PEDIATRIC ANTIRETROVIRAL DRUG INFORMATION

Members of the Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children have developed this Antiretroviral Drug Information Hyperlink document. As new information becomes available, the hyperlink will be up-dated. This document contains detailed information about the different classes of antiretroviral agents. Promising investigational agents currently under study in adults and/or children will be included. This document should be used in conjunction with the Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection (**http://AIDSinfo.nih.gov/**). Dosing information can be found in the **Appendix to the Guidelines**. Additionally, antiretroviral drug information updates, labeling changes and safety warnings may be accessed by subscribing to the U.S. Food and Drug Administration (FDA) HIV/AIDS E-mail list at: **http://www.fda.gov/oashi/aids/email.html.**

In the past seventeen years, therapeutic strategies to treat pediatric patients with HIV infection have expanded dramatically from treatment with a single medication to combination therapy that includes up to four different classes of antiretroviral agents. As of January 2004, there were twenty antiretroviral agents approved for use in HIV-infected adults and adolescents in the United States; twelve of these have an approved pediatric treatment indication. The agents available fall into four major classes, the nucleoside analogue reverse transcriptase inhibitors NRTI'S (abacavir*, didanosine*, emtricitabine, lamivudine*, stavudine*, zalcitabine, and zidovudine*) and nucleotide reverse transcriptase inhibitors (tenofovir); nonnucleoside analogue reverse transcriptase inhibitors NNRTI'S (nevirapine*, efavirenz*, and delavirdine); protease inhibitors PI's (amprenavir*, atazanavir, fosamprenavir, indinavir, lopinavir/ritonavir*, nelfinavir*, ritonavir*, and saquinavir hard and soft gel capsules); and fusion inhibitors (enfuvirtide*).

In order to successfully suppress HIV viral replication without disruption of normal cellular function, it is essential to target specific components unique to the virus. Theoretically, antiretroviral agents that target the initial stages of the viral replicative cycle (prior to provirus formation), should prevent primary infection of cells, yet be ineffective in cells that have already integrated virus and drugs that inhibit steps after viral integration should block new virus production by virally infected cells. Currently FDA approved antiretroviral medications include fusion inhibitors, which prevent viral entry; reverse transcriptase inhibitors (nucleoside, nucleotide, and non-nucleoside), which act at the early stage of replication; and inhibitors of viral protease, which work in the later stage after viral integration. Fusion inhibitors are the newest class of antiretroviral drugs, and act by inhibiting binding or fusion of HIV to target host cells. The NRTIs are potent inhibitors of the HIV reverse transcriptase enzyme, which is responsible for the reverse transcription of viral RNA into DNA; this process occurs prior to integration of viral DNA into the chromosomes of the host cell. The NRTIs require intracellular phosphorylation to their active forms by cellular kinases. The phosphorylated drug acts to competitively inhibit viral reverse transcriptase and to terminate further elongation of viral DNA following incorporation of the drug into the growing DNA chain. Since these drugs act at a pre-integration step in the viral life cycle, they have little to no effect on chronically infected cells in which proviral DNA has already been integrated into cellular chromosomes. Nucleotide reverse transcriptase inhibitors also competitively inhibit the viral reverse transcriptase, like the NRTIs, but because the nucleotide drugs already possess a phosphate molecule (and the NRTIs do not), the nucleotide drugs bypass the rate-limiting initial phosphorylation step required for activation of NRTIs. NNRTIs specifically inhibit reverse transcriptase activity by binding directly to the active site of the enzyme without requiring prior activation. Protease inhibitors inhibit the HIV protease enzyme that is required to cleave viral polyprotein precursors and generate functional viral proteins. The protease enzyme is crucial for the assembly stage of viral replication, which occurs after transcription of proviral DNA to viral RNA, and subsequent translation into viral proteins. Because protease inhibitors act at a post-integration step of the viral life cycle, they are effective in inhibiting replication in both newly infected and chronically infected cells *[1]*.

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*denotes pediatric treatment indication

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors

The NRTIs were the first class of antiretroviral drugs available for the treatment of HIV infection. Their antiviral activity depends upon intracellular serial phosphorylation to the triphosphate active drug by host cellular kinases *[2]*. Although resistance eventually develops to these agents during the course of long-term single drug therapy, combination therapy with these drugs may prevent, delay or reverse the development of resistance *[3]*. One notable exception to this is lamivudine (3TC) and emtricitabine (FTC), where a single point mutation can confer resistance to these agents in as little as 4 to 8 weeks when given as monotherapy or in combination with an antiretroviral regimen that does not fully suppress viral replication (e.g. dual NRTI therapy with ZDV/3TC). NRTIs may increase the risk of mitochondrial dysfunction due to inhibition of mitochondrial DNA polymerase gamma *[4]*. Unusual but significant serious toxicities that can occur in patients exposed to these agents include lactic acidosis, hepatic steatosis, pancreatitis, myopathy, cardiomyopathy and peripheral neuropathy. Additionally, rapidly ascending muscular weakness has recently been reported as a new symptom of nucleoside related lactic acidosis and hyperlactataemia (BMS letter to doctors. 28 September 2001). Interestingly, although some toxicities may be seen with all NRTI drugs (e.g. lactic acidosis), other toxicities (such as peripheral neuropathy) may predominately occur with specific NRTIs, suggesting diverse mitochondrial effects of the drugs that may be dependent on varying ability to penetrate particular cell types. The relative potency of the nucleosides in inhibiting mitochondrial gamma DNA polymerase in vitro is highest for zalcitabine (ddC), followed by didanosine (ddI), stavudine (d4T), lamivudine (3TC), zidovudine (ZDV) and abacavir (ABC) *[5]*. The prevalence of these side effects in children is unknown.

Nucleotide reverse transcriptase inhibitors (NtRTIs) possess a phosphate molecule that the NRTI drugs do not. NRTI drugs require three intracellular phosphorylation steps to the active triphosphate form of the drug. In contrast, nucleotide analogues contain a phosphonate group and do not require the first, often rate-limiting, intracellular phosphorylation step. Both NRTI and the nucleotide reverse transcriptase inihibitors are competitive inhibitors of the HIV reverse transcriptase, resulting in premature termination of viral DNA synthesis. Tenofovir disoproxil fumerate is the first drug approved in the nucleotide reverse transcriptase inhibitor class for treatment of HIV. Other nucleotide analogue drugs include cidofovir (used to treat cytomegalovirus) and adefovir, active against HIV and hepatitis B virus; both of these latter drugs have high rates of renal toxicity, particularly proximal tubule dysfunction and Fanconi syndrome.

References:

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Abacavir (ABC, Ziagen®)

URL:http://www.fda.gov/cder/foi/label/2000/20978s2lbl.pdf
URL: link to Guideline Appendix-ABC

Overview
In December of 1998, abacavir (ABC) was approved by the FDA for combination therapy in adults and children age 3 months or older, based on controlled trials in adults and children.

Abacavir (ABC) is a guanosine analogue nucleoside reverse transcriptase inhibitor. ABC is anabolized intracellularly to its active triphosphate form utilizing enzymes that do not phosphorylate other NRTIs *[1]*. ABC demonstrates *in vitro* synergy with 3TC, ZDV, nevirapine and amprenavir and additive activity in combination with ddI, 3TC, d4T and ddC.

It crosses the blood-brain barrier, with CSF-to-plasma concentration ratios of 18%-25%. Bioavailability is 83% and serum half-life is 1.5 hours. In humans, cytochrome P450 enzymes do not significantly metabolize abacavir and it in turn does not inhibit human CYP3A4, CYP2D6 or CYP2C activity at clinically relevant concentrations. The primary routes of elimination are metabolism by alcohol dehydrogenase and glucuronyl transferase.

Resistance
Prior treatment with multiple NRTIs and the development of mutations associated with resistance to multiple NRTIs are associated with a blunted HIV RNA response to ABC combination therapy *[2, 3]*. Resistance mutations have been seen at RT codons 65, 74, 115, and 184 both *in vitro* and in patients taking ABC. At least 2 to 3 of the mutations are required to reduce susceptibility by 10-fold. Mutations at codons 184 and 74 were most frequently observed in clinical isolates. ABC-resistant virus will be resistant to 3TC. While virus resistant to AZT or 3TC alone may remain susceptible to ABC, virus resistant to both ZDV and 3TC is more likely to be cross-resistant with ABC.

Adverse Effects
A potentially fatal hypersensitivity reaction occurs in approximately 5% of adults and children receiving ABC (see: Adult Guidelines Document: Table 18-Black Box warnings) *. Symptoms include flu-like symptoms, respiratory symptoms, fever, rash, fatigue, malaise, nausea, vomiting, diarrhea, and abdominal pain. Patients developing these symptoms should have ABC stopped and not restarted, since hypotension and death have occurred with rechallange. In a randomized study comparing ABC/ZDV/3TC to ZDV/3TC alone, 4 of 146 children receiving ABC and 2 of 44 children in the ZDV/3TC group who switched to open-label ABC therapy developed a hypersensitivity reaction, which resolved upon discontinuation of therapy *[4]*. Onset of the hypersensitivity reaction occurred between 1 to 2 weeks after ABC was started. Nausea and vomiting alone may occur in as many as one-third of children receiving ABC in combination with other antiretroviral agents.
When using ABC, parents and patients must be cautioned about the risk of a serious hypersensitivity reaction; a medication guide and warning card should be provided to parents. Patients should also be advised to consult their physician immediately if signs or symptoms consistent with a hypersensitivity reaction occur. Children experiencing a hypersensitivity reaction should be reported to the Abacavir Hypersensitivity Registry (1-800-270-0425). While ABC may be included as a component of a treatment regimen for children who have failed prior antiretroviral therapy, it should be recognized that it is less likely to be active in children with extensive prior treatment with NRTIs. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including ABC.

> * ***The updated version of the adult-adolescents guidelines, containing the new Table 18, Adverse Drug Reactions Related "Black Box Warnings" in Product Labeling for Antiretrovirals Agents.***

Pediatric Experience
In adults, ABC has been studied in dual and triple combinations with a protease inhibitor (PI). Dual combination therapy with various PIs reduced the viral load to <400 copies/mL in 54-85% of treatment-naïve adults *[5]* . ABC has also been studied in combination with other NRTIs without a PI. In an ongoing study of treatment-naïve adults, combination therapy with ABC/ZDV/3TC resulted in a viral load of <400 copies/mL in 75% of subjects at 16 weeks of treatment and this result was sustained through 48 weeks of therapy *[6, 7]*. In a study of 205 treatment-experienced children ranging in age from 0.7 – 13 years, the combination of ABC/ZDV/3TC resulted in a greater fall in viral load and increase in $CD4^+$ cell count than did ZDV/3TC. However, only 10% of 102 children receiving ABC/ZDV/3TC had HIV RNA levels <400 copies/mL at 48 weeks of therapy *[4]*. It is therefore unclear what role triple NRTI combinations may have in the pediatric population.

References:

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Didanosine (ddI, Videx®)

URL:http://www.fda.gov/cder/foi/label/2001/videxlbl.pdf
URL:http://www.fda.gov/cder/foi/label/2001/videxec.pdf
URL: link to Guideline Appendix-ddI

Overview
Didanosine (ddI) received FDA approval in 1991 for adults and pediatric patients older than 6 months of age with advanced HIV infection who were intolerant to or deteriorating on ZDV. Since that time the indications have been broadened and dosage recommendations reduced. In October 2000 a new delayed-release formulation of enteric-coated beadlets was approved for use in adults allowing for once-daily ddI administration in selected patients.

ddI is a purine dideoxynucleoside analogue that requires intracellular phosphorylation in resting cells to become active. Despite lower CSF penetration than ZDV (CSF/plasma ratio = 0.05), there was a 46% (range 12-85%) improvement in neuropsychometric testing scores observed in some children that were correlated with ddI plasma concentration *[1, 2]*. ddI is unstable at acidic pH and is rapidly degraded unless given as an enteric formulation (EC) or combined with buffering agents or antacids. Bioavailability ranges from 20% to 40% depending upon the formulation used. ddI's plasma half-life is 0.5 to 1 hour in contrast to its intracellular half-life of 25 to 40 hours. The long intracellular half-life allows for the extended dosing interval. Recent data from PACTG 144 has suggested that systemic exposure to ddI (i.e. AUC) in children remains similar in the both the presence and absence of food *[3]*. This may allow for the relaxation of fasting state requirement in certain instances.

Resistance
Genotypic mutations at codons 65, 74 and 184 have been associated with ddI resistance. The most common mutation, L74V is most frequently associated with diminished antiviral activity of ddI. Interestingly, isolates with this resistance mutation have increased susceptibility to ZDV *[4]*. 3TC-resistant virus may have reduced susceptibility to ddI but cross-resistance is not complete.

Adverse Effects
Fatal and nonfatal pancreatitis has occurred during therapy with this agent used alone or in combination regimens in both treatment-naïve and treatment-experienced patients, regardless of degree of immunosuppression (see: Adult Guidelines Document: Table 18-Black Box warnings) *.
Didanosine should be suspended in patients with suspected pancreatitis and discontinued in patients with confirmed pancreatitis. Pancreatitis appears to be more common in adult patients and may be dose-related. It has occurred more commonly in patients with predisposing factors including a prior history of pancreatitis, baseline elevation of serum trans-aminases, and concurrent administration of other drugs known to cause pancreatitis, such as pentamidine and d4T *[5]*. Hydroxyurea appears to increase the risk of pancreatitis when co-administered with ddI. Didanosine may cause peripheral sensory neuropathy. Asymptomatic peripheral retinal depigmentation has been observed in <5% of children receiving ddI, is not associated with loss of vision, and appears to reverse with discontinuation of therapy *[6]*. Diarrhea has been reported, and may be more related to the antacid/buffer with which the drug is formulated than to ddI itself. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including didanosine.

Pediatric Experience
Results of long-term follow-up of infected children receiving ddI for a median duration of almost two

years show that ddI appears safe, and is associated with clinical improvement, increase in $CD4^+$ count and decrease in p24 antigenemia, persisting in some cases for several years *[7]*. In PACTG 152, ddI (administered either as a single agent or in combination with ZDV) was shown to be superior to ZDV monotherapy as initial therapy for symptomatic children over 3 months of age as measured by length of time to death or to progression of HIV disease *[8]*. PACTG 300 found that in symptomatic children, combination therapy with either ddI and ZDV or 3TC and ZDV was more effective than ddI monotherapy *[9]*. PACTG 327, a randomized trial to evaluate the safety, tolerance and antiviral activity of ddI and d4T in combination or d4T alone, found the combination to be superior to d4T monotherapy in 108 antiretroviral experienced children who had been previously enrolled in PACTG 240 (d4T monotherapy versus ZDV monotherapy) or who had received ZDV monotherapy for at least 6 months *[10]*. Importantly, no children were discontinued from study due to toxicity and there were no cases of pancreatitis or peripheral neuropathy identified when this combination of agents was used. ddI has also been studied as part of a treatment regimen including ZDV and ritonavir in highly retroviral-experienced pediatric patients and as part of a combination regimen with d4T and nelfinavir *[11, 12]*.

**** The updated version of the adult-adolescents guidelines, containing the new Table 18, Adverse Drug Reactions Related "Black Box Warnings" in Product Labeling for Antiretrovirals Agents.***

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Emtricitabine (FTC, Emtriva™)

URL:http://www.fda.gov/cder/foi/label/2003/21500_emtriva_lbl.pdf
URL: link to Guideline Appendix FTC

Overview

Emtricitabine (FTC) was approved in July 2003 for treatment of HIV infection in adults aged 18 years or older. Approval in adults was based on 48-week data from 2 clinical trials in adults. The first trial was in antiretroviral naïve patients; FTC in combination with ddI and efavirenz was compared to d4T, ddI and efavirenz. The proportion of patients with HIV RNA <400 copies/mL at 48 weeks was 81% with the FTC-based regimen compared to 61%

for the d4T-based regimen *[1]*. The second trial was in treatment-experienced patients who had HIV RNA <400 copies/mL on 3TC-based triple drug therapy; patients either continued on 3TC or switched to FTC. At 48 weeks, the proportion of patients with HIV RNA <400 copies/mL was 77% in the FTC group compared to 82% in the 3TC group *[2]*. Safety and effectiveness of FTC in pediatric patients is under study.

FTC is a synthetic cytosine nucleoside analog (nucleotide 2'deoxycytidine). It differs only slightly in structure from 3TC (5-fluoro substitution), although its potency is on average five times higher in *in-vitro* tests against HIV strains from primary clinical isolates; concentrations required for 50% inhibition of HIV-1 are 10-20 nanomols/liter. Like other NRTI drugs, FTC requires intracellular phosphorylation to become active. FTC is metabolized intracellularly and its primary route of elimination is via renal excretion without significant metabolic interactions with other antiretroviral drugs.

FTC is rapidly and well-absorbed following oral administration. Systemic exposure (area under the curve, AUC) is unaffected by administration of FTC with food. The plasma level of FTC follows linear pharmacokinetics over a wide dosage range. The terminal half-life of FTC in plasma is 8-10 hours. This NRTI is expected to be most effective against HIV-1 when used in combination regimens with other antiretroviral therapy agents. *In-vitro* data have shown that FTC is synergistic with zidovudine, didanosine, stavudine, abacavir, nevirapine, delavirdine, efavirenz, indinavir, nelfinavir and amprenavir. However, resistance to 3TC confers cross-resistance to FTC.

Limited data suggest FTC is active against hepatitis B virus, although the safety and efficacy of FTC in HIV-infected patients co-infected with hepatitis B has not been established. "Flare-ups" of hepatitis B have been reported in HIV/hepatitis B coinfected patients after discontinuation of FTC therapy. Such patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping FTC treatment.

Resistance
Like 3TC, resistance to FTC is associated with a single genotypic mutation at codon 184. FTC-resistant isolates have been recovered from some patients treated with FTC alone or in non-suppressive combination with other antiretroviral drugs. FTC-resistant isolates are cross-resistant to 3TC and ddC, but retain sensitivity to ABC, ddI, d4T, tenofovir, ZDV and NNRTI drugs. HIV-1 isolates containing the K65R mutation, selected *in vivo* by ABC, ddI, TFV, and ddC, have reduced susceptibility to FTC.

Adverse Effects
FTC is well-tolerated. The most common adverse events reported in clinical trials were headache, diarrhea, nausea, and rash, which were generally of mild-moderate severity and required drug discontinuation in only 1% of patients. Skin discoloration, manifested by hyperpigmentation of the palms and/or soles, can be observed, predominantly in non-Caucasian patients. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including FTC.

Pediatric Experience
A single dose pharmacokinetic study of FTC liquid solution and capsules was performed in 23 HIV-infected children 2-17 years of age *[3]*. FTC was found to be well-absorbed following oral administration, with a mean elimination half-life of 11 hours (range 9.7-11.6 hours). Based on this dose-finding study, FTC was given at a dose of 6 mg/kg once daily in combination with other antiretroviral drugs in a phase II study in 82 HIV-infected children *[4]*. Antiretroviral naïve children received FTC plus d4T and lopinavir/ritonavir, and treatment-experienced children were changed from a 3TC to FTC-based regimen. The 6 mg/kg once daily dose regimens achieved a plasma area under the curve (AUC) equivalent to median values in adults receiving a standard 200 mg dose *[4]*. In PACTG 1021, FTC 6 mg/kg (maximum 200 mg/day) in combination with ddI and efavirenz, given once daily, is under study in antiretroviral-naïve HIV-infected children aged 3 months to 21 years. This regimen has been well tolerated and FTC and ddI concentrations met the desired target study concentrations *[5]*.

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Lamivudine (3TC, Epivir®)

URL:http://www.fda.gov/cder/foi/label/2001/20596S12LBL.pdf
URL: link to Guideline Appendix 3TC

Overview
Lamivudine (3TC) was approved in November 1995 for use in infants greater than 3 months of age and children based on efficacy studies in adults in conjunction with safety and pharmacokinetic studies in children. In September 1997 it was approved as a fixed combination of 3TC/ZDV for adults and adolescents greater than 12 years old. In November 2000 it was approved as a fixed-dose combination of 3TC/ZDV/abacavir for adolescents and adults weighing greater than 40 kg.

3TC is the negative enantiomer of a synthetic cytidine analogue. 3TC requires intracellular phosphorylation to become active and does so preferentially, like ddI and ddC, in resting cells. 3TC has activity against HIV-1, HIV-2 as well as hepatitis B virus. The CSF/plasma ratio in children is relatively low (0.11) compared with that of ZDV (0.25), but higher than that of ddI (0.05) *[1]*. The bioavailability is approximately 66% in children and 86% in adolescents and adults. Its plasma half-life is 2 hours and its intracellular half-life is 10-15 hours allowing for twice daily dosing.

Resistance
When 3TC is administered as monotherapy, resistance emerges rapidly and is associated with a single genotypic mutation at codon 184. Resistance also develops rapidly (within weeks) when 3TC is used in non-suppressive combination antiretroviral regimens, such as dual NRTI therapy with ZDV/3TC *[2]*. Therefore optimal use of 3TC is within a combination of at least three antiretroviral medications capable of providing full suppression of viral replication. 3TC-resistant virus may be partially cross-resistant to ddI and ddC. *In vitro*, development of the codon 184 3TC resistance mutation is associated with increased fidelity of the viral reverse transcriptase enzyme for its substrate *[3]*. It is speculated that this could influence the evolution of the virus and may prevent or delay the generation of drug resistant variants. For example, the 184 mutation is reported to suppress ZDV resistance *in vitro* and when introduced into the background of a ZDV-resistant reverse transcriptase gene to suppress the effect of some ZDV resistance mutations *[4]*. Additionally, the M184I/V mutation is associated with diminished viral replicative fitness *[5]*.

Adverse Effects
3TC is very well tolerated. The major reported toxicities are pancreatitis and peripheral neuropathy *[1, 6]*. Headache, fatigue and gastrointestinal upset have also been described. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including 3TC.

Pediatric Experience
Phase I/II study of 3TC showed that the agent could decrease viral burden by 0.77 logs when used as monotherapy *[1]*. In PACTG 300, children receiving ZDV and 3TC had a lower risk of HIV disease progression or death than those receiving ddI alone *[7]*. In the European PENTA-4 double-blind randomized trial of the addition of 3TC or placebo to NRTI therapy in pediatric patients with advanced disease, 3TC was well tolerated when coupled with ZDV, ddI or ZDV plus ddC *[8]* . In PACTG 338, 42% of children receiving triple combination ZDV, 3TC plus ritonavir had undetectable HIV-RNA at week 48 compared with 27% receiving a single NRTI plus ritonavir.

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Stavudine (d4T, Zerit®)

URL:http://www.fda.gov/cder/foi/label/2001/zeritwng.pdf
URL: link to Guideline Appendix-d4T

Overview
Stavudine (d4T) was approved in September 1996 for use in infants and children greater than six months of age based on evidence from controlled trials in adults and on safety and pharmacokinetic data from children.

d4T, like ZDV, is a thymidine analogue. It is preferentially phosphorylated and exerts more potent antiviral activity in activated rather than in resting cells. CSF concentrations of d4T varied widely (16-97% of plasma concentrations) in a study of eight pediatric patients receiving chronic dosing *[1]*. Drug absorption is reliable with bioavailability greater than 80%. The plasma half-life is 1.4 hours while the intracellular half-life is 3.5 hours. In pediatric patients, the plasma half-life is 0.96 hours.

Resistance
High-level resistance to d4T has been difficult to demonstrate; genotypic mutations at codon 50 and 75 have been reported to be associated with diminished *in vitro* susceptibility to d4T.

Emergence of genotypic mutations associated with ZDV resistance in ZDV-naïve individuals receiving therapy with d4T-based regimens has been reported *[2]*.

Adverse Effects
d4T's most significant toxicity is peripheral neuropathy, but this appears to be less common in children than adults *[1, 3]*. Elevated hepatic transaminases are seen in about 11% and pancreatitis in 1% of adults enrolled in clinical trials of d4T. d4T has been studied in pediatric patients in combination with ddI; no pharmacokinetic interactions were observed and there were no cases of peripheral neuropathy *[4]*. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including d4T. ZDV is a potent inhibitor of the intracellular phosphorylation of d4T in vitro, and at least one adult clinical trial indicates that there may also be in vivo antagonism associated with this combination *[5, 6]*. Therefore, d4T and ZDV should not be co-administered.

Pediatric Experience
Many clinicians use d4T as a replacement for ZDV when combination drug regimens are changed. In a phase II study comparing monotherapy with either d4T or ZDV in 212 infected children between 3 months and 6 years of age (median age, 14 months), d4T and ZDV were largely comparable in terms of safety and tolerance *[3]*. Neutropenia occurred significantly less commonly among children receiving d4T than ZDV. d4T has been studied in combination with ddI in HIV-infected children *[4, 7]*. This combination was well tolerated; in PACTG 327,

plasma RNA levels showed larger average declines in children receiving d4T/ddI than d4T monotherapy *[7]*. However, while these declines were maintained through 48 weeks of therapy, virologic suppression was incomplete in both groups, with fewer than 8% of patients having RNA levels <200 copies/mL at any time point. d4T has also been studied in children in combination with a protease inhibitor; the dual combination of d4T and ritonavir produced comparable virologic effects to the triple combination of ZDV, 3TC and ritonavir in 12- and 36-week analyses from PACTG 338 *[8, 9]*. However, after 48 weeks of follow-up, the proportion of children with undetectable viral load was significantly higher in the triple than dual drug regimen.

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Tenofovir Disoproxil Fumarate (Viread®)

URL: http://www.fda.gov/cder/foi/label/2002/21356slr001_Viread_lbl.pdf
URL: link to Guideline Appendix-ddC

Overview

Tenofovir was approved for use in combination with other antiretroviral agents for treatment of adults in October 2001; it is not approved for use in pediatric patients <18 years old. Tenofovir is an acyclic nucleotide analog with activity against retroviruses, including HIV-1 and HIV-2, and hepatitis B virus. Tenofovir disoproxil fumarate, an orally active ester prodrug of tenofovir, is rapidly hydrolyzed to tenofovir by plasma esterases, and metabolized intracellularly to the active drug, tenofovir diphosphate, which competitively inhibits the HIV reverse transcriptase enzyme, and terminates the growing DNA chain. Oral bioavailability in fasted patients is 25% but increases to 39% after a high-fat meal *[1]*; the drug should be taken with a meal for optimal bioavailability. Tenofovir is excreted unchanged by the kidneys by a combination of glomerular filtration and active tubular secretion, and should not be given to patients with renal insufficiency; there is a potential for interaction with other drugs that undergo renal excretion. There is no hepatic metabolism of tenofovir. There is a poorly understood drug-drug interaction between tenofovir and ddI that results in significantly increased ddI levels, and coadministration should be undertaken with caution and attention to symptoms of ddI toxicity, such as pancreatitis and lactic acidosis. The drug is has a long half-life, allowing once daily dosing in adults, and is active against many viruses resistant to NRTIs, NNRTIs and PIs. The drug is currently in phase I/II studies in the pediatric population, and an oral suspension formulation is under study. Animal toxicology studies have demonstrated a potential for bone and renal toxicity.

Resistance
While tenofovir is sensitive against many viruses that are resistant to other drugs, HIV isolates with reduced susceptibility to tenofovir have been selected *in vitro*; these viruses expressed at K65R mutation in reverse transcriptase and have a 3 to 4-fold reduction in susceptibility to tenofovir. The K65R mutation can also be selected *in vivo* in patients receiving ddI, ddC, or ABC; thus, patients who develop the K65R mutation following treatment with ddI, ddC or ABC may have some cross-resistance to tenofovir. Viruses containing multiple thymidine analogue mutations (e.g., mutations at codons 41 and 210, which also confer resistance to d4T, ZDV and ABC), a mutation at codon 74 (which confers resistance to ABC, ddI and ddC), or the T69S double insertion resistance mutation also have reduced susceptibility to tenofovir *[1]*.

Adverse Effects
The principal target organs of toxicity in animal studies were the renal tubular epithelium, and bone. Of particular concern in children, tenofovir, when given in high doses, causes bone toxicity (osteomalacia and reduced bone density) in juvenile monkeys as well as rats and dogs. These effects have not been seen in adult patients taking tenofovir for up to one year, but it is not known if these effects will be seen in persons taking tenofovir for more than one year or in children.

Evidence of renal toxicity, including increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia, and/or calcuria and decreases in serum phosphate, has been observed in animal studies at high exposure levels. Tenofovir-associated renal toxicity has not been observed in clinical studies of adults on treatment for up to one year, although there have been some case reports of nephrotoxicity in adults *[2, 3]*. The long-term renal effects are not known but patients at risk should be closely monitored.

Tenofovir appears less likely than NRTI drugs to be associated with mitochondrial toxicity *[4]*; tenofovir inhibits HIV reverse transcriptase at concentrations about 3,000-fold lower than needed to inhibit DNA polymerases beta and gamma, and is also only a weak inhibitor of the alpha, beta and gamma DNA polymerase. In adult studies, the rate of mitochondrial side effects was 3% among tenofovir recipients compared to 11% among those taking d4T *[5]*. However, cases of lactic acidosis have been reported with use of tenofovir *[3]*.

Pediatric Experience
Tenofovir has been evaluated in both treatment-experienced and treatment naïve adults; several intensification studies have shown that adding tenofovir to an existing regimen can provide benefit for treatment-experienced adults with detectable viral load, and a regimen of tenofovir/3TC/efavirenz was found to have equivalent virologic and immunologic efficacy as a regimen of d4T/3TC/efavirenz in treatment-naïve adults *[5]*. Three phase I safety and pharmacokinetic trials of tenofovir in a small number of pediatric patients are ongoing in France and the US; an oral suspension formulation is under study in younger children. Based on the results of the studies in older children, a phase III trial in HIV-infected, treatment experienced children over age 8 years is planned, using a dose of 175 mg/meter^2 body surface area once daily, which achieves tenofovir exposure similar to that seen in adults with a dose of 300 mg once daily.

Lumbar spine densitometry measured by dual-energy absorptiometry (DEXA) scan is being evaluated in one pediatric phase I study. Preliminary data indicated that over half of the 12 HIV-infected children had lumbar bone density that was at least 1 standard deviation from the norm at baseline, indicating a high prevalence of osteopenia prior to receiving tenofovir. Preliminary data indicated a decrease in bone mineral density of >6% from baseline in 4 children after 24 weeks of tenofovir therapy. No studies have been performed in treatment naïve children. Given the potential for bone toxicity, the drug may have greater utility for treatment of children in whom other antiretroviral drugs have failed than for initial therapy of treatment naïve children.

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Zalcitabine (ddC, Hivid®)

URL:http://www.rocheusa.com/products/hivid/pi.html
URL: link to Guideline Appendix-ddC

Overview
In August 1994 zalcitabine (ddC) was approved for use in adults and adolescents older than 13 years of age. It is not FDA-approved for use in pediatric patients.

ddC is a cytidine analogue that undergoes intracellular phosphorylation to its active form in resting cells. It is well adsorbed from the gut with approximately 70 to 80% bioavailability in adults. The plasma half-life in HIV-infected adults ranges from 1.2 to 2 hours while the intracellular half-life is approximately 2.6 hours. There are limited pharmacokinetic data in children. Oral bioavailability in children is approximately 54% compared with almost 90% in adults. Plasma half-life in a limited study of children ranging in age from 6 months to 13 years, was 0.2-1.9 hours. ddC is less than 4% protein bound and therefore drug interactions involving displacement at binding sites are unlikely.

Resistance
Genotypic mutations at reverse transcriptase codons 65, 69 and 184 are associated with ddC resistance. Mutations occurring together at codons 75, 77, 116 (multinucleoside resistant) plus 151 are associated with high-level ddC resistance.

Adverse Effects
Although uncommon, peripheral neuropathy was observed in some children in PACTG 138. ddC has similar toxicities as ddI; combination with ddI is not recommended due to overlapping genotypic resistance mutations and enhanced risk of peripheral neuropathy and pancreatitis. Rashes and oral ulcerations have also been reported with ddC therapy in children *[1]*. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including ddC.

Pediatric Experience
Initial studies of ddC monotherapy and of alternating ddC and ZDV therapy in pediatric patients demonstrated evidence of antiretroviral activity, with increase in $CD4^+$ lymphocyte count and decrease in p24 antigenemia in some patients; however, IQ scores appeared to fall during ddC monotherapy *[1-3]*. The combination of ddC and ZDV has been studied in pediatric patients, and appears to be well tolerated *[4]*.

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Zidovudine (ZDV, AZT, Retrovir®)

URL:http://www.fda.gov/cder/foi/label/2001/20518s4lbl.pdf
URL: link to Guideline Appendix-ZDV

Overview
Zidovudine (ZDV) was the first NRTI studied in adult and pediatric clinical trials and the first antiretroviral agent approved for therapy of HIV infection. ZDV first received FDA approval for the treatment of HIV infection in adults in 1987. It was

approved for use in children ages 3 months to 12 years in May 1990. Perinatal trial PACTG 076 established that a ZDV prophylactic regimen given during pregnancy, labor and to the newborn reduced the risk of perinatal HIV transmission by nearly 70% *[1]*. Zidovudine received FDA approval for that indication in August 1994.

ZDV is a thymidine analogue that has its greatest activity in replicating cells. It has good central nervous system (CNS) penetration (CSF/plasma ratio = 0.25) and is the NRTI of choice when treating children with HIV-related CNS disease *[2]*. ZDV is metabolized by the liver, primarily by glucuronidation, and then excreted by the kidneys. It is well absorbed in the gut with an average bioavailability of approximately 60%, and is approximately 35% protein bound. The serum half-life is 1.1 hours and the intracellular half-life is 3 hours.

Resistance
The antiretroviral activity of ZDV as monotherapy is limited by emergence of resistance, which generally occurs after months to years of treatment, depending on the patient's disease stage *[3]*. ZDV resistance is a consequence of a stepwise accumulation of genotypic mutations in the viral reverse transcriptase enzyme, including substitutions at codons 41, 70, 67, 210, 215, and 219. The quantity and pattern of mutations influence the level of phenotypic resistance. The codon 184 mutation associated with 3TC resistance is reported to suppress ZDV resistance *in vitro* and, when introduced into the background of a virus containing a ZDV-resistant reverse transcriptase gene, to suppress the effect of some ZDV resistance mutations *[4, 5]* . A small proportion of patients taking ZDV may develop a "multi-drug resistance" genotype, leading to cross-resistance to all NRTI drugs *[6]*.

Adverse Effects
ZDV is generally well tolerated in children with its major toxicities being macrocytic anemia and neutropenia *[7]*. Dose reduction and hematopoietic growth factors such as erythropoietin and filgrastim (NEUPOGEN, G-CSF) have been used to mitigate these toxicities. ZDV has also been associated with reversible myopathy and cardiomyopathy. Other reported toxicities of ZDV include fatigue, headache, and nausea. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including ZDV.

Pediatric Experience
ZDV has been extensively studied in both adult and pediatric trials, initially as monotherapy, and more recently in combination with other agents. ZDV monotherapy was associated with weight gain and improved neurological status in pediatric clinical trials *[8, 9]*. ZDV as monotherapy had modest effect on viral load and $CD4^+$ lymphocyte counts. ZDV is currently used in combination with other antiretroviral drugs when used for treatment of HIV disease. PACTG 152 showed that the combination ZDV/ddI was superior to ZDV monotherapy *[10]*. ZDV has also been studied in dual combination with the NRTI 3TC and found to significantly improve weight for age and length for age z-scores in young treatment-naïve children *[8]*. This study concluded that a combination regimen containing ZDV and 3TC or ddI was superior both clinically and by laboratory measurements to monotherapy with didanosine (ddI). ZDV has been studied as part of a PI-sparing, three-drug nucleoside analogue regimen (ZDV, 3TC and abacavir) in antiretroviral-experienced children. Increased virologic benefit was found in those patients who had two new NRTIs added to their regimen *[11]*. Viral suppression was not sustained however and it is unclear what role triple NRTI combinations may have in the pediatric population. ZDV is often a component of combination therapy including NNRTIs or PIs. For example, dramatic decreases in viral load and increases in $CD4^+$ count have been observed when ZDV has been combined with ddI and the PI ritonavir *[12]*. Long term (greater than 96 weeks) immunologic improvement and reconstitution with a naïve T-cell phenotype ($CD4^+CD45RA^+$) has been seen in some children receiving the combination ZDV, 3TC and the PI indinavir *[13]*. Some children in this study continued to have significant increases in $CD4^+$ cell counts even with virologic rebound.

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Non-Nucleoside Analogue Reverse Transcriptase Inhibitors

The non-nucleoside reverse transcriptase inhibitors (NNRTIs) have substantial and specific activity against HIV-1, although not HIV-2 or other retroviruses. Unlike the dideoxynucleoside NRTIs, which require intracellular phosphorylation to become active and then cause premature chain termination, this class of agents inhibits DNA polymerase activities by noncompetitively binding to and disrupting a unique catalytic site of the reverse transcriptase enzyme *[1]*. There are currently three NNRTIs approved for the treatment of HIV infection: nevirapine (NVP), delavirdine (DLV), and efavirenz (EFV). All members of this class are metabolized by the cytochrome P450 enzyme system, particularly CYP34A, and depending on the agent may affect (either induce or inhibit) the metabolism of other medications.

NNRTIs rapidly reduce viral load. However, drug resistance develops rapidly after initiation of monotherapy or with use of non-suppressive combination regimens, and cross-resistance is likely between the drugs in this class *[2]*. Sustained suppression of viral load has been observed in some patients who have been treated with regimens combining NNRTIs plus NRTIs as well as NNRTIs plus PIs. A two-dose intrapartum/newborn nevirapine regimen has been shown to reduce the risk of perinatal transmission by nearly 50% compared to an ultrashort intrapartum/1 week infant ZDV regimen *[3]*.

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Delavirdine (DLV, Rescriptor®)

URL:http://www.fda.gov/cder/foi/label/2001/20705s8lbl.pdf
URL: link to Guideline Appendix-DLV

Overview
Delavirdine (DLV) was approved in April 1997 for use in adolescents 16 years and older and adults in combination with other antiretroviral agents. This agent, similar to others in its class has no activity against HIV-2 but is specific for HIV-1. This NNRTI has had very limited study in pediatric patients under age 13 years.

Delavirdine is metabolized in part by the hepatic cytochrome P450 3A (CYP3A) enzyme system. In general, delavirdine is considered an inhibitor of these cytochrome P450 isoenzymes and may decrease the metabolism of certain drugs resulting in increased drug levels and potential toxicity. Because of its ability to delay clearance of some protease inhibitors, delavirdine is being studied for use in combination with indinavir or saquinavir to increase trough plasma concentrations of those agents. However, concerns about NNRTI cross-resistance may limit the utility of such combinations, and they are not currently recommended.

Resistance
As with the other NNRTIs, DLV resistance can be induced by a single point mutation. DLV has primary resistance mutations at reverse transcriptase codons 103 and 181, so resistance to delavirdine predicts resistance to nevirapine and efavirenz. The highest degree of resistance to DLV however, is found with the combination of mutations at codons 181 and 236.

Adverse Effects
Skin rash is the most common toxicity observed with DLV, as observed with the other NNRTIs. Skin rash attributable to DLV was observed in 18% of all adults receiving combination regimens with DLV in phase II and III trials; an incidence rate as high as 50% was reported in some trials (Rescriptor label) *[1]*. Dose titration did not significantly reduce the incidence of rash, but the rash was more common in adults with lower $CD4^+$ cell counts and typically appeared within one to three weeks of treatment. Severe rash such as Stevens Johnson Syndrome, while rare, does occur; like the other NNRTIs, DLV should be discontinued if severe rash or severe rash with constitutional findings occurs. Other toxicities were uncommon; elevated liver transaminases were observed in 2-7% of adults receiving DLV but did not differ from comparison groups receiving regimens not including DLV. In the one phase I study involving children, the most frequently reported adverse effects were rash in 40% (all grade 1 or 2) and vomiting in 40% *[1, 2]*.

Pediatric Experience
DLV has been evaluated children in only one phase I study in 15 children aged 5 months to 15 years. DLV was administered twice daily as an oral suspension or as a tablet/tablet dispersion at doses ranging from 12 to 28 mg/kg body weight *[2]*. Doses of 16 mg/kg twice daily in children 5 months or older produced systemic DLV exposure similar to that achieved in adults receiving doses of 400 mg three times daily. No other pediatric studies are available at this time.

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Efavirenz (DMP-266, EFV, Sustiva™)

URL:http://www.fda.gov/cder/foi/label/2000/20972S7LBL.PDF
URL: link to Guideline Appendix-EFV

Overview
Efavirenz (EFV) was approved in September 1998 for children older than 3 years of age, adolescents and adults.

Like the protease inhibitors, EFV is metabolized via the cytochrome P450 pathway (CYP3A4 and CYP2B6, primarily). EFV has been shown to induce its own metabolism and to be a mixed inducer/inhibitor of cytochrome P450 isoenzymes. Therefore concentrations of concomitant drugs can be increased or decreased depending on the specific enzyme pathway involved. In addition, concomitantly administered medications that induce or inhibit cytochrome P450 isoenzymes may affect the plasma concentrations of efavirenz. Efavirenz is highly protein bound (>99%), and may therefore interact with other highly protein bound drugs like phenobarbital and phenytoin.

Resistance
EFV, like other NNRTIs, has a low genetic barrier to resistance, with high-level resistance seen with a single mutation (lysine to asparagine), typically in the 103 position. Other known mutations conferring phenotypic resistance include those at codons 100, 108 or 225. Cross-resistance to EFV is likely with DLV-resistant virus and also with NVP-resistant virus in some cases; the extent of resistance may vary depending on which mutations are present. Therefore, EFV should never be used as monotherapy. EFV appears to offer an alternative to the protease inhibitors as an element of initial therapy when combined with 2 NRTIs and should be active in the secondary treatment of patients initially treated with a protease inhibitor, but not with an NNRTI (due to cross resistance).

Adverse Effects
The toxicity profile for efavirenz differs for adults and children. In adults, a central nervous system (CNS) complex of confusion, agitation, sleep disturbance, nightmares, hallucinations or other symptoms has been reported in more than 50% of patients *[1]*. These symptoms usually occur early in treatment and rarely require drug discontinuation. Bedtime dosing, particularly during the first several weeks of therapy appears to decrease the occurrence and severity of this side effect. Adverse CNS effects occurred in 14% of children receiving EFV in clinical studies *[2]*. The principal side effect of EFV seen in children is rash, which was seen in up to 40% of children compared to 27% of adults. The rash is usually maculopapular, pruritic, and mild to moderate in severity and rarely requires drug discontinuation. Onset is typically in the first 2 weeks of treatment *[1, 2]*. While severe rash and Stevens Johnson Syndrome have been reported, this is rare. Other reported adverse events include diarrhea, nausea, and increased aminotransferase levels.

Pediatric Experience
EFV has been found to have potent antiviral effects in vivo when combined with either two NRTIs, a protease inhibitor or an NRTI and a protease inhibitor, in three controlled trials conducted in 928 infected adults followed for 24 weeks *[1, 3, 4]*. The EFV containing regimens were comparable in efficacy to the dual NRTI-PI containing combinations over 16 to 72 weeks of therapy as measured by decrease in HIV-RNA and increase in $CD4^+$ cell counts *[1, 3]*. An open label study of EFV combined with nelfinavir and one or two NRTIs was performed in fifty-seven pediatric patients (PACTG 382), some as young as age 3 years *[2]* . In an intent-to-treat analysis, at 48 weeks of therapy, 76% of children had plasma HIV RNA levels <400 copies/mL, and 63% had HIV RNA levels <50 copies/mL *[2]*. The median times to achieve those levels were 4 and 20 weeks, respectively. Therefore, children with detectable HIV RNA of greater than 50 copies/mL by the ultra sensitive RNA assay after one month of therapy continued to accrue some virologic benefit through 5 months of treatment with this regimen *[5]*. A liquid formulation of EFV is under study in children under the age of 3 years or who weigh less than 13 kg, but data are not yet available.

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Nevirapine (NVP, Viramune®)

URL:http://www.fda.gov/cder/foi/label/2000/viramunelabel.pdf
URL: link to Guideline Appendix-NVP

Overview
Nevirapine (NVP) is approved for use in children greater than 2 months old. NVP is a dipyridodiazepinone derivative and is specific for HIV-1. It does not inhibit any of the human cellular DNA polymerases *[1]*.

NVP is highly lipophilic and widely distributed in the body; CSF/plasma concentration ratio is approximately 0.45. NVP undergoes extensive hepatic metabolism by way of hepatic cytochrome P450 metabolic enzymes, which NVP itself induces. During the course of the first 2 weeks of administration, plasma clearance increases while half-life decreases. NVP clearance in children is greater than in adults, and clearance in children under 9 years of age is greater than in older children *[2]*. Due to induction of cytochrome P450 hepatic enzymes, concomitantly administered medications that induce or inhibit cytochrome P450 enzymes may affect the plasma concentration of NVP. Medications that undergo hepatic metabolism by cytochrome P450 enzymes may have levels increased or decreased by concomitant NVP administration.

Resistance
NVP has potent antiviral activity but drug resistance develops rapidly when NVP is administered as monotherapy *[3, 4]*. Genotypic mutations associated with viral resistance to NVP typically occur within one to six weeks after initiation of NVP in situations where viral production is not effectively controlled. High-level resistance has been associated with a single point mutation at codon 103, 106, 108, 181, and 188 in the reverse transcriptase gene, with a mutation at codon 181 being the most common *[5, 6]*. Mutations associated with resistance to nevirapine can confer cross-resistance to other NNRTIs. HIV subtype B viruses that contain the K103N compared to the Y181C mutation may differ in their cross-resistance to efavirenz *[7, 8]*. Viruses with the Y181C mutation alone have little resistance to efavirenz (although Y181C can enhance the level of resistance of viruses containing additional NVP mutations), whereas viruses with the single K103N mutation are cross-resistant to other non-nucleosides *[9]*. With the exception of the use of the two-dose intrapartum/newborn NVP prophylaxis regimen to reduce perinatal HIV transmission, NVP should only be used in combination with other antiretroviral drugs *[10]*.

Adverse Effects
The most common adverse events reported in adults include headache, nausea, fever, and skin rashes *[11]*. In initial clinical trials of NVP treatment in HIV-infected children, rash was observed in 24% *[12]*. When a 2-week lower dose "lead in" period was used, the incidence of rash is decreased *[2]*. In a study of 4-drug therapy including nevirapine (given with 2 week "lead in"), rash was observed in only 6% of children. Granulocytopenia was the second most frequent adverse event, seen in 16%. However, it should be noted the children were also receiving ZDV, a known cause of granulocytopenia. The skin rash typically presents in the first 28 days after initiating therapy and in rare cases has progressed to Stevens-Johnson syndrome, toxic epidermal necrolysis, a severe skin rash accompanied by hypersensitivy reactions (characterized by rash, constitutional symptoms such as fever, arthalgia, myalgia, and lymphadenopathy, and visceral involvement such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction) or death. NVP should be discontinued if severe rash or severe rash with constitutional findings occurs. Patients experiencing rash during the 14-day lead-in period should not have their NVP dose increased until the rash has resolved. (see: Adult Guidelines Document: Table 18-Black Box warnings) *. Severe, life-threatening and in some cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis and hepatic failure, has been reported in NVP-treated patients. Increased serum transaminases levels or a history of hepatitis B or C infection prior to starting nevirapine are associated with higher risk for hepatic adverse events. The majority of cases has occurred during the first 12 weeks of NVP therapy, and frequent and intensive clinical and laboratory monitoring, including liver function tests, is important during this time period. However, about one third of cases occurred after 12 weeks of treatment, so continued periodic monitoring of liver function tests is needed. In some cases, patients presented with non-specific prodromal signs or symptoms of hepatitis and progressed to hepatic failure; patients with symptoms or signs of hepatitis should have liver function tests performed. NVP should be permanently discontinued and not restarted in patients who develop clinical hepatitis (FDA 12/00).

Pediatric Experience
Treatment of therapy naïve adults with a triple antiretroviral regimen demonstrated comparable results for dual nucleoside combinations with either indinavir or NVP *[13]*. Nevirapine administered as a single 200 mg oral dose to the mother intrapartum and a single 2mg/kg oral dose to the infant at age 48 hours reduced perinatal transmission by approximately 50% when compared to an intrapartum/ one week infant regimen of ZDV in a trial in a breastfeeding population in Uganda *[14]*. Combination therapy with NVP, ZDV and ddI in young infected infants has been associated with sustained viral suppression in a small number of children *[15]*. PACTG Protocol 377 randomized 181 PI-naïve, NNRTI-naïve mild-moderately suppressed children to one of four combination treatment regimens. All of the regimens contained d4T and a PI (either ritonavir or nelfinavir); three of the four regimens also included NVP as part of combination therapy. Children in the NVP containing arms experienced moderate or worse skin rash more frequently than those not receiving NVP. Importantly, those children receiving a quadruple regimen containing both NVP and a PI had a significantly greater increase in $CD4^+$ cell count from baseline to Week 24, then those receiving other regimens *[16]*.

**** The updated version of the adult-adolescents guidelines, containing the new Table 18, Adverse Drug Reactions Related "Black Box Warnings" in Product Labeling for Antiretrovirals Agents.***

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PROTEASE INHIBITORS

The protease inhibitors (PIs) are potent antiretroviral agents, especially when used in combination with NRTI and/or NNRTI therapy *[1]*. This class of antiretroviral agent has the distinct advantage of blocking HIV-1 infection in both acutely and chronically infected cells by preventing the production of mature, infectious virions. Unlike the NRTI drugs, intracellular conversion of the parent compound is not required for activity of any of the protease inhibitors. Resistance has been reported with all protease inhibitors when used as monotherapy, and can rapidly develop even with combination therapy in the presence of subtherapeutic drug levels (as can occur when there is inadequate dosing, poor drug absorption, rapid drug clearance, or not adequate adherence to the prescribed drug regimen). The patterns of resistance mutations are more complex than observed with the NRTIs and NNRTIs. A larger number of genotypic mutation sites are observed and there is greater variability in the temporal pattern of development of these mutations and in the combination of mutations that lead to drug resistance. The mutation patterns associated with protease inhibitor resistance overlap; resistance to one drug may result in reduced susceptibility to some or all of the other currently available protease inhibitors. Therapeutic regimens consisting of two protease inhibitors (e.g., ritonavir and saquinavir or nelfinavir and saquinavir soft gel capsules) combined with one or two NRTIs are under evaluation in adults and children; early results are promising, showing potent antiviral activity. However, with the exception of the co-formulated protease inhibitor lopinavir-ritonavir (Kaletra™), there are neither safety data nor appropriate recommendations regarding dosage of combination protease inhibitor regimens in children available at this time. The practitioner should consider many factors when considering the short- and long-term risks and benefits of utilizing protease inhibitor therapy. Among the most important in this regard is the capacity of the patient and family to maintain adherence to the prescribed regimen.

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus and hyperglycemia have been reported in HIV-infected patients treated with any of the currently available protease inhibitors *[2-4]*. In some cases, diabetic ketoacidosis has occurred. A causal relationship between protease inhibitor therapy and these events has not been established, but health care providers should be aware of the possibility of hyperglycemia in patients receiving these drugs and monitor appropriately. Caregivers and patients should be informed how to recognize the early symptoms of hyperglycemia to ensure prompt health care if such symptoms develop. There have also been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia A and B treated with protease inhibitors *[5]*. In some patients additional Factor VIII was given, and in more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. Additionally, the protease inhibitors have been associated with fat redistribution, lipodystrophy syndrome, and hyperlipidemia in both adults and children receiving therapy *[6]*. A potentially increased risk of cardiovascular disease and bone disorders such as osteoporosis and avascular necrosis are currently being investigated.

Protease inhibitors are metabolized in the liver via the cytochrome P450 enzyme system. A direct human liver microsomal comparison with other protease inhibitors showed the following rank order of CYP3A4 inhibition: ritonovir >> indinavir = nelfinavir = amprenavir > saquinavir *[7, 8]*. Clinically significant drug interactions may occur when a PI is administered concomitantly with other agents metabolized by the cytochrome p450 system, especially those metabolized by CYP3A, CYP2D6, CYP2C9 and CYP2C19, as well as, to a lesser extent, CYP2A6, CYP1A2 and CYP2E1. Increased or decreased plasma concentrations of either drug may occur and consequent clinical abnormalities may be seen. Please go to **Antiretroviral Drug Appendix of Pediatric Guidelines** for a list of contraindicated medications. A complete list of potential drug interactions is provided by the PI manufacturer in the prescribing information and should be consulted prior to initiating PI therapy or starting any new concomitant therapy in patients receiving PI-based regimens.

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Amprenavir (APV, Agenerase®)

URL:http://www.fda.gov/cder/foi/label/2001/21039s6lbl.pdf
URL: link to Guideline Appendix-APV

Overview
The Food and Drug Administration in April 1999 approved amprenavir (APV) for use in combination with other antiretrovirals in adults and children over 4 years of age. This approval was based upon the results of controlled trials of up to 24 weeks duration in treatment naïve and experienced adults. Pediatric approval was based upon analysis of two open label trials in treatment experienced children, one after 8 weeks of therapy and one after 4 weeks of therapy. APV is available in both liquid and solid formulations.

Approximately 90% of APV is protein bound, primarily by alpha$_1$-acid glycoprotein (AAG). Like other agents in this class APV is metabolized by cytochrome P450 isoenzyme CYP3A4 and has the potential for multiple drug interactions (see product label). Although the absolute bioavailability of APV has not been determined, the APV solution was found to be 14% less bioavailable than the capsule formulation and therefore the two are not interchangeable.

Resistance
APV therapy induces mutations in HIV-1 protease gene at codons 46, 47, 50, 54, and 84 and at the viral protease p1/p6 cleavage site. A mutation at codon 50 may be unique to this agent. At least 2-3 mutations are required at amino acid resides 46, 47 and 50 to produce >10 fold decrease in sensitivity. Cross-resistance to other PIs is low when mutation at codon 50 alone is present. IDV or RTV-resistant virus is likely to be resistant to APV.

Adverse Effects
Data compiled from 30 phase I-III studies of amprenavir in 1330 adult and pediatric patients revealed the following most frequently reported adverse events: nausea, diarrhea, rash, headache, oral paresthesia, and fatigue. The majority of adverse events were mild to moderate. Nausea, rash, including Stevens-Johnson Syndrome, and vomiting were the most common adverse events associated with discontinuation of treatment *[1]*. The most common drug related adverse events in trials of pediatric patients are vomiting, nausea, diarrhea, and rash *[2]*. APV should be discontinued for severe rash including Stevens-Johnson Syndrome or moderate rash with systemic symptoms. APV is related to the sulfonamides and the potential for cross-sensitivity of sulfonamides and APV is unknown. APV should therefore be used with caution in patients with sulfonamide allergy. Signs of lipodystrophy have been reported in a few patients on amprenavir. As with all agents in this class, new onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, hyperglycemia, and diabetic ketoacidosis may occur.

The FDA approved formulation of APV contains 46 IU of vitamin E/ml of oral solution and 109 IU vitamin E per 150 mg capsule. The recommended dose of APV results in a dose of 138 IU/kg/day of vitamin E using the oral solution with a maximum dose of 8,587 IU vitamin E per day. Patients receiving the recommended adult dose of APV in capsule form receive 1,744 IU/day of vitamin E. There is a paucity of data regarding the use of extremely high doses of vitamin E on a chronic daily basis. The Reference Daily Intake for vitamin E is 30 IU per day for adults and approximately 10 IU per day for children. In a study using vitamin E in premature infants, 20% of infants receiving

100mg/kg/day of vitamin E had serum levels of tocopherol ≥ 4.5 mg/dl. This level was associated with an increased incidence of bacterial sepsis and necrotizing enterocolitis *[3]*. Excess ingestion or administration of vitamin E in adults and animals has been associated with creatinuria, decreased platelet aggregation, impaired wound healing, prolongation of Prothrombin Time, hepatomegaly and the potentiation of vitamin K deficiency coagulopathy. Adult and pediatric patients receiving APV should be advised not to take supplemental vitamin E.

(See: Adult Guidelines Document: Table 18-Black Box warnings) *. The FDA approved liquid formulation of APV contains propylene glycol in a concentration that exceeds WHO standards for use in infants. Young infants have immature levels of alcohol dehydrogenase enzymes, which are involved in the metabolism of propylene glycol. There is concern that the propylene glycol contained in the liquid formulation may not be metabolized adequately and could cause toxicity. High levels of propylene glycol have been associated with hyperosmolality, lactic acidosis, seizures and respiratory depression (American Academy of Pediatrics). Therefore, APV should not be used in its current liquid formulation in children under the age of 4 years.

Pediatric Experience
In a Phase III study in treatment naïve adults 53% of patients receiving APV with two NRTIs had HIV RNA < 400 copies/mL after 24 weeks of therapy *[4]*. In an open label phase III study of eighty-one treatment experienced children 3-17 years of age receiving APV in combination with 2 NRTIs, 41% had plasma HIV RNA < 400 copies/mL and 65% had plasma HIV RNA < 10,000 copies/mL after 8 weeks of therapy. In this study, PI naïve children had a greater antiviral response than PI experienced children with a median reduction in HIV RNA of 1.41 and 0.38 log copies/mL in PI naïve and PI experienced children respectively *[2]*.

**** The updated version of the adult-adolescents guidelines, containing the new Table 18, Adverse Drug Reactions Related "Black Box Warnings" in Product Labeling for Antiretrovirals Agents.***

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Atazanavir (ATV, Reyataz™)

URL:http://www.fda.gov/cder/foi/label/2003/21567_reyataz_lbl.pdf
URL: link to Guideline Appendix ATV

Overview
Atazanavir (ATV) was approved in June 2003 for treatment of HIV infection in individuals over 16 years of age. Approval in adults was based on 48-week data from controlled trials in antiretroviral naïve patients and 24-week data from a trial in antiretroviral-experienced patients. In a trial in 810 antiretroviral naïve patients, treatment with ATV was compared to treatment with efavirenz, both in combination with ZDV/3TC. The proportion of patients with HIV RNA <400 copies/mL at 48 weeks was 70% with the ATV-based regimen compared to 64% with the efavirenz-based regimen *[1]*. A separate study in 272 antiretroviral naïve patients compared ATV to nelfinavir-based therapy, both in combination with d4T/3TC; at 48 weeks of therapy, 67% those receiving ATV-based therapy had HIV RNA <400 copies/mL compared to 59% of those receiving nelfinavir-based therapy *[2]*. In an ongoing trial in treatment-experienced patients, ATV plus 2 NRTIs is being compared to lopinavir/ritonavir plus 2 NRTIs. The proportion of patients with HIV RNA <400 copies/mL at 24 weeks was 54% with ATV-based therapy compared to 75% with lopinavir/ritonavir-based therapy *[3]*. Unlike other protease inhibitors, minimal effect on lipid levels has been observed in adults treated with ATV *[4]*. Safety and effectiveness of ATV in

pediatric patients is under study, but appropriate dosage has not yet been determined.

ATV is an azapeptide aspartyl protease inhibitor that differs structurally from other approved peptidomimetic protease inhibitors. ATV is rapidly absorbed following oral administration, and should be administered with food to increase bioavailability and reduce pharmacokinetic variability: administration with a light meal resulted in a 70% increase in systemic ATV exposure (AUC) and a 57% increase in peak levels relative to the fasting state, and administration with a high-fat meal resulted in a mean increase in AUC of 35% and no change in peak levels relative to the fasting state. ATV is extensively metabolized via the hepatic CYP3A enzyme pathway, and primarily excreted in the feces in the form of metabolites. The median half-life in adults is 6.5 hours, allowing once daily administration. In a multiple-dose study in HIV infected patients, the cerebrospinal fluid/plasma ratio for ATV ranged between 0.0021 and 0.0226 *[3]*.

Decreased ATV exposure has been observed when coadministered with efavirenz and with tenofovir. Augmentation of ATV concentration by coadministration of ATV with a low-dose ritonavir boost (300 mg ATV plus 100 mg ritonavir once daily) increases ATV concentration to acceptable levels in adults, and is recommended if ATV is administered with either of these agents.

Resistance
Like other protease inhibitors, several mutations are generally required to result in clinically significant drug resistance *[5]*. ATV has a unique resistance profile. Treatment-naive patients developed a characteristic I50L mutation that is associated with increased susceptibility to other protease inhibitors *[6]*. In contrast, treatment-experienced patients did not develop the I50L mutation; rather, these patients developed mutations (I84V, L90M, A71V/T, N88S/D, and M46I) that reduced response to atazanavir and conferred high cross-resistance to other protease inhibitors. Generally, if there were pre-existing protease inhibitor mutations in the patient's virus population prior to ATV initiation, ATV resistance developed through mutations associated with resistance to other protease inhibitors instead of the I50L mutation. While HIV isolates resistant to only 1 or 2 protease inhibitors may remain sensitive to ATV, as isolates exhibit increasing resistance to multiple protease inhibitors, cross-resistance with ATV increases. ATV resistant isolates are highly cross-resistant to other protease inhibitors.

Adverse Effects
The most common side effects associated with ATV include gastrointestinal symptoms (e.g., nausea, vomiting, abdominal pain, diarrhea), headache, rash, tingling in hands and feet, and depression. Unlike other protease inhibitors, ATV does not appear to be associated with an increase in total cholesterol and triglycerides. As with other protease inhibitors, new onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, hyperglycemia, and diabetic ketoacidosis may occur.

ATV inhibits the hepatic glucuronidation enzyme uridine diphosphate glucuronosyl transferase (UGT1A1) that conjugates bilirubin; ATV administration is frequently associated with asymptomatic hyperbilirubinemia, which may be accompanied by scleral icterus and/or jaundice. This is not accompanied by elevations in hepatic transaminase levels, and is reversible following discontinuation of ATV therapy. ATV has been reported to prolong the PR interval of the electrocardiogram. In the majority of patients, abnormalities in atrio-ventricular (AV) conduction were asymptomatic and limited to first-degree AV block; no second or third degree AV block has been observed. However, because experience with ATV is limited, caution should be exercised when ATV is used in patients with pre-existing conduction system disease and/or receiving other drugs that prolong the PR interval (e.g., most beta-blockers, digoxin, verapamil).

Pediatric Experience
ATV pharmacokinetics, safety, and preliminary efficacy are being studied in a phase II study, PACTG 1020A, in HIV-infected children 3 months to 21 years of age. In addition to capsules, a powder formulation is being evaluated. Preliminary data in 44 children indicate difficulty in achieving adequate ATV concentrations in children even using higher ATV dosage, and therefore use of ATV with a low-dose ritonavir boost is currently under evaluation.

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Fosamprenavir (f-APV, Lexiva®)

URL: http://www.fda.gov/cder/foi/label/2003/21548_lexiva_lbl.pdf
URL: link to Guideline Appendix f-APV

Overview
In October 2003, fosamprenavir calcium (f-APV), a prodrug of amprenavir (APV), was approved for use in combination with other antiretrovirals for the treatment of HIV infection in adults. This approval was based on results from two studies in antiretroviral-naïve adults and one study in protease inhibitor-experienced adults. Pediatric trials are ongoing at this time.

In the two clinical trials (APV 30001 [NEAT trial] and APV 30002 [SOLO trial]) in which f-APV was used to treat antiretroviral-naïve adult patients, it was used in combination with abacavir and lamivudine *[1, 2]*. In APV 30001, f-APV 1400 mg twice daily was compared to NFV 1250 mg twice daily. After 48 weeks of therapy, the proportions of patients who achieved HIV RNA < 400 copies/mL (< 50 copies/mL) were 66% (57%) for the f-APV group and 52% (42%) for the NFV group, respectively *[1,3]*. There were comparable rates of increases from baseline in $CD4^+$ cell counts between the two groups *[1]*. In APV 30002, f-APV 1400 mg once daily was combined with RTV 200 mg once daily and compared to NFV 1250 mg twice daily. After 48 weeks of therapy, the proportions of patients who achieved HIV RNA < 400 copies/mL (<50 copies/mL) was 69% (58%) for the f-APV group and 68% (55%) for the NFV group, respectively *[2, 3, 5]*. There were comparable rates of increases from baseline in $CD4^+$ cell counts between the two groups *[5]*. In the SOLO study, more patients discontinued the trial in the f-APV arm than the NFV arm (25% vs. 15%) *[5]*.

APV 30003 (CONTEXT trial) studied protease inhibitor-experienced adults using two different dosing regimens of f-APV: f-APV 700 mg twice daily plus RTV 100 mg twice daily or f-APV 1400 mg once daily plus RTV 200 mg once daily *[3, 4]*. This was compared to LPV/RTV (400 mg/100 mg twice daily) in 315 patients who had experienced virologic failure to 1 or 2 prior protease inhibitor-containing regimens. After 48 weeks of therapy, the proportions of patients who achieved HIV RNA <400 copies/mL (<50 copies/mL) were 58% (46%) for twice daily f-APV/RTV and 61% (50%) for LPV/RTV, respectively *[3, 4]*. The median increases from baseline in $CD4^+$ cell counts were 81 cells/mm^3 for twice daily f-APV/RTV and 91 cells/mm^3 for LPV/RTV [3]. There were not enough patients in this study to conclude that twice daily f-APV/RTV and LPV/RTV are clinically equivalent. However, the once daily administration f-APV/RTV group had a poorer response rate than either of the other treatment groups. After 48 weeks of therapy, the proportion of patients who achieved HIV RNA <400 copies/mL (<50 copies/mL) was 50% (37%) for the once daily treatment group *[3]*.

Based on the results of these adult studies, the recommendations for dosing antiretroviral-naïve adults with f-APV in combination with other antiretroviral agents is as follows: 1400 mg twice daily (without RTV); or 1400 mg once daily plus RTV 200 mg once daily; or 700 mg twice daily plus RTV 100 mg twice daily. For protease inhibitor-experienced adults, once daily administration of f-APV plus RTV is not recommended, and the recommendation is for f-APV 700 mg twice daily plus RTV 100 mg twice daily.

The prodrug f-APV is rapidly and almost completely hydrolyzed to APV by cellular phosphatases in the gut as it is absorbed *[6, 7]*. The drug can be administered with or without food without any significant effects on pharmacokinetic parameters. Peak APV serum concentrations are reached between 1.5 and 4 hours (mean 2.5 hours). Approximately 90% of APV is plasma protein bound, primarily by alpha 1-acid glycoprotein (AAG). APV is extensively metabolized by cytochrome P450 isoenzyme CYP3A4 and has the potential for multiple drug interactions. RTV inhibits the metabolism of APV, resulting in increases in both AUC and trough drug concentrations. The pharmacokinetics of f-APV in adults has been studied when administered as once daily administration (f-APV 1400 mg), once daily administration in combination with RTV (f-APV 1400 mg plus RTV 200 mg), and twice daily administration with RTV (f-APV 700 mg plus RTV 100 mg). The AUC 24 (mcg-hr/mL) for f-APV once daily, f-APV plus RTV once daily, and f-APV plus RTV twice daily were 33.0, 69.4, and 79.2 mcg-hr/mL, respectively.

Administration of f-APV with low-dose RTV boosting may result in an increased number and magnitude of drug interactions due to the additive effect of RTV on drug metabolism (see RTV drug label for more information). F-APV has not been studied in patients with hepatic insufficiency, but these patients may require a dose reduction. Pediatric pharmacokinetic data are incomplete at this time and further investigations are underway.

Resistance
Genotypic analysis of isolates from APV-treated patients shows that mutations are induced in the HIV protease gene at codons 32, 46, 47, 50, 54, 84, and at the viral protease p1/p6 cleavage site. At least 2-3 mutations are required at amino acid resides 46, 47, and 50 to produce >10 fold decrease in sensitivity. Varying degrees of cross-resistance among HIV-1 protease inhibitors have been observed.

Viral resistance studies performed on patients receiving unboosted f-APV during the NEAT trial detected protease mutations similar to those observed in patients receiving APV *[8]*. In the SOLO study, no protease mutations were detected with boosted f-APV, suggesting that the addition of ritonavir decreases the likelihood of the development of resistance *[8]*.

Adverse Effects
F-APV is generally well tolerated. The most common side effects associated with f-APV include gastrointestinal symptoms (nausea, vomiting, diarrhea), perioral paresthesias, headache, and rash *[9,10]*. When compared to nelfinavir, there is a lower rate of gastrointestinal adverse effects *[1, 2]*. Although rash was reported in approximately 19% of patients in the efficacy trials, life-threatening rash, including Stevens-Johnson syndrome, are rare, reported in <1% of patients *[9, 10]*. F-APV should be discontinued for severe rash, including Steven-Johnson syndrome, or moderate rash with systemic symptoms. APV is related to the sulfonamides and the potential for cross-sensitivity of sulfonamides and APV is unknown. F-APV should therefore be used with caution in patients with a history of sulfonamide allergy. Fat redistribution and lipid abnormalities have been reported. As with other protease inhibitors, new onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, hyperglycemia, and spontaneous bleeding in hemophiliacs may occur.

Pediatric Experience
A multicenter, international study of the use of f-APV plus RTV is currently underway in pediatric patients using both the 700 mg tablets and an investigational suspension. Both once daily and twice daily administration are being investigated in treatment naïve and protease inhibitor-experienced children.

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Indinavir (IDV, Crixivan®)

URL:http://www.fda.gov/cder/foi/label/2001/20685s41lbl.pdf
URL: link to Guideline Appendix-IDV

Overview
Indinavir (IDV) was approved in 1996 for use in adolescents and adults older than 18 years of age. Like the other PIs, IDV is prone to multiple drug interactions due to its interaction with the cytochrome P450 system (see product label). A liquid formulation is not yet available. Administration of IDV with a meal high in calories, fat and protein results in a reduction in plasma IDV concentrations; administration with lighter meals (e.g. dry toast with jelly, apple juice and coffee with skim milk and sugar) results in little to no change in IDV pharmacokinetics.

Resistance
Resistance to IDV is associated with mutations at codons 10, 32, 54, 63, 71, 82, 84 and 90. Virus resistant to IDV may also be resistant to RTV. IDV-resistant virus may be broadly cross-resistant to all other PIs.

Adverse Effects
The most serious side effect observed in both adults and children is nephrolithiasis. In double-blind clinical trials in adults, the incidence of nephrolithiasis was 9.3% in IDV-containing groups. Abnormal renal function (including acute renal failure) has been observed in a small number of patients with nephrolithiasis; abnormal renal function was generally transient and temporally related to the acute episode. Interstitial nephritis has also been observed in patients receiving IDV. If signs and symptoms such as flank pain with or without hematuria occur, temporary interruption of therapy (for 1-3 days) during the acute episode may be considered. Adequate hydration is essential when IDV is administered. Nephrolithiasis may be somewhat more frequent among children, likely due to the difficulty in maintaining adequate hydration; in an IDV study in fifty-four children, 13% developed hematuria *[1]*.

Asymptomatic mild elevation of bilirubin, due to an increase in indirect bilirubin, has also been reported in adults and children receiving IDV. In adult trials, about 10% of IDV-receiving patients had bilirubin values $\geq$2.5 mg/dL at some point during treatment; in most cases, the maximum bilirubin elevations were observed after 1 or more weeks of treatment. Clinical adverse effects such as jaundice or elevations in serum transaminase levels have only rarely been reported. As with all agents in this class, new onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, hyperglycemia, and diabetic ketoacidosis have been reported.

Pediatric Experience
In clinical trials in infected adults, IDV in combination with NRTIs has been shown to retard clinical progression and to decrease mortality and to dramatically reduce HIV RNA levels and increase $CD4^+$ lymphocyte counts compared to dual nucleoside therapy *[2, 3]*. This protease inhibitor has

been studied in small, uncontrolled pediatric trials but has not been approved in this age group. It has been studied in dosage ranges of 300-600 mg/m^2 given every 8 hours *[1, 4-10]*. In general, IDV regimens were well-tolerated and both virologic and immunologic responses were observed. In an open-label study in twenty-eight children receiving IDV/ZDV/3TC, 70% of children had HIV RNA levels of <500 copies/mL after 6 months of therapy *[7]*. In an open-label study of IDV/d4T/3TC treatment in twenty-five Italian children, HIV RNA levels were maintained at <400 copies/mL after 18 months of therapy in 87% of children who entered the study with CD4$^+$ cell counts in CDC Immune Class 2 and 72% of those who entered with CDC Immune Class 3 *[8]*. In a study in thirty-three infected children who had received ≥96 weeks of treatment with IDV/ZDV/3TC (with an initial 16 weeks of IDV monotherapy), a median increase in CD4$^+$ cell count of 199/mm^3 and a median decrease in HIV RNA of 0.74 log was observed at 96 weeks *[11]*. Virologic response in this study may have been impacted by the prolonged period of IDV monotherapy received prior to combination with ZDV/3TC.

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Lopinavir/Ritonavir (LPV/RTV, ABT-378/r, Kaletra™)

URL:http://www.fda.gov/cder/foi/label/2001/21251s2lbl.pdf
URL: link to Guideline Appendix-LPV/RTV

Overview

Lopinavir/Ritonavir (LPV/RTV) is a fixed combination of these two protease inhibitors (133.3 mg of lopinavir plus 33.3 mg of ritonavir). LPV/RTV received FDA approval in 2000 for combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients age six months and older. It is available in both liquid and solid formulations. Like other PIs, LPV/RTV is metabolized by the hepatic cytochrome P450 system and multiple drug interactions are possible (see product label). Administration of LPV/RTV with food increases plasma concentrations; to enhance bioavailability and minimize pharmacokinetic variability, LPV/RTV should be taken with food.

Resistance
Resistance to LPV/RTV has been associated with genotypic mutations at 11 positions of the protease enzyme including codons 10, 20, 24, 46, 53, 54, 63, 71, 82, 84, and 90 *[1]*. Importantly, high-level resistance generally requires at least 6 mutations. Cross-resistance among protease inhibitors is likely.

Adverse Effects
The most common side effects associated with LPV/RTV have been diarrhea, asthenia, and triglyceride and cholesterol elevations. Pancreatitis has been reported in adult patients taking LPV/RTV. High triglyceride levels may be a risk factor for pancreatitis to develop. As with all agents in this class, new onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, hyperglycemia, and diabetic ketoacidosis may occur.

Pediatric Experience
The use of dual protease inhibitors that include ritonavir (RTV) have been studied in adults. In these combinations, rather than being used for its antiretroviral activity, RTV acts as a pharmacokinetic enhancer by inhibiting the metabolism of other protease inhibitor and therefore increasing its plasma concentrations. Ritonavir inhibits the metabolism of lopinavir and thus increases its plasma concentration. Data on combination protease inhibitors in children is more limited. ABT Study M98-940 is a Phase I/II open-label study that evaluated the pharmacokinetic profile, tolerability, safety, and efficacy of LPV/RTV oral solution and either two NRTIs or NVP plus up to two NRTIs in 100 pediatric patients. Through 24 weeks of therapy, the proportion of patients with HIV RNA <400 copies/mL was 82% for antiretroviral naïve patients and 66% for antiretroviral experienced patients. Follow up at 60 weeks was 77% and 70% for naïve and experienced patients, respectively *[2]*. The mean increase from baseline in $CD4^+$ cell count was 328 cells/mm^3 for antiretroviral naïve and 335 cells/mm^3 for antiretroviral experienced patients treated through 24 weeks. This increased to 404 cells/mm^3 for naïve patients and 238 cells/mm^3 for treatment experienced patients at week 60.

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Nelfinavir (NFV, Viracept®)

URL:http://www.fda.gov/cder/foi/label/2001/20779s32lbl.pdf
URL: link to Guideline Appendix-NFV

Overview
Nelfinavir (NFV) is approved for use in children over two years of age in combination with NRTIs and NNRTIs. It is available in both oral powder and tablet formulations. Like other agents in this class it is an inhibitor of the HIV-1 protease enzyme, which results in preventing cleavage of the gag-pol polyprotein. This inhibits viral replication by producing and releasing immature, non infectious virions. NFV is active against HIV-1 and HIV-2 strains. Oral bioavailability of NFV has been reported to be 70-80% when administered with food; bioavailability is significantly reduced when the drug is taken in a fasting state. Like other PIs, NFV is metabolized by the cytochrome P450 enzyme system in the liver, inhibits CYP3A4 and is associated with a number of clinically significant pharmacologic drug interactions (see product label).

Resistance
NFV-resistant virus contains a unique protease enzyme mutation at codon 30 and does not confer cross-resistance to other PIs. However, continued use of NFV in the presence of viremia and PI mutations may result in the selection of additional mutations, which may decrease susceptibility to other PIs. There is some data suggesting that changing from NFV to another protease inhibitor may be effective if multiple PI mutations have not developed. However, NFV is not effective in virus with high-level resistance to RTV or SQV, and IDV-resistant virus is often also NFV resistant.

Adverse Effects
NFV in children has been relatively well tolerated, even when dosing schemes exceed adult recommended amounts. The most common adverse effects include diarrhea, abdominal pain, flatulence and rash. As with other protease inhibitors, new onset diabetes mellitus and exacerbations of previous hyperglycemia have been reported, as has the occurrence of the lipodystrophy syndrome. The

long-term safety, durability of virologic efficacy, and the feasibility of children taking this drug for long periods of time is still under investigation.

Pediatric Experience
Virologic efficacy of NFV in combination with a NNRTI and/or a protease inhibitor has been evaluated in various pediatric trials, typically in children who have been NRTI experienced. In an open-label study of fifty five antiretroviral-experienced children aged 3 months to 13 years, combination of NRTIs with NFV, dosed as 20-30 mg/kg three times daily, resulted in an initial decrease in HIV RNA of at least 0.7 log in 71%, however, suppression of viral load to <400 copies/mL was observed in only 28% *[1]*. In a study in sixteen antiretroviral naïve children, NFV in combination with either ZDV/3TC or d4T/ddI resulted in a median decrease in HIV RNA of 2.8 logs, and RNA levels were <500 copies/mL in 69% and<50 copies/mL in 44% of children after 12 months of therapy *[2]*.

PACTG Protocol 377 was a phase II, multicenter, randomized, open-label study of 4 different d4T-containing regimens in 181 clinically stable, PI naïve children; three of the arms contained NFV, and two of these also contained NVP. Overall, 57% of children in the four main treatment arms had an initial suppression of plasma HIV-1 RNA to ≤ 400 copies/mL or ≥ 2 log units from baseline *[3]*. Of children still on their study therapy at week 48, 30 to 52% of patients receiving a NFV containing regimen maintained HIV-1 RNA suppression to ≤ 400 copies/mL.

Optimal dosing of NFV in children has not been well defined. In a small substudy of PACTG 377, NFV given as 55 mg/kg twice a day provided improved serum NFV levels compared to NFV given as 30 mg/kg three times daily. Additionally, the week 24 virologic response of decrease in RNA <400 copies/mL was higher among children receiving NFV 55 mg/kg twice daily combined with d4T/3TC than those receiving NFV 30 mg/kg three times daily combined with d4T/3TC (64% vs. 46%, respectively) *[3]*. Baseline HIV RNA was an important predictor of viral suppression. No increase in toxicity was observed with the twice-daily NFV dosing regimen.

NFV in the absence of NVP resulted in less than half the drug exposure in children who were <25 kg compared with children >25 kg. NFV dosed at 55 mg/kg twice daily in children who are <30 kg provided comparable exposure to that measured in children >25 kg and who received NFV dosed as 30 mg three times daily *[4]*. NFV pharmacokinetics in the presence of NVP did not differ between the <25 kg and >25 kg groups.

PACTG Protocol 382 studied fifty-seven antiretroviral experienced, PI and NNRTI-naïve children given a combination of NFV, EFV and at least one NRTI. Overall, the combination was well tolerated by most children in the study. Viral suppression to less than 50 copies/mL was seen in 53% of the children studied at 48 weeks of treatment *[5]*.

A logistic model analysis of PACTG 377, using RNA status at week 8 (<400 vs. >400 copies/ml) as outcome and EFV and NFV area under the curve (AUC) measures as predictors, revealed that the AUC value of both drugs significantly predicted RNA outcome, even when controlling for one another. These findings indicate that EFV and NFV exposure is significantly associated with virologic effect and that, in this study, each drug acts independently in producing the virologic response. These data support the practice of ensuring that pediatric dosing regimens achieve concentrations above threshold values for all children *[6]*.

However, NFV concentrations in infants are highly variable and lower than those seen for adults or pediatric populations receiving the labeled dosing regimen. In a pharmacokinetic study of 22 HIV-infected infants between 15 days and 2 years of age in PACTG 356 given the recommended NFV dose of 20 to 30 mg/kg three times a day, clearance was significantly higher than in older children (2.7 L/h/kg vs 1.2 L/h/kg in older children and 0.6 L/h/kg in adults), and the peak NFV levels were less than half those reported in older children *[7]*. As a consequence, doses of 55 to 65 mg/kg twice daily are currently under study in the young children in this protocol.

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Ritonavir (RTV, Norvir®)

URL:http://www.fda.gov/cder/foi/label/2001/20659s26lbl.pdf
URL: link to Guideline Appendix-RTV

Overview
Ritonavir (RTV) is approved for use in children over the age of 2 years in combination with other antiretroviral agents. It was the first PI approved for use in children and is available as liquid and capsule formulations. It has specific activity for HIV-1, and to a lesser extent, HIV-2.

RTV is a potent inhibitor of the cytochrome P450 enzyme pathway and significantly interferes with the metabolism of several common medications including macrolides and certain antihistamines (see product label). Although RTV inhibits cytochrome P450 CYP3A, it induces its own metabolism. It is well absorbed with a half-life of 2 to 4 hours in children *[1]*. Pharmacokinetic studies in HIV-infected children 2-14 years of age indicate that ritonavir clearance is greater than that seen in adults.

Resistance
The most significant genotypic resistance mutations associated with RTV are those found at codons 82, 84, 71 and 46. Multiple genotypic mutations are required for resistance to develop, although the 82 mutation appears to be necessary but not sufficient to confer phenotypic resistance. There may be cross-resistance between RTV and indinavir, and many isolates resistant to indinavir may also be resistant to saquinavir. Use of one of these agents following the failure of another is not routinely recommended unless viral resistance status is known for the specific PI.

Adverse Effects
One small phase I study in children demonstrated a high rate of gastrointestinal intolerance *(1)*. However, larger studies (e.g., PACTG 338) have shown better tolerance of the drug, particularly when dose escalation is used when initiating therapy. In PACTG 338, approximately 80% of children were able to tolerate RTV at 24 weeks of therapy *[2]*. Circumoral paresthesia and taste perversion have been reported in adults receiving the drug. Hepatic transaminase elevations exceeding 5 times the upper limit of normal, clinical hepatitis and jaundice have been reported in adults receiving RTV alone or in combination with other antiretroviral drugs. There may be an increased risk for transaminase elevation in patients with underlying hepatitis B or C virus infection. Caution should be exercised when administering RTV to patients with pre-existing liver disease.

Pediatric Experience
RTV monotherapy is associated with substantial decreases in HIV RNA levels and increases in $CD4^+$ lymphocyte counts *[3, 4]*, but resistance develops with its continued use as a single agent *[5]*. Addition of RTV to established antiretroviral regimens significantly decreased clinical progression and mortality in a 6-month clinical trial in infected adults with advanced disease *[6]*. Addition of a single drug, including a PI, to a failing regimen is not advised; at least two new drugs should be given when changing a regimen.

An interim analysis of PACTG 338 demonstrated that children receiving RTV and one or two NRTIs had a mean decrease of >1.5 log in viral RNA levels after 12 weeks of therapy. After 48 weeks of RTV plus two NRTIs 42% of children maintained HIV-RNA levels below the limits of detection of the assay compared with 27% of children receiving

RTV plus one NRTI *[7]*. Another small study of protease inhibitor naïve children receiving RTV with two NRTIs showed an increase of greater than 400 $CD4^+$ cells/mm^3 after 12 months of therapy *[8]*. PACTG Protocol 377 randomized antiretroviral experienced, PI and NNRTI-naïve children to four different treatment regimens including RTV/d4T/NVP. The median increase in $CD4^+$ cell count for those on this regimen was 254 cells/mm^3 and 41% of children had HIV RNA less than 400 copies/mL at 24 weeks of treatment *[9]*.

Similar to that found with other agents of its class, clearance of RTV is greater in young infants than that seen in older children and adults. Preliminary data from PACTG 345, which looked at RTV alone and in combination with 3TC and ZDV in children less then 2 years of age, showed that concentrations are highly variable and doses of 350 to 450 mg/m^2 twice a day may not be sufficient to suppress viral replication in this age group.

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Saquinavir (SQV, hard gel capsule, Invirase®); soft gel capsule, Fortovase®)

URL:http://www.fda.gov/cder/OGD/rld/20828S8.PDF
URL: link to Guideline Appendix SQV

Overview
In 1995, saquinavir (SQV) became the first protease inhibitor approved for use in adolescents and adults older then 16 years, in combination therapy with NRTIs. In its original formulation, as a hard gel capsule (Invirase), it had very limited bioavailability (~ 4%) following oral administration. In 1997, the FDA approved a soft gel capsule preparation (Fortovase) with significantly enhanced oral bioavailability. SQV has not been formally approved for use in children and is not yet available in a liquid preparation. Absorption of SQV soft gel capsule is enhanced by food.

Saquinavir is more than 90% metabolized by cytochrome P450 3A4 isoenzymes, the same enzyme system which metabolizes ritonavir. RTV and NFV have been shown to inhibit the metabolism of SQV; plasma levels of SQV are increased when it is co-administered with these agents *[1, 2]*. As with the other PIs, multiple pharmacological interactions are possible with coadministered agents that are also metabolized by cytochrome P450 3A4 (see product label).

Resistance
Resistance to SQV is associated with a unique mutation pattern in the HIV-protease gene primarily in codons 48 and 90, and viral isolates resistant to SQV are not necessarily resistant to the other protease inhibitors. However, phenotypic resistance to NFV has been demonstrated following SQV use, despite the lack of the usual NFV resistance

mutations. Additional codons associated with viral resistance to this agent include those at codons 84 and 82. Continued use of SQV without complete virologic suppression may lead to cross-resistance with other PIs due to the accumulation of secondary mutations. Viral isolates resistant to RTV and IDV are usually also resistant to SQV.

Adverse Effects
The drug appears to be well tolerated, with mild gastrointestinal disturbances (diarrhea, nausea, abdominal pain) and reversible elevations in liver function tests being the most common side effects reported in adults. As with all agents in this class, new onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, hyperglycemia, and diabetic ketoacidosis have been reported.

Pediatric Experience
Despite the low oral bioavailability of the hard gel capsule form of SQV, the drug has demonstrated virologic efficacy in clinical trials of combination therapy with ZDV and ddC in adults; a 0.8 log decrease in HIV RNA after 48 weeks of therapy was observed *[3]*. In a monotherapy regimen of high dose SQV, the maximum decrease in HIV RNA was 1.3 logs *[4]*. Initial pharmacokinetic studies in children found pharmacokinetics of the soft gel formulation similar to that in adults *[5]*. SQV soft gelatin capsule was studied in combination with 2 NRTIs in fourteen children; while combination therapy was well tolerated, in this study SQV plasma concentrations were lower than expected *[6]*. After 48 weeks of therapy with SQV plus dual NRTIs, median change in HIV RNA was –2.12 log, with 36% of children having RNA <50 copies/mL.

SQV administered in combination with low dose RTV, using the RTV as a pharmacologic "booster" of SQV level, has been studied in adults, but have had limited evaluations in children. Studies to find the most effective dose combination of SQV and RTV with the least toxicity are underway. The soft gel formulation of SQV in combination with NRTIs and RTV or NFV is currently being studied in pediatric patients *[6-8]*. In a study of thirteen children, the addition of NFV to a regimen of SQV with one or two NRTIs resulted in significant increase in SQV concentrations, and median change in HIV RNA levels was 2.58 log, with 62% of children having HIV RNA levels <50 copies/mL at 48 weeks *[9]*. In another study in eleven HIV-infected children with intensive prior therapy, salvage therapy with combination SQV/RTV and SQV/NFV with at least one NRTI were well tolerated; reduction in viral load and increase in $CD4^+$ cell count was more pronounced in the group receiving SQV/RTV combination *[8]*. However, safety and appropriate dosing information for children remains limited.

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Fusion Inhibitors

Enfuvirtide (T-20) is the first drug of the fusion inhibitor class of antiretroviral drugs to be approved; these drugs interact with components of the HIV envelope to prevent fusion of the virus with the host cell membrane. The normal fusion process involves binding of the viral envelope glycoprotein gp120 to the $CD4^+$ receptor, which induces conformational changes that enable gp120 to interact with a chemokine receptor on the host cell. Binding of gp120 to the coreceptor causes subsequent conformational changes in the viral transmembrane glycoprotein gp41, exposing the "fusion peptide" of gp41, which inserts into the cell membrane. A helical region of gp41, called HR1, then interacts with a similar helical region, HR2, on gp41, resulting in a "zipping" together of the two helices and mediating the fusion of cellular and viral membranes. T-20 is a synthetic peptide derived from a naturally occurring motif within the HR2 domain of viral gp41; as a molecular mimic of the HR2 region, the drug binds to the HR1 region, preventing the HR1-HR2 interaction and correct folding of gp41 into its secondary structure, thereby inhibiting virus-cell fusion. A number of additional fusion inhibitors are under study, including T-1249, which corresponds to a region of HR2 from diverse HIV strains that overlaps the T-20 sequence, and shows activity against viruses that are resistant to enfuvirtide.

Enfuvirtide (Fuzeon™, T-20)

URL:http://www.fda.gov/cder/foi/label/2003/021481lbl.pdf
URL: link to Guideline Appendix-EFV

Overview
Enfurvirtide (T-20) was approved in March 2003 for HIV-infected adults and children 6 years or older for use in combination with other antiretroviral drugs for the treatment of HIV infection in treatment-experienced patients with evidence of HIV replication despite ongoing antiretroviral therapy. T-20 is a novel, synthetic, 36-amino-acid peptide that binds to a region of the HIV envelope glycoprotein gp41, which prevents fusion of the virus envelope with the membrane of the $CD4^+$ host cell. It is a potent and selective inhibitor of HIV-1 entry *in vitro*, and has induced virologic responses in phase III clinical trials in adults and phase I/II trials in children *[1-3]*. T-20 comes as a sterile powder that must be reconstituted with sterile water and administered by subcutaneous injection. Each injection should be given at a site different from the preceding injection site, and should not be injected into moles, scar tissue, bruises, or the navel. T-20 is approximately 92% protein bound, predominantly to albumin. As a peptide, T-20 undergoes catabolism to its constituent amino acids, with subsequent recycling of the amino acids into the general body pool. T-20 does not affect the metabolism of drugs metabolized by liver CYP450 enzymes.

Resistance
Clinical isolates of HIV that are resistant to NRTIs, NNRTIs, and protease inhibitors remain susceptible to T-20 in cell culture. However, HIV isolates with reduced susceptibility to T-20 have been selected *in vitro*, although primary resistance to T-20 in treatment naïve patients is very rare *[4]*. The results from *in vitro* studies indicate that two amino acid substitutions (G to S at position 36 and V to M at position 38 in gp41) within the HR1 region of the HIV gp41 glycoprotein can lead to T-20 resistance *[5]*. In clinical trials in adults, HIV isolates with reduced susceptibility to T-20 have been recovered, demonstrating that HIV quasispecies in infected patients can undergo *in vivo* selection of resistant variants as a result of T-20 therapy. Decreases in susceptibility ranging from 4-fold to 422-fold relative to baseline virus have been observed with genotypic changes in gp41 amino acids 36 to 45.

Adverse Effects
Local injection site reactions are common, with such reactions occurring in 98% of adults, although only 3% required T-20 discontinuation. Symptoms included pain and discomfort, induration, erythema, nodules and cysts, pruritis, and ecchymosis. Although infection is uncommon (1% of patients), caregivers should monitor injection sites carefully for signs or symptoms of cellulitis or local infection. An increased rate of bacterial pneumonia was observed in T-20-treated adults in phase III studies (4.7 pneumonia events per 100-patient-years) compared to the control arm; the relation of this finding to T-20 use is uncertain. However, patients should be monitored for signs and symptoms of pneumonia, particularly if they have a low initial $CD4^+$ cell count, high initial viral load, history of prior lung disease, intravenous drug use or smoking (in adolescents). Other adverse events reported in trials include insomnia, myalgia, peripheral neuropathy, and depression.

Serious hypersensitivity reactions are rare. Symptoms include rash, fever, nausea and vomiting, chills, hypotension, and elevated liver transaminases; other presumably immune-mediated symptoms include respiratory distress, glomerulonephritis with hematuria, and Guillain-Barre syndrome. If such symptoms occur, therapy with T-20 should not be restarted, as hypersensitivity may recur on rechallenge. Treatment-related eosinophilia occurred in 11.2% of adults in a phase III trial, compared to only 2.4% of control patients *[1]*. However, eosinophilia was not associated with clinical events suggestive of systemic hypersensitivity.

In a trial of chronic T-20 in 14 children (see below), no life-threatening adverse events were identified, and no systemic serious toxicities were related to T-20 administration. Six wheezing episodes were noted in 4 children, and one episode of bacteremia was identified but none were judged related to T-20. As in adult trials, injection site reactions were frequent, observed in 79% of children, but were generally mild *[2]*.

Pediatric Experience
T-20 was studied in 14 HIV-infected children aged 4-12 years with incomplete viral suppression on their current antiretroviral regimen (plasma HIV RNA levels >10,000 copies/mL while receiving a stable combination of 2 NRTIs plus an NNRTI or a PI for at least 16 weeks) *[2]*. In the part A, dose-finding part of the study, a single dose of T-20 at 15, 30 or 60 mg per meter^2 body surface area was administered subcutaneously, with pharmacokinetic studies, and then intravenously, with pharmacokinetic studies. Based on findings in part A, part B evaluated the safety and antiretroviral activity of chronic twice daily subcutaneous T-20 administration at 30 or 60 mg per meter^2 body surface area per dose. For 7 days, the drug was added to the child's background antiretroviral regimen; at day 7, each child's background therapy was changed to a regimen that was predicted to be virologically active, while T-20 was continued. One child discontinued T-20 due to aversion to injections but no child discontinued because of adverse effects. Seventy-nine percent of children achieved the protocol-specified endpoint of at least a 0.7 $\log_{10}$ reduction in HIV RNA copies by day 7, and 71% had virologic suppression of at least 1.0 $\log_{10}$ by 24 weeks; 43% had suppression to <400 copies/mL and 21% to <50 copies/mL at 24 weeks. In continued follow-up through 48 weeks of therapy, 43% of children maintained virologic suppression (>1.0 $\log_{10}$ decrease in HIV RNA) *[3]*. Additionally, significant improvements in CD4$^+$ percentage and height z-score were observed in children receiving T-20 for 48 weeks. The dose of T-20 that reliably resulted in the target trough concentration (1,000 ng/mL) was 60 mg per meter^2 body surface area per dose, the approximate "equivalent" of 90 mg dose delivered to a typical adult with a body surface area of 1.7 m^2. The recommended pediatric label dose in children aged 6 to 16 years is 2 mg/kg (maximum 90 mg) twice daily administered subcutaneously. In a second pediatric study of 18 children aged 6 to 16 years, the 2 mg/kg dose was found to yield drug concentrations similar to the 60 mg per meter^2 body surface area dose; further data are needed in children under age 6 years *[6]*.

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