Specific Issues in Antiretroviral Therapy for Adolescents Living with HIV Infection  (Last updated April 27, 2017; last reviewed April 27, 2017)

Panel's Recommendations

- Antiretroviral therapy (ART) selection should take into account the adolescent’s individual needs and preferences (AIII).
- Reproductive health including preconception care and contraceptive methods, and safe sex techniques to prevent HIV transmission should be discussed regularly (AI).
- All adolescents, including those who are considering pregnancy, should be receiving maximally suppressive ART (AII).
- Providers should be aware of potential interactions between ART and hormonal contraceptives that could lower contraceptive efficacy (AII*).
- 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

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 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/adolescents, but not studies limited to post-pubertal adolescents

Background

Most individuals in the United States who acquired HIV infection through perinatal transmission are now adolescents or young adults. Of the individuals who acquired HIV infection through perinatal transmission in the United States—1,999 are aged less than 13 years with an estimated 9,131 adults and adolescents (aged >13 years) as of December 2013.1 Most have had a long clinical course with an extensive history of treatment with antiretroviral therapy (ART).2,3 Many older youth initially received non-suppressive mono- or dual therapy prior to the availability of combination regimens. Challenges in the treatment of adolescents with perinatally acquired HIV infection include extensive drug resistance, complex regimens, and the long-term consequences of HIV and ART exposure.

Most post-pubertal adolescents living with HIV in the United States acquired their infection by horizontal rather than perinatal transmission. They generally follow a clinical course similar to that of adults and the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents (Adult and Adolescent Guidelines) should be used for treatment recommendations.4

Dosing of Antiretroviral Therapy for Adolescents Living with HIV

Puberty is a time of somatic growth and sexual maturation, with females developing more body fat and males more muscle mass. These physiologic changes may affect drug pharmacokinetics (PK), which is especially important for medications (e.g., the protease inhibitor atazanavir) that have a narrow therapeutic index that are used in combination with protein-bound medicines or hepatic enzyme inducers or inhibitors.5

In addition, many antiretroviral (ARV) drugs (e.g., abacavir, emtricitabine, lamivudine, tenofovir disoproxil fumarate [TDF], and some protease inhibitors [PIs]) are administered to children at higher body weight- or body surface area-based doses than would be predicted by direct extrapolation of adult doses. This is based upon reported PK data indicating more rapid drug clearance in children.

The choice of ART, specifically for TDF is based on sexual maturity rating (SMR, formerly Tanner staging) and not on age, related to concerns for associated toxicity.

Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection
Timing and Selection of ART

All individuals, including adolescents living with HIV, should initiate ART promptly. Optimal dosing recommendations for initial therapy that are pertinent to adolescents whose SMR is between I and III are available in Appendix A: Pediatric Antiretroviral Drug Information and What to Start. Recommendations for initial therapy for adolescents and young adults whose SMR is between IV and V are available in the What to Start section of the Adult and Adolescent Guidelines. These recommendations also reflect results from two key, randomized controlled trials in adults (START and TEMPRANO) which both demonstrated that the clinical benefits of ART are greater when ART is started early, with pre-treatment CD4 T lymphocyte (CD4) counts >500 cells/mm³, than when initiated at a lower CD4 cell count threshold.6,7

Adherence Concerns in Adolescents

Adolescents living with HIV are especially vulnerable to adherence problems resulting from their psychosocial and cognitive developmental trajectory. Comprehensive systems of care are required to serve both the medical and psychosocial needs of adolescents living with HIV, who are frequently inexperienced with personally managing health care systems and may lack health insurance. Compared with adults, these youth have lower rates of viral suppression and higher rates of virologic rebound and loss to follow up.8-10 For a further discussion of interventions to promote adherence in adolescents, see the HIV-Infected Adolescents section of the Adult and Adolescent Guidelines and a review by Agwu and Fairlie.11

A particular challenge is presented by youth who, despite interventions, remain unable to adhere to therapy. In these cases, alternative considerations to initiating or changing ARV therapy can include: reminders to the patient through cell phone alerts, a short-term deferral of treatment until adherence is improved or while adherence-related problems are aggressively addressed, an adherence testing and training period in which a placebo (e.g., vitamin pill) is administered, and the avoidance of any regimens with low genetic resistance barriers. Such decisions should be individualized and the patient’s clinical and laboratory status monitored carefully.

Sexually Transmitted Diseases in Adolescents

Sexually transmitted diseases (STDs), including human papilloma virus (HPV), should be addressed in all adolescents. In young men who have sex with men, screening for STDs often requires sampling from several body sites, including the oropharynx, rectum, and urethra, since multiple sites of infection are common.12 For a more detailed discussion of STDs, see the most recent Centers for Disease Control and Prevention guidelines,13 the Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents (Adult and Adolescent OI Guidelines), and Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children (Pediatric OI Guidelines) on HPV among youth living with HIV.14,15 All female adolescents living with HIV who are sexually active should receive gynecologic care and all adolescents should be immunized with HPV vaccination.

Adolescent Contraception, Pregnancy, and Antiretroviral Therapy

Adolescents living with HIV may initiate sexual activity before or after puberty. Family planning counseling, including a discussion of the risks of perinatal transmission of HIV and methods for reducing risks, should be provided to all youth. Reproductive health options including pregnancy planning, preconception care, contraception methods, and safer sex techniques (including the correct and consistent use of condoms) for prevention of secondary HIV transmission should be discussed regularly (see U.S. Medical Eligibility Criteria for Contraceptive Use).16 For additional information readers are referred to The 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 (Perinatal Guidelines) section entitled Reproductive Options for HIV-Concordant and Serodiscordant Couples.17

The possibility of planned and unplanned pregnancy should also be considered when selecting an ART regimen for an adolescent female. The most vulnerable period in fetal organogenesis is the first trimester, often before
pregnancy is recognized. Concerns about specific ARV drugs and birth defects should be promptly addressed (for additional information please see the Perinatal Guidelines).17 Readers should consult the Perinatal Guidelines for guidance in selection of ARV drugs during pregnancy.

**Contraceptive-Antiretroviral Drug Interactions**

Women living with HIV can use all available contraceptive methods, including the transdermal patch and vaginal ring.

Several PI and non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs alter metabolism of oral contraceptives, which may reduce the efficacy of oral contraceptive agents or increase the risk of estrogen- or progestin-related adverse effects (see the Adult and Adolescent Guidelines and http://www.hiv-druginteractions.org).18-20 Integrase inhibitors (specifically raltegravir) appear to have no interaction with estrogen-based contraceptives.21 For more information about potential interactions between ARVs and hormonal contraceptives please see Table 3 in the Perinatal Guidelines.

Concerns about loss of bone mineral density (BMD) with long-term use of depot medroxyprogesterone acetate (DMPA) with or without ART (specifically TDF) should not preclude use of DMPA as an effective contraceptive, unless there is clinical evidence of bone fragility. However, monitoring of BMD in young women on DMPA should be considered.22

**Pregnant Adolescents Living with HIV**

Adolescents who want to become pregnant should be referred for preconception counseling and care, including discussion of special considerations for use of ART during pregnancy (see Perinatal Guidelines).17 Pregnancy should not preclude the use of optimal therapeutic regimens. However, because of considerations related to prevention of perinatal transmission and maternal and fetal safety, selection of regimens may be different for pregnant women or women planning to become pregnant than for non-pregnant women. Details regarding choice of ART regimen in pregnant women living with HIV, including adolescents, are provided in the Perinatal Guidelines.17 Pregnancies are currently being reported as girls with perinatally acquired HIV infection enter adolescence and young adulthood.23,24 Some studies suggest higher rates of adverse pregnancy outcome, such as small-for-gestational-age infants, among pregnant women with perinatal compared to horizontal infection, and unplanned pregnancy appears frequent.24-26 However, the rate of perinatal transmission among pregnant women with perinatally acquired HIV infection who are receiving ART appears similar to that among women on ART who acquired HIV by horizontal transmission.27-31

**Transition of Adolescents into Adult HIV Care Settings**

Facilitating a seamless transition of adolescents living with HIV from their pediatric/adolescent medical home to adult care is important but challenging. Pediatric and adolescent providers and their multidisciplinary teams should have a formal written plan in place to transition adolescents to adult care. While transition generally occurs when individuals are in their late teens or early 20s, the transition process should be initiated early in the second decade of life. Transition is “a multifaceted, active process that attends to the medical, psychosocial, cognitive and educational, or vocational needs of adolescents as they move from the child-focused to the adult-focused health-care system.”32 Care models for children and adolescents with perinatal HIV tend to be family-centered, consisting of a multidisciplinary team that often includes pediatric or adolescent physicians, nurses, social workers, and mental health professionals. These providers generally have long-standing relationships with patients and their families, and care is rendered in discreet, more intimate settings. Although expert care is also provided under the adult HIV care medical model, an adolescent may be unfamiliar with the more individual-centered, busier clinics typical of adult medical providers and uncomfortable with providers with whom they do not have a long-standing relationship. Providing adolescents and their new adult medical care providers with support and guidance regarding expectations for each partner in the patient-provider relationship may be beneficial. In this situation, it may be helpful for a pediatric and an adult provider to share joint care of a patient for a period of time.
The adolescent provider should have a candid discussion with the transitioning adolescent to understand what qualities the adolescent considers most important in choosing an adult care setting (e.g., confidentiality, small clinic size, after-school appointments). Additional factors that should be considered during transition include social determinants such as developmental status, behavioral/mental health issues, housing, family support, employment, recent discharge from foster care, peer pressure, illicit drug use, and incarceration. Psychiatric comorbidities and their effective management predict adherence to medical care and therapy.\textsuperscript{33-36}

Currently there is no definitive model of transition to adult HIV care and only limited reports about outcomes following transition. In some settings, youth followed in adult care settings have had higher rates of attrition from care than those remaining in pediatric/adolescent care; in one U.S. study, only 42\% of youth receiving care in an adult clinic remained in care after 12 months compared to 75\% of those receiving care in a pediatric clinic.\textsuperscript{10} A report from the United Kingdom suggests an increased risk of mortality after transition.\textsuperscript{35} In a report from a Baltimore clinic on 50 youth (31 non-perinatally and 19 perinatally-acquired HIV), although 86\% were successfully transitioned and linked to adult care, only 50\% were retained in care 12 months after transition.\textsuperscript{37} Another study that examined the continuum of care for youth with perinatally acquired HIV, using surveillance data in New York city, reported worsening rates of retention and lower rates of viral suppression with increasing age. Rates of continuous engagement in care and viral suppression were 89\% and 67\%, respectively, for individuals aged 13 to 19 years decreasing to 76\% and 58\% for those aged 20 to 29 years, underscoring the need to critically examine transition and determine best mechanisms to optimize the long-term outcomes for youth with perinatal HIV infection.\textsuperscript{1}

Some general guidelines, mostly based on anecdotal evidence and consensus expert opinion, are available about transitional plans and who might benefit most from them.\textsuperscript{38-45} To maximize the likelihood of success, providers should prepare adolescents for transition long before it occurs. Attention to the following key areas could improve retention in care and minimize the risk of interruptions to ART:

\begin{itemize}
\item Developing a written individualized transition plan to address comprehensive care needs including medical, psychosocial, and financial aspects of transitioning;
\item Optimizing provider communication between pediatric/adolescent and adult clinics;
\item Identifying adult care providers who have expertise in providing care to adolescents and young adults;
\item Addressing patient/family barriers caused by lack of information, stigma or disclosure concerns, and differences in practice styles;
\item Preparing youth for life skills development, including counseling them on the appropriate use of a primary care provider and appointment management, the importance of prompt symptom recognition and reporting, and the importance of self-efficacy in managing medications, insurance, and entitlements;
\item Identifying an optimal clinic model for a given setting (i.e., simultaneous transition of mental health and/or case management versus a gradual phase-in);
\item Implementing ongoing evaluation to measure the success of a selected model;
\item Engaging in regular multidisciplinary case conferences between adult and adolescent care providers;
\item Implementing interventions that may be associated with improved outcomes, such as support groups and mental health consultation;
\item Incorporating a family planning component into clinical care;
\item Educating HIV care teams and staff about transitioning; and
\item Beginning discussions regarding transition early and before the actual transition process.
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\section*{References}
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