newly diagnosed infants under age 12 months, particularly if the mother has known or suspected infection with drug-resistant virus. There are no definitive data that demonstrate that resistance testing in this setting correlates with greater success of initial antiretroviral therapy, however.

AVAILABLE ANTIRETROVIRAL DRUGS

As of January 2004, there were 20 antiretroviral drugs approved for use in HIV-infected adults and adolescents; 12 of these have an approved pediatric treatment indication. These drugs fall into several major classes: nucleoside analogue or nucleotide reverse transcriptase inhibitors (NRTIs, NtRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, and fusion inhibitors. Brief information on drug formulation, pediatric dosing, and toxicity for the individual drugs can be found in the **Appendix - Characteristics of Available Antiretroviral Drugs.** For more detailed discussion of major classes of antiretroviral drugs and individual drugs for treatment of pediatric HIV infection, go to the **Pediatric Antiretroviral Drug Information** hyperlink**.** The advantages and disadvantages of individual drugs for children are presented in **Tables 8-10**.

Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTIs) (Table 8)

The NRTIs were the first class of antiretroviral drugs that became available for treatment of HIV infection. These drugs include ZDV, ddI, 3TC, d4T, zalcitabine (ddC), abacavir (ABC), and emtricitabine (FTC). All except ddC and FTC are available in liquid formulations. Additionally, two fixed-dose drug combination preparations are available in solid formulations — a fixed-dose combination of ZDV/3TC (Combivir) and a fixed-dose formulation of ZDV/3TC/ABC (Trizivir). These latter two drug formulations are approved for use in adolescents and adults but are not recommended for use in children less than 12 years old, for whom the adult dosage may not be appropriate.

Dual NRTI combinations form the “backbone” of HAART regimens for both adults and children. Dual NRTI combinations that have been studied in children include ZDV and ddI; ZDV and 3TC; d4T and ddI; d4T and 3TC; ZDV and ddC; and ABC in combination with ZDV, 3TC, d4T or ddI *[91, 121-125]*. The choice of specific dual NRTI combinations for children is based upon the:

- Extent of pediatric experience with the specific drug combination;
- Potency of the NRTI combination;
- Availability of pediatric formulations;
- Potential drug interactions; and
- Short- and long-term toxicity.

The most experience in children is with combination ZDV/3TC, ZDV/ddI, and d4T/3TC, which are the Strongly Recommended dual NRTI combinations for inclusion in initial therapy regimens in children. Alternative dual NRTI combinations include ZDV/ABC, 3TC/ABC, and ddI/3TC. ABC-containing regimens have been shown to be as or possibly more potent than ZDV/3TC *[125]*, but have the potential for ABC-associated life-threatening hypersensitivity reactions in a small proportion of patients *[126, 127]*. Thus, ABC-containing regimens are listed as Alternative rather than as Strongly Recommended dual NRTI combinations for inclusion in initial therapy regimens in children. While the dual NRTI combination of ddI/3TC has been well tolerated, there is less pediatric experience with ddI/3TC than the preferred regimens, and it is thus recommended as an Alternative as well.

The dual NRTI combinations d4T/ddI and ZDV/ddC are recommended for Use in Special Circumstances. In small pediatric studies, d4T/ddI has been shown to have virologic efficacy and was well tolerated *[124, 128]*. However, in studies in adults, d4T/ddI-based combination regimens were associated with greater rates of neurotoxicity, hyperlactatemia and lactic acidosis, and lipodystrophy than therapies based on ZDV/3TC *[129, 130]*; additionally, cases of fatal and non-fatal lactic acidosis with pancreatitis/hepatic steatosis have been reported in women receiving this combination during pregnancy *[6, 7]*. ZDV/ddC has been studied in children *[123]*, but ddC is less potent than the other NRTI drugs and has greater toxicity, and thus would not be first choice for inclusion in an initial therapy regimen.

Certain dual NRTI drug combinations are Not Recommended. These include ZDV and d4T, due to pharmacologic interactions that can result in potential virologic antagonism, and dual regimens combining ddC with ddI, d4T or 3TC, as pediatric experience

with these combinations is limited and there is overlapping neurotoxicity between the drugs. FTC is approved for use in adults age 18 years or older. Although FTC is under study in children, pharmacokinetic, safety and efficacy data in pediatric patients are not yet available and no pediatric formulation is commercially available. Therefore, there are Insufficient Data to Recommend use of FTC for initial therapy in children.

Nucleotide Reverse Transcriptase Inhibitors (NtRTIs) (Table 8)

Tenofovir disoproxil fumerate is a nucleotide analogue; like the NRTI drugs, tenofovir inhibits HIV reverse transcriptase. However, because the drug already possesses a phosphate molecule, it bypasses the rate-limiting initial phosphorylation step required for activation of NRTIs. 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. The drug is currently in phase I/II studies in the pediatric population, and an oral suspension formulation is under study. However, animal toxicology studies have demonstrated a potential for bone and renal toxicity. Preliminary data from pediatric phase I studies indicate that decreased bone mineral density as measured by dual-energy x-ray absorptiometry (DEXA) scans has been observed in some children. Thus, there are Insufficient Data to Recommend use of this drug for initial therapy in infected 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. Additionally, a recent study in antiretroviral-naïve adults found sub-optimal early virologic response to a regimen containing tenofovir in combination with 3TC and ABC, and this combination regimen should not be used for initial treatment of therapy-naïve adults or children *[131]*.

Non-Nucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs) (Table 9)

There are currently 3 NNRTIs approved for treatment of HIV infection: nevirapine, efavirenz, and delavirdine. Nevirapine has a liquid formulation and is approved for pediatric use in children aged 2 months or older. The capsule formulation of efavirenz is approved for use in children over 3 years of age; a liquid formulation is under study and is available through an expanded access program *[132]*. Delavirdine is only available in a tablet preparation and is not approved for use in children. The NNRTI class of drugs rapidly reduces viral load; however, drug resistance develops quickly after initiation of monotherapy or with combination therapy that does not fully suppress viral replication, and cross-resistance between drugs in this class is common. Thus, NNRTI drugs should only be used in the context of a HAART regimen, and never as mono- or dual therapy (with the exception of single-dose nevirapine prophylaxis to reduce mother-to-child HIV transmission *[133]*).

Efavirenz is the Strongly Recommended NNRTI for use in a combination regimen for initial treatment of children over age 3 years who can swallow capsules. Efavirenz in combination with 1 or 2 NRTIs plus nelfinavir has been shown to produce sustained and durable viral suppression in a large proportion of treated children *[134]*. Although there are not data in children, a protease inhibitor-sparing regimen of efavirenz plus 2 NRTIs has had similar efficacy in infected adults *[135]*. Based on these adult data, the latter protease inhibitor-sparing combination offers an alternative to children when issues of adherence or use of protease inhibitors are problematic. There are currently no pharmacokinetic data available on appropriate dosage of efavirenz in children under age 3 years. A liquid preparation has been studied in children over age 3 years *[132]* and is available by expanded access, but only a capsular formulation is currently commercially available. Because efavirenz is currently only available in a capsule, while nevirapine is available in a liquid formulation, for children who require a liquid formulation or who are under age 3 years, nevirapine would be the recommended NNRTI.

For children over age 3 years, nevirapine is Recommended as an Alternative NNRTI for initial therapy. Combination therapy with nevirapine, ZDV and ddI in a small number of young, antiretroviral therapy-naïve infants was associated with substantial and sustained viral suppression in some of the infants *[94, 104]*. Treatment of therapy-naïve adults with nevirapine plus dual NRTI regimen demonstrated comparable results to triple therapy with the protease inhibitor indinavir *[136]*, but no similar comparative studies have been performed in children. Results of studies comparing nevirapine-based versus efavirenz-based regimens in adults are conflicting (see