Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

Downloaded from http://aidsinfo.nih.gov/guidelines on 2/21/2013 EST.

Choice of Next Antiretroviral Regimen for Virologic Treatment Failure with Evidence of Drug Resistance (Last updated November 1, 2012; last reviewed November 1, 2012)

Panel's Recommendations

- Antiretroviral (ARV) regimens should be chosen based on treatment history and drug-resistance testing, including both past and current resistance test results **(AI*)**.
- The new regimen should include at least two, but preferably three, fully active ARV medications with assessment of anticipated ARV activity based on past treatment history and resistance test results **(AII*)**.
- Interpretation of resistance test results showing complex combinations of mutations and assessment of future treatment options should be made in collaboration with a pediatric HIV specialist **(AI*)**.
- Use of novel agents with limited available pharmacokinetic and/or safety data in pediatric populations should be undertaken only in collaboration with a pediatric HIV specialist **(AIII)**.

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

General

After reaching a decision that a change in therapy is needed, a clinician should attempt to identify at least two, but preferably three, fully active antiretroviral (ARV) agents from at least two different classes on the basis of resistance test results, prior ARV exposure, acceptability to the patient, and likelihood of adherence.[1-5] This often requires using agents from one or more drug classes that are new to the patient. Substitution or addition of a single drug to a failing regimen should not be done because it is unlikely to lead to durable virologic suppression and will likely result in additional drug resistance. A drug may be new to the patient but have diminished antiviral potency because of the presence of drug-resistance mutations that confer cross resistance within a drug class. In children who are changing therapy owing to the occurrence or progression of abnormal neurodevelopment, the new treatment regimen should include agents (such as zidovudine) that are known to achieve higher concentrations in the central nervous system.[6-10]

A change to a new regimen must include an extensive discussion of treatment adherence and potential toxicity with a patient in an age- and development-appropriate manner and with a patient's caregivers. Clinicians must recognize that conflicting requirements of some medications with respect to food and concomitant medication restrictions may complicate administration of a regimen. Timing of medication administration is particularly important to ensure adequate ARV drug exposures throughout the day. Palatability, size and number of pills, and dosing frequency all need to be considered when choosing a new regimen.[11]

Choice of Therapy with Viral Resistance to Current Therapy: Goal of Complete Virologic Suppression

Determination of a new regimen with the best chance for complete virologic suppression in children who

have already experienced treatment failure should be made in collaboration with a pediatric HIV specialist. ARV regimens should be chosen based on treatment history and drug-resistance testing to optimize ARV drug potency in the new regimen. A general strategy for regimen change is shown in Table 20, although as additional agents are licensed and studied for use in children, newer strategies that are better tailored to the needs of each patient may be constructed.

If a child has received initial therapy with a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen, a change to a protease inhibitor (PI)-based regimen is recommended. Resistance to the NNRTI nevirapine results in cross-resistance to the NNRTI efavirenz, and vice versa. However, the newer NNRTI etravirine retains activity against nevirapine- or efavirenz-resistant virus (see below). If a child received initial therapy with a PI-based regimen, a change to an NNRTI-based regimen is generally recommended. Lopinavir/ritonavir-based regimens have also been shown to have durable ARV activity in some PI-experienced children.[12-14] Choice of the new dual-nucleoside reverse transcriptase inhibitor (NRTI) component is particularly important when constructing a regimen because the choice of an insufficiently potent NRTI may result in selection of additional NRTI-related drug-resistance mutations. Resistance testing is essential to properly select a potent NRTI combination, and interpretation of these results should take place in collaboration with an expert in pediatric HIV infection (see Antiretroviral Drug-Resistance Testing).

The availability of new drugs in existing classes (e.g., the NNRTI etravirine) and new classes of drugs (e.g., integrase inhibitors) increases the likelihood of finding three active drugs, even for children with extensive drug resistance (Table 20). In studies of adults, etravirine retains activity against nevirapine- or efavirenz-resistant viruses when used in a regimen that also contains darunavir/ritonavir and if the number of NNRTI resistance-associated mutations is limited.[15, 16] Etravirine in combination with ritonavir-boosted darunavir, as part of a new combination antiretroviral therapy (cART) regimen, has been shown to be a safe and effective option for children in whom cART fails.[17, 18] Etravirine is approved for use in children aged ≥6 years;[17, 19] studies in younger children are under way. Studies of treatment-experienced adult and adolescent patients have shown that using one or more new class(es) of drug (e.g., integrase inhibitors, entry inhibitors), often coupled with a ritonavir-boosted PI (e.g., darunavir) in PI-experienced patients with multidrug-resistant virus, is associated with good virologic responses.[20-23] Raltegravir, in combination with optimized background therapy, was safe and effective in treatment-experienced children aged 2 to 16 years,[24] for whom it is Food and Drug Administration (FDA)-approved. Use of newer agents in novel combinations is becoming more common in aging perinatally infected youth in the United States.[25] It is important to review individual drug profiles for information about drug interactions and dose adjustment when devising a regimen for children with multi-class drug resistance. Appendix A: Pediatric Antiretroviral Drug Information provides more detailed information on drug formulation, pediatric and adult dosing, and toxicity, as well as discussion of available pediatric data for the approved ARV drugs, including new drugs in existing classes such as darunavir and agents in new classes of drugs such as CCR5 antagonists (e.g., maraviroc, approved for use in adolescents aged ≥16 years) and integrase inhibitors (e.g., raltegravir, approved for use in children aged ≥2 years [FDA, December 21, 2011]).

Previously prescribed drugs that were discontinued because of poor tolerance or poor adherence may sometimes be reintroduced if ARV resistance did not develop and if prior difficulties with tolerance and adherence can be overcome (such as by switching from a liquid to pill formulation or to a new formulation [such as ritonavir tablet]). Limited data in adults suggest that continuation of lamivudine can contribute to suppression of HIV replication despite the presence of lamivudine resistance mutations and can maintain lamivudine mutations (184V) that can partially reverse the effect of other mutations conferring resistance to zidovudine, stavudine, and tenofovir.[26-28] The use of new drugs that have been evaluated in adults but have not been fully evaluated in children may be justified and ideally is done in the framework of a clinical trial (see The Use of Antiretroviral Agents Not Approved for Use in Children). Expanded access programs or clinical trials may be available. New drugs should be used in combination with at least one, and ideally two, additional active agents.

The HIV entry inhibitor enfuvirtide is approved for use in heavily treatment-experienced patients based on potent ARV activity in heavily treatment-experienced adults; it has been approved for use in children aged ≥6 years.[29, 30] Studies have helped establish safety, appropriate dosing, and efficacy of enfuvirtide in treatment-experienced children aged ≥6 years.[31, 32] Enfuvirtide must be administered by subcutaneous injection twice daily, a disadvantage that presents a greater challenge to adherence in adolescents than in younger children. Enfuvirtide can be considered an option when designing a new regimen for children in whom multiple classes of ARV medications have failed, but newer and better tolerated agents have largely supplanted use of enfuvirtide.

Pharmacokinetic (PK) studies of certain dual-boosted PI regimens (lopinavir/ritonavir with saquinavir and lopinavir/ritonavir with atazanavir/ritonavir) suggest that PK targets for both PIs can be achieved or exceeded when used in combination in adults[33-35] and in children.[36-38] PK studies of other dual-boosted PI combinations are limited but suggest inadequate drug levels of one or both PIs.[39, 40] A study in Thailand of 50 PI-naive but NRTI +/- NNRTI-experienced children treated with a combination of lopinavir/ritonavir (230/57.5 mg/m^2 twice daily) and saquinavir (50 mg/kg twice daily, maximum dose 1000 mg) demonstrated trough levels of both PIs at or above therapeutic targets and complete viral suppression at 48 weeks in ≥50% of patients. The use of multidrug regimens, sometimes including up to 3 PIs and/or 2 NNRTIs, has shown efficacy in a pediatric case series;[41] however, multidrug regimens should be used cautiously because of their complexity, poor tolerability, and unfavorable drug-drug interactions. Therapeutic drug monitoring may be helpful for confirming therapeutic PI levels when using PIs in combinations that result in complex drug interactions or when there is partially reduced PI activity because of the presence of drug-resistance mutations (see Role of Therapeutic Drug Monitoring in Management of Treatment Failure). Availability of newer potent PIs and new classes of ARV drugs (integrase and CCR5 inhibitors) may lessen the need for dual-PI regimens.

When searching for at least two fully active agents in cases of extensive drug resistance, clinicians should consider the potential availability and future use of newer therapeutic agents that may not be studied or approved in children or may be in clinical development (see The Use of Antiretroviral Agents Not Approved for Use in Children). Information concerning potential clinical trials can be found at http://aidsinfo.nih.gov/clinical-trials and through collaboration with a pediatric HIV specialist. Children should be enrolled in clinical trials of new drugs whenever possible.

Therapeutic Options When Two Fully Active Agents Cannot Be Identified or Administered

It may be impossible to provide an effective and sustainable therapeutic regimen because no combination of currently available agents is active against extensive drug-resistant virus in a patient or because a patient is unable to adhere to or tolerate cART.

In such cases, non-suppressive regimens (or holding regimens) are sometimes used pending availability of additional active, tolerable drugs or improvement in ability to adhere. This interim strategy allows for the overall objective of preventing clinical and immunological deterioration until new agents are available to design a regimen that can be expected to achieve undetectable plasma viral load. This approach should be regarded as acceptable but not ideal. Such patients should be followed more closely than those with stable virologic status, and the potential to successfully initiate a fully suppressive cART regimen should be reassessed at every opportunity.

Even when NRTI drug-resistance mutations are present, patients can derive immunologic and clinical benefit despite persistent viremia from treatment with lamivudine monotherapy or with lamivudine or emtricitabine in combination with one or more other NRTIs, such as zidovudine, stavudine, abacavir, or tenofovir.[42, 43]

The newer NNRTI etravirine retains activity against many nevirapine- or efavirenz-resistant viruses with a limited number of NNRTI resistance-associated mutations. Ongoing use of efavirenz or nevirapine as part of a failing regimen should be avoided because it may lead to accumulation of additional NNRTI resistance

mutations that will reduce etravirine activity and preclude its use in a future, suppressive regimen,[44] and it may allow for accumulation of additional NRTI resistance.[45]

Continued use of a PI in the face of persistent viremia can lead to accumulation of additional mutations conferring resistance to that PI as well as other, newer PIs. Such acquisition of additional PI drug resistance occurs slowly, especially if the viral load is relatively low.[46-49] However, continued PI use in the presence of resistance may limit viral replication and be beneficial to some patients.

When clinical or immunologic deterioration occurs while patients are receiving such holding regimens, it is important to re-assess patient readiness and regimen availability. It may be appropriate to use investigational agents or agents approved for older age groups as second fully active drugs in the new regimen (see The Use of Antiretroviral Agents Not Approved for Use in Children). In general, a single, new, fully active agent should not be added to non-suppressive holding regimens because resistance is likely to develop quickly.

Table 20. Options for Regimens with at Least Two Fully Active Agents with Goal of Virologic Suppression in Patients With Failed Antiretroviral Therapy and Evidence of Viral Resistance[a]

Prior Regimen	Recommended Change (in order of relative preference)[a]
2 NRTIs + NNRTI	• 2 NRTIs + PI • 2 NRTI + integrase inhibitor[b]
2 NRTIs + PI	• 2 NRTIs + NNRTI • 2 NRTIs + alternative RTV-boosted PI • 2 NRTIs + integrase inhibitor[b] • NRTI(s) + integrase inhibitor + (NNRTI *or* alternative RTV-boosted PI)
3 NRTIs	• 2 NRTIs + (NNRTI or PI) • 2 NRTIs + integrase inhibitor[b] • Integrase inhibitor[b] + 2 other active agents (chosen from NNRTI, PI, NRTI[s])
Failed regimen(s) that included NRTI(s), NNRTI(s), and PI(s)	• > 1 NRTI + RTV-boosted PI • NRTI(s) + RTV-boosted PI + integrase inhibitor[b] (consider adding T-20 and/or MVC,[c] if additional active drug[s] needed) • NRTI(s) + RTV-boosted DRV, LPV or SQV + ETR (consider adding one or more of MVC,[c] T-20, or integrase inhibitor,[b] if additional active drug[s] needed) • > 1 NRTI + 2 RTV-boosted PIs (LPV/r + SQV, LPV/r + ATV) (consider adding T-20 or an integrase inhibitor[b] if additional active drug[s] needed)

[a] ARV regimens should be chosen based on treatment history and drug-resistance testing to optimize ARV drug effectiveness. This is particularly important in selecting NRTI components of an NNRTI-based regimen where drug resistance to the NNRTI can occur rapidly if the virus is not sufficiently sensitive to the NRTIs. Regimens should contain at least two, but preferably three, fully active drugs for durable, potent virologic suppression. *Please see individual drug profiles for information about drug interactions and dose adjustment when devising a regimen for children with multi-class drug resistance.* Collaboration with a pediatric HIV specialist is especially important when choosing regimens for children with multi-class drug resistance. Regimens in this table are listed in relative order of preference and are provided as examples but the list is not exhaustive.

[b] Caution advised when using raltegravir in children aged ≤6 years because pharmacokinetic and efficacy data are particularly limited in this age group.

[c] No current FDA-approved pediatric indication for maraviroc.

Key to Acronyms: ATV = atazanavir, DRV = darunavir, ETR = etravirine, LPV = lopinavir, LPV/r = lopinavir/ritonavir, MVC = maraviroc, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, RTV = ritonavir, SQV = saquinavir, T-20 = enfuvirtide

References

1. Katlama C, Haubrich R, Lalezari J, et al. Efficacy and safety of etravirine in treatment-experienced, HIV-1 patients: Pooled 48 week analysis of two randomized, controlled trials. *AIDS*. Nov 13 2009;23(17):2289-2300. Available at http://www.ncbi.nlm.nih.gov/pubmed/19710593.
2. Steigbigel RT, Cooper DA, Teppler H, et al. Long-term efficacy and safety of Raltegravir combined with optimized background therapy in treatment-experienced patients with drug-resistant HIV infection: Week 96 results of the BENCHMRK 1 and 2 Phase III trials. *Clin Infect Dis*. Feb 15 2010;50(4):605-612. Available at http://www.ncbi.nlm.nih.gov/pubmed/20085491.
3. De Luca A, Di Giambenedetto S, Cingolani A, Bacarelli A, Ammassari A, Cauda R. Three-year clinical outcomes of resistance genotyping and expert advice: Extended follow-up of the Argenta trial. *Antivir Ther*. 2006;11(3):321-327. Available at http://www.ncbi.nlm.nih.gov/pubmed/16759048.
4. Baxter JD, Mayers DL, Wentworth DN, et al. A randomized study of antiretroviral management based on plasma genotypic antiretroviral resistance testing in patients failing therapy. CPCRA 046 Study Team for the Terry Beirn Community Programs for Clinical Research on AIDS. *AIDS*. Jun 16 2000;14(9):F83-93. Available at http://www.ncbi.nlm.nih.gov/pubmed/10894268.
5. Tural C, Ruiz L, Holtzer C, et al. Clinical utility of HIV-1 genotyping and expert advice: The Havana trial. *AIDS*. Jan 25 2002;16(2):209-218. Available at http://www.ncbi.nlm.nih.gov/pubmed/11807305.
6. Antinori A, Giancola ML, Grisetti S, et al. Factors influencing virological response to antiretroviral drugs in cerebrospinal fluid of advanced HIV-1-infected patients. *AIDS*. Sep 27 2002;16(14):1867-1876. Available at http://www.ncbi.nlm.nih.gov/pubmed/12351946.
7. Antinori A, Perno CF, Giancola ML, et al. Efficacy of cerebrospinal fluid (CSF)-penetrating antiretroviral drugs against HIV in the neurological compartment: Different patterns of phenotypic resistance in CSF and plasma. *Clin Infect Dis*. Dec 15 2005;41(12):1787-1793. Available at http://www.ncbi.nlm.nih.gov/pubmed/16288405.
8. Capparelli EV, Letendre SL, Ellis RJ, Patel P, Holland D, McCutchan JA. Population pharmacokinetics of abacavir in plasma and cerebrospinal fluid. *Antimicrob Agents Chemother*. Jun 2005;49(6):2504-2506. Available at http://www.ncbi.nlm.nih.gov/pubmed/15917556.
9. Letendre S, Marquie-Beck J, Capparelli E, et al. Validation of the CNS Penetration-Effectiveness rank for quantifying antiretroviral penetration into the central nervous system. *Arch Neurol*. Jan 2008;65(1):65-70. Available at http://www.ncbi.nlm.nih.gov/pubmed/18195140.
10. Patel K, Ming X, Williams PL, et al. Impact of HAART and CNS-penetrating antiretroviral regimens on HIV encephalopathy among perinatally infected children and adolescents. *AIDS*. Sep 10 2009;23(14):1893-1901. Available at http://www.ncbi.nlm.nih.gov/pubmed/19644348.
11. Lin D, Seabrook JA, Matsui DM, King SM, Rieder MJ, Finkelstein Y. Palatability, adherence and prescribing patterns of antiretroviral drugs for children with human immunodeficiency virus infection in Canada. *Pharmacoepidemiol Drug Saf*. Dec 2011;20(12):1246-1252. Available at http://www.ncbi.nlm.nih.gov/pubmed/21936016.
12. Galan I, Jimenez JL, Gonzalez-Rivera M, et al. Virological phenotype switches under salvage therapy with lopinavir-ritonavir in heavily pretreated HIV-1 vertically infected children. *AIDS*. Jan 23 2004;18(2):247-255. Available at http://www.ncbi.nlm.nih.gov/pubmed/15075542.
13. Ramos JT, De Jose MI, Duenas J, et al. Safety and antiviral response at 12 months of lopinavir/ritonavir therapy in human immunodeficiency virus-1-infected children experienced with three classes of antiretrovirals. *Pediatr Infect Dis J*. Oct 2005;24(10):867-873. Available at http://www.ncbi.nlm.nih.gov/pubmed/16220083.
14. Resino S, Bellon JM, Munoz-Fernandez MA, Spanish Group of HIVI. Antiretroviral activity and safety of lopinavir/ritonavir in protease inhibitor-experienced HIV-infected children with severe-moderate immunodeficiency. *J Antimicrob Chemother*. Mar 2006;57(3):579-582. Available at http://www.ncbi.nlm.nih.gov/pubmed/16446377.

15. Vingerhoets J, Peeters M, Azijn H, et al. An update of the list of NNRTI mutations associated with decreased virological response to etravirine: Multivariate analyses on the pooled DUET-1 and DUET-2 clinical trial data. Abstract 24. *Antivir Ther*. 2008;13(Suppl 3):A26.

16. Scherrer AU, Hasse B, von Wyl V, et al. Prevalence of etravirine mutations and impact on response to treatment in routine clinical care: the Swiss HIV Cohort Study (SHCS). *HIV Med*. Nov 2009;10(10):647-656. Available at http://www.ncbi.nlm.nih.gov/pubmed/19732174.

17. Briz V, Palladino C, Navarro M, et al. Etravirine-based highly active antiretroviral therapy in HIV-1-infected paediatric patients. *HIV Med*. Aug 2011;12(7):442-446. Available at http://www.ncbi.nlm.nih.gov/pubmed/21395964.

18. 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.

19. Konigs C, Feiterna-Sperling C, Esposito S, et al. Pharmacokinetics and short-term safety and tolerability of etravirine in treatment-experienced HIV-1-infected children and adolescents. *AIDS*. Feb 20 2012;26(4):447-455. Available at http://www.ncbi.nlm.nih.gov/pubmed/22156961.

20. 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.

21. Temesgen Z, Cainelli F, Poeschla EM, Vlahakis SA, Vento S. Approach to salvage antiretroviral therapy in heavily antiretroviral-experienced HIV-positive adults. *Lancet Infect Dis*. Aug 2006;6(8):496-507. Available at http://www.ncbi.nlm.nih.gov/pubmed/16870528.

22. Thuret I, Chaix ML, Tamalet C, et al. Raltegravir, etravirine and r-darunavir combination in adolescents with multidrug-resistant virus. *AIDS*. Nov 13 2009;23(17):2364-2366. Available at http://www.ncbi.nlm.nih.gov/pubmed/19823069.

23. Yazdanpanah Y, Fagard C, Descamps D, et al. High rate of virologic suppression with raltegravir plus etravirine and darunavir/ritonavir among treatment-experienced patients infected with multidrug-resistant HIV: results of the ANRS 139 TRIO trial. *Clin Infect Dis*. Nov 1 2009;49(9):1441-1449. Available at http://www.ncbi.nlm.nih.gov/pubmed/19814627.

24. Nachman S, Acosta E, Zheng N, et al. Interim Results from IMPAACT P1066: RAL Oral Chewable Tablet Formulation for 2- to 5-Year-olds. Abstract 715. Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI) 2011; February 27, 2011–March 3, 2011; Boston, MA. Available at http://www.retroconference.org/2011/Abstracts/40427.htm.

25. Van Dyke RB, Patel K, Siberry GK, et al. Antiretroviral treatment of US children with perinatally acquired HIV infection: temporal changes in therapy between 1991 and 2009 and predictors of immunologic and virologic outcomes. *J Acquir Immune Defic Syndr*. Jun 1 2011;57(2):165-173. Available at http://www.ncbi.nlm.nih.gov/pubmed/21407086.

26. Campbell TB, Shulman NS, Johnson SC, et al. Antiviral activity of lamivudine in salvage therapy for multidrug-resistant HIV-1 infection. *Clin Infect Dis*. Jul 15 2005;41(2):236-242. Available at http://www.ncbi.nlm.nih.gov/pubmed/15983922.

27. Nijhuis M, Schuurman R, de Jong D, et al. Lamivudine-resistant human immunodeficiency virus type 1 variants (184V) require multiple amino acid changes to become co-resistant to zidovudine in vivo. *J Infect Dis*. Aug 1997;176(2):398-405. Available at http://www.ncbi.nlm.nih.gov/pubmed/9237704.

28. 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.

29. Church JA, Cunningham C, Hughes M, et al. Safety and antiretroviral activity of chronic subcutaneous administration of T-20 in human immunodeficiency virus 1-infected children. *Pediatr Infect Dis J*. Jul 2002;21(7):653-659. Available at http://www.ncbi.nlm.nih.gov/pubmed/12237598.

30. Church JA, Hughes M, Chen J, et al. Long term tolerability and safety of enfuvirtide for human immunodeficiency virus 1-infected children. *Pediatr Infect Dis J*. Aug 2004;23(8):713-718. Available at

http://www.ncbi.nlm.nih.gov/pubmed/15295220.

31. Wiznia A, Church J, Emmanuel P, et al. Safety and efficacy of enfuvirtide for 48 weeks as part of an optimized antiretroviral regimen in pediatric human immunodeficiency virus 1-infected patients. *Pediatr Infect Dis J*. Sep 2007;26(9):799-805. Available at http://www.ncbi.nlm.nih.gov/pubmed/17721374.
32. Zhang X, Lin T, Bertasso A, et al. Population pharmacokinetics of enfuvirtide in HIV-1-infected pediatric patients over 48 weeks of treatment. *J Clin Pharmacol.* Apr 2007;47(4):510-517. Available at http://www.ncbi.nlm.nih.gov/pubmed/17389560.
33. Ribera E, Azuaje C, Lopez RM, et al. Atazanavir and lopinavir/ritonavir: pharmacokinetics, safety and efficacy of a promising double-boosted protease inhibitor regimen. *AIDS*. May 12 2006;20(8):1131-1139. Available at http://www.ncbi.nlm.nih.gov/pubmed/16691064.
34. Stephan C, von Hentig N, Kourbeti I, et al. Saquinavir drug exposure is not impaired by the boosted double protease inhibitor combination of lopinavir/ritonavir. *AIDS*. Feb 20 2004;18(3):503-508. Available at http://www.ncbi.nlm.nih.gov/pubmed/15090803.
35. van der Lugt J, Autar RS, Ubolyam S, et al. Pharmacokinetics and short-term efficacy of a double-boosted protease inhibitor regimen in treatment-naive HIV-1-infected adults. *J Antimicrob Chemother*. May 2008;61(5):1145-1153. Available at http://www.ncbi.nlm.nih.gov/pubmed/18285316.
36. Ananworanich J, Kosalaraksa P, Hill A, et al. Pharmacokinetics and 24-week efficacy/safety of dual boosted saquinavir/lopinavir/ritonavir in nucleoside-pretreated children. *Pediatr Infect Dis J*. Oct 2005;24(10):874-879. Available at http://www.ncbi.nlm.nih.gov/pubmed/16220084.
37. Kosalaraksa P, Bunupuradah T, Engchanil C, et al. Double boosted protease inhibitors, saquinavir, and lopinavir/ritonavir, in nucleoside pretreated children at 48 weeks. *Pediatr Infect Dis J*. Jul 2008;27(7):623-628. Available at http://www.ncbi.nlm.nih.gov/pubmed/18520443.
38. 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.
39. Collier AC, Tierney C, Downey GF, et al. Randomized study of dual versus single ritonavir-enhanced protease inhibitors for protease inhibitor-experienced patients with HIV. *HIV Clin Trials*. Mar-Apr 2008;9(2):91-102. Available at http://www.ncbi.nlm.nih.gov/pubmed/18474494.
40. Walmsley SL, Katlama C, Lazzarin A, et al. Pharmacokinetics, safety, and efficacy of tipranavir boosted with ritonavir alone or in combination with other boosted protease inhibitors as part of optimized combination antiretroviral therapy in highly treatment-experienced patients (BI Study 1182.51). *J Acquir Immune Defic Syndr*. Apr 1 2008;47(4):429-440. Available at http://www.ncbi.nlm.nih.gov/pubmed/18176328.
41. King JR, Acosta EP, Chadwick E, et al. Evaluation of multiple drug therapy in human immunodeficiency virus-infected pediatric patients. *Pediatr Infect Dis J*. Mar 2003;22(3):239-244. Available at http://www.ncbi.nlm.nih.gov/pubmed/12634585.
42. 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.
43. Deeks SG, Hoh R, Neilands TB, et al. Interruption of treatment with individual therapeutic drug classes in adults with multidrug-resistant HIV-1 infection. *J Infect Dis*. Nov 1 2005;192(9):1537-1544. Available at http://www.ncbi.nlm.nih.gov/pubmed/16206068.
44. Agwu A, Lindsey JC, Ferguson K, et al. Analyses of HIV-1 drug-resistance profiles among infected adolescents experiencing delayed antiretroviral treatment switch after initial nonsuppressive highly active antiretroviral therapy. *AIDS Patient Care STDS*. Jul 2008;22(7):545-552. Available at http://www.ncbi.nlm.nih.gov/pubmed/18479228.

45. 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.

46. Garcia-Gasco P, Maida I, Blanco F, et al. Episodes of low-level viral rebound in HIV-infected patients on antiretroviral therapy: frequency, predictors and outcome. *J Antimicrob Chemother*. Mar 2008;61(3):699-704. Available at http://www.ncbi.nlm.nih.gov/pubmed/18192682.

47. Napravnik S, Edwards D, Stewart P, Stalzer B, Matteson E, Eron JJ, Jr. HIV-1 drug resistance evolution among patients on potent combination antiretroviral therapy with detectable viremia. *J Acquir Immune Defic Syndr*. Sep 1 2005;40(1):34-40. Available at http://www.ncbi.nlm.nih.gov/pubmed/16123679.

48. Nettles RE, Kieffer TL, Kwon P, et al. Intermittent HIV-1 viremia (Blips) and drug resistance in patients receiving HAART. *JAMA*. Feb 16 2005;293(7):817-829. Available at http://www.ncbi.nlm.nih.gov/pubmed/15713771.

49. Eshleman SH, Krogstad P, Jackson JB, et al. Analysis of human immunodeficiency virus type 1 drug resistance in children receiving nucleoside analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir (Pediatric AIDS Clinical Trials Group 377). *J Infect Dis*. Jun 15 2001;183(12):1732-1738. Available at http://www.ncbi.nlm.nih.gov/pubmed/11372025.