Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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What's New in the Pediatric Guidelines (Last updated November 5, 2012; last reviewed November 1, 2012)

Key changes made to update the August 11, 2011, *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* are summarized below. Minor revisions have been made in toxicity tables and other sections of the document; all changes are highlighted throughout the guidelines. Throughout the document, references have been updated to include new publications where relevant.

Diagnosis of HIV infection

- New section on diagnostic testing in children with perinatal HIV exposure in exceptional situations: late seroreversion up to 24 months of age, postnatal exposure in children with prior negative virologic tests for whom there are additional HIV transmission risks (e.g., breastfeeding, feeding premasticated food), and non-subtype B HIV-1 infection and HIV-2 infection.
- New section on diagnostic testing in children with non-perinatal exposure.

When to Start Antiretroviral Therapy

- CD4 T lymphocyte (CD4 cell) count and CD4 percentage thresholds for initiation of treatment are now offered for children aged >12 months, but in the case of discordance between CD4 cell counts and percentages, decisions should be based on the lower value.
- Although CD4 percentage had been preferentially used to monitor immunologic status in children aged <5 years, recent analyses show that CD4 cell counts provide greater prognostic value than CD4 percentage for short-term disease progression in children aged <5 years as well as in older children.
- CD4 thresholds for treatment have been further subdivided into age groups 1 to <3, 3 to <5, and ≥5 years to more precisely link them to age-related changes in absolute CD4 cell count.
- The Panel continues to recommend treatment of all HIV-infected infants aged <12 months, regardless of clinical status, CD4 percentage, or viral load (**AI** for infants aged <12 weeks and **AII** for infants aged ≥12 weeks to 12 months).
- The Panel discusses current adult antiretroviral (ARV) guidelines and similarities and differences between children and adults. Adult guidelines have been modified to recommend treatment for all HIV-infected individuals, with the strength of the recommendation based on the pre-treatment CD4 cell count.
- In addition to recommending treatment for all children with AIDS or significant HIV-related symptoms **(AI*)**, the Panel also generally recommends treatment for all children aged ≥1 year with minimal or no symptoms (Clinical Categories N and A, or Clinical Category B disease due to a single episode of bacterial infection), with the strength of recommendation based on age and CD4 cell count/percentage. However, on a case-by-case basis, providers may elect to defer therapy based on clinical and/or psychosocial factors.
  - ART should be initiated in HIV-infected children aged ≥1 year with minimal or no symptoms with the following CD4 values:
    - Aged 1 to <3 years:
      - With CD4 cell count <1000 cells/mm^3 or CD4 percentage <25% **(AII)**
    - Aged 3 to <5 years:
      - With CD4 cell count <750 cells/mm^3 or CD4 percentage <25% **(AII)**

- Aged ≥5 years:
  - With CD4 cell count ≤500 cells/mm^3 (**AI*** for CD4 cell count <350 cells/mm^3, **BII*** for CD4 cell count 350–500 cells/mm^3)

- ART should be considered for HIV-infected children aged ≥1 year with minimal or no symptoms with the following CD4 values:
  - Aged 1 to <3 years:
    - With CD4 cell count ≥1000 cells/mm^3 or CD4 percentage ≥25% **(BIII)**
  - Aged 3 to <5 years:
    - With CD4 cell count ≥750 cells/mm^3 or CD4 percentage ≥25% **(BIII)**
  - Aged ≥5 years:
    - With CD4 cell count >500 cells/mm^3 **(BIII)**
- In children with lower-strength (B level) recommendations for treatment, plasma HIV RNA levels >100,000 copies/mL provide stronger evidence for initiation of treatment **(BII)**.

What Drugs to Start: Initial Combination Therapy for Antiretroviral Treatment-Naive Children

- Tenofovir disoproxil fumarate (tenofovir) has recently been FDA-approved for children as young as age 2 years. The Panel has modified its recommendations for use of tenofovir in children based on Tanner staging. Tenofovir, in combination with lamivudine or emtricitabine, is part of a Recommended nucleoside reverse transcriptase inhibitor (NRTI) combination for adolescents who are Tanner stage 4 or 5 **(AI*)**, an Alternative choice for those who are Tanner stage 3, and reserved for Special Circumstances for those aged ≥2 years and Tanner stage 1 or 2.
- Etravirine and rilpivirine are also FDA-approved but are not recommended as initial therapy at this time because of lack of experience and dosing information in children.
- Boosted fosamprenavir is now FDA-approved for infants as young as age 4 weeks, provided that they were born at ≥38 weeks' gestation. However, because of palatability and lower drug exposure in young infants, boosted fosamprenavir, when used in combination with 2 NRTIs, is an Alternative option only in infants and children aged 6 months and older.
- Darunavir with low-dose ritonavir is now FDA-approved and, when used in combination with 2 NRTIs, an Alternative regimen in children aged ≥3 years. Once-daily dosing of boosted darunavir in children aged <12 years is not recommended.
- Raltegravir is now FDA-approved for children aged ≥2 years, but are not recommended for initial therapy at this time because of insufficient data. Elvitegravir, another integrase inhibitor, is only available as a fixed-dose combination tablet containing elvitegravir/cobicistat/emtricitabine/tenofovir, and is FDA-approved for HIV-1-infected ARV treatment-naive adults, but not children aged <18 years. Given the lack of data in individuals aged <18 years, it cannot be considered for use as initial therapy in children at this time.
- Although emerging information about the use of efavirenz in pregnancy is reassuring, the Panel awaits additional safety information and recommends that alternative regimens that do not include efavirenz 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 a woman's health **(BIII)**.

Management of Treatment-Experienced Infants, Children, and Adolescents

- Management of treatment failure has been more clearly limited to management of virologic treatment failure. There is no consensus on how to manage immunologic or clinical treatment failure in the absence of virologic treatment failure.
- Newer individual drugs and classes of ARV drugs have been incorporated into both the discussion and the table of new regimen options for children with treatment failure (Table 20).

Specific Issues in Adolescents

- Updates have been provided in the section on contraceptive and ARV drug interactions.
- An update was provided regarding pregnancy outcomes in adolescent girls.

Pediatric Antiretroviral Drug Information

Updates with new pediatric data are provided when relevant for specific drugs.

- **Emtricitabine:** The Panel provides neonatal pharmacokinetic (PK) data at a dose of 3mg/kg/day, and PK data in children indicating that the oral solution has 20% lower plasma exposure than the capsule formulation. Information is provided on Complera (fixed-dose combination of tenofovir, emtricitabine, and rilpivirine) for adolescents aged >18 years and adults.
- **Lamivudine:** The Panel provides information on generic tablet formulations and weight band dosing for children who weigh ≥14 kg, using 150-mg scored tablets. The Panel discusses switching from twice-daily to once-daily dosing at 8 to10 mg/kg, based on review of data from the PENTA 13 and 15 and ARROW trials.
- **Stavudine:** The Panel recommends a maximum dose of 30 mg of stavudine.
- **Tenofovir:** The Panel provides information on the newly available pediatric oral powder and tablets of lower milligram amounts (150, 200, and 250 mg), and dosing by weight band starting at age 2 years and 10 kg, with a discussion of the recommended pediatric dose of 8 mg/kg/dose once daily and results of the studies that led to registration of the drug. The Panel notes Truvada (emtricitabine/tenofovir) is now FDA-approved for use in adolescents aged ≥12 years and who weigh ≥35 kg; and Atripla (emtricitabine/tenofovir/efavirenz) is now FDA-approved for use in adolescents aged ≥12 years and who weigh ≥40 kg.
- **Zidovudine:** Dosing recommendations for zidovudine used as prophylaxis for prevention of mother-to-child HIV transmission and in infants have been updated.
- **Efavirenz:** Additional detail has been added involving the precaution against using efavirenz in women of childbearing potential.
- **Etravirine:** Pediatric dosing recommendations have been updated to reflect FDA approval for treatment-experienced children aged 6 to <18 years.
- **Nevirapine:** The Panel notes data showing a three-fold increased risk of rash and hepatotoxicity in children with CD4 percentage >15% when initiating nevirapine.
- **Rilpivirine:** The Panel notes the availability of Complera (fixed-dose combination of tenofovir, emtricitabine, and rilpivirine) for adolescents aged >18 years and adults. A pediatric trial is under way in treatment-naive adolescents aged 12 to 18 years. The Panel recommends that rilpivirine should be administered with a meal that contains at least 500 calories, and notes that rilpivirine should not be used with proton pump inhibitors.

- **Atazanavir:** Modifications have been made in the dosing table and new dosing recommendations are discussed.
- **Darunavir:** Additional dosing down to a weight of 10 kg and PK of this dosing by weight band are described. The caveat against darunavir use in children aged <3 years was strengthened and explained more fully: Do not use darunavir in children aged <3 years because of concerns related to seizures and death in infant rats due to immaturity of the blood-brain barrier and liver metabolic pathways.
- **Fosamprenavir:** The Panel added information on FDA approval in infants as young as 4 weeks but notes that the Panel does not recommend use in infants aged <6 months, given concerns about palatability and low drug level exposures. Details about PK have also been added and a dosing table was added for children aged 6 months to 18 years.
- **Lopinavir/ritonavir:** The Panel discusses a preference for dosing in children at 300 mg lopinavir/m^2 twice daily rather than 230 mg/m^2 twice daily, particularly for ARV-experienced patients.
- **Raltegravir:** Information has been added on the newly available pediatric chewable tablets (25 and 100 mg), dosing by weight band starting at age 2 years, and results from the trials that led to FDA approval in children are summarized.
- **Elvitegravir:** Information has been added on the newly available fixed-dose combination tablet containing the integrase strand transfer inhibitor elvitegravir plus the PK booster cobicistat and the NRTIs emtricitabine and tenofovir. The Panel notes there are no data on its use in individuals aged <18 years.