Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Specific Issues in Antiretroviral Therapy for HIV-Infected Adolescents
(Last updated November 1, 2012; last reviewed November 1, 2012)

Panel's Recommendations
• Antiretroviral therapy (ART) regimens must be individually tailored to the adolescent **(AIII)**.
• Appropriate dosing of ART for adolescents is complex, not always predictable, and dependent upon multiple factors, including body mass and composition and pubertal development **(AII)**.
• Effective and appropriate methods should be selected to reduce the likelihood of unintended pregnancy and to prevent secondary transmission of HIV to sexual partners **(AI)**.
• Providers should be aware of potential interactions between ART and hormonal contraceptives, which could lower contraceptive efficacy **(AII*)**.
• Alternative regimens that do not include efavirenz should be strongly considered in adolescent females who are trying to conceive or who are not using effective and consistent contraception because of the potential for teratogenicity with first-trimester efavirenz exposure, assuming these alternative regimens are acceptable to the provider and will not compromise the woman's health **(BIII)**.
• Adolescent girls who require treatment with efavirenz should undergo pregnancy testing before initiation of treatment and receive counseling about potential fetal risk and desirability of avoiding pregnancy while receiving efavirenz-containing regimens **(AIII)**.
• 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 and adolescents but not studies limited to postpubertal adolescents

Background

An increasing number of HIV-infected children who acquired HIV infection through perinatal transmission are now surviving into adolescence. They generally have had a long clinical course and extensive antiretroviral therapy (ART) treatment history.[1] Adolescents with non-perinatally acquired HIV infection generally follow a clinical course similar to that in adults. Because non-perinatally infected adolescents are usually at the initial stages of their HIV disease, they are potential candidates for early intervention and treatment.[2]

Dosing of Antiretroviral Therapy for HIV-Infected Adolescents

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 drugs with a narrow therapeutic index that are used in combination with protein-bound medicines or hepatic enzyme inducers or inhibitors.[3] Dosages of medications for HIV infection and

opportunistic infections are prescribed according to Tanner staging of puberty[4] rather than strictly on the basis of age.[2] Using the Tanner method, adolescents in early puberty (i.e., Tanner stages I and II) are administered doses using pediatric schedules, whereas those in late puberty (i.e., Tanner stage V) are administered doses using adult schedules. However, Tanner stage and age are not necessarily directly predictive of drug PK, and dosing of antiretroviral (ARV) drugs during Tanner stages III and IV may be more challenging. Puberty may be delayed in children who were infected with HIV perinatally,[5] adding to discrepancies between Tanner stage-based and age-based dosing, although delayed onset of puberty appears to be uncommon in those in whom potent combination ART was initiated at an early age.[6]

Many ARV drugs (e.g., abacavir, emtricitabine, lamivudine, tenofovir, and some protease inhibitors [PIs]) are administered to children at higher weight- or surface area-based doses than would be predicted by direct extrapolation of adult doses. This is based upon reported PK data indicating more rapid drug clearance in children. Continued use of these pediatric weight- or surface area-based doses as a child grows during adolescence can result in medication doses that are higher than the usual adult doses. Data suggesting optimal doses for every ARV drug in adolescents are not available. Appendix A: Pediatric Antiretroviral Drug Information includes a discussion of data relevant to adolescents for individual drugs and notes the age listed on the drug label for adult dosing, when available.

Adolescent Contraception, Pregnancy, and Antiretroviral Therapy

HIV-infected adolescents may be sexually active regardless of how they acquired the virus. Reproductive plans including preconception care, contraception methods, and safer sex techniques for prevention of secondary HIV transmission should be discussed with them regularly (see U.S. Medical Eligibility Criteria for Contraceptive Use).[7] For additional information please see Health and Human Services (HHS) *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States* (Preconception Care and Reproductive Options for HIV-Concordant and Serodiscordant Couples section).[8]

The possibility of an unplanned pregnancy should also be considered when selecting an ART regimen for an adolescent female. The most vulnerable period in fetal organogenesis is early in gestation, often before pregnancy is recognized. In addition, concerns about specific ARV drugs and birth defects should be addressed immediately to preclude misinterpretations or lack of adherence by adolescents with unexpressed plans for pregnancy.[9] For additional information please see HHS *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States* (Special Considerations Regarding the Use of Antiretroviral Drugs by HIV-Infected Pregnant Women and their Infants: Teratogenicity section).[8] Alternative regimens that do not include efavirenz should be strongly considered in adolescent females who are trying to conceive or who are not using effective and consistent contraception because of the potential for teratogenicity with first-trimester efavirenz exposure, assuming these alternative regimens are acceptable to the provider and will not compromise the woman's health.

Contraceptive-Antiretroviral Drug Interactions

Several PI and non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs alter metabolism of oral contraceptives, resulting in possible decreases in ethinyl estradiol or increases in estradiol or norethindrone levels (see the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* available at http://aidsinfo.nih.gov) (http://www.hiv-druginteractions.org/).[10-12] These changes may decrease the effectiveness of the oral contraceptives or potentially increase the risk of estrogen- or progestin-related adverse effects. Some newer agents, such as integrase inhibitors (specifically raltegravir), appear to have no interaction with estrogen-based contraceptives.[13] Providers should be aware of these drug interactions and consider alternative or additional contraceptive methods for patients receiving ART with such interactions.

Whether interactions with ART would compromise the contraceptive effectiveness of progestogen-only injectable contraceptives (such as depot medoxyprogesterone acetate [DMPA]) is unknown because these methods produce higher blood hormone levels than other progestogen-only oral contraceptives and combined oral contraceptives. In one study, the efficacy of DMPA was not altered in women receiving concomitant nelfinavir-, efavirenz-, or nevirapine-based treatment, with no evidence of ovulation during concomitant administration for 3 months, no additional adverse effects, and no clinically significant changes in ARV drug levels.[14, 15] At this time, concerns about loss of bone mineral density (BMD) with long-term use of DMPA with or without ART (specifically tenofovir)[16] should not preclude use of DMPA as an effective contraceptive. However, more active monitoring of BMD in young women on DMPA may need to be considered.[16] Minimal information exists about drug interactions with use of newer hormonal contraceptive methods (e.g., the patch and vaginal ring).[17] Intrauterine device (IUD) use while on ART is not restricted by current guidelines; however, IUD users with AIDS should be closely monitored for pelvic infection.[7] Adolescents who want to become pregnant should be referred for preconception counseling and care, including discussion of special considerations with ART use during pregnancy (see HHS *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States* available at http://aidsinfo.nih.gov).[8]

HIV-Infected Pregnant Adolescents and Outcomes

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, timing of initiation of treatment and selection of regimens may be different for pregnant women than for nonpregnant adults or adolescents. Details regarding choice of ART regimen in pregnant HIV-infected women, including adolescents, are provided in HHS *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States* available at http://aidsinfo.nih.gov.[8] Although information is limited about the pregnancies of adolescents who were HIV-infected perinatally, perinatal HIV transmission outcomes in this population appear similar to those in adult cohorts;[18-21] however, there may be differences in pregnancy-related morbidities. Kenny et al[22] reported pregnancy outcomes from the United Kingdom and Ireland in a group of 30 adolescents who were perinatally HIV-infected or who acquired HIV infection at a young age. Few of these pregnancies were planned and in many cases, the partner was unaware of the mother's HIV status. Rates of elective termination, miscarriage, and prematurity were high. The rate of prematurity was twice that in the general adolescent population of Europe. Many of the women had an AIDS diagnosis before pregnancy, but only one infant was HIV-infected. Although the rate of perinatal transmission is reassuring, this study highlights some of the major challenges in caring for pregnant, perinatally HIV-infected youth.

Comparisons of pregnancy incidence and outcomes between perinatally infected and non-perinatally infected youth are few and may offer special insight into the effects of prolonged HIV infection on pregnancy-related sequelae. Agwu et al[23] retrospectively evaluated pregnancies at four clinics. Non-perinatally infected youth were more likely to have one or more pregnancies despite similar age at first pregnancy between groups. They also appeared to have more premature births and spontaneous abortions, but that is tempered by the fact that the perinatally infected youth were more likely to have an elective termination. The perinatal transmission rate for the entire cohort was 1.5%. Similar results were found in several other studies.[24, 25] However, in a single-center review of perinatal versus non-perinatal birth outcomes, infants born to women with perinatal HIV infection were more likely to be small for gestational age, indicating the potential for future adverse health outcomes.[26]

Transition of Adolescents into Adult HIV Care Settings

Facilitating a smooth transition of adolescents with chronic health conditions from their pediatric/adolescent medical home to adult care can be difficult and is especially challenging for HIV-infected adolescents.

Transition is described as "a multifaceted, active process that attends to the medical, psychosocial, and educational or vocational needs of adolescents as they move from the child-focused to the adult-focused health-care system."[27] Care models for children and adolescents with perinatally acquired 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, more 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 uncomfortable with providers with whom he or she often does not have a long-standing relationship. Providing an adolescent and an adult medical care provider with support and guidance regarding expectations for each partner in the patient-provider relationship may be helpful. In this situation, it may also be helpful for a pediatric and an adult provider to share joint care of a patient for a period of time. Providers should also have a candid discussion with a transitioning adolescent to understand what qualities the adolescent considers most important in a provider (such as confidentiality, small clinic size, after-school appointments). Some general guidelines about transitional plans and who might benefit most from them are available.[28-32] Pediatric and adolescent providers should have a formal plan to transition adolescents to adult care.

Outcomes are variable in young adult patients transitioned to adult care. Definitions of "successful transition" have ranged from the ability to maintain a certain level of follow-up in the new clinic, to laboratory measures of stability, to comparisons of younger and older adult patients.[33-35] Factors that should be taken into consideration during transition include social determinants such as developmental status, behavioural/mental health issues, housing, family support, employment, recent discharge from foster care, peer pressure, illicit drug use, and incarceration. Currently there is no definitive model of transition to adult care, but in one study, adherence to medical visits just prior to the transition was predictive of successful transfer.[33] Psychiatric co-morbidities and their effective management also predict adherence to medical care and therapy.[36, 37] With more perinatally infected children surviving into adulthood, transitioning these patients to adult care settings remains challenging.

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