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

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HIV-Infected Women (Last updated February 12, 2013; last reviewed February 12, 2013)

Panel's Recommendations
• The indications for initiation of antiretroviral therapy (ART) and the goals of treatment are the same for HIV-infected women as for other HIV-infected adults and adolescents **(AI)**.
• Women taking antiretroviral (ARV) drugs that have significant pharmacokinetic interactions with oral contraceptives should use an additional or alternative contraceptive method to prevent unintended pregnancy **(AIII)**.
• In pregnant women, an additional goal of therapy is prevention of perinatal transmission of HIV, with a goal of maximal viral suppression to reduce the risk of transmission of HIV to the fetus and newborn **(AI)**.
• When selecting an ARV combination regimen for a pregnant woman, clinicians should consider the known safety, efficacy, and pharmacokinetic data on use during pregnancy for each agent **(AIII)**.
• Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz (EFV) and receive counseling about the potential risk to the fetus and desirability of avoiding pregnancy while on EFV-based regimens **(AIII)**.
• Alternative regimens that do not include EFV should be strongly considered in women who are planning to become pregnant or sexually active and not using effective contraception, assuming these alternative regimens are acceptable to the provider and are not thought to compromise the woman's health **(BIII)**.
• Because the risk of 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, EFV can be continued in pregnant women receiving an EFV-based regimen who present for antenatal care in the first trimester, provided the regimen produces virologic suppression **(CIII)**.
• When designing a regimen for a pregnant woman, clinicians should consult the most current Health and Human Services (HHS) Perinatal Guidelines **(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*

This section provides discussion of some basic principles and unique considerations to follow when caring for HIV-infected women, including during pregnancy. Clinicians who provide care for pregnant women should consult the current *Perinatal Guidelines*[1] for more in-depth discussion and management assistance. Additional guidance on the management of HIV-infected women can be found at http://hab.hrsa.gov/deliverhivaidscare/clinicalguide11.

Gender Considerations in Antiretroviral Therapy

In general, studies to date have not shown gender differences in virologic responses to antritretroviral therapy (ART),[2-4] but a number of studies have suggested that gender may influence the frequency, presentation, and severity of selected antiretroviral (ARV)-related adverse events.[5] Although data are limited, evidence also exists that pharmacokinetics for some 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.[6-8]

Adverse Effects:

- ***Nevirapine (NVP)-associated hepatotoxicity:*** NVP has been associated with an increased risk of symptomatic, potentially fatal, and often rash-associated liver toxicity in ARV-naive individuals; women with higher CD4 counts (>250 cells/mm^3) or elevated baseline transaminase levels appear to be at

greatest risk.[9-12] It is generally recommended that NVP not be prescribed to ARV-naive women who have CD4 counts >250 cells/mm^3 unless there is no other alternative and the benefit from NVP outweighs the risk of hepatotoxicity **(AI)**.

- ***Lactic acidosis:*** There is a female predominance in the increased incidence of symptomatic and even fatal lactic acidosis associated with prolonged exposure to nucleoside reverse transcriptase inhibitors (NRTIs). Lactic acidosis is most common with stavudine (d4T), didanosine (ddI), and zidovudine (ZDV) but it can occur with other NRTIs.[13]
- ***Metabolic complications:*** A few studies have compared women and men in terms of metabolic complications associated with ARV use. Compared with HIV-infected men, HIV-infected women are more likely to experience increases in central fat with ART and are less likely to have triglyceride elevations on treatment.[14, 15] Women have an increased risk of osteopenia/osteoporosis, particularly after menopause, and this risk is exacerbated by HIV and ART.[16, 17] At the present time, none of these differences requires women-specific recommendations regarding treatment or monitoring.

Women of Childbearing Potential

All women of childbearing potential should be offered pre-conception counseling and care as a component of routine primary medical care. Counseling should include discussion of special considerations pertaining to ARV use when trying to conceive and during pregnancy (see *Perinatal Guidelines*[1]). Safe sexual practices, reproductive desires and options for conception, HIV status of sexual partner(s), and use of effective contraception to prevent unintended pregnancy should be discussed. An HIV-infected woman who wishes to conceive with an HIV-uninfected male partner should be informed of options to prevent sexual transmission of HIV while attempting conception. Interventions include initiation of maximally suppressive ART, which significantly decreases the risk of sexual transmission (see Preventing Secondary Transmission of HIV), and artificial insemination, including the option to self-inseminate with the partner's sperm during the periovulatory period[18] (for more extensive discussion on this topic, see the Reproductive Options for HIV-Concordant and Serodiscordant Couples section of the *Perinatal Guidelines*.[1]

Efavirenz (EFV) is teratogenic in non-human primates. Women of childbearing potential should undergo pregnancy testing before initiation of EFV and receive counseling about the potential risk to the fetus and desirability of avoiding pregnancy while on EFV-based regimens **(AIII)**. Alternative regimens that do not include EFV should be strongly considered in women who are planning to become pregnant or who are sexually active and not using effective contraception, assuming these alternative regimens are acceptable to the provider and are not thought to compromise the woman's health **(BIII)**. The most vulnerable period in fetal organogenesis is early in gestation, before pregnancy is recognized.

Hormonal Contraception

Safe and effective reproductive health and family planning services to reduce unintended pregnancy and perinatal transmission of HIV are an essential component of care for HIV-infected women of childbearing age. Counseling about reproductive issues should be provided on an ongoing basis.

Providers should be aware of potential interactions between ARV drugs and hormonal contraceptives that could lower contraceptive efficacy. Several protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) have drug interactions with combined oral contraceptives (COCs). Interactions include either a decrease or an increase in blood levels of ethinyl estradiol, norethindrone, or norgestimate (see Tables 15a and 15b), which potentially decreases contraceptive efficacy or increases estrogen- or progestin-related adverse effects (e.g., thromboembolism). Small studies of HIV-infected women receiving injectable depot-medroxyprogesterone acetate (DMPA) while on ART showed no significant interactions between DMPA and EFV, NVP, nelfinavir (NFV), or NRTI drugs.[19-21] Contraceptive failure of the etonogestrel

implant in two patients on EFV-based therapy has been reported and a study has shown EFV may decrease plasma progestin concentrations of COCs containing ethinyl estradiol and norgestimate.[22, 23] Several RTV-boosted PIs decrease oral contraceptive estradiol levels.[24, 25] A small study from Malawi showed that NVP use did not significantly affect estradiol or progestin levels in HIV-infected women.[26] Overall, data are relatively limited and the clinical implications of these findings are unclear. The magnitudes of change in drug levels that may reduce contraceptive efficacy or increase adverse effects are unknown. Concerns about pharmacokinetic interactions between oral and implant hormonal contraceptives and ARVs should not prevent clinicians from prescribing hormonal contraceptives for women on ART if that is their preferred contraceptive method. However, when women wish to use hormonal contraceptives and drug interactions with ARVs are known, additional or alternative contraceptive methods may be recommended (see drug interaction Tables 15a, 15b, and 15d and *Perinatal Guidelines*[1]). Consistent use of male or female condoms to prevent transmission of HIV and protect against other sexually transmitted diseases (STDs) is recommended for all HIV-infected women and their partners, regardless of contraceptive use.

The data on the association between hormonal contraception and the risk of acquisition of HIV are conflicting.[27] 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 vast majority using injectable DMPA) had a twofold increased risk of acquiring HIV (for HIV-infected male/HIV-uninfected female couples) or transmitting HIV (HIV-infected female/HIV-uninfected male couples). HIV-infected women using hormonal contraception had higher genital HIV RNA concentrations than did women not using hormonal contraceptives.[28] 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. It is important to note that not all studies have supported a link between hormonal contraception and transmission or acquisition of HIV and that the individuals in this study were not receiving ART. 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.[27, 29]

Intrauterine devices (IUDs) appear to be a safe and effective contraceptive option for HIV-infected women.[30-33] Although studies have focused primarily on non-hormone-containing IUDs (e.g., copper IUD), several small studies have also found levonorgestrel-releasing IUDs to be safe and not associated with increased genital tract shedding of HIV.[31, 34, 35]

Pregnant Women

Clinicians should review the *Perinatal Guidelines*[1] for a detailed discussion of the management of HIV-infected pregnant women. The use of combination ARV regimens is recommended for all HIV-infected pregnant women, regardless of virologic, immunologic, or clinical parameters **(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. A woman's decision regarding ARV use should be respected. Coercive and punitive approaches undermine provider-patient trust and could discourage women from seeking prenatal care and adopting health care behaviors that optimize maternal, fetal, and neonatal well-being.

Prevention of Perinatal Transmission of HIV. The use of ARVs and the resultant reduction of HIV RNA levels decrease perinatal transmission of HIV.[36-38] The goal of ARV use is to achieve maximal and sustained suppression of HIV RNA levels during pregnancy.

As in non-pregnant individuals, genotypic resistance testing is recommended for all pregnant women before ARV initiation **(AIII)** and for pregnant women with detectable HIV RNA levels while on therapy **(AI)**. Optimal prevention of perinatal transmission may require initiation of ARV drugs before results of resistance testing are available. If results demonstrate the presence of significant mutation(s) that may confer resistance to the prescribed ARV regimen, the regimen should be modified.

Long-term follow-up is recommended for all infants born to women who have received ARVs during pregnancy, regardless of the infant's HIV status (see the *Perinatal Guidelines*[1]).

Regimen Considerations. Pregnancy should not preclude the use of optimal drug regimens. Because recommendations on ARVs to use for treatment of HIV-infected pregnant women are subject to unique considerations, recommendations specific to the timing of therapy initiation and the choice of ARVs for pregnant women may differ from those for non-pregnant individuals. These considerations include the following:

- Potential changes in pharmacokinetics and, thus, dosing requirements, which result from physiologic changes associated with pregnancy;
- potential ARV-associated adverse effects in pregnant women and the woman's ability to adhere to a particular regimen during pregnancy; and
- potential short- and long-term effects of the ARV on the fetus and newborn, which are unknown for many drugs.

Combination drug regimens are considered the standard of care in pregnancy, both for the treatment of HIV infection and for the prevention of perinatal transmission of HIV. Because the risk of 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, and unnecessary changes in ARV drugs during pregnancy may be associated with loss of viral control and increased risk of perinatal transmission, EFV can be continued in pregnant women receiving an EFV-based regimen who present for antenatal care in the first trimester, provided the regimen produces virologic suppression **(CIII)**. Detailed recommendations on ARV choice in pregnancy are discussed in detail in the Perinatal Guidelines (see *Perinatal Guidelines*[1]).

Intravenous (IV) zidovudine (ZDV) infusion to the mother during labor is recommended if maternal HIV RNA is ≥400 copies/mL (or with unknown HIV RNA levels) near delivery, regardless of antepartum regimen or mode of delivery **(AI)**. Consideration can be given to omitting IV ZDV infusion during labor for HIV-infected women receiving combination ART regimens who have HIV RNA <400 copies/mL near delivery **(BII)**; however, the combination ART should continue to be administered during labor.

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-approved ARV drugs during pregnancy for the purpose of assessing potential teratogenicity. For more information regarding selection and use of ART during pregnancy, refer to the *Perinatal Guidelines*.[1]

Postpartum Management

Following delivery, clinical, immunologic, and virologic follow-up should continue as recommended for non-pregnant 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 also be counseled to avoid breastfeeding.[1] HIV-infected women should avoid pre-mastication of food fed to their infants because the practice has been associated with transmission of HIV from mother to child.[39] Considerations regarding continuation of ART for maternal therapeutic indications are the same as those for ART use in other non-pregnant individuals. For more information regarding postpartum discontinuation of ART, refer to the *Perinatal Guidelines*.[1]

Several studies have demonstrated that adherence to ART may worsen in the postpartum period.[40-44] Clinicians caring for women postpartum who are receiving ART should specifically address adherence, including an evaluation of specific facilitators and barriers to adherence. Clinicians may consider an intervention to improve adherence (see Adherence to Antiretroviral Therapy).

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