Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

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Older children and adolescents now make up the largest percentage of HIV-infected children 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 new HIV infections diagnosed in 2010 were among youth 13 to 24 years of age. In this age group, 57% of the infections were among young black/African Americans and 75% among young gay and bisexual men who have sex with men (MSM).\textsuperscript{1} Among youth living with HIV infection in 2010, CDC estimates that almost 60% had undiagnosed infections and were unaware they were HIV-infected.\textsuperscript{2} Trends in HIV/AIDS prevalence indicate that the disproportionate burden of AIDS among racial minorities is even greater among minority youth 13 to 24 years of age (64% to 66% of cases) than among those older than 24 years (48% of cases).\textsuperscript{3} 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. HIV-infected adolescents represent a heterogeneous group in terms of socio-demographics, mode of HIV infection, 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 are infected through sex. Many of them are recently infected and unaware of their HIV infection status. Thus, 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.\textsuperscript{4} High grade viremia was reported in a cohort of youth identified as HIV-infected 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.\textsuperscript{5} A study among HIV-infected adolescents and young adults presenting for care identified primary genotypic resistance mutations to ARV medications in up to 18% of the evaluable sample of recently infected youth, as determined by the detuned antibody testing assay strategy that defined recent infection as occurring within 180 days of testing.\textsuperscript{6} Substantial multiclass resistance was noted in a cohort of non-perinatally infected, treatment-naive youth

<table>
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<tr>
<th>Key Summary and Panel's Recommendations</th>
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<td>HIV-infected adolescents 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.</td>
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<td>ART is recommended for all HIV-infected individuals (AI) to reduce morbidity and mortality. Thus, ART is also recommended for ART-naive adolescents. However, 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).</td>
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<td>Once ART is initiated, appropriate support is essential to reduce potential barriers to adherence and maximize the success in achieving sustained viral suppression (AII).</td>
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<td>The adolescent sexual maturity rating can be helpful to guide regimen selection for initiation of or changes in ART as recommended by either these Adult and Adolescent ART Guidelines or the Pediatric ART Guidelines. These Adult/Adolescent Guidelines are more appropriate for postpubertal adolescents (i.e., sexual maturity rating IV or V) (AIII).</td>
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<td>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 insure adolescents’ successful transition and continued engagement in care (AIII).</td>
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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
who were screened for an ARV treatment trial. As these youth were naive to all ART, this reflects transmission of resistant virus. This transmission dynamic reflects that a substantial proportion of youth’s sexual partners are likely older and may be more ART experienced; thus, using baseline resistance testing to guide initial therapy in recently infected youth naive to ART is imperative.

A limited but increasing number of HIV-infected adolescents are long-term survivors of HIV infection 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 infected later in life. Adolescents infected 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 section).

Adolescents are developmentally at a difficult crossroad. Their needs for autonomy and independence and their evolving decisional capacity intersect and 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 challenges with youth remaining in care and achieving long-term viral suppression, additional considerations may be given to more intensive case management approaches. Adolescents may seek care in several settings including pediatric-focused HIV clinics, adolescent/young adult clinics, and adult-focused clinics. Where youth services are available, they may be helpful to consider as one approach to enhancing HIV care engagement and retention among adolescents. Regardless of the setting, expertise in caring for adolescents is critical to creating a supportive environment for engaging youth in care.

**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 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 similar to those observed in adults. Given the psychosocial turmoil that may occur frequently in the lives of HIV-infected American youth, 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 success in achieving sustained viral suppression.

The adolescent sexual maturity rating (SMR) (also known as Tanner stage) can be helpful when ART initiation is being considered for this population (see SMR table). Adult guidelines for ART initiation or regimen changes (see Adult Guidelines, What to Start) are usually appropriate for postpubertal adolescents (SMR IV or V) because the clinical course of HIV infection in postpubertal adolescents who were infected 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 were perinatally infected and whose long-term HIV infection has not affected their sexual maturity (SMR IV or V). Pediatric guidelines for ART may be more appropriate for adolescents infected with HIV during their teen years (e.g., through sex), but who are sexually immature (SMR III or less) and for perinatally infected adolescents with stunted sexual maturation (i.e., delayed puberty) from long-standing HIV infection or other co-morbidities (SMR III or less) (see What to Start in the Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection).
Perinatally infected, postpubertal youth 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 Recovery, Regimen Switching in the Setting of Virologic Suppression, and Adverse Effects of Antiretroviral Agents). Perinatally infected postpubertal adolescents may also have comorbid cognitive impairments that compound adherence challenges common among youth.15

Dosage of ARV drugs should be prescribed according to the SMR and not solely on the basis of age.16,17 Adolescents in early puberty (i.e., SMR I-III) should be administered doses on pediatric schedules, whereas those in late puberty (i.e., SMR IV-V) should follow adult dosing schedules. However, SMR stage and age are not necessarily directly predictive of drug pharmacokinetics. Because puberty may be delayed in children who were infected with HIV perinatally,18 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., Tanner Stage III in females and Tanner Stage IV in males) 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 selected circumstances to help guide therapy decisions. Pharmacokinetic studies of drugs in youth are needed to better define appropriate dosing. For a more detailed discussion, see Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection.19

**Adherence Concerns in Adolescents**

HIV-infected adolescents are especially vulnerable to specific adherence problems because of their psychosocial and cognitive developmental trajectory. Comprehensive systems of care are required to serve both the medical and psychosocial needs of HIV-infected adolescents, who frequently lack both health insurance and experience with health care systems. Studies in adolescents infected in their teen years and in adolescents infected through perinatal transmission demonstrate that many adolescents in both groups face numerous barriers to adherence.20-22 Compared with adults, these youth have lower rates of viral suppression and higher rates of virologic rebound and loss to follow up.23 Reasons that HIV-infected adolescents often have difficulty adhering to medical regimens include the following:

- Denial and fear of their HIV infection;
- 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 infection if parental health insurance is used.

Clinicians selecting treatment regimens for adolescents must balance the goal of prescribing a maximally potent ART regimen with realistic assessment of existing and potential support systems to facilitate adherence. Adolescents benefit from reminder systems (e.g., apps, beepers, timers, and pill boxes) that are stylish and/or inconspicuous.24 In a randomized controlled study among non-adherent youth 15 to 24 years of age, youth who

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received cell phone medication reminders demonstrated significantly better adherence and lower viral loads than youth who did not receive the reminder calls. It is important to make medication adherence as user friendly and the least stigmatizing as possible for the older child or adolescent. The concrete thought processes of adolescents make it difficult for them to take 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. Directly observed therapy may be considered for some HIV-infected adolescents such as those with mental illness.

Difficult Adherence Problems

Because adolescence is characterized by rapid changes in physical maturation, cognitive processes, and lifestyle, predicting long-term adherence in an adolescent can be very challenging. The ability of youth to adhere to therapy needs to be considered as part of therapeutic decision making concerning the risks and benefits of starting treatment. Erratic adherence may result in the loss of future regimens because of the development of resistance mutations. Clinicians who care for HIV-infected adolescents frequently manage youth who, although needing therapy, 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 treatment 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 genetic resistance barriers.

Such decisions are ideally individualized to each patient and should be made carefully in context with the individual’s clinical status. For a more detailed discussion on specific therapy and adherence issues for HIV-infected adolescents, see the Adherence to ART section of these guidelines and the Guidelines for Use of Antiretroviral Agents in Pediatric HIV Infection.

Special Considerations in Adolescents

All adolescents should be screened for sexually transmitted diseases (STDs), in particular human papilloma virus (HPV). In young MSM, screening for STDs may require sampling from several body sites because oropharyngeal, rectal, and urethral infections may be present in this population. For a more detailed discussion on STDs, see the most recent CDC guidelines and the adult and pediatric opportunistic infection treatment and prevention guidelines on HPV among HIV-infected adolescents. Family planning counseling, including a discussion of the risks of perinatal transmission of HIV and methods to reduce risks, should be provided to all youth. Providing gynecologic care for HIV-infected female adolescents is especially important. Contraception, including the interaction of specific ARV drugs with hormonal contraceptives, and the potential for pregnancy also may alter choices of ART. As an example, efavirenz (EFV) should be used with caution in females of childbearing age and should only be prescribed after intensive counseling and education about the potential effects on the fetus, the need for close monitoring—including periodic pregnancy testing—and a commitment on the part of the teen to use effective contraception. For a more detailed discussion, see HIV-Infected Women and the Perinatal Guidelines. Finally, HIV-infected transgender youth represent an important population that requires additional psychosocial and healthcare considerations. For a more detailed discussion, see Adolescent Trials Network (ATN) 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 HIV-infected children, adolescents, and young adults. A successful transition requires an awareness of some
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 referral of the patient to separate subspecialty care settings, such as gynecology. Transitioning the care of an emerging young adult includes considerations of areas such as 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, HIV-infected adolescents belong to two epidemiologically distinct subgroups with unique biomedical and psychosocial considerations and needs:

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

To maximize the likelihood of a successful transition, interventions to facilitate transition are best implemented early on. 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 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 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 and before the actual transition process. Attention to the key interventions noted above will likely improve adherence to appointments and avert the potential for a youth to fall through the cracks, as it is commonly referred to in adolescent medicine. For a more detailed discussion on specific topics on transitioning care for adolescents and young adults, see http://www.hivguidelines.org/clinical-guidelines/adolescents/transitioning-hiv-infected-adolescents-into-adult-care/.

References


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