Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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What Drugs to Start: Initial Combination Therapy for Antiretroviral Treatment-Naive Children (Last updated November 1, 2012; last reviewed November 1, 2012)

General Considerations

Panel's Recommendations
• Combination therapy consisting of a dual-nucleoside/nucleotide reverse transcriptase inhibitor backbone with either a non-nucleoside reverse transcriptase inhibitor or a protease inhibitor is recommended for initial treatment of HIV-infected children **(AI)**. • The goal of therapy in treatment-naive children is to reduce plasma HIV RNA levels to below the limits of quantitation using the most sensitive assays and to preserve or normalize immune status **(AI)**. • Antiretroviral (ARV) drugs initiated for chemoprophylaxis of maternal-child transmission of HIV should be discontinued in infants who are confirmed to be HIV-infected **(AI)**. • ARV drug-resistance testing is recommended before initiation of therapy in all treatment-naive infants, children, and adolescents (**AII** infants; **AIII** children and adolescents).
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional* ***Rating of Evidence:*** *I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion* *† Studies that include children or children and adolescents but not studies limited to postpubertal adolescents*

More than 20 antiretroviral (ARV) drugs are Food and Drug Administration-approved for use in HIV-infected adults and adolescents and 19 have an approved pediatric treatment indication.[1] The majority of the agents approved for use in pediatric patients are available as a liquid, powder, chewable tablet, or small capsule or tablet suitable for pediatric use. ARV drugs fall into several major drug classes: nucleoside/nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, entry inhibitors (including fusion inhibitors and CCR5 antagonists), and integrase inhibitors. Information on drug formulation, pediatric dosing, and toxicity for the individual drugs and detailed information on drug interactions can be found in Appendix A: Pediatric Antiretroviral Drug Information. Over time, new drugs and drug combinations that demonstrate sustainable viral load suppression and acceptable toxicity and dosing profiles will likely become available, which will increase treatment options for children.

Combination antiretroviral therapy (cART) with at least three drugs from at least two drug classes is recommended for initial treatment of HIV-infected infants, children, and adolescents because it provides the best opportunity to preserve immune function and delay disease progression.[2-5] The goal of cART is to maximally suppress viral replication, preferably to below the limits of quantification, for as long as possible while preserving and/or restoring immune function and minimizing drug toxicity. Combination therapy slows disease progression and improves survival, results in a greater and more sustained virologic and immunologic

response, and delays development of viral mutations that confer resistance to the drugs being used.[4-6]

If an infant is confirmed to be HIV-infected while receiving chemoprophylaxis to prevent mother-to-child transmission (PMTCT) of HIV, prophylactic ARV drugs should be discontinued promptly and treatment initiated with a combination regimen of at least three drugs. Zidovudine can be included as a component of the treatment regimen if zidovudine drug resistance is not detected.

Treatment-naive infants and children with perinatal HIV infection can have drug-resistant virus either because it was transmitted perinatally or during breastfeeding or because resistance developed while they were receiving ARV prophylaxis. Thus, ARV drug-resistance testing is recommended before initiation of therapy in all treatment-naive infants and children. In infants receiving prophylactic ARV drugs for PMTCT, ARV drug resistance testing can be performed at the same time as confirmatory HIV testing or when prophylactic ARV drugs are discontinued. In a study in New York State, genotypic drug resistance was identified in 12% of 91 HIV-infected infants born from 1998 to 1999 and in 19% of 42 infants born from 2000 to 2001.[7, 8] Detection of resistance in the infants was not significantly associated with a history of maternal and infant ARV prophylaxis. Similarly, following initiation of treatment, mutations associated with drug-resistance were detected in 24% of 21 infants at a median age of 9.7 weeks. Most of the mutations were not associated with maternal/infant prophylaxis regimens and resistant virus was persistently archived in the resting CD4 cell reservoir in all the infants. In a study in Africa, infants, regardless of whether they were exposed to nevirapine as part of PMTCT, had higher rates of virologic failure on nevirapine-based regimens compared with lopinavir/ritonavir-based regimens.[9-11] In a Spanish cohort of children, resistance mutations were detected in 13% of treatment-naive children.[12] In the United States and Europe, drug-resistant virus has been identified in 6% to 16% of ARV-naive adults and 18% of adolescents with recently acquired HIV infection.[13-17] For ARV-naive children beyond infancy, limited available data do not demonstrate that resistance testing before initiation of therapy correlates with greater success of initial ART.[18] Nevertheless, because the prevalence of resistance in HIV-infected children is sufficiently high and on the basis of expert opinion, the Panel recommends ARV drug-resistance testing with a genotypic assay before initiation of therapy in all treatment-naive infants and children and use of resistance testing results to select the initial drug combination.[19] (See Antiretroviral Drug-Resistance Testing.) Resistance testing in HIV-infected adolescents and adults is also recommended at entry into care.

References

1. Food and Drug Administration. Approved antiretroviral drugs for pediatric treatment of HIV infection. Accessed on June 20, 2012. http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm118951.htm.
2. Nachman SA, Stanley K, Yogev R, et al. Nucleoside analogs plus ritonavir in stable antiretroviral therapy-experienced HIV-infected children: A randomized controlled trial. Pediatric AIDS Clinical Trials Group 338 Study Team. *JAMA*. Jan 26 2000;283(4):492-498. Available at http://www.ncbi.nlm.nih.gov/pubmed/10659875.
3. Chiappini E, Galli L, Gabiano C, Tovo PA, de Martino M, Italian Register for HIVIiC. Early triple therapy vs. mono or dual therapy for children with perinatal HIV infection. *JAMA*. Feb 8 2006;295(6):626-628. Available at http://www.ncbi.nlm.nih.gov/pubmed/16467231.
4. de Martino M, Tovo PA, Balducci M, et al. Reduction in mortality with availability of antiretroviral therapy for children with perinatal HIV-1 infection. Italian Register for HIV Infection in Children and the Italian National AIDS Registry. *JAMA*. Jul 12 2000;284(2):190-197. Available at http://www.ncbi.nlm.nih.gov/pubmed/10889592.
5. Gortmaker SL, Hughes M, Cervia J, et al. Effect of combination therapy including protease inhibitors on mortality among children and adolescents infected with HIV-1. *N Engl J Med*. Nov 22 2001;345(21):1522-1528. Available at http://www.ncbi.nlm.nih.gov/pubmed/11794218.
6. Violari A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J*

Med. Nov 20 2008;359(21):2233-2244. Available at http://www.ncbi.nlm.nih.gov/pubmed/19020325.

7. Karchava M, Pulver W, Smith L, et al. Prevalence of drug-resistance mutations and non-subtype B strains among HIV-infected infants from New York State. *J Acquir Immune Defic Syndr*. Aug 15 2006;42(5):614-619. Available at http://www.ncbi.nlm.nih.gov/pubmed/16868498.
8. Parker MM, Wade N, Lloyd RM Jr., et al. Prevalence of genotypic drug resistance among a cohort of HIV-infected newborns. *J Acquir Immune Defic Syndr*. Mar 1 2003;32(3):292-297. Available at http://www.ncbi.nlm.nih.gov/pubmed/12626889.
9. Palumbo P, Lindsey JC, Hughes MD, et al. Antiretroviral treatment for children with peripartum nevirapine exposure. *N Engl J Med*. Oct 14 2010;363(16):1510-1520. Available at http://www.ncbi.nlm.nih.gov/pubmed/20942667.
10. Violari A, Lindsey JC, Hughes MD, et al. Nevirapine versus ritonavir-boosted lopinavir for HIV-infected children. *N Engl J Med*. Jun 21 2012;366(25):2380-2389. Available at http://www.ncbi.nlm.nih.gov/pubmed/22716976.
11. Persaud D, Palumbo P, Ziemniak C, et al. Early archiving and predominance of nonnucleoside reverse transcriptase inhibitor-resistant HIV-1 among recently infected infants born in the United States. *J Infect Dis*. May 15 2007;195(10):1402-1410. Available at http://www.ncbi.nlm.nih.gov/pubmed/17436219.
12. de Mulder M, Yebra G, Martin L, et al. Drug resistance prevalence and HIV-1 variant characterization in the naive and pretreated HIV-1-infected paediatric population in Madrid, Spain. *J Antimicrob Chemother*. Oct 2011;66(10):2362-2371. Available at http://www.ncbi.nlm.nih.gov/pubmed/21810838.
13. Cane P, Chrystie I, Dunn D, et al. Time trends in primary resistance to HIV drugs in the United Kingdom: multicentre observational study. *BMJ*. Dec 10 2005;331(7529):1368. Available at http://www.ncbi.nlm.nih.gov/pubmed/16299012.
14. Novak RM, Chen L, MacArthur RD, et al. Prevalence of antiretroviral drug resistance mutations in chronically HIV-infected, treatment-naive patients: implications for routine resistance screening before initiation of antiretroviral therapy. *Clin Infect Dis*. Feb 1 2005;40(3):468-474. Available at http://www.ncbi.nlm.nih.gov/pubmed/15668873.
15. Viani RM, Peralta L, Aldrovandi G, et al. Prevalence of primary HIV-1 drug resistance among recently infected adolescents: a multicenter adolescent medicine trials network for HIV/AIDS interventions study. *J Infect Dis*. Dec 1 2006;194(11):1505-1509. Available at http://www.ncbi.nlm.nih.gov/pubmed/17083034.
16. Weinstock HS, Zaidi I, Heneine W, et al. The epidemiology of antiretroviral drug resistance among drug-naive HIV-1-infected persons in 10 US cities. *J Infect Dis*. Jun 15 2004;189(12):2174-2180. Available at http://www.ncbi.nlm.nih.gov/pubmed/15181563.
17. Wensing AM, van de Vijver DA, Angarano G, et al. Prevalence of drug-resistant HIV-1 variants in untreated individuals in Europe: implications for clinical management. *J Infect Dis*. Sep 15 2005;192(6):958-966. Available at http://www.ncbi.nlm.nih.gov/pubmed/16107947.
18. Fiscus SA, Kovacs A, Petch LA, et al. Baseline resistance to nucleoside reverse transcriptase inhibitors fails to predict virologic response to combination therapy in children (PACTG 338). *AIDS Res Ther*. 2007;4:2. Available at http://www.ncbi.nlm.nih.gov/pubmed/17280617.
19. Hecht FM, Grant RM. Resistance testing in drug-naive HIV-infected patients: is it time? *Clin Infect Dis*. Nov 1 2005;41(9):1324-1325. Available at http://www.ncbi.nlm.nih.gov/pubmed/16206109.

Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children (Table 8) (Last updated November 15, 2012; last reviewed November 1, 2012)

Panel's Recommendations

- The Panel recommends initiating combination antiretroviral therapy in treatment-naive children using one of the following agents plus a dual-nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) backbone combination (in alphabetical order):
    - For children aged ≥6 years: atazanavir/ritonavir **(AI*)**
    - For children aged ≥3 years: efavirenz **(AI*)**
    - For children aged ≥42 weeks postmenstrual and ≥14 days postnatal: lopinavir/ritonavir **(AI)**
- The Panel recommends the following preferred dual-NRTI backbone combinations (in alphabetical order):
    - For children aged ≥3 months: abacavir + (lamivudine or emtricitabine) **(AI)**
        - HLA-B*5701 genetic testing should be performed before initiating abacavir-based therapy, and abacavir should not be given to a child who tests positive for HLA-B*5701 **(AII*)**.
    - For adolescents, Tanner Stage 4 or 5: tenofovir + (lamivudine or emtricitabine) **(AI*)**
    - For children of any age: zidovudine + (lamivudine or emtricitabine) **(AI*)**
- Table 8 provides a list of Panel-recommended alternative and acceptable regimens.
- Selection of an initial regimen should be individualized based on a number of factors including characteristics of the proposed regimen, patient characteristics, and results of viral resistance testing **(AIII)**.
- Alternative regimens may be preferable for some patients based on their individual characteristics and needs.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion*

† Studies that include children or children and adolescents but not studies limited to postpubertal adolescents

Criteria Used for Recommendations

In general, Panel recommendations are based on review of pediatric and adult clinical trial data published peer-reviewed journals (the Panel may also review data prepared by manufacturers for Food and Drug Administration review and data presented in abstract format at major scientific meetings). Few randomized, Phase III clinical trials of combination antiretroviral therapy (cART) in pediatric patients exist that provide direct comparison of different treatment regimens. Most pediatric drug data come from Phase I/II safety and pharmacokinetic (PK) trials and non-randomized, open-label studies. In general, even in studies in adults, assessment of drug efficacy and potency is primarily based on surrogate marker endpoints, such as CD4 T lymphocyte (CD4 cell) count and HIV RNA levels. The Panel continually modifies recommendations on optimal initial therapy for children as new data become available, new therapies or drug formulations are developed, and additional toxicities are recognized.

Information considered by the Panel for recommending specific drugs or regimens includes:

- 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;
- The extent of pediatric experience with the particular drug or regimen;
- Incidence and types of short- and long-term drug toxicity with the regimen, with special attention to toxicity reported in children;
- Availability and acceptability of formulations appropriate for pediatric use, including palatability, ease of preparation (such as powders), volume of syrups, and pill size and number of pills;
- Dosing frequency and food and fluid requirements; and
- Potential for drug interactions with other medications.

The Panel classifies drugs or drug combinations into one of several categories as follows:

- ***Preferred:*** Drugs or drug combinations are designated as *preferred* for use in treatment-naive children when clinical trial data in children or, more often, in adults have demonstrated optimal and durable efficacy with acceptable toxicity and ease of use, and pediatric studies demonstrate that safety and efficacy are suggested using surrogate markers; additional considerations are listed above.
- ***Alternative:*** Drugs or drug combinations are designated as *alternatives* for initial therapy when clinical trial data in children or adults show efficacy but there are disadvantages compared with preferred regimens in terms of more limited experience in children; the extent of antiviral efficacy or durability is less well defined in children or less than a preferred regimen in adults; there are specific toxicity concerns; or there are dosing, formulation, administration, or interaction issues for that drug or regimen.
- ***Use in Special Circumstances:*** Some drugs or drug combinations are recommended for use as initial therapy only in special circumstances when preferred or alternative drugs cannot be used.
- ***Not Recommended:*** Some drugs and drug combinations are not recommended for initial therapy in children because of inferior virologic response, potential serious safety concerns (including potentially overlapping toxicities), or pharmacologic antagonism. These drugs and drug combinations are listed in Table 9.
- ***Insufficient Data to Recommend:*** For a number of drugs and drug combinations approved for use in adults, PK or safety data in children are unavailable or too limited to make a recommendation on use of the drugs as initial therapy in children. Some of these drugs and drug combinations may be appropriate for consideration in management of treatment-experienced children, even though they are not recommended for initial therapy in children (see Management of Treatment-Experienced Infants, Children, and Adolescents).

Factors to Consider When Selecting an Initial Regimen

Choice of a regimen should be individualized based on a number of factors including characteristics of the proposed regimen, patient characteristics, and results of viral resistance testing. Advantages and disadvantages of each class-based regimen are delineated in detail in the sections that follow and in Tables 10-14. In addition, because cART will need to be administered lifelong, considerations related to the choice of initial antiretroviral (ARV) regimen should also include an understanding of barriers to adherence, including the complexity of schedules and food requirements for different regimens; differing formulations; palatability problems; and potential limitations in subsequent treatment options, should resistance develop. Treatment should only be initiated after assessment and counseling of caregivers about adherence to therapy.[1, 2]

Choice of NNRTI- Versus PI-Based Initial Regimens

Preferred regimens for initial therapy include both non-nucleoside reverse transcriptase inhibitor (NNRTI)- and protease inhibitor (PI)-based regimens. The selection of an NNRTI- or PI-based regimen should be based on patient characteristics and preferences, results of viral drug resistance testing, and information cited below.

Recent clinical trial data in children provide some guidance for choosing between an NNRTI-based regimen and a PI-based regimen for initial therapy. P1060 compared a nevirapine-based regimen to a lopinavir-based regimen in HIV-infected infants and children aged 2 to 35 months in 7 African countries. Infants and children in this study were stratified at entry based on either prior maternal or infant exposure to single-dose nevirapine prophylaxis for prevention of mother-to-child transmission (PMTCT) and randomized to receive either zidovudine, lamivudine, and nevirapine or zidovudine, lamivudine, and lopinavir/ritonavir. Among infants and children with prior exposure to nevirapine, 39.6% of children in the nevirapine group reached a study endpoint of death, virologic failure, or toxicity by Week 24 compared with 21.7% of children in the lopinavir/ritonavir group.[3] Among infants and children with no prior nevirapine exposure, 40.1% of children treated with nevirapine met a study endpoint after 24 weeks in the study compared with 18.4% of children who received lopinavir/ritonavir.[4] Additional nonrandomized studies have also indicated that infants exposed to nevirapine in the peripartum period as part of PMTCT strategy had a higher risk of treatment failure because of nevirapine resistance.[5-7]

A comparison of a PI-based regimen and a NNRTI-based regimen was also undertaken in HIV-infected treatment-naive children aged 30 days to <18 years in PENPACT-1 (PENTA 9/PACTG 390) (the study did not dictate the specific NNRTI or PI initiated). In the PI-based group, 49% of children received lopinavir/ritonavir and 48% received nelfinavir; in the NNRTI-based group, 61% of children received efavirenz and 38% received nevirapine. Efavirenz was recommended only for children aged >3 years. After 4 years, 73% of children randomized to PI-based therapy and 70% randomized to NNRTI-based therapy remained on their initial cART regimen. In both groups, 82% of children had viral loads <400 copies/mL, suggesting that selection of an NNRTI or a PI did not influence outcome. Although the age of participants overlapped somewhat between P1060 and PENPACT-1 (in PENPACT-1, the lowest quartile was aged <2.8 years), PENPACT-1 generally enrolled older children.[8]

Results of the P1060 study support the recommendation that a PI-based regimen containing lopinavir/ritonavir should be the preferred initial regimen for children aged <3 years based on superior virologic suppression. However, in both single-dose nevirapine-exposed and -unexposed children in the P1060 study, participants receiving the nevirapine-based regimen demonstrated better immunologic response and growth than those receiving a lopinavir/ritonavir-based regimen, although these differences did not achieve statistical significance. Similarly, in the NEVEREST study, children switched to a nevirapine regimen showed better immune and growth responses than those continuing a lopinavir/ritonavir regimen.[9] Based on these findings, the potential for improved lipid profiles with nevirapine use,[9, 10] and the poor palatability of liquid lopinavir/ritonavir, liquid nevirapine remains an acceptable alternative for infants who were not exposed to single-dose nevirapine for PMTCT and who cannot tolerate lopinavir/ritonavir.

In children aged ≥3 years, either an NNRTI-based or a PI-based regimen is acceptable.

NNRTI-Based Regimens (one NNRTI + two-NRTI backbone)

Summary: NNRTI-Based Regimens

Nevirapine and efavirenz both have an FDA-approved pediatric indication. In the United States, nevirapine is available in a liquid formulation but efavirenz is not. Advantages and disadvantages of different NNRTI drugs are delineated in Table 11. Use of NNRTIs as initial therapy preserves the PI class for future use and

confers lower risk of dyslipidemia and fat maldistribution than use of some agents in the PI class. In addition, for children taking solid formulations, NNRTI-based regimens generally have a lower pill burden than PI-based regimens. The major disadvantages of the current NNRTI drugs FDA-approved for use in children are that a single viral mutation can confer high-level drug resistance, and cross resistance develops between nevirapine and efavirenz.

In infants, regardless of whether nevirapine is used as part of PMTCT, nevirapine-based regimens demonstrate higher rates of virologic failure than with lopinavir/ritonavir-based regimens.[3, 4] Rare but serious and potentially life-threatening skin and hepatic toxicity can occur with all NNRTI drugs, but is most frequent with nevirapine, at least in HIV-infected adults. Like PIs, NNRTIs have the potential to interact with other drugs also metabolized via hepatic enzymes; however, these drug interactions are less frequent with NNRTIs than with boosted PI regimens.

Efavirenz, in combination with 2 NRTIs, is the preferred NNRTI for initial therapy of children aged ≥3 years based on clinical trial experience in children and because higher rates of toxicity have been observed with nevirapine in clinical trials in adults. Results of studies comparing virologic response to nevirapine- versus efavirenz-based regimens in adults are conflicting, and no randomized studies have been done in children. Because nevirapine therapy is associated with the rare occurrence of significant hypersensitivity reactions (HSRs), including Stevens-Johnson syndrome and rare but potentially life-threatening hepatitis,[11, 12] nevirapine is recommended as an alternative, rather than a preferred, NNRTI for initial treatment of ARV-naive children.

Etravirine is an NNRTI approved by the FDA for treatment of HIV-1 infection in treatment-experienced patients aged ≥6 years. Rilpivirine, also an NNRTI, is FDA-approved for treatment of HIV-1 infection in treatment-naive adults only. At this time, there is insufficient information to consider either of these agents as initial therapy in children.

Preferred NNRTI

Efavirenz as preferred NNRTI (AI*): In clinical trials in HIV-infected adults, a PI-sparing regimen of efavirenz in combination with zidovudine and lamivudine was associated with an excellent virologic response; 70% of treated adults had plasma HIV RNA <400 copies/mL at 48 weeks.[13] In randomized controlled trials in treatment-naive adults, efavirenz-treated patients had superior or similar virologic activity compared with those receiving PI- or triple NRTI-based regimens.[14-19] Clinical trials in adults are conflicting in terms of comparative efficacy of efavirenz and nevirapine (see discussion below).[20-24] In PENPACT-1, subjects receiving efavirenz or nevirapine showed comparable virologic suppression after 4 years.[8] An analysis of children and adults starting first-line cART in Uganda demonstrated the superiority of an efavirenz-based regimen compared with a nevirapine-based regimen in 222 children and adolescents (mean age, 9.2 years).[25] Few had received nevirapine as part of a PMTCT regimen. In addition, a recent report of 761 children aged 3 to 16 years who received either efavirenz (n = 398) or nevirapine (n = 363) in the Botswana national treatment program demonstrated increased rates of virologic failure among those receiving nevirapine (OR = 2.2, 95% CI 1.5–3.4). Time to virologic failure also favored an efavirenz regimen.[26]

Efavirenz in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) or with an NRTI and a PI has been studied in HIV-infected children.[27-33] Results are comparable to those seen in adults. The appropriate dose of efavirenz for children aged <3 years has not been determined; therefore, efavirenz is not recommended for children in this age group. For children aged ≥3 years, who are unable to swallow pills, some clinicians recommend breaking open efavirenz capsules and adding the contents to food or liquid. Bioequivalence data based on bioavailability and PK support this option.[34]

The major limitations of efavirenz are central nervous system (CNS) side effects in both children and adults;

reported adverse effects include fatigue, poor sleeping patterns, vivid dreams, poor concentration, agitation, depression, and suicidal ideation. Although in most patients this toxicity is transient, in some patients the symptoms may persist or occur months after initiating efavirenz. In several studies, the incidence of such adverse effects was correlated with efavirenz plasma concentrations and the occurrence was more frequent in adults with higher levels of drug.[35-38] In patients with pre-existing psychiatric conditions, efavirenz should be used cautiously for initial therapy. Rash may also occur with efavirenz treatment; it is generally mild and transient but appears to be more common in children than adults.[31, 33] In addition, first-trimester exposure to efavirenz is potentially teratogenic (see Appendix A: Pediatric Antiretroviral Drug Information for detailed information). Although emerging information about the use of efavirenz in pregnancy is reassuring,[39] alternative regimens that do not include efavirenz should be strongly considered in adolescent females who are trying to conceive or who are not using effective and consistent contraception because of the potential for teratogenicity with first-trimester efavirenz exposure, assuming these alternative regimens are acceptable to the provider and will not compromise the woman's health **(BIII)**.

Alternative NNRTI

Nevirapine as alternative NNRTI (AI): Nevirapine has extensive clinical and safety experience in HIV-infected children and has shown ARV efficacy in a variety of combination regimens (see Appendix A: Pediatric Antiretroviral Drug Information for detailed information).[40] Nevirapine in combination with two NRTIs or with an NRTI and a PI has been studied in HIV-infected children.[41-43]

In a large adult trial (2NN trial), although virologic efficacy was comparable between nevirapine and efavirenz (plasma HIV RNA <50 copies/mL at 48 weeks in 56% of those receiving nevirapine vs. 62% of those receiving efavirenz), serious hepatic toxicity was more frequent in the nevirapine arm than the efavirenz arm (hepatic laboratory toxicity in 8%−14% of those on nevirapine, compared with 5% on efavirenz).[24] In the ARTEN trial, antiretroviral therapy-naive participants were randomized to nevirapine 200 mg twice daily, nevirapine 400 mg once daily, or ritonavir-boosted atazanavir, all in combination with tenofovir disoproxil fumarate (tenofovir)/emtricitabine. By 48 weeks, similar proportions of subjects in each group had at least 2 consecutive plasma HIV RNA levels <50 copies/mL (66.8% for nevirapine vs. 65.3% for ritonavir-boosted atazanavir) but more participants in the nevirapine arms discontinued study drugs because of adverse events (13.6% vs. 2.6%, respectively) or lack of efficacy (8.4% vs. 1.6%, respectively).[44]

Other studies in adults have indicated potentially increased risk of hepatic toxicity with nevirapine-based compared with efavirenz-based regimens.[45] In addition, data in adults indicate that symptomatic hepatic toxicity is more frequent in individuals with higher CD4 T lymphocyte (CD4 cell) counts and in women, particularly women with CD4 cell counts >250 cells/mm^3 and men with CD4 cell counts >400 cells/mm^3. A more recent study including 820 women in Kenya, Zambia, and Thailand demonstrated that hepatic toxicity was associated with elevated baseline liver function tests and not CD4 cell count at the time of nevirapine initiation.[46] In the published literature, hepatic toxicity appears to be less frequent in children receiving chronic nevirapine therapy than in adults.[42, 43, 47] In an FDA review of 783 HIV-infected pediatric patients, there was only 1 case of hepatitis, which was reported in a 17-year-old child; there was no evidence of a serious hepatic event associated with nevirapine use in any child before adolescence.[47] A recent report of 1,434 children in Malawi receiving treatment with a nevirapine-based regimen noted that only 0.14% of the children discontinued the regimen because of hepatic toxicity.[48] In contrast, skin reactions and HSRs associated with nevirapine use have been reported in children.[49] However, it should be noted that data are limited about the relationship between CD4 cell count and percentage in children at the time they initiate nevirapine and the development of toxicity. In a study of 201 HIV-infected children in Asia initiating cART (137 randomized to a nevirapine-containing regimen), the development of overall toxicities, including rash and hepatotoxicity, was almost three-fold higher in children initiating cART when CD4 percentage was ≥15%.[50] The safety of substituting efavirenz for nevirapine in patients who have experienced nevirapine-associated hepatic toxicity is unknown. Efavirenz use in this situation has been well tolerated in the very

limited number of patients in whom it has been reported but this substitution should be attempted with caution.[51]

Because of the greater potential for toxicity and possibly increased risk of virologic failure, nevirapine-based regimens are considered an alternative rather than the preferred NNRTI in children aged ≥3 years. In children aged <3 years, nevirapine is considered an alternative because of increased risk of virologic failure. Even if not exposed to nevirapine as part of PMTCT, infants on nevirapine-based regimens had higher rates of virologic failure than infants on lopinavir/ritonavir-based regimens.[3-5, 52] However, infants treated with nevirapine showed a trend toward greater improvement in both immunologic status and growth.[3]

A recent study randomized infants exposed to nevirapine who had achieved viral suppression for an average of 9 months using lopinavir/ritonavir-based therapy as part of a PMTCT regimen to continuation of the lopinavir/ritonavir regimens or a switch to a nevirapine-based regimen. After 52 weeks of follow up, plasma viremia ≥50 copies/mL occurred less frequently in the switched group compared with the continuation group. CD4 response was also better in the switched group. However, 20% of the switched group experienced breakthrough viremia (confirmed viral load >1,000 copies/mL) and subsequent analysis demonstrated that failure was associated with higher (>25%) frequencies of pretreatment NNRTI mutations.[53] These findings suggest this strategy may be an option for children in whom standard genotyping before treatment detects no NNRTI mutations but should be undertaken with careful monitoring of viral load.[9]

Similar to recommendations in adults, nevirapine also should not be used in postpubertal adolescent girls with CD4 cell counts >250/mm^3 because of the increased risk of symptomatic hepatic toxicity, unless the benefit clearly outweighs the risk.[12] Nevirapine also should be used with caution in children with elevated pretreatment liver function tests.

PI-Based Regimens (PIs [boosted or unboosted] + two-NRTI backbone)

Summary: PI-Based Regimens

Nine PIs are currently FDA-approved for use and 7 are approved for use in children. Advantages of PI-based regimens include excellent virologic potency, high barrier for development of drug resistance (requires multiple mutations), and sparing of the NNRTI drug class. However, because PIs are metabolized via hepatic enzymes the drugs have potential for multiple drug interactions. They may also be associated with metabolic complications such as dyslipidemia, fat maldistribution, and insulin resistance. Factors to consider in selecting a PI-based regimen for treatment-naive children include virologic potency, dosing frequency, pill burden, food or fluid requirements, availability of palatable pediatric formulations, drug interaction profile, toxicity profile (particularly related to metabolic complications), and availability of data in children. (Table 12 lists the advantages and disadvantages of PIs. See Appendix A: Pediatric Antiretroviral Drug Information for detailed pediatric information on each drug.)

Ritonavir acts as a potent inhibitor of the cytochrome P450 3A4 (CYP3A4) isoenzyme, thereby inhibiting the metabolism of other PIs coadministered with ritonavir. The drug has been used in low doses combined with another PI as a PK booster, increasing drug exposure by prolonging the half-life of the second, boosted PI. Boosted PI-based regimens are commonly used in treatment of adults and pediatric data are available for several combinations. Co-formulated lopinavir/ritonavir has been studied in infants as young as age 25 days[54] and is FDA-approved for use in infants after a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days. Fosamprenavir with low-dose ritonavir is FDA-approved in infants and children aged ≥4 weeks, although the Panel only recommends use in those aged 6 months and older. Darunavir with low-dose ritonavir is FDA-approved in children aged ≥3 years and atazanavir and tipranavir with low-dose ritonavir are FDA-approved in children aged ≥6 years. In addition, the use of low-dose ritonavir increases the potential for hyperlipidemia[55] and drug-drug interactions.

The Panel recommends either atazanavir with low-dose ritonavir or coformulated lopinavir/ritonavir as the preferred PI for initial therapy in children based on virologic potency in adult and pediatric studies, high barrier to development of drug resistance, excellent toxicity profile in adults and children, availability of appropriate dosing information, and experience as initial therapy in both resource-rich and resource-limited areas. Although lopinavir/ritonavir can be used in children aged ≥42 weeks postmenstrual and aged ≥14 days postnatal, at the current time, atazanavir with low-dose ritonavir should be used only in children aged ≥6 years. Two additional PIs—fosamprenavir and darunavir—can be considered as alternative PIs for use in children. Fosamprenavir is FDA-approved for treatment of HIV infection in infants aged ≥4 weeks and older. However, because of low drug exposure in infants aged <6 months, the Panel recommends use only in patients aged ≥6 months. Darunavir can also be used for children aged ≥3 years. Both fosamprenavir and darunavir should be used in combination with low-dose ritonavir. Other PIs that can be considered in special circumstances when preferred and alternative drugs are not available or are not tolerated include fosamprenavir without boosting ritonavir in children aged ≥2 years, atazanavir without boosting ritonavir in adolescents aged ≥13 years and weighing >39 kg, and nelfinavir in children aged ≥2 years. A saquinavir/ritonavir (1000/100 mg twice daily)-based regimen compared with a lopinavir/ritonavir-based regimen demonstrated comparable virologic and immunologic outcomes when used as initial therapy in treatment-naive adults.[56] However, saquinavir is not recommended for initial therapy in children because the agent is not available in a pediatric formulation and dosing and outcome data on saquinavir use in children are limited. Although good virologic and immunologic responses have been observed with indinavir-based regimens in adults, the drug is not available in a liquid formulation and high rates of hematuria, sterile leukocyturia, and nephrolithiasis in pediatric patients using indinavir have been reported.[57-60] The incidence of hematuria and nephrolithiasis with indinavir therapy may be higher in children than adults.[57, 60] Therefore, indinavir alone or with ritonavir boosting is not recommended as initial therapy in children. Tipranavir currently is not recommended for initial therapy in treatment-naive children because experience with the drug is limited.

Preferred PIs

Atazanavir with low-dose ritonavir as preferred PI (for children ≥6 years) (AI*): Atazanavir is a once-daily PI that was FDA-approved in March 2008 for use in children aged ≥6 years. It has efficacy equivalent to efavirenz-based and lopinavir/ritonavir-based combination therapy when given in combination with zidovudine and lamivudine in treatment-naive adults.[18, 61-63] Seventy-three percent of 48 treatment-naive South African children achieved viral load <400 copies/mL by 48 weeks when given atazanavir with or without low-dose ritonavir in combination with 2 NRTIs.[64] Among 43 treatment-naive children aged 6 to18 years in IMPAACT/PACTG P1020A who received the capsule formulation of atazanavir with or without ritonavir, 51% and 47% achieved viral load <400 copies/mL and <50 copies/mL, respectively, by 96 weeks.[65, 66] When given with low-dose ritonavir boosting, atazanavir achieves enhanced concentrations compared with the unboosted drug in adults and children aged ≥6 years[67-69] and in ARV-naive adults appears to be associated with fewer PI-resistance mutations at virologic failure compared with atazanavir given without ritonavir boosting.[70] The main adverse effect associated with atazanavir/low-dose ritonavir is indirect hyperbilirubinemia, with or without jaundice or scleral icterus, but without concomitant hepatic transaminase elevations. Although atazanavir is associated with fewer lipid abnormalities than other PIs, lipid levels are higher with low-dose ritonavir boosting than with atazanavir alone.[55]

Lopinavir/ritonavir as preferred PI (for infants with a postmenstrual age ≥42 weeks and postnatal age ≥14 days) (AI): In clinical trials in adults, regimens containing lopinavir/ritonavir plus 2 NRTIs have been found to have potent virologic activity in treatment-naive patients. In a comparative trial of lopinavir/ritonavir versus nelfinavir (both combined with stavudine/lamivudine), lopinavir/ritonavir had virologic efficacy superior to nelfinavir (plasma HIV RNA <400 copies/mL in 84% vs. 66% of patients, respectively), and drug-resistant virus in patients with detectable plasma viral load at 48 weeks was detected

in none of 51 lopinavir/ritonavir-treated patients, compared with 45% of 43 nelfinavir-treated patients.[71, 72] The groups had similar rates of toxicity. Lopinavir/ritonavir has been studied in both ARV-naive and -experienced children and has demonstrated durable virologic activity and low toxicity (see Appendix A: Pediatric Antiretroviral Drug Information for detailed information).[3, 73-80] In addition, dosing and efficacy data in infants as young as 25 days of age are available.[54, 77] Post-marketing reports of lopinavir/ritonavir-associated cardiac toxicity (including complete atrioventricular block, bradycardia, and cardiomyopathy), lactic acidosis, acute renal failure, CNS depression, and respiratory complications leading to death have been reported, predominantly in preterm neonates. These reports have resulted in a change in lopinavir/ritonavir labeling including a recommendation to not administer the combination to neonates until they reach a postmenstrual age of 42 weeks and a postnatal age of at least 14 days. In addition, although once-daily lopinavir/ritonavir is FDA-approved for initial therapy in adults,[81] PK data in children do not support a recommendation for once-daily dosing in children.[82, 83]

Alternative PIs

Darunavir with low-dose ritonavir as alternative PI (for children aged ≥3 years) (AI*): Darunavir combined with low-dose ritonavir is FDA-approved for ARV-naive and -experienced adults and for ARV-naive and -experienced children aged ≥3 years. In a randomized, open-label trial in adults, darunavir/ritonavir (800/100 mg once daily) was found to be non-inferior to lopinavir/ritonavir (once or twice daily), when both boosted PIs were administered in combination with tenofovir/emtricitabine. Plasma HIV RNA levels were <50 copies/mL in 84% of darunavir/ritonavir recipients and 78% of lopinavir/ritonavir recipients at 48 weeks and 79% of darunavir/ritonavir recipients and 71% of lopinavir/ritonavir recipients at 96 weeks (P <0.001, for each comparison). Adverse events were also less common in the darunavir/ritonavir group (P <0.01).[84, 85] In a study of treatment-experienced children (aged 6–17 years), twice-daily darunavir/ritonavir-based therapy was well tolerated and 48% of the children achieved HIV-1 RNA <50 copies/mL by 48 weeks.[86] In another study of treatment-experienced pediatric subjects (aged 3–<6 years and weight ≥10 kg–<20 kg), 57% of subjects had HIV-1 RNA less than 50 copies/mL and 81% were less than 400 copies/mL after 24 weeks of treatment.[87] Twenty children completed the trial; one stopped prematurely because of vomiting. Once-daily darunavir/ritonavir has been studied in treatment-naive adolescents aged 12 to 18 years (mean age, 14.6 years). After 24 weeks of treatment, 11 of 12 subjects had HIV-1 RNA <50 copies/mL.[88] Darunavir with low-dose ritonavir is recommended as an alternative initial therapy in HIV-infected children based on data from these studies and the finding of high potency and low toxicity in adults. Some experts would only recommend boosted darunavir for treatment-experienced children and reserve its use for patients with PI-resistant mutations. While twice-daily dosing of darunavir with ritonavir boosting is recommended as an alternative PI for children aged ≥3 years, once-daily dosing of darunavir currently should only be considered for treatment-naive adolescents aged >12 years.

Fosamprenavir with low-dose ritonavir as alternative PI (for children aged ≥6 months) (AI*): Fosamprenavir (the prodrug of amprenavir) is now available in a pediatric liquid formulation and a tablet formulation. Amprenavir is no longer manufactured. In June 2007, fosamprenavir suspension was FDA-approved for use in pediatric patients aged ≥2 years. The approval was based on two open-label studies in pediatric patients aged 2 to 18 years.[89, 90] In 2012, fosamprenavir was FDA-approved for use in PI-naive children as young as 4 weeks who were born at ≥38 weeks' gestation and had attained a postnatal age of 28 days. Overall, fosamprenavir was well tolerated and effective in suppressing viral load and increasing CD4 cell count (see Appendix A: Pediatric Antiretroviral Drug Information for detailed information). There is less pediatric experience with fosamprenavir than with lopinavir/ritonavir. In an adult clinical trial, fosamprenavir with low-dose ritonavir was demonstrated to be noninferior to lopinavir/ritonavir.[91] In children aged ≥4 weeks, fosamprenavir should be used in combination with low-dose ritonavir boosting to ensure adequate drug levels. In addition, because of low drug exposure, the Panel recommends fosamprenavir with low-dose ritonavir only for children aged ≥6 months. Once-daily dosing of fosamprenavir is not recommended for pediatric patients.

PIs for Use in Special Circumstances

Atazanavir without ritonavir boosting in children age ≥13 years (BII*): Although unboosted atazanavir is FDA-approved for treatment-naive adolescents aged ≥13 years who weigh >39 kg and are unable to tolerate ritonavir, data from the IMPAACT/PACTG 1020A study indicate that higher doses of unboosted atazanavir (on a mg/m^2 basis) are required in adolescents than in adults to achieve adequate drug concentrations[69] (see Appendix A: Pediatric Antiretroviral Drug Information for detailed information on dosing used in IMPAACT/PACTG P1020A). If using unboosted atazanavir in treatment-naive patients, clinicians should consider using a dual-NRTI combination other than didanosine/emtricitabine because this combination demonstrated inferior virologic response in adults in ACTG 5175.[92] If didanosine, emtricitabine, **and** atazanavir are used in combination, patients should be instructed to take didanosine and atazanavir at least 2 hours apart, to take atazanavir with food, and to take didanosine on an empty stomach.

Fosamprenavir without ritonavir boosting in children aged ≥2 years (BII*): Fosamprenavir without ritonavir boosting has been studied in children aged ≥2 years but is only recommended in special circumstances when preferred or alternative PI-based regimens cannot be used.

Nelfinavir for children aged ≥2 years (BI*): Nelfinavir in combination with two NRTIs is an acceptable PI choice for initial treatment of children aged ≥2 years in special circumstances. The pediatric experience with nelfinavir-based regimens in ARV-naive and -experienced children is extensive, with follow-up in children receiving the regimen for as long as 7 years.[93] The drug has been well tolerated—diarrhea is the primary adverse effect; however, in clinical studies the virologic potency of nelfinavir has varied greatly, with reported rates of virologic suppression ranging from 26% to 69% (see Appendix A: Pediatric Antiretroviral Drug Information for detailed information). Several studies have shown a correlation between nelfinavir trough concentrations and virologic response in treatment-naive pediatric patients.[94] In one such study, virologic response at Week 48 was observed in 29% of children with subtherapeutic nelfinavir troughs (<0.8 mg/L) versus 80% of children with therapeutic nelfinavir troughs (>0.8 mg/L).[94] The interpatient variability in plasma concentrations is great in children, with lower levels in younger children.[95-100] The optimal dose of nelfinavir in younger children, particularly in those aged <2 years, has not been well defined. These data, combined with data in adults showing inferior potency of nelfinavir compared with other PIs and efavirenz, balanced against the advantage of a PI that is not coadministered with low-dose ritonavir for boosting,[72, 101-104] make nelfinavir an agent for use in special circumstances in treatment-naive children aged ≥2 years and not recommended for treatment of children aged <2 years.

Nelfinavir is currently available only as tablets, which can be dissolved in water or other liquids to make a slurry that is then ingested by children unable to swallow whole tablets. Dissolving nelfinavir tablets in water and swallowing whole tablets resulted in comparable PK parameters in a study in adults.[105]

Selection of Dual-NRTI Backbone as Part of Initial Combination Therapy

Summary: Selection of Dual-NRTI Backbone Regimen

Currently, seven NRTIs (zidovudine, didanosine, lamivudine, stavudine, abacavir, emtricitabine, and tenofovir) are FDA-approved for use in children <13 years of age. Tenofovir is FDA-approved for use in children and adolescents aged ≥2 years. Because of decreases in bone mineral density (BMD) observed in adults and children receiving tenofovir, the Panel has opted to consider use of tenofovir based on Tanner stage and only in children aged ≥2 years. We have reserved our strongest recommendation for adolescents who are in the late stages of or who have completed puberty (Tanner stages 4 and 5). Tenofovir can be used in younger children after weighing potential risks of decreased BMD versus benefits of therapy. It is important to note that although decreases in BMD are observed, the clinical significance of these changes is not yet known. Dual-NRTI combinations form the backbone of combination regimens for both adults and children. Dual-NRTI combinations that have been studied in children include zidovudine in combination

with abacavir, didanosine, or lamivudine; abacavir in combination with lamivudine, stavudine, or didanosine; emtricitabine in combination with stavudine or didanosine; and tenofovir in combination with lamivudine or emtricitabine.[1, 29, 67, 93, 99, 106, 107, 114-119] Advantages and disadvantages of different dual-NRTI backbone options are delineated in Table 10.

Preferred Dual-NRTI Regimens

The dual-NRTI combinations preferred for initial therapy in children are abacavir or zidovudine combined with either lamivudine or emtricitabine, and in adolescents who are Tanner Stage 4 or 5, tenofovir combined with either lamivudine or emtricitabine. The most extensive experience in children is with zidovudine in combination with lamivudine **(AI*)**. Data on the safety of this combination in children are extensive and the combination is generally well tolerated. The major toxicity associated with zidovudine/lamivudine is bone marrow suppression, manifested as macrocytic anemia and neutropenia; minor toxicities include gastrointestinal toxicity and fatigue.

Both lamivudine and emtricitabine are well tolerated with few adverse effects. Although there is less experience in children with emtricitabine than with lamivudine, it is similar to lamivudine and can be substituted for lamivudine as one component of a preferred dual-NRTI backbone (that is, emtricitabine in combination with abacavir or zidovudine). The advantages of emtricitabine are that it can be administered once daily and it is available as an oral solution. Both lamivudine and emtricitabine select for the M184V resistance mutation, which is associated with high-level resistance to both drugs; a modest decrease in susceptibility to abacavir and didanosine; and improved susceptibility to zidovudine, stavudine, and tenofovir based on decreased viral fitness.[108, 109]

Abacavir in combination with lamivudine **(AI)** has been shown to be as potent or, possibly, more potent than zidovudine in combination with lamivudine in both children and adults.[110, 111] However, abacavir/lamivudine has the potential for abacavir-associated life-threatening HSRs in a small proportion of patients. In 5 years of follow-up, abacavir plus lamivudine maintained significantly better viral suppression and growth in children than did zidovudine plus lamivudine and zidovudine plus abacavir.[111] Abacavir hypersensitivity is more common in individuals with certain HLA genotypes, particularly HLA-B*5701 (see Appendix A: Pediatric Antiretroviral Drug Information); however, in the United States, the prevalence of HLA-B*5701 is much lower in African Americans and Hispanics (2%–2.5%) than in whites (8%).[112] Pretreatment screening for HLA-B*5701 before initiation of abacavir treatment resulted in a significant reduction in the rate of abacavir HSRs in HIV-infected adults (from 7.8% to 3.4%).[113] Before initiating abacavir-based therapy in HIV-infected children, genetic screening for HLA-B*5701 should be performed and children who test positive for HLA-B*5701 should not receive abacavir **(AII*)**.

Tenofovir has been studied in HIV-infected children in combination with other NRTIs and as an oral sprinkle/granule formulation.[114-117] The use of tenofovir in pediatric patients aged 2 to <18 years is approved by the FDA based on data from two randomized studies. In study 321, 87 treatment-experienced subjects aged 12 to <18 years, were randomized to receive tenofovir or placebo plus optimized background regimen (OBR) for 48 weeks. Although there was no difference in virologic response between the two groups, the safety and PKs of tenofovir in children in the study were similar to those in adults receiving tenofovir.[118] In study 352, 92 treatment-experienced children, aged 2 to <18 years with virologic suppression on stavudine- or zidovudine-containing regimens were randomized to either replace stavudine or zidovudine with tenofovir or continue their original regimen. After 48 weeks, 89% of subjects receiving tenofovir and 90% of subjects continuing their original regimen had HIV-1 RNA concentrations <400 copies/mL.[119]

Tenofovir in combination with lamivudine or emtricitabine is a preferred dual-NRTI combination for use in adolescents Tanner Stage 4 or 5 **(AI*)**. The fixed-dose combination of tenofovir and emtricitabine and the fixed-dose triple combination of tenofovir, emtricitabine, and efavirenz both allow for once-daily dosing,

which may help improve adherence in older adolescents. In studies in adults, tenofovir when used with lamivudine or emtricitabine in combination with efavirenz had potent viral suppression for up to 3 years and was superior to zidovudine/lamivudine/efavirenz in viral efficacy.[120, 121] In ACTG 5202, adults were randomly assigned to tenofovir/emtricitabine versus abacavir/lamivudine in combination with boosted atazanavir versus efavirenz (in factorial design). Among adults with screening HIV-1 RNA ≥100,000 copies per mL, the time to virologic failure and to first adverse event were both significantly shorter in patients randomly assigned to abacavir/lamivudine than in those assigned to tenofovir/emtricitabine. Results for patients with lower entry viral loads and for comparisons by assignment to efavirenz or boosted atazanavir are not yet available.[122] A study of 688 adults receiving lopinavir/ritonavir in addition to the randomized backbone of either tenofovir/emtricitabine or abacavir/lamivudine showed no difference in antiviral efficacy, safety, or tolerability at 48 weeks.[123] In nonrandomized studies, 48-week virologic efficacy of tenofovir/emtricitabine in combination with lopinavir/ritonavir was similar to that seen in trials with other dual-NRTI backbones in treatment-naive adults.[124] Also, no difference in virologic response was demonstrated in a meta-analysis of combination regimens containing tenofovir or zidovudine. However, tenofovir-containing regimens demonstrated better immunologic response, adherence, and less resistance.[125]

In some, but not all, studies, decreases in BMD have been observed in both adults and children taking tenofovir for 48 weeks.[114-117, 126, 127] At this time, data are insufficient to recommend use of tenofovir as part of a preferred regimen for initial therapy in infected children in Tanner Stages 1 through 3, for whom the risk of bone toxicity may be greatest.[114, 117] (See Appendix A: Pediatric Antiretroviral Drug Information for more detailed pediatric information.) Renal toxicity has been reported in children receiving tenofovir.[128-131] Given the potential for bone and renal toxicity, tenofovir may be more useful for treatment of children in whom other ARV drugs have failed than for initial therapy of treatment-naive younger children. Numerous drug-drug interactions with tenofovir and other ARV drugs, including didanosine, lopinavir/ritonavir, atazanavir, and tipranavir, complicate appropriate dosing of tenofovir.

Alternative Dual-NRTI Regimens

Alternative dual-NRTI combinations include zidovudine in combination with abacavir or didanosine **(BII)**, didanosine in combination with lamivudine or emtricitabine **(BI*)** and tenofovir in combination with lamivudine or emtricitabine in children and adolescents who are Tanner Stage 3 (as opposed to Tanner Stages 4 and 5, where this is a preferred dual-NRTI regimen) **(BI*)**. There is considerable experience with use of these dual-NRTI regimens in children, and in a large pediatric study, the combination of zidovudine and didanosine had the lowest rate of toxicities.[132] However, zidovudine/abacavir and zidovudine/lamivudine had lower rates of viral suppression and more toxicity leading to drug modification than did abacavir/lamivudine in 1 European pediatric study.[99, 111] The combination of didanosine and emtricitabine allows for once-daily dosing. In a study of 37 treatment-naive children aged 3 to 21 years, long-term virologic suppression was achieved with a once-daily regimen of didanosine, emtricitabine, and efavirenz; 72% of subjects maintained HIV RNA suppression to <50 copies/mL through 96 weeks of therapy.[29] Prescribing information for didanosine recommends administration on an empty stomach. However, this is impractical for infants who must be fed frequently and it may decrease medication adherence in older children because of the complexity of the regimen. A comparison of didanosine given with or without food in children found that systemic exposure was similar but with slower and more prolonged absorption with food.[133] To improve adherence, some practitioners recommend administration of didanosine without regard to timing of meals for young children. However, data are inadequate to allow a strong recommendation at this time, and it is preferable to administer didanosine under fasting conditions when possible.

Dual-NRTI Regimens for Use in Special Circumstances

The dual-NRTI combinations of stavudine with lamivudine or emtricitabine in children of any age are recommended for use in special circumstances. Stavudine is recommended for use only in special circumstances because the ARV is associated with a higher risk of lipoatrophy and hyperlactatemia than

other NRTI drugs.[134-136] Children receiving dual-NRTI combinations containing stavudine had higher rates of clinical and laboratory toxicities than children receiving zidovudine-containing combinations.[132] In children with anemia in whom there are concerns related to abacavir hypersensitivity and who are too young to receive tenofovir, stavudine may be preferable to zidovudine for initial therapy because of its lower incidence of hematologic toxicity.

In children aged ≥2 who are prepubertal or in the early stages of puberty (Tanner Stages 1 and 2), tenofovir in combination with lamivudine or emtricitabine is also recommended for use in special circumstances. As discussed above, the use of tenofovir during puberty when bone toxicity may be greatest may require caution. However, tenofovir may be a reasonable choice for initial therapy in children with demonstrated resistance to other NRTIs, co-infection with hepatitis B virus, or in those desiring a once-daily NRTI where abacavir is not an option. The Panel awaits additional safety data, especially with the recently licensed powder formulation, before providing a broader recommendation in younger children.

Dual-NRTI Regimens Not Recommended

Certain dual-NRTI drug combinations are not recommended. These include zidovudine plus stavudine because of virologic antagonism. The drug structure of emtricitabine is similar to lamivudine and the same single resistance mutation confers cross resistance, so these drugs should not be used in combination. The dual-NRTI combination of stavudine/didanosine is also not recommended for use as initial therapy because of potentially greater toxicity. In small pediatric studies, stavudine/didanosine demonstrated virologic efficacy and was well tolerated.[106, 107, 137] However, in studies in adults, stavudine plus didanosine-based combination regimens were associated with greater rates of neurotoxicity, pancreatitis, hyperlactatemia and lactic acidosis, and lipodystrophy than therapies based on zidovudine plus lamivudine;[138, 139] in addition, cases of fatal and nonfatal lactic acidosis with pancreatitis/hepatic steatosis have been reported in women receiving this combination during pregnancy.[134, 140] Abacavir/didanosine, abacavir/tenofovir, and didanosine/tenofovir are not recommended as dual-NRTI backbones in initial therapy on the basis of insufficient data in children.

All-NRTI Regimens

Triple-NRTI regimens are attractive for use in HIV-infected pediatric patients as initial therapy because of the ease of administration, availability of palatable liquid formulations, demonstrated tolerance, and avoidance of many drug interactions. Data on the efficacy of triple-NRTI regimens for treatment of ARV-naive children are limited; in small observational studies, response rates of 47% to 50% have been reported.[141, 142] In adult trials, these regimens have shown less potent virologic activity when compared with NNRTI- or PI-based regimens. Based on the results of these clinical trials, the Panel recommends that a three-NRTI-based regimen consisting of zidovudine plus lamivudine plus abacavir should be used only in special circumstances when a preferred or alternative NNRTI-based or PI-based regimen cannot be used as first-line therapy in treatment-naive children (such as because of significant drug interactions or concerns related to adherence) **(BI*)**.

Following is a discussion of findings in clinical trials of triple-NRTI regimens.

Zidovudine + lamivudine + abacavir: The triple-NRTI combination of zidovudine + lamivudine + abacavir has been demonstrated to have virologic efficacy comparable to indinavir-[143] or nelfinavir-containing regimens[144] but was inferior to an efavirenz-based regimen.[14, 145] In a study of this regimen in previously treated children, the combination showed evidence of only modest viral suppression, with only 10% of 102 children maintaining a viral load of <400 copies/mL at 48 weeks of treatment.[146]

Other triple-NRTI regimens: Clinical trials in adults also have investigated triple-NRTI regimens consisting of stavudine + didanosine + lamivudine, stavudine + lamivudine + abacavir, and didanosine + stavudine + abacavir.[147, 148] The virologic response to all these regimens was inferior to viral suppression achieved in comparator regimens. In addition, the M184V lamivudine drug-resistance mutation was seen more frequently

in patients treated with triple-NRTI regimens containing lamivudine. Tenofovir + abacavir + lamivudine and tenofovir + didanosine + lamivudine demonstrate significantly increased rates of virologic failure and are not recommended.[149-151] The tenofovir + zidovudine + lamivudine combination demonstrated antiviral activity in adults; however, no comparative data are available and the regimen is not recommended.[152]

Regimens Not Recommended for Initial Therapy of Antiretroviral-Naive Children

Not Recommended for Initial Therapy for Children Because of Insufficient Data

A number of ARV drugs and drug regimens are not recommended for initial therapy of ARV-naive children because of insufficient pediatric data **(AIII)**. These are summarized below.

Regimens containing three drug classes: Data are insufficient to recommend initial regimens containing agents from three drug classes (e.g., NRTI plus NNRTI plus PI). Although efavirenz plus nelfinavir plus one or two NRTIs was shown to be safe and effective in HIV-infected children with prior NRTI therapy, this regimen was not studied as initial therapy in treatment-naive children and has the potential for inducing resistance to three drug classes, which could severely limit future treatment options.[30-32]

Regimens containing three NRTIs and an NNRTI: Data are currently insufficient to recommend a regimen of three NRTIs plus an NNRTI in young infants. A recent review of nine cohorts from 13 European countries contributed data on HIV-infected infants born from 1996 through 2008 who initiated therapy before age 12 months. Superior responses to this four-drug regimen were observed compared to boosted PI or three-drug NRTI regimens.[153] It is speculated that poor tolerance and adherence to a PI-based regimen may account for differences. Based on demonstated benefits of recommended three-drug regimens and lack of additional safety and efficacy data on the four-drug regimen, the Panel currently does not recommend this regimen.

New agents without sufficient pediatric data to recommend use as initial therapy (Tables 13 and 14): At this time several new agents that appear promising for use in adults do not have sufficient pediatric PK and safety data to recommend their use as components of an initial therapeutic regimen in children. These agents include maraviroc (a CCR5 antagonist), raltegravir and elvitegravir (both integrase inhibitors), and etravirine and rilpivirine (both NNRTIs). Raltegravir is FDA-approved for treatment of HIV-1-infected children aged ≥2 years and weight ≥10 kg. It is available in film-coated tablets and chewable tablets. Oral granules for suspension are currently under investigation. Safety and efficacy data are promising, but at this time, data are insufficient to recommend as initial therapy.[154-156] In June 2008, FDA approved tipranavir boosted with ritonavir for use in treatment-experienced children aged 2 to 18 years; however, data are insufficient to consider use of the agent for initial therapy. Elvitegravir, another integrase inhibitor, is only available as a fixed-dose combination tablet containing elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate, and is FDA-approved for use as a complete ARV regimen in HIV-1-infected ARV treatment-naive adults. It is not FDA-approved for use in children aged <18 years. There are no data on its use in individuals younger than age 18 years, and it cannot be considered for use as initial therapy for children at this time (http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203100s000lbl.pdf).

Enfuvirtide, a fusion inhibitor, is FDA-approved for use in combination with other ARV drugs to treat children aged ≥6 years who have evidence of HIV replication despite ongoing cART (that is, treatment-experienced children on nonsuppressive regimens). The drug must be administered subcutaneously twice daily and is associated with a high incidence of local injection site reactions (98%). Currently, data are insufficient to recommend use of enfuvirtide for initial therapy of children.

Antiretroviral Drug Regimens that Should Never be Recommended (Table 9)

Several ARV drugs and drug regimens are not recommended for use in therapy of children or adults. These are summarized below. Clinicians should be aware of the components of fixed-drug combinations so that

patients do not inadvertently receive a double dose of a drug contained in such a combination.

The following regimens or regimen components should <u>never</u> be offered to HIV-infected children:

- *A single ARV drug (monotherapy)* **(AII)**
- *Two NRTIs alone* **(AI)**
- *Certain dual-NRTI combinations as part of a combination regimen:*
  - *Lamivudine + emtricitabine because of similar resistance patterns and no additive benefit* **(AIII)**
  - *Zidovudine + stavudine because of virologic antagonism* **(AII)**
- *Dual-NNRTI combinations* **(AI*)**
- *Unboosted saquinavir, darunavir, or tipranavir* **(AII*)**
- *Atazanavir + indinavir* **(AIII)**
- *Certain NRTI-only regimens*
  - *Tenofovir + didanosine + (lamivudine or emtricitabine)* **(AI*)**
  - *Tenofovir + abacavir + (lamivudine or emtricitabine)* **(AI*)**

Monotherapy: Therapy with a single ARV drug is not recommended for HIV treatment because monotherapy is unlikely to result in sustained viral suppression, leading to development of viral resistance to the drug used and cross resistance to other drugs in the same drug class. However, use of zidovudine alone is appropriate for prophylaxis for the newborn of an HIV-infected mother. In this setting, 6 weeks of monotherapy with zidovudine is recommended for the infant. In the event the infant is identified as HIV infected, zidovudine should be discontinued and standard triple therapy initiated.[140]

In a child with treatment failure associated with drug resistance and persistent nonadherence, monotherapy using an interim bridging regimen of lamivudine alone can be considered. Bridging regimens have been reported to be effective in delaying immunologic decline in adults with failing combination therapy, often because of to nonadherence.[157, 158] Bridging regimens should not be considered as initial therapy and should only be used in the interim as a clinician works intensively with the patient and caregivers to improve adherence before initiating a new, suppressive cART regimen (see Approach to the Management of Antiretroviral Treatment Failure).

Dual-nucleoside regimens alone: Dual-NRTI therapy alone is not recommended for initial therapy because it is unlikely to result in sustained viral suppression, leading to development of viral resistance to the drugs being used and cross resistance to other drugs within the same drug class. For children who have achieved viral suppression on a previously initiated dual-NRTI regimen, it is reasonable to either continue on this therapy or to add a PI or a NNRTI to the regimen. However, a child remaining on a dual-NRTI regimen should be switched to a 3-or-more drug combination if viral rebound occurs (see Management of Treatment-Experienced Infants, Children, and Adolescents).

Certain dual-nucleoside backbone combinations: Certain dual-NRTI combinations (zidovudine + stavudine, emtricitabine + lamivudine) are not recommended for therapy at any time because of antagonism or inferior virologic response. Emtricitabine should not be used in combination with lamivudine because the NRTIs share a similar drug structure and the same single resistance mutation (M184V) induces resistance to both drugs.

Dual NNRTIs: An adult study (2NN) demonstrated increased toxicity with the combination of nevirapine plus efavirenz.[24]

Certain PIs: The combination of atazanavir plus indinavir has the potential for additive hyperbilirubinemia. Unboosted saquinavir, darunavir, and tipranivir have low bioavailablity and do not achieve adequate drug levels; therefore, they should not be used without ritonavir boosting.

Three-NRTI regimen of tenofovir + (didanosine or abacavir) + (lamivudine or emtricitabine): The triple-NRTI combinations of tenofovir with (didanosine or abacavir) plus (lamivudine or emtricitabine) have a high rate of early virologic nonresponse when used as initial therapy in treatment-naive adults and are not recommended as combination therapy for children at any time.[149-151]

Table 8. ARV Regimens Recommended for Initial Therapy for HIV Infection in Children (page 1 of 2)

A combination ARV regimen in treatment-naive children generally contains 1 NNRTI plus a 2-NRTI backbone or 1 PI plus a 2-NRTI backbone. Regimens should be individualized based on advantages and disadvantages of each combination (see Tables 10–14).

Preferred Regimens	
Children aged ≥14 days to <3 years[a]	Two NRTIs ***plus*** LPV/r
Children aged ≥3 years	Two NRTIs ***plus*** EFV[b] Two NRTIs ***plus*** LPV/r
Children aged ≥6 years	Two NRTIs ***plus*** ATV ***plus*** low-dose RTV Two NRTIs ***plus*** EFV[b] Two NRTIs ***plus*** LPV/r
Alternative Regimens	
Children of any age	Two NRTIs ***plus*** NVP[c]
Children aged ≥3 years	Two NRTIs ***plus*** DRV ***plus*** low-dose RTV
Children aged ≥6 months[d]	Two NRTIs ***plus*** FPV ***plus*** low-dose RTV
Regimens for Use in Special Circumstances	
Two NRTIs ***plus*** ATV unboosted (for treatment-naive adolescents aged ≥13 years and weight >39 kg) Two NRTIs ***plus*** FPV unboosted (children aged ≥2 years) Two NRTIs ***plus*** NFV (children aged ≥2 years) Zidovudine ***plus*** 3TC ***plus*** ABC	
2-NRTI Backbone Options for Use in Combination with Additional Drugs (in alphabetical order)	
Preferred	ABC ***plus*** (3TC ***or*** FTC) (children aged ≥3 months) TDF ***plus*** (3TC ***or*** FTC) (adolescents, Tanner Stage 4 or 5) ZDV ***plus*** (3TC ***or*** FTC)
Alternative	ddI ***plus*** (3TC ***or*** FTC) TDF ***plus*** (3TC ***or*** FTC) (adolescents,Tanner Stage 3) ZDV ***plus*** ABC ZDV ***plus*** ddI
Use in Special Circumstances	d4T ***plus*** (3TC ***or*** FTC) TDF ***plus*** (3TC ***or*** FTC) (prepubertal children aged ≥2 years and adolescents, Tanner Stage 1 or 2)
Not Recommended for Initial Therapy	
ETR-containing regimens EFV-containing regimens for children aged <3 years TPV-containing regimens SQV-containing regimens	

Table 8. ARV Regimens Recommended for Initial Therapy for HIV Infection in Children (page 2 of 2)

Not Recommended for Initial Therapy
IDV-containing regimens
Dual (full-dose) PI regimens
Full-dose RTV or use of RTV as the sole PI
Unboosted ATV-containing regimens in children aged <13 years and/or weight <39 kg
NFV-containing regimens for children aged <2 years
Unboosted DRV-containing regimens
Once-daily dosing of boosted DRV in children aged <12 years
Once-daily dosing of LPV/r or boosted or unboosted FPV
Triple-NRTI regimens other than ABC + ZDV + 3TC
Triple-class regimens, including NRTI ***plus*** NNRTI ***plus*** PI
Four-drug regimens with three NRTIs ***plus*** NNRTI
Regimens with dual-NRTI backbones of ABC + ddI, ABC + TDF, and ddI + TDF
TDF-containing regimens in children aged <2 years
MVC-containing regimens
RPV-containing regimens
RAL-containing regimens
T-20-containing regimens
EVG-containing regimens

[a] LPV/r should not be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days.

[b] EFV should be used only in children aged ≥3 years with weight ≥10 kg. Unless adequate contraception can be ensured, EFV-based therapy is not recommended for adolescent females who are sexually active and may become pregnant.

[c] NVP should not be used in postpubertal girls with CD4 count >250/mm^3, unless the benefit clearly outweighs the risk.

[d] FPV with low dose ritonavir should only be administered to infants born at ≥38 weeks gestation who have attained a postnatal age of 28 days and to infants born before 38 weeks gestation who have reached a postmenstrual age of 42 weeks.

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, ARV = antiretroviral, ATV = atazanavir, d4T = stavudine, ddI = didanosine, DRV = darunavir, EFV = efavirenz, ETR = etravirine, EVG = elvitegravir, FPV = fosamprenavir, FTC = emtricitabine, IDV = indinavir, LPV/r = lopinavir/ritonavir, MVC = maraviroc, NFV = nelfinavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, RAL = raltegravir, RTV = ritonavir, SQV = saquinavir, T-20 = enfuvirtide, TDF = tenofovir, RPV = rilpivirine, TPV = tipranavir, ZDV = zidovudine

Table 9. ARV Regimens or Components that Should Never Be Recommended for Treatment of HIV Infection in Children

	Rationale	Exceptions
ARV regimens never recommended for children		
One ARV drug alone (monotherapy)	• Rapid development of resistance • Inferior antiviral activity compared with combination including ≥3 ARV drugs	• HIV-exposed infants (with negative viral testing) during 6-week period of prophylaxis to prevent perinatal transmission of HIV • 3TC or FTC interim "bridging regimen" in special circumstances of children with treatment failure associated with drug resistance and persistent nonadherence
Two NRTIs alone	• Rapid development of resistance • Inferior antiviral activity compared with combination including ≥3 ARV drugs	• Not recommended for initial therapy • For patients currently on 2 NRTIs alone who achieve virologic goals, some clinicians may opt to continue this treatment.
TDF ***plus*** ABC ***plus*** (3TC ***or*** FTC) as a triple-NRTI regimen	• High rate of early viral failure when this triple-NRTI regimen used as initial therapy in treatment-naive adults	• No exceptions
TDF ***plus*** ddI ***plus*** (3TC ***or*** FTC) as a triple-NRTI regimen	• High rate of early viral failure when this triple-NRTI regimen used as initial therapy in treatment-naive adults	• No exceptions
ARV components never recommended as part of an ARV regimen for children		
ATV ***plus*** IDV	• Potential additive hyperbilirubinemia	• No exceptions
Dual-NNRTI combinations	• Enhanced toxicity	• No exceptions
Dual-NRTI combinations: • 3TC ***plus*** FTC • d4T ***plus*** ZDV	• Similar resistance profile and no additive benefit • Antagonistic effect on HIV	• No exceptions • No exceptions
EFV in first trimester of pregnancy or for sexually active adolescent girls of childbearing potential when reliable contraception cannot be ensured	• Potential for teratogenicity	• When no other ARV option is available and potential benefits outweigh risks
NVP in adolescent girls with CD4 count >250 cells/mm^3 or adolescent boys with CD4 count >400 cells/mm^3	• Increased incidence of symptomatic (including serious and potentially fatal) hepatic events in these patient groups	• Only if benefit clearly outweighs risk
Unboosted SQV, DRV, or TPV	• Poor oral bioavailablity • Inferior virologic activity compared with other PIs	• No exceptions

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, ARV = antiretroviral, ATV = atazanavir, d4T = stavudine, ddI = didanosine, DRV = darunavir, EFV = efavirenz, FTC = emtricitabine, IDV = indinavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, SQV = saquinavir, TDF = tenofovir, TPV = tipranavir, ZDV = zidovudine

Table 10. Advantages and Disadvantages of Different NRTI Backbone Combinations for Use in Combination ARV Regimens for Initial Therapy in Children (page 1 of 2) (see Pediatric Antiretroviral Drug Information Appendix for more information)

	Advantages	Disadvantages
Preferred Combinations		
ABC ***plus*** (3TC ***or*** FTC)	• Palatable liquid formulations • Can give with food • ABC and 3TC are coformulated as a single pill for older/larger patients.	• Risk of ABC HSR; perform HLA-B*5701 screening before initiation of ABC treatment.
ZDV ***plus*** (3TC ***or*** FTC)	• Extensive pediatric experience • ZDV and 3TC are coformulated as single pill for older/larger patients. • Palatable liquid formulations • Can give with food • FTC is available as a palatable liquid formulation administered once daily.	• Bone marrow suppression with ZDV • Lipoatrophy with ZDV
TDF ***plus*** (3TC ***or*** FTC) for adolescents, Tanner Stage 4 or 5	• Resistance slow to develop • Once-daily dosing for TDF • Less mitochondrial toxicity than other NRTIs • Can give with food • Bone toxicity may be less in postpubertal children. • TDF and FTC are coformulated as single pill for older/larger patients.	• Limited pediatric experience • Potential bone and renal toxicity • Appropriate dosing is complicated by numerous drug-drug interactions with other ARV agents including ddI, LPV/r, ATV, and TPV.
Alternative Combinations		
ddI ***plus*** (3TC ***or*** FTC)	• Delayed-release capsules of ddI may allow once-daily dosing in older children able to swallow pills and who can receive adult dosing along with once-daily FTC. • FTC available as a palatable liquid formulation administered once daily.	• Food effect (ddI is recommended to be taken 1 hour before or 2 hours after food). Some experts give ddI without regard to food in infants or when adherence is an issue (ddI can be coadministered with FTC or 3TC). • Limited pediatric experience using delayed-release ddI capsules in younger children • Pancreatitis, neurotoxicity with ddI
TDF ***plus*** (3TC ***or*** FTC) for adolescents, Tanner Stage 3	• Resistance slow to develop • Once-daily dosing for TDF • Less mitochondrial toxicity than other NRTIs • Can give with food • TDF and FTC are coformulated as single pill for older/larger patients. • Available as reduced-strength tablets and oral powder for use in younger children	• Limited pediatric experience • Potential for bone and renal toxicity • Numerous drug-drug interactions with other ARV agents including ddI, LPV/r, ATV, and TPV complicate appropriate dosing.

Table 10. Advantages and Disadvantages of Different NRTI Backbone Combinations for Use in Combination ARV Regimens for Initial Therapy in Children (page 2 of 2) (see Pediatric Antiretroviral Drug Information Appendix for more information)

	Advantages	Disadvantages
Alternative Combinations, continued		
ZDV ***plus*** ABC	• Palatable liquid formulations • Can give with food	• Risk of ABC HSR; perform HLA-B*5701 screening before initiation of ABC treatment. • Bone marrow suppression and lipoatrophy with ZDV
ZDV ***plus*** ddI	• Extensive pediatric experience • Delayed-release capsules of ddI may allow once-daily dosing of ddI in older children able to swallow pills and who can receive adult doses.	• Bone marrow suppression and lipoatrophy with ZDV • Pancreatitis, neurotoxicity with ddI • ddI liquid formulation is less palatable than 3TC or FTC liquid formulation. • Food effect (ddI is recommended to be taken 1 hour before or 2 hours after food). Some experts give ddI without regard to food in infants or when adherence is an issue.
Use in Special Circumstances		
d4T ***plus*** (3TC ***or*** FTC)	• Extensive pediatric experience • Palatable liquid formulations • Can give with food • FTC is available as a palatable liquid formulation administered once daily.	• d4T associated with higher incidence of hyperlactatemia/lactic acidosis, lipoatrophy, peripheral neuropathy, hyperlipidemia • Limited pediatric experience with d4T plus FTC
TDF ***plus*** (3TC ***or*** FTC) for children, Tanner Stage 1 or 2	• Resistance slow to develop • Once-daily dosing for TDF • Less mitochondrial toxicity than other NRTIs • Can give with food • Bone toxicity may be less in postpubertal children. • TDF and FTC are coformulated as single pill for older/larger patients. • Available as reduced strength tablets and oral powder for use in younger children	• Limited pediatric experience • Potential bone and renal toxicity • Numerous drug-drug interactions with other ARV agents including ddI, LPV/r, ATV, and TPV complicate appropriate dosing.
Not Recommended		
3TC ***plus*** FTC	• None	• Similar drug structure • Single mutation (M184V) associated with resistance to both drugs
d4T ***plus*** ddI	• Has shown antiviral activity in small studies in children • Although not recommended for initial therapy, it can be considered for use in ARV-experienced children who require a change in therapy.	• Significant toxicities including lipoatrophy, peripheral neuropathy, hyperlactatemia including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis
ZDV ***plus*** d4T	• None	• Pharmacologic and antiviral antagonism

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, ARV = antiretroviral, ATV = atazanavir, d4T = stavudine, ddI = didanosine, FTC = emtricitabine, HSR = hypersensitivity reaction, LPV/r = lopinavir/ritonavir, NRTI = nucleoside reverse transcriptase inhibitor, PK = pharmacokinetic, TDF = tenofovir, TPV = tipranavir, ZDV = zidovudine

Table 11. Advantages and Disadvantages of Different NNRTIs for Use in Combination ARV Regimens for Initial Therapy in Children (page 1 of 2) (see Pediatric Antiretroviral Drug Information Appendix for more information)

	Advantages	Disadvantages
General Issues		
NNRTI-based Regimens	**NNRTI Class Advantages:** • Less dyslipidemia and fat maldistribution than PIs • PI sparing • Lower pill burden than PIs for children taking solid formulation; easier to use and adhere to than PI-based regimens.	**NNRTI Class Disadvantages:** • Single mutation can confer resistance, with cross resistance between EFV and NVP. • Rare but serious and potentially life-threatening cases of skin rash, including SJS, and hepatic toxicity with all NNRTIs (but highest with nevirapine) • Potential for multiple drug interactions due to metabolism via hepatic enzymes (e.g., CYP3A4)
Preferred		
EFV (for children aged ≥3 years who can take capsules)	• Potent ARV activity • Once-daily administration • Can give with food (but avoid high-fat meals)	• Neuropsychiatric adverse effects (bedtime dosing recommended to reduce CNS effects) • Rash (generally mild) • No commercially available liquid • No data on dosing for children aged <3 years • Teratogenic in primates; use with caution in adolescent females of childbearing age.
Alternative		
NVP	• Liquid formulation available • Dosing information for young infants available • Can give with food	• Reduced virologic efficacy in young infants, regardless of exposure to NVP as part of a PMTCT regimen • Higher incidence of rash/HSR than other NNRTIs • Higher rates of serious hepatic toxicity than EFV • Decreased virologic response compared with EFV • Need to initiate therapy with a lower dose and increase in a stepwise fashion. This is to allow for auto-induction of NVP metabolism and is associated with a lower incidence of toxicity. • Twice-daily dosing
Not Recommended		
EFV (for children aged <3 years)	• Potent ARV activity • Once-daily administration • Can give with food (but avoid high-fat meals)	• Neuropsychiatric adverse effects (bedtime dosing recommended to reduce CNS effects) • Rash (generally mild) • No commercially available liquid • No data on dosing for children aged <3 years • Teratogenic in primates; use with caution in adolescent females of childbearing age.

Table 11. Advantages and Disadvantages of Different NNRTIs for Use in Combination ARV Regimens for Initial Therapy in Children (page 2 of 2) (see Pediatric Antiretroviral Drug Information Appendix for more information)

	Advantages	Disadvantages
Not Recommended, continued		
ETR	• Three or more baseline NNRTI mutations result in a decreased virologic response. • Patients with a history of NNRTI-related rash do not appear to be at increased risk of ETR-related rash.	• Limited data on pediatric dosing or safety • No pediatric formulation available • Food effect (should be given with food) • No data in treatment-naive patients • Multiple drug interactions with PIs and other medications • Twice-daily dosing • Skin rash
RPV	• Once-daily administration • Reduced CNS effects compared with EFV • Not associated with embryofetal abnormalitites	• No data on pediatric dosing or safety • No pediatric formulation available • Compared with EFV, has higher rate of treatment failure and cross resistance to the NNRTI class in adults • Adults with viral loads >100,000 copies/mL are more likely to experience virologic failure than are patients with viral loads <100,000 copies/mL.

Key to Abbreviations: ARV = antiretroviral, CNS = central nervous system, CYP3A4 = cytochrome P450, EFV = efavirenz, ETR = etravirine, HSR = hypersensitivity reaction, NNRTI = non-nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, PMTCT = prevention of mother-to-child transmission, SJS = Stevens-Johnson syndrome, RPV= rilpivirine

Table 12. Advantages and Disadvantages of Different PIs for Use in Combination ARV Regimens for Initial Therapy in Children (page 1 of 4) (see Pediatric Antiretroviral Drug Information Appendix for more information)

	Advantages	Disadvantages
General Issues		
PI-based Regimens	**PI Class Advantages:** • NNRTI sparing • Clinical, virologic, and immunologic efficacy well documented • Resistance to PIs requires multiple mutations • Targets HIV at 2 steps of viral replication (viral reverse transcriptase and protease enzymes)	**PI Class Disadvantages:** • Metabolic complications including dyslipidemia, fat maldistribution, insulin resistance • Potential for multiple drug interactions because of metabolism via hepatic enzymes (e.g., CYP3A4) • Higher pill burden than NRTI- or NNRTI-based regimens for patients taking solid formulations • Poor palatability of liquid preparations, which may affect adherence to treatment regimen
Preferred		
ATV in combination with low-dose RTV in children aged ≥6 years	• Once-daily dosing • ATV has less effect on TG and total cholesterol levels than other PIs (but RTV boosting may be associated with elevations in these parameters).	• No liquid formulation • Food effect (should be administered with food) • Indirect hyperbilirubinemia common but asymptomatic • Must be used with caution in patients with pre-existing conduction system defects (can prolong PR interval of ECG)
LPV/r	• Coformulated liquid and tablet formulations • Tablets can be given without regard to food but may be better tolerated when taken with meal or snack.	• Poor palatability of liquid formulation (bitter taste), although palatability of combination better than RTV alone • Food effect (liquid formulation should be administered with food) • RTV component associated with large number of drug interactions (see RTV) • Should not be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days • Must be used with caution in patients with pre-existing conduction system defects (can prolong PR and QT interval of ECG)
Alternative		
DRV in combination with low-dose RTV in children aged ≥3 years	• Effective in PI-experienced children when given with low-dose RTV boosting	• Pediatric pill burden high with current tablet dose formulations • No liquid formulation • Food effect (should be given with food) • Must be given with RTV boosting to achieve adequate plasma concentrations • Contains sulfa moiety. The potential for cross sensitivity between DRV and other drugs in sulfonamide class is unknown. • Cannot administer once daily in children aged <12 years

Table 12. Advantages and Disadvantages of Different PIs for Use in Combination ARV Regimens for Initial Therapy in Children (page 2 of 4) (see Pediatric Antiretroviral Drug Information Appendix for more information)

	Advantages	Disadvantages
FPV in combination with low-dose RTV in children aged ≥6 months	• Oral prodrug of APV with lower pill burden • Pediatric formulation available, which should be given to children with food	• Skin rash • More limited pediatric experience than preferred PI • Must be given with food to children • RTV component associated with large number of drug interactions (see RTV) • Contains sulfa moiety. Potential for cross sensitivity between FPV and other drugs in sulfonamide class is unknown. • Should only be administered to infants born at ≥38 weeks' gestation and who have attained a postnatal age of 28 days
Use in Special Circumstances		
ATV (unboosted) in treatment-naive adolescents aged ≥13 years and weight >39 kg who are unable to tolerate RTV	• Once-daily dosing • Less effect on TG and total cholesterol levels than other PIs	• No liquid formulation • Food effect (should be administered with food) • Indirect hyperbilirubinemia common but asymptomatic • Must be used with caution in patients with pre-existing conduction system defects (can prolong PR interval of ECG) • May require RTV boosting in treatment-naive adolescent patients to achieve adequate plasma concentrations • Unboosted ATV cannot be used with TDF
FPV (unboosted) in children aged ≥2 years	• Oral prodrug of APV with lower pill burden • Pediatric formulation available • Can give with food	• Skin rash • More limited pediatric experience than preferred PI • May require boosted regimen to achieve adequate plasma concentrations; PK data to define appropriate dosing not yet available.
NFV in children aged ≥2 years	• Can give with food • Simplified 2-tablet (625 mg) twice-daily regimen has a reduced pill burden compared with other PI-containing regimens in older patients where the adult dose is appropriate.	• Diarrhea • Food effect (should be administered with food) • Appropriate dosage for younger children not well defined • Need for 3-times-daily dosing for younger children • Adolescents may require higher doses than adults • Less potent than boosted PIs

Table 12. Advantages and Disadvantages of Different PIs for Use in Combination ARV Regimens for Initial Therapy in Children (page 3 of 4) (see Pediatric Antiretroviral Drug Information Appendix for more information

	Advantages	Disadvantages
Not Recommended		
ATV (unboosted) in children aged <13 years and/or weight <39 kg	• Once-daily dosing (aged >13 years) • Less effect on TG and total cholesterol levels than other PIs	• Drug levels low if used without RTV boosting • No liquid formulation • Food effect (should be administered with food) • Indirect hyperbilirubinemia common but asymptomatic • Must be used in caution in patients with pre-existing conduction system defects (can prolong PR interval of ECG) • May require RTV boosting in treatment-naive adolescent patients to achieve adequate plasma concentrations
IDV (unboosted or boosted)	• Can be considered for use as component of a regimen in combination with low-dose RTV in postpubertal adolescents who weigh enough to receive adult dosing	• Only available in capsule • Possible higher incidence of nephrotoxicity in children • Requires 3-times-daily dosing unless boosted with RTV • High fluid intake required to prevent nephrolithiasis • Food effect (should be taken 1 hour before or 2 hours after food) • Limited pediatric PK data
NFV in children aged <2 years	• Can give with food	• Diarrhea • Food effect (should be administered with food) • Appropriate dosage for younger children not well defined • Need for 3-times-daily dosing for younger children • Adolescents may require higher doses than adults • Less potent than boosted PIs
RTV (full dose as single PI)	• Liquid formulation • Can give with food	• Poor palatability of liquid (bitter taste) • GI intolerance • Food effect (should be administered with food) • Large number of drug interactions (most potent inhibitor of CYP3A4)
SQV (unboosted or boosted)		• Low bioavailability, should never be used as sole PI • Limited pediatric PK data; will require boosting with another PI (e.g., RTV) to achieve adequate concentrations. • No liquid formulation • High pill burden • Must be taken with food • Potential for photosensitivity reactions

Table 12. Advantages and Disadvantages of Different PIs for Use in Combination ARV Regimens for Initial Therapy in Children (page 4 of 4) (see Pediatric Antiretroviral Drug Information Appendix for more information)

	Advantages	Disadvantages
TPV	• Effective in PI-experienced children and adults when given with low-dose RTV boosting • Liquid formulation	• Limited data in treatment-naive patients • Food effect (should be administered with food) • Must be given with RTV boosting to achieve adequate plasma concentrations

Key to Abbreviations: APV = amprenavir, ARV = antiretroviral, ATV = atazanavir, CYP3A4 = cytochrome P450, DRV = darunavir, ECG = electrocardiogram, FPV = fosamprenavir, GI = gastrointestinal, IDV = indinavir, LPV/r = lopinavir/ritonavir, NFV = nelfinavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, PK = pharmacokinetic, RTV = ritonavir, SQV = saquinavir, TDF = tenofovir, TG = triglyceride, TPV = tipranavir

Table 13. Advantages and Disadvantages of Entry Inhibitors for Use in Combination ARV Regimens (see Pediatric Antiretroviral Drug Information Appendix for more information)

	Advantages	Disadvantages
General Issues		
Entry Inhibitors	**Entry Inhibitor Class Advantages:** • Susceptibility of HIV to a new class of ARVs	**Entry Inhibitor Class Disadvantages:** • Rapid development of resistance with T-20 • CCR5 inhibitors are ineffective against CXCR4 virus, mixed CCR5 and CXCR4 viral populations, or dual-tropic virus.
Use in Special Circumstances		
T-20	• Susceptibility of HIV to a new class of ARVs • Route of administration ensures adequate drug levels	• Twice-daily subcutaneous injections • 98%–100% incidence of local injection site reactions • Poor adherence and limited levels of success in adolescents because of local site reactions
Insufficient Data to Recommend		
MVC	• Susceptibility of HIV to a new class of ARVs • Can give with food	• Ineffective against CXCR4 or mixed/dual-tropic viral populations • Limited data on pediatric dosing or safety • No pediatric formulation • Multiple drug interactions; different dosing depending on NNRTI or PI coadministered with MVC.

Key to Abbreviations: ARV = antiretroviral, MVC = maraviroc, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, T-20 = enfuvirtide

Table 14. Advantages and Disadvantages of Integrase Inhibitors for Use in Combination ARV Regimens

	Advantages	Disadvantages
General Issues		
Integrase Inhibitors	**Integrase Inhibitor Class Advantages:** • Susceptibility of HIV to a new class of ARVs	**Integrase Inhibitor Class Disadvantages:** • Limited data on pediatric dosing or safety
Insufficient Data to Recommend		
EVG only available as a coformulated product containing EVG/COBI/FTC/TDF	• One tablet, once daily • The single tablet is a complete combination regimen in antiretroviral-naive patients.	• No data on use in patients aged <18 years • Potential bone and renal toxicity • Potential for many drug interactions from cobicistat (COBI), a CYP3A4 inhibitor with pharmacokinetic actions similar to RTV • Must be taken with food
RAL	• Susceptibility of HIV to a new class of ARVs • Can give with food • Available in a chewable tablet	• Limited data on pediatric dosing or safety • Potential for rare systemic allergic reaction or hepatitis

Key to Abbreviations: ARV = antiretroviral, COBI = cobicistat, EVG = elvitegravir, FTC = emtricitabine, RAL = raltegravir, RTV= ritonavir, TDF = tenofovir disoproxil fumarate

References

1. McKinney RE Jr., Johnson GM, Stanley K, et al. A randomized study of combined zidovudine-lamivudine versus didanosine monotherapy in children with symptomatic therapy-naive HIV-1 infection. The Pediatric AIDS Clinical Trials Group Protocol 300 Study Team. *J Pediatr*. Oct 1998;133(4):500-508. Available at http://www.ncbi.nlm.nih.gov/pubmed/9787687.
2. Nachman SA, Stanley K, Yogev R, et al. Nucleoside analogs plus ritonavir in stable antiretroviral therapy-experienced HIV-infected children: A randomized controlled trial. Pediatric AIDS Clinical Trials Group 338 Study Team. *JAMA*. Jan 26 2000;283(4):492-498. Available at http://www.ncbi.nlm.nih.gov/pubmed/10659875.
3. Palumbo P, Lindsey JC, Hughes MD, et al. Antiretroviral treatment for children with peripartum nevirapine exposure. *N Engl J Med*. Oct 14 2010;363(16):1510-1520. Available at http://www.ncbi.nlm.nih.gov/pubmed/20942667.
4. Violari A, Lindsey JC, Hughes MD, et al. Nevirapine versus ritonavir-boosted lopinavir for HIV-infected children. *N Engl J Med*. Jun 21 2012;366(25):2380-2389. Available at http://www.ncbi.nlm.nih.gov/pubmed/22716976.
5. Lockman S, Shapiro RL, Smeaton LM, et al. Response to antiretroviral therapy after a single, peripartum dose of nevirapine. *N Engl J Med*. Jan 11 2007;356(2):135-147. Available at http://www.ncbi.nlm.nih.gov/pubmed/17215531.
6. Musiime V, Ssali F, Kayiwa J, et al. Response to non-nucleoside reverse transcriptase inhibitor-based therapy in HIV-infected children with perinatal exposure to single-dose nevirapine. *AIDS Res Hum Retroviruses*. Oct 2009;25(10):989-996. Available at http://www.ncbi.nlm.nih.gov/pubmed/19778270.
7. MacLeod IJ, Rowley CF, Thior I, et al. Minor resistant variants in nevirapine-exposed infants may predict virologic failure on nevirapine-containing ART. *J Clin Virol*. Jul 2010;48(3):162-167. Available at http://www.ncbi.nlm.nih.gov/pubmed/20427228.
8. Babiker A, Castro nee Green H, Compagnucci A, et al. First-line antiretroviral therapy with a protease inhibitor versus non-nucleoside reverse transcriptase inhibitor and switch at higher versus low viral load in HIV-infected children: An open-label, randomised phase 2/3 trial. *Lancet Infect Dis*. Apr 2011;11(4):273-283. Available at

http://www.ncbi.nlm.nih.gov/pubmed/21288774.

9. Coovadia A, Abrams EJ, Stehlau R, et al. Reuse of nevirapine in exposed HIV-infected children after protease inhibitor-based viral suppression: A randomized controlled trial. *JAMA*. Sep 8 2010;304(10):1082-1090. Available at http://www.ncbi.nlm.nih.gov/pubmed/20823434.

10. Hazra R, Cohen RA, Gonin R, et al. Lipid levels in the second year of life among HIV-infected and HIV-exposed uninfected Latin American children. *AIDS*. Jan 14 2012;26(2):235-240. Available at http://www.ncbi.nlm.nih.gov/pubmed/22008654.

11. Kontorinis N, Dieterich DT. Toxicity of non-nucleoside analogue reverse transcriptase inhibitors. *Semin Liver Dis*. May 2003;23(2):173-182. Available at http://www.ncbi.nlm.nih.gov/pubmed/12800070.

12. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Accessed on August 17, 2012.

13. Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. *N Engl J Med*. Dec 16 1999;341(25):1865-1873. Available at http://www.ncbi.nlm.nih.gov/pubmed/10601505.

14. Gulick RM, Ribaudo HJ, Shikuma CM, et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. *N Engl J Med*. Apr 29 2004;350(18):1850-1861. Available at http://www.ncbi.nlm.nih.gov/pubmed/15115831.

15. Lucas GM, Chaisson RE, Moore RD. Comparison of initial combination antiretroviral therapy with a single protease inhibitor, ritonavir and saquinavir, or efavirenz. *AIDS*. Sep 7 2001;15(13):1679-1686. Available at http://www.ncbi.nlm.nih.gov/pubmed/11546943.

16. Pulido F, Arribas JR, Miro JM, et al. Clinical, virologic, and immunologic response to efavirenz-or protease inhibitor-based highly active antiretroviral therapy in a cohort of antiretroviral-naive patients with advanced HIV infection (EfaVIP 2 study). *J Acquir Immune Defic Syndr*. Apr 1 2004;35(4):343-350. Available at http://www.ncbi.nlm.nih.gov/pubmed/15097150.

17. Torti C, Maggiolo F, Patroni A, et al. Exploratory analysis for the evaluation of lopinavir/ritonavir-versus efavirenz-based HAART regimens in antiretroviral-naive HIV-positive patients: Results from the Italian MASTER Cohort. *J Antimicrob Chemother*. Jul 2005;56(1):190-195. Available at http://www.ncbi.nlm.nih.gov/pubmed/15917286.

18. Squires K, Lazzarin A, Gatell JM, et al. Comparison of once-daily atazanavir with efavirenz, each in combination with fixed-dose zidovudine and lamivudine, as initial therapy for patients infected with HIV. *J Acquir Immune Defic Syndr*. Aug 15 2004;36(5):1011-1019. Available at http://www.ncbi.nlm.nih.gov/pubmed/15247553.

19. Riddler SA, Haubrich R, DiRienzo AG, et al. Class-sparing regimens for initial treatment of HIV-1 infection. *N Engl J Med*. May 15 2008;358(20):2095-2106. Available at http://www.ncbi.nlm.nih.gov/pubmed/18480202.

20. Carr A. Antiretroviral therapy for previously untreated HIV-1-infected adults: 2NN, or just one? *Lancet*. Apr 17 2004;363(9417):1248-1250. Available at http://www.ncbi.nlm.nih.gov/pubmed/15094265.

21. Cozzi-Lepri A, Phillips AN, d'Arminio Monforte A, et al. Virologic and immunologic response to regimens containing nevirapine or efavirenz in combination with 2 nucleoside analogues in the Italian Cohort Naive Antiretrovirals (I.Co.N.A.) study. *J Infect Dis*. Apr 15 2002;185(8):1062-1069. Available at http://www.ncbi.nlm.nih.gov/pubmed/11930316.

22. Manfredi R, Calza L, Chiodo F. Efavirenz versus nevirapine in current clinical practice: A prospective, open-label observational study. *J Acquir Immune Defic Syndr*. Apr 15 2004;35(5):492-502. Available at http://www.ncbi.nlm.nih.gov/pubmed/15021314.

23. Manosuthi W, Sungkanuparph S, Vibhagool A, Rattanasiri S, Thakkinstian A. Nevirapine- versus efavirenz-based highly active antiretroviral therapy regimens in antiretroviral-naive patients with advanced HIV infection. *HIV Med*. Mar 2004;5(2):105-109. Available at http://www.ncbi.nlm.nih.gov/pubmed/15012650.

24. van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: A randomised open-label trial, the 2NN Study. *Lancet*. Apr 17 2004;363(9417):1253-1263. Available at http://www.ncbi.nlm.nih.gov/pubmed/15094269.

25. Kamya MR, Mayanja-Kizza H, Kambugu A, et al. Predictors of long-term viral failure among ugandan children and adults treated with antiretroviral therapy. *J Acquir Immune Defic Syndr*. Oct 1 2007;46(2):187-193. Available at http://www.ncbi.nlm.nih.gov/pubmed/17693883.

26. Lowenthal E, Ellenberg J, et al. Virologic outcomes in children receiving efavirenz-based and nevirapine-based cART in a large African cohort. Abstract 965. Presented at: 19th Conference on Retroviruses and Opportunistic Infections (CROI); 2012; Seattle, WA. Available at http://www.retroconference.org/2012b/PDFs/965.pdf.

27. Fraaij PL, Neubert J, Bergshoeff AS, et al. Safety and efficacy of a NRTI-sparing HAART regimen of efavirenz and lopinavir/ritonavir in HIV-1-infected children. *Antivir Ther*. Apr 2004;9(2):297-299. Available at http://www.ncbi.nlm.nih.gov/pubmed/15134193.

28. Funk MB, Notheis G, Schuster T, et al. Effect of first line therapy including efavirenz and two nucleoside reverse transcriptase inhibitors in HIV-infected children. *Eur J Med Res*. Dec 7 2005;10(12):503-508. Available at http://www.ncbi.nlm.nih.gov/pubmed/16356864.

29. McKinney RE Jr, Rodman J, Hu C, et al. Long-term safety and efficacy of a once-daily regimen of emtricitabine, didanosine, and efavirenz in HIV-infected, therapy-naive children and adolescents: Pediatric AIDS Clinical Trials Group Protocol P1021. *Pediatrics*. Aug 2007;120(2):e416-423. Available at http://www.ncbi.nlm.nih.gov/pubmed/17646352.

30. Spector SA, Hsia K, Yong FH, et al. Patterns of plasma human immunodeficiency virus type 1 RNA response to highly active antiretroviral therapy in infected children. *J Infect Dis*. Dec 2000;182(6):1769-1773. Available at http://www.ncbi.nlm.nih.gov/pubmed/11069252.

31. Starr SE, Fletcher CV, Spector SA, et al. Combination therapy with efavirenz, nelfinavir, and nucleoside reverse-transcriptase inhibitors in children infected with human immunodeficiency virus type 1. Pediatric AIDS Clinical Trials Group 382 Team. *N Engl J Med*. Dec 16 1999;341(25):1874-1881. Available at http://www.ncbi.nlm.nih.gov/pubmed/10601506.

32. Starr SE, Fletcher CV, Spector SA, et al. Efavirenz liquid formulation in human immunodeficiency virus-infected children. *Pediatr Infect Dis J*. Jul 2002;21(7):659-663. Available at http://www.ncbi.nlm.nih.gov/pubmed/12237599.

33. Teglas JP, Quartier P, Treluyer JM, Burgard M, Gregoire V, Blanche S. Tolerance of efavirenz in children. *AIDS*. Jan 26 2001;15(2):241-243. Available at http://www.ncbi.nlm.nih.gov/pubmed/11216933.

34. Kaul S, Ji P, Lu M, Nguyen KL, Shangguan T, Grasela D. Bioavailability in healthy adults of efavirenz capsule contents mixed with a small amount of food. *Am J Health Syst Pharm*. Feb 1 2010;67(3):217-222. Available at http://www.ncbi.nlm.nih.gov/pubmed/20101064.

35. Gutierrez F, Navarro A, Padilla S, et al. Prediction of neuropsychiatric adverse events associated with long-term efavirenz therapy, using plasma drug level monitoring. *Clin Infect Dis*. Dec 1 2005;41(11):1648-1653. Available at http://www.ncbi.nlm.nih.gov/pubmed/16267739.

36. Marzolini C, Telenti A, Decosterd LA, Greub G, Biollaz J, Buclin T. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. *AIDS*. Jan 5 2001;15(1):71-75. Available at http://www.ncbi.nlm.nih.gov/pubmed/11192870.

37. Treisman GJ, Kaplin AI. Neurologic and psychiatric complications of antiretroviral agents. *AIDS*. Jun 14 2002;16(9):1201-1215. Available at http://www.ncbi.nlm.nih.gov/pubmed/12045485.

38. Zugar A. Studies disagree on frequency of late cns side effects from efavirenz. *AIDS Clin Care*. 2006;4(1).

39. World Health Organization. Technical update on treatment optimization: Use of efavirenz during pregnancy: A public health perspective. Accessed June 25, 2012. Available at http://www.who.int/hiv/pub/treatment2/efavirenz/en/.

40. Bardsley-Elliot A, Perry CM. Nevirapine: A review of its use in the prevention and treatment of paediatric HIV infection. *Paediatr Drugs*. Sep-Oct 2000;2(5):373-407. Available at http://www.ncbi.nlm.nih.gov/pubmed/11022799.

41. Luzuriaga K, Bryson Y, Krogstad P, et al. Combination treatment with zidovudine, didanosine, and nevirapine in infants with human immunodeficiency virus type 1 infection. *N Engl J Med*. May 8 1997;336(19):1343-1349. Available at http://www.ncbi.nlm.nih.gov/pubmed/9134874.

42. Luzuriaga K, McManus M, Mofenson L, et al. A trial of three antiretroviral regimens in HIV-1-infected children. *N Engl J Med*. Jun 10 2004;350(24):2471-2480. Available at http://www.ncbi.nlm.nih.gov/pubmed/15190139.

43. Verweel G, Sharland M, Lyall H, et al. Nevirapine use in HIV-1-infected children. *AIDS*. Jul 25 2003;17(11):1639-1647. Available at http://www.ncbi.nlm.nih.gov/pubmed/12853746.

44. Soriano V, Arasteh K, Migrone H, et al. Nevirapine versus atazanavir/ritonavir, each combined with tenofovir disoproxil fumarate/emtricitabine, in antiretroviral-naive HIV-1 patients: The ARTEN Trial. *Antivir Ther*. 2011;16(3):339-348. Available at http://www.ncbi.nlm.nih.gov/pubmed/21555816.

45. Sulkowski MS, Thomas DL, Mehta SH, Chaisson RE, Moore RD. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. *Hepatology*. Jan 2002;35(1):182-189. Available at http://www.ncbi.nlm.nih.gov/pubmed/11786975.

46. Peters PJ, Stringer J, McConnell MS, et al. Nevirapine-associated hepatotoxicity was not predicted by CD4 count >/=250 cells/muL among women in Zambia, Thailand and Kenya. *HIV Med*. Nov 2010;11(10):650-660. Available at http://www.ncbi.nlm.nih.gov/pubmed/20659176.

47. Baylor M, Ayime O, Truffa M, et al. Hepatotoxicity associated with nevirapine use in HIV-infected children. Paper presented at: 12th Conference on Retroviruses and Opportunistic Infections; 2005; Boston, MA.

48. Buck WC, Kabue MM, Kazembe PN, Kline MW. Discontinuation of standard first-line antiretroviral therapy in a cohort of 1434 Malawian children. *J Int AIDS Soc*. 2010;13:31. Available at http://www.ncbi.nlm.nih.gov/pubmed/20691049.

49. Wiznia A, Stanley K, Krogstad P, et al. Combination nucleoside analog reverse transcriptase inhibitor(s) plus nevirapine, nelfinavir, or ritonavir in stable antiretroviral therapy-experienced HIV-infected children: Week 24 results of a randomized controlled trial--PACTG 377. Pediatric AIDS Clinical Trials Group 377 Study Team. *AIDS Res Hum Retroviruses*. Aug 10 2000;16(12):1113-1121. Available at http://www.ncbi.nlm.nih.gov/pubmed/10954886.

50. Kea C, Puthanakit T, et al. Incidence and risk factors for nevirapine related toxicities among HIV-infected Asian children randomized to starting ART at different CD4%. Abstract MOPE240. 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention; July 17-20, 2011, 2011; Rome, Italy. Available at: http://pag.ias2011.org/abstracts.aspx?aid=3248.

51. Mehta U, Maartens G. Is it safe to switch between efavirenz and nevirapine in the event of toxicity? *Lancet Infect Dis*. Nov 2007;7(11):733-738. Available at http://www.ncbi.nlm.nih.gov/pubmed/17961859.

52. Davies MA, Moultrie H, Eley B, et al. Virologic failure and second-line antiretroviral therapy in children in South Africa—the IeDEA Southern Africa collaboration. *J Acquir Immune Defic Syndr*. Mar 2011;56(3):270-278. Available at http://www.ncbi.nlm.nih.gov/pubmed/21107266.

53. Moorthy A, Kuhn L, Coovadia A, et al. Induction therapy with protease-inhibitors modifies the effect of nevirapine resistance on virologic response to nevirapine-based HAART in children. *Clin Infect Dis*. Feb 15 2011;52(4):514-521. Available at http://www.ncbi.nlm.nih.gov/pubmed/21258105.

54. Chadwick EG, Pinto J, Yogev R, et al. Early initiation of lopinavir/ritonavir in infants less than 6 weeks of age: Pharmacokinetics and 24-week safety and efficacy. *Pediatr Infect Dis J*. Mar 2009;28(3):215-219. Available at http://www.ncbi.nlm.nih.gov/pubmed/19209098.

55. Gatell J, Salmon-Ceron D, Lazzarin A, et al. Efficacy and safety of atazanavir-based highly active antiretroviral therapy in patients with virologic suppression switched from a stable, boosted or unboosted protease inhibitor treatment regimen: The SWAN Study (AI424-097) 48-week results. *Clin Infect Dis*. Jun 1 2007;44(11):1484-1492. Available at http://www.ncbi.nlm.nih.gov/pubmed/17479947.

56. Walmsley S, Avihingsanon A, Slim J, et al. Gemini: A noninferiority study of saquinavir/ritonavir versus lopinavir/ritonavir as initial HIV-1 therapy in adults. *J Acquir Immune Defic Syndr*. Apr 1 2009;50(4):367-374.

Available at http://www.ncbi.nlm.nih.gov/pubmed/19214123.

57. Fraaij PL, Verweel G, van Rossum AM, Hartwig NG, Burger DM, de Groot R. Indinavir/low-dose ritonavir containing HAART in HIV-1 infected children has potent antiretroviral activity, but is associated with side effects and frequent discontinuation of treatment. *Infection*. Jun 2007;35(3):186-189. Available at http://www.ncbi.nlm.nih.gov/pubmed/17565462.

58. Jankelevich S, Mueller BU, Mackall CL, et al. Long-term virologic and immunologic responses in human immunodeficiency virus type 1-infected children treated with indinavir, zidovudine, and lamivudine. *J Infect Dis*. Apr 1 2001;183(7):1116-1120. Available at http://www.ncbi.nlm.nih.gov/pubmed/11237839.

59. van Rossum AM, Geelen SP, Hartwig NG, et al. Results of 2 years of treatment with protease-inhibitor—containing antiretroviral therapy in dutch children infected with human immunodeficiency virus type 1. *Clin Infect Dis*. Apr 1 2002;34(7):1008-1016. Available at http://www.ncbi.nlm.nih.gov/pubmed/11880968.

60. van Rossum AM, Dieleman JP, Fraaij PL, et al. Persistent sterile leukocyturia is associated with impaired renal function in human immunodeficiency virus type 1-infected children treated with indinavir. *Pediatrics*. Aug 2002;110(2 Pt 1):e19. Available at http://www.ncbi.nlm.nih.gov/pubmed/12165618.

61. Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. *Lancet*. Aug 23 2008;372(9639):646-655. Available at http://www.ncbi.nlm.nih.gov/pubmed/18722869.

62. Malan DR, Krantz E, David N, et al. Efficacy and safety of atazanavir, with or without ritonavir, as part of once-daily highly active antiretroviral therapy regimens in antiretroviral-naive patients. *J Acquir Immune Defic Syndr*. Feb 1 2008;47(2):161-167. Available at http://www.ncbi.nlm.nih.gov/pubmed/17971713.

63. Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir compared with twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 96-week efficacy and safety results of the CASTLE study. *J Acquir Immune Defic Syndr*. Mar 2010;53(3):323-332. Available at http://www.ncbi.nlm.nih.gov/pubmed/20032785.

64. Meyers T, Rutstein R, Samson P, et al. Treatment responses to atazanavir-containing HAART in a drug-naive paediatric population in South Africa. Abstract 582. Paper presented at: 15th Conference on Retroviruses and Opportunistic Infections (CROI); February 3-6, 2008; Boston, MA. Available at http://www.retroconference.org/2008/PDFs/582.pdf.

65. Deeks ED. Atazanavir: In Pediatric Patients with HIV-1 Infection. *Paediatr Drugs*. Apr 1 2012;14(2):131-141. Available at http://www.ncbi.nlm.nih.gov/pubmed/22292486.

66. Bristol-Myers Squibb. Reyataz Package Insert. 2012; http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021567s028lbl.pdf.

67. Kiser JJ, Fletcher CV, Flynn PM, et al. Pharmacokinetics of antiretroviral regimens containing tenofovir disoproxil fumarate and atazanavir-ritonavir in adolescents and young adults with human immunodeficiency virus infection. *Antimicrob Agents Chemother*. Feb 2008;52(2):631-637. Available at http://www.ncbi.nlm.nih.gov/pubmed/18025112.

68. Kiser J, Rutstein R, Aldrovandi G, et al. Pharmacokinetics of atazanavir/ritonavir in HIV-infected infants, children, and adolescents: PACTG 1020. Abstract 774. Paper presented at: 12th Conference on Retroviruses and Opportunistic Infections (CROI); February 22-25 2005; Boston, MA. Available at http://www.retroconference.org/2005/cd/PDFs/774.pdf.

69. Kiser JJ, Rutstein RM, Samson P, et al. Atazanavir and atazanavir/ritonavir pharmacokinetics in HIV-infected infants, children, and adolescents. *AIDS*. Jul 31 2011;25(12):1489-1496. Available at http://www.ncbi.nlm.nih.gov/pubmed/21610486.

70. Stebbing J, Nathan B, Jones R, et al. Virological failure and subsequent resistance profiles in individuals exposed to atazanavir. *AIDS*. Aug 20 2007;21(13):1826-1828. Available at http://www.ncbi.nlm.nih.gov/pubmed/17690587.

71. Kempf DJ, King MS, Bernstein B, et al. Incidence of resistance in a double-blind study comparing lopinavir/ritonavir plus stavudine and lamivudine to nelfinavir plus stavudine and lamivudine. *J Infect Dis*. Jan 1 2004;189(1):51-60.

Available at http://www.ncbi.nlm.nih.gov/pubmed/14702153.

72. Walmsley S, Bernstein B, King M, et al. Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. *N Engl J Med*. Jun 27 2002;346(26):2039-2046. Available at http://www.ncbi.nlm.nih.gov/pubmed/12087139.

73. Chadwick EG, Capparelli EV, Yogev R, et al. Pharmacokinetics, safety and efficacy of lopinavir/ritonavir in infants less than 6 months of age: 24 week results. *AIDS*. Jan 11 2008;22(2):249-255. Available at http://www.ncbi.nlm.nih.gov/pubmed/18097227.

74. De Luca M, Miccinesi G, Chiappini E, Zappa M, Galli L, De Martino M. Different kinetics of immunologic recovery using nelfinavir or lopinavir/ritonavir-based regimens in children with perinatal HIV-1 infection. *Int J Immunopathol Pharmacol*. Oct-Dec 2005;18(4):729-735. Available at http://www.ncbi.nlm.nih.gov/pubmed/16388722.

75. Havens P, Frank M, Cuene B, et al. Pharmacokinetics and safety of lopinavir/ritonavir doses greater than 300 mg/m2/dose in children and adolescents with HIV infection. Abstract 937. Paper presented at: 11th Conference on Retroviruses and Opportunistic Infections; February 8–11, 2004; San Francisco, CA. Available at http://www.retroconference.org/2004/cd/Abstract/937.htm.

76. Saez-Llorens X, Violari A, Deetz CO, et al. Forty-eight-week evaluation of lopinavir/ritonavir, a new protease inhibitor, in human immunodeficiency virus-infected children. *Pediatr Infect Dis J*. Mar 2003;22(3):216-224. Available at http://www.ncbi.nlm.nih.gov/pubmed/12634581.

77. Violari A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J Med*. Nov 20 2008;359(21):2233-2244. Available at http://www.ncbi.nlm.nih.gov/pubmed/19020325.

78. Reitz C, Coovadia A, Ko S, et al. Initial response to protease-inhibitor-based antiretroviral therapy among children less than 2 years of age in South Africa: Effect of cotreatment for tuberculosis. *J Infect Dis*. Apr 15 2010;201(8):1121-1131. Available at http://www.ncbi.nlm.nih.gov/pubmed/20214476.

79. Chadwick EG, Yogev R, Alvero CG, et al. Long-term outcomes for HIV-infected infants less than 6 months of age at initiation of lopinavir/ritonavir combination antiretroviral therapy. *AIDS*. Mar 13 2011;25(5):643-649. Available at http://www.ncbi.nlm.nih.gov/pubmed/21297419.

80. Robbins BL, Capparelli EV, Chadwick EG, et al. Pharmacokinetics of high-dose lopinavir-ritonavir with and without saquinavir or nonnucleoside reverse transcriptase inhibitors in human immunodeficiency virus-infected pediatric and adolescent patients previously treated with protease inhibitors. *Antimicrob Agents Chemother*. Sep 2008;52(9):3276-3283. Available at http://www.ncbi.nlm.nih.gov/pubmed/18625762.

81. Gathe J, da Silva BA, Cohen DE, et al. A once-daily lopinavir/ritonavir-based regimen is noninferior to twice-daily dosing and results in similar safety and tolerability in antiretroviral-naive subjects through 48 weeks. *J Acquir Immune Defic Syndr*. Apr 15 2009;50(5):474-481. Available at http://www.ncbi.nlm.nih.gov/pubmed/19225400.

82. la Porte C, van Heeswijk R, Mitchell CD, Zhang G, Parker J, Rongkavilit C. Pharmacokinetics and tolerability of once- versus twice-daily lopinavir/ritonavir treatment in HIV-1-infected children. *Antivir Ther*. 2009;14(4):603-606. Available at http://www.ncbi.nlm.nih.gov/pubmed/19578247.

83. van der Flier M, Verweel G, van der Knaap LC, et al. Pharmacokinetics of lopinavir in HIV type-1-infected children taking the new tablet formulation once daily. *Antivir Ther*. 2008;13(8):1087-1090. Available at http://www.ncbi.nlm.nih.gov/pubmed/19195335.

84. Ortiz R, Dejesus E, Khanlou H, et al. Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1-infected patients at week 48. *AIDS*. Jul 31 2008;22(12):1389-1397. Available at http://www.ncbi.nlm.nih.gov/pubmed/18614861.

85. Mills AM, Nelson M, Jayaweera D, et al. Once-daily darunavir/ritonavir vs. lopinavir/ritonavir in treatment-naive, HIV-1-infected patients: 96-week analysis. *AIDS*. Aug 24 2009;23(13):1679-1688. Available at http://www.ncbi.nlm.nih.gov/pubmed/19487905.

86. Blanche S, Bologna R, Cahn P, et al. Pharmacokinetics, safety and efficacy of darunavir/ritonavir in treatment-experienced children and adolescents. *AIDS*. Sep 24 2009;23(15):2005-2013. Available at

http://www.ncbi.nlm.nih.gov/pubmed/19724191.

87. Janssen Pharmaceuticals. Prezista Package Insert. 2012. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021976s022lbl.pdf.

88. Flynn P, Blanche S, et al. 24-week efficacy, safety, tolerability and pharmacokinetics of darunavir/ritonavir once daily in treatment-naïve adolescents aged 12 to <18 years in DIONE. AbstractWEPDB0101. Paper presented at: 6th IAS Conference on HIV Pathogenesis, Treatment, and Prevention; 17-20 July, 2011, 2011; Rome, Italy. Available at http://pag.ias2011.org/abstracts.aspx?aid=3385.

89. Chadwick E, Borkowsky W, Fortuny C, al e. Safety and antiviral activity of fosamprenavir/ritonavir once daily regimens in HIV-infected pediatric subjects ages 2 to 18 years (48-week interim data, study apv20003). Abstract 719. 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Available at http://www.retroconference.org/2007/Abstracts/30293.htm.

90. Cunningham C, Freedman A, Read S, al e. Safety and antiviral activity of fosamprenavir-containing regmens in HIV-infected 2- to 18-year-old pediatric subjects (interim data, study apv29005). Abstract 718. 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, CA. Available at http://www.retroconference.org/2007/Abstracts/30184.htm.

91. Eron J, Jr., Yeni P, Gathe J, Jr., et al. The KLEAN study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomised non-inferiority trial. *Lancet*. Aug 5 2006;368(9534):476-482. Available at http://www.ncbi.nlm.nih.gov/pubmed/16890834.

92. National Institute of Allergy and Infectious Diseases (NIAID). Bulletin monitoring board recommends stopping experimental treatment regimen in international study of patients new to HIV treatment. 2008; http://www.niaid.nih.gov/news/newsreleases/2008/Pages/ACTG_5175.aspx.

93. Scherpbier HJ, Bekker V, van Leth F, Jurriaans S, Lange JM, Kuijpers TW. Long-term experience with combination antiretroviral therapy that contains nelfinavir for up to 7 years in a pediatric cohort. *Pediatrics*. Mar 2006;117(3):e528-536. Available at http://www.ncbi.nlm.nih.gov/pubmed/16481448.

94. Burger DM, Bergshoeff AS, De Groot R, et al. Maintaining the nelfinavir trough concentration above 0.8 mg/L improves virologic response in HIV-1-infected children. *J Pediatr*. Sep 2004;145(3):403-405. Available at http://www.ncbi.nlm.nih.gov/pubmed/15343199.

95. Capparelli EV, Sullivan JL, Mofenson L, et al. Pharmacokinetics of nelfinavir in human immunodeficiency virus-infected infants. *Pediatr Infect Dis J*. Aug 2001;20(8):746-751. Available at http://www.ncbi.nlm.nih.gov/pubmed/11734735.

96. Floren LC, Wiznia A, Hayashi S, et al. Nelfinavir pharmacokinetics in stable human immunodeficiency virus-positive children: Pediatric AIDS Clinical Trials Group Protocol 377. *Pediatrics*. Sep 2003;112(3 Pt 1):e220-227. Available at http://www.ncbi.nlm.nih.gov/pubmed/12949316.

97. Hirt D, Urien S, Jullien V, et al. Age-related effects on nelfinavir and M8 pharmacokinetics: a population study with 182 children. *Antimicrob Agents Chemother*. Mar 2006;50(3):910-916. Available at http://www.ncbi.nlm.nih.gov/pubmed/16495250.

98. Litalien C, Faye A, Compagnucci A, et al. Pharmacokinetics of nelfinavir and its active metabolite, hydroxy-tert-butylamide, in infants perinatally infected with human immunodeficiency virus type 1. *Pediatr Infect Dis J*. Jan 2003;22(1):48-55. Available at http://www.ncbi.nlm.nih.gov/pubmed/12544409.

99. Paediatric European Network for Treatment of AIDS (PENTA). Comparison of dual nucleoside-analogue reverse-transcriptase inhibitor regimens with and without nelfinavir in children with HIV-1 who have not previously been treated: the PENTA 5 randomised trial. *Lancet*. 2002;359(9308):733-740. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11888583&query_hl=42.

100. van Heeswijk RP, Scherpbier HJ, de Koning LA, et al. The pharmacokinetics of nelfinavir in HIV-1-infected children. *Ther Drug Monit*. Aug 2002;24(4):487-491. Available at http://www.ncbi.nlm.nih.gov/pubmed/12142631.

101. Rodriguez-French A, Boghossian J, Gray GE, et al. The NEAT study: a 48-week open-label study to compare the antiviral efficacy and safety of GW433908 versus nelfinavir in antiretroviral therapy-naive HIV-1-infected patients. *J Acquir Immune Defic Syndr*. Jan 1 2004;35(1):22-32. Available at http://www.ncbi.nlm.nih.gov/pubmed/14707788.

102. Gathe JC, Jr., Ive P, Wood R, et al. SOLO: 48-week efficacy and safety comparison of once-daily fosamprenavir /ritonavir versus twice-daily nelfinavir in naive HIV-1-infected patients. *AIDS*. Jul 23 2004;18(11):1529-1537. Available at http://www.ncbi.nlm.nih.gov/pubmed/15238771.

103. Robbins GK, De Gruttola V, Shafer RW, et al. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med*. Dec 11 2003;349(24):2293-2303. Available at http://www.ncbi.nlm.nih.gov/pubmed/14668455.

104. Resino S, Larru B, Maria Bellon J, et al. Effects of highly active antiretroviral therapy with nelfinavir in vertically HIV-1 infected children: 3 years of follow-up. Long-term response to nelfinavir in children. *BMC Infect Dis*. 2006;6:107. Available at http://www.ncbi.nlm.nih.gov/pubmed/16834769.

105. Regazzi MB, Seminari E, Villani P, et al. Nelfinavir suspension obtained from nelfinavir tablets has equivalent pharmacokinetic profile. *J Chemother*. Oct 2001;13(5):569-574. Available at http://www.ncbi.nlm.nih.gov/pubmed/11760223.

106. Kline MW, Van Dyke RB, Lindsey JC, et al. A randomized comparative trial of stavudine (d4T) versus zidovudine (ZDV, AZT) in children with human immunodeficiency virus infection. AIDS Clinical Trials Group 240 Team. *Pediatrics*. Feb 1998;101(2):214-220. Available at http://www.ncbi.nlm.nih.gov/pubmed/9445494.

107. Kline MW, Van Dyke RB, Lindsey JC, et al. Combination therapy with stavudine (d4T) plus didanosine (ddI) in children with human immunodeficiency virus infection. The Pediatric AIDS Clinical Trials Group 327 Team. *Pediatrics*. May 1999;103(5):e62. Available at http://www.ncbi.nlm.nih.gov/pubmed/10224206.

108. Borroto-Esoda K, Vela JE, Myrick F, Ray AS, Miller MD. In vitro evaluation of the anti-HIV activity and metabolic interactions of tenofovir and emtricitabine. *Antivir Ther*. 2006;11(3):377-384. Available at http://www.ncbi.nlm.nih.gov/pubmed/16759055.

109. Ross L, Parkin N, Chappey C, et al. Phenotypic impact of HIV reverse transcriptase M184I/V mutations in combination with single thymidine analog mutations on nucleoside reverse transcriptase inhibitor resistance. *AIDS*. Aug 20 2004;18(12):1691-1696. Available at http://www.ncbi.nlm.nih.gov/pubmed/15280780.

110. DeJesus E, Herrera G, Teofilo E, et al. Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naive HIV-infected adults. *Clin Infect Dis*. Oct 1 2004;39(7):1038-1046. Available at http://www.ncbi.nlm.nih.gov/pubmed/15472858.

111. Green H, Gibb DM, Walker AS, et al. Lamivudine/abacavir maintains virological superiority over zidovudine/lamivudine and zidovudine/abacavir beyond 5 years in children. *AIDS*. May 11 2007;21(8):947-955. Available at http://www.ncbi.nlm.nih.gov/pubmed/17457088.

112. Phillips EJ. Genetic screening to prevent abacavir hypersensitivity reaction: are we there yet? *Clin Infect Dis*. Jul 1 2006;43(1):103-105. Available at http://www.ncbi.nlm.nih.gov/pubmed/16758425.

113. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med*. Feb 7 2008;358(6):568-579. Available at http://www.ncbi.nlm.nih.gov/pubmed/18256392.

114. Gafni RI, Hazra R, Reynolds JC, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy: impact on bone mineral density in HIV-infected children. *Pediatrics*. Sep 2006;118(3):e711-718. Available at http://www.ncbi.nlm.nih.gov/pubmed/16923923.

115. Giacomet V, Mora S, Martelli L, Merlo M, Sciannamblo M, Vigano A. A 12-month treatment with tenofovir does not impair bone mineral accrual in HIV-infected children. *J Acquir Immune Defic Syndr*. Dec 1 2005;40(4):448-450. Available at http://www.ncbi.nlm.nih.gov/pubmed/16280700.

116. Hazra R, Balis FM, Tullio AN, et al. Single-dose and steady-state pharmacokinetics of tenofovir disoproxil fumarate in human immunodeficiency virus-infected children. *Antimicrob Agents Chemother*. Jan 2004;48(1):124-129. Available at

http://www.ncbi.nlm.nih.gov/pubmed/14693529.

117. Hazra R, Gafni RI, Maldarelli F, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy for pediatric HIV infection. *Pediatrics*. Dec 2005;116(6):e846-854. Available at http://www.ncbi.nlm.nih.gov/pubmed/16291735.

118. Della Negra M, de Carvalho AP, de Aquino MZ, et al. A randomized study of tenofovir disoproxil fumarate in treatment-experienced HIV-1 infected adolescents. *Pediatr Infect Dis J*. May 2012;31(5):469-473. Available at http://www.ncbi.nlm.nih.gov/pubmed/22301477.

119. Gilead Sciences. *Viread Package Insert*. http://www.gilead.com/pdf/viread_pi.pdf. Accessed on June 20, 2012.

120. Arribas JR, Pozniak AL, Gallant JE, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz compared with zidovudine/lamivudine and efavirenz in treatment-naive patients: 144-week analysis. *J Acquir Immune Defic Syndr*. Jan 1 2008;47(1):74-78. Available at http://www.ncbi.nlm.nih.gov/pubmed/17971715.

121. Gallant JE, DeJesus E, Arribas JR, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med*. Jan 19 2006;354(3):251-260. Available at http://www.ncbi.nlm.nih.gov/pubmed/16421366.

122. Sax PE, Tierney C, Collier AC, et al. Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV-1 therapy. *N Engl J Med*. Dec 3 2009;361(23):2230-2240. Available at http://www.ncbi.nlm.nih.gov/pubmed/19952143.

123. Smith KY, Patel P, Fine D, et al. Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment. *AIDS*. Jul 31 2009;23(12):1547-1556. Available at http://www.ncbi.nlm.nih.gov/pubmed/19542866.

124. Loutfy MR, Ackad N, Antoniou T, et al. Randomized controlled trial of once-daily tenofovir, lamivudine, and lopinavir/ritonavir versus remaining on the same regimen in virologically suppressed HIV-infected patients on their first PI-containing HAART regimen. *HIV Clin Trials*. Sep-Oct 2007;8(5):259-268. Available at http://www.ncbi.nlm.nih.gov/pubmed/17956827.

125. Spaulding A, Rutherford GW, Siegfried N. Tenofovir or zidovudine in three-drug combination therapy with one nucleoside reverse transcriptase inhibitor and one non-nucleoside reverse transcriptase inhibitor for initial treatment of HIV infection in antiretroviral-naive individuals. *Cochrane Database Syst Rev*. 2010(10):CD008740. Available at http://www.ncbi.nlm.nih.gov/pubmed/20927777.

126. Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. *JAMA*. Jul 14 2004;292(2):191-201. Available at http://www.ncbi.nlm.nih.gov/pubmed/15249568.

127. Vigano A, Bedogni G, Manfredini V, et al. Long-term renal safety of tenofovir disoproxil fumarate in vertically HIV-infected children, adolescents and young adults: A 60-month follow-up study. *Clin Drug Investig*. 2011;31(6):407-415. Available at http://www.ncbi.nlm.nih.gov/pubmed/21528939.

128. Papaleo A, Warszawski J, Salomon R, et al. Increased beta-2 microglobulinuria in human immunodeficiency virus-1-infected children and adolescents treated with tenofovir. *Pediatr Infect Dis J*. Oct 2007;26(10):949-951. Available at http://www.ncbi.nlm.nih.gov/pubmed/17901802.

129. Riordan A, Judd A, Boyd K, et al. Tenofovir use in human immunodeficiency virus-1-infected children in the United kingdom and Ireland. *Pediatr Infect Dis J*. Mar 2009;28(3):204-209. Available at http://www.ncbi.nlm.nih.gov/pubmed/19209091.

130. Andiman WA, Chernoff MC, Mitchell C, et al. Incidence of persistent renal dysfunction in human immunodeficiency virus-infected children: associations with the use of antiretrovirals, and other nephrotoxic medications and risk factors. *Pediatr Infect Dis J*. Jul 2009;28(7):619-625. Available at http://www.ncbi.nlm.nih.gov/pubmed/19561425.

131. Pontrelli G, Cotugno N, Amodio D, et al. Renal function in HIV-infected children and adolescents treated with tenofovir disoproxil fumarate and protease inhibitors. *BMC Infect Dis*. 2012;12:18. Available at http://www.ncbi.nlm.nih.gov/pubmed/22269183.

132. Van Dyke RB, Wang L, Williams PL, Pediatric ACTGCT. Toxicities associated with dual nucleoside reverse-transcriptase inhibitor regimens in HIV-infected children. *J Infect Dis*. Dec 1 2008;198(11):1599-1608. Available at http://www.ncbi.nlm.nih.gov/pubmed/19000014.

133. Stevens RC, Rodman JH, Yong FH, Carey V, Knupp CA, Frenkel LM. Effect of food and pharmacokinetic variability on didanosine systemic exposure in HIV-infected children. Pediatric AIDS Clinical Trials Group Protocol 144 Study Team. *AIDS Res Hum Retroviruses*. Mar 20 2000;16(5):415-421. Available at http://www.ncbi.nlm.nih.gov/pubmed/10772527.

134. Dieterich DT. Long-term complications of nucleoside reverse transcriptase inhibitor therapy. *AIDS Read*. Apr 2003;13(4):176-184, 187. Available at http://www.ncbi.nlm.nih.gov/pubmed/12741368.

135. Falco V, Rodriguez D, Ribera E, et al. Severe nucleoside-associated lactic acidosis in human immunodeficiency virus-infected patients: Report of 12 cases and review of the literature. *Clin Infect Dis*. Mar 15 2002;34(6):838-846. Available at http://www.ncbi.nlm.nih.gov/pubmed/11850865.

136. Joly V, Flandre P, Meiffredy V, et al. Increased risk of lipoatrophy under stavudine in HIV-1-infected patients: results of a substudy from a comparative trial. *AIDS*. Dec 6 2002;16(18):2447-2454. Available at http://www.ncbi.nlm.nih.gov/pubmed/12461419.

137. de Mendoza C, Ramos JT, Ciria L, et al. Efficacy and safety of stavudine plus didanosine in asymptomatic HIV-infected children with plasma HIV RNA below 50,000 copies per milliliter. *HIV Clin Trials*. Jan-Feb 2002;3(1):9-16. Available at http://www.ncbi.nlm.nih.gov/pubmed/11819180.

138. Blanco F, Garcia-Benayas T, Jose de la Cruz J, Gonzalez-Lahoz J, Soriano V. First-line therapy and mitochondrial damage: Different nucleosides, different findings. *HIV Clin Trials*. Jan-Feb 2003;4(1):11-19. Available at http://www.ncbi.nlm.nih.gov/pubmed/12577192.

139. Shafer RW, Smeaton LM, Robbins GK, et al. Comparison of four-drug regimens and pairs of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med*. Dec 11 2003;349(24):2304-2315. Available at http://www.ncbi.nlm.nih.gov/pubmed/14668456.

140. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf. Accessed on September 25, 2012.

141. Saavedra J, Mccoig C, Mallory M, et al. Clinical experience with triple nucleoside (NRTI) combination ZDV/3TC/abacavir (ABC) as initial therapy in HIV-infected children. Paper presented at: 41st Interscience Conference on Antimicrobial Agents and Chemotherapy; September 22-25, 2001; Chicago, IL.

142. Wells C, Sharland M, Smith C, et al. Triple nucleoside analogue therapy with zidovudine (AZT), lamivudine (3TC), and abacavir (ABC) in the paediatric HIV London south network (phils-net) cohort. Abstract TuPeB4625. Paper presented at: XIV International AIDS Conference; July 7-12, 2002; Barcelona, Spain. Available at http://www.iasociety.org/Default.aspx?pageId=11&abstractId=1582.

143. Staszewski S, Keiser P, Montaner J, et al. Abacavir-lamivudine-zidovudine vs indinavir-lamivudine-zidovudine in antiretroviral-naive HIV-infected adults: A randomized equivalence trial. *JAMA*. Mar 7 2001;285(9):1155-1163. Available at http://www.ncbi.nlm.nih.gov/pubmed/11231744.

144. Kumar PN, Rodriguez-French A, Thompson MA, et al. A prospective, 96-week study of the impact of Trizivir, Combivir/nelfinavir, and lamivudine/stavudine/nelfinavir on lipids, metabolic parameters and efficacy in antiretroviral-naive patients: Effect of sex and ethnicity. *HIV Med*. Mar 2006;7(2):85-98. Available at http://www.ncbi.nlm.nih.gov/pubmed/16420253.

145. Moyle GJ. Where now for Trizivir? Role of the triple-NRTI pill post-ACTG 5095. *AIDS Read*. May 2003;13(5):223-224, 227, 244. Available at http://www.ncbi.nlm.nih.gov/pubmed/12800825.

146. Saez-Llorens X, Nelson RP, Jr., Emmanuel P, et al. A randomized, double-blind study of triple nucleoside therapy of

abacavir, lamivudine, and zidovudine versus lamivudine and zidovudine in previously treated human immunodeficiency virus type 1-infected children. The CNAA3006 Study Team. *Pediatrics*. Jan 2001;107(1):E4. Available at http://www.ncbi.nlm.nih.gov/pubmed/11134468.

147. Gerstoft J, Kirk O, Obel N, et al. Low efficacy and high frequency of adverse events in a randomized trial of the triple nucleoside regimen abacavir, stavudine and didanosine. *AIDS*. Sep 26 2003;17(14):2045-2052. Available at http://www.ncbi.nlm.nih.gov/pubmed/14502007.
148. van Leeuwen R, Katlama C, Murphy RL, et al. A randomized trial to study first-line combination therapy with or without a protease inhibitor in HIV-1-infected patients. *AIDS*. May 2 2003;17(7):987-999. Available at http://www.ncbi.nlm.nih.gov/pubmed/12700448.
149. Balestre E, Dupon M, Capdepont S, et al. Virological response to HIV-1 nucleoside/nucleotide reverse transcriptase inhibitors-based, tenofovir DF-including regimens in the ANRS Aquitaine Cohort. *J Clin Virol*. Jun 2006;36(2):95-99. Available at http://www.ncbi.nlm.nih.gov/pubmed/16556509.
150. Gallant JE, Rodriguez AE, Weinberg WG, et al. Early virologic nonresponse to tenofovir, abacavir, and lamivudine in HIV-infected antiretroviral-naive subjects. *J Infect Dis*. Dec 1 2005;192(11):1921-1930. Available at http://www.ncbi.nlm.nih.gov/pubmed/16267763.
151. Jemsek J, Hutcherson P, Harper E. Poor virologic responses and early emergence of resistance in treatment naive, HIV-infected patients receiving a once daily triple nucleoside regimen of didanosine, lamivudine, and tenofovir DF. Abstract 51. 11th Conference on Retroviruses and Opportunistic Infections; February, 2004; San Francisco, CA. Available at http://www.retroconference.org/2004/cd/Abstract/51.htm.
152. Group DV, Trial T. Virological response to a triple nucleoside/nucleotide analogue regimen over 48 weeks in HIV-1-infected adults in Africa. *AIDS*. Jun 26 2006;20(10):1391-1399. Available at http://www.ncbi.nlm.nih.gov/pubmed/16791013.
153. Judd A, European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) study group in EuroCoord. Early antiretroviral therapy in HIV-1-infected infants, 1996–2008: Treatment response and duration of first-line regimens. *AIDS*. Nov 28 2011;25(18):2279-2287. Available at http://www.ncbi.nlm.nih.gov/pubmed/21971357.
154. Nachman S, Acosta E, Samson P, et al. Interim results from IMPAACT P1066: Raltegravir (RAL) oral chewable tablet (OCT) formulation in children 6 to 11 years. Abstract 161LB. 17th Conference on Retroviruses and Opportunistic Infections (CROI); February 16-19, 2010; San Francisco, CA. Available at http://www.retroconference.org/2010/Abstracts/39677.htm.
155. Nachman S, Samson P, Acosta E, et al. Pharmacokinetic (PK), safety, and efficacy data on cohort IIA; youth aged 6 to 11 years from IMPAACT P1066: A phase I/II study to evaluate raltegravir (RAL) in HIV-1 infected youth. Abstract 873. Paper presented at: 17th Conference on Retroviruses and Opportunistic Infections (CROI); February 16–19, 2010; San Francisco, CA. Available at http://www.retroconference.org/2010/PDFs/873.pdf.
156. Briz V, Leon-Leal JA, Palladino C, et al. Potent and sustained antiviral response of raltegravir-based highly active antiretroviral therapy in HIV type 1-infected children and adolescents. *Pediatr Infect Dis J*. Mar 2012;31(3):273-277. Available at http://www.ncbi.nlm.nih.gov/pubmed/22330165.
157. Castagna A, Danise A, Menzo S, et al. Lamivudine monotherapy in HIV-1-infected patients harbouring a lamivudine-resistant virus: a randomized pilot study (E-184V study). *AIDS*. Apr 4 2006;20(6):795-803. Available at http://www.ncbi.nlm.nih.gov/pubmed/16549962.
158. Opravil M, Klimkait T, Louvel S, et al. Prior therapy influences the efficacy of lamivudine monotherapy in patients with lamivudine-resistant HIV-1 infection. *J Acquir Immune Defic Syndr*. May 1 2010;54(1):51-58. Available at http://www.ncbi.nlm.nih.gov/pubmed/19838125.