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

Recommendation section) and no comparative studies have been done in children. Because nevirapine therapy is associated with the rare occurrence of significant hypersensitivity reactions, including Stevens-Johnson syndrome, and rare but potentially life-threatening hepatitis *[5, 137, 138]*, nevirapine is therefore Recommended as an Alternative, as opposed to Strongly Recommended, NNRTI for initial treatment of antiretroviral-naïve children, except for those children under age 3 years or who cannot swallow a capsule. Since delavirdine has not been studied in or approved for children, there are Insufficient Data to Recommend it for use as initial therapy in children.

Protease Inhibitors (Table 10)

Protease inhibitors with formulations appropriate for infants and children who cannot swallow pills or capsules include nelfinavir, ritonavir, amprenavir, and lopinavir/ritonavir. Nelfinavir is available as a powder formulation that can be mixed with water or food, while the others are available in liquid formulations. Indinavir, saquinavir, atazanavir, and fosamprenavir are only available in capsule formulations. Two capsule formulations of saquinavir are available: the hard-gel capsule (saquinavir-HGC; Invirase™) has limited bioavailability, while the soft-gel capsule (saquinavir-SGC; Fortavase™) has enhanced bioavailability and is the predominant saquinavir formulation now used for therapy. However, both formulations require boosting with ritonavir to achieve adequate levels in children (see below).

Clinical trials involving antiretroviral-naïve children (some as young as 15 days of age) as well as antiretroviral-experienced children provide evidence that the combination of 2 NRTIs and a protease inhibitor may reduce HIV RNA to undetectable levels in a substantial proportion of children *[104, 105, 125, 139-142]* although somewhat less than that observed with similar treatments in infected adults. Nelfinavir, ritonavir, or lopinavir/ritonavir are considered Strongly Recommended protease inhibitors for use in combination with 2 NRTIs as initial therapy in infected children. These drugs have the greatest clinical experience in the pediatric population, and are available in pediatric formulations.

Indinavir and amprenavir when used in combination with 2 NRTIs are Recommended as Alternative protease inhibitors for initial therapy due to more limited experience in children, lack of approved liquid dosage formulations and/or issues of toxicity. The incidence of hematuria and nephrolithiasis with indinavir therapy may be higher in children than adults *[139]*. Amprenavir should not be used in children <4 years of age because of the lack of data for children in this age group, the uncertain impact of extremely high levels of vitamin E found in the liquid formulation (46 IU of vitamin E per mL; the recommended daily dose of vitamin E in children is 10 IU), and the presence of propylene glycol in the oral liquid preparation in a concentration that exceeds WHO standards for use in infants.

Atazanavir is approved for use in HIV-infected adults (in adults, atazanavir coadministration with tenofovir requires low-dose ritonavir boosting to achieve adequate atazanavir drug levels) *[143]*. Although atazanavir is under study in children, pharmacokinetic, safety and efficacy data in pediatric patients are not yet available and no pediatric formulation is commercially available; it is likely that co-administration of atazanavir with a low-dose ritonavir boost will be needed to achieve adequate drug levels in children. Therefore, there are Insufficient Data to Recommend use of atazanavir for initial therapy in children.

Fosamprenavir calcium is a prodrug of amprenavir that is approved for use in combination therapy for HIV-infected adults. Pediatric trials are ongoing at this time, but at present there are Insufficient Data to Recommend use of fosamprenavir for initial therapy in children.

Studies of infected adults have indicated that some drugs that inhibit the cytochrome P450 system, including the protease inhibitor ritonavir, can produce substantial increases in the drug levels of other protease inhibitors. Low-dose, non-therapeutic doses of ritonavir when combined with saquinavir, amprenavir, and indinavir have been shown to act as a pharmacological “booster” to produce elevated therapeutic plasma concentrations of the second drug. The protease inhibitor fixed-dose combination lopinavir/ritonavir is a preparation that takes advantage of this pharmacokinetic enhancement by using a low dose of ritonavir to produce sustained therapeutic levels of lopinavir. However, while combinations of ritonavir with saquinavir-SGC, saquinavir-HGC, indinavir, or nelfinavir in infected adults have shown evidence of virologic suppression when combined with dual NRTIs, these studies have been predominantly conducted among treatment-experienced adults, and it is unclear whether dual protease inhibitors offer any substantial benefit over