Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Identification of Perinatal HIV Exposure (Last updated November 1, 2012; last reviewed November 1, 2012)

Panel's Recommendations
• HIV testing early in pregnancy is recommended as standard of care for all pregnant women in the United States **(AII)**.
• Repeat HIV testing in the third trimester should be considered for all HIV-seronegative pregnant women and is recommended for pregnant women who are at high risk of HIV infection (such as those with a known HIV-infected partner, personal or partner history of injection drug use, diagnosis with a sexually transmitted disease [STD], signs or symptoms of acute HIV infection or who reside in a high-prevalence area) **(AIII)**.
• Rapid HIV antibody testing at the time of labor or delivery should be performed on women with undocumented HIV status, and intrapartum antiretroviral (ARV) prophylaxis should be initiated in those who test positive **(AII)**.
• For pregnant women who are suspected to have acute HIV infection, a virologic test such as a plasma HIV RNA assay should be performed because serologic testing may be negative at this early stage of infection **(AII)**.
• Women who have not been tested for HIV before or during labor should undergo rapid HIV antibody testing during the immediate postpartum period or their newborns should undergo rapid HIV antibody testing. If results in mother or infant are positive, infant ARV prophylaxis should be initiated as soon as possible and the mothers should not breastfeed unless confirmatory HIV antibody testing is negative **(AII)**.
• Results of maternal HIV testing should be documented in the newborn's medical record and communicated to the newborn's primary care provider **(AIII)**.
• Infant HIV antibody testing to determine HIV exposure should be considered for infants in foster care and adoptees for whom maternal HIV infection status is unknown **(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

Diagnosis of HIV Infection in Infants and Children (Last updated November 1, 2012; last reviewed November 1, 2012)

Panel's Recommendations
• Virologic assays that directly detect HIV must be used to diagnose HIV infection in infants younger than 18 months **(AII)**.
• Virologic diagnostic testing in infants with known perinatal HIV exposure is recommended at ages 14 to 21 days, 1 to 2 months, and 4 to 6 months **(AII)**.
• Virologic diagnostic testing at birth should be considered for infants at high risk of HIV infection **(BIII)**.
• HIV DNA polymerase chain reaction and HIV RNA assays are recommended as preferred virologic assays **(AII)**.
• A positive virologic test should be confirmed as soon as possible by a repeat virologic test on a second specimen **(AII)**.
• Definitive exclusion of HIV infection in nonbreastfed infants is based on two or more negative virologic tests, with one obtained at ≥1 month of age and one at ≥4 months of age, or two negative HIV antibody tests from separate specimens obtained at ≥6 months of age **(AII)**.
• Some experts confirm the absence of HIV infection at 12 to 18 months of age in infants with prior negative virologic tests by performing an antibody test to document loss of maternal HIV antibodies **(BIII)**.
• HIV antibody assays alone can be used for diagnosis of HIV infection in children with perinatal exposure who are ≥18 months of age and in children with non-perinatal exposure (see text for exceptions) **(AII)**.
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*
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Laboratory Monitoring of Pediatric HIV Infection Prior to Therapy Initiation (Last updated November 1, 2012; last reviewed November 1, 2012)

Panel's Recommendations
• The age of the child must be considered when interpreting the risk of disease progression based on CD4 percentage or CD4 T lymphocyte (CD4 cell) count and plasma HIV RNA level **(AII)**. For any given CD4 percentage and count, younger children, especially those in the first year of life, face higher risk of progression than do older children **(AII)**.
• In children younger than 5 years of age, CD4 percentage is generally preferred for monitoring immune status because of age-related changes in absolute CD4 cell count in this age group although absolute CD4 count may also be used **(AII)**.
• CD4 percentage and/or CD4 cell count should be measured at the time of diagnosis of HIV infection and at least every 3 to 4 months thereafter **(AIII)**.
• Plasma HIV RNA should be measured to assess viral load at the time of diagnosis of HIV infection and at least every 3 to 4 months thereafter **(AIII)**.
• More frequent CD4 cell and plasma HIV RNA monitoring should be considered in children with suspected clinical, immunologic, or virologic deterioration or to confirm an abnormal value **(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*

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Treatment Recommendations for Initiation of Therapy in Antiretroviral-Naive HIV-Infected Infants and Children

Panel's Recommendations

- Antiretroviral therapy (ART) should be initiated in all children with AIDS or significant symptoms (Clinical Category C or most Clinical Category B conditions) **(AI*)**.
- ART should be initiated in HIV-infected infants <12 months of age regardless of clinical status, CD4 percentage or viral load (**AI** for infants <12 weeks of age and **AII** for infants ≥12 weeks to 12 months).
- ART should be initiated in HIV-infected children ≥1 year who are asymptomatic or have mild symptoms with the following CD4 values:
    - Age 1 to <3 years
        - with CD4 T lymphocyte (CD4 cell) count <1000 cells/mm^3 or CD4 percentage <25% **(AII)**
    - Age 3 to <5 years
        - with CD4 cell count <750 cells/mm^3 or CD4 percentage <25% **(AII)**
    - Age ≥5 years
        - with CD4 cell count <350 cells/mm^3 **(AI*)**
        - with CD4 cell count 350–500 cells/mm^3 **(BII*)**
- ART should be considered for HIV-infected children ≥1 year who are asymptomatic or have mild symptoms with the following CD4 values:
    - Age 1 to <3 years
        - with CD4 cell count ≥1000 cells/mm^3 or CD4 percentage ≥25% **(BIII)**
    - Age 3 to <5 years
        - with CD4 cell count ≥750 cells/mm^3 or CD4 percentage ≥25% **(BIII)**
    - Age ≥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)**.
- Issues associated with adherence should be assessed and discussed with an HIV-infected child's caregivers before initiation of therapy **(AIII)**. Patients/caregivers may choose to postpone therapy, and on a case-by-case basis, providers may elect to defer therapy based on clinical and/or psychosocial factors.

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*

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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)

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*

Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children (Table 8) (Last updated November 1, 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*

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Monitoring of Children on Antiretroviral Therapy (Last updated November 1, 2012; last reviewed November 1, 2012)

Panel's Recommendations
• Within 1 to 2 weeks after starting a new antiretroviral (ARV) regimen, children should be evaluated to screen for clinical side effects and to ensure patient and caretaker adherence to the regimen **(AIII)**. Evaluations can be conducted in person or over the phone. • After starting or changing therapy, more frequent evaluation may be needed to support adherence to the regimen **(AIII)**. • At least every 3 to 4 months thereafter, children should have a monitoring evaluation to assess both effectiveness and potential toxicity of their ARV regimens **(AII*)**.

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*

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Specific Issues in Antiretroviral Therapy for HIV-Infected Adolescents

(Last updated November 1, 2012; last reviewed November 1, 2012)

Panel's Recommendations
• Antiretroviral therapy (ART) regimens must be individually tailored to the adolescent **(AIII)**.
• Appropriate dosing of ART for adolescents is complex, not always predictable, and dependent upon multiple factors, including body mass and composition and pubertal development **(AII)**.
• Effective and appropriate methods should be selected to reduce the likelihood of unintended pregnancy and to prevent secondary transmission of HIV to sexual partners **(AI)**.
• Providers should be aware of potential interactions between ART and hormonal contraceptives, which could lower contraceptive efficacy **(AII*)**.
• 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)**.
• Adolescent girls who require treatment with efavirenz should undergo pregnancy testing before initiation of treatment and receive counseling about potential fetal risk and desirability of avoiding pregnancy while receiving efavirenz-containing regimens **(AIII)**.
• Pediatric and adolescent care providers should prepare adolescents for the transition into adult care settings **(AIII)**.

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

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Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents (Last updated November 1, 2012; last reviewed November 1, 2012)

Panel's Recommendations
• Strategies to maximize adherence should be discussed before initiation of antiretroviral therapy (ART) and again before changing regimens **(AIII)**. • Adherence to therapy must be stressed at each visit, along with continued exploration of strategies to maintain and/or improve adherence **(AIII)**. • At least one method of measuring adherence to ART (such as quantitative and/or qualitative self-report, pharmacy refill checks, pill counts) should be used in addition to monitoring viral load **(AII)**. • When feasible, once-daily antiretroviral regimens should be prescribed **(AI*)**. • To improve and support adherence, providers should maintain a nonjudgmental attitude, establish trust with patients/caregivers, and identify mutually acceptable goals for care **(AII*)**.

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Management of Medication Toxicity or Intolerance (Last updated November 1, 2012; last reviewed November 1, 2012)

Panel's Recommendations
• In children who have severe or life-threatening toxicity, all components of their drug regimen should be stopped immediately **(AIII)**. Once symptoms of toxicity have resolved, antiretroviral therapy (ART) should be resumed with substitution of a different antiretroviral (ARV) drug or drugs for the offending agent(s) **(AII*)**. • When modifying therapy because of toxicity or intolerance to a specific drug in children in whom virus has been suppressed, changing one drug in a multidrug regimen is permissible; if possible, an agent with a different toxicity and side-effect profile should be chosen **(AI*)**. • The toxicity and the medication presumed responsible should be documented in the medical record and the caregiver and patient advised of the drug-related toxicity to facilitate future medication choices if care is transferred **(AIII)**. • Dose reduction is not a recommended option in the setting of ARV toxicity, except when therapeutic drug monitoring (TDM) indicates a drug concentration above the normal therapeutic range **(AII*)**.
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*

Management of Treatment-Experienced Infants, Children, and Adolescents (Last updated November 1, 2012; last reviewed November 1, 2012)

Panel's Recommendations
• The goal of therapy following treatment failure is to achieve and maintain virologic suppression, as measured by a plasma viral load below the limits of quantification using the most sensitive assay **(AI*)**. • When complete virologic suppression cannot be achieved, the goals of therapy are to preserve or restore immunologic function (as measured by CD4 lymphocyte values), prevent clinical disease progression, and prevent development of additional drug resistance that could further limit future antiretroviral options **(AII)**. • Not all instances of treatment failure require an immediate change in therapy; careful assessment, especially of adherence, is required to evaluate the etiology of the treatment failure and determine an appropriate management strategy **(AII)**. • Children who require evaluation for treatment failure should be managed in collaboration with a pediatric HIV specialist **(AI*)**.

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

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Assessment of Patients with Virologic Failure of Antiretroviral Treatment (Last updated November 1, 2012; last reviewed November 1, 2012)

Panel's Recommendations
• Assess adherence to therapy; address barriers and develop interventions to improve adherence **(AII)**. • Assess medication intolerance **(AIII)**. • Assess issues related to pharmacokinetics because developmental and individual differences in drug absorption, distribution, metabolism, and elimination can cause inadequate antiretroviral (ARV) drug exposure that can result in combination antiretroviral therapy failure **(AII)**. • Perform ARV drug-resistance testing when virologic failure occurs, while a patient is still taking the failing regimen and before changing to a new regimen **(AI*)**. • Perform assessment in collaboration with a pediatric HIV specialist **(AI*)**.
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*

Approach to the Management of Virologic Failure of Antiretroviral Treatment (Last updated November 1, 2012; last reviewed November 1, 2012)

Panel's Recommendations
• The causes of virologic treatment failure, which include poor adherence, drug resistance, poor absorption of medications, inadequate dosing, and drug-drug interactions, should be assessed and addressed **(AII)**. • When deciding how to treat a child with virologic treatment failure, the probability of achieving durable virologic suppression should be considered, as well as the future options for treatment, should durable suppression not be achieved **(AII)**. • Children who experience treatment failure should be managed in collaboration with a pediatric HIV specialist **(AI*)**.

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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)**.

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The Use of Antiretroviral Agents Not Approved for Use In Children (Last updated November 1, 2012; last reviewed November 1, 2012)

Panel's Recommendations

- Children may need to use antiretroviral (ARV) drugs that are not yet approved for their age because many of the recently approved, more convenient, and potent agents are approved for use in adults before pharmacokinetic (PK), safety, and efficacy data are available in children **(AII)**.
- Dosing in a child of ARVs only approved for adults cannot simply be inferred from a simple calculation using the adult dose and the child's weight **(AII)**. Such use of ARVs should always be done in collaboration with a pediatric HIV specialist, who may have access to unpublished data about safety and PKs of ARVs that are not yet Food and Drug Administration (FDA)-approved for children **(AI*)**.
- Whenever possible, use of ARVs that are not yet FDA-approved for children should be done in the context of clinical trials that can generate the data needed for pediatric approval **(AIII)**.

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

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Antiretroviral Drug-Resistance Testing (Last updated November 1, 2012; last reviewed November 1, 2012)

Panel's Recommendations

- Antiretroviral (ARV) drug-resistance testing is recommended before initiation of therapy in all treatment-naive children **(AII)**. Genotypic resistance testing is preferred for this purpose **(AIII)**.
- ARV drug resistance testing is recommended before changing therapy because of treatment failure **(AI*)**.
- Resistance testing in patients with virological failure should be done while they are still on the failing regimen or within 4 weeks of discontinuation **(AII*)**.
- Phenotypic resistance testing should be used (usually in addition to genotypic resistance testing) for patients with known or suspected complex drug resistance mutation patterns, which generally arise after virologic failure of successive ARV therapy regimens **(BIII)**.
- The absence of detectable resistance to a drug does not ensure that use of the drug will be successful. Consequently, previously used ARV agents and previous resistance test results should be reviewed when making decisions regarding the choice of new agents for patients with virologic failure **(AII)**.
- Viral coreceptor (tropism) assays should be used whenever the use of a CCR5 antagonist is being considered **(AI*)**. Tropism assays should also be considered for patients who demonstrate virologic failure while receiving therapy that contains a CCR5 antagonist **(AI*)**.
- Consultation with a specialist in pediatric HIV infection is recommended for interpretation of resistance assays when considering starting or changing an ARV regimen in pediatric patients **(AI*)**.

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

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