*, 2/4/02; downloaded from http://www.aidsinfo.nih.gov/

Resistance Testing

Definitions:

As of early 2003, there are two major types of resistance testing available:

a) **Genotypic testing,** which looks at genetic mutations, takes 1-2 weeks to complete. Must be correlated with what is known about specific mutation sites as relates to individual drugs. Based on PCR technology, it can generally detect mutations in plasma samples with more than 1000 copies of HIV RNA per ml. Species comprising 20% or more of amplified product can usually be detected by current techniques. Expert clinical interpretation is necessary to put results in their proper perspective, including an appreciation of the patient's previous history and available options for further treatment. A compilation of the most common HIV-1 mutations selected by the three classes of ARV agents is available at http://hiv-web.lanl.gov

b) **Phenotypic testing**, which looks at viral replication in the presence of specific antiretroviral agents, takes 2-3 weeks, and measures the 50% to 90% inhibitory concentrations of a drug against the virus in vitro. Results can be reported as fold-change in IC-50 or IC-90, as compared to a drug-susceptible control strain, or to a previous test of the same patient's blood. Again, resistant variants with few copies may be undetected, and expert interpretation is helpful to determine the significance of results.

Modifying factors: Viral population in any person is changed by selective resistance to drugs in the patient's system. This may include early mutations that precede the appearance of detectable increases in inhibitory concentrations, and mutations that have decreased in number after discontinuation of previous medication(s), which is why this test is drawn while the patient is still on the failing regimen.

The presence of viral resistance suggests that a particular drug (and drugs with similar resistance patterns, e.g., cross-resistant) are likely to be unsuccessful in suppressing viral replication. In contrast, the absence of resistance to a drug does not necessarily indicate that it will be successful, particularly if that drug (or drugs sharing cross-resistance) have been used previously. In such situations, minority populations of resistant viruses may exist in reservoirs, and may emerge rapidly under selective pressure when the drug is started.

Changing therapy for HAART regimen failure: As discussed in the section on antiretroviral therapy, adherence should always be assessed first when a HAART regimen fails. Other factors beyond non-adherence and resistance may cause failure of antiretroviral therapy, such as drug-drug interactions and malabsorption. If resistance is still suspected, **testing should be done while the patient is taking the failing regimen**, for reasons noted above.

Resistance testing recommendations:

Clinical Setting/Recommendation	Rationale
Recommended	
Virologic failure during HAART	Determine the role of resistance in drug failure and maximize the number of active drugs in the new regimen if indicated
Suboptimal suppression of viral load after initiation of HAART	Determine the role of resistance and maximize the number of active drugs in the new regimen if indicated
Consider	
Acute or primary HIV infection	Determine if drug resistant virus was transmitted and change regimen accordingly
Not generally recommended	
Chronic HIV infection prior to starting therapy	Uncertain prevalence of resistant virus; minor drug-resistant species may not be detectable
After discontinuation of drugs	Drug resistance mutations may decrease in number and become undetectable on assays
Plasma viral load <1000 HIV RNA copies/mL	Resistance assays unreliable due to low number of RNA copies

Reference:

USPHS/IDSA Guidelines for use of Antiretroviral agents in HIV-infected adults and adolescents. February 4, 2002, downloaded from http://www.aidsinfo.nih.gov/

Fat Redistribution on HAART

Definition: Fat maldistribution associated with HIV antiretroviral therapy can be difficult to describe, as there is no standard case definition. Sometimes referred to as lipodystrophy, this syndrome includes body composition changes of central fat accumulation and peripheral fat atrophy. Most common morphologic changes include fat accumulation across the abdomen, gynecomastia in males, breast enlargement in females, and buffalo hump in both sexes. Also reported are fat depletion (lipoatrophy) in the face, buttocks, and limbs, with venous prominence. These changes are variable, with some patients reporting only lipoatrophy and some complaining of fat accumulation, while others present a mixed picture. Fat maldistribution happens gradually, usually months after initiation of HAART, and may damage self-image and quality of life.

Background: Initially associated with PIs, it is now recognized that the condition develops in some PI-naïve patients, and mitochondrial dysfunction probably plays a role. Both PIs and NRTIs are likely to contribute to the problem. One of the few specific associations of symptoms with drugs is that stavudine seems to be more associated with fat atrophy. Host factors are also thought to affect its presentation. For example, individuals with a higher BMI at baseline are more likely to notice fat accumulation, and those with lower BMIs are more likely to notice fat loss.

S: Patient may report some manifestations of the following: abdominal fat accumulation, increased neck size, buffalo hump, enlarged breasts; women may note increased bra size. Patient may also c/o decreased arm and/or leg circumference, sunken cheeks, buttock flattening, temporal wasting, and even pain in walking due to atrophy around soles of feet. Patient may volunteer that changes are causing emotional distress.

Hx: If body habitus changes noted, query about above factors, including level of emotional distress with the situation. Medication history, duration of each, recent adherence

O: Compare past and current weights. Review lab history: glucose, cholesterol triglycerides (see lactic acidosis and dyslipidemia).
PE: Measure and document waist and hip; check ratio. Values > 0.95 in men and > 0.85 in women are associated with increase CHD risk. Some suggest that an abdominal circumference > 100 cm. (~39 inches) is a better diagnostic tool. Examine for buffalo hump, temporal and extremity fat wasting. If calipers are available, skin-fold measures can be taken.

A: HAART-related fat redistribution; specify peripheral fat depletion and/or central fat accumulation. Assess for other toxicities of HAART, such as dyslipidemia, dysglycemia, lactic acidosis (see relevant topics, this section.)

P: Labs: Fasting lipid profile, blood glucose to rule out metabolic disorders. (See *Dyslipidemia* and *Insulin Resistance,* this section, for further information on workup and treatment.)

Evaluate effect of body shape changes on self-esteem, medication adherence, and interpersonal relationships. If patient is sufficiently distressed to consider discontinuing or interrupting HAART, review with the patient any gains they have made on HAART; discuss other measures that may be taken to reduce maldistribution effects; go over the risks and benefits of a supervised treatment interruption, and refer to mental health as needed.

TX:
The lack of case definition combined with individual variances in metabolic and morphologic changes create difficulty in identifying and managing these syndromes, although the following are considered reasonable approaches:

Drug Substitutions
Currently there is no standard recommendation for reversing fat redistribution. Studies to date have shown mixed results when substituting a new drug for the suspected offending agent(s), although patients on stavudine (d4t) may benefit from switching to another drug.

Non-Pharmacologic measures
Diet: If overall weight reduction is needed, avoid rapid weight loss plans, since lean body mass is often disproportionately lost. Refer to dietician, with consideration of any lipid or glucose abnormalities, to help patient decrease intake of saturated fat, simple sugars, and alcohol.

One option is the incorporation of **exercise (muscle-building)** training to improve the ratio between fat and muscle composition in body areas of muscle wasting and fat accumulation. Some studies using this intervention have shown some improvement in fat redistribution. Moderate exercise should be encouraged in all patients.

Some clinicians have used **anabolic steroids** or **growth hormone** to improve morphologic appearance; however, once these agents are discontinued, morphologic changes re-appear. Growth hormone has the added disadvantage of fostering insulin resistance, which is already a problem for some patients on PIs. These drugs are investigational and recommendations on types, dosages, frequency, and duration are unavailable.

Another option for the treatment of morphologic changes is the use of **plastic and reconstructive surgery**, including liposuction, breast reduction, cheek implants, etc. However, such procedures are extensive, costly, not covered by private or public payer sources, and in some cases, may only be a temporary solution, as abnormalities may re-appear following surgery.

Antidiabetic drugs
Studies of HIV-infected patients with fat accumulation along with insulin resistance have shown success with metformin. In addition to its main indication of reducing blood glucose, it seems to have modestly reduced central adiposity in a couple of studies. If used for these patients, it must be given cautiously and monitored carefully, given its association with lactic acidosis and hepatotoxicity.

Studies of troglitazone, a thiazolidinedione that is no longer available, on fat atrophy in diabetic individuals showed partial restoration of subcutaneous fat. Although clinical trials on HIV-infected individuals are underway using other thiazolidinediones, one small pilot study recently found improvement in fat redistribution and insulin resistance with rosiglitazone.

Patient education:

1. (If patient decides to stay on HAART) Review schedule and affirm adherence to regimen.
2. If you decide you need to come off HAART for any reason, please call and discuss it. In the event that you do, you will need to stop all HAART drugs at once. We will need to change some of your laboratory monitoring and may need to add other medications to try and avoid opportunistic infections.
3. Exercise to build muscle may be helpful to you (assess resources in your area for safe muscle-strengthening possibilities).
4. If weight reduction is needed, follow dieticians' recommendations. Quick weight loss diets may result in excessive muscle loss.

References:

CDC. Guidelines for Using Antiretroviral Agents among HIV-Infected Adults and Adolescents: Recommendations of the Panel on Clinical Practices for Treatment of HIV. *MMWR* 2002; 51 (No. RR-7)

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Gelato MC, Mynarik DC, Quick JL, et al. Improved insulin sensitivity and body fat distribution in HIV-infected patients treated with rosiglitazone: A pilot study. *JAIDS*, 2002:31(2), 163-170

Dyslipidemias on HAART

Definition: Elevations of triglycerides and low-density lipoprotein (LDL) cholesterol and decreases in high-density lipoprotein (HDL) cholesterol, compared to pre-treatment baseline levels, in patients receiving HAART. HIV infection itself plays a role in lipid abnormalities; in untreated patients, low HDL, low total cholesterol, and elevated triglycerides are common. Patients on protease inhibitors are more likely to have elevations in LDL and further increases in triglyceride levels. Patients on NNRTIs have increases in total cholesterol and LDL, which are often partially offset by increased HDL. In general, patients on HAART show lipid abnormalities after a few months of therapy, although patients on any dose of ritonavir may begin to show changes within a month, especially in triglyceride levels. These lipid abnormalities suggest a higher risk for coronary artery disease, and elevated triglycerides may be associated with pancreatitis as well. Patients with a family history and other risk factors for CHD, as well as fat redistribution abnormalities, may have higher incidence of dyslipidemia.

Background: Randomized clinical trials to determine optimal management of HAART-related hyperlipidemia have not been completed. Risk estimates and information from the National Cholesterol Education Project (Adult Treatment Panel III) are based on non-HIV-infected patients in the Framingham cohort, and may not correspond exactly to HAART-related hyperlipidemia, although expert panels working with HIV-infected patients generally recommend similar treatment methods and goals in dealing with HAART related dyslipidemia. LDL cholesterol is generally the target of interventions.

S: Evaluate for factors which contribute to CHD risk: hypothyroidism, hypogonadism, liver disease, alcohol abuse. Check cardiac risk factor history, as well as family history for all of the factors below. Check medications the patient is taking, especially anabolic androgenic steroids, which have been shown to increase LDL.

The following are CHD risk or CHD equivalents, in that patients with these conditions have a high risk of a serious cardiac event and can benefit from intensive LDL-lowering therapy.

Personal hx of CHD or CHD equivalents (peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease)
Diabetes
Multiple risk factors which confer a >20% CHD risk over the next 10 years (see website under "assessment" or last page of *Dyslipidemi*a to quantify risk for patients without CHD or diabetes)

Additional risk factors

Cigarette smoking
Hypertension ≥ 140/90, or on antihypertensive medication
HDL <40
Patient age >45 for males, or >55 for females
Family hx of early CHD in first degree relatives (males <55, females < 65)

O: Review baseline labs prior to starting antiretroviral therapy, specifically lipid profile and blood glucose. See blood pressure history, weight changes.

A: For patients who do not have diabetes or pre-existing CHD (or CHD equivalents, above), and who have 2 or more risk factors, perform a "10-year-risk of cardiovascular event" by using the risk estimate page at end of this protocol , or visit: http://hin.nhlbi.nih.gov/atpiii/calculator.asp

P: Labs:

- Measure serum lipids after fasting 8 hours minimum (ideally 12 hours), to include total cholesterol, HDL cholesterol, and triglycerides with calculated LDL and VLDL cholesterol prior to starting HAART.
- Repeat lipid profile within 3-6 months after starting HAART regimen, and sooner (1-2 months) in those with elevated triglycerides prior to therapy. Patients with normal follow-up profiles will need annual screening, and those with abnormal values will need more intensive monitoring (q 4-6 weeks) until LDL goal is met; after which monitoring ever 4-6 months is adequate. Any time a new HAART regimen is begun, re-check lipids at 3-6 months, sooner if pre-existing abnormalities.

Treatment for hypertriglyceridemia

In cases of isolated hypertriglyceridemia, non-drug interventions such as smoking cessation, aerobic exercise, and diet modification should be tried before using drug therapy. Those with CHD/CHD equivalents or high risk of CHD may need pharmacologic therapy if diet and exercise fail. See Table 3.

Fibrates are first-line drug treatment in isolated hypertriglyceridemia and are an alternate option in concurrent hypertriglyceridemia and hypercholesterolemia. Gemfibrozil or micronized fenofibrate reduce triglyceride levels effectively in patients on PIs, and are not metabolized by Cytochrome P-450.

- Standard gemfibrozil dose: 600 mg po bid 30 min ac
- Standard micronized fenofibrate dose: 200 mg po qd

If use of a fibrate alone is inadequate in reducing triglycerides or LDL cholesterol, the cautious addition of a statin should be considered; note increased risk of skeletal muscle toxicity with concomitant use. Rhabdomolysis has been associated with elevated statin levels. Statin level elevation is also a concern in patients taking protease inhibitors that inhibit CYP3A4. (See Table 4:Statin Agents and HAART Interactions.)

Treatment for Hypercholesterolemia

Therapeutic lifestyle modification should be used prior to using drug therapies. In patients with serum triglycerides > 400 mg/dL, the LDL cholesterol calculation is unreliable. For those individuals, dietary intervention is warranted if total cholesterol > 240 mg/dl or HDL cholesterol < 35 mg/dl. For those with triglycerides < 400, use LDL and table below for intervention levels. If non-pharmacologic intervention fails, HMG-CoA reductase inhibitors (statins) reduce total and LDL cholesterol levels in HIV infected patients on PIs.

Drug Interactions: Of all the statin drugs, pravastatin is least affected by PIs. Although ritonavir/saquinavir combination therapy decreased statin levels by 50%, lower doses of ritonavir and other PIs do not seem to substantially affect levels. **Atorvastatin may be used at the lowest possible dose**, although ritonavir/saquinavir combination therapy raised blood levels of atorvastatin and its metabolites as well.

Standard dose Pravastatin: 20 mg po qd
Standard dose Atorvastatin: 10 mg po qd

Bile acid sequestrants are avoided due to potential for interference with drug absorption, and may increase triglyceride levels. **Niacin may worsen insulin resistance**, a common concomitant with dyslipidemia. **Fibric acids and statins together have an increased risk of rhabdomyolysis,** and must be used with caution and careful monitoring.

Effect of Switching Antiretroviral Therapy. Data suggest that replacing PIs with an NNRTI, NRTI, or NtRTI may be associated with improved lipid profiles. There are no study reports available comparing switching strategies versus addition of lipid-lowering agents to successful antiretroviral therapy. Long-term virologic effects of switching therapy remain unknown, especially in treatment-experienced patients.

Table 1. Intervention Criteria for Elevated LDL Cholesterol

Risk factors, 10 year risk estimate	Consider Therapeutic Lifestyle Changes	Consider Drug Therapy	LDL-C Goal
Without CHD or CHD equivalents and < 2 risk factors	LDL ≥ 160 mg/dL	≥ 190 mg/dL	<160 mg/dL
Without CHD or CHD equivalents and ≥2 risk factors, with 10 year estimated risk <10%	LDL ≥ 130 mg/dL	≥ 160 mg/dL	< 130 mg/dL
Without CHD or CHD equivalents and ≥2 risk factors and 10-year estimated risk between 10-20%	LDL ≥ 130 mg/dL	≥ 130 mg/dL	< 130 mg/dL
With CHD or CHD equivalents	LDL ≥ 100 mg/dL	≥ 130 mg/dL	< 100 mg/dL

Table 2. Choice of initial drug treatment for lipid abnormalities

Lipid abnormality	First choice	Second choice	Comments
Isolated ↑ LDL	Statin	Fibrate	• Start with lower statin doses and titrate up; patients on PIs may have ↑ risk of myopathy
Isolated ↑ triglycerides	Fibrate	Statin	• Combined statin and fibrate may further increase myopathy risk
↑ cholesterol and ↑ triglyerides	Fibrate or statin	Fibrate or statin*	• Combined statin and fibrate may further increase myopathy risk

*if started with fibrate add statin, and vice versa

Table 3. Interventions for isolated hypertriglyceridemia

	Diet and exercise	Consider Drug therapy	Drug therapy Indicated
no pre-existing pancreatitis	≥200 mg/dL (fasting)	≥1000 mg/dL (fasting)*	≥2000 mg/dL (fasting)**
previous episode of pancreatitis, or if non-reponsive to diet and exercise	--	>500 mg/dL (fasting)**	> 1000 mg/dL (fasting)**

* If unresponsive to non-pharmacologic interventions
** Pharmacologic and non-pharmacologic intervention may be initiated simultaneously
-- Although no specific recommendations have been made, prudent practice would suggest lower action levels for patients with pre-existing pancreatitis

Table 4. Statin Agents and HAART Interactions

Agent	Considerations
Lovastatin Simvastatin	Extensive metabolization by CYP3A4 Toxicity likely when combined with Protease Inhibitors
Fluvastatin	Metabolized by CYP2C9 Decreased levels of nelfinavir likely
Cerivastatin	Limited data on drug interactions Low likelihood of interactions
Atorvastatin	Some CYP3A4 metabolism Increased AUC of Atorvastatin when given with ritonavir-saquinavir
Pravastatin	No significant p450 interactions; primarily renal excretion Slightly decreased AUC when given with ritonavir-saquinavir

Calculations for estimate of 10 year risk of cardiac event for men (and women)

Add up points from the top five tables (Age, HDL, B/P, Total Cholesterol, Smoking Status). Note that women's points are in parentheses. After adding points from all tables, consult the Cardiac Risk Estimate for Men and Women table, below.

Age	Points Men	(Women)
20-34	-9	(-7)
35-39	-4	(-3)
40-44	0	(0)
45-49	3	(3)
50-54	6	(6)
55-59	8	(8)
60-64	10	(10)
65-69	11	(12)
70-74	12	(14)
75-79	13	(16)

HDL(mg/dL)	Points Men	(Women)
≥ 60	-1	(-1)
50-59	0	(0)
40-49	1	(1)
<40	2	(2)

Systolic B/P	If Untreated (W)	If Treated (W)
<120	0 (0)	0 (0)
120-129	0 (1)	1 (3)
130-139	1 (2)	2 (4)
140-159	2 (3)	3 (5)
≥ 160	2 (4)	3 (6)

Total Cholesterol	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
< 160	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
160-199	4 (4)	3 (3)	2 (2)	1 (1)	0 (1)
200-239	7 (8)	5 (6)	3 (4)	1 (2)	0 (1)
240-279	9 (11)	6 (8)	4 (5)	2 (3)	1 (2)
≥ 280	11 (13)	8 (10)	5 (7)	3 (4)	1 (2)

	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Smoker	8 (9)	5 (7)	3 (4)	1 (2)	1 (1)

Cardiac Risk Estimate for Men and Women

Add points from each table above (women's values in parentheses), and compare to risk % below:

Men		**Women**	
Point Total	10-Year Risk %	Point Total	10-Year Risk %
< 0	<1	<9	<1
0	1	9	1
1	1	10	1
2	1	11	1
3	1	12	1
4	1	13	2
5	2	14	2
6	2	15	3
7	3	16	4
8	4	17	5
9	5	18	6
10	6	19	8
11	8	20	11
12	10	21	14
13	12	22	17
14	16	23	22
15	20	24	27
16	25	≥ 25	≥ 30
≥ 17	≥ 30		

Adapted from: National Cholesterol Education Program, Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) May 2001.

References:

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Adult AIDS Clinical Trials Metabolic Guides: *Lipid disturbances*. Downloaded 10/30/02 from http://aactg.s-3.com/

Drug manufacturer's product information.

Insulin Resistance/Hyperglycemia on HAART

Background and definitions: Patients on HAART, particularly on PI-containing regimens, appear to have increased risk of dysglycemia. Hyperglycemia with or without diabetes has been reported in 3-17% of patients, occurring at a median of ~60 days, with a range from 2 days to over a year after starting therapy. Disorders of glucose metabolism may present as:

- insulin resistance, in which higher concentrations of insulin are required to exert normal effects, in which case blood glucose levels may be normal but fasting insulin levels will be high due to compensatory insulin secretion by the pancreas;
- impaired glucose tolerance, a glucose of 140-199 two hours after a 75 gram oral glucose load;
- impaired fasting glucose, that is 110-125mg/dl; and
- diabetes mellitus, which is diagnosed when the fasting blood sugar is ≥ 126 mg/dl, or the 2-hour glucose level is ≥ 200 mg/dl and confirmed with repeat testing.

The onset of new-onset hyperglycemia on HAART has been reported as 5%, although some cohorts have reported hyperglycemia rates as high as 17%. Even if fasting glucose levels remain normal in patients on HAART, up to 40% of those on a PI-containing regimen will show impaired glucose tolerance. Patients who have pre-existing diabetes must be closely monitored when starting HAART; some experts would consider a PI sparing regimen for these patients. Those with no history of diabetes should be advised about the warning signs of hyperglycemia (polydipsia, polyuria, and polyphagia) and the need to use diet and exercise to maintain an ideal body weight.

S: Patient considering HAART or has been on HAART regimen which includes a protease inhibitor. Often asymptomatic, patients with hyperglycemia may note polydipsia, polyuria, and polyphagia. Take history of:

- fat redistribution on HAART (see *Fat Redistribution* section)
- family history of diabetes, obesity or habitual physical inactivity
- racial or ethnic heritages at higher risk: African, Hispanic, Native American, Asian-Pacific Islander
- hypertension
- low HDL
- elevated triglycerides
- history of gestational diabetes or delivery of infant > 9 lbs
- polycystic ovarian syndrome
- current pregnancy

O: Review previous/baseline blood glucose levels. Document weight and any weight changes or fat redistribution.

A: Determine if normal blood glucose, impaired fasting glucose, or diabetes (see lab recommendations and definitions below)

P: **Labs:** Some experts (IAS-USA) recommend routine fasting blood glucose levels at baseline and 3-6 months after starting therapy if baseline is normal. Others recommend 2 hour post-prandial measurements within the first 3 to 4 months and every 3-4 months thereafter (more frequently if abnormalities detected), especially if any additional risk factors exist as noted above. Patients with these risk factors should also be carefully counseled about prevention prior to starting HAART.

Treatment: Drug treatment is not indicated for patients with insulin resistance and normal blood glucose levels, although lifestyle modification can be recommended. Some studies are underway, however, and patients with access to clinical trials may meet inclusion criteria. Evidence to date is inadequate to recommend drug treatment for patients with impaired glucose tolerance and normal fasting blood sugar, although weight loss is strongly recommended if the patient is overweight. Refer to dietician.

Drug treatment of insulin resistance and hyperglycemia is more problematic in that oral hypoglycemic agents may increase the risk of renal and hepatic abnormalities. When drug treatment is required, for patients who meet the standard for diagnosis of diabetes and in whom lifestyle changes are not adequate, metformin or thiazolidinediones (pioglitazone or rosiglitazone) should be considered, because of their insulin-sensitizing ability. Monitoring for hepatic toxicity (thiazolidinediones) and lactic acidosis (metformin) should be increased in these patients, and

patients with significant liver disease should not take thiazolidinediones. Patients with elevated serum creatinine or lactic acidemia should not take metformin. Caution is warranted when using sulfonylureas along with hepatotoxic agents. In some cases, insulin may be the safest drug therapy for symptomatic hyperglycemia, although episodes of hypoglycemia are much more common than with most oral agents.

Recommendations for patients with diabetes:

- Measure urine microalbumin
- Maintain HbA1c < 7%
- Maintain triglyceride levels < 200 mg/dL
- Maintain LDL < 100 mg/dL
- Maintain B/P < 130/85
- Lifestyle modification: smoking and alcohol cessation, increase exercise, weight loss, nutritional counseling
- Annual retinal exam by ophthalmologist
- Annual oral health exam
- Annual foot exam
- Aspirin therapy for evidence of macrovascular disease, family history of CHD, history of smoking, or secondary prevention after vascular events

See American Diabetes Association, Clinical Practice Recommendations. *Diabetes Care*, at http://care.diabetesjournals.org

Patient education:

1. HAART can increase the risk of diabetes in some individuals. Report any difficulty with excessive hunger and thirst, and increased urination. We will monitor your blood glucose when we do lab work, but it is important to know if you have any symptoms.
2. Review exercise possibilities with patient to determine what activities might be realistic and acceptable for the patient.
3. For lifestyle modifications (minor blood glucose abnormalities): Review eating habits and explain the need to work with dietician to keep blood glucose (and triglycerides) within normal limits to avoid permanent damage to blood vessels of the eye, kidney, and brain, as well as reduce risk of heart attack.
4. Do medication-specific education, especially if patient will be on metformin.
5. Consider referral to diabetic clinic for specialty needs.

References:

Shambelan M, Benson CA, Carr A, et al. Management of Metabolic Complications Associated with Antiretroviral Therapy for HIV-1 Infection: Recommendations of an International AIDS Society-USA Panel. *J AIDS* 2002, 31:257-275.

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New York State Department of Health AIDS Institute. *Side effects of antiretroviral therapy*. Downloaded 10/30/02 from http://www.hivguidelines.org/public_html

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Lactic Acidosis and Hyperlactatemia on HAART

Definition: Lactic acidosis (LA) and hyperlactatemia are related to mitochondrial dysfunction, and associated with NRTI therapy. Manifestations range from asymptomatic elevations in lactate to lactic acidosis and rapid progression to death. May present with or without pancreatitis. Risk factors for LA include African-American ethnicity, obesity, female gender, chronic Hepatitis C, ethanol use, and prolonged NRTI use, especially with regimens that include stavudine, didanosine, or zalcitabine. Typical laboratory abnormalities include:

- Elevated lactate levels
- Elevated anion gap: $Na - [Cl + CO2] > 16$
- Elevated aminotransferases, CPK, LDH, lipase and amylase

S: Early symptoms may be subtle and variable, including GI symptoms without dramatic elevations of liver enzymes. Symptoms of LA are non-specific, and may include two or more of the following: Abdominal pain, anorexia, N/V, malaise, myalgias, generalized weakness, abdominal distention, paresthesias, ascending neuromuscular weakness, and SOB. Ask about medications and duration.

O: Tachypnea, weight loss, hepatomegaly. Check previous liver enzyme history and anion gap trends. Asymptomatic hyperlactatemia may show only elevated lactate with normal HCO3.

A: Prolonged NRTI use with symptoms and laboratory abnormalities suggests possible lactic acidosis. Low grade hyperlactatemia without symptoms is not thought to be predictive of subsequent lactic acidosis.

P: Measure lactate levels, electrolytes, aminotransferases, CPK, LDH, lipase and amylase.
Serum Lactate levels from 2 to 5 mmol/dL are considered elevated and need to be correlated with symptoms. Levels above 5 are clearly abnormal, and >10 indicates a severe and potentially life-threatening situation.

> **Lab Collection Note:** pre-chilled fluoride-oxalate tubes must be used to collect lactate levels, which are then transported on ice to the lab ASAP (at least within 4 hours of collection.) Blood should be drawn without using a tourniquet or fist-clenching, and if possible, without stasis. If tourniquet must be used, apply lightly and draw lactate first with the tourniquet still in place.

Tx: Patients with lactic acidosis need to have NRTIs discontinued immediately; see *HAART* in Antiretroviral section for information on discontinuation of medications. Patients with shortness of breath and tachypnea may progress to respiratory failure and require mechanical ventilation. Admission is often indicated for IV fluids, supportive care, and close monitoring.

Definitive treatment for lactic acidosis has not been established. Although no controlled clinical trial reports are available as of this writing, anecdotal reports have suggested use of antioxidants and nutrients such as some or all of these. Expert consultation is recommended as quickly as available.

1) Thiamine (vitamin B-1), 50-100 mg per day
2) Riboflavin (B-2), 50-200 mg/day
3) L-Carnitine, pharmaceutical grade, 990 mg tid
4) Co-enzyme Q-10; dose not established, but <50 mg/day is probably insufficient
5) Other agents, such as vitamins A, C, and E may be helpful, in doses dependent on patient's height and weight, preferably with nutritional consultation
6) Idabenone, a Co-enzyme Q analogue, may be available from its Japanese manufacturer. It has been used in some cases of mitochondrial dysfunction when the CNS was involved.
7) Hemodialysis may help clear lactic acid

Asymptomatic patients: Routine monitoring of serum lactate levels is not indicated in asymptomatic patients with lactate level <5, normal NaCO3, and normal anion gap.

References:

CDC. Guidelines for Using Antiretroviral Agents among HIV-Infected Adults and Adolescents: Recommendations of the Panel on Clinical Practices for Treatment of HIV. *MMWR* 2002; 51 (No. RR-7)

Adult AIDS Clinical Trials Metabolic Guides: Hyperlactatemia and lactic acidosis. Downloaded 10/30/02 from http://aactg.s-3.com/

New York State Department of Health AIDS Institute. *Side effects of antiretroviral therapy*. Downloaded 10/30/02 from http://www.hivguidelines.org/public_html

Fischbach F. A Manual of Laboratory and Diagnostic Tests, 6th ed. 2000; New York, Lippincott.

CHAPTER 7: Common HIV Drugs

This section is intended for brief review of selected common medications used in HIV and AIDS care, and their primary usages in the adult and adolescent HIV-infected population.

NOTE: The following drug list and information is neither comprehensive nor all-inclusive. This information is not intended to supplant detailed review of clinical trials, labeling, packaging materials, and other sources of information, particularly for side effects, drug interactions, new drugs, and new indications for old drugs. Especially in the area of drug interactions, new sources must be consulted frequently, because new problems surface frequently. Consultation from a clinical pharmacist is often essential for determining whether drugs can be used concomitantly, and what dosage adjustments or additional monitoring might be required.

Before using any drug during pregnancy or otherwise, refer to full prescribing information available on the drug. All drug-related adverse events can be reported to FDA's MedWatch, at **1-800-FDA-1088**.

Pregnancy Categories: Brief information on pregnancy categories has been added to medications listed in this section. Even though this data is almost always much less than clinicians need to know, especially for Category C drugs, it tells a little about what testing has been performed on animals during gestation. This information is somewhat helpful in considering the medication's possible effect on human fetal development. Interestingly, animal teratogenicity does not necessarily mean that a drug is teratogenic in humans; out of 1200 known animal teratogens, only about 30 are known to be teratogenic in humans (USPHS, 1997). However, because of some serious incidents with prescription drugs and birth defects, drug companies are reluctant to perform clinical trials on pregnant women.

Collecting More Information: Because of the lack of information, a group of drug companies have set up a confidential registry to help collect data on the fetal effects of antiretroviral exposure in utero, to try and help fill in the gaps on what clinicians need to know to care for pregnant women. For information on the registry, go to http://www.apregistry.com, or call the number below. Clinicians are encouraged to use this service, and help contribute information on the antiretroviral drugs *(see Treatment During Pregnancy* in the Health Maintenance section). This effort will eventually help clinicians, but much more is needed. While we await more observations, the clinician must offer optimal treatment to pregnant women despite limited information on possible fetal effects. To enroll a pregnant woman whose fetus was exposed to antiretroviral medications in utero, **call prior to the infant's birth** at **1-800-258-4263**

Treatment During Pregnancy, in the Health Maintenance section, contains more information on how medications should be used during gestation, including some data on animal teratogenicity and crossing of the placental barrier. **Note that no information is given in this manual about the presence of medications in breast milk, since breast feeding is not recommended for HIV-infected women due to the additional risk of HIV infection.**

The following **Pregnancy Category** codes are used in this section:

Category A - Adequate, well-controlled studies in pregnant women have failed to show fetal risk.

Category B - No evidence of risk in humans. Either animal findings show risk, but human findings do not; or no adequate human studies have been done, and animal studies show no risk.

Category C - Risk to fetus cannot be ruled out. Human studies are lacking, and animal studies either haven't been done, or are positive for fetal risk. Consider use if benefit outweighs potential risk.

Category D - Possible evidence of risk. Investigational or post-marketing data show risk to the fetus. However, potential benefits may outweigh the potential risk. Generally this rating is reserved for drugs with no safer alternatives.

Category X - Contraindicated in pregnancy. Studies have shown fetal risk clearly outweighs any possible benefit to the patient.

ABACAVIR (Ziagen®, 152U89)

Abacavir is also a component of Trizivir®, which contains abacavir, zidovudine, and lamivudine; and Combivir®, which contains zidovudine and lamivudine)

Classification: Antiretroviral, nucleoside reverse transcriptase inhibitor

Indications: HIV infection, in combination therapy with other antiretrovirals

Adult Dose: 300 mg po bid;
For patients with cirrhosis and a Childs-Pugh score of 5-6, consider decreasing dose to 150 mg. po bid

Contraindications: Previous hypersensitivity to abacavir or any ingredient in tablet or liquid. (See Side Effects below.)

Drug Interactions: **Alcohol** increases abacavir levels by 40%; abacavir has no effect on alcohol.
Methadone levels may be reduced by abacavir.

Side effects: typically mild: nausea, anorexia, headache, malaise, abdominal pain, diarrhea, and rash. Fever, chills or symptoms below call for discontinuation of the drug.

Potentially fatal hypersensitivity response in ~5% of patients, generally present within the first few days to six weeks, but have been observed up to 10 months after starting: flu-like symptoms, which may include fever, malaise, fatigue, abdominal cramps, nausea, diarrhea, with or without a cutaneous rash. Less often, cough, shortness of breath, pharyngitis, itching, swelling, and joint aches may occur. Easily mistaken for acute respiratory infection, gastroenteritis, or allergy to other drugs; does not resemble anaphylaxis. These symptoms tend to worsen until the drug is discontinued, then resolve in 1-2 days. Once discontinued due to suspected hypersensitivity, the drug should not be restarted. Re-challenge can result in life-threatening hypotension and death.

Report hypersensitivity reactions to 1-800-270-0425 as well as to MedWatch (1-800-FDA-1088).

Note that once the drug is **discontinued for any reason other than symptoms suspicious of hypersensitivity, it should be restarted, in a safe place**, such as the clinic or office, where emergency intervention can be instituted immediately. If the clinical presentation of any acute illness on abacavir cannot be clearly differentiated from a hypersensitivity reaction, abacavir must be permanently discontinued.

Lactic acidosis and severe hepatomegaly with steatosis have been reported with use of nucleoside reverse transcriptase inhibitors alone or in combination with other antiretroviral (ARV) drugs. This has happened more often in women and obese patients, most often after prolonged ARV exposure.

Use in Pregnancy: Category C: Risk to fetus cannot be ruled out. Anasarca, low birth weight and skeletal malformations during organogenesis in rodents at 35X human dosage. Report women who have taken abacavir at any time during pregnancy to the Antiretroviral Pregnancy Registry, at 1-800-258-4263.

Monitoring: CBC, differential, LFTs, CPK
Observe for hypersensitivity reaction: fever, fatigue, respiratory symptoms, GI symptoms (N/V/D, or abdominal pain), skin rash, lymphadenopathy, and/or mouth ulcerations.

ACYCLOVIR (Zovirax®)

Classification: Antiviral

Indications: Herpes genitalis, herpes simplex, herpes zoster

Adult Dose: Should be started ASAP, within 48-72 hours of outbreak:
- Genital herpes (initial): 400 mg po 3 to 5 times/day until lesions heal
- Genital herpes (recurrent): 400mg tid for 5-10 days until lesions heal
- Genital herpes (suppressive therapy): 200 mg po tid for up to 12 months, then re-evaluate
- Herpes zoster (VZV), shingles: 800mg 5 times/day x 7 days
- Herpes zoster, chickenpox: 800 mg qid X 5 days
- Severe VZV or complications: 5-10mg/kg IV q 8 hours x 7-14 days. Administer at a constant rate over 1 hour.

Side effects:

Parenteral

1. Renal toxicity; precipitation of acyclovir crystals can occur in renal tubules if the maximum solubility of free acyclovir (2.5mg/ml at 37° C in water) is exceeded or if the drug is given by bolus injection. Serum creatinine and BUN rise and creatinine clearance decreases.

2. Encephalopathic changes: Approximately 1% of patients receiving IV acyclovir manifested encephalopathic changes characterized by lethargy, obtundation, tremors, confusion, hallucinations, agitation, seizures or coma.

3. Other: transient elevation of serum creatinine; rash or hives; diaphoresis; hematuria; hypotension; headache and nausea; thrombocytopenia.

Oral: (GI side effects reduced if taken with meals).
Short-term therapy: nausea/vomiting, diarrhea, headache, dizziness, fatigue, skin rash, edema, inguinal adenopathy, anorexia, leg pain, medication taste, sore throat.
Long-term therapy: nausea/vomiting, diarrhea, headache, vertigo, insomnia, irritability, depression, skin rash, acne, accelerated hair loss, arthralgia, fever, palpitations, sore throat, muscle cramps, menstrual abnormalities, lymphadenopathy.

Contraindications: Sensitivity to acyclovir or valacyclovir

Drug interactions: **Other nephrotoxic agents and probenecid.** Reports of 30% decreased clearance of acyclovir when used with probenecid; reduce acyclovir dose.

Monitoring: BUN, serum creatinine.

Use in Pregnancy: Category B. No evidence of risk in humans. Consider use if benefit outweighs potential risk.

Amdoxovir (DAPD)

Classification: Investigational drug: antiretroviral, nucleoside analog reverse transcriptase inhibitor (NRTI)

Indication: Not approved by FDA as of 1/03; may be useful in NRTI resistance

Adult Dose: expected to be 500mg twice daily*

Side Effects: no data*

Contraindications: no data*

Use in Pregnancy: no data*

Drug Interactions: no data*

Monitoring: no data*

Note: Phase II

**provisional information only; may be incomplete. Drug not approved by the FDA. Contact manufacturer for further information: Triangle 919-493-5980*

AMIKACIN SULFATE (Amikin®)

Classification: Antimycobacterial

Indication: Treatment of DMAC or MTB.

Adult Dose: MTB: 7.5mg/kg BID (to max of 1 gm/day) IV or IM 5 days/week x 8 weeks
DMAC: 7.5mg/kg QD or BID IV or IM x 1 month
Dose adjustment required in renal failure; see full prescribing information.
Note: in obese patients, Ideal Body Weight (IBW) may be more accurate dose requirement indicator than total body weight.

Side effects: Ototoxicity (including vertigo, tinnitus, and dizziness, which may not be reversible), nephrotoxicity, hepatotoxicity, rash, leukopenia. Sulfites in injectable solution may precipitate anaphylaxis.

Contraindications: Hypersensitivity to amikacin or components. Cross-sensitivity may exist with other aminoglycosides.

Drug interactions: Amphotericin B, loop diuretics (such as furosemide and ethacrynic acid), vancomycin, aminoglycosides, radiographic contrast material, muscle relaxants, NSAIDs due to nephrotoxicity.

Use in Pregnancy: Category C. No serious fetal effects have been reported, but some potential for harm.

Monitoring: Peak and trough drug levels, urinalysis, urine protein, BUN and serum creatinine. Hearing parameters should be checked by audiologist if treatment exceeds 10 days.

AMPHOTERICIN B (Fungizone®, AMB) injectable

[Note: Liposomal amphotericin formulations may be used in those intolerant to the conventional formulation. Dosing is different for each formulation; for example, Abelcet dose is 5 mg/kg/day, given over 2 hours; Amphotec dose is 3-4 mg/kg/day; AmBisone dose is 3-6 mg/kg/day, depending on type of systemic fungal infection. Consult full prescribing information.]

Classification: Antifungal

Indication: Treatment of deep-seated mycotic infection, including cryptococcosis, histoplasmosis, blastomycosis, coccidioidomycosis, candida, and aspergillosis (invasive disease).

Adult Dose: Highly individualized. Test dose with 1-5mg infusions. If test dose is tolerated, dose at 0.7-1.0 mg/kg/day IV slowly every 24 hours, with longer dosage interval for renal failure. Average daily dose is 50-70mg/day. Duration of therapy depends on the infection. Prehydrate, may require potassium and magnesium. Do not use IV filters with any formulation of amphotericin.

Side effects: Rigors/chills, hypotension, renal failure, azotemia, hypokalemia, hypomagnesemia, neutropenia, fever, anorexia, headache, vomiting, diarrhea. If patients experience significant chills, premedicate with Benadryl or Demerol and Tylenol.

Drug interactions: **Use extreme caution when patient is on other nephrotoxic drugs such as aminoglycosides,** high dose/IV **acyclovir, ganciclovir, foscarnet, flucytosine, cidofovir, cyclosporine, antineoplastic drugs, and pentamidine**. **Corticosteroids, diuretics, vancomycin,** and **ACTH** may potentiate hypokalemia; digoxin toxicity possible if potassium level drops. May potentiate bone marrow toxicity of **ganciclovir**. **Probenecid** may increase levels of Amphotericin-B.

Use in Pregnancy: Category B--No evidence of risk in humans. Drug should be used only if clearly indicated.

Monitoring: Daily BUN and creatinine, potassium, magnesium, LFTs, and CBC. Observe for symptoms of hypokalemia.

AMPRENAVIR (Agenerase®, 141W94, VX-478)

Classification: Antiretroviral, protease inhibitor

Indication: HIV infection in combination therapy with other antiretrovirals

Adult Dose: 1200 mg po bid, eight 150-mg capsules per dose
caps also come in 50 mg strength
oral solution contains 15 mg/ml
Food decreases absorption somewhat; drug should not be taken with a high-fat meal
Patients with impaired hepatic function (Childs-Pugh score <13) require dose adjustment

Boosted dosing options include
Amprenavir (APV) 600 mg q 12 hours with ritonavir (RTV) 100-200 mg q 12 hours; or
APV 1200 mg po qd plus RTV 200 mg po qd

Side effects: nausea, vomiting, diarrhea, headache; rash may occur, possibly Stevens-Johnson syndrome; (severe or life-threatening rash in 1%) Diabetes may be worsened or precipitated in patients on combination therapy.

Contraindications: **astemizole, bepridil, carbamazepine, cisapride, dihydroergotamine, ergotamine, lovastatin, midazolam, phenobarbital, phenytoin, pimozide, rifampin, simvastatin, St. John's Wort, terfenadine, triazolam.** Not to be used with **disulfiram or metronidazole.**
The liquid form of amprenavir is contraindicated in pregnant women and children < 4 years old due to its propylene glycol content. Disulfiram and metronidazole should not be used with liquid amprenavir.
Use with caution in patients with known **sulfonamide hypersensitivity**.
Supplemental **vitamin E** should not be taken due to high vitamin E content of amprenavir capsule and solution. High doses may cause bleeding.

Drug interactions: **See Drug Interactions Tables 2-3 in HAART, Antiretroviral section, for dosing adjustments with NNRTIs and other PIs**.

Serious and/or life-threatening interactions could occur between amprenavir and **amiodarone, lidocaine, tricyclic antidepressants, and quinidine** - therapeutic drug monitoring is required.

Space amprenavir 1 hour before or after **buffered ddI or antacids.**
Delavirdine increases APV levels and APV decreases Delavirdine. No dosing adjustment available.
Amprenavir may increase **sildenafil (Viagra)** levels by 2-to-11-fold. Use with caution, and do not exceed 25 mg sildenafil in a 48 hour period.
APV raises levels of **atorvastatin, cerivastatin** and **calcium channel blockers**.
Corticosteroids, carbamazepine, phenytoin and phenobarbital decrease APV levels.
Itraconazole and ketaconazole levels may be increased with APV. Use lower doses of antifungals.
APV raises **rifabutin** levels by 193%. Rifabutin dose should be↓ to 150 mg qd or 300 mg 3x/week.
Warfarin may be affected, and must be monitored carefully.
Theoretical risk of decreased **oral contraceptive** levels. Alternate or additional contraception should be used.

Use in Pregnancy: Category C. In rabbits abortions and minor skeletal variations were noted; in rats, low birth weight in 10-20%. Should be used in pregnancy only if benefit justifies potential risk. Enroll pregnant women whose fetuses were exposed to antiretrovirals in utero by calling 1-800-258-4263 so that infants can be followed up for adverse effects.

Monitoring: LFTs, blood glucose, lipid profile, body fat changes.

Atazanavir (Zrivada, BMS)

Classification: Investigational drug: antiretroviral, protease inhibitor*

Indication: Not approved by FDA as of 12/02*

Adult Dose: probably 400mg (2 capsules) daily with food to improve bioavailability*

Side Effects: diarrhea (17%), hyperbilirubinemia, low incidence of hyperlipidemia compared to other protease inhibitors*

Contraindications: no data*

Use in Pregnancy: no data*

Drug Interactions: **simvastatin, St. John's Wort**. **Ritonavir** and **saquinavir** slow atazanavir excretion.
Buffers/antacids may decrease atazanavir levels, although adding ritonavir may counter this effect.
Rifabutin, clarithromycin, and diltiazem doses may need to be lowered.*

Monitoring: no data*

Note: Phase III; New Drug Application submitted in December 2002*
**provisional information only; may be incomplete. Drug not approved by the FDA. Contact manufacturer for further information: Bristol Myers Squibb, 800-426-7644. Expanded access program call 1-877-726-7327.*

ATOVAQUONE (Mepron®) suspension

Classification: Antiprotozoal

Indications: Primary or secondary prophylaxis for Pneumocystis pneumonia
Mild – moderate pneumocystis pneumonia, if intolerant to TMP-SMX.
Toxoplasmosis prevention and treatment
May also be used for some types of microsporidial diarrhea

Adult Dose: 750 mg (5 mL) po tid for 21 days for PCP treatment;
750 mg po q6 hours for toxoplasmosis treatment
750 mg tid for microsporidia; chronic suppressive therapy is necessary.
1500 mg po qd for PCP prophylaxis; same dose for toxoplasmosis prophylaxis
Take with meals that include fatty foods.

Side Effects: N/V, diarrhea, rash, cough; allergic reactions, including erythema multiforme, pancreatitis, renal impairment

Drug Interactions: Highly protein bound and has potential to interfere with other drugs requiring protein binding, such as aspirin or warfarin. Phenytoin does not present a problem with this effect. **Rifampin** speeds excretion atovaquone, as may **rifabutin** although it has not been tested. Atovaquone dose may need increase. **Fluconazole** increases atovaquone levels.

Use in Pregnancy: Category C - no adequate, well-controlled studies in pregnant women; should be used in pregnancy only if the benefit justifies potential risk.

Monitoring: Be sure patient is able to take with food. Monitor closely for improvement in PCP symptoms, particularly after 4-6 days of atovaquone. Change of therapy may be indicated if no improvement.

AZITHROMYCIN (Zithromax® tablets, capsules, oral suspension)

Classification: Macrolide antibiotic

Indication: prophylaxis and treatment of DMAC (for treatment, is used with other drugs); pneumonias, STDs and other infections that are attributed to susceptible organisms. Some anecdotal reports that it helps in cryptosporidiosis, although studies are incomplete at this time.

Adult Dose: 500 mg-600 mg po qd for DMAC treatment, along with other drugs;
DMAC prophylaxis dose is 1200 mg po q week; 1 gm powder/suspension package may be used weekly. Other doses depending on infection and site.

Contraindications: **Pimozid**e. Any hypersensitivity to this or other macrolide antibiotics.

Drug Interactions: Increased **digoxin, theophyllin and warfarin** levels, **ergot** toxicity, increased effect and slowed excretion of **triazolam**, elevated levels of **carbamazepine, cyclosporine, hexobarbital, phenytoin. Antacids** decrease azithromycin absorption; separate doses by at least 2 hours. Food decreases absorption of capsule form by 40-50%.

Side Effects: N/V/D and abdominal pain, may be somewhat reduced by taking tablets with food (capsules should not be taken with food). Allergic reactions, including anaphylaxis, may recur after treatment and drug discontinuation because of the drug's long half-life. Rare, potentially serious effects include angioedema and cholestatic jaundice. Also rarely, (1-2%) elevated LFTs, CPK, potassium.

Use in Pregnancy: Category B. No evidence of risk in animal studies.

Monitoring: Chemistries and electrolytes, CBC and diff.

BETAMETHASONE Syrup (Celestone®)

Classification: Corticosteroid, anti-inflammatory

Indication: In HIV, used as topical for oral ulceration (many other indications)

Adult Dose: 5 ml (0.6 mg) swish, hold for >1 minute, expectorate. Systemic side effects may occur due to **limited absorption**. Be sure patient knows to expectorate rather than swallowing topical doses.

Side Effects: Fluid/electrolyte disturbances, muscle weakness, GI ulceration, mood alteration, exacerbation of herpetic outbreaks, masking of infection, impaired wound healing, cushingoid syndrome, anergy to skin tests, and adrenal insufficiency (usually with longer tx and higher doses)

Drug Interactions: None noted (unless dose is swallowed, in which case it can induce CYP 450 enzymes and can influence or be influenced by the metabolism of many other drugs

Use in Pregnancy: Inadequate information

Monitoring: Watch for worsening of lesions, indicating possible viral ulceration.

Capravirine (AG1549)

Classification: Investigational drug: antiretroviral, non-nucleoside reverse transcriptase inhibitor (NNRTI)*

Indication: Not approved by FDA as of 1/03; may be useful in NNRTI resistance conferred by K103N (mainly applies to efavirenz resistance; Nevirapine resistance would confer capravirine resistance)*

Adult Dose: to be determined; food increases drug levels*

Side Effects: nausea, vomiting, diarrhea, headache, metallic taste*

Contraindications: no data*

Drug Interactions: *in vitro* synergy with ZDV, DDI, DDC, 3TC, SQV*

Use in Pregnancy: no data*

Monitoring: no data*

Note: structurally unrelated to other NNRTIs; 1/01 FDA temporarily halted some clinical trials due to vasculitis in dogs

*provisional information only; may be incomplete. Drug not approved by the FDA. Contact manufacturer for further information: Agouron, 888-847-2237

CIDOFOVIR injection (Vistide®)

Classification: Antiviral

Indication: CMV retinitis in AIDS

Adult Dose: **Induction:** 5 mg/kg IV q week x 2
Maintenance: 5 mg/kg IV q 2 weeks
Dose reduction in renal failure

Pre-hydrate with at least 1 liter of NS over 1-2 hours, immediately before dosing; second liter can be given during or after cidofovir dose.
All doses must be given with probenecid, 2 gm po 3 hours before cidofovir, 1 gm 2 hours after dose, and 1 gm 8 hours after dose of cidofovir.
Cidofovir must be diluted in at least 100 cc of NS and infused over 1 hour. Before each dose, check u/a; hold if ≥ 2+ protein.

Contraindications: Baseline serum creatinine > 1.5 mg/dL, or creatinine clearance ≤ 55 mL/min, or urine protein ≥ 100 mg/dL (≥ 2+ proteinuria). Contraindicated in patients receiving other **nephrotoxic drugs**, which should be discontinued at least 7 days before cidofovir is begun. This includes NSAIDS, amphotericin, foscarnet, aminoglycosides, IV pentamidine. Contraindicated in patients with allergy to probenecid or other sulfa-containing medications.

Drug Interactions: Probenecid slows excretion of **ZDV** resulting in 80% increased exposure to ZDV; give only 1/2 dose ZDV on cidofovir days. Also, increases the half-life of many drugs, including **penicillins, oral hypoglycemics, rifampin, NSAIDs, ciprofloxacin, acetaminophen, acyclovir, benzodiazepines, ganciclovir, theophylline, barbiturates, furosemide, famotidine, bumetidine, clofibrate, angiotensin-converting-enzyme inhibitors, theophylline, and other**

Side effects: Nephrotoxicity (may be irreversible), metabolic acidosis with pancreatitis, liver dysfunction, iritis, uveitis, ocular hypotony, neutropenia, N/V/D, asthenia, rash, fever, chills, anaphylaxis. Probenecid may cause headache, dizziness, and occasionally anaphylaxis.

Use in Pregnancy: Category C; no adequate, well-controlled studies in pregnant women; should be used in pregnancy only if the benefit justifies potential risk. In animal studies it appears to be carcinogenic, teratogenic, and cause hypospermia.

Monitoring: Serum creatinine (if increases ≥ 0.5 mg/dL above baseline, d/c drug) and urine protein; CBC with differential, LFTs, electrolytes; intraocular pressure

CIPROFLOXACIN (Cipro®)

Classification: Antibiotic

Indication: Treatment of sinusitis, otitis media, urinary tract infections, prostatitis, DMAC, skin and bone infections, enterotoxigenic E. coli, shigella, campylobacter.

Adult Dose: 500mg q12h for most infections; for DMAC, 750 mg po q12h, plus other drugs.
Dose adjustment in renal impairment, see prescribing info

Drug interactions: **NSAIDs** increase the risk of seizures; **probenecid, theophylline** (decreased theophylline clearance), **warfarin** (increases PT); may affect **phenytoin** levels; may interfere with insulin or oral hypoglycemic drugs. Slows clearance of caffeine.

Antacids, ddI, sucralfate, iron, magnesium, zinc, and calcium supplements will decrease absorption of cipro--take at least two hours apart. (Note that many multiple vitamin/mineral supplements contain these cations and should be spaced accordingly.)

Side effects: GI intolerance (nausea, vomiting, diarrhea); photosensitivity; rash, anaphylaxis; occasionally, patients manifest CNS toxicity, marked by dizziness and tremors.

Use in Pregnancy: Category C. Risk to fetus cannot be ruled out. Use if benefits outweigh potential risk.

Monitoring: BUN and creatinine weekly, CBC weekly, monitor theophylline levels.

CLARITHROMYCIN (Biaxin®)

Classification: Macrolide antibiotic

Indication: Prophylaxis or treatment of MAI or DMAC; strep pharyngitis, sinusitis, bronchitis, community-acquired pneumonias

Adult Dose: DMAC treatment: 500mg po bid, in combination with other drugs
DMAC prophylaxis: 500 mg po bid alone
Toxoplasmosis: 1 gm po q12h (with pyrimethamine and folinic acid)
Dose adjustment for renal insufficiency (creatinine clearance <30 mL/min); see prescribing info

Contraindications: **Astemizole, cisapride, pimozide, and terfenadine** are contraindicated in patients on clarithromycin. Any hypersensitivity to erythromycin or other macrolides

Drug interactions: **Digoxin, oral anticoagulant levels** are increased on clarithromycin**.** Decreased **carbamazepine & theophylline** metabolism. Increased **triazolam, omeprazole, cisapride, phenytoin, valproate, lovastatin, simvastatin,** and **ergot alkaloid** levels, and other drugs metabolized via cytochrome P450 pathway. May increase **sildenafil** (Viagra) levels.

Side effects: Nausea, vomiting, abdominal pain, abnormal taste, diarrhea, headache, pseudomembranous colitis, hearing loss, usually reversible, mainly in elderly patients.

Use in Pregnancy: Category C. Risk to fetus cannot be ruled out. Use if benefit outweighs potential risk.

Monitoring: Theophylline and carbamazepine levels. Prothrombin times if patient is on oral anticoagulants, monitor digoxin levels.

CLINDAMYCIN (Cleocin®)

Classification: Anti-protozoal, antibiotic

Indications: As part of combination therapy, with pyrimethamine and folinic acid, for toxoplasmosis; occasionally used for PCP, in combination with primaquine. Also, other infections caused by susceptible organisms in patients who are penicillin-allergic, usually in lower doses.

Adult Dose: Toxoplasmosis, acute phase: 900mg IV Q 8 hours, then 600mg po q 6 hours along with pyrimethamine (25-50mg/day) and folinic acid (leukovorin) 10 mg po qd.
Toxoplasmosis, maintenance: 300-450 mg q6h or q8h, with pyrimethamine 25-50 mg po qd and folinic acid 10 mg po qd, for life, to prevent recurrence
PCP treatment: 300-450 mg po q8h + primaquine base 15 mg po qd x 21 days

Drug interactions: **Erythromycin, Kaolin-pectin** (decreases clindamycin absorption); **antiperistaltic agents** increase the risk of pseudomembranous colitis; muscle relaxants, including **diazepam, baclofen, and atracurium** may increase risk/duration of respiratory paralysis. Theophyllin levels may be increased.

Side effects: N/V/D, esophagitis; pseudomembranous colitis; rash; rarely erythema multiforme or anaphylaxis.

Use in Pregnancy: Category B. No evidence of risk in humans. However, there are no adequate and well-controlled studies in pregnant women, so the drug should be used in pregnancy if clearly needed.

Monitoring: LFTs, jaundice. If diarrhea occurs, culture for C. *difficile* and do not prescribe anti-diarrheals. Pseudomembranous colitis may be life-threatening.

CLOTRIMAZOLE (Lotrimin®, Mycelex®)

Classification: Antifungal (broad spectrum)

Indication: Treatment of superficial or mucous membrane candidal infections.

Adult Dose:
Oral: one 10mg troche dissolved in mouth five times a day
Vaginal: 100mg vaginal tablet or 5gm applicator cream; 1 dose PV per night. Standard therapy is 7 days, but treat until symptom relief is achieved or therapy has failed. Three day courses are available OTC containing 2% clotrimazole.
Topical cream for cutaneous infection: apply BID.

Side effects: Troches: nausea, vomiting, bad medication taste, elevated liver function tests.
Cream and vaginal preparations: erythema, burning, irritation. May reduce latex condom effectiveness

Use in Pregnancy: Category C--risk to fetus can't be ruled out. Consider use if benefit outweighs potential risk. No teratogenicity in rats, mice and rabbits. Some embryotoxicity in rodents at 100x the adult human dose.

Monitoring: Troches: liver function tests.

DAPSONE

Classification: Antiparasitic

Indication: 1.) Pneumocystis pneumonia (PCP) treatment, in combination with trimethoprim;
2.) prophylaxis for PCP;
3.) toxoplasmosis prophylaxis, in combination with other drugs

Adult Dose: 1.) PCP treatment: 100mg PO QD in combination with Trimethoprim
2.) PCP prophylaxis: 100mg PO QD
3.) PCP and toxo prophylaxis: 50 mg qd along with pyrimethamine 50 mg and folinic acid (leucovorin) 25 mg po q week (for those who cannot take sulfa). Alternatively, Dapsone 200 mg + pyrimethamine 75 mg + folinic acid 25 mg p.o. all once per week.

Contraindications: Relative contraindication with G6PD deficiency. Monitor Hct and methemoglobin levels if anemia develops.

Drug interactions: **ZDV** (increased bone marrow toxicity); buffered **ddI** (decreased Dapsone absorption--administer at least two hours apart); **pyrimethamine/primaquine** (hemolysis and increased bone marrow toxicity); **probenecid** (decreased dapsone clearance); **trimethoprim** (decreased TMP clearance and increased dapsone levels); **rifampin and rifabutin** (increased dapsone clearance); **warfarin** may have increased effect; may decrease effectiveness of **oral contraceptives**; use additional or substitute method.

Side effects: Rash, including erythema multiforme and other manifestations; itching, hemolytic anemia, methemoglobinemia, photosensitivity, nausea, vomiting, headache, peripheral neuropathy, agranulocytosis, aplastic anemia.

Use in Pregnancy: Category C. Risk to fetus cannot be ruled out. Use only if benefit outweighs potential risk.

Monitoring: CBC, LFTs. Check baseline G6PD levels in males, especially those of African, Asian, Mediterranean or Sephardic Jewish descent.

DELAVIRDINE (Rescriptor®)

Classification: Antiretroviral, non-nucleoside reverse transcriptase inhibitor

Indication: HIV infection in combination with other antiretrovirals

Adult Dose: 400 mg po q 8 hours, in combination with other antiretroviral drugs; absorption is better if allowed to dissolve in water just prior to taking. Only the 100 mg. tablets disperse well in water.
Dose adjustment for renal insufficiency**.**

Contraindications: rifabutin (reduces delavirdine levels by >90%), **rifampin, non-sedating antihistamines, sedative hypnotics, antiarrhythmics, calcium channel blockers, simvastatin, lovastatin, ergot alkaloid preparations, amphetamines, cisapride, astemizole, terfenadine.**

Drug Interactions: **See Drug Interactions Tables 2-3 in HAART, Antiretroviral section, for dosing adjustments with NNRTIs and other PIs**.

Phenytoin, phenobarbital, and carbamazepine may cause substantial reduction in plasma Delavirdine levels, so these combinations are not recommended. Monitor anticonvulsant levels.

H2 blockers such as **Cimetidine, famotidine, nizatidine, ranitidine** may reduce delavirdine absorption, as may proton pump inhibitors. **Ketaconazole** may increase delavirdine concentration.

Buffered didanosine and antacids may decrease DLV absorption; separate doses by at least 1 hour. The following drugs may have increased plasma concentrations if administered with delavirdine (see Tables 2, 4, and 6 at end of Antiretrovirals section): **benzodiazepines, calcium channel blockers clarithromycin, dapsone, ergot alkaloids, ethinyl estradiol, methadone, quinidine, sildenafil, warfarin. Atorvastatin, cerivastatin**, and **amphetamines** may have increased blood levels; use with caution.

Side Effects: rash, occasional Stevens-Johnson; most rashes mild and resolve spontaneously within two weeks; N/V/D, headache, fatigue, pruritis

Use in Pregnancy: Category C. Risk to fetus cannot be ruled out; consider use if benefits outweigh potential risk. Rats showed ventricular septal defects, and rabbits had embryotoxicity at 6x human doses. Enroll pregnant women whose fetuses were exposed to antiretrovirals in utero by calling 1-800-258-4263 so that infants can be followed up for adverse effects.

Monitoring: LFTs, WBC; observe for rash

DIDANOSINE (Videx®, ddI)

Classification: Antiretroviral, nucleoside reverse transcriptase inhibitor (NRTI)

Indication: HIV infection in combination with other antiretrovirals

Adult Dose: Dose is weight-dependent: Videx EC (enteric coated) 400 mg po qd (patients > 60 kg), or 250 mg qd (< 60 kg.), must be taken on an empty stomach, 1 hour before or 2 hours after a meal; capsules must be swallowed intact; **or**
Tablets and powder: tablets must be chewed, crushed thoroughly, or dispersed in water; powder is mixed with 4 oz. water, and stirred until completely dissolved.
Two 100 mg tabs (or 250 mg powder) po q12h for patients > 60 kg;
One 100mg and one 25mg tab (or 167 mg powder) po q12h for patients < 60 kg.
Tablets and powder contain a buffer, which is needed to increase absorption; proper buffer dosing depends on taking a minimum of 2 tablets per dose, on an empty stomach.
Dose is adjusted in renal impairment if creatinine clearance <60 mL/min

Contraindications: Acute pancreatitis or pancreatitis history; recurrent seizures; current heavy alcohol use. Allopurinol increases ddI concentrations and should not be used concomitantly.

Drug interactions: DdI buffer will cause decreased absorption of **dapsone, ketoconazole, delavirdine, indinavir, itraconazole, quinolones** (such as cipro) or **tetracyclines**; give two hours before didanosine. The following drugs have decreased absorption and will increase ddI absorption: **cimetidine, ganciclovir, INH, metronidazole, propanalol, digoxin. Increased risk of pancreatitis with IV pentamidine, ganciclovir, ribavirin, stavudine, or tenofovir.** Use with caution, or avoid, **other drugs that have the potential to cause peripheral neuropathy**, such as ddC, d4t, INH, phenytoin, hydralazine. **Methadone** will decrease ddI levels by 41%; consider ddI dose adjustment.

Side effects: **Life-threatening pancreatitis**; lactic acidosis and severe hepatomegaly with steatosis, peripheral neuropathy; hepatitis; insomnia; headache, N/V/D, abdominal pain, chills, fever, rash, retinal changes with optic neuritis. Use with caution in patients with other risks of pancreatitis or on other drugs, such as ethambutol or IV pentamidine, which increase risk of pancreatitis.

Use in Pregnancy: Category B. No evidence of risk in animal studies, although no adequate controlled trials have been done in humans. Not recommended in combination with stavudine during pregnancy due to risk of lactic acidosis. Enroll pregnant women whose fetuses were exposed to antiretrovirals in utero by calling 1-800-258-4263 so that infants can be followed up for adverse effects.

Monitoring: Serum amylase, LFTs, WBC; observe for neuropathy, abdominal pain, diarrhea, seizures and confusion, nausea or vomiting, skin rash.

DRONABINOL (Marinol®)

Classification: Cannabinoid

Indication: Anorexia, weight loss, wasting, nausea

Adult Dose: 2.5mg/day to 20 mg/day, increasing or decreasing as below:
Starting dose is 2.5 mg po bid before lunch and supper. CNS effects usually resolve 1-3 days after starting, but if they do not, reduce dose to 2.5 mg before supper. If adverse effects (of 2.5 mg bid) are minimal and further appetite stimulation is needed, increase dose to 2.5 mg before lunch and 5 mg before supper, or to 5 mg before lunch and 5 mg before supper. Most patients respond satisfactorily at the 2.5 mg bid dose, but some have been raised to 10 mg bid and tolerated it well. Adverse effects tend to increase with dosage, however.

Contraindications: Allergy to cannabinoids or sesame oil.

Drug Interactions: Dronabinol is highly protein bound and may displace other protein-bound drugs. All protease inhibitors may increase levels of dronabinol, with increased heart rate, decreased B/P, dizziness, etc. Additive hypertension might occur with **amphetamines, cocaine, and other sympathomimetic agents; additive tachycardia with atropine, antihistamines and other anticholinergic agents;** additive drowsiness and CNS depression with **benzodiazepines, barbiturates, antihistamines, alcohol, methadone, muscle relaxants and other CNS depressants**. Increased tachycardia, hypertension, and drowsiness if used with **tricyclic antidepressants such as amitriptyline or amoxapine**.

Side Effects: CNS effects: somnolence, dizziness, euphoria, paranoid reactions, feeling "high." Anxiety, asthenia, facial flushing, palpitations and tachycardia may also occur, as may N/V and abdominal pain. Blood pressure elevations may occur initially but tolerance tends to occur by 2 weeks. When using the higher doses, some amnesia, ataxia and hallucinations have been reported.

Use in Pregnancy: Category C. Risk cannot be ruled out. Dronabinol should only be used in pregnancy if the benefit justifies potential risk to the fetus.

Monitoring: For adverse responses and magnitude of therapeutic effects. Drug may be habit forming, and mild withdrawal symptoms have occasionally been reported.

EFAVIRENZ (Sustiva®,DMP-266)

Classification: Antiretroviral, non-nucleoside reverse transcriptase inhibitor (NNRTI)

Indication: HIV infection, combination therapy

Adult Dose: 600 mg po qd (3 caps/dose or 1 tab per dose)

Contraindications: S**aquinavir as only PI;** pregnancy. **Terfenadine, cisapride, astemizole, midazolam, triazolam, ergot alkaloids, clarithromycin.**

Drug Interactions: **See Drug Interactions Tables 2-3 in HAART, Antiretroviral section, for dosing adjustments with NNRTIs and other PIs**.

Protease inhibitors--dose adjustments required for some PIs (See Table 2 at end of antiretrovirals section). **Clarithromycin and rifabutin** levels are reduced by efavirenz; dosage adjustment required for rifabutin; clarithromycin should be avoided; see tables in *HAART*, Antiretroviral section. Monitor **warfarin and anticonvulsant (phenytoin, carbamazepine, phenobarbital)** levels; uncertain effect on **oral contraceptives**. Rifampin decreases efavirenz levels by 25%; rifabutin levels are decreased by EFV; adjust rifabutin dose to 450-600 qd or use 600 mg 3x/week.

Patients on **methadone** may experience opiate withdrawal, usually starting around day 7-10 of efavirenz, due to enzyme inducer effect; methadone dose may need to be titrated up for effect. (Note that neurologic effects of efavirenz can be differentiated because they usually begin earlier in therapy.) Likewise, if efavirenz is discontinued for any reason, the methadone dose should be gradually decreased over a 2 to 3 week period to the pre-efavirenz dose. Careful monitoring and assessment are essential during this period to prevent opiate intoxication or overdose.

Side effects: Dizziness, nightmares, depersonalization, mostly during the first few weeks. Serious psychiatric symptoms, including aggression, depression, paranoia, and psychotic symptoms may occur.

Use in Pregnancy: Category C: gross abnormalities reported in monkeys, such as anencephaly, anophthalmia, cleft palate, receiving standard doses of efavirenz; avoid in women of child-bearing potential unless on reliable birth control plus a barrier method, and it should not be used in pregnant women or women trying to become pregnant. Enroll pregnant women whose fetuses were exposed to antiretrovirals in utero by calling 1-800-258-4263 so that infants can be followed up for adverse effects.

Monitoring: CNS effects/psychiatric symptoms; LFTs, cholesterol

Emtricitabine (Coviracil, FTC)

Classification: Investigational drug: nucleoside analog with activity against HIV and HBV*

Indication: Not approved by FDA; new drug application submitted September 2002. Note that the drug shows cross resistance with 3TC (lamivudine) via mutation at M184V. Resistance to FTC promotes susceptibility to ZDV, similar to 3TC*

Adult Dose: probably to be ~200 mg po qd*

Contraindications: no data*

Drug Interactions: no data*

Side effects: elevated CPK and LFTs; one study was discontinued due to hepatotoxicity in combination with Nevirapine. Diarrhea, rash, CNS symptoms such as dizziness, sleep disturbances, depression, h/a.

Use in pregnancy: no data*

Monitoring: no data*

*provisional information only; may be incomplete. Drug not approved by the FDA. Contact manufacturer for further information: Triangle Pharmaceuticals, and Gilead Sciences, 800 445-3235.

Emvirine (MKC-442, Coactinon)

Classification: Investigational drug: non-nucleoside reverse transcriptase inhibitor

Indication: Not approved by FDA as of 1/03

Adult Dose: 500 mg bid or 750 mg bid are being evaluated

Contraindications: **Nelfinavir** went below therapeutic level when co-administered with emvirine; **delavirdine** trough levels were also decreased greatly*

Drug Interactions: Emvirine is metabolized by the CYP 3A4/5 isoenzymes of the P450 pathway. Emvirine also induces this pathway, and may lower plasma concentrations of other drugs metabolized by the same path, such as **oral contraceptives, protease inhibitors, rifampin and rifabutin***

Side effects: nausea, headache, dizziness, rash, diarrhea, abdominal pain, asthenia. Elevations of LFTs*

Use in pregnancy: inadequate information*

Monitoring: LFTs*

*provisional information only; may be incomplete. Drug not approved by the FDA. Contact manufacturer for further information: Triangle Pharmaceuticals, and Gilead Sciences, 800 445-3235.

Enfuvirtide (Fuzeon, Pentafuside, T-20)

Classification: Investigational drug: fusion inhibitor (inhibits fusion of HIV to host cell), New Drug Application submitted in 2002

Indication: Not approved by FDA as of 1/03; may be helpful in multi-drug-resistant HIV

Adult Dose: 50 mg to 100 mg bid under investigation; drug must be injected subcutaneously*

Contraindications: anticoagulants; patients unable to mix and self-inject*

Drug Interactions: no data*

Side effects: rash, pain, redness, induration at injection site, cysts or nodules in many patients*

Use in pregnancy: no data*

Monitoring: no data*

*provisional information only; may be incomplete. Drug not approved by the FDA. Contact manufacturer for further information: Trimeris, 919-419-6050; ask for Medical Department, or visit website at trimeris.com for clinical trials listing. Expanded access may be available at www.T20eap.com

ERYTHROPOIETIN ALFA, (Epogen®, Procrit®)

Classification: Hematopoietic hormone

Indication: Treatment of anemia secondary to ZDV- or Ganciclovir-induced bone marrow suppression (most effective in patients with endogenous EPO levels. 500 IU/ml).

Adult Dose: 100-250 U/kg 3 times/week, IV or SC; do not shake bottle. Time to response: 2-8 weeks. Titrate frequency of dosage downward for maintenance after anemia is corrected. Hold dose if Hct >36%, until Hct begins to fall, then reinstitute at a lower dosage.

Contraindications: Uncontrolled hypertension, albumin hypersensitivity.

Drug Interactions: none known

Side effects: Hypertension, thrombosis, increased seizure risk, arthralgias, N/V/D, fever, H/A.

Use in Pregnancy: Category C. Risk to fetus cannot be ruled out. Use if benefit outweighs potential risk.

Monitoring: Check Hct at least 2 x/week after dose adjustment, for 2-6 weeks; patients may fail to respond in the event of Fe or B_{12} deficiency, hemolysis, and other conditions. CBC, B/P.

ETHAMBUTOL (Myambutol®)

Classification: Antimycobacterial
Indication: Active disease caused by susceptible mycobacteria; always used with other antimycobacterial drugs

Adult Dose: 15-20 mg/kg given po in a single daily dose, max 2.5 gm/day. For retreatment of patients who have previously received treatment for TB, a higher dose may be appropriate: 25 mg/kg/day in single oral dose. Consult with Infectious Disease specialist. Dose adjustment in renal failure.

Drug Interactions: **Aluminum-containing antacids (including buffer in ddI tablets and powder)** decrease absorption of ethambutol; separate dosing by 2 hours. **Verapamil** levels are decreased by ethambutol. Concomitant administration with other **antituberculous** drugs may have synergistic effect on LFTs

Side Effects: Decreases in visual acuity (one or both eyes; test eyes separately and together) which appear to be due to optic neuritis, apparently related to dose and duration of treatment. This effect usually subsides if drug is promptly discontinued. Vision testing with Snellen chart and color testing should be undertaken prior to and periodically during drug administration (monthly if on high doses). See product information for more specifics on testing. Other effects include anaphylactoid reactions, pruritis and joint pain, anorexia, N/V, GI upset and pain; fever, malaise, headache and dizziness; confusion and disorientation. Elevations in serum uric acid levels have been reported and acute gout episodes precipitated.

Use in Pregnancy: Unknown. Rats and rabbits given high doses of ethambutol showed higher risks of fetal mortality, and a low incidence of exancephaly, cleft palate, and abnormal vertebral development. There are published reports of five women who received the drug during pregnancy with no ill effects. The benefits of using this drug during pregnancy must be weighed against potential risks to the fetus.

Monitoring: Visual acuity (test eyes separately), uric acid, LFTs; monitoring indicated by concurrent drug therapy.

FAMCICLOVIR (Famvir®)

Classification: Antiviral

Indication: Acute herpes zoster (shingles); recurrent genital herpes

Adult Dose: Shingles: 500 mg po q8h x 7 days, starting within 72 hrs after lesions erupt
Recurrent genital herpes: 500 mg bid x 5-10 days, preferably within 6 hours of symptom onset
Dose adjustment for renal failure

Drug Interactions: Clearance of famciclovir metabolite decreased while on **theophylline**; however, the magnitude of this effect is considered clinically unimportant. **Cimetidine** may increase famciclovir levels; **digoxin** level may increase by nearly 20%.

Side Effects: Minor--headache, nausea, fatigue, N/V/D, abdominal pain

Use in Pregnancy: Category B. No evidence of risk in humans.

Monitoring: any interacting drug

FILGRASTIM (G-CSF, Neupogen®)

Classification: Recombinant human granulocyte colony stimulating factor

Indication: Neutropenia

Adult Dose: 5 mcg/kg/day SC; if no response after one week, raise dose to 7.5 mcg/kg/day for 7 days; if no response, increase to 10 mcg/kg/day. Dose must be adjusted frequently based on response. Avoid shaking bottle or diluting with saline.

Contraindications: hypersensitivity to e. coli-derived proteins or other ingredients in filgrastim. Do not give within 24 hours of cancer chemotherapy drugs

Drug Interactions: Lithium and corticosteroids my increase myeloproliferative effect.

Side Effects: Mild-moderate bone pain, splenomegaly, ↑ in other WBCs; ↑ uric acid, LDH, and alkaline phosphatase; mild ↓ platelet count

Use in Pregnancy: Category C. Risk to fetus cannot be ruled out. Use if benefit outweighs potential risk.

Monitoring: WBC and differential for response to therapy, platelet count, biochemical profile.

FLUCONAZOLE (Diflucan®)

Classification: Antifungal

Indication: Treatment of oropharyngeal, esophageal, or systemic candidiasis; cryptococcosis, and coccidioidomycosis. Vaginal candidiasis.

Adult Dose: 200-400mg PO per day. Also available in injectable form. Dose adjustment required in renal failure.

Contraindications: cisapride, pimozide

Drug interactions: Inhibits CYP 450 and increases levels of **atovaquone, benzodiazepines**. **Oral contraceptives**: minor increase in level of **levonorgestrel and ethinyl estradiol.** Decreased metabolism of **phenytoin, warfarin;** decreased renal clearance of fluconazole when used with **hydrochlorothiazide;** increased hypoglycemia with sulfonylureas. Cimetidine and rifampin decrease flucon level. **Rifabutin** has increased levels and toxicity. Phenytoin levels may increase, as may **zidovudine, delavirdine, and theophylline; oral hypoglycemics** of the sulfonylurea type may have increased level, producing hypoglycemia. May increase **sildenafil** (Viagra) levels.

Side effects: GI intolerance, abdominal pain, rash, headache.

Use in Pregnancy: Category C: risk to fetus cannot be ruled out. Should be avoided if possible.

Monitoring: CBC, blood glucose, BUN, creatinine, LFTs, potassium.

FLUCYTOSINE (Ancobon®)

Classification: Antifungal

Indication: Adjunctive treatment for susceptible fungal infections, such as cryptococcus

Adult Dose: 37.5 mg/kg po q6h in conjunction with amphotericin B, until patient is afebrile and culture-negative. Increase the dosing interval for renal failure. Nausea may be decreased if caps are given a few at a time over a 15-minute period.

Contraindications: Use with extreme caution and close monitoring in impaired renal function or bone marrow depression

Drug interactions: Antacids decrease absorption; give 2 hours after any antacids or ddI. Drugs which impair glomerular filtration; **Chemotherapeutic drugs, dapsone, ganciclovir, primaquine, pyrimethamine, TMP-SMX, sulfadiazine, ZDV, cidofovir** may increase risk of hematologic toxicity. Flucytosine is synergistic with amphotericin B but may also increase toxicities.

Side effects: Rash, abdominal pain, anorexia, N/V/D, anemia or other cytopenias, hepatitis, renal impairment or failure, ataxia, hearing loss, paresthesias, peripheral neuropathy, seizures, headache, fatigue, hypoglycemia, allergic reactions

Use in pregnancy: Category C: risk to fetus cannot be ruled out; consider use if benefits outweigh potential risk

Monitoring: serum flucytosine levels, CBC, BUN, creatinine, LFTs, electrolytes

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Fosamprenavir (GW 433908; VX 175)

Classification: Investigational drug: protease inhibitor*

Indication: not approved by FDA as of 1/03; this is a pro-drug form of amprenavir, which is metabolized to amprenavir at the intestinal wall before entering circulation. Will not contain vitamin E, as the current formulation does.

Adult Dose: probably 1400 mg po daily if given with ritonavir; if given without ritonavir, 1400 mg bid*

Contraindications: see amprenavir*

Drug Interactions: see amprenavir*

Side effects: see amprenavir*

Use in Pregnancy: insufficient data*

Monitoring: see amprenavir*

*provisional information only; may be incomplete. Drug not approved by the FDA. Contact Glaxo Smith Kline at 1-800 334-0089

FOSCARNET (Foscavir®)

Classification: Antiviral

Indication: For treatment of severe herpesvirus infections which have become resistant to acyclovir (for HSV, ZVZ) or ganciclovir (for CMV)

Adult Dose: For CMV retinitis (Predose hydration must be used, NS or D5NS, 1 liter before 1st dose. Later doses hydration may be concurrent with foscarnet infusion.
Induction: 180mg/kg/day IV in divided doses seven days a week. May be given as 90 mg/kg q 12 hours or 60 mg/kg q 8 hours. A metered pump is used to infuse at a rate no greater than 1mg/kg/min to avoid excessive plasma levels.
Maintenance: 90-120mg/kg/day IV as a single dose seven days a week.
Dosage should be adjusted based on creatinine clearance; use with caution due to increased blood levels of the drug with potential for increasing renal impairment.

For GI CMV infections:
same induction dose as for retinitis, re-scope before discontinuing. Maintenance not generally used

For acyclovir-resistant HSV or VZV: 40 mg/kg IV q8h for 14-26 days

Drug interactions: Nephrotoxic agents, **furosemide, NSAIDs, amphotericin B, cidofovir, aminoglycosides, or ritonavir** may increase risk of nephrotoxicity; **IV pentamidine** may increase risk of both nephrotoxicity and hypocalcemia; **ciprofloxacin and imipenim may increase risk of seizures.**

Side effects: Hypocalcemia, hypomagnesemia, hypokalemia, hypo- or hyperphosphatemia. Renal impairment is a common effect of therapy, and may progress to renal failure. Fever, headache, seizures due to changes in minerals and electrolytes, N/V/D, anemia, fatigue, malaise, confusion, anxiety, granulocytopenia, leukopenia, weakness.

Use in Pregnancy: Category C. Risk to fetus cannot be ruled out. Skeletal abnormalities and deviations occurred in rats and rabbits. Use if benefit outweighs potential risk.

Monitoring: Baseline and periodic recheck of 24 hour creatinine clearance is recommended to assure correct dosing. **Daily** creatinine and BUN during induction, along with calcium, magnesium electrolytes, and phosphorus. Follow these parameters weekly on maintenance therapy. Check Hgb/Hct monthly. Electrolyte disturbances, sometime severe, can develop even after therapy is discontinued. Monitor also for perioral tingling or numbness in extremities, which can indicate low calcium levels and require immediate labs and intervention.

GANCICLOVIR (Cytovene®)

Classification: Antiviral

Indication: CMV retinitis; also used for active CMV in other sites (e.g., radiculopathy, encephalitis, GI ulcerations)
Oral form also used for prevention of CMV disease in advanced AIDS for patients at high risk, although not generally recommended. See also valganciclovir.

Adult Dose: Induction phase, 5 mg/kg IV q12 hours x 14-21 days;
Maintenance phase, 5 mg/kg IV qd, **OR**, 6 mg/kg IV 5 days a week.
Adjust dose based on creatinine clearance.
Oral form may be used with intraocular treatment (injections or inserts) to reduce risk of disease in other organs, but has extremely poor bioavailability

Contraindications: Absolute granulocyte count <500, platelet count <25,000, or Hgb <8

Drug Interactions: **Didanosine** may decrease ganciclovir levels and increased **ddI** levels may occur with ganciclovir. Ganciclovir levels increase if given with **probenecid. ZDV, dapsone, amphotericin B, chemotherapeutic agents, hydroxyurea, flucytosine, pentamidine, primaquine, pyrimethamine, sulfadiazine, TMP/SMX, trimetrexate and other nucleoside analogues** may potentiate ganciclovir's bone marrow toxicity; **nephrotoxic and bone marrow depressant drugs** should be administered with caution due to possible additive effects. **Imipenem-cilastatin + ganciclovir** may result in seizures, and should not be used together unless benefit clearly outweighs risk.

Side Effects: Neutropenia, anemia, thrombocytopenia, ↑ creatinine, headache, confusion, fever, rash, paresthesia, tremor, retinal detachment, dyspnea

Use in Pregnancy: Category C. Risk to fetus cannot be ruled out; birth defects were observed in animals, as well as decreased sperm production and decreased fertility. Contraception is recommended for both sexes during use, and for men, at least 90 days after last dose. Consider use if benefit outweighs potential risk.

Monitoring: Serum creatinine; if ↑, repeat creatinine clearance to re-adjust dose
Magnesium, biochemical profile (3x/week during induction, then q wk if stable); CBC with diff and platelet count weekly during induction, then q 2 weeks if stable. Monitor for visual disturbances which may indicate progression of retinal CMV; regular ophthalmology F/U is essential for early detection of disease reactivation.

HYDROXYUREA (Hydrea®)

Classification: anti-neoplastic, ribonucleotide reductase inhibitor

Indication: antineoplastic drug. Sometimes used off-label as an adjunct to ddI in combination antiretroviral therapies, **although not approved for HIV treatment**.

Adult Dose: 500 mg po bid

Contraindications: severe anemia or bone marrow depression

Drug interactions: Increased effects of ZDV, ddC, ddI, especially bone marrow toxicity

Side effects: Bone marrow toxicity (7-21 days to recover after drug discontinued), drowsiness, N/V/D, constipation, mucositis, anorexia, stomatitis, alopecia, skin changes, abnormal LFTs, creatinine, BUN, decreased spermatogenesis in men. Some experts report poorer CD4 recovery on HAART with hydroxyurea.

Use in pregnancy: Category D - investigational or post-marketing data show risk to the fetus. However, potential benefits may outweigh the potential risk. Generally this rating is reserved for drugs with no safer alternatives.

Monitoring: CBC, diff, renal and LFTs, uric acid, watch for unusual bleeding or bruising

INDINAVIR (Crixivan®)

Classification: Protease inhibitor

Indication: HIV infection, in combination with other antiretrovirals

Adult Dose: 800 mg q 8 hours with water. In patients with mild to moderate hepatic insufficiency, dose may be decreased to 600 mg q8 hours. Take 1 hour before or 2 hours after a meal; requires acid environment for absorption. Drug is moisture-sensitive and should be stored in bottle (with dessicant in place) until taken.

Contraindications: **Rifampin, carbamazepine, cisapride, astemizole, triazolam, midazolam, pimozide, amiodarone, quinidine, ergot alkaloids, benzodiazepines, simvastatin, lovastatin, terfenadine, St. John's Wort**

Drug interactions: **See Drug Interactions Tables 2-3 in HAART, Antiretroviral section, for dosing adjustments with NNRTIs and other PIs**.

Buffer in **didanosine** inhibits absorption - give 1 hour apart on empty stomach. **Cisapride, triazolam, and midazolam** may be life-threatening if given with indinavir. Taken with rifabutin, causes increased **rifabutin** levels and decreased indinavir levels--consider halving rifabutin dose (150 mg qd or 300 mg every other day) and increasing indinavir to 1000 mg q8 hours. **Rifampin** causes decreased indinavir levels; do not use concomitantly. **Clarithromycin** increases indinavir levels and indinavir increases **clarithromycin** levels. **Ketaconazole** and **itraconazole** cause increased indinavir levels--consider indinavir dose reduction to 600 mg q 8 hrs. **Fluconazole** decreases indinavir levels. **Dronabinol** levels may be higher if given with indinavir. Indinavir may increase **sildenafil** (Viagra) levels; do not exceed 25 mg in 48 hours. **Venlafaxine** causes 28-36% decrease in indinavir levels. Grapefruit juice decreases indinavir levels by ~26%

Side effects: Nephrolithiasis - adequate hydration is necessary for prevention. Patients on indinavir must drink 1.5 liters of non-alcoholic liquid per day (6 glasses of water). Reversible asymptomatic hyperbilirubinemia, abdominal pain, N/V/D; hyperglycemia, diabetes; "buffalo hump," "protease paunch," round facies, and other symptoms of fat redistribution; increased cholesterol and triglyceride levels, acute hemolytic anemia.

Use in pregnancy: Category C. Risk to fetus cannot be ruled out. Consider use if benefits outweigh potential risk. Enroll pregnant women whose fetuses were exposed to antiretrovirals in utero by calling 1-800-258-4263 so that infants can be followed up for adverse effects.

Monitor: LFTs, including bilirubin. Lipid profile, blood glucose, body fat distribution. Observe for flank pain or other symptoms of nephrolithiasis.

ISONIAZID

Classification: Antimycobacterial

Indication: Mycobacterium tuberculosis infection; in combination with other antitubercular agents for active TB disease

Adult Dose: 300 mg po qd (should be given with 25-50 mg pyridoxine qd to prevent peripheral neuropathy)

Contraindications: acute liver disease; previous history of hepatic damage from INH

Drug Interactions: **Antacids** decrease absorption of INH; take at least 2 hours after antacids. **Alcohol**, especially daily use, increases hepatic hazards of INH; INH may ↑ **phenytoin** levels, which should be closely monitored and adjusted; increased levels of **oral anticoagulants, carbamazepine, ethionamide, theophylline, phenytoin, cycloserine, disulfiram, benzodiazepines.** May increase **sildenafil** (Viagra) levels. **Ketaconazole or itraconazole** may have diminished effect.

Side Effects: Peripheral neuropathy, anorexia, nausea, vomiting, GI distress, elevated LFTs and occasional hepatitis (especially in older patients), agranulocytosis, aplastic or hemolytic anemia, fever, rash, dizziness, slurred speech, gynecomastia, rheumatic syndromes; rarely, CNS effects such as seizures, optic neuritis, encephalopathy.

Use in Pregnancy: Category C - possible risk to fetus must be weighed against benefit of drug. US Public Health Service recommends use of INH in HIV-infected pregnant women in most cases (see *LTBI* in Health Maintenance section and *MTB* in Disease-specific section.)

Monitoring: Monthly LFTs, CBC. Watch for symptoms of hepatitis.

ITRACONOZOLE (Sporanox®)

Classification: Antifungal

Indication: Histoplasmosis, blastomycosis; aspergillosis if intolerant to amphotericin B

Adult Dose: 200 mg po qd (blastomycosis) to 200 mg po bid (histoplasmosis); take with full meal. In life-threatening situations may require loading dose for first 2-3 days. Dose adjustment for renal failure.

Contraindications: Itraconazole should not be given with **terfenadine, cisapride, pimozide, lovastatin, simvastatin, triazolam, midazolam, or astemizole**; may result in cardiac dysrhythmias and death.

Drug Interactions: **Rifabutin, benzodiazepines, statin drugs, oral hypoglycemics, protease inhibitors, saquinavir, sildenafil or digoxin** levels may ↑ on itra. **Indinavir** levels may increase on itraconazole; indinavir dose may be reduced to 800 mg q8 hours. **Isoniazid, nevirapine, phenobarbital, phenytoin, rifampin, or rifabutin** may ↓ itra levels. **Cyclosporine or tacrolimus** levels may be ↑on itra, and **warfarin** may show ↑ anticoagulant effects.
Itraconazole levels may increase if given with **macrolides, indinavir, and ritonavir.**
Absorption requires gastric acidity, and **sucralfate**, **proton pump inhibitors** and **H2 antagonists such as cimetidine** should not be co-administered with itraconazole. **Antacids**, including the one in **ddI tablets and powder**, inhibit itraconazole absorption.

Side Effects: N/V/D, rash, pruritis, edema, headache, hypertension, hypokalemia, hepatitis

Use in Pregnancy: Category C. Risk to fetus cannot be ruled out. Consider use if benefit outweighs the risk
Monitoring: Liver function, symptoms of congestive heart failure

KETOCONAZOLE (Nizoral®)

Classification: Antifungal

Indication: candidiasis

Adult Dose: 200-400mg PO daily; acid required for absorption. Patients with hypochlorhydria should take dose with cola or orange juice

Contraindications: **Terfenadine, astemizole, pimozide, triazolam, cisapride** (prolonged Q-T interval and life-threatening ventricular arrhythmias)

Drug interactions: **Antacids, including the buffer in ddI tablets and powder, H_2 antagonists,** and **proton pump inhibitors** decrease ketoconazole absorption; separate administration of ddI or antacids by 2 hours. **Indinavir** levels may be increased by 70%; reduce indinavir dose to 600 mg po q8h. **Isoniazid and rifampin** cause increased ketoconazole metabolism and decreased rifampin effect. **Midazolam** has elevated plasma concentration. **Cyclosporine, tacrolimus, and methylprednisone** may have elevated plasma levels. **Phenytoin, warfarin, and oral hypoglycemic** agents may be potentiated. May increase **sildenafil (Viagra)** levels. **Indinavir** levels are increased (reduce dose to 600 mg q8hours), **ritonavir** increases ketaconazole levels (do not give > 200 mg. ketaconazole/day). Do not use with **nevirapine** due to 63% decrease in ketoconazole levels.

Side effects: Hepatotoxicity, GI intolerance, headache. Gynecomastia and decreased testosterone in males.

Use in Pregnancy: Category C. Risk to fetus cannot be ruled out. Use only if benefit outweighs potential risk.

Monitoring: Liver function tests.

LAMIVUDINE (3TC, Epivir®)

Classification: Antiretroviral (nucleoside analogue, reverse transcriptase inhibitor)

Indication: HIV infection, in combination therapy with other antiretrovirals. Hepatitis B infection.

Adult Dose: 300 mg po qd **or** 150 mg po bid for adults ≥ 50 kg. If < 50 kg or 110 lbs, use 2 mg/kg bid. Dosage adjustment required in renal impairment

Drug Interactions: Resistance to lamivudine promotes susceptibility to ZDV. TMP-SMX slows clearance of lamivudine; clinical implication uncertain.

Side effects *(in combination studies with ZDV)***:**
Headache, nausea, malaise and fatigue, peripheral neuropathy, nasal symptoms, cough, diarrhea, N&V, musculoskeletal pain, insomnia, fever or chills, anorexia, elevated LFTs, lactic acidosis, hepatomegaly and steatosis, pancreatitis. Note that patients with chronic HBV may experience a flare when lamivudine is D/Ced. Some experts recommend continuing lamivudine if it keeps HBV viral loads down, even though it is no longer working for HIV; this would require a full antiretroviral regimen in addition to the lamivudine.

Use in pregnancy: Category C. Risk to fetus cannot be ruled out. Consider use if benefit outweighs risk. Enroll pregnant women whose fetuses were exposed to antiretrovirals in utero by calling 1-800-258-4263 so that infants can be followed up for adverse effects.

Monitoring: CBC and diff, LFTs, amylase.

LOPINAVIR + RITONAVIR (Kaletra™, ABT-378/r)

Classification: Antiretroviral, protease inhibitor

Indication: HIV infection, in combination with other antiretrovirals

Adult Dose: 400/100 mg po bid (400 mg of lopinavir, plus ritonavir 100 mg to boost lopinavir levels. Each capsule contains 133.3 mg of lopinavir and 33.3 mg of ritonavir). Take with food to enhance absorption

Contraindications: **astemizole, cisapride, pimozide, dihydroergotamine, ergotamine, midazolam, triazolam, rifampin, simvastatin, lovastatin, bepridil, amiodarone, flecainide, phenytoin, Phenobarbital, carbamazepine, propafenone, quinidine. Do not use Kaletra oral solution with disulfuram or metronidazole; contains alcohol. (See also ritonavir)**

Drug Interactions: **See Drug Interactions Tables 2-3 in HAART, Antiretroviral section, for dosing adjustments with NNRTIs and other PIs**.

Lopinavir is metabolized by the cytochrome P 450 pathway, primarily the 3A4 pathway. Other drugs metabolized in this way may interact with lopinavir. **Pravastatin** levels increase by 33%; use with caution. **Atorvastatin** levels increase nearly 6-fold. **Ethinyl estradiol** levels decrease; use alternative or additional methods. **Rifabutin** levels increase; reduce RFB dose to 150 mg every other day. **Methadone** levels may decrease on lopinavir; monitor for withdrawal and titrate dose up if needed. **Ketoconazole** levels increase 3-fold. **Sildenafil** levels increase. **Phenobarbital, phenytoin, and carbamazepine** decrease lopinavir levels. Mild increase in **clarithromycin**; dose adjustment needed if renal insufficiency. **Ketaconazole and itraconazole** levels increase on lopinavir. High doses (>200 mg/day) not recommended. Atovaquone levels decrease; calcium channel blockers increased level with lopinavir. Steroids decrease lopinavir level. Separate **ddI** dose from lopinavir dose.

Side effects: pancreatitis, diabetes, hyperglycemia, diarrhea, headache, nausea, vomiting, abdominal pain, fatigue, dry mouth, and ritonavir's adverse effects (which see). Increased risk of rhabdomyolysis on **atorvastatin or cerivastatin**.

Use in Pregnancy: Category C. Risk to fetus cannot be ruled out; some fetal development toxicity in rats and rabbits at maternally toxic doses. Enroll pregnant women whose fetuses were exposed to antiretrovirals in utero by calling 1-800-258-4263 so that infants can be followed up for adverse effects

Monitoring: LFTs, lipid profile, blood glucose, body fat distribution

MEGESTROL (Megace®) suspension

Classification: Appetite enhancer

Indication: Anorexia, cachexia

Adult Dose: up to 800 mg (20 mL) po qd. Take 30 minutes before meals

Drug Interactions: Not studied. May increase insulin requirements.

Side Effects: Diarrhea, rash, impotence, males may have feminizing effects; carpal tunnel syndrome

Use in Pregnancy: Category X. Do not use.

Monitoring: Weight.

NELFINAVIR (Viracept®)

Classification: Antiretroviral, protease inhibitor

Indication: HIV infection, in combination with other antiretrovirals

Adult Dose: 50 mg po tid; or 1250 mg po q 12 h with a meal or snack

Contraindications: **Carbamazepine, phenytoin, phenobarbitol (which may substantially decrease nelfinavir levels), rifampin, simvastatin, lovastatin, quinidine, midazolam, triazolam, cisapride, terfenadine, astemizole, amiodarone, ergot alkaloids, and St. John's Wort** should not be given with nelfinavir.

Drug interactions: **See Drug Interactions Tables 2-3 in HAART, Antiretroviral section, for dosing adjustments with NNRTIs and other PIs**.

Metabolized by cytochrome P-450, CYP 3-A. **Dronabinol** levels may be higher if given with nelfinavir. **Rifabutin** levels are increased by 200%; dose must be reduced to 150 mg per day. **Rifabutin** reduces nelfinavir levels by 32%; no dosage adjustment recommendation for nelfinavir has been developed. **Ritonavir** increases nelfinavir levels. Reduced effectiveness of **oral contraceptives**, use additional or alternative methods. May increase **sildenafil** (Viagra) levels; do not exceed 25 mg in 48 hours. **Methadone** levels may decrease in some patients, requiring methadone dosage increase in some patients; monitor for signs of withdrawal. Atorvastatin levels are increased 74%; use lowest dose, with caution.

Side effects: soft stools or diarrhea - often controllable with loperamide; hyperglycemia, diabetes, elevations in triglycerides and cholesterol; "buffalo hump," "protease paunch," round facies, and other symptoms of fat redistribution.

Use in pregnancy: Category B - no evidence of risk to fetus. Enroll pregnant women whose fetuses were exposed to antiretrovirals in utero by calling 1-800-258-4263 so that infants can be followed up for adverse effects

Monitoring: baseline biochemical profile, then every 3 months if normal; blood sugar, LFTs, lipid profile, body fat redistribution

NEVIRAPINE (Viramune®)

Classification: Antiretroviral (Non-nucleoside reverse transcriptase inhibitor, NNRTI)

Indication: HIV infection in combination with other antiretrovirals

Adult Dose: Start on 200 mg po qd for 14 days before escalating to 200 mg po bid

Contraindications: Do not use with **ketaconazole, rifampin, or St. John's Wort (hypericum**).

Drug Interactions: **See Drug Interactions Tables 2-3 in *HAART*, Antiretroviral section, for dosing adjustments with NNRTIs and other PIs**.

Cytochrome P-450 inducer. Hormonal contraceptives, beta blockers, doxycycline, griseofulvin, methadone, metronidazole, ketaconazole, nifedipine, quinidine, steroids, theophyllin, and warfarin may have decreased plasma levels. **Rifabutin** decreases nevirapine concentrations (see Table 6 in antiretroviral section) though no dosage adjustment is usually recommended; if used with a PI that increases rifabutin levels, the effect on nevirapine may be magnified. **Macrolides and cimetidine** may somewhat increase nevirapine levels.

Note that patients on **methadone** may experience withdrawal, usually starting around day 7-10 of efavirenz; methadone dose may need to be titrated up, at a rate of ~10 mg/day, for effect. Average increase is 22% above pre-nevirapine dose. ***Warn patients not to discontinue nevirapine while on the increased methadone dose because of risk of methadone overdose after isoenzymes normalize.*** Likewise, if nevirapine is discontinued for any reason, the methadone dose should be gradually decreased over a 2 to 3 week period to the pre-nevirapine dose. Careful monitoring and assessment are essential during this period to prevent opiate intoxication or overdose.

Side Effects: Rash, usually within first six weeks of therapy. D/C drug for severe rash or rash accompanied by other symptoms; Stevens-Johnson syndrome has occurred. Severe liver complications have occurred, including cholestatic hepatitis, hepatic necrosis, and hepatic failure. Fever, headache, nausea, diarrhea, abdominal pain, thrombocytopenia, anemia, leukopenia, ulcerative stomatitis, hepatitis, peripheral neuropathy, paresthesia, or myalgia may also occur.

Use in Pregnancy: Category C - risk to fetus cannot be ruled out; some rat and rabbit neonates had decreased weight. Consider use if benefits outweigh risk. Enroll pregnant women whose fetuses were exposed to antiretrovirals in utero by calling 1-800-258-4263 so that infants can be followed up for adverse effects

Monitoring: LFTs, rash

PENTAMIDINE AEROSOLIZED (NebuPent® Inhalation)

Classification: Anti-parasitic

Indication: For primary and secondary prevention of PCP pneumonia (see *PCP prophylaxis* in Health Maintenance section)

Adult Dose: 300mg Q month via Respirgard/Economist nebulizer.

Side effects: Metallic taste, coughing, wheezing; bronchospasm in heavy smokers and asthmatics; increased incidence of spontaneous pneumothorax in patients with previous PCP infection or pnuematoceles; hypoglycemia.

Use in Pregnancy: Category C. Risk to fetus cannot be ruled out. Use only if benefit outweighs potential risk.

Monitoring: Auscultate for bronchospasm during administration. Watch CXR for pneumatoceles.
Rule out active TB or active PCP before administering. Administer in negative pressure area. Take careful respiratory history. Evaluate for pre- or post-treatment with bronchodilators such as albuterol.

PENTAMIDINE injectable (Pentam®)

Classification: Anti-parasitic

Indication: Treatment of PCP pneumonia. See *Pneumocystis Pneumonia* in Disease Specific section.

Adult Dose: 4mg/kg IV in a single dose per day x 21 days (full course); usually IV therapy x 6-7 days, then switch to oral medication. Dose modification required for renal failure

Drug interactions: Possible synergy with other **nephrotoxic agents**, especially f**oscarnet, aminoglycosides, and amphotericin B**. Do not mix with normal saline or any other drug.

Side effects: Sudden severe hypotension, hypoglycemia, renal failure, cardiac arrhythmias, acute pancreatitis, nausea and vomiting. Chest pain, rash, hyperkalemia, wheezing, dyspnea. Long term possibility of pancreatic failure. Tissue necrosis has been reported with extravasation of IV pentamidine.

Use in Pregnancy: Category C. Risk to fetus cannot be ruled out. Use only if benefit outweighs potential risk.

Monitoring: B/P during and after each dose, blood glucose by fingerstick at least QD; daily BUN and creatinine. Liver function tests, EKG, and serum potassium and calcium every few days. CBC with differential and platelet count once a week, hydrate prn. Nutritional counseling: small, frequent meals. The metallic taste of this drug may depress appetite. Monitor glucose, pancreatic function studies at least monthly for at least 3 months after induction.

PRAVASTATIN (Pravachol®)

Class: antihyperlipidemic, HMG CoA reductase inhibitor

Indication: hypercholesterolemia (increased LDL and triglycerides, as an adjunct to dietary changes

Adult dose: 10-20 mg q hs po, may increase to 40-80 mg. if LDL goal not reached. (See *Hyperlipidemia* in Antiretroviral section)

Contraindications: acute liver disease, unexplained persistent LFT abnormalities, pregnancy

Drug Interactions: Cholestyrene decreases pravastatin absorption. Lopinavir/ritonavir increases pravastatin levels ~33%. No dosage adjustment necessary.

Side Effects: Headache, fatigue, N/V/D, rash, rarely rhabdomyolysis and acute renal failure. Fibrates increase risk of myopathy and rhabdomyolysis

Use in Pregnancy: Category X. Do not use.

Monitor: LFT's, muscle pain or tenderness, fatigue, CPK if symptoms. Baseline lipid profile and q 4 weeks to measure effect.

PYRAZINAMIDE

Classification: Antituberculous agent

Indication: Active tuberculosis (in combination with other agents); second line treatment of latent TB infection (see *LTBI* Health Maintenance section)

Adult Dose: 5-30 mg/kg/day, maximum 2 gms/day if on daily regimen, may be administered in thrice-weekly doses of 50-70 mg/kg. Higher dosages may be used in multi-drug-resistant TB.

Contraindications: severe hepatic damage, acute gout. Use with caution in patients with chronic gout, porphyria, diabetes, renal failure

Drug Interactions: Interferes with urine tests Acetest® and Ketostix®

Side Effects: Hepatotoxicity, N/V, anorexia, sideroblastic anemia, thrombocytopenia, rash, urticaria, pruritis, dysuria, interstitial nephritis, malaise, photosensitivity, mild arthralgia and myalgia; rarely porphyria, fever

Use in Pregnancy: Category C. Risk to fetus cannot be ruled out, and drug should only be used if clearly needed.

Monitoring: LFTs, uric acid before and during treatment, follow-up of TB symptoms, CXR and sputum

PYRIMETHAMINE (Daraprim®)

Classification: Anti-protozoal

Indication: In combination with sulfadiazine or clindamycin for treatment of cerebral toxoplasmosis; primary prophylaxis of toxoplasmosis

Adult Dose: Induction therapy, toxoplasmosis: 100-200 mg loading dose, then 50-75 mg po qd + folinic acid (leukovorin) 10-50 mg po qd x 6 weeks, then maintenance
Maintenance therapy, toxoplasmosis: 25-50mg qd. Must be given with sulfadiazine or clindamycin; also, use 10-50 mg folinic acid (leucovorin) qd to ameliorate bone marrow suppression during high-dose or prolonged treatment with pyrimethamine; may decrease to 10 mg/day when pyrimethamine dose is reduced.
Primary toxoplasmosis prophylaxis in toxo IgG+ patients: 50mg PO q week in combination with leukovorin 25mg PO q week and dapsone 200 mg q week (or with dapsone 50 - 100 mg qd)

Contraindications: Megaloblastic anemia due to folate deficiency; seizure disorders. Use with caution in patients with renal or hepatic insufficiency.

Drug interactions: Do not give dose within 2 hours of **antacids, buffered drugs, or kaolin. ZDV, TMP-SMX, sulfonamides, dapsone, amphotericin B, flucytosine, ganciclovir, primaquine, sulfadiazine, trimetrexate, methotrexate, and cidofovir** may increase bone marrow toxicity.

Side effects: Anorexia, N/V, abdominal cramps, bone marrow suppression, anemia in patients with G6PD deficiency. Hypersensitivity reactions, such as anaphylaxis and erythema multiforme can occur, especially when co-administered with sulfonamides. Lorazepam may increase hepatotoxicity.

Use in Pregnancy: Category C. Risk to fetus cannot be ruled out; teratogenicity in pigs, hamsters, and rats when used at 2 to >5x human doses. Use only if benefit outweighs potential risk; **do not use without folinic acid**.

Monitoring: CBC with differential and platelet counts. Check G6PD prior to use in males, particularly those of African, Mediterranean, Asian, and Sephardic Jewish descent.

RIFABUTIN (Mycobutin®)

Classification: Anti-mycobacterial

Indication: Treatment of tuberculosis when patient is on antiretrovirals that contraindicate rifampin use
Treatment of DMAC disease in combination with other drugs
Primary prophylaxis for DMAC disease in people with CD4 <50/mm^3 and no evidence of active tuberculosis, although this is no longer the preferred drug

Adult Dose: TB treatment or DMAC treatment (as a substitute for rifampin): 150 mg po qd (or 300 mg three times a week) when given with **indinavir, nelfinavir, or amprenavir** which raise rifabutin levels.
If on **ritonavir, lopinavir/ritonavir, or saquinavir + ritonavir**, use 150 mg rifabutin every other day or 300 mg three time a week.
With **efavirenz**, which decreases rifabutin levels, use rifabutin 450 mg qd**.**
DMAC prophylaxis: 300mg po qd, although this is not the preferred drug; dose would be modified as above if on interacting drugs.
Dose adjustment in renal failure

Contraindications: **Saquinavir without ritonavir, delavirdine**; WBC <1000/mm^3 or platelet count <50,000/mm^3
Tuberculosis organisms which are resistant to rifampin will be resistant to rifabutin, and vice versa.

Drug interactions: Many **antiretrovirals** require dose adjustment with rifabutin. See Tables 4, 5 and 6, from *HAART* in Antiretroviral section, and *Mycobacterium TB* in Disease-specific section for antiretroviral dosage adjustments and rifabutin dose changes. Rifabutin can induce hepatic enzymes that decrease the activity of other drugs, including **clarithromycin and delavirdine**. Reduces activity of **dapsone, methadone, narcotics, warfarin, corticosteroids, cyclosporine, cardiac glycosides, quinidine, oral contraceptives, digoxin, oral hypoglycemics, and analgesics.** May also decrease effect of **ketaconazole, itraconazole, diazepam, barbiturates, verpamil, beta-adrenergic blockers, clofibrate, progestins, disopyramide, mexiletine, theophyllin, chloramphenicol, and anticonvulsants.** Rifabutin decreases plasma concentrations of **ZDV. Fluconazole** may increase serum concentrations of rifabutin.

See table on **rifamycin-antiretroviral drug interactions** on page 143, for dosage adjustments.

Side effects: Rash, gastrointestinal symptoms, leukopenia, anemia, thrombocytopenia, muscle and joint aches, discolored urine; uncommonly: hepatitis, fever, and chest pain with dyspnea.

Use in Pregnancy: Category B. No evidence of risk, although adequate, well-controlled studies in humans have not been carried out. Animal studies show no teratogenicity.

Monitoring: Liver function tests, BUN, creatinine, CBC with differential and platelet count

RIFAMPIN (Rifadin®)

Classification: Anti-mycobacterial

Indication: Treatment of susceptible mycobacterial infections (DMAC or MTB), including latent TB infection

Adult Dose: 10mg/kg PO qd (usual/maximum dose: 600mg po qd); must be taken as a single dose, not divided. May be given three times a week on directly observed therapy regimens.

Contraindications: Do not use with **indinavir, saquinavir (unless used with ritonavir), nelfinavir, amprenavir, lopinavir, or delavirdine**. Not recommended with **nevirapine**. (See Rifabutin entry; see also Tables 4, 5 and 6, from *HAART* in Antiretroviral section, and *Mycobacterium TB* in Disease-specific section for dosage adjustments and substitutions.)

Drug interactions: Decreases effect of **nevirapine, efavirenz, oral contraceptives, delavirdine, nevirapine, acetaminophen, atovaquone, benzodiazepines, dapsone, fluconazole, methadone, coumadin, digoxin, steroids, sulfones, quinidine and verapamil.** May reduce activity of **anticoagulants, corticosteroids, cyclosporine, quinidine, oral hypoglycemics, narcotics, and analgesics**. Also may reduce effects of **barbiturates, diazepam, verapamil, beta-adrenergic blockers, clofibrate, progestins, disopyramide, mexiletine, theophylline, chloramphenicol, macrolides, and anticonvulsants. Ketaconazole** may reduce both drug levels. **PAS** (para aminosalicylic acid) may reduce serum levels of rifampin, and doses should be given 8 hours apart. **Rifampin may precipitate acute withdrawal when given with methadone.** Use caution with other **hepato- or nephro-toxic agents**, or in patients with severe **hepatic impairment**, and patients with **porphyria**. May decrease **sildenafil** (Viagra) levels.

See table on **rifamycin-antiretroviral drug interactions** on page 143, for dosage adjustments.

Side effects: Flu-like symptoms (fever, chills, bone and muscle pain, nausea/vomiting, headache); thrombocytopenia, anemia, hepatotoxicity, rash, discoloration of body fluids and plastic contact lenses, nephrotoxicity.

Use in Pregnancy: Category C. Risk to fetus cannot be ruled out. Use only if benefits outweigh potential risks.

Monitoring: Liver function tests, BUN and creatinine, CBC; TB symptoms, sputum, and CXR

RITONAVIR (Norvir®)

Classification: Protease inhibitor

Indication: Treatment of HIV infection in combination with other antiretrovirals

Adult Dose: 600 mg po bid; dosage adjustments are often needed with other antiretrovirals. Lower doses may be used to boost blood levels of other PIs. Take with meals; refrigerate. Dose reduction in renal failure

Contraindicated: **Amiodarone, astemizole, bepridil, bupropion, cisapride, clozapine, encainide, ergotamine and ergot alkaloids, flecainide, flurazepam, loratadine, lovastatin, meperidine, midazolam, pimozide, piroxicam, propafenone, propoxyphene, quinidine, rifabutin, simvastatin, and terfenadine** all are elevated by ritonavir and should not be used concomitantly. Blood levels of **alprazolam, clorazepate, diazepam, estazolam, flurazepam, midazolam, triazolam, and zolpidem** are highly elevated by ritonavir and should not be used concomitantly due to increased sedation and CNS effects. Ritonavir cannot be used with **disulfiram** due to ethanol content in caps and solution.

Drug interactions: **See Drug Interactions Tables 2-3 in HAART, Antiretroviral section, for dosing adjustments with NNRTIs and other PIs**.

Clarithromycin - increased clarithro levels; reduce dose if decreased renal function. **Theophylline** level reduced by 47%; monitor levels. **Ethinyl** estradiol level reduced; consider substitution or additional method. **Desipramine** levels increased; may need to reduce desipramine dose. **Dronabinol and sildenafil** (Viagra) levels higher if given with ritonavir; max 25 mg sildenafil in 48 hours. **Rifabutin** dose must be reduced to 150 mg every other day; **rifampin** reduces ritonavir levels by 35%. **Metronidazole** may interact with the ethanol in ritonavir, but may be used with caution.

The following drugs may have 3-fold increases if given with ritonavir; use with caution: **alfentanil, amlodipine, carbamazepine, clonazepam, coumadin, cyclosporine, dexamethasone, diltiazem, disopyramide, dronabinol, erythromycin, ethosuximide, etoposide, fentanyl, felodipine, isradipine, ketaconazole, lidocaine, lovastatin, nefazodone, nicardipine, nifedipine, nimodipine, nisoldipine, ondansetron, paclitaxel, pravastatin, prednisone, quinine, sertraline, tamoxifen, trazodone, verapamil, vinblastine, vincristine.**

The following drugs have 1.5-3-fold increases when given with ritonavir: **amitriptyline, chlorpromazine, clomipramine, desipramine, fluoxetine, haloperidol, hydrocodone, imipramine, maprotiline, methamphetamine, metoprolol, mexiletine, nortriptyline, oxycodone, paroxetine, perphenazine, pindolol, propranolol, risperidone, thioridazine, timolol, tramadol, venlafaxine.**

Other drugs with increase or decrease: **diclofenac, glipizide, glyburide, ibuprofen, indomethacin, lansoprazole, omeprazole, losartan, phenytoin, proguanil, tolbutamide, warfarin s-enantiomer. Methadone** levels are decreased ~36%; consider increasing methadone dose.

Side effects: Elevated liver enzymes, anorexia, taste perversion, asthenia, peripheral and circumoral paresthesias, nausea (may be handled with dose escalation, starting at 300 mg bid for one day, then 400 bid for two days, then 500 bid for one day, then to usual dose of 600 mg bid); hyperglycemia, diabetes; hyperlipidemia, elevated triglycerides, fat redistribution.

Use in pregnancy: Category B. No evidence of risk to fetus, although no adequate, well-controlled studies have been done in humans. Some developmental toxicity (resorptions and decreased birth weight) noted in rats and rabbits. Enroll pregnant women whose fetuses were exposed to antiretrovirals in utero by calling 1-800-258-4263 so that infants can be followed up for adverse effects

Monitor: LFTs, blood glucose, lipid panel, body fat changes, interacting drugs including recreational drugs (see Appendix A: Recreational Drugs and HAART.)

SAQUINAVIR (Fortovase®)

Classification: Antiretroviral (protease inhibitor)

Indication: Approved for use in combination with nucleoside analogues for the treatment of HIV infection

Adult Dose: 1200 mg po q 8 hours for soft gel formula (older, hard-gel formula was branded Invirase® and, due to poor bioavailability, is no longer recommended for use except with ritonavir)
400 mg po bid if given with ritonavir

Contraindications: **efavirenz, rifampin, rifabutin, simvastatin, lovastatin, cisapride, midazolam, triazolam, ergot alkaloids, St. John's Wort, terfenadine, astemizole.**

Drug interactions: **See Drug Interactions Tables 2-3 in HAART, Antiretroviral section, for dosing adjustments with NNRTIs and other PIs**.

Dronabinol levels may be higher if given with saquinavir. **Rifampin** decreases saquinavir levels by 80%, **rifabutin** by 40%. Other drugs that induce metabolic enzymes which may decrease saquinavir levels include **phenobarbital, phenytoin, dexamethasone, carbamazepine.** Clarithromycin increases saquinavir levels by 177%; and saquinavir increases clarithromycin by 45%; use standard doses. Other compounds, such as **calcium channel blockers, clindamycin, dapsone, quinidine or triazolam (that are substrates of CYP3A4)** may have increased plasma concentrations when given with saquinavir; therefore, patients should be monitored for toxicities with these drugs. **Saquinavir** may increase **sildenafil** (Viagra) levels; do not exceed 25 mg in 48 hour period. **Garlic supplements** may decrease saquinavir levels, and **grapefruit juice** increases saquinavir levels.

Side effects: Diarrhea, abdominal discomfort, nausea, asthenia; hyperglycemia, diabetes; "buffalo hump," "protease paunch," round facies, and other symptoms of fat redistribution.

Use in pregnancy: category B. No evidence of risk in humans. Enroll pregnant women whose fetuses were exposed to antiretrovirals in utero by calling 1-800-258-4263 so that infants can be followed up for adverse effects

Monitoring: Baseline biochemical profile then q 3 months if normal; LFTs, lipid profile, blood glucose, body fat changes.

SARGRAMOSTIM (GM-CSF, Leukine®)

Class: Recombinant human granulocyte macrophage colony stimulating factor

Indication: Neutropenia

Adult dose: 250 mcg/m2 subcutaneously qd x 2-4 weeks. Some use 5 mcg/kg. Round dose up to nearest vial size Adjust dose to response. Do not shake vial or filter product

Contraindications: Hypersensitivity to drug or yeast-derived products

Drug Interactions: Lithium and corticosteroids may increase myeloproliferative effects

Side Effects: mild-moderate bone pain, myalgia, nausea, vomiting, polydipsia, headache

Use in Pregnancy: Category C

Monitoring: WBC, differential for response to therapy. Watch renal and hepatic function in patients with pre-existing abnormalities

STAVUDINE (Zerit®, Zerit XR®, D4T)

Classification: Antiretroviral, nucleoside reverse transcriptase inhibitor

Indication: HIV infection in combination with other antiretrovirals

Adult Dose: 40 mg po q 12 hours for patients ≥ 60 kg; 30 mg po q 12 hours for patients < 60 kg.
Zerit XR 100 mg po qd for patients ≥ 60 kg; and 75 mg po qd for patients < 60 kg.
Dosage adjustment required for creatinine clearance ≤50

Drug Interactions: **dapsone, INH, hydralazine, or ethionamide** may increase risk of peripheral neuropathy. Concomitant use of **ZDV** is not recommended due to competitive inhibition. **Methadone** decreases d4t levels by 27%.

Side effects: Peripheral neuropathy, diarrhea, headache, chills, fever, N&V, rash, myalgias, asthenia, abdominal or back pain, insomnia, anxiety, arthralgias, malaise, depression, dyspnea, pruritis, fat redistribution, anorexia; increased risk of fatal and non-fatal pancreatitis, especially when given with didanosine. Lactic acidosis with severe hepatomegaly and steatosis have occurred. Elevations of ALT and AST (SGPT, SGOT), Alk phos, and neutropenia have occurred.

Use in pregnancy: Category C. Risk to fetus cannot be ruled out. Consider if benefit outweighs risk; do not use with didanosine in pregnancy due to increased risk of lactic acidosis. Enroll pregnant women whose fetuses were exposed to antiretrovirals in utero by calling 1-800-258-4263 so that infants can be followed up for adverse effects

Monitoring: LFTs and CBC with differential, neuropathy, fat redistribution, pancreatitis

T-1249

Classification: Investigational drug: antiretroviral, fusion inhibitor (targets gp41)*

Indication: Not approved by FDA as of 1/03; may be useful in patients with strains resistant to PI, RTI and T-20 resistance; in Phase II trials as of early 2003*

Adult Dose: once or twice a day, subcutaneously injected*

Contraindications: anticoagulants, inability to mix, draw up, and self-inject drug*

Drug Interactions: no data*

Side effects: pain, redness, induration, abscess at injection site; hypersensitivity reaction with oral ulcers, rash, fever, neutropenia, headache, dizziness, diarrhea*

Use in pregnancy: no data*

Monitoring: no data*

*provisional information only; may be incomplete. Drug not approved by the FDA. Contact manufacturer for further information: Roche, 800-526-6367.

TENOFOVIR (Viread™, BisPOC PMPA)

Classification: antiretroviral, nucleotide reverse transcriptase inhibitor

Indication: HIV infection, in combination with other antiretroviral drugs

Adult Dose: 300 mg po qd; take with a meal. Do not use in patients with creatinine clearance < 60 mL/min until more data available

Contraindications: none known

Drug Interactions: Increases ddI levels by 46-49%; if given with food, increases by 60-64%. **Lopinavir** increases tenofovir levels; co-administration with other **renally-excreted drugs** such as **acyclovir, ganciclovir, cidofovir, valganciclovir** may result in increased blood levels of either or both drugs; monitor for dose-related toxicities.

Side effects: dizziness, headache, lactic acidosis with severe hepatomegaly and steatosis, fatigue, proteinuria; co-administration with ddI increases risk of pancreatitis and peripheral neuropathy.

Use in pregnancy: Category B. No evidence of risk in humans. Enroll pregnant women whose fetuses were exposed to antiretrovirals in utero by calling 1-800-258-4263 so that infants can be followed up for adverse effects

Monitoring: CBC with differential, renal function

TERBINAFINE (Lamisil®)

Classification: Antifungal

Drug Interactions: rifampin increases clearance of terbinafine 100%. May slow excretion of beta blockers, tricyclic antidepressants, SSRIs, and MAO inhibitors.

Side Effects: headache, dizziness, rash, nausea, taste disturbance, hepatitis, neutropenia, urticaria, pruritis

Indication: Onychomycosis

Dose: 250 mg po qd; for toenails x 12 weeks; for fingernails, 6 weeks

Use in Pregnancy: Category B. No evidence of risk in humans.

Monitoring: CBC, differential, LFTs, symptoms of hepatitis

Tipranavir (PNU-140690)

Classification: Investigational drug: antiretroviral, protease inhibitor

Indication: Not approved by FDA; may be useful in patients with strains resistant to protease inhibitors; saquinavir resistance enhances susceptibility to tipranavir*

Adult Dose: probable dose will be 500 mg with ritonavir 200 mg BID, taken with a fatty meal. Drug must be refrigerated*

Contraindications: Delavirdine (reduces levels by 95%)*

Drug Interactions: tipranavir is a CYP 3A4 enzyme inducer; **ritonavir** (100mg bid) increased the trough tipranavir level by 10-fold, which is why it is likely to be dosed with ritonavir. Not to be taken with antacids or buffered drugs. Decreases other PI concentrations.*

Side effects: N/V/D, abdominal discomfort, fatigue*

Use in pregnancy: no data*

Monitoring: no data*

*provisional information only; may be incomplete. Drug not approved by the FDA. Contact manufacturer for further information: Boehringer-Ingleheim, 800-542-6257.

TRIMETHOPRIM SULFAMETHOXAZOLE (Bactrim®, Septra®, TMP-SMX)

Classification: Antibacterial

Indication: Primary treatment of PCP pneumonia
Primary & secondary prophylaxis of PCP pneumonia;
Prophylaxis against toxoplasmosis.
Urinary tract infection, prostatitis, enteric infections (shigella, salmonella) certain STD's

Adult Dose: Depends on organism and renal function. For IV treatment of PCP in the hospitalized patient, 15-20 mg/kg/day of TMP and 75-100 mg of the SMX component, in divided doses IV x 21 days. . Switch patient to oral medication after improvement of clinical status. Dose generally works out to ~2 DS tablets q 6-8 hours. Dose adjustment in renal failure, with creatinine clearance ≤30.

Contraindications: **porphyria, megaloblastic anemia** due to folate deficiency

Drug interactions: **Dilantin** prolongs TMP-SMX half-life. **Pyrimethamine** may cause megaloblastic anemia. Increased PTT with **warfarin**; increased effect of o**ral hypoglycemic agents**; increased neutropenia with **ganciclovir.** Increased levels of **phenytoin, procainamide.**

Side effects: Skin rash; Stevens-Johnson syndrome; exfoliative dermatitis; renal failure; neutropenia, agranulocytosis, aplastic anemia; nausea, vomiting, anorexia, photosensitivity, hepatitis, hepatic necrosis; hyperkalemia and hyponatremia on higher doses. Use with caution in patients with impaired kidney or liver function, and patients with folate deficiency. May cause hemolysis inpatients with G6PD deficiency.

Use in Pregnancy: Category C - should be used in pregnancy only if the benefit justifies potential risk. Small studies have shown no increase in adverse pregnancy outcomes in humans. TMP-SMX is the preferred PCP prophylaxis during pregnancy

Monitoring: Close monitoring for skin rash; serum iron; CBC with differential (q 3 days on IV therapy); BUN, creatinine, sodium and potassium levels q 4-5 days on IV therapy.

TRIMETREXATE (Neutrexin®)

Classification: Growth-inhibitor of pneumocystis organisms, folate antagonist, derivative of antineoplastic drug

Indication: Moderate-to-severe pneumocystis pneumonia

Adult Dose: 45mg/m^2 IV over 60-90 minutes qd for 21 days; must be accompanied by leucovorin (folinic acid) 20 mg/ m^2 IV q 6 hours for 24 days to prevent lethal toxicity (leukovorin must extend 3 days beyond last dose of trimetrexate). The drugs cannot be mixed with each other. Trimetrexate must be filtered after mixing, and cannot be mixed with NaCl solutions or other anions. Use D5W flush before and after.

Contraindications: Severe bone marrow depression, hypersensitivity to methotrexate.

Drug Interactions: **Erythromycin, fluconazole, and ketoconazole, cimetidine, and clotrimazole** may increase plasma trimetrexate concentrations; **rifampin and rifabutin** may decrease trimetrexate levels. ZDV may increase bone marrow suppression.

Side Effects: Neutropenia, anemia, thrombocytopenia, hepatotoxicity, fever, rash, seizures, stomatitis, N/V, peripheral neuropathy, flu-like illness, hypersensitivity reaction.

Use in Pregnancy: Category D. Possible evidence of risk to fetus.

Monitoring: CBC and platelet count, LFTs, electrolytes, calcium level, creatinine, BUN

VALACYCLOVIR (Valtrex®)

Classification: Antiviral, with activity against herpes virus family

Indication: Herpes zoster, if treated within 72 hours after vesicle appearance; genital herpes

Adult Dose: Herpes zoster (shingles): 1 gm po q 8 hours x 7 days, started within 72 hours of lesion appearance;
Recurrent genital herpes: Valtrex 1 gm po bid x 5-10 days, preferably within 24 hours of outbreak;
Genital herpes suppression: 500 mg po bid.
All dosing must be adjusted in patients with renal disease

Drug Interactions: Cimetidine and probenecid both increase blood levels of valacyclovir, but dosage adjustment not required if renal function normal.

Side Effects: nausea, headache, vomiting, diarrhea; dizziness, abdominal pain, rash; AIDS patients on high dosages (8 gm/day) were more likely to experience thrombotic thrombocytopenic purpura/hemolytic uremic syndrome than immunocompetent patients. Other nephrotoxic drugs may increase risk of renal toxicity.

Use in Pregnancy: Category B. No evidence of risk in humans.

Monitoring: Platelet counts, renal function with long term use

VALGANCICLOVIR (Valcyte®)

Classification: antiviral, prodrug of acyclovir

Indication: CMV retinitis

Adult Dose: Induction: 900 mg bid with food x 3 weeks
Maintenance: 600 mg po qd with food

Contraindications: absolute neutrophil count <500, platelet count <25,000, or hemoglobin <8 g/dL. Not recommended for use in dialysis patients.

Drug Interactions: caution when administering with other myelosuppressive drugs (such as TMP/SMX, pyrimethamine, sulfadiazine, flucytosine, hydroxyurea, antineoplastic drugs.) Probenecid increases ganciclovir levels.

Side Effects: Bone marrow suppression, diarrhea, nausea, vomiting, headache, rash

Use in Pregnancy: Category C – should be used in pregnancy only if the benefit justifies the potential risk. Animal studies have shown teratogenicity in rats.

Monitoring: CBC with differential, platelet count; serum creatinine; follow CMV disease for visual disturbances and frequent f/u with ophthalmologist for early detection of disease progression.

ZALCITABINE (HIVID®, ddC)

Classification: Antiretroviral, nucleoside reverse transcriptase inhibitor

Indication: HIV infection, in combination with other antiretrovirals

Adult Dose: 0.75 mg po q 8 hours
Dose adjustment required in renal failure with creatinine clearance ≤40

Drug Interactions: Any drug which **increases risk of pancreatitis** (e.g., **IV pentam**) or **peripheral neuropathy (e.g., amphotericin B, aminoglycosides, ddI, d4T, foscarnet, ethambutol, cloramphenicol, hydralazine, INH, dapsone, metronidazole, phenytoin** and others) should be avoided when possible. **Antacids** decrease ddC absorption, as does food; **probenecid and cimetidine** decrease elimination of ddC and may increase chance of toxicity

Side Effects: Pancreatitis and peripheral neuropathy, which may become irreversible if drug is not discontinued immediately; hepatic toxicity, lactic acidosis with severe hepatomegaly and steatosis; gastrointestinal symptoms, oral and esophageal ulceration, rash, urticaria, anaphylaxis, anemia, leukopenia, fatigue, fever, headache, N/V/D, abdominal pain, and fat redistribution

Use in Pregnancy: Category C. Risk to fetus cannot be ruled out. Consider use if benefits outweighs potential risk. Enroll pregnant women whose fetuses were exposed to antiretrovirals in utero by calling 1-800-258-4263 so that infants can be followed up for adverse effects

Monitoring: CBC, biochemical profile, LFTs, serum amylase; symptoms of pancreatitis or peripheral neuropathy

ZIDOVUDINE - AZT, ZDV (Retrovir®)

Classification: Anti-retroviral, nucleoside analog

Indication: Treatment of HIV infection when CD4 count is <500/mm^3 or symptomatic. Also approved for use in HIV-infected pregnant women in 2nd and 3rd trimesters, along with IV ZDV during labor and delivery, and ZDV syrup to newborn for 6 weeks.

Adult Dose: 200 mg PO TID or 300mg PO BID

Contraindications: should not be used with ribavirin

Drug interactions: **Acyclovir, alpha interferon, dipyridamole** (increased in vitro antiretroviral activity); **amphotericin B, dapsone, pentamidine, TMP/SMX, acyclovir, ganciclovir, pentamidine, sulfadiazine/pyrimethamine** (increased bone marrow toxicity); methadone (decreased ZDV metabolism); **phenytoin** (increased or decreased phenytoin levels); **Nephrotoxic drugs or cytotoxic drugs, such as flucytosine, vincristine, or interferon,** may increase ZDV toxicity. **Acetaminophen, probenecid, cimetidine, indomethacin, lorazepam, or aspirin** may inhibit excretion and contribute to toxicity.

Side effects: headache, insomnia, nausea, GI upset, myalgia, malaise. More serious effects include neutropenia, anemia, occasional hepatotoxicity, peripheral neuropathy, myositis

Use in Pregnancy: Category C. Risk to fetus cannot be ruled out, although short-term effects of use after first trimester appear negligible. Enroll pregnant women whose fetuses were exposed to antiretrovirals in utero by calling 1-800-258-4263 so that infants can be followed up for adverse effects.

Monitoring: CBC, liver function tests, serum creatinine

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Manufacturers' product labeling.

Appendices

APPENDIX A Recreational Drugs and HAART

INTERACTIONS BETWEEN PRESCRIPTION MEDICATIONS AND RECREATIONAL DRUGS

B. A. Farrington, RN, NP-C, ANP, ACRN; updated by Mark Hebert, FNP

Key Points to Consider

- There is very little data regarding medication interactions with recreational drugs. No controlled trial to date has been performed due to the legal and ethical issues regarding the use of illicit agents in clinical trials. Most information available is either postulated or deduced from laboratory pharmacokinetic studies and/or case reports.
- The majority of issues relative to drug-drug interactions are associated with the pharmacokinetic properties of each interacting agent, specifically metabolism and excretion.
- Some agents have stronger impact on liver enzymes necessary in metabolizing (breaking-down) the active form of other agents, specifically cytochrome p450 (CY P450) enzymes.
- **Inducers** are agents that **increase** the level of these enzymes resulting in **decreased** serum concentration of the active drug form. This may potentially cause loss of therapeutic efficacy of the interacting drug.
- **Inhibitors** are agents that **decrease** the level of these enzymes resulting in **increased** serum concentration of the active drug form. This may potentially cause drug toxicities with the interactive agent.
- Some agents have **both** inhibiting and inducing activity, making assessment of drug interactions more complicated.
- Some agents are not metabolized by the liver but travel via the kidneys where they are combined with enzymes to be dissolved and excreted in the urine.
- Other agents use similar metabolic pathways competing with the same pathways of another agent, thus causing an increase blood level of one agent and a potential decrease in the interacting agent.
- In the presence of hepatic (liver) and renal (kidney) pathologies metabolism and excretion of single agents may be impaired, thus possibly increasing the amount of drug in the body or the amount of its toxic metabolites (breakdown byproducts). There is also the potential for worsening of drug-drug interactions in the presence of these pathologies, especially inhibitors of cytochrome.
- Some of the laboratory data, however, may actually be converse to observations in the clinical setting (i.e., drug interactions between ritonavir and methadone).
- Street drugs are often not what they are thought to be. They are frequently cut with substances that may interact with drugs themselves and their potency can vary widely, even with the same batch.

The following table lists potential and documented drug interactions between more commonly used and available recreational drugs. Pharmacokinetic properties are briefly discussed as well as the interacting agents.

Drug	Pharmacokinetics	Interaction(s)	Significance	Comments
Cocaine	Largely metabolized by tissue and plasma enzymes. Small amount (10%) metabolized by P450 enzymes (CYP3A3/4, CYB2B1) May also induce some P450 enzymes with chronic use and inhibit others with acute use	Potential interaction between: 1) protease inhibitors 2) macrolide antibiotics (erythromycin, clarithromycin) 3) NNRTI's (nevirapine, efavirenz)	Inhibition or induction of P450 enzymes can lead to potential hepatotoxicities, but due to the minor role these enzymes play in drug metabolism, clinical significance is unlikely	While the likelihood of drug interactions with cocaine is low, cocaine is also a known immunotoxic agent, significantly decreasing CD4+ cell production by as much as 3-4 fold, and increasing the rate of HIV reproduction up to 20-fold
Amphetamine Compounds	Under normal conditions, approximately. 15% of dose is eliminated renally, but as urine becomes more acidic, renal excretion may increase up to 55%. Majority metabolized by cytochrome P450 (CYP P2D6)	Inhibition of CYP2D6 can significantly interfere with hepatic metabolism of the amphetamine compound. Such inhibitors include: 1) Ritonavir (↑ amphet-amine levels 2-3 fold) 2) SSRIs (fluoxetine, fluvoxamine, sertraline, paroxetine) 3) Haloperidol 4) Delavirdine	Inhibition of amphetamine metabolism leads to increased levels of the compound. Effects similar to those seen with large doses may be anticipated. Response variable from patient to patient: intense exhilaration, euphoria, agitation, panic, angina, C-V collapse, convulsions, cerebral hemorrhage	Although no data to date exists regarding amphetamine compounds and the prevalence of drug interactions, it is recommended that the best way to manage this interaction is to avoid the combination of the amphetamine compound and the inhibiting agent.
Ecstasy (X, MDMA) **GHB (gammahydro-xybutyrate)**	This is an amphetamine-like compound that has similar metabolism as that of amphetamine compounds. GHB is also thought to be metabolized similarly to Ecstasy.	Inhibition of CYP2D6 will most likely impair detoxification of Ecstasy and lead to large increases in serum levels. Drugs that inhibit CYP2D6 are the same as those listed in "amphetamine" section, above; for ex., ritonavir can ↑ ecstasy levels by 5-10 fold. Alcohol and GHB can cause coma and death	Similar problems associated with amphetamines can be seen with Ecstasy. At least two deaths from the combination of ritonavir and Ecstasy have been reported. Heatstroke, dehydration may occur with ecstasy, which would ↑ with RTV. Dehydration could ↑ risk of renal stones with indinavir	Strongly recommend avoiding the combination of Ecstasy with inhibiting agents. Recent research has also shown that Ecstasy interferes with serotonin neurons, and can increase the potential for depression and anxiety disorders in individuals at risk. At least 68 deaths have been attributed to Ecstasy + alcohol.
LSD **Mescaline** **Psilocin** **Methyltrypta-mine**	Information about P450 metabolism is not available. LSD is structurally similar to serotonin and thus may be metabolized similarly. This means LSD might be eliminated by MAO, aldehyde dehydrogenase and alcohol dehydrogenase. Mescaline, psilocin, dimethyltryptamine may have similar metabolic pathways.	Based on the postulated metabolism of LSD, MAO inhibitors could cause serious interactions. Abacavir could either interfere or be interfered with by LSD, as its pathway also involves alcohol dehydrogenase.	Possible events with retained high doses of LSD include respiratory insufficiency, acute anxiety, fear, vascular spasm and potentially-fatal malignant hyperthermia.	As there is no data to validate these interactions in humans, the prudent recommendation is to avoid combinations of LSD with MAO inhibitors or abacavir.

Drug	Pharmacokinetics	Interaction(s)	Significance	Comments
Tetrahydro-cannibinol (THC, marijuana, hashish and hashish oil)	Rapidly metabolized in the liver to an active metabolite form (11-hydroxyl THC) which is then converted to inactive metabolites and excreted in the urine and stool. Levels of the active metabolite vary with route of administration. Oral route produces more of the active metabolite than either IV or inhaled route. P450 isoenzymes are thought to be important in THC metabolism (CYP3A3/4, 2C9, 2C6)	Inhibiting agents that affect CYP3A3/4 could affect THC metabolism thus increasing THC levels: 1) Protease inhibitors 2) Macrolide antibiotics 3) Delavirdine Inducing agents of the same isoenzymes could reduce THC levels: 1) Nevirapine, efavirenz 2) rifampicin compounds Fluconazole is an inhibitor of 2C9 and can potentially increase THC levels	Inhibition of selected isoenzymes may potentially increase THC levels producing effects of higher THC doses: frank hallucinations, delusions, paranoia, altered time sense, anxiety, panic, orthostatic hypotension, increased heart rate. However, inhibition may actually decrease the amount of the active THC metabolite, thus decreasing THC effects. Induction may increase active metabolite thus increasing the response or may accelerate metabolism to inactive forms	Recommend to closely monitor response in combinations with inhibitors and inducers with THC compounds.
Benzodiaze-pines, group I (alprazolam, clorazepate, clonazepam, diazepam, midazolam)	These agents are extensively metabolized in the liver by CYP3A4 isoenzymes	Drugs inhibiting CYP3A4 could theoretically interfere with metabolism of these agents, causing large increase in the area under the time-concentration curve (AUC). See above list of inhibiting drugs	Large increases in the AUC (>3 fold) of some of these compounds could have serious consequences including sedation and respiratory depression	These agents are contraindicated with ritonavir, although alprazolam has been safely administered with ritonavir, with close monitoring and dose adjustment. See Drug Contraindications chart for other PI info
Benzodiaze-pines, group II (lorazepam, oxazepam, temazepam)	These benzodiazepines are metabolized primarily by conjugation with glucuronic acid which is mediated by glucuronosyltranferase enzymes	Agents that increase glucuronsyltranferase enzyme activity may increase the metabolism of these compounds. Ritonavir is capable of increasing the metabolism of these drugs by this mechanism	Concomitant use of these agents with ritonavir may decrease therapeutic effectiveness of these agents. In patients who are abusing these agents, reduction in serum levels may cause symptoms of withdrawal including: rebound insomnia, tremors, irritability, dysphoria, panic/paranoia, convulsions	Patients receiving these benzodiazepine agents for therapeutic purposes should be monitored for loss of effectiveness in the presence of ritonavir therapy. Patients who are known to be actively abusing these agents should either be given an alternate protease inhibitor or monitored for withdrawal

Drug	Pharmacokinetics	Interaction(s)	Significance	Comments
Alcohol	Principally metabolized by alcohol dehydrogenase may induce activity of CYP2E1 and CYP3A	Due to the induction of CYP3A it is possible that alcohol may induce drugs which are metabolized by the 3A system such as protease inhibitors, NNRTIs Due to common pathway used by abacavir, alcohol may compete for metabolism thus increasing abacavir serum concentrations.	Inducing metabolism of specific agents may result in subtherapeutic levels, predisposing to resistance and decreasing efficacy Elevated abacavir serum concentrations may result in increasing preponderance to toxicity or hypersensitivity reaction	While the information regarding the induction of CYP3A is of some concern, only one study noted such association. There may be little or no significance in the interaction with alcohol and these agents. Alcohol abuse and concomitant use of such hepatotoxic agents may increase the risk of early and more severe liver damage. Additionally, chronic alcohol abuse in the presence of didanosine markedly increases the risk of developing pancreatitis
Heroin **Morphine** **Hydromor-phone** **Codeine**	Morphine and hydro-morphone are extensively metabolized to glucon-nuronides mediated by gluconuronosyltranferases Codeine is mainly metabolized by gluconuronidation, but minor pathways include a process mediated by CYP2D6. Heroin is rapidly converted to morphine in the blood and is similarly metabolized.	Plasma concentrations of all these agents may be decreased by agents that increase activity of gluconuronosyl-tranferases (e.g. ritonavir). Administration of codeine with a CYP 2D6 inhibitor may inhibit the bioactivation of codeine into morphine. In the presence of ritonavir, heroin serum concentrations are reduced by as much as 50%.	Decreased levels of all these agents may result in loss of therapeutic effect when administered with ritonavir. Patients abusing these agents may develop withdrawal symptoms if ritonavir is added to their regimen: lacrimation, rhinorrhea, irritability, tachycardia, elevated blood pressure, chills, flushing, sweating, seizures, myalgias, arthralgias. There is potential for an increased effect with morphine as one gluconuride metabolite is 45 times more potent than the parent compound. Therefore, in some cases, no loss of effect may be seen.	Patients taking these agents with ritonavir or a CYP2D6 inhibitor (of codeine) should be monitored for either loss of therapeutic effect or withdrawal symptoms. It is also known that some opiate compounds act conversely in vivo to what may be seen in vitro, therefore monitoring for toxicities with these agents may also be warranted

Drug	Pharmacokinetics	Interaction(s)	Significance	Comments
Caffeine	Thought to be extensively metabolized by CYP1A2 enzyme group. Minor pathways include CYP2D6 and CYP3A4	Drugs most likely to affect caffeine metabolism include those that inhibit its major metabolizing isoenzymes: ciprofloxacin (and potentially other fluoroquinolones) and macrolide antibiotics	Elevations in caffeine levels may result in accentuated effects: increased blood pressure, increased CNS stimulation, tremors, atrial dysrhythmias, pressor responses. CYP3A4 inhibitors like ritonavir could potentially elevate caffeine levels, but unlikely as this is a very minor pathway in caffeine metabolism	Recommend decreasing caffeine intake while concomitantly using agents that inhibit CYP1A2. No documented interaction between caffeine and protease inhibitors has been reported
Ketamine (Special K)	Undergoes extensive demethylation and hydroxylation in liver and excreted in the urine. It is unclear what P450 isoenzyme is involved with metabolism. As CYP3A4 inhibitors prolong ketamine effects in laboratory animals it is speculated that this pathway may play a significant role. Ketamine is structurally similar to phencyclidine and may also undergo similar metabolism	It is possible that CYP 3A4 inhibitors could inhibit metabolism of ketamine resulting in an elevated serum concentration of the compound. A wide range of CYP3A4 inhibitors can play a significant role in interactions with ketamine: protease inhibitors, benzodiazepines, macrolide antibiotics, delavirdine	Ketamine has a reported wide margin of safety; however, elevated serum concentrations could result in increased heart rate, increased BP or respiratory depression. Theoretically, patients using benzodiazepines that are CYP3A4 metabolized (Group I) could experience adverse effects from elevations in these compounds as well. Chronic use of ketamine in the presence of ritonavir may increase the potential for hepatotoxicity and drug-induced hepatitis	It is recommended that caution be exercised with concomitant use of ketamine and agents that are CYP3A4 inhibitors. Two case reports of drug-induced hepatitis have been reported in patients concomitantly using ketamine and ritonavir. Ketamine is often added to other illegal psychoactive substances, e.g., ecstasy, marijuana, and others.
Phencyclidine (PCP)	PCP is mainly metabolized in the liver mediated by CYP2C11. It is also speculated that PCP may inhibit CYP2B1.	Given the pharmacokinetic profile, it is difficult to predict significant drug interactions as the affinity of other drug interactions as the affinity of other drugs for these agents are not known.		No case reports have been documented involving PCP and P450 inhibitors to date. Caution should be exercised if combining PCP or ketamine with ritonavir

Drug	Pharmacokinetics	Interaction(s)	Significance	Comments
Amyl Nitrate (poppers)	Completely and rapidly metabolized in the liver by first-pass mechanism.	Pharmacodynamic property of this agent creates rapid and system-wide vasodilation. Agents that also cause vasodilation may create additive effect. The use of sildenafil (Viagra) and amyl nitrate may significantly decrease cardiac circulation.	Combinations of nitrates and sildenafil can cause severe hypotension, and may lead to loss of consciousness, ischemic angina, unstable angina and myocardial infarction.	Nitrates and nitric oxide compounds with sildenafil are contraindicated. Caution should be exercised with concomitant use of other vasodilators.

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APPENDIX B Adherence Strategies in Antiretroviral Therapy

Advances in HIV science have clearly brought newer understandings of HIV dynamics, utilization of advanced monitoring techniques, and the introduction of effective multiple drug regimens. However, with these advances there have emerged new issues on old themes: adherence to treatment regimens that are error-prone but have no forgiveness for such errors.

Effectiveness of HIV therapies are globally impacted by the dynamic nature of HIV mutations, resistance patterns, and the accuracy/frequency of virologic monitoring. All of these factors are impacted by adherence to treatment regimens. Adherence, which is essential for regimen effectiveness, is closely influenced by 3 dynamic factors itself: the regimen itself, patient dynamics, and the patient-provider relationship. This section will discuss the role of the clinician, and suggest a practice model for primary care incorporating adherence strategies for therapeutic success.

I. Patient Dynamics

No clinical trial to date has been able to predict adherence based on sociodemographic information, such as race, age, gender, social status, educational status. Factors to consider in assessing the ability of the patient to adhere to regimen, including:

A. Life Stressors

1. Competing demands
- a. job or unemployment
- b. responsibilities to family, children
- c. housing
- d. financial situation
- e. daily schedule
- f. transportation
- g. pre-existing illnesses, medications, drugs
- h. other issues of daily living

2. Unresolved issues, stressful events
- a. when did they learn they had HIV?
- b. family reaction/support
- c. her infected family members

B. Past Experiences

1. What were their experiences in taking medications in the past?

2. Have they ever taken complicated multiple drug regimens before?
- a. For how long?
- b. How successfully were they able to adhere?

3. Have they ever had an adverse drug reaction?
- a. How did they handle it?
- b. Were they able to resume appropriate treatment?

4. How have they dealt with drug side effects?

C. Attitudes about medications/treatment

1. How do they feel about taking medications?

2. What have they heard about HIV therapies, and what do they believe about them?

3. What are their feelings about swallowing several pills multiple times/day?

D. Knowledge about HIV

1. What do they know about HIV disease?
- a. pathogenesis
- b. drug resistance
- c. treatment

2. How interested are they in learning about this disease?

3. What understanding do they have of the importance of treatment on disease progression?

E. Co-existing morbidity

1. History of alcoholism
- a. active or in recovery
- b. patterns of use
- c. how long?
- d. When did they last use?
- e. Have they ever been in treatment program or sought addictions counseling?
  - i. When?
  - ii. How many times?

2. Other addictive substance use: drug(s) of choice; route of use
- a. Active or in recovery
- b. Patterns of use
- c. How long?
- d. when did they last use?
- e. Have they ever been in treatment program or sought addictions counseling?
  - i. When?
  - ii. How many times?

3. Psychiatric illnesses (depression, bipolar, anxiety disorder, PTSD, other)
- a. history of treatment
- b. currently under treatment?

F. Trust in the provider and medical community

1. What has been their previous experience with the health care system?
2. What has been their experience with the health care system since their diagnosis?
3. What "ticks them off" about the health care system now?
4. Do they feel their provider cares about their issues and health care?
5. What would they like to see changed or different about their health care?

G. Cultural and Health beliefs

1. What is their ethnic and racial background?
- a. Are there any ethnic beliefs or values that impact their view of health care?
- b. How do they feel about health care with relationship to their ethnicity?
  - i. Discrimination?
  - ii. Professional bias?

2. Have they ever sought health care from "folk medicine" practitioner of their ethnicity?
- a. Do they still do this?
- b. How do they perceive the difference in care between traditional medicine and folk medicine of their ethnicity?
  - i. Better, worse and which?
- c. How do you (the clinician) feel about their seeking non-traditional care?

3. What is their belief about health and illness?
- a. How do they feel they become ill?
- b. How do they feel they become well and stay well?
- c. Why did they seek medical attention with you, the clinician?
- d. What are their expectations of what treatment can do for them?

The patient's real and perceived place in the world around them has great influence upon the willingness and ability to adhere to drug regimens. Stressors, such as job and housing, set different priorities for different clients. Homeless people, for example, have the priority of finding shelter and food for that day, not taking their medications on an empty stomach or with a meal. There may be negative attitudes toward medications secondary to past experiences, either personally or from others. Co-morbid addictions require addressing the issue that addictions are generally the priority in an individual's life, not taking medications on a strict schedule.

It may take time for patients to build trust in the provider or the medical community. This is influenced by past experiences as well as the individual's health beliefs and cultural influences. This requires considerable empathy and cultural competency on the part of the clinician in order to ascertain the issues of treatment for each individual patient.

II. Treatment Regimen

Characteristics of the treatment regimen impact adherence as well. The larger the number, the greater the frequency, and the tighter the medication restrictions, the greater the chance of non-adherence. Other issues of importance include the cost and availability of drug and the client's financial resources, the amount of behavior change demanded of the individual, how this impacts on the individual's life, and whether the person feels the effect is worth the inconvenience.

Therefore, the clinician and the patient need to assess jointly the following:

A. Drug availability and resource considerations
1. Can we get the drugs we need for this patient?
2. What will be the resource issues for the drug regimens we have chosen?

B. Number of medications
1. How many different medications will be taken with the new regimen?
    a. Consider all meds for OI prophylaxis, current HIV-associated sequelae and other non-HIV-related illnesses; complementary therapies and non-prescription supplements

C. Dosing frequency and timing with meals
1. How many different times will medicines need to be taken?
2. How late is "too late" when a dose is missed?
3. What medications can be taken together?
4. What medications cannot be taken at all while on certain medications?
5. What medications must be separated?
6. What medications have fluid or diet requirements/restrictions?
    a. Does this increase or change the frequency of dosing with the regimen?

D. Duration of therapy
1. What is meant by "life-long" treatment?
2. What happens if the patient has "had it" and can no longer tolerate taking complex medications?
3. What is meant by "treatment failure?"
    a. Does this always mean the patient did not follow instructions or failed to adhere?

E. Side effects
1. What types of side effects are expected with each drug?
2. What are the possible drug-drug interactions and side effects that might be experienced?
3. What interventions can be initiated for certain side effects and drug interactions?
4. How does the patient feel about the potential for drug side effects, toxicities, and interactions?

F. Storage requirements
1. What medications must be refrigerated?
    a. Does the patient have a refrigerator?
    b. How does medication refrigeration impact the patient when they are not at home?
        i. How long can they be left at room temperature?
        ii. Effect of heat (closed car, body heat) on the medication
2. What medications must be kept in a bottle with desiccant?
        i. Effect of humidity on medication
3. How can storage issues, such as refrigeration, impact the patient's confidentiality?
4. How does the patient feel about different storage requirements for multiple medications?
5. What strategies can be employed to ensure proper storage, access to drug with storage requirements, and maintain confidentiality?

G. Intrusion on life
1. All these issues of treatment regimens impact on the individual's life
2. What strategies can be employed to assure adherence and maintain adequate continuance of the patient's life without interfering with its quality?
3. Is the patient ready or willing to make such changes?

4. What preparations should be necessary prior to the start of therapy?
5. What have they done so far to prepare for such changes?

Williams and Friedland (1997) report, "It is clear that expecting most patients to comply with complex antiretroviral regimens without thoughtful and practical support is naive and perhaps arrogant, particularly if patients who fail are then characterized as 'noncompliant.'"

III. Patient-Provider Relationship

There are many factors that impact the patient-provider relationship and become important determinants of adherence. Some of these factors cannot be controlled as they are irrespective of the style of the provider. However, the provider has the opportunity to address all issues relative to their relationship with the patient. Aspects of the relationship that should be addressed include:

A. Respect and trust

1. The central factors in all relationships
2. Does the clinician feel the client trusts his/her judgment and care?
   a. How did the clinician arrive at this decision?
   b. What key evidence is available to support trust or mistrust?
3. Factors that foster trust
   a. honest discussion of difficulties of following regimen
   b. disclosure of potential side effects before they occur
   c. respect for the client's readiness
4. Does the clinician trust the client?
   a. Why do they trust or mistrust the client?
   b. What key evidence is available to support this assessment?
5. What strategies may be employed to encourage open dialogue about trust issues?
   a. What stance would the clinician need to assume in order for the client to feel safe in self-disclosure?
   b. How does the clinician feel about personal self-disclosure?
6. What strategies may be employed to establish a trusting relationship?
   a. Same provider for every visit
   b. Make only promises that you can keep

B. Client-provider responsibility: Client must become a full partner in implementing treatment regimen

a. open dialogue of client expectations and provider expectations
b. discussion of treatment (or non-treatment) options and consequences
c. giving client as much choice over regimen as possible
d. therapeutic contract
e. mutual limit setting
f. elicit feedback from client at every visit

C. Commonalities

1. What factors does the clinician have that are shared by the client?
   a. Age, race, gender, ethnic background, sexual orientation
   b. Similar past health history
      - How willing would the clinician be to self-disclose those facts?
      - How necessary would it be for the clinician to self-disclose those facts?
2. There may be subtle, but unique commonalities that can be shared by the client and the provider: hobbies, sports, music, dancing, arts, politics. It does not need to be a physical attribute, but the more commonalities between the provider and the client, the greater the affectivity between the individuals in the relationship

D. Accessibility

1. How easy is it to contact the clinician?
2. Does the clinician return all patient calls?
3. Does the clinician respond rapidly or do clients wait?
4. Is there a back-up when the clinician is not able to be contacted or unavailable?

5. Does the clinician offer and encourage as much contact as the patient feels is necessary?
6. What office hours does the clinician keep?
7. Is the clinician flexible with his/her availabilities?
8. Does/did the clinician express the limits of his/her availability on the initial encounter?

E. Continuity of care and extent of collaboration

1. What is the clinician's style of practice?
2. Is it mutually participatory or authoritative?
   a. What style of practice is the patient seeking?
3. Does the clinician follow up on patient requests?
4. Does the patient see a different provider each clinic visit? How many times does the patient see his/her provider as opposed to some other covering provider?
5. Does the clinician ask the patient how they feel about treatment decisions?
   a. Does the provider encourage and enlist the patient's assistance and opinion on their medical care and treatment regimen?
6. Does the clinician allow the client choices in treatment and interventions?

F. Communication

1. How do the clinician and the patient communicate?
2. How much empathy is expressed by the clinician?
   a. Does the clinician express to the patient that he/she has heard and understood what they are saying?
   b. How does the clinician express this to the client?
3. Does the clinician explain medical issues in terms that the patient can understand?
   a. How are client questions encouraged or elicited?
   b. How willing is the clinician to answer questions?
4. What is the atmosphere of both verbal and non-verbal communication?
   a. Is it rigidly professional, relaxed, apathetic?
5. Is the clinician assessing the communication of client in response to the encounter?
   a. What cues does the clinician identify to help communication improve?

G. Clinician skills

1. How does the clinician feel about his/her own clinical skills?
2. Is there a degree of confidence expressed to the client about the competency of the clinician?
3. Is the clinician honest with the patient about his/her limitations?
   a. Does the clinician confer and refer when he/she is uncertain of a clinical issue?
   b. Does the clinician communicate the need for conferring and referring to the patient?
4. What is the patient's perception of the clinician and his/her skill?

H. Patient satisfaction

1. All factors above impact patient satisfaction of care which impacts adherence to treatment
2. Patients should be asked without fear of repercussions how they feel about their care
3. They should also be allowed the opportunity to express specifically what it is about their care with which they are dissatisfied
4. What strategies can be employed to improve the patient's satisfaction with their care?
5. Is there a mechanism to solve issues between the client and their provider?

The clinician who uses understandable language, encourages open patient-provider exchange, fosters participation by patients in their own medical care, and creates a friendly, efficient, and supportive environment enhances the likelihood of adherence.

APPENDIX B Adherence

Putting the Pieces Together: The MATEP Adherence Initiative
RIME/EARS: A Model For Therapeutic Success

The Tools for Assessment and Practice workgroup of the Midwest Aids Training and Education Partners (MATEP) Adherence Initiative developed a clinical practice model for improving therapeutic success in HIV/AIDS care: the RIME/EARS Model. **RIME** is an acronym for a dynamic stage-based model of treatment and stands for:

Readiness
Initiation
Maintenance and **E**valuation

EARS is an acronym for the interactive stages within RIME as a process between patient and provider that supports the patient's ability to adhere to a regimen and stands for:

Engage
Assess
Recommend
Support

This model addresses non-emergent HIV/AIDS care that allows some time before starting therapy in order to give the patient time and freedom in preparing for the changes associated with highly active antiretroviral therapy (HAART).

I. Readiness

A. Engage
   1 Begin establishing a partnership
   2. Learn more about each other
      a. What are the patient's expectations?
      b. What are the provider's expectations?
      c. Begin establishing the therapeutic contract
   3. Educate about HIV
      a. Clear up misconceptions
      b. Give basic information about HIV
      c. Discuss the importance of treatment and the impact on progression
   4. Build trust
      a. Encourage open communication
      b. Offer accessibility
      c. Emphasize partnership and the therapeutic contract
   5. Instill hope
      a. Emphasize successes
      b. Emphasize the fact they don't have to do this alone
      c. Dispel the old media myths about HIV/AIDS
      d. Mental health referrals for unresolved psych-emotional barriers to therapy

B. Assess
   1. Identify obstacles to adherence
      a. Explore with the patient factors related to personal dynamics, treatment regimens, and client-provider relationships
      b. Assist the patient in his/her identification of what they perceive to be their obstacles in adherence
   2. Identify potential supports and enhancers to adherence
      a. Explore with the patient his/her perception of tools and concepts they could use to assist them in adhering to treatment

C. Recommend
   1. Establish if the patient is ready for HAART
      a. Very rarely is the patient ready on the first follow-up visit
      b. Readiness may take as much as 6 weeks and in some cases upward of 2-3 years
      c. Do they know what regimen they want?
      d. How have they prepared for the start of the regimen?
   2. Establish which regimen will be best for the ready patient
      a. Review all treatment options with the patient

b. Review all pros and cons of treatment with the patient
c. Review side effects, storage and dosing restrictions of each drug
d. Provide graphic demonstration of various drug combinations for the patient to review

D. Support
1. Facilitate interpersonal support systems
a. Utilizing community-based agencies, family, partners
b. Adherence and treatment support groups
2. Provide use of tangible support products
a. Pill boxes and setup practice
b. Electronic timers
c. Pocket sized med schedules
d. Trial runs with placeboes (mints, small candies) so that patient knows what it's like to use them before therapy begins

II. Initiation

A. Engage
1. Reaffirm the relationship between the provider and the patient
a. Review mutual expectations and limitations and change accordingly
b. Discuss any issues of care impacting satisfaction and measures to intervene

B. Assess
1. Determine potential barriers to adherence
a. Review what was previously addressed in "Readiness" and discuss any new issues emerging.
b. If new barriers are evident and hold the start of therapy, then the patient returns to "Readiness" stage of therapy
2. Determine characteristics that will contribute to success
a. Review what techniques will be used by patient to adhere to regimens
b. Identify any new methods that have emerged that will contribute to adherence

C. Recommend
1. Arrive at a joint decision regarding the most compatible therapeutic regimen
2. If this regimen doesn't work (either for client or virologically), what will future options be?

D. Support
1. Provide necessary educational material and tools to reinforce plan
2. Develop and implement effective follow-up plans tailored to each individual
a. phone call 2 days post-initiation
b. clinic visit at 1 week

III. Maintenance and Evaluation

A. Engage
1. Strengthen the relationship between provider and patient
a. Review mutual goals and expectations; change accordingly
b. Air any new issues regarding care or satisfaction.

B. Assess
1. Determine what is and what is not working in the treatment plan
a. Don't ask, "are you taking your pills?"
b. Ask, "how many times in the past 24 hours have you missed a dose?, past 72 hours?, past week?"
c. What strategies that were thought to be helpful are no longer helpful?
d. What changes in the patient's life have impacted their adherence?
e. What strategies do they find helpful in treatment adherence?

C. Recommend
1. Change therapies or adherence strategies as needed
a. If treatment failure is evident, do not immediately assume the patient is nonadherent, as failure is not always an adherence or personal issue of the patient
b. If therapy requires changing in this model, a shift to "Readiness" is required before beginning new therapy regimen

D. Support
   1. Implement plans based on strategies that are working and problem-solve what is not working
   2. Develop and implement pro-active planning approach and system of support for providers addressing adherence issues

The dynamic nature of adherence strategies implies a fluid staged process, not a linear process. If changes occur in any stage a shift back to "Readiness" is mandated by the model.

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APPENDIX C Primary HIV Infection

Acute/Primary HIV Infection. In patients who are newly infected with HIV, it takes a median of 25 days before the HIV antibody test becomes positive. The typical sequence of routine antibody testing for an individual with HIV exposure in the community is 6 weeks, then 3 months after the most recent potential exposure, although some test to 6 months after the last exposure. Patients who have been infected with HIV generally seroconvert well within this time frame. There have been rare occasions in which occupationally-acquired HIV has taken somewhat longer to show up on serologic testing.

In the setting of an HIV treatment clinic, clinicians do not generally see the primary HIV phenomenon, other than phone inquiries and the rare occasions when a patient brings in sex or needle-sharing partner who experienced a recent accidental exposure. Any patient who reports a recent incident of accidentally exposing a partner should be informed of testing options for the partner, as well as whom to call in the event the partner shows symptoms.

For many patients, symptoms consistent with primary (acute) HIV infection may appear a few days to a few weeks after infection with Human Immunodeficiency Virus, and may include:

- erythematous maculopapular (morbilliform) rash
- Fever
- Pharyngitis
- generalized lymphadenopathy
- Urticaria
- myalgia/arthralgia
- Anorexia
- mucocutaneous ulceration
- headache, retro-orbital pain
- neurologic symptoms

The HIV antibody test is most likely to be negative or indeterminate during this symptomatic phase, which is usually limited to 2-4 weeks or less, although lymphadenopathy generally persists. If the HIV antibody test is negative or indeterminate* during this symptomatic phase, and HIV is still strongly suspected – in clients with recent strong risk history for HIV exposure and whose symptoms are still unexplained – an HIV-1 viral load test can be performed. Of note, a low viral load (<3,000) usually indicates a false positive result at this stage, since viral loads run very high in acute infection.

Patients who come in for an HIV antibody test very soon after exposure, or those coming for STD treatment should be offered an HIV test, but also must be apprised that a negative HIV test does not rule out recent infection. Some clinicians request that the client observe for symptoms noted above, and return to clinic immediately in the event they occur.

On the basis of primary HIV symptoms, a recent exposure to HIV, and a viral load >3,000 copies/ml, some clinicians will offer combination antiretroviral therapy to the client in hope of preserving HIV-specific immune function that may be otherwise lost if the infection runs its course. (See antiretroviral therapy section for complete discussion of HAART and drug selection.) Other clinicians would offer a slot in a clinical trial, since starting HAART at this early stage has very little data to support it at this time; clearly, more information is needed to understand optimal management of the client with very early HIV infection. Nationally, the AIDS Clinical Trials Information Service (ACTIS) may have information on PHIV trials, at 1-800-HIV-0440 noon to 5 p.m. Eastern; or their website at http://www.aidsinfo.nih.gov may be accessed.

In the Atlanta area, Emory University has clinical trials for primary HIV infection; contact Ericka Patrick, RN, BSN at (404) 616-6313 or beep Jeff Lennox, MD, at (404) 560-0034.

The HIV antibody test should still be repeated in 4-6 weeks for documentation of HIV status, although presumptive treatment may have already begun.

*Note that patients who have **indeterminate HIV antibody test results without clear HIV risk factors or PHIV symptoms** should have repeat antibody testing in 2-3 months, without other intervention. Only rarely do indeterminate results indicate evolving seropositivity, and are followed up with HIV viral load testing only in when there is clear history of a recent HIV exposure event and current symptoms of primary HIV.

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APPENDIX D Occupational HIV Exposure

Occupational HIV exposure, background: Of the 57 documented cases of occupationally-acquired HIV/AIDS reported to Centers for Disease Control (CDC) as of year-end 2000, 48 involved sticks or cuts with contaminated sharps. Another 5 were mucocutaneous exposures, all involving large blood volumes or long exposures; 2 had both percutaneous and mucocutaneous exposures. Several of the mucocutaneous exposures involved people working with concentrated virus in virology labs; others were exposures to blood or visibly bloody fluid. After a needlestick with an HIV-contaminated hollow-bore needle, the average HIV seroconversion rate is 0.3%. Risk for any particular incident may be higher or lower, depending on type of exposure. (For evaluation information on other bloodborne pathogens and more on HIV, see full guidelines, first reference.)

When individuals with occupational HIV infection (cases) were retrospectively compared to a group of individuals (controls) with occupational HIV exposure who did not seroconvert, the following odds ratios emerged. Note that only risk factors with P value < 0.1 reported below:

Risk Factor	% of cases with risk factor	% of controls with risk factor	Odds Ratio
large gauge (<18) hollow-bore needle	15	1.2	14
deep injury	52	6.8	15
visible blood on the device	84	35	10
procedure with needle in blood vessel	73	31	5.9
terminal AIDS in source patient	48	16	4.8

Risk factors significantly associated with increased infection appear to be indirect measures of the volume of blood transferred and possibly also the concentration of virus in the inoculum, since endstage patients tend to have much higher viral loads. After control for confounding, the logistic regression analysis showed that the cases were significantly less likely to have used zidovudine after their exposure. These findings and others prompted the US Public Health Service to recommend that health care workers who were occupationally exposed to HIV receive antiretroviral therapy under certain circumstances.

After any potential HIV exposure at work...

Exposed Worker:

- Decontaminates injured/exposed skin with soap and water, or flushes exposed mucous membranes with copious amounts of water or saline
- Reports exposure immediately

Institution:*

- Evaluates circumstances of exposure, including type of fluid, possible entry points, and evaluates source patient
- Counsels on post-exposure prophylaxis (PEP); employee makes final decision
- Offers or recommends post-exposure prophylaxis within an hour or two, or a.s.a.p.
- Obtains baseline HIV antibody test after appropriate pre-test counseling
- Reports exposure as required by federal and state regulations (including OSHA requirements)
- Counsels worker about avoiding potential secondary transmission to others, safer sex
- Supports and maintains confidentiality of worker and partner(s)
- Repeats HIV testing at 6 weeks, 3 months, 6 months; some also test at 1 year

*Legal issues vary from state to state, and there is frequently no obligation from institutions or clinics to students and non-employees who have HIV exposures in their settings. In such situations, clinical supervisors or school/university officials are often the first contact for notification. However, the student/volunteer should make every attempt to avoid delay in treatment by being familiar with the procedure and financial responsibility for exposure management.

In the 2001 occupational exposure guidelines, the US Public Health Service recommended assessing the source patient and circumstances of the exposure, in order to assign a risk status code to each exposure. For source patients whose HIV status is unknown, a rapid HIV test may be helpful in determining need for PEP. While a positive rapid test requires confirmation before treating the source patient, the occupational counselor would presume, for purposes of PEP, that it is truly positive until proven otherwise. A negative test is generally considered accurate, unless the source reports recent HIV exposure or primary HIV symptoms. For complete information on evaluating source patients and other bloodborne pathogen information, see text of Reference #1.

The drugs may be *considered* for the exposed worker, or *recommended* to the exposed worker, depending on the assessed risk. Two different types of regimens were selected, again based on potential risk-benefit ratio, with a "basic regimen" for most exposures, and an "expanded regimen" for those categorized as highest in risk.

Antiretroviral drugs and doses used for the four-week post-exposure prophylaxis period will generally include 2 nucleoside reverse transcriptase inhibitors (NRTIs) for the basic regimen. The expanded regimen consists of the basic regimen plus a protease inhibitor (PI). As with all treatments, the patient (in this case the health care worker) has the right to refuse all drugs. Health care workers who are pregnant at the time of their exposure must weigh fetal risk of exposure and infection against potential risks of the drugs. If antiretroviral drugs are given to pregnant health care workers, it is recommended that the gestating infant be enrolled in a follow-up observational study (see: *Treatment during Pregnancy* in Health Maintenance section.)

Doses of common antiretroviral drugs for PEP:

NRTIs	zidovudine 300 mg + lamivudine 150 mg po bid	
	stavudine 40 mg bid + lamivudine 150 mg bid	These combinations are *basic* regimens
	didanosine 200 mg bid + stavudine 40 mg bid*	
PIs	indinavir 800 mg po q 8 hours	
	nelfinavir 750 mg po tid, or 1250 mg po bid	Add one of these to a basic regimen
	abacavir 300 mg bid	to set up an *expanded* regimen
	lopinavir/ritonavir combination, 400/100 mg bid	
NNRTI	efavirenz 600 mg qd*	

*not recommended in pregnant women

Other antiretrovirals may be used as well, and are given in the same doses as for people with known HIV infection (see antiretroviral drug section). None of the antiretroviral drugs are FDA-approved for post-exposure treatment, but are expected to reduce infection risk based on viral kinetics and animal trials which successfully aborted some HIV infections even when medications were given after exposure to HIV. Side effects and toxicities of drugs may not always warrant their use, depending on circumstances of exposure. Refer to full-text CDC article (first on reference list) for more complete discussion.

Primary HIV Infection in Occupational Exposure:

Source patients recently infected with HIV may have symptoms of primary HIV before their HIV antibody tests become positive, although generally speaking, patients with negative HIV testing do not need further follow-up. These patients with a recent HIV exposure may exhibit acute onset of symptoms such as fever, lymphadenopathy, pharyngitis, and maculopapular (morbilliform) rash, which occurs in 70% or more of symptomatic patients. Less common symptoms include arthralgias, myalgias, malaise, N/V/D, headache, unexplained neurologic symptoms, urticaria, and oral or mucocutaneous ulcerations. Consultation with HIV-expert clinician would be helpful. See further information in Reference #1, or *Appendix C: Primary HIV Infection.* Source patients with symptoms and positive risk history should be considered SC 2 (see Step 2: Determine the HIV Source's Status Code), pending confirmatory labs, and exposed health care workers treated accordingly.

Symptoms of primary HIV infection may also occur in health care workers who have become infected with HIV. If such symptoms appear within 4-6 weeks after an occupational exposure, immediate follow-up is indicated; the employee should be counseled to return as soon as possible after onset of symptoms for re-evaluation.

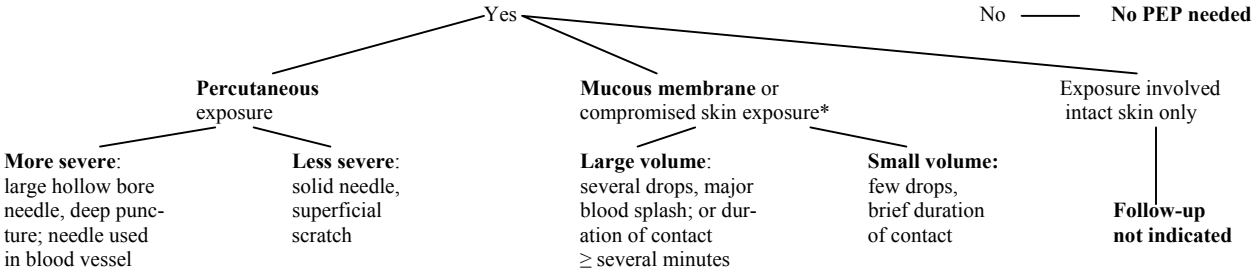
For free consultation on treatment of occupational exposures to HIV and other bloodborne pathogens, have the clinician managing the exposed patient call the national PEPline at 1-888-HIV-4911. This line is available 24 hours a day, although the consultant may have to call back. PEPline support may be especially useful when drug-resistant HIV strains are suspected. More information is available on the Internet at http://hivinsite.ucsf.edu; see also Reference #1 for the full text of the USPHS guidelines for PEP.

For information resources on post-exposure prophylaxis for non-occupational exposures, see *HIV Prevention* in Health Maintenance section

Appendix D — Occupational HIV Exposure

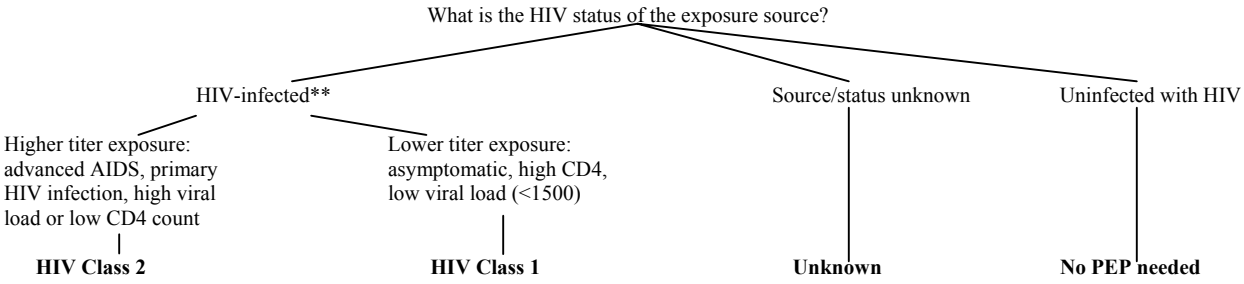
Step 1: Determine the Exposure Type and Severity

Is the source material blood, bloody fluid (including pus or vesicle fluid), semen, vaginal secretions; or potentially-infectious material such as cerebrospinal, synovial, pleural, peritoneal, pericardial, or amniotic fluids; or tissue?



* Skin integrity is considered compromised if there is evidence of chapping, dermatitis, abrasion, or open wound/lesion.

Step 2: Determine the Source Patient's HIV Infectivity Class



**A source is considered infected with HIV if there is or has been a positive HIV antibody, HIV PCR, P-24 antigen, HIV-RNA test, diagnosed AIDS, or symptoms and history consistent with primary HIV infection.

Step 3: Determine the PEP Recommendation

Exposure Type	HIV Status Class	PEP Recommendation
Small-volume mucous membrane	1	*Consider* basic regimen (2 NRTIs, see front)
Small-volume mucous membrane	2	*Recommend* basic regimen
Less-severe percutaneous or Large-volume mucous membrane	1	*Recommend* basic regimen
Less-severe percutaneous or Large-volume mucous membrane	2	*Recommend* expanded regimen: basic regimen plus protease inhibitor or non-nucleoside reverse transcriptase inhibitor
More-severe percutaneous	1 or 2	*Recommend* expanded regimen
Any type	Unknown	Generally, no PEP is warranted. If the source or setting where the exposure occurred suggests a possible risk for HIV, *consider* basic regimen. If source is later learned to be HIV-negative, PEP should be discontinued

Algorithms and tables adapted from reference 1 (below), pp 24-25

Note that exposed health care workers should be re-evaluated in 72 hours, and again at 2 weeks, at a minimum. Health care workers should be advised at their initial visit to report any new febrile illnesses immediately, as well as in the event of rash, back or abdominal pain, painful urination or hematuria, or other unexplained symptoms. Some medications may cause fairly severe side effects, of which health care worker should be apprised. Most minor drug effects do not necessitate discontinuation of the PEP regimen, and can be managed with symptomatic therapy. The health care worker should be informed of drug interactions between antiretrovirals and their current medications as well as what medications to avoid during PEP. Pregnant health care workers should be informed of risks and benefits of HIV medications, and those who are

breastfeeding should be advised to consider interruption of breastfeeding during the course of PEP, since several of the drugs are present in breast milk. See reference 1 below, for more complete discussion; see also Antiretrovirals in Pregnancy table in *Treatment During Pregnancy*, in Health Maintenance section.

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Index