Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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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 16% are aged <13 years. Most have had a long clinical course with an extensive history of treatment with antiretroviral therapy (ART). Many older youth and adults initially received nonsuppressive mono- or dual-therapy prior to the availability of combination 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, social determinants, and psychosocial factors.

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 Adult and Adolescent Guidelines should be used for treatment recommendations.

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 [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- 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. The choice of some ARVs, specifically TDF, is based on sexual maturity rating (SMR, formerly Tanner staging) and not on age, due to concerns about associated toxicity.
Timing and Selection of Antiretroviral Therapy

All individuals who are living with HIV, including adolescents, should initiate ART promptly. Optimal dosing recommendations for initial therapy that are pertinent to adolescents whose SMRs are between 1 and 3 are available 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 Guidelines. These recommendations 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, 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.¹¹,¹²

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.¹³⁻¹⁵ For further discussion of interventions to promote adherence in adolescents, see the Adolescents and Young Adults with HIV section of the Adult and Adolescent Guidelines and a 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 initiating or changing ARV therapy can include, but are not limited to: 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, more frequent appointments, directly observed therapy, and the avoidance of 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.

Sexually Transmitted Infections in Adolescents

Sexually transmitted infections (STIs), including human papilloma virus (HPV), should be addressed in all adolescents. 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.¹⁶ For all adolescents, there should be a detailed sexual history (to elicit practices that may place them at increased risk for STI acquisition) and to inform appropriate screening. For a more detailed discussion of STIs, see the most recent Centers for Disease Control and Prevention guidelines and the Human Papillomavirus Disease section in the Adult and Adolescent Opportunistic Infections Guidelines and the Human Papillomavirus section in the Pediatric Opportunistic Infections Guidelines.¹⁸,¹⁹ All female adolescents living with HIV who are sexually active should receive gynecologic care, and all adolescents should be immunized with the HPV vaccination.

Adolescent 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. Data indicate that approximately half of pregnancies in the United States, including those among women with HIV, are unintended or unplanned.²⁰,²¹ Providers should regularly assess adolescents’ desires to become pregnant or avoid pregnancy (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, 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 U.S. Medical Eligibility Criteria for Contraceptive Use). For additional information, readers are referred to sections of the Perinatal Guidelines entitled Preconception Counseling and Care for Women of Childbearing Age Living with HIV and Reproductive Options for Couples with the Same or Differing HIV Status. The American Academy of Pediatrics Committee on Adolescence offers guidance about the integration of sexual and reproductive health care in pediatric clinical settings.

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. Concerns about specific ARV drugs and birth defects should be promptly addressed (for additional information please see the Teratogenicity section of the Perinatal Guidelines). Readers should consult the 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.

**Contraceptive-Antiretroviral Drug Interactions**

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- or progestin-related adverse effects (see the Adult and Adolescent 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 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.

**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 for use of ART during pregnancy (see the Perinatal Guidelines). 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 nonpregnant women. See the Perinatal Guidelines for more details about choosing an ART regimen for pregnant women living with HIV, including adolescents. Pregnancies are currently being 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 perinatal infection than among those with horizontal infection, and unplanned pregnancy appears frequent. However, the rate of perinatal transmission among pregnant women with perinatally acquired HIV who are receiving ART appears similar to that 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. 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 second decade of life 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 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, 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 may be 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 the 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-care 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, low patient-to-provider ratio, availability of after-school or evening appointments). Additional factors that should be considered during transition include social determinants, such as developmental status, behavioral/mental health issues, housing, family support, employment status, 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. Currently, there is no definitive model of transition to adult HIV care and only a limited number of reports about outcomes following transition, though research in this area is ongoing. In some studies, youth followed into 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. A report from the United Kingdom suggests an increased risk of mortality after transition. In a report from a Baltimore clinic on 50 youth (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 to 19 years. These rates decreased to 76% and 58% for those aged 20 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. Pretransition 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 transitional 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:

- 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 have expertise in providing care to adolescents and young adults;
- Addressing patient or family barriers caused by lack of information, stigma or disclosure concerns, and differences in practice styles;
- Preparing youth for life skills development, 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 self-efficacy in managing medications, insurance, and state and federal benefits;

- 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);

- 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 selected 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;

- Incorporating a family-planning component into clinical care;

- Educating HIV care teams and staff about transitioning; and

- Beginning discussions regarding transition early, before the actual transition process.

References


