HIV in Women

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Section 6: Key Populations
Topic 3: HIV in Women

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Background

Women comprise more than half of the people living with HIV worldwide and almost 25% of people living with HIV in the United States.[1,2] Medical providers who care for women with HIV should be aware of the unique healthcare needs of this special population. This Topic Review will explore several of the most important clinical issues for women living with HIV, including selection of appropriate antiretroviral therapy in women, contraception options, management of conception in serodiscordant couples desiring pregnancy, gynecologic disorders, menopause, and gender-based violence. The following topics also pertain to women living with HIV infection but are addressed in separate Topic Reviews: (1) transgender women (HIV in Sexual and Gender Minority Populations), (2) HIV in pregnancy (Preventing Perinatal HIV Transmission), and (3) cervical and breast cancer screening (Essentials of Primary Care Management in Persons Living with HIV).
HIV Epidemiology in Women

The following summarizes key features of HIV epidemiology of women in the United States. These data are for cisgender (person whose gender identity and assigned sex at birth correspond) women.

- **Living with Diagnosed and Undiagnosed HIV (Estimated HIV Prevalence):** At year end 2015 in the United States, an estimated 22.8% (256,500 of 1,122,900) of persons living with HIV in the United States were women.[1] These HIV prevalence estimates include women living with diagnosed and undiagnosed HIV.[1] In 2015, an estimated 11.5% of women living with HIV in the United States had undiagnosed infection. For all women living with HIV in the United States, 78% acquired HIV through heterosexual sex and 21% from injection drug use.[1] Overall, an estimated 1 in 250 women in the United States will have a lifetime diagnosis of HIV.[3]

- **Living with Diagnosed HIV:** At year end 2015, 24.0% (232,692 of 971,524) of persons 13 years of age and older living with diagnosed HIV in the United States were women.[4] Approximately 75% of women living with diagnosed HIV acquired HIV through heterosexual contact and 22% by injection drug use (Figure 1).[4] In the United States, black/African American women comprise, by far, the highest number of HIV infections in women living with diagnosed HIV (Figure 2).[4] Indeed, although black/African American women comprise about 13% of the female population in the United States, they account for approximately 59% of women living with diagnosed HIV.[4,5] These data show the HIV epidemic in women profoundly and disproportionately impacts black/African American women.

- **New HIV Infections (Estimated HIV Incidence):** Women accounted for approximately 18% of the new HIV infections during 2015 in the United States.[1] In 2015, 58% (4,000 of 6,900) of women with new HIV infections were black/African Americans and 15.9% (1,100 of 6,900) were Hispanic/Latina.[1] From 2010-2015, the number of new HIV infections in the United States among women decreased significantly (from a high of 8,700 in 2010 to a low of 6,700 in 2014) (Figure 3).[1]

- **New HIV Diagnoses:** Among the 39,782 persons newly diagnosed with HIV in 2016 in the United States, 7,529 (19%) were women.[4] Among women newly diagnosed with HIV in 2016, 87% were infected through heterosexual contact and 13% were infected through injection drug use (Figure 4).[4] In 2016, when comparing different racial/ethnic groups, the number of women newly diagnosed with HIV (Figure 5) and rate (per 100,000 population) (Figure 6) were by far the highest in black/African American women. For example the rate of new diagnoses of HIV infection among African American females was more than 15 times higher than the rate for white females (1.7).[4] In 2016, although black/African American women comprised 13% of the female population in the United States, they accounted for 61% of new diagnoses of HIV infection among females.[4,5] From 2011-2016, the number of new HIV diagnoses in women in the United States fell by 15% (Figure 7).[4]

- **Deaths in Women with Diagnosed HIV Infection:** In the United States in 2015, there were 3,816 deaths in women who had diagnosed HIV infection. From 2011-2015, the number of deaths in women with diagnosed HIV declined by approximately 11%.[4]
Antiretroviral Therapy in Women

Indications for Antiretroviral Therapy

The Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV (Adult and Adolescent Antiretroviral Therapy Guidelines) recommend antiretroviral therapy for all women living with HIV to improve the health of the individual woman and to decrease the risk of sexual and perinatal transmission of HIV.[6] This recommendation is the same as for all other adults and adolescents living with HIV.[7] Women who are pregnant have the additional goal of using antiretroviral therapy to prevent perinatal transmission of HIV.[6]

Gender Considerations

Available evidence suggests that virologic responses to antiretroviral therapy are comparable among women and men.[8,9,10,11] There are, however, some differences in women and men with respect to antiretroviral medication pharmacokinetics and adverse effects.[6,12,13,14] For example, women have greater risk of developing nevirapine-associated hepatotoxicity than men; nevirapine is contraindicated for use in women with a CD4 count greater than 250 cells/mm$^3$, whereas for men it is contraindicated when the CD4 count is greater than 400 cells/mm$^3$.[6,15]

Selecting an Antiretroviral Regimen in Women of Childbearing Age

Healthcare providers working with women of childbearing age with HIV should engage these women in discussions about their reproductive goals and contraceptive options prior to starting antiretroviral therapy. For women of childbearing age, it is important to carefully choose an antiretroviral regimen, taking into consideration the regimen should also be safe and effective in the event the woman becomes pregnant (either intentionally or inadvertently). For all pregnant women with HIV, the Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States (Perinatal Guidelines) recommend using combination antiretroviral therapy (with at least 3 drugs) to reduce the risk of HIV transmission to the child and to prevent disease in the mother.[16,17] In the Adult and Adolescent Antiretroviral Guidelines, only one preferred regimen for antiretroviral-naïve persons with HIV is also considered a preferred regimen in the Perinatal Guidelines for use in pregnancy: tenofovir DF-emtricitabine plus raltegravir.[17,18] The use of antiretroviral medications in pregnant women is discussed in detail in the topic Preventing Perinatal HIV Transmission in Module 5. The following highlights commonly used preferred antiretroviral medications in adults and adolescents that may have specific issues in women if they become pregnant.

- **Dolutegravir**: On May 18, 2018, the United States Food and Drug Administration issued a Safety Alert regarding a potential association of neural tube defects in babies born to mothers who initiated a dolutegravir-based regimen prior to pregnancy, and who were still receiving it at the time of conception. On May 30, 2018, the U.S. Department of Health and Human Services Antiretroviral Therapy Guidelines Panels issued Recommendations Regarding the Use of Dolutegravir in Adults and Adolescents with HIV who are Pregnant or of Child Bearing Potential.[19] Several key points in these recommendations are: (1) prior to initiating dolutegravir for any woman not known to be pregnant, documentation of a negative pregnancy test is recommended, (2) women of childbearing age who are taking dolutegravir or considering starting dolutegravir should receive counseling about the possible risk of neural tube defects if they are taking dolutegravir near the time of conception, and (3) women who are pregnant and within 8 weeks of their last menstrual period should switch to a non-dolutegravir regimen if other good options are available; if 8 weeks or more have elapsed since their last menstrual period, dolutegravir can be initiated or continued, as neural tube defects occur within the first 6 weeks after the last menstrual period.

- **Efavirenz**: In the Adult and Adolescent Antiretroviral Therapy Guidelines, efavirenz with
2NRTIs is included in the category of Recommended Initial Regimens in Certain Clinical Situations.[18] Previous concerns about teratogenicity associated with efavirenz have largely been quelled due to reassuring findings in several systematic reviews and meta-analyses.[20,21] Nonetheless, the Perinatal Guidelines still recommend that women of childbearing age undergo pregnancy testing prior to starting efavirenz and receive counseling about the possible fetal risks associated with taking efavirenz during pregnancy, though pregnant women already on suppressive regimens containing efavirenz may continue these regimens throughout their pregnancies.[6]

- **Elvitegravir-Cobicistat**: Limited data with use of regimens containing elvitegravir-cobicistat in pregnancy suggest that elvitegravir and cobicistat levels are significantly decreased during the second and third trimesters of pregnancy and therefore regimens containing elvitegravir-cobicistat are not recommended for use in pregnancy. For women who become pregnant while receiving a regimen containing elvitegravir-cobicistat, the regimen should be switched to a preferred regimen.[22] For these reasons, regimens such as elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine or elvitegravir-cobicistat-tenofovir DF-emtricitabine are not ideal choices in women of childbearing age.

- **Tenofovir alafenamide**: In the Adult and Adolescent Antiretroviral Therapy Guidelines, tenofovir alafenamide-emtricitabine is included as the backbone component of multiple regimens in the category of Recommended Initial Regimens for Most People with HIV.[18] There are, however, insufficient data regarding the use of tenofovir alafenamide in pregnancy to recommend its routine use in this situation.[16]
Contraception in Women with HIV

Healthcare providers should offer all women living with HIV counseling about family planning, reproductive goals, and contraception options, and they should emphasize the importance of HIV prevention measures, including treatment as prevention, limiting numbers of sexual partners, correct and consistent use of condoms, and availability of preexposure (PrEP) and postexposure (PEP) prophylaxis for their partners, regardless of the method of contraception chosen. Discussing risks of HIV transmission with different forms of contraception, as well as possible drug interactions with contraceptives and antiretroviral therapy, is also critical.

Guidance for Hormonal Contraceptive Use

There are a number of excellent resources for guidance related to contraception in women living with HIV including the CDC’s U.S. Medical Eligibility Criteria for Contraceptive Use (CDC U.S. MEC), the Perinatal Guidelines, and the Adult and Adolescents Antiretroviral Therapy Guidelines.[6,23,24,25] These resources provide recommendations about safety and efficacy of different methods of contraception, prescribing recommendations, drug interactions, and counseling about family planning for women living with or at risk for HIV. All of these guidelines concur that women living with HIV should be offered a full array of contraception choices, including hormonal options.[23,24] Selection of a contraceptive method in women living with HIV should take into account the patient’s desires about family planning and preferred contraceptive method, antiretroviral therapy regimen, other medications and comorbid conditions, and risk of transmission of HIV to other partners.[23,25] The following summarizes the CDC U.S. MEC recommendations for use of contraception in women living with HIV:[23,25]

CDC U.S. MEC Categories for Classifying Contraceptive Methods

The CDC U.S. MEC uses a rating system to categorize the relative risks and benefits of each method of contraception depending on a woman’s medical comorbidities or medication use.[25]

- 1 = A condition for which there is no restriction for the use of the contraceptive method.
- 2 = A condition for which the advantages of using the method generally outweigh the theoretical or proven risks.
- 3 = A condition for which the theoretical or proven risks usually outweigh the advantages of using the method.
- 4 = A condition that represents an unacceptable health risk if the contraceptive method is used.

CDC U.S. MEC Recommendations for Contraceptive Methods

- **Hormonal Contraceptives**: In these guidelines, hormonal contraceptives consist of combined hormonal contraceptives (including combined oral contraceptives, combined hormonal patches, and the combined vaginal ring), progestin-only pills, and implants. In women living with HIV who are not clinically well or not on antiretroviral therapy, combined hormonal contraceptives, progestin-only pills, and implants may be used without restriction (category 1). In women with HIV who are taking antiretroviral therapy, these contraceptives are considered safe and the advantages of their use are thought to outweigh the risks. These are rated either CDC U.S. MEC category 1 or 2, depending on which antiretroviral therapy regimen the woman is using, due to concerns about drug interactions between contraceptives and some antiretroviral medications, especially protease inhibitors, pharmacologic boosters, and efavirenz.
- **Progestin-Only Injectable Contraceptives**: In women living with HIV, progestin-only injectable contraceptives are considered safe to use without restriction (category 1). Most often, depot-medroxyprogesterone acetate (DMPA) is the progestin-only injectable contraceptive used. Antiretroviral medication drug interactions with DMPA are generally not
clinically significant. There has been some concern that DMPA use may increase risk of HIV transmission and acquisition, but the CDC continues to recommend DMPA (without restriction) in women living with HIV. The CDC has updated their recommendations about the use of DMPA in women at high risk for HIV.[23,26]

- **Intrauterine devices (IUDs):** Intrauterine devices (IUDs) are considered safe and effective in women living with HIV, and these may be used without restriction in women clinically well and on antiretroviral therapy (category 1) (Table 1). Although IUDs are still considered reasonable options in women living with HIV who are not clinically well or not on antiretroviral therapy, the CDC U.S. MEC ranks initiation of IUDs as category 2 and continuation of IUDs previously inserted as category 1. The use of IUDs in women has not been associated with increased HIV disease progression, risk of HIV transmission, or genital viral shedding. In addition, there is no evidence to suggest increased risks of infectious complications, such as pelvic inflammatory disease (PID), associated with IUD use in women living with HIV.[23,25]

- **Condoms:** Women living with HIV using any contraceptive method other than condoms should receive counseling regarding the use of condoms to reduce the risk of transmission of sexually transmitted infections and HIV, as well as to prevent pregnancy. This is particularly important for women living with HIV on antiretroviral therapy regimens that may decrease the efficacy of their method of contraception.

- **Spermicides:** The use of spermicides containing nonoxynol-9 should be avoided in women with or at risk for HIV due to concerns about this spermicide causing genital lesions which could lead to increased risk of transmission and acquisition of HIV. Whether used alone, with condoms, or with a diaphragm, spermicides are rated category 3 (the risks of this method are thought to outweigh the benefits) in women living with HIV.[25,27]

### Hormonal Contraception Interactions with Antiretroviral Medications

Since some antiretroviral medications and hormonal contraceptives are metabolized by the same enzyme pathways, drug interactions are a concern in women with HIV who are of childbearing age. The most common interactions between these classes of medications may cause compromised efficacy of the contraceptive method, but fortunately rarely diminish the potency of the antiretroviral medications. In general, significant interactions with antiretroviral medications are more likely to occur with combined oral contraceptives and transdermal contraceptives compared with intrauterine devices (IUDs) and injectable DMPA.[28] Some of the most significant potential drug interactions between hormonal contraceptives and antiretroviral medications are highlighted below:[6,24,25]

- **Nucleoside Reverse Transcriptase Inhibitors (NRTIs):** There are no significant drug interactions expected between NRTIs and hormonal contraceptive methods.

- **Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs):** Among the NNRTIs, efavirenz is the most likely to interact with hormonal contraceptives. Efavirenz is metabolized by the CYP3A4 enzyme pathway and may decrease blood levels of hormonal contraceptives, leading to decreased contraceptive efficacy, including the efficacy of emergency postcoital contraception. The NNRTIs etravirine and rilpivirine do not have this effect.[25] Although the main drug interactions of concern is with efavirenz and combined oral contraceptives, one study showed a non-significant increase in pregnancy rates in women who were taking efavirenz and were using the etonogestrel implant.[29] There are no known significant interactions between NNRTIs and DMPA or levonorgestrel-releasing IUDs.[28]

- **Protease inhibitors (PIs):** Protease inhibitors undergo metabolism via the same CYP3A4 enzyme pathway as many hormonal contraceptives and can alter hormone levels.[6] Although PIs generally inhibit CYP3A4 and would therefore be expected to increase hormone levels, most ritonavir-boosted PIs actually decrease levels of ethinyl estradiol and have unpredictable effects on progestins, norethindrone and norgestimate, potentially decreasing contraceptive efficacy. No significant interactions have been identified between protease inhibitors and injectable DMPA.[28] When women on hormonal contraceptives take protease inhibitors in the absence of a boosting agent, levels of the estrogen and progestin
components of the contraceptive may increase, potentially raising the risk of associated adverse effects of the contraceptive.

- **Cobicistat**: Although relatively little is known about drug interactions between hormonal contraceptives and cobicistat, this pharmacologic booster is a potent inhibitor of CYP3A and CYP2D6 hepatic enzymes and theoretically could increase contraceptive hormone levels. In addition, the effect of cobicistat on hormonal contraceptives, when used with other antiretrovirals, is not clearly understood, and theoretically it may actually decrease hormone levels similar to the effect caused by ritonavir-boosted protease inhibitors.

- **Integrase Strand Transfer Inhibitors (INSTIs)**: The INSTIs are not substrates for CYP enzymes and thus have lower potential for drug interactions with hormonal contraceptives. Raltegravir and dolutegravir have both been studied with combined oral contraceptive pills and no significant drug interactions have been identified.[30] In contrast, when elvitegravir is given in a fixed-dose combination with cobicistat, levels of ethinyl estradiol decrease and levels of norgestimate increase significantly; consequently, clinicians should consider using an alternative hormonal contraceptive in patients taking elvitegravir in combination with cobicistat. If these medications are taken together, patients should be counseled about possible increased risk of progestin side effects, including insulin resistance, dyslipidemia, acne, and venous thrombosis.[28,30]

- **CCR5 Co-Receptor Antagonists and Fusion inhibitors**: There are no significant drug interactions expected between these antiretroviral therapies and hormonal contraceptive methods.

**Contraception Use and Risk of HIV Transmission**

There are limited, high-quality data that address the potential impact of contraception on HIV transmission for women living with HIV. The following summarizes available data.

- A European study involving 563 HIV-serodiscordant couples found no association between hormonal contraception and HIV transmission to the uninfected male partner.[31]
- A prospective cohort analysis in Africa that included 3790 HIV-serodiscordant couples (of which 2476 had a female partner with HIV) found that women with HIV taking hormonal contraception (primarily injectable methods) had an approximately two-fold risk of transmitting HIV to their male partner compared with women who did not use hormonal contraception.[26] Women using injectable contraception had higher HIV levels in their endocervical secretions and this finding provided a plausible mechanism for the increased transmission risk.[26] In a multivariate analysis adjusted for age, pregnancy, unprotected sex, and plasma HIV RNA level, the investigators concluded that any hormonal contraceptive use by female partners with HIV increased the HIV acquisition risk in uninfected male partners, but the effect was statistically significant only for injectable contraceptives; the women in this study were not on antiretroviral therapy.[26]
- Several other studies have investigated the effect of hormonal contraception on HIV viral load set points, as well as cervical and vaginal HIV shedding; although some of these studies provide indirect evidence for a hormonally-mediated increase in infectivity (higher plasma RNA and higher rates of genital HIV shedding), the results have been mixed, with several studies showing no association or even inverse association.[32,33]
- A recent systematic review of women living with HIV and using IUDs (either levonorgestrel- or copper-containing) found no difference in disease progression or genital viral shedding compared with women using other forms of contraception.[34]

**Effect of Hormonal Contraception on HIV Disease Progression**

Data on the impact of hormonal contraception on HIV disease progression is also contradictory. A study of 599 postpartum women with HIV infection in Zambia found that hormonal contraception was associated with more rapid disease progression whereas the copper-containing IUD was safe and effective; secondary analysis of the data confirmed this relationship.[35,36] The same author,
however, also reported that a study of 4,109 women found that neither implants/injectables nor oral contraceptive pills were associated with HIV disease progression.\cite{35} Subsequently, a systematic review of 10 cohort studies and one randomized trial concluded that hormonal contraception is not associated with accelerated HIV disease progression; a variety of outcome measures were used to determine HIV progression, including mortality, onset of clinical AIDS, time to a CD4 cell count below 200 cells/mm$^3$, CD4 count decline below a defined threshold, time to initiation of antiretroviral therapy, and increase in HIV RNA level.\cite{37} A prospective study of 2,269 women with HIV infection similarly found no association between the use of hormonal contraception and accelerated HIV disease progression, and another small study that specifically evaluated the levonorgestrel-releasing intrauterine device (LNG-IUD) also reported the LNG-IUD does not have any adverse impact on HIV progression.\cite{38,39} Importantly, most of the patients in clinical studies evaluating the effect of hormonal contraception on HIV progression were not taking antiretroviral therapy, so it remains unclear whether having a suppressed viral load on therapy would negate the potentially negative effects of hormonal contraception on HIV progression.\cite{36}
Contraception Considerations for Women at Risk for HIV

Healthcare providers should offer all women at risk for acquiring HIV counseling about reproductive goals and contraception options, and they should emphasize the importance of HIV prevention measures, including treatment as prevention strategies in partners living with HIV, limiting numbers of sexual partners, correct and consistent use of condoms, and availability of preexposure (PrEP) and postexposure (PEP) prophylaxis, regardless of the method of contraception chosen.

Hormonal Contraception Use and Risk of HIV Acquisition

Systematic reviews of available data have concluded that no clear association exists between the use of non-injectable hormonal contraceptives, such as oral contraceptive pills, intrauterine devices, and implants, and the risk of HIV acquisition.[23,40,41,42] In contrast, several observational studies have suggested a possible increased risk of HIV acquisition with the use of the injectable progestin-only contraceptive DMPA.[26,43,44,45,46,47] In addition, a pooled estimate of the association between DMPA and HIV acquisition based on data from a meta-analysis concluded DMPA increases a woman’s chance of acquiring HIV by 40%, and this is consistent with two additional systematic reviews that found hazard ratios between 1.4 and 1.5.[40,43,48] Other studies, however, have contradicted these findings and several recent systematic reviews found no increased risk of HIV acquisition with the non-DMPA injectable progestin norethisterone enanthate (NET-EN).[43,48,49,50]

Possible Mechanisms for Enhanced HIV Risk Acquisition with DMPA

Experts have proposed several possible mechanisms for the observed increased risk of HIV acquisition associated with DMPA, including biologic changes (thinning of the vaginal epithelium or changes in vaginal flora), immune system changes (alteration in cytokines and antimicrobial peptides, increased inflammation, increased frequency of activated HIV target cells in the cervix, and changes in CCR5 expression), and behavioral factors (decreased condom use in the setting of reliable contraception).[42,45,51,52] In contrast, in a trial of 34 HIV women without HIV who were randomized to either a levonorgestrel-containing IUD or a copper-containing IUD, women using either type of IUD had reduced expression of CCR5 receptors and a decrease in activated T-cells in the endometrium and cervix compared with expression prior to IUD placement.[53]

CDC U.S. MEC Guidance for Hormonal Contraception in Women at Risk for HIV

In September 2017, the CDC released an update to the 2016 CDC U.S. MEC guidance pertaining to the use of hormonal contraception in women at high risk for HIV infection.[23,25] After careful review of the current data and the updated World Health Organization (WHO) MEC guidance from March 2017, the CDC decided to adopt the WHO recommendations, which are summarized below (Table 2):[23,54]

- All hormonal contraceptive options should be available to women at high risk for HIV infection.
- Despite conflicting data about increased risk of HIV acquisition in women using progestin-only injectable contraception (including DMPA), the advantages of these methods outweigh the theoretical or proven risks (category 2) and may be initiated or continued in women at high risk for HIV.
- Women considering progestin-only injectable contraception should be counseled about the concerns of increased risk of HIV acquisition in women using these methods, the unclear causal relationship, and strategies to minimize risk of HIV infection.
- There are no restrictions for the use of other hormonal contraceptive methods (including combined hormonal methods, implants, and progestin-only pills) in women at high risk for HIV infection (category 1).
IUD use (both initiation and continuation) is rated category 2 (the advantages of these methods outweigh the theoretical or proven risks) in women at risk for HIV. Finally, spermicides containing nonoxynol-9 should not be used in women with or at risk for HIV due to concerns about this spermicide causing genital lesions which could lead to increased risk of transmission and acquisition of HIV. Whether used alone, with condoms, or with a diaphragm, spermicides are rated category 4 (unacceptable health risk) in women at risk for HIV.

Contraception in Women Using Preexposure Prophylaxis (PrEP)

Women taking combination tenofovir DF-emtricitabine for PrEP who do not currently desire pregnancy may use any effective method of contraception. There are no significant drug interactions expected with tenofovir DF-emtricitabine and any of the available forms of contraception, and PrEP was not associated with increased pregnancy rates in women using hormonal contraception compared to women not using PrEP.[55] Women on PrEP should be counseled to use condoms in addition to hormonal contraceptives, particularly if they are using injectable progestin-only contraceptives such as DMPA, due to some concerns related to increased risk of acquisition of HIV with the use of these; however, a recent study showed that PrEP was equally effective in reducing risk of HIV acquisition in women using DMPA compared to women who were not using hormonal contraception.[56] Ongoing research and development of products that will have the dual purpose of providing contraception and PrEP may provide more options for women who want simpler methods of preventing pregnancy and HIV acquisition.[57, 58]
Serodiscordant Couples Desiring Pregnancy

Several options exist for HIV serodiscordant couples seeking pregnancy. [59] Serodiscordant couples who wish to conceive a child should first ensure the partner with HIV infection achieves virologic suppression on an effective antiretroviral regimen and that both partners undergo screening and treatment for sexually transmitted infections (untreated sexually transmitted infections can increase HIV shedding).[24] Several studies have now shown that the risk of HIV transmission in discordant couples is exceedingly low when the partner with HIV is taking antiretroviral therapy and has consistently suppressed HIV RNA levels.[24] The following will review a variety of strategies for safer conception depending on which partner is living with HIV.

Female Partner with HIV Infection

When the female partner has HIV and the male partner does not, the risk of female-to-male HIV transmission can be avoided entirely if the couple utilizes impregnation techniques without having condomless intercourse. In this situation, the safest and recommended method of conception is periovulatory artificial insemination, whether by self-insemination with the partner’s semen, such as with a plastic (needleless) syringe or with the assistance of a medical professional using intrauterine insemination.[24] In vitro fertilization is considered another very safe option, but it is cost-prohibitive for many couples and not usually necessary unless fertility problems exist. In some instances, especially for cultural or philosophical reasons, couples may not be willing to utilize any self-insemination techniques. If, despite counseling, the serodiscordant couple elects to try to conceive via unprotected sexual intercourse, they should be advised to proceed only after the woman has attained suppressed plasma HIV RNA levels on antiretroviral therapy and the conception attempts should consist of selected, timed, periovulatory condomless intercourse, with use of condoms at all other times.[24, 60, 61] In this scenario, it would be reasonable to consider giving the male partner preexposure prophylaxis (PrEP), especially if the female partner did not have suppressed HIV RNA levels.

Male Partner with HIV Infection

When the male partner in an HIV-serodiscordant relationship is living with HIV, the safest conception option is to use donated sperm from another man who is not infected with HIV. If this is not a desired or acceptable option for the couple, experts recommend a multipronged approach to minimize the risk of HIV transmission during conception attempts. First, and most importantly, the male partner should be taking antiretroviral therapy and have suppressed HIV RNA levels prior to having unprotected intercourse. Second, both partners should undergo screening and treatment for any sexually transmitted genital tract infections. Third, if possible, the couple should consider assisted reproductive technologies, such as in vitro fertilization, intrauterine insemination after sperm preparation techniques, and sperm washing, to decrease the risk of HIV transmission to the female partner.[24] Fourth, the use of PrEP for the woman should be discussed with the couple. In addition, with HIV serodiscordant couples, many experts recommend performing a basic semen analysis, including sperm count, volume, and mobility, in order to make sure the couple has substantial likelihood of achieving conception, especially if they elect to pursue conception through condomless intercourse.[24] Unfortunately, many of the assisted reproductive technologic services are often not an option for serodiscordant couples due to prohibitive cost or lack of access to an in vitro fertilization center. In these cases, couples should be counseled that engaging in timed periovulatory condomless intercourse may decrease, but not eliminate, the risk of HIV transmission.[24] For these couples, condoms should be used at all other times. If the female partner of a man living with HIV becomes pregnant, she should undergo HIV testing and close monitoring during the pregnancy.

Periconception Preexposure Prophylaxis (PrEP)

The use of periconception PrEP has provided a new adjunctive option for HIV-serodiscordant couples
attempting conception.\[61, 62\] Limited data exist regarding the efficacy and optimal use of PrEP in serodiscordant couples planning pregnancy. Although several large randomized PrEP trials have involved heterosexual women of childbearing age, PrEP was promptly stopped if the woman in the trial became pregnant. A subanalysis of the data from the Partners PrEP Study (conducted at multiple sites in Kenya and Uganda) showed no significant differences in pregnancy incidence, birth outcomes, or infant growth among women who were taking PrEP at the time of conception.\[63, 64\] The CDC Clinical Practice Guideline for the use of PrEP and the HHS Perinatal Guidelines both note that PrEP may offer an additional tool to reduce the risk of sexual transmission of HIV during attempts at conception, regardless of which partner is living with HIV.\[24, 65, 66\] If periconception PrEP is used, the CDC recommends the uninfected partner initiate PrEP one month before conception is attempted and continue for one month after the couple's last attempt at conception.\[66\] Of note, most of the PrEP studies have been conducted outside of the United States, and some researchers have found that within the United States, HIV-related stigma and lack of provider awareness may lead to missed opportunities for using PrEP for safer conception.\[67, 68\]
Vaginitis in Women with HIV

Although most women will experience at least one episode of vaginitis in their lifetime, women living with HIV develop vaginal infections more commonly than women without HIV infection. These infections can influence susceptibility to sexually transmitted infections and increase the risk of HIV transmission to uninfected partners. Three of the most common vaginal infections that occur in women living with HIV are addressed in this section: bacterial vaginosis, vulvovaginal candidiasis, and trichomoniasis. A more comprehensive discussion of female genitourinary infections, including sexually transmitted infections, is available in the CDC 2015 STD Treatment Guidelines.

Bacterial Vaginosis

Bacterial vaginosis is a condition in which the predominant vaginal hydrogen peroxide-producing *Lactobacillus* species bacteria are overgrown with abundant anaerobic bacteria. Women with bacterial vaginosis may be asymptomatic or they may develop a malodorous vaginal discharge. Bacterial vaginosis tends to occur (and recur) more frequently in women with HIV infection compared with women who do not have HIV infection; bacterial vaginosis increases the risk of acquiring other sexually transmitted diseases, and it can also increase the risk of HIV transmission to partners without HIV.[70,71,72]

- **Diagnosis:** The gold standard for diagnosing bacterial vaginosis is a Gram’s stain of the vaginal discharge, which reveals a low concentration of lactobacilli, with multiple gram-negative and gram-variable rods and cocci. Alternatively, bacterial vaginosis can be diagnosed clinically by Amsel’s Diagnostic Criteria, which requires that three of the following are met: (1) homogenous thin discharge coating the vaginal walls, (2) vaginal epithelial cells studded with adherent coccobacilli on microscopy (clue cells), (3) vaginal pH greater than 4.5, and (4) a fishy (amine) odor to the vaginal discharge that occurs when adding 10% potassium hydroxide (positive whiff test).[70] Other acceptable, but less frequently used, diagnostic tests include a DNA probe test for *Gardnerella vaginalis*, a proline aminopeptidase test card, the OSOM BV Blue test, and the recent FDA-approved BD MAX Vaginal Panel real-time PCR assay.

- **Treatment:** There are three recommended treatment options for bacterial vaginosis in the 2015 STD Treatment Guidelines: metronidazole 500 mg orally twice daily for 7 days, metronidazole gel 0.75% applied in one full applicator (5 g) intravaginally once a day for 5 days, or clindamycin cream 2% applied in one full applicator (5 g) intravaginally at bedtime for 7 days.[70] Alternative regimens include the use of tinidazole or oral clindamycin. The treatment is the same for women with HIV as for women without HIV. A new nitroimidazole antibiotic, secnidazole, was approved by the FDA in September 2017 for the treatment of bacterial vaginosis based on data from randomized controlled trials that found secnidazole was well-tolerated, superior to placebo, and at least as effective as multiday metronidazole therapy.[73,74,75] There are no published data about the use of secnidazole to treat bacterial vaginosis in women with HIV infection, and there are no CDC recommendations regarding secnidazole since it was approved for use after the most recent 2015 issue of the STD Guidelines.

Trichomoniasis

Trichomoniasis is a common sexually transmitted infection in the United States caused by a protozoan pathogen, *Trichomonas vaginalis*, and some studies have found that more than half of women with HIV infection are coinfected with *T. vaginalis* at some point in their lives.[76] In women living with HIV, *T. vaginalis* infection increases the risk of pelvic inflammatory disease and it increases shedding of HIV from the genital tract, which may increase the risk of HIV transmission.[76] Among sexually active women without HIV, *T. vaginalis* infection is also an independent risk factor for acquiring HIV.[76]
• **Diagnosis:** Women with trichomoniasis may present with malodorous, yellow-green vaginal discharge, vulvar irritation, or they may be asymptomatic. The use of nucleic acid amplification testing (NAAT) in vaginal, endocervical, or urine specimens has become the gold standard for diagnosing trichomoniasis in women, replacing the wet mount preparation and culture for this purpose when available.[76]

• **Treatment:** According to the 2015 STD Treatment Guidelines, the preferred treatment option for trichomoniasis in women with HIV infection is metronidazole 500 mg orally twice daily for 7 days.[76] A single dose of metronidazole 2 g (or tinidazole 2 g) is considered first-line therapy for women without HIV, but a randomized clinical trial found that single-dose therapy was less effective than the 7-day regimen for women with HIV and trichomoniasis (Figure 8).[77]

**Vulvovaginal Candidiasis**

Vulvovaginal candidiasis is a common problem among women living with HIV, occurring more frequently in this population than in women without HIV.[78,79] Recurrent vulvovaginal candidiasis may be the initial clinical presentation in women with HIV; with more advanced HIV disease vulvovaginal candidiasis often is more severe and may recur more frequently.[79,80] Vulvovaginal candidiasis can impact the vaginal epithelium and increase susceptibility to sexually transmitted infections, including HIV. In addition, women with HIV and vulvovaginal candidiasis have higher concentrations of HIV in genital fluids; it is not clear, however, if treatment of vulvovaginal candidiasis alters the risk of HIV acquisition or transmission.[79]

• **Diagnosis:** Women with early stages of HIV usually have manifestations of vulvovaginal candidiasis that are similar to women without HIV, namely mucosal burning and itching with evidence of white adherent plaques.[80] The diagnosis is confirmed by examining a wet mount of vaginal secretions and finding hyphal forms after applying 10% potassium hydroxide (KOH). In the absence of other causes of vaginitis, such as bacterial vaginosis or trichomoniasis, a woman with candida infection should have a normal vaginal fluid pH (less than 4.5).

• **Treatment:** The preferred treatment options for treatment of vulvovaginal candidiasis consist of single-dose fluconazole 150 mg orally or short-course topical azoles.[79,80] If topical therapies are chosen, it is especially important to counsel women with HIV that the available creams and suppositories are oil-based and might weaken latex condoms. Available data suggest that vulvovaginal candidiasis is rarely refractory to oral azoles, such as fluconazole.[80] If a woman has recurrent (greater than four episodes per year) vulvovaginitis or symptoms without evidence of yeast on wet mount, fungal cultures and susceptibility testing should be considered. The 2015 STD Guidelines notes that for women with frequent or severe recurrences of vulvovaginal candidiasis, some experts recommend using a long treatment course (e.g. oral fluconazole 100-200 mg orally every third day for 3 doses), followed by a maintenance regimen of fluconazole 100-200 mg weekly for 6 months.[79]

• **Prophylaxis:** Long-term prophylactic fluconazole therapy can reduce colonization and recurrent symptoms of vulvovaginal candidiasis, but routine primary prophylaxis with fluconazole is not recommended in women living with HIV.[79]
Women with HIV and Gender-Based Violence

Gender-based violence, defined as a woman’s experience of childhood or adult physical, sexual, or psychological abuse, increases a woman’s likelihood of engaging in sexual risk behavior and substance use, which in turn increases her risk of acquiring HIV infection.[81] If a woman is infected with HIV, the syndemic of gender-based violence (often intimate partner violence), substance use, and HIV infection places her at high risk of attendant mental health disorders.[81,82,83,84] Studies have found that 60 to 90% women who are victims of gender-based violence develop anxiety disorders, including post-traumatic stress disorder, and as many as 50% develop depression; these numbers are likely higher for women with HIV who already suffer higher rates of psychological disease at baseline.[85,86] Transgender women are also at significant risk of gender-based violence against them.[87,88] Clinicians caring for cis- and transgender women with HIV should be vigilant in screening for gender-based violence, as well as screening for accompanying mental health symptoms, given that depression and posttraumatic stress disorder decrease quality of life and have been linked to poor adherence with antiretroviral therapy and subsequent treatment failure.[89,90]
Menopause in Women with HIV

Age at Menopause

With the widespread availability of effective antiretroviral therapy, women with HIV are living longer and more are reaching menopause.\[91,92\] Available data suggest that menopause occurs at an earlier age in women with HIV than in the general population; however, the results are confounded by many other factors that affect age at menopause and are common in women living with HIV (e.g. smoking, low body mass index, coinfection with hepatitis C virus, and low socioeconomic status).\[91,92,93\] In one multivariate analysis of data collected from a prospective cohort of 667 women with HIV, the presence of a CD4 count less than 50 cells/mm\(^3\) conferred a three-fold risk of early menopause.\[91\] Women with HIV also appear to experience a greater burden of menopausal symptoms compared with women without HIV.\[93\]

Effect of Menopause on HIV Acquisition and Transmission

There are concerns that age-related vaginal epithelial changes (such as atrophy and decreased mucosal integrity) might enhance risk for HIV acquisition and transmission, in much the same way that mucosal ulcers disrupt the mucosal barrier and can enhance HIV susceptibility and shedding.\[94,95\] Despite these concerns, postmenopausal women with HIV infection have not been found to have increased genital HIV shedding compared with younger women.\[95\]

Antiretroviral Therapy in Peri- and Postmenopausal Women

Estrogen appears to have a protective effect on immune function, as evidenced by the fact that premenopausal women have higher CD4 counts and lower HIV RNA levels compared with age-matched men.\[96\] Despite concerns that postmenopausal women might have suboptimal immunologic and virologic responses to antiretroviral therapy as a result of decreasing estrogen levels, two studies have demonstrated equivalent responses to antiretroviral therapy regardless of menopausal status.\[96\] Unfortunately, given the higher rates of menopausal symptoms in women with HIV infection, there are limited data on the safety and efficacy of hormone replacement therapy in women with HIV infection, including limited information on drug interactions between hormonal therapies and antiretroviral medications.\[93\] Because current guidelines stress the need to weigh the risks and benefits of using hormone replacement therapy for the treatment of menopausal symptoms, women living with HIV may not be ideal candidates for hormonal replacement therapy given the increased rates of cardiovascular disease in the population living with HIV.\[93,97\]

Impact of Menopause on Other Conditions

Earlier onset of menopause requires heightened vigilance for conditions that are associated with postmenopausal status, such as osteoporosis and cardiovascular disease, especially since HIV infection (and antiretroviral therapy, in some cases) may directly increase a woman’s risk of developing these disorders.\[91,92,93,98\] There are no HIV-specific surveillance recommendations for these conditions in women with HIV, but clinicians should emphasize the importance of age-appropriate screening and counsel about secondary prevention measures, including smoking cessation and regular exercise.
Summary Points

- In the United States, women comprise an estimated 23% of all persons living with HIV and approximately 19% of new HIV diagnoses. Black/African American and Latina women are disproportionately affected.
- In recent years, 78% women of women living with HIV identified heterosexual contact and 21% reported injection drug use as their risk factor for HIV acquisition.
- Women and men have similar virologic responses to antiretroviral therapy, though women are more likely to experience antiretroviral-related adverse effects.
- Women with HIV who become pregnant should be on a suppressive antiretroviral regimen for their personal health and to prevent transmission of HIV to the fetus and newborn. Certain antiretroviral therapies should be avoided due to concerns about teratogenicity or lack of data.
- Women living with HIV should be offered the full array of contraceptive options and counseled about potential drug interactions with antiretroviral therapy.
- Systematic reviews of available data have concluded no association exists between the use of oral contraceptives and HIV acquisition, but there is a possible increased risk of HIV acquisition and transmission with the use of the injectable DMPA; the benefits of DMPA are thought to outweigh the risks in women at risk for HIV, and these women should be counseled accordingly.
- Multiple options exist for serodiscordant couples seeking pregnancy. The strategies should be individualized and the approach may differ based on which partner is living with HIV.
- Women with HIV experience vaginal infections more often than women without HIV infection and these infections can influence susceptibility to sexually transmitted infections and increase the risk of HIV transmission to uninfected partners.
- Menopause may be earlier and more symptomatic in women with HIV compared to women without HIV, but there is no data to support a link between menopause-related vaginal mucosal changes and increased risk of HIV transmission.
- Women with HIV (both cisgender and transgender) experience high rates of gender-based violence, particularly intimate partner violence, and should be screened routinely as part of their comprehensive care.
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Figures

Figure 1 Women Living with Diagnosed HIV in United States, by Transmission Category, Year-End 2015


Other = hemophilia, blood transfusion, or risk factor not reported or identified.

Estimate for females ≥13 years of age living with diagnosed HIV infection
Figure 2 Women Living with Diagnosed HIV in United States, by Race/Ethnicity, Year-End 2015

Figure 3 Estimated HIV Incidence in Women United States, 2010-2015

Figure 4 Transmission Categories for Women with New Diagnosis of HIV in United States, 2016


Total for Females = 7,529

- Heterosexual Contact: 86.9%
- Injection Drug Use: 12.5%
- Other: 0.4%
**Figure 5 Number of New HIV Diagnoses in Women in United States, 2016, by Race/Ethnicity**

The number of new HIV diagnoses among women in 2016 is not the same as the number of new HIV infections since women newly diagnosed in 2016 could have acquired HIV prior to 2016 and remained undiagnosed for years while living with HIV.

Figure 6 Rate of New HIV Diagnoses in Women in United States, 2016, by Race/Ethnicity

This graph shows the rate (per 100,000) of new HIV diagnoses in women in 2016. The rate of new HIV diagnoses among women in 2016 is not the same as the rate of new HIV infections since women newly diagnosed in 2016 could have acquired HIV prior to 2016 and remained undiagnosed for years while living with HIV.

Figure 7: Number of New HIV Diagnoses in Women in United States, 2011-2016

Overall, the number of new HIV diagnoses among women in the United States decreased approximately 15% during the years 2011-2016.

Figure 8 Treatment of Trichomoniasis in Women with HIV Infection

In this trial, investigators randomized women with trichomoniasis and HIV infection to receive either a 7-day course of metronidazole (500 mg twice daily) or a single 2-gram dose of metronidazole. More treatment failures occurred in women who received single-dose therapy.

<table>
<thead>
<tr>
<th>Device</th>
<th>Component in IUD</th>
<th>Pregnancy Rate Year 1*</th>
<th>Approved Duration^</th>
</tr>
</thead>
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<tr>
<td>Non-Hormonal Copper IUD</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Paragard</td>
<td>Copper coil</td>
<td>0.60-0.80%</td>
<td>10 years</td>
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<tr>
<td>Levonorgestrel-Releasing IUDs</td>
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<td></td>
<td></td>
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<tr>
<td>Mirena</td>
<td>52 mg levonorgestrel</td>
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<td>5 years</td>
</tr>
<tr>
<td>Liletta</td>
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<td>4 years</td>
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<tr>
<td>Kyleena</td>
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<td>0.16%</td>
<td>5 years</td>
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<tr>
<td>Skyla</td>
<td>18 mg levonorgestrel</td>
<td>0.41%</td>
<td>3 years</td>
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</table>

* These year 1 pregnancy rates are based on information provided in prescribing information.
^ Approved Duration = United States Food and Drug Administration (FDA) approved duration of use.

Source:
Table 2.

<table>
<thead>
<tr>
<th></th>
<th>Copper-Containing IUD</th>
<th>LNG-IUD</th>
<th>Implants</th>
<th>DMPA*</th>
<th>POP</th>
<th>CHCs</th>
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<td>1</td>
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<tr>
<td>Continuation</td>
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<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: IUD = intrauterine device; LNG-IUD = levonorgestrel-releasing intrauterine device; DMPA = depot medroxyprogesterone acetate; POP = progestin-only pill; CHC = combined hormonal contraceptive

*Clarification for (DMPA): There continues to be evidence of a possible increased risk of acquiring HIV among progestin-only injectable users. Uncertainty exists about whether this is due to methodological issues with the evidence or a real biological effect. In many settings, unintended pregnancies and/or pregnancy-related morbidity and mortality are common, and progestin-only injectables are among the few types of methods widely available. Women should not be denied the use of progestin-only injectables because of concerns about the possible increased risk. Women considering progestin-only injectables should be advised about these concerns, about the uncertainty over whether there is a causal relationship, and about how to minimize their risk of acquiring HIV.

Source:
