Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Specific Issues in Antiretroviral Therapy for Adolescents Living with HIV  
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**Background**

The majority of individuals in the United States who acquired HIV through perinatal transmission are now adolescents or young adults; only about <20% are aged <13 years. Most have had a long clinical course with an extensive antiretroviral treatment (ART) history. Many older youth and adults initially received nonsuppressive monotherapy or dual-therapy prior to the availability of fixed-dose combination (FDC) regimens. Challenges that affect the treatment of adolescents with perinatally acquired HIV include extensive drug resistance, complex regimens, the long-term consequences of HIV and ART exposure, unfavorable socioeconomic circumstances, and psychosocial factors.

In the United States, most adolescents aged ≥14 years who recently received HIV diagnoses acquired their infection by horizontal, rather than perinatal, transmission. They generally follow a clinical course similar to that of adults, and the Adult and Adolescent Antiretroviral Guidelines should be used for treatment recommendations. Additional information that is specific to the care of post-pubertal adolescents can be found in Adolescents and Young Adults with HIV.

**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 (PKs), which is especially important for medications (e.g., the protease inhibitor [PI] atazanavir) that have a narrow therapeutic index and that are used in combination with protein-bound medicines or hepatic enzyme inducers or inhibitors.

In addition, many antiretroviral (ARV) drugs (e.g., abacavir, emtricitabine, lamivudine, tenofovir disoproxil fumarate [TDF], and some PIs) are administered to children at higher body weight-based or body surface area-based doses than would be predicted by direct extrapolation of adult doses. These doses are based on reported PK data that indicates more rapid drug clearance in children than in adults. TDF should only be
used in patients with certain sexual maturity ratings (SMRs, formerly Tanner staging), due to concerns about associated toxicity.

**Timing and Selection of Antiretroviral Therapy**

All individuals who are living with HIV, including adolescents, should initiate ART as soon as possible. Recommendations for doses to use when initiating therapy in adolescents whose SMRs are between 1 and 3 can be found in Appendix A: Pediatric Antiretroviral Drug Information and What to Start. Recommendations for initial therapy for adolescents and young adults whose SMRs are between 4 and 5 are available in the What to Start section of the Adult and Adolescent Antiretroviral Guidelines. These recommendations reflect the results from two key randomized controlled trials in adults (START and TEMPRANO). These studies demonstrated that the clinical benefits of ART are greater when ART is started early, when a patient’s pretreatment CD4 T lymphocyte (CD4) count is >500 cells/mm³, than when ART is initiated at a lower CD4 cell count threshold.12,13 Clinicians who are treating adolescents of childbearing potential should consider some additional factors before initiating ART, including potential drug interactions with contraception and the safety of using certain ARV drugs before conception or during pregnancy (see the Contraception, Pregnancy, and Antiretroviral Therapy section below).

**Adherence Concerns in Adolescents**

Poor adherence to ART is a common problem among adolescents with HIV. Both psychosocial and cognitive developmental factors may contribute to adherence challenges and should be assessed regularly. The adolescent’s individual needs and preferences should also be considered when making decisions about initiating or changing ART. Comprehensive systems of care are required to serve both the medical and psychosocial needs of adolescents living with HIV, who are frequently inexperienced with managing their own health care and may lack health insurance. Many are also at risk for mental health issues, including psychiatric, behavioral, and substance use disorders that may interfere with their adherence.14,15 Compared with adults, these youth have lower rates of viral suppression and higher rates of virologic rebound and loss to follow up.16-18 For further discussion of interventions to promote adherence in adolescents, see the Adolescents and Young Adults with HIV section of the Adult and Adolescent Antiretroviral Guidelines and a 2013 review by Agwu and Fairlie.4

A specific challenge is presented by youth who, despite interventions, remain unable to adhere to therapy. In these cases, alternatives to changing ARV therapy can include, but are not limited to: simplifying treatment to a once-daily regimen or an FDC tablet, using cell phone alerts and other eHealth approaches to remind patients about taking their medication and attending clinic visits, initiating a short-term deferral of treatment until adherence improves or while adherence-related problems are aggressively addressed, initiating an adherence testing and training period in which a placebo (e.g., vitamin pill) is administered, scheduling appointments more frequently, employing directly observed therapy, and avoiding any regimens with a low genetic resistance threshold. Such decisions should be individualized, and the patient’s clinical and laboratory status should be monitored carefully while using any of these interventions.

**Mental Health Concerns in Adolescents**

Many factors can increase the risk of adverse mental health outcomes among adolescents with perinatally acquired HIV, including long-term medical treatment for a chronic disease, hospitalizations, stigma, the neurocognitive impacts of HIV, parental psychiatric and substance use disorder, and family and caregiver stress and loss. The prevalence of mental health disorders in youth with perinatally acquired HIV is high, with nearly 70% of these adolescents meeting the criteria for a psychiatric disorder at some point in their lives.14,19-21 The most common conditions include anxiety and behavioral disorders, mood disorders (including depression), and attention deficit hyperactivity disorder. Effectively managing psychiatric comorbidities can improve a patient’s adherence to medical care, including ART, and lead to better academic performance and interpersonal relationships.15,22-24
Interventions that address mental health problems in youth with perinatally acquired HIV are not well studied, but some studies have evaluated pharmacologic interventions; behavioral modification; and individual, family, and group counseling.\textsuperscript{25-27} Providers who are caring for adolescents with HIV should incorporate screening for psychiatric and substance use disorders into routine care and refer patients to age-appropriate services as needed. The \textit{American Academy of Pediatrics policy statement} provides some guidance and screening tools, particularly for depression. Screening tools for substance use, such as \textit{Screening, Brief Intervention, and Referral to Treatment (SBIRT)} or \textit{Car, Relax, Alone, Forget, Friends, and Trouble (CRAFFT)}, may be used.\textsuperscript{38}

**Sexually Transmitted Infections in Adolescents**

Clinicians should discuss the risk of sexually transmitted infections (STIs) with all adolescents who are living with HIV and screen and treat appropriately. \textbf{Clinicians should regularly obtain a detailed sexual history for adolescent patients in order to determine which STI screening tests are appropriate.} In young men who have sex with men, screening for STIs often requires sampling from several body sites, including the oropharynx, rectum, and urethra, since multiple sites of infection are common. Furthermore, a negative assay at a single site does not exclude infection at another site.\textsuperscript{29} For a more detailed discussion of STIs, see the most recent \textit{Centers for Disease Control and Prevention guidelines},\textsuperscript{30} \textit{Human Papillomavirus Disease} in the \textit{Adult and Adolescent Opportunistic Infection Guidelines}, and \textit{Human Papillomavirus} in the \textit{Pediatric Opportunistic Infection Guidelines}.\textsuperscript{31,32} All female adolescents living with HIV who are sexually active should receive gynecologic care, and all adolescents should receive the HPV vaccination.

**Contraception, Pregnancy, and Antiretroviral Therapy**

Adolescents living with HIV may initiate sexual activity before or after puberty. Sexually active adolescents are at risk for unintended pregnancy. Approximately half of pregnancies in the United States, including those among women with HIV, are unintended or unplanned.\textsuperscript{33,34} Providers should regularly assess adolescents’ desires to become pregnant or avoid pregnancy (also known as their fertility intentions). Family planning counseling, including a discussion of the risks of sexual HIV transmission, perinatal HIV transmission, and methods for reducing these risks, should be provided to all youth. Reproductive health options, such as pregnancy planning, preconception care, contraception methods, \textit{pre-exposure prophylaxis for partners}, and safer sex techniques (including instruction on the correct and consistent use of condoms) for prevention of secondary HIV transmission, should be discussed regularly (see \textit{U.S. Medical Eligibility Criteria for Contraceptive Use}).\textsuperscript{35} For additional information, readers are referred to the following sections of the \textit{Perinatal Guidelines: Preconception Counseling and Care for Women of Childbearing Age Living with HIV and Reproductive Options for Couples in Which One or Both Partners are Living with HIV}.\textsuperscript{36} The American Academy of Pediatrics Committee on Adolescence offers guidance about the integration of sexual and reproductive health care in pediatric clinical settings.\textsuperscript{37}

The possibility of planned and unplanned pregnancy should 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. When treating adolescents of childbearing potential, clinicians should carefully review the potential toxicities of ARV drugs and consider making any necessary changes to a regimen as promptly as possible (e.g., before conception, when possible). For additional information, please see \textit{Teratogenicity} in the \textit{Perinatal Guidelines}.\textsuperscript{36} Readers should consult the \textit{Recommendations for Use of Antiretroviral Drugs During Pregnancy} in the \textit{Perinatal Guidelines} for information about the selection and management of ARV drugs before and during pregnancy for women with HIV who are of childbearing age (see \textit{Table 7}). Recent safety concerns about the potential for neural tube defects in infants born to women who conceived while taking regimens that contained \textit{dolutegravir} should be considered when discussing ART regimen options with female adolescents and their caregivers. Specific recommendations about the initiation and use of dolutegravir in women of childbearing potential and in pregnant women are available in the \textit{Adult and Adolescent Antiretroviral Guidelines} (see \textit{Table 6b} and \textit{Adolescents and Young Adults with HIV}) and...
Interactions Between Contraceptives and Antiretroviral Drugs

Women living with HIV can use all available contraceptive methods, including hormonal contraceptives, implantable devices, intrauterine devices, the transdermal patch, and vaginal ring. Several PI and non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs alter the metabolism of oral contraceptives, which theoretically may reduce the efficacy of oral contraceptive agents or increase the risk of estrogen-related or progesterin-related adverse effects (see the Drug-Drug Interactions in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker). Integrase strand transfer inhibitors (specifically raltegravir) appear to have no interaction with estrogen-based contraceptives. For more information about potential interactions between ARV drugs and hormonal contraceptives, please see Table 3 in the Perinatal Guidelines.

Concerns about loss of bone mineral density with long-term use of depot medroxyprogesterone acetate (DMPA), with or without ART (specifically TDF), should not preclude the use of DMPA as an effective contraceptive, unless there is clinical evidence of bone fragility.

Pregnant Adolescents Living with HIV

Adolescents who want to become pregnant should receive preconception counseling and care, including a discussion of pregnancy planning and special considerations when using ARV drugs during pregnancy (see the Perinatal Guidelines). Pregnancy should not preclude the use of optimal therapeutic regimens. Clinicians need to consider maternal and fetal safety as well as the need to prevent perinatal transmission when selecting regimens for pregnant women or women who are planning to become pregnant. See the Perinatal Guidelines for more details about choosing an ART regimen for pregnant women living with HIV, including adolescents, and guidance regarding the use of dolutegravir during pregnancy. Pregnancies have been reported as girls with perinatally acquired HIV enter adolescence and young adulthood. Some studies suggest higher rates of adverse pregnancy outcomes, such as small-for-gestational-age infants, among pregnant women with perinatally acquired HIV than among those with horizontal HIV infection, and unplanned pregnancy appears to be a frequent occurrence. However, the rate of perinatal transmission among pregnant women with perinatally acquired HIV who are receiving ART appears to be similar to the rate among women on ART who acquired HIV by horizontal transmission.

Transition of Adolescents into Adult HIV Care Settings

Facilitating a seamless transition for adolescents living with HIV from their pediatric/adolescent medical home to adult care is important but challenging. Many adolescents disengage from care during the transition to adult care, putting them at risk for HIV progression and transmission to partners. 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, discussion of and planning for the transition process should be initiated early in the teen years, with involvement from both the adolescent and his or her parents and/or caregivers. 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.” Care models for children and adolescents with perinatally acquired HIV tend to be family-centered, consisting of a multidisciplinary team that often includes 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, intimate settings. Although expert care is also provided under the adult HIV care medical model, adolescents and their caregivers may be unfamiliar with the busier, more individual-centered clinics that are typical of adult medical providers. These providers often expect patients to assume a greater level of responsibility for their care, and adolescents may be uncomfortable with providers with whom they do not have a long-standing relationship.
One multisite study in the United States found that adolescents who transitioned to adult care at an older age reported greater satisfaction with their care than those who transitioned at a younger age. Additionally, adolescents who reported being able to perform certain tasks that were related to their care (e.g., making appointments, requesting prescriptions, arranging transportation to appointments) were more likely to be engaged in adult care. Providing adolescents, caregivers, and their new adult medical care providers with support and guidance regarding the expectations for each person involved in the patient-provider relationship may be beneficial. In this situation, it may be helpful for a pediatric provider and an adult provider to share joint care of a patient for a period of time.

The adolescent-care provider should have a candid discussion with the transitioning adolescent and their caregivers to understand what qualities the adolescent considers most important when choosing an adult care setting (e.g., confidentiality, small clinic size, low patient-to-provider ratio, availability of after-school or evening appointments). Social determinants, such as the patient’s developmental status, behavioral/mental health issues, housing, family support, employment status, recent discharge from foster care, peer pressure, illicit drug use, and incarceration, should also be considered during transition.

Currently, there is no definitive model of transition to adult HIV care, and only a limited number of studies have reported on outcomes following transition, though research in this area is ongoing. Several studies have shown that youth who transitioned into adult care settings had higher rates of attrition from care than those who remained 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. Another multisite study in the United States showed that only 37% of youth had successfully transitioned to adult care after a follow-up period of 9 months. A report from the United Kingdom suggests that the mortality rate of adolescents with HIV increases after transition. In a report on 50 youth from a Baltimore clinic (31 with non-perinatally acquired HIV and 19 with perinatally acquired HIV), only 50% were retained in care 12 months after transition, although 86% of participants were successfully transitioned and linked to adult care. Another study used surveillance data in New York City to examine the continuum of care for youth with perinatally acquired HIV. Rates of continuous engagement in care and viral suppression were 89% and 67%, respectively, for individuals aged 13 years to 19 years. These rates decreased to 76% and 58% for those aged 20 years to 29 years, underscoring the need to critically examine transition and determine the best mechanisms to optimize the long-term outcomes for youth with perinatal HIV infection. A recent retrospective study from Atlanta reported that, while retention rates were initially high once adolescents entered adult care, they had declined significantly by the second year after transition. Pre-transition viral suppression and shorter linkage time between the pediatric and adult clinic were associated with better outcomes post-transition.

Some general guidelines, mostly based on anecdotal evidence and consensus expert opinion, are available about transition plans and who might benefit most from them. 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 ART interruptions:

- Educating HIV care teams and staff about transitioning;
- Beginning discussions about transition early, before the actual transition process;
- Developing a written, individualized transition plan to address comprehensive care needs, including medical, psychosocial, and financial aspects of transitioning;
- Optimizing provider communication between pediatric/adolescent clinics and adult clinics;
- Identifying adult care providers who are experts in providing care to adolescents and young adults;
- Addressing barriers caused by a lack of information, stigma, or disclosure concerns, and discussing the differences between the practice styles of adult clinics and pediatric/adolescent clinics.
• Helping youth develop the skills needed to manage their own care, including counseling them on appointment management, the appropriate use of a primary care provider, the importance of prompt symptom recognition and reporting, and the importance of managing medications, insurance, and state and federal benefits;

• Identifying an optimal clinic model for a given setting (e.g., simultaneous transition of mental health and/or case management versus a gradual phase-in);

• Clearly defining the desired outcomes for the transition, such as retention in care, ongoing access to other services (e.g., case management, mental health), clinical outcomes (e.g., viral suppression), and patient satisfaction;

• Implementing ongoing evaluations to measure the success of a transition model;

• Engaging in regular multidisciplinary case conferences between adult and adolescent care providers;

• Implementing interventions that may be associated with improved outcomes, such as support groups and mental health consultation; and

• Identifying a care navigator who can provide support during the transition.

References


