Special Considerations for Antiretroviral Therapy Use in Adolescents With HIV

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Panel's Recommendations
• All adolescents with HIV should receive maximally suppressive antiretroviral (ARV) therapy; this is urgent for those who are sexually active, considering pregnancy, or pregnant (AII). • ARV regimen selection should include consideration of the adolescent's individual needs and preferences (AIII). See What to Start: Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children and Management of Children Receiving Antiretroviral Therapy for more information. • All adolescents with HIV should be screened for mental health disorders and substance use disorders (AII). • Reproductive and sexual health issues—including pregnancy intentions, contraceptive methods, safer sex techniques to prevent transmission of HIV and other sexually transmitted infections (STIs), regular STI screening, pre-exposure prophylaxis for partners, pregnancy planning, and preconception care—should be discussed regularly (AII). • Adolescents with HIV can use all available hormonal contraceptive methods (e.g., pill, patch, ring, injection, implant); however, providers should consider potential drug–drug interactions between hormonal contraceptives and ARV medications that could affect contraceptive efficacy (AII*). See Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives in the Perinatal Guidelines. • 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 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/adolescents, but not studies limited to postpubertal adolescents.*

Background

Most individuals in the United States who acquired HIV through perinatal transmission are now adolescents or young adults. Most have had a long clinical course with an extensive antiretroviral (ARV) treatment history.[1,2] Older youth and adults may have initially received nonsuppressive monotherapy or dual therapy prior to the availability of combination ARV regimens, including fixed-dose combination (FDC) formulations. Challenges that affect the treatment of adolescents with perinatally acquired HIV include extensive drug resistance, complex regimens, the long-term consequences of HIV and antiretroviral therapy (ART) exposure,[3] the developmental transition to adulthood, and psychosocial factors.[4-7]

In the United States, most adolescents aged ≥14 years who recently received HIV diagnoses acquired their infection through non-perinatal transmission.[8] They generally follow a clinical course similar to that of adults, and the Adult and Adolescent Antiretroviral Guidelines should be consulted for treatment recommendations for these patients. Additional information that is specific to the care of post-pubertal adolescents can be found in Adolescents and Young Adults With HIV.

Timing and Selection of Antiretroviral Therapy

All adolescents with HIV (like all people with HIV) should initiate ART as soon as possible after HIV diagnosis. Recommendations for ART selection in adolescents with sexual maturity ratings (SMRs) between 1 and 3 can be found in What to Start: Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children and Appendix A: Pediatric Antiretroviral Drug Information. ART recommendations for adolescents and young adults with SMRs between 4 and 5 are available in the What to Start: Initial Combination Antiretroviral Regimens for People With HIV section of the Adult and Adolescent Antiretroviral Guidelines. Optimizing and simplifying treatment may be especially important when treating adolescents, because this can help improve adherence (see Modifying Antiretroviral Regimens in Children With Sustained Virologic Suppression on Antiretroviral Therapy). Clinicians who are treating adolescents of childbearing potential should consider 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).

Dosing of Antiretroviral Therapy for Adolescents With HIV

Clinical providers need to pay attention to the transition of adolescents from pediatric to adult ART dosing. Many ARV drugs (e.g., abacavir, emtricitabine, lamivudine, tenofovir disoproxil fumarate [TDF], and some protease inhibitors [PIs]) are administered to children at higher body weight–based doses or body surface area–based doses than would be predicted by direct extrapolation of adult doses. These doses are based on reported pharmacokinetic data that indicate more rapid drug clearance in children than in adults. Therefore, failure to ensure weight-appropriate dosing in adolescents can result in an increased risk of drug toxicity if higher pediatric dosing is not transitioned to lower adult dosing (often between 25 kg and 40 kg, depending on the particular drug).[9]

Adherence Concerns in Adolescents

Low adherence to ART is a common problem among adolescents with HIV. Both psychosocial and cognitive developmental factors may contribute to adherence challenges, and these factors should be assessed regularly. Assessment of antiretroviral adherence in adolescents with HIV can be challenging, and discordance between self-report and other adherence measures—such as viral load and therapeutic or cumulative drug levels—should prompt open discussions with the adolescent and their caregiver. In one study conducted in Botswana, adolescents whose self-reported adherence and electronic adherence monitoring were discordant reported reasons for not disclosing non-adherence that included fear of disappointing caregivers and providers and a desire to avoid negative feedback or punitive adherence counseling.[10] Providers should encourage open discussions that normalize the difficulties of taking life-long medications and provide positive reinforcement of disclosing adherence challenges. The adolescent's individual needs and preferences also should 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 with HIV, because they are frequently inexperienced with managing their health care and may also lack health insurance. Adolescents with perinatally acquired HIV infection are at risk for neurocognitive impairment, which also can interfere with medication adherence.[11,12] Many also are at risk for mental health comorbidities, including psychiatric, behavioral, and substance use disorders that may interfere with adherence to ART.[7,13] Compared with adults, youth have lower rates of viral suppression and higher rates of virologic rebound and loss to follow-up.[14,15] For further discussion of interventions to promote adherence in adolescents, see the Adolescents and Young Adults With HIV section of the Adult and Adolescent Antiretroviral Guidelines and a 2013 review by Agwu and Fairlie.[3]

A specific challenge is presented by youth who, despite interventions, remain unable to adhere to therapy. In these cases, simplifying treatment to a once-daily regimen, an FDC tablet, or a long-acting injectable ARV regimen may improve adherence. The first long-acting injectable ARV regimen (cabotegravir and rilpivirine) was recently approved for use in adolescents aged ≥12 years and weighing ≥35 kg who are virally suppressed; however, data on use in adolescents are limited to safety, pharmacokinetics, and acceptability (see Cabotegravir and Rilpivirine).[16,17] Data are not yet available on the use of this combination ARV in adolescents and its potential use in those with adherence concerns. Alternatives to changing the ARV regimen can include, but are not limited to, using cellphone alerts and other mHealth approaches to remind patients to take their medication and attend clinic visits[18]; initiating a short-term deferral of treatment until adherence improves or while adherence-related problems (including mental health and substance use disorders) are aggressively addressed; initiating an adherence testing and training period during which a placebo (e.g., vitamin pill) is administered; scheduling appointments more frequently; employing directly observed therapy; and avoiding regimens with a low genetic resistance threshold. Such decisions should be individualized, and the patient's clinical and laboratory status monitored carefully, integrating transportation support and telemedicine options for flexible care engagement. Of note, even small and short-term improvements in virologic suppression may have longer-term clinical value for adolescents with HIV.[19]

Mental Health and Substance Use Concerns in Adolescents

Adolescent mental distress is a growing concern that has been exacerbated by the COVID-19 pandemic (see Background: The COVID-19 Pandemic's Impact on the Mental Health of Children and Youth in *Protecting Youth Mental Health: The U.S. Surgeon General's Advisory*). 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 disorders, 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.[7,20-22] The most common conditions include anxiety and behavioral disorders, mood disorders (including depression), and attention deficit hyperactivity disorder. Additionally, although data are sparse, the prevalence of attempted suicide has been notably higher in adolescents with HIV compared to those that have been exposed to HIV but are uninfected.[23] In at least one cohort, the risk of psychosis and severe chronic mental health disorders was higher in adolescents with perinatally acquired HIV than expected in the general young adult population.[24] Effectively managing psychiatric comorbidities can improve a patient's adherence to medical care, including ART, and can lead to better academic performance and interpersonal relationships (see Substance Use Disorders and HIV in the Adult and Adolescent Antiretroviral Guidelines).[13,25-27]

Interventions that address mental health in youth with perinatally acquired HIV include pharmacologic interventions; behavioral modification; and individual, family, and group counseling. The use of telehealth or counseling via videoconferencing may be feasible and acceptable and may improve access to mental health treatment for adolescents with HIV.[28] Current evidence suggests that a combination of tailored psychotherapy—such as cognitive behavioral therapy—and pharmacotherapy can reduce depressive symptoms in adolescents with HIV; however, clinicians who prescribe pharmacotherapy for depression must take potential interactions with ARV drugs into account.[29,30] One recent study randomized 13 U.S. sites to either a cognitive behavioral therapy and medication management algorithm (COMB-R) tailored for adolescents with HIV or enhanced standard of care, including standard psychotherapy and medication management, for adolescents with HIV who have depressive symptoms. After 6 months, sites using the COMB-R intervention showed

decreased depressive symptoms and higher remission from depression than the enhanced standard of care; however, mean HIV viral load and CD4 cell count were not significantly different between arms.[31]

There is evidence that adolescents with perinatally acquired HIV are more likely to have substance use disorders compared to the general population.[32] However, available studies on substance use among adolescents with perinatally acquired HIV show age of initiation and rates of substance use similar to age-matched peers without HIV.[33] In a comparison of 390 youth with perinatal exposure to HIV versus 211 youth living with perinatally acquired HIV, investigators from the Pediatric HIV/AIDS Cohort Study (PHACS) found that nearly half of both groups had ever used alcohol or marijuana, with a majority having used either substance in the last 3 months, and one out of five marijuana users reporting at least daily use.[34] In another study, there was no difference in substance use between adolescents exposed to HIV and adolescents living with HIV. While rates of substance use may not be higher in adolescents with perinatally acquired HIV, the impact on health outcomes—including interference with medication adherence and increased risk taking and decreased safe sex practices—and the potential for comorbid mental health concerns make addressing substance use in adolescents with HIV an important consideration for HIV care providers.[35,36]

Providers who are caring for adolescents with HIV should incorporate screening for psychiatric (including suicidality) and substance use disorders into routine care and refer patients to age-appropriate services as needed. The American Academy of Pediatrics Guidelines for Adolescent Depression in Primary Care policy statement provides some guidance and screening tools, particularly for depression. Screening tools for substance use—such as Screening, Brief Intervention, and Referral to Treatment (SBIRT) or Car, Relax, Alone, Forget, Friends, and Trouble (CRAFFT)—may be used.[37] Providers also should consider emerging substance use trends when screening adolescents with HIV. Further guidance on screening tools for substance use and mental health is provided by the National Institute on Drug Abuse's Screening and Assessment Tools Chart.

Sexually Transmitted Infections in Adolescents

At least half of new sexually transmitted infections (STIs) in the United States occur in youth aged 15 to 24. An analysis of three Adolescent Medicine Trials Network for HIV/AIDS Interventions studies conducted between 2009 and 2015 identified rates of STIs in adolescents with HIV that were higher than national averages for those without HIV.[38] Although adolescents with either non-perinatally or perinatally acquired HIV had elevated rates of STIs, those with non-perinatally acquired HIV had higher rates than those with perinatally-acquired HIV. In addition, STIs were more frequent during times when viral load was > 400 copies/mL. Clinicians should discuss the risk of STIs with their patients. All adolescents with HIV should be screened for STIs and treated appropriately. Clinicians should regularly obtain a detailed sexual history for adolescents to determine which STI screening tests are appropriate. Screening for STIs in sexually active adolescents with HIV often requires sampling from several body sites—including the oropharynx, rectum, and urethra—because multiple sites of infection are common.[39] Furthermore, a negative assay at a single site does not preclude the possibility of infection at another site.[40] For a more detailed discussion of STIs, see the Centers for Disease Control and Prevention STI Treatment Guidelines,[41] Human Papillomavirus Disease in the Adult and Adolescent Opportunistic Infection Guidelines, and Human Papillomavirus in the Pediatric Opportunistic Infection Guidelines. All female adolescents with HIV who are sexually active should receive gynecologic services. All adolescents with HIV should receive three doses of the 9-valent human papillomavirus vaccination.

Contraception, Pregnancy, and Antiretroviral Therapy

Adolescents 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.[42,43] Providers should regularly assess adolescents' desires to become pregnant or avoid pregnancy (also known as their pregnancy 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, contraceptive methods, pre-exposure prophylaxis for partners, the concept of Undetectable = Untransmittable (U=U),[44,45] and safer sex techniques (including instruction on the correct and consistent use of condoms) for prevention of sexual HIV transmission—should be discussed regularly (see U.S. Medical Eligibility Criteria for Contraceptive Use). Access to sexual health care, including contraception and abortion care, varies by state. To provide complete guidance, providers must be familiar with local laws and regulations. For additional information, refer to the following sections of the Perinatal Guidelines: Prepregnancy Counseling and Care for Persons of Childbearing Age With HIV and Reproductive Options When One or Both Partners Have HIV. The American Academy of Pediatrics Committee on Adolescence offers guidance about the integration of sexual and reproductive health care in pediatric clinical settings.[46]

The possibility of planned and unplanned pregnancy should be considered when selecting an ARV regimen for a female adolescent. 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 information about the selection and management of ARV drugs before and during pregnancy for people with HIV who are of childbearing age, see Table 7 in the Recommendations for Use of Antiretroviral Drugs During Pregnancy section of the Perinatal Guidelines. When discussing ART options with female adolescents and their caregivers, it is important to consider the benefits and risks of all ARV drugs and to provide the information and counseling needed to support informed decision-making (see Appendix C: Antiretroviral Counseling Guide for Health Care Providers).

Interactions Between Contraceptives and Antiretroviral Drugs

People living with HIV can use all available contraceptive methods, including hormonal contraceptives, implantable devices, intrauterine devices, the transdermal patch, and a vaginal ring.[47]

Several PIs and non-nucleoside reverse transcriptase inhibitors alter the metabolism of oral contraceptives, which theoretically may reduce the efficacy of oral contraceptive agents or increase the risk of estrogen-related or progestin-related adverse effects[48-50] (see Drug–Drug Interactions in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker). Integrase strand transfer inhibitors appear to have no interaction with estrogen-based contraceptives.[51,52] For more information about potential interactions between ARV drugs and hormonal contraceptives, see Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives in the Perinatal Guidelines.

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

Pregnant Adolescents 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 Prepregnancy Counseling and Care for Persons of Childbearing Age With HIV in the Perinatal Guidelines). Pregnancy should not preclude the use of optimal therapeutic ARV regimens. Clinicians need to consider maternal and fetal safety, as well as the need to prevent perinatal transmission of HIV, when selecting regimens for pregnant people or adolescents who are planning to become pregnant. See the Prepregnancy Counseling and Care for Persons of Childbearing Age With HIV for more details about choosing an ARV regimen for pregnant people with HIV, including adolescents. Pregnancies occur as adolescents with perinatally acquired HIV enter adolescence and young adulthood.[53,54] Some studies suggest higher rates of adverse pregnancy outcomes—such as small-for-gestational-age infants—among pregnant people with perinatally acquired HIV than among those who acquired HIV by non-perinatal transmission. Unplanned pregnancy is not uncommon in youth living with perinatally acquired HIV.[54-56] One site serving pregnant women with HIV in Baltimore reported higher rates of unintended pregnancy (83.6% vs. 68.8%, p = 0.016), lower viral suppression, and higher marijuana use during pregnancy in adolescents with HIV compared to adults with HIV.[57] Pregnant adolescents with perinatally acquired HIV also may be more likely to have complex ARV histories, virologic failure, and drug resistance at the time of pregnancy.[57-59] However, the rate of perinatal transmission among pregnant people with perinatally acquired HIV who are receiving ART appears to be similar to the rate among people on ART who acquired HIV by non-perinatal transmission.[60-64]

Special Considerations for Adolescents With HIV Who Are Sexual Minorities

Adolescence is a period of emerging recognition of sexual identity. Adolescents with HIV who are lesbian, gay, bisexual, transgender, or nonbinary require both culturally competent providers and tailored medical care. Health care providers should ask patients nonjudgmental questions about their sexual and gender identity to determine whether they require specific medical and support services. It is important to consider the possibility of drug–drug interactions in adolescents who are receiving both ART and gender-affirming hormone therapy. Additional resources for the care of these adolescents can be found in the Adolescents and Young Adults With HIV section and the Transgender People With HIV section of the Adult and Adolescent Antiretroviral Guidelines.

Transitioning Adolescents Into Adult HIV Care Settings

Transition to adult care is defined by Reiss et. al. as "a multifaceted, active process that attends to the medical, psychosocial, cognitive and educational, or vocational needs of adolescents as they move from the child- to the adult-focused health care system."[65] Facilitating a successful transition for adolescents with HIV from their pediatric/adolescent care clinic to adult care is important, but challenging.[66-69] Many adolescents disengage from care during the transition to adult care, putting them at risk for HIV progression and transmission to partners.[70-72] Pediatric and adolescent care providers and their multidisciplinary teams should have a formal written plan in place to transition adolescents to adult care. Although 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 their parents and/or caregivers. 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. A recent qualitative metasynthesis of adolescent transition studies demonstrated that established patient–provider relationships among

adolescents with HIV and their providers are integral to HIV care engagement and that collaborative approaches to build trusted, new patient–provider relationships is necessary to support successful transition.[73] Although expert care also is 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 care 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.[74] Assessments of transition readiness using standardized tools are emerging as a potentially helpful part of the transition process and may be predictive of HIV outcomes, including virologic failure post-transition.[75,76] It may be beneficial to provide 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. In this situation, it may be helpful for a pediatric care provider and an adult care provider to share joint care of a patient for a period.

Adolescent care providers 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 comorbidities, housing, family support, employment status, recent discharge from foster care, peer pressure, illicit drug use, and incarceration—should be considered during transition.

No definitive model of transition to adult HIV care currently exists, and only a limited number of studies have reported on outcomes following transition, although research in this area is ongoing. However, emerging qualitative research has revealed the importance of the patient–provider relationship, including trust, the need for developmentally appropriate preparation for transition, and opportunities for growth and independence.[69,77] Recent studies have shown potential for successful transition and ongoing retention using models that include a multidisciplinary approach, which utilizes providers co-trained in both internal medicine and pediatrics, peer navigators, social workers, mental health support, and a youth-focused care model for adolescents who were already attending adult HIV clinics.[78,79]

Several studies have shown that youth with HIV who transitioned into adult care settings had higher rates of attrition from care than those who remained in pediatric/adolescent care; U.S. studies show that less than half of youth who transitioned care to an adult clinic remained in care after 9 to 12 months.[70,71,80] In addition to poor retention in care, several studies have identified poor viral suppression rates in transitioned youth and young adults with HIV.[2] Pre-transition virologic failure and longer linkage times have been associated with worse outcomes post-transition.[69,72] Furthermore, some reports from the United Kingdom suggest that the mortality rate of adolescents with HIV increases after transition,[26,72,81] underscoring the need to critically examine transition and determine the best mechanisms to optimize the long-term outcomes for youth with perinatally acquired HIV.[70]

Some general guidelines, mostly based on anecdotal evidence and consensus expert opinion, are available about transition plans and who might benefit most from them.[67,82-89] 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 communication between providers at pediatric/adolescent clinics and providers at adult clinics;
- Identifying adult care providers who are experts in providing care to adolescents and young adults;
- Fostering a trusting patient–provider relationship with new adult care providers;
- Addressing barriers caused by a lack of information, stigma, or disclosure concerns;
- Discussing the differences between the practice styles of adult clinics and pediatric/adolescent clinics;
- Helping youth develop the skills needed to manage their 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 services 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.

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