



Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV

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Adolescents and Young Adults with HIV (Last updated October 25, 2018; last reviewed October 25, 2018)

Key Summary and Panel's Recommendations

- Adolescents living with HIV largely belong to two distinct groups—those who acquired HIV in infancy and are heavily antiretroviral therapy (ART)-experienced, and those who acquired HIV more recently during their teens.
- ART is recommended for all individuals with HIV (AI) to reduce morbidity and mortality. Thus, ART is also recommended for ART-naive adolescents. Before initiation of therapy, adolescents' readiness and ability to adhere to therapy within their psychosocial context need to be carefully considered as part of therapeutic decision making (AIII).
- Once ART is initiated, appropriate support is essential to reduce potential barriers to adherence and maximize the likelihood of achieving sustained viral suppression (AI).
- Preliminary data from Botswana suggested that infants born to women who were receiving dolutegravir (DTG) at the time of conception have an increased risk of neural tube defects. Until more information is available, DTG should not be prescribed for adolescents:
 - Who are pregnant and within 12 weeks post-conception;
 - Who are of childbearing potential, are sexually active, and who are not using effective contraception; or
 - Who are contemplating pregnancy.
- The adolescent sexual maturity rating (SMR) can be helpful to guide regimen selection for initiation of or changes in ART as recommended by either these Adult and Adolescent Antiretroviral Guidelines or the [Pediatric Guidelines](#). These Adult and Adolescent Guidelines are more appropriate for postpubertal adolescents (i.e., those with SMRs of 4 or 5) (AIII).
- Pediatric and adolescent care providers should prepare adolescents for the transition into adult care settings. Adult providers should be sensitive to the challenges associated with such transitions, consulting and collaborating with adolescent HIV care providers to ensure adolescents' successful transition and continued engagement in care (AIII).

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

Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Older children and adolescents now make up the largest percentage of children with HIV who are cared for at pediatric HIV clinics in the United States. The Centers for Disease Control and Prevention (CDC) estimates that 26% of the approximately 50,000 people newly diagnosed with HIV in 2010 were youth 13 to 24 years of age. In this age group, 57% of the infections were among young black/African Americans and 75% were among young men who have sex with men (MSM).¹ Among youth living with HIV in 2010, CDC estimates that almost 60% had undiagnosed infections and were unaware they had HIV.¹ Trends in HIV/AIDS prevalence indicate that the disproportionate burden of HIV among racial minorities is even greater among minority youth 13 to 24 years of age than among those older than 24 years.² Furthermore, trends for all HIV diagnoses among adolescents and young adults in 46 states and 5 U.S.-dependent areas from 2007 to 2010 decreased or remained stable for all transmission categories except among young MSM. Adolescents with HIV represent a heterogeneous group in terms of socio-demographics, mode of HIV acquisition, sexual and substance abuse history, clinical and immunologic status, psychosocial development, and readiness to adhere to medications. Many of these factors may influence decisions concerning when to start antiretroviral therapy (ART) and what antiretroviral (ARV) medications to use.

Most adolescents who acquire HIV do so through sex. Many of them are recently infected and unaware of their HIV status. Many are in an early stage of HIV infection, which makes them ideal candidates for early interventions, such as prevention counseling, linkage to and engagement in care, and initiation of ART.³ High-grade viremia was reported in a cohort of youth living with HIV who were identified by adolescent HIV specialty clinics in 15 major metropolitan U.S. cities. The mean HIV viral load for the cohort was

94,398 copies/mL; 30% of the youth were not successfully linked to care.⁴ In a study of youths with recent HIV infection, primary genotypic resistance mutations were reported in 18% of the samples, as determined by the detuned antibody testing assay strategy that defined recent infection as occurring within 180 days of testing.⁵ In an ARV treatment trial, a cohort of ART-naive youth who had behaviorally acquired HIV showed substantial multiclass resistance.⁶ As these youth were naive to all ARV drugs, this reflects transmission of resistant virus. This transmission dynamic indicates that a substantial proportion of the study participants' sexual partners were likely to be older and ART-experienced; thus, using baseline resistance testing to guide initial therapy in youth who have recently acquired HIV and are naive to ART is imperative.

A limited but increasing number of adolescents with HIV are long-term survivors of HIV acquired perinatally or in infancy through blood products. These adolescents are usually heavily ART-experienced and may have a unique clinical course that differs from that of adolescents who acquire HIV later in life.⁷ Adolescents who acquired HIV perinatally or in infancy were often started on ART early in life with mono- or dual-therapy regimens, resulting in incomplete viral suppression and emergence of viral resistance. If these heavily ART-experienced adolescents harbor resistant virus, optimal ARV regimens should be selected on the basis of the same guiding principles used for heavily ART-experienced adults (see [Virologic Failure](#)).

Developmentally, adolescents are at a difficult crossroad. Their needs for autonomy and independence and their evolving decisional capacity compete with their concrete thinking processes, risk-taking behaviors, preoccupation with self-image, and need to fit in with their peers. This makes it challenging to attract and sustain adolescents' focus on maintaining their health, particularly for those with chronic illnesses. These challenges are not specific to any particular transmission mode or stage of disease. Thus, irrespective of disease duration or mode of HIV transmission, every effort must be made to engage and retain adolescents in care so they can improve and maintain their health for the long term. Given the challenges of retaining youth in care and achieving long-term viral suppression,⁸ more intensive case management approaches may be considered for adolescents with HIV.^{9,10} Adolescents may seek care in several settings, including pediatric-focused HIV clinics, adolescent/young adult clinics, and adult-focused clinics.¹¹ When available, youth services may be helpful to consider as one approach to enhancing HIV care engagement and retention among adolescents.¹² Regardless of the setting, expertise in caring for adolescents is critical to creating a supportive environment for engaging youth in care.¹¹

Antiretroviral Therapy Considerations in Adolescents

The results from the START and TEMPRANO trials that favor initiating ART in all individuals who are able and willing to commit to treatment, and who can understand the benefits and risks of therapy and the importance of excellent adherence, are discussed elsewhere in these guidelines (see [Initiation of Antiretroviral Therapy](#)). Neither of these trials included adolescents; however, recommendations based on these trials have been extrapolated to adolescents based on the expectation that they will derive benefits from early ART that are similar to those observed in adults. Given the psychosocial turmoil that may occur frequently in the lives of American youth with HIV, their ability to adhere to therapy needs to be carefully considered as part of therapeutic decision making concerning the risks and benefits of starting treatment. Once ART is initiated, appropriate support is essential to reduce potential barriers to adherence and maximize the likelihood of achieving sustained viral suppression.

The adolescent sexual maturity rating (SMR; also known as the Tanner stage) can be helpful when ART initiation is being considered for this population (see this [SMR table](#)). Adult guidelines for ART initiation (see [What to Start](#)) or regimen changes are usually appropriate for postpubertal adolescents (SMR 4 or 5) because the clinical course of HIV infection in postpubertal adolescents who acquired HIV sexually or through injection drug use during adolescence is more similar to that in adults than that in children. Adult guidelines can also be useful for postpubertal youth who acquired HIV perinatally and whose long-term HIV infection has not affected their sexual maturity (SMR 4 or 5). Pediatric guidelines for ART may be

more appropriate for adolescents who acquired HIV during their teen years (e.g., through sex), but who are sexually immature (SMR 3 or less) and for adolescents who acquired HIV perinatally with stunted sexual maturation (i.e., delayed puberty) from long-standing HIV infection or other comorbidities (SMR 3 or less) (see [What to Start](#) in the [Pediatric Guidelines](#)). Postpubertal youth who acquired HIV perinatally often have treatment challenges associated with the long-term use of ART that mirror those of ART-experienced adults, such as extensive resistance, complex regimens, and adverse drug effects (see also [Virologic Failure](#), [Poor CD4 Cell Recovery](#), [Optimizing Antiretroviral Therapy in the Setting of Viral Suppression](#), and [Adverse Effects of Antiretroviral Agents](#)). Postpubertal adolescents who acquired HIV perinatally may also have comorbid cognitive impairments that compound adherence challenges that are common among youth.¹³

Dosage of ARV drugs should be prescribed according to the SMR and not solely on the basis of age. Adolescents in early puberty (i.e., SMR 3 or less) should be administered doses on pediatric schedules, whereas those in late puberty (i.e., SMR 4 or 5) should follow adult dosing schedules. However, SMR and age are not necessarily directly predictive of drug pharmacokinetics (PKs). Because puberty may be delayed in children with perinatally acquired HIV,¹⁴ continued use of pediatric doses in puberty-delayed adolescents can result in medication doses that are higher than the usual adult doses. Because data are not available to predict optimal medication doses for each ARV medication for this group of children, issues such as toxicity, pill or liquid volume burden, adherence, and virologic and immunologic parameters should be considered in determining when to transition youth from pediatric to adult doses. Youth who are in their growth spurt period (i.e., SMR 3 in females and SMR 4 in males) and who are following adult or pediatric dosing guidelines and adolescents who have transitioned from pediatric to adult doses should be closely monitored for medication efficacy and toxicity. Therapeutic drug monitoring can be considered in each of these circumstances to help guide therapy decisions. PK studies of drugs in youth are needed to better define appropriate dosing. For a more detailed discussion, see the [Pediatric Guidelines](#).¹⁵

Preliminary data from a study on birth outcomes among pregnant women on ART in Botswana suggested an increased rate of neural tube defects (NTDs) among infants born to women who initiated a dolutegravir (DTG)-based regimen prior to pregnancy and who were still receiving it at the time of conception.^{16,17} Until more information is available, DTG is not recommended for adolescents who are pregnant and within 12 weeks post-conception. It is also not recommended for those of childbearing potential who are sexually active and not using effective contraception or those who are contemplating pregnancy.

It is not known whether this possible risk of NTDs is shared by other integrase strand transfer inhibitors (i.e., a class effect). Bictegravir (BIC) is structurally similar to DTG, but there are no safety data on the use of BIC near the time of conception. For those who are of childbearing potential, but who are not pregnant, an approach similar to that outlined for DTG should be discussed before considering the use of BIC-containing ART. Clinicians should refer to the [Perinatal Guidelines](#) for information on the safety and efficacy of ARV use in pregnancy.

Adherence Concerns in Adolescents

Adolescents with HIV are especially vulnerable to specific adherence problems because of their psychosocial and cognitive developmental trajectory. To meet the medical and psychosocial needs of adolescents with HIV, who frequently lack both health insurance and experience with health care systems, comprehensive systems of care are required. Studies of adolescents who acquired HIV during their teen years and adolescents with perinatal acquisition demonstrate that many adolescents in both groups face numerous barriers to adherence.¹⁸⁻²⁰ Compared with adults, these youth have lower rates of viral suppression and higher rates of virologic rebound and loss to follow up.²¹ Reasons that adolescents with HIV often have difficulty adhering to medical regimens include the following:

- Denial and fear of their HIV diagnosis;
- Misinformation;

- Distrust of the medical establishment;
- Fear of ART and lack of confidence in the effectiveness of medications;
- Low self-esteem;
- Unstructured and chaotic lifestyles;
- Mood disorders and other mental illness;
- Lack of familial and social support;
- Lack of or inconsistent access to care or health insurance; *and*
- Risk of inadvertent disclosure of their HIV status if parental health insurance is used.

Clinicians selecting treatment regimens for adolescents must balance the goal of prescribing a maximally potent ART regimen with a realistic assessment of existing and potential support systems to facilitate adherence. Adolescents benefit from reminder systems (e.g., apps, timers, and pill boxes) that are stylish and/or inconspicuous.²² In a randomized controlled study among nonadherent youth aged 15 years to 24 years, youth who received medication reminders through their cell phones demonstrated significantly better adherence and lower viral loads than youth who did not receive the reminder calls.²³ It is important to make medication adherence user-friendly and to avoid HIV-related stigma as much as possible for the older child or adolescent. Adolescents may not understand the importance of taking medications when they are asymptomatic, particularly if the medications have side effects. Adherence to complex regimens is particularly challenging at a time of life when adolescents do not want to be different from their peers.²⁴⁻²⁶ Directly observed therapy may be considered for some adolescents with HIV, such as those with mental illness.²⁷⁻³¹

Difficult Adherence Problems

Because adolescence is characterized by rapid changes in physical maturation, cognitive processes, and life style, predicting long-term adherence in an adolescent can be very challenging. A young person's ability to adhere to therapy needs to be considered as part of therapeutic decision making when considering the risks and benefits of starting ART. Erratic adherence may result in the loss of future regimens due to the development of resistance mutations. Clinicians who care for adolescents with HIV frequently manage youth who pose significant concerns regarding their ability to adhere to therapy. In these cases, the following strategies can be considered:

1. A short-term deferral of ART until adherence is more likely or while adherence-related problems are aggressively addressed;
2. An adherence testing period in which a placebo (e.g., vitamin pill) is administered; *and*
3. The avoidance of any regimens with low resistance barriers.

Such decisions should ideally be individualized to reflect each patient's clinical status. For a more detailed discussion on specific therapy and adherence issues for adolescents with HIV, see [Adherence to the Continuum of Care](#) in these guidelines and the [Pediatric Guidelines](#).¹⁵

Special Considerations in Adolescents

All adolescents should be screened for sexually transmitted infections (STIs), especially human papilloma virus (HPV). In young MSM, screening for STIs may require sampling from several body sites because oropharyngeal, rectal, and urethral infections may be present in this population.³² For a more detailed discussion on STIs, see the most recent CDC guidelines,³³ [Adult and Adolescent Opportunistic Infections Guidelines](#), and [Pediatric Opportunistic Infections Guidelines](#) on HPV among adolescents with HIV.^{34,35} Family planning counseling, including a discussion of the risks of perinatal transmission of HIV and methods to reduce those risks, should be provided to all youth. Providing gynecologic care for female adolescents with HIV is especially important. Choice of ART may also be affected by a patient's potential for pregnancy

and use of contraception, since some ARV drugs can interact with hormonal contraceptives (see [Drug-Drug Interaction](#) tables). Finally, transgender youth with HIV represent an important population that requires additional psychosocial and health care considerations. For a more detailed discussion, see [Adolescent Trials Network Transgender Youth Resources](#).

Transitioning Care

Given lifelong infection with HIV and the need for treatment through several stages of growth and development, HIV care programs and providers need flexibility to appropriately transition care for children, adolescents, and young adults with HIV. A successful transition requires an awareness of the fundamental differences between many adolescent and adult HIV care models. In most adolescent HIV clinics, care is more teen-centered and multidisciplinary, with primary care highly integrated into HIV care. Teen services, such as sexual and reproductive health, substance abuse treatment, mental health, treatment education, and adherence counseling are all found in one clinic setting. In contrast, some adult HIV clinics may rely more on referring the patient to separate subspecialty care settings, such as gynecology. Transitioning the care of an emerging young adult includes considering areas such as access to medical insurance; the adolescent's degree of independence/autonomy and decisional capacity; patient confidentiality; and informed consent. Also, adult clinic settings tend to be larger and can easily intimidate younger, less-motivated patients. As an additional complication to this transition, adolescents with HIV belong to two epidemiologically distinct subgroups with unique biomedical and psychosocial considerations and needs:

- Adolescents who acquired HIV perinatally, who likely have a longer history of disease burden, complications, and chronicity; less functional autonomy; a greater need for ART; and a higher mortality risk; and
- Youth who more recently acquired HIV during their adolescence, who are likely to be in earlier stages of HIV infection and have higher CD4 T lymphocyte cell counts; these adolescents would be less likely to have viral drug resistance and may benefit from simpler treatment regimen options.

Interventions to facilitate transition should be implemented early to ensure a successful transition.³⁶ These interventions include the following:

- Developing an individualized transition plan to address comprehensive care needs, including medical, psychosocial, and financial aspects of transitioning;
- Optimizing provider communication between adolescent and adult clinics;
- Identifying adult care providers that are willing to care for adolescents and young adults;
- Addressing patient and family resistance to transition of care caused by lack of information, concerns about stigma or risk of disclosure, and differences in practice styles;
- Helping youth develop life skills, including counseling them on the appropriate use of a primary care provider and how to manage appointments; the importance of prompt symptom recognition and reporting; and the importance of self-efficacy in managing medications, insurance, and assistance benefits;
- Identifying an optimal clinic model based on specific needs (i.e., simultaneous transition of mental health and/or case management versus a gradual phase-in);
- Implementing ongoing evaluation to measure the success of a selected clinic model;
- Engaging adult and adolescent care providers in regular multidisciplinary case conferences;
- Implementing interventions that may improve outcomes, such as support groups and mental health consultation;
- Incorporating a family planning component into clinical care; *and*
- Educating HIV care teams and staff about transitioning.

Discussions regarding transition should begin early, before the actual transition process.³⁷ Attention to the key interventions noted above will likely improve adherence to appointments and allow the youth to be retained in care. For a more detailed discussion on specific topics on transitioning care for adolescents and young adults, see HIV Clinical Guidelines Program's [Adolescent Transition to Adult Care](#).

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