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

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This section discusses some unique issues to consider and basic principles to follow when caring for HIV-infected women, including during pregnancy. Clinicians who care for pregnant women should consult the current 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 for a more in-depth discussion and guidance on managing these patients.

**Gender Considerations in Antiretroviral Therapy**

In general, studies to date have not shown gender differences in virologic responses to antiretroviral therapy (ART).\(^1\)\(^\text{-}^4\) However, there are limited data showing that pharmacokinetics (PKs) for some antiretroviral (ARV) drugs may differ between men and women, possibly because of variations between men and women in factors such as body weight, plasma volume, gastric emptying time, plasma protein levels, cytochrome P (CYP) 450 activity, drug transporter function, and excretion activity.\(^5\)\(^\text{-}^7\)

**Adverse Effects**

Several studies have suggested that gender may influence the frequency, presentation, and severity of some ARV-related adverse events. Most notably, women are more likely to develop severe symptomatic hepatotoxicity with nevirapine (NVP) use,\(^5\)\(^\text{-}^9\) and are more likely to develop symptomatic lactic acidosis with prolonged use of older nucleoside reverse transcriptase inhibitors (NRTIs) such as zidovudine (ZDV), stavudine (d4T), and didanosine (ddI).\(^10\) These agents are no longer recommended for use in HIV-infected patients in the United States; although ZDV is still administered intravenously to women during delivery, it is not generally recommended for long-term use.
Some studies have compared women and men in relation to metabolic complications associated with ARV use. Over 96 weeks following initiation of ART, HIV-infected women are less likely to have decreases in limb fat but more likely to have decreases in bone mineral density (BMD) than HIV-infected men.\textsuperscript{11,12}

Women have an increased risk of osteopenia, osteoporosis, and fractures, particularly after menopause, and this risk is exacerbated by HIV and ART.\textsuperscript{13-16} ART regimens that contain tenofovir disoproxil fumarate (TDF), ritonavir-boosted protease inhibitors (PI/r), or both are associated with a significantly greater loss of BMD than regimens containing other NRTIs and raltegravir (RAL).\textsuperscript{17-20} Abacavir (ABC), NRTI-sparing regimens, and tenofovir alafenamide (TAF; a new oral tenofovir prodrug that induces less bone loss than TDF) may be considered as alternatives to TDF in patients who are at risk of osteopenia or osteoporosis. Recommendations for management of bone disease in HIV-infected patients have been published.\textsuperscript{21}

**HIV-Infected Women of Childbearing Potential**

All HIV-infected women of childbearing potential should be offered comprehensive reproductive and sexual health counseling and care as part of routine primary medical care. Topics for discussion should include safe sex practices, reproductive desires and options for conception, the HIV status of sex partner(s), and use of effective contraception to prevent unintended pregnancy. Counseling should also include discussion of special considerations pertaining to ARV use when using hormonal contraceptives, when trying to conceive, and during pregnancy (see Perinatal Guidelines).

**Reproductive Options for Serodiscordant Couples**

HIV infected and uninfected women who wish to conceive with an HIV-uninfected or infected male partner (respectively) should be informed of options to prevent sexual transmission of HIV while attempting conception. Interventions include screening and treating both partners for sexually transmitted infections (STIs), ART to maximally suppress and maintain the infected partner’s viral load, use of pre-exposure prophylaxis by the uninfected partner,\textsuperscript{22,24} male circumcision, and/or self-insemination with the HIV-uninfected partner’s sperm during the HIV-infected woman’s periovulatory period.\textsuperscript{25}

Efavirenz (EFV) is teratogenic in nonhuman primates. Nonpregnant women of childbearing potential should have a pregnancy test before starting EFV and be advised of potential EFV-related risks to the fetus and the desirability of avoiding conception while on an EFV-based regimen (AIII). Regimens that do not include EFV should be considered in women who are planning to become pregnant or who are sexually active and not using effective contraception (BIII). The most vulnerable period in fetal organogenesis is early in gestation, usually before pregnancy is recognized. Efavirenz use after the first 8 weeks of pregnancy appears safe.

**Hormonal Contraception**

Safe and effective reproductive health and family planning services to prevent unintended pregnancies and perinatal transmission of HIV are an essential component of care for HIV-infected women of childbearing age. These women should receive ongoing counseling on reproductive issues. Regardless of hormonal contraceptive use, HIV-infected women should be advised to consistently use condoms (male or female) during sex and adhere to an HIV regimen effective in maintaining viral suppression. Both strategies are crucial to prevent transmission of HIV to uninfected partners and to protect against infection with other STIs. The following are some considerations when hormonal contraceptives are used.

**Drug-Drug Interactions**

PK interactions between ARV drugs and hormonal contraceptives may reduce contraceptive efficacy. However, there are limited clinical data regarding drug interactions between ARVs and hormonal contraceptives and the clinical implications of these interactions are unclear. The magnitudes of changes in drug levels that may reduce contraceptive efficacy or increase adverse effects are unknown.
• **Combined Oral Contraceptives (COCs):** Several PIs, EFV, and elvitegravir/cobicistat (EVG/c)-based regimens have drug interactions with COCs. Interactions include either a decrease or an increase in blood levels of ethinyl estradiol, norethindrone, or norgestimate (see Tables 19a, 19b, and 19d), which potentially decreases contraceptive efficacy or increases estrogen- or progestin-related adverse effects (e.g., thromboembolism). EFV can decrease etonogestrel bioavailability and plasma progestin concentrations of COCs containing ethinyl estradiol and norgestimate.26 Several PI/r and EVG/c decrease oral contraceptive estradiol levels.27-30 Several PK studies have shown that ETR, RPV, and NVP use did not significantly affect estradiol or progestin levels in HIV-infected women using COCs.31-33

• **Injectable Contraceptives:** Small studies of HIV-infected women receiving injectable depot-medroxyprogesterone acetate (DMPA) while on ART showed no significant interactions between DMPA and EFV, lopinavir/ritonavir (LPV/r), NVP, nelfinavir (NFV), or NRTI drugs.34-37

• **Contraceptive Implants:** Contraceptive failure of the etonogestrel implant in women on EFV-based therapy has been reported.38,39 Two studies identified lower exposure of levonorgestrel and etonogestrel released from an implant when combined with EFV-based ART.40,41 These PK studies did not identify any change in hormone concentrations when the implants were used in women taking NVP40 or LPV/r.41 Similarly, two retrospective cohort evaluations conducted in Swaziland and Kenya showed an increased risk of contraceptive failure in women using contraceptive implants and receiving EFV.42,43

Concerns about PK interactions between oral or implantable hormonal contraceptives and ARVs should not prevent clinicians from prescribing hormonal contraceptives for women on ART who prefer this contraceptive method. However, an alternative or additional effective contraceptive method is recommended when there are significant drug interactions between hormonal contraceptives and ARVs (see drug interaction Tables 19a, 19b, and 19d and Perinatal Guidelines).

### Risk of HIV Acquisition and Transmission

Studies have produced conflicting data on the association between hormonal contraception and the risk of acquisition of HIV.44 Most of the retrospective studies were done in the setting where the HIV-infected partners were not taking ART. A retrospective secondary analysis of two studies of serodiscordant couples in Africa in which the HIV-infected partner was not receiving ART found that women using hormonal contraception (the majority using injectable DMPA) had a twofold increased risk of acquiring or transmitting HIV. HIV-infected women using hormonal contraception had higher genital HIV RNA concentrations than those not using hormonal contraceptives.45 Oral contraceptive use was not significantly associated with transmission of HIV; however, the number of women using oral contraceptives in this study was insufficient to adequately assess risk. A World Health Organization expert group reviewed all available evidence regarding hormonal contraception and HIV transmission to an uninfected partner and recommended that women living with HIV can continue to use all existing hormonal contraceptive methods without restriction.46 Further research is needed to definitively determine if hormonal contraceptive use is an independent risk factor for acquisition and transmission of HIV, particularly in the setting of ART. Regardless, the potential association of hormonal contraception use and HIV transmission in the absence of ART underscores the importance of ART-induced viral suppression to reduce transmission risk.

Intrauterine devices (IUDs) appear to be a safe and effective contraceptive option for HIV-infected women.47-49 Although studies have focused primarily on non-hormone-containing IUDs (e.g., copper IUD), several small studies have found that levonorgestrel-releasing IUDs are also safe and not associated with increased genital tract shedding of HIV.50-52

### Pregnant Women

Clinicians caring for HIV-infected pregnant women should review the Perinatal Guidelines. The use of combination ARV regimens is recommended for all HIV-infected pregnant women, regardless of virologic,
immunologic, or clinical parameters, for their own health and to prevent transmission of HIV to the fetus (AI). Pregnant HIV-infected women should be counseled regarding the known benefits and risks of ARV use during pregnancy to the woman, fetus, and newborn. Women should be counseled and strongly encouraged to receive ART for their own health and that of their infants. Open, non-judgmental and supportive discussion should be used to encourage women to adhere to care.

Prevention of Perinatal Transmission of HIV

The use of ART and the resultant reduction of HIV RNA levels decrease perinatal transmission of HIV. The goal of ART is to achieve maximal and sustained viral suppression throughout pregnancy. Long-term follow-up is recommended for all infants born to women who receive ART during pregnancy, regardless of the infant’s HIV status (see the Perinatal Guidelines).

ARV Regimen Considerations

Pregnancy should not preclude the use of optimal ARV regimens. As in nonpregnant individuals, genotypic resistance testing is recommended for all pregnant women before ARV initiation (AIII) and for pregnant women with detectable HIV RNA while on ART (AI). ART initiation should not be delayed in pregnant women pending genotypic resistance testing results. The ARV regimen can be modified, if necessary, once the resistance testing results are available (BIII). Unique considerations that influence recommendations on ARVs to use to treat HIV-infected pregnant women include the following:

- Physiologic changes associated with pregnancy that potentially result in changes in PKs, which may affect ARV dosing at different stages of pregnancy;
- Potential ARV-associated adverse effects in pregnant women and the potential for adherence to a particular regimen during pregnancy; and
- Potential short- and long-term effects of an ARV on the fetus and newborn, which are unknown for many drugs.

ART is considered the standard of care for HIV-infected pregnant women, both to treat HIV infection and prevent perinatal transmission of HIV. If a pregnant woman receiving an EFV-based regimen presents to prenatal care during the first trimester with suppressed HIV RNA, EFV can be continued. This is because the risk of fetal neural tube defects is restricted to the first 5 to 6 weeks of pregnancy and pregnancy is rarely recognized before 4 to 6 weeks of pregnancy. Unnecessary changes in ARV drugs during pregnancy may be associated with loss of viral control and increased risk of perinatal transmission. Detailed recommendations on ARV choice in pregnancy are discussed in detail in the Perinatal Guidelines.

If maternal HIV RNA is ≥1,000 copies/mL (or unknown) near delivery, intravenous (IV) infusion of ZDV during labor is recommended regardless of the mother’s antepartum regimen and resistance profile, and the mode of delivery (AI). Administration of combination ART should continue during labor and before a cesarean delivery (oral medications can be continued with sips of water).

Clinicians who are treating HIV-infected pregnant women are strongly encouraged to report cases of prenatal exposure to ARVs (either administered alone or in combinations) to the Antiretroviral Pregnancy Registry (http://www.apregistry.com). The registry collects observational data regarding exposure to Food and Drug Administration (FDA)-approved ARV drugs during pregnancy to assess potential teratogenicity. Analysis of the Antiretroviral Pregnancy Registry data indicates that there is no clear association between first-trimester exposure to any ARV drug and increased risk of birth defects. For more information regarding selection and use of ART during pregnancy, refer to the Perinatal Guidelines.
Postpartum Management

Following delivery, clinical, immunologic, and virologic follow-up should continue as recommended for nonpregnant adults and adolescents. Because maternal ART reduces but does not eliminate the risk of transmission of HIV in breast milk and postnatal transmission can occur despite maternal ART, women should be counseled to avoid breastfeeding.56 HIV-infected women should not premasticate food and feed it to their infants because the practice has been associated with mother-to-child transmission of HIV.57 ART is currently recommended for all HIV-infected individuals (AI); therefore, maternal ART should be continued after delivery. For more information regarding postpartum management, refer to the Perinatal Guidelines.

Several studies have demonstrated that adherence to ART may decline in the postpartum period.58-60 Clinicians caring for postpartum women who are receiving ART should address adherence, including an evaluation of specific facilitators and barriers to adherence. Clinicians may recommend an intervention to improve adherence (see Adherence to Antiretroviral Therapy).

References


49. U.S. Medical Eligibility Criteria for Contraceptive Use. Recommendations and Reports June 18, 2010 / 59(RR04);1-6; Prepared by Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion: [http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5904a1.htm?s_cid=rr5904a1_e](http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5904a1.htm?s_cid=rr5904a1_e). 2010.


