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

a single protease inhibitor for initial therapy of antiretroviral naïve individuals *[144-147]*.

In children, available pharmacokinetic data indicate that administration of saquinavir SGC does not result consistently in efficacious plasma levels, possibly due to increased systemic clearance and reduced oral bioavailability. Therefore, saquinavir should not be used as a sole protease inhibitor in combination therapy in children. To achieve adequate drug levels in children, saquinavir-SGC must be administered with a second protease inhibitor that inhibits saquinavir metabolism (e.g., ritonavir or nelfinavir); however, there are only limited pediatric data on appropriate dosing for such combinations *[148]*. Similarly, saquinavir HGC requires a second protease inhibitor boost to achieve adequate drug levels in children, but no data on appropriate pediatric dosage are available.

Studies of saquinavir in combination with ritonavir or nelfinavir and studies of other dual protease inhibitor combinations are ongoing in treatment-experienced children, but complete data are not yet available *[124, 149, 150]*. Because information on the pharmacokinetics, safety, and efficacy of dual protease inhibitor combinations in children are limited, with the exception of the co-formulated lopinavir/ritonavir, there are Insufficient Data to Recommend use of dual protease inhibitors as a component of initial therapy in children, although such combinations may have utility as a component of secondary treatment regimens for children who have failed initial therapy.

Fusion Inhibitors

A new class of antiretroviral agents called fusion inhibitors have been identified that inhibit viral binding or fusion to host target cells; the available drugs in this class must be administered subcutaneously. Single and chronic-dosing phase I/II studies of the fusion inhibitor enfuvirtide (T-20) in combination with other antiretroviral drugs in treatment-experienced children have been completed, and have demonstrated that the drug is safe and has an additive anti-viral effect *[151]*. Enfuvirtide 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. There are currently Insufficient Data to Recommend use of enfuvirtide for initial therapy of HIV infection in children, although the drug may have utility in the treatment of children failing alternative antiretroviral regimens.

RECOMMENDATIONS ON ANTIRETROVIRAL REGIMENS FOR INITIAL THERAPY (Table 11)

There are few randomized, phase III clinical trials of HAART among pediatric patients that provide direct comparison of different treatment regimens; most pediatric drug data come from phase I/II safety and pharmacokinetic trials and non-randomized, open-label studies. Recommendations on the optimal initial therapy for children are continually being modified as new data become available, new therapies or drug formulations are developed, and late toxicities become recognized. Criteria used by the Working Group for recommending specific drugs or regimens include:

- Data demonstrating durable viral suppression, immunologic improvement, and clinical improvement (when such data are available) with the regimen, preferably in children as well as adults;
- Incidence and types of drug toxicity with the regimen;
- Availability and palatability of formulations appropriate for pediatric use;
- Dosing frequency, and food and fluid requirements; and
- Potential for drug interactions.

The most extensive clinical trial data on initial therapy regimens in adults and children are available for three types of regimens based on drug class: protease inhibitor-based (2 NRTIs plus a protease inhibitor); NNRTI-based (2 NRTIs plus an NNRTI); and NRTI-based (3 NRTI drugs). Each class-based regimen has advantages and disadvantages. Protease inhibitor-based regimens, while highly potent, have a high pill burden and palatability challenges in children (**Table 10**). NNRTI-based regimens are palatable and effective, but a low genetic barrier to resistance leads to rapid development of drug resistance mutations when therapy does not fully suppress viral replication, and there is cross-resistance among members of this drug class (**Table 9**). Triple NRTI-based regimens, while sparing of other drug classes, may have lower potency than other regimens (**Table 8**). As discussed earlier, within each drug class, some drugs may be preferred over other drugs for treatment of children, based on: the extent of pediatric experience; drug formulation,