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

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Preconception Counseling and Care for Women of Childbearing Age Living with HIV  
(Last updated November 14, 2017; last reviewed November 14, 2017)

Panel’s Recommendations

- Discuss childbearing intentions with all women of childbearing age on an ongoing basis throughout the course of their care (AII).
- Provide information about effective and appropriate contraceptive methods to reduce the likelihood of unintended pregnancy (AI).
- During preconception counseling, include information on safer sexual practices and elimination of alcohol, tobacco, and other drugs of abuse; if elimination is not feasible, appropriate treatment (e.g., methadone) and prevention (e.g., access to syringe services program) should be provided (AII).
- All women living with HIV who are contemplating pregnancy should be receiving antiretroviral therapy (ART), and have a plasma viral load below the limit of detection prior to conception (AII).
- When selecting or evaluating ART for women of childbearing age living with HIV, consider a regimen’s effectiveness, a woman’s hepatitis B status, teratogenic potential of the drugs in the ART regimen, and possible adverse outcomes for the mother and fetus (AII).
- HIV infection does not preclude the use of any contraceptive method; however, drug-drug interactions between hormonal contraceptives and ART should be considered (AII).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Overview

The Centers for Disease Control and Prevention (CDC), the American College of Obstetricians and Gynecologists (ACOG), and other national organizations recommend offering all women of childbearing age comprehensive family planning and the opportunity to receive preconception counseling and care as a component of routine primary medical care. The purpose of preconception care is to improve the health of each woman before conception by identifying risk factors for adverse maternal or fetal outcomes, providing education and counseling targeted to patients’ individual needs, and treating or stabilizing medical conditions to optimize maternal and fetal outcomes. Preconception care is not something that occurs in a single clinical visit but, rather, a process of ongoing care and interventions integrated into primary care to address the needs of women during the different stages of reproductive life. Because more than half of all pregnancies in the United States are unintended, it is important that comprehensive family planning and preconception care be integrated into routine health visits. Providers should initiate and document a nonjudgmental conversation with all women of reproductive age concerning their reproductive desires because women may be reluctant to bring this up themselves. Health care providers who routinely care for women of reproductive age living with HIV play an important role in promoting preconception health and informed reproductive decisions.

The fundamental principles of preconception counseling and care are outlined in the CDC Preconception Care Work Group’s Recommendations to Improve Preconception Health and Health Care. In addition to the general components of preconception counseling and care that are appropriate for all women of reproductive age, women living with HIV have specific needs that should be addressed. Issues that impact pregnancy should be addressed before conception during their routine medical care for HIV disease because many women are aware of their HIV status before becoming pregnant. In addition to the principles outlined by the CDC Preconception Care Work Group, the following components of preconception counseling and care are specifically recommended for women living with HIV. Health care providers should:

- Discuss reproductive options, actively assess women’s pregnancy intentions on an ongoing basis throughout the course of care, and, when appropriate, make referrals to experts in HIV and women’s health, including experts in reproductive endocrinology and infertility when necessary.
Counsel on safer sexual practices (including condoms) that prevent HIV transmission to sexual partners, protect women from acquiring sexually transmitted diseases, and reduce the potential to acquire resistant strains of HIV (see Reproductive Options section).

Encourage sexual partners to receive HIV counseling and testing so they can seek HIV care if they have HIV infection and seek advice about oral pre-exposure prophylaxis (PrEP) and other measures to prevent HIV acquisition if they do not have HIV infection.

Counsel on eliminating alcohol, tobacco, and other drugs of abuse or appropriately treat and prevent when elimination is not feasible (e.g., methadone program, access to syringe services program).

Counsel women contemplating pregnancy to take a daily multivitamin that contains 400 mcg of folic acid to help prevent certain birth defects. Women who are at higher risk of having a child with an neural tube defects than the baseline population are candidates for higher (1 to 4 mg) dose folic acid supplementation.

Educate and counsel women about risk factors for perinatal transmission of HIV, strategies to reduce those risks, potential effects of HIV or of antiretroviral (ARV) drugs given during pregnancy on pregnancy course and outcomes, and the recommendation that women living with HIV in the United States not breastfeed because of the risk of transmission of HIV to their infants and the availability of safe and sustainable infant feeding alternatives.

When prescribing antiretroviral therapy (ART) to women of childbearing age, consider the regimen’s effectiveness, an individual’s hepatitis B virus (HBV) status, the potential for teratogenicity, and possible adverse outcomes for mother and fetus.¹⁹-²¹

Use the preconception period in women who are contemplating pregnancy to modify their ART regimen to optimize virologic suppression and minimize potential adverse effects.

Make a primary treatment goal for women who are on ART and who are planning a pregnancy attainment of sustained suppression of plasma viral load below the limit of detection prior to conception for the health of the woman and to decrease the risk of perinatal transmission and of sexual transmission to a partner that does not have HIV infection.

Evaluate and manage therapy-associated side effects (e.g., hyperglycemia, anemia, hepatotoxicity) that may adversely impact maternal-fetal health outcomes.

Administer all vaccines as indicated (see http://www.cdc.gov/vaccines/acip/committee/guidance/rec-vac-preg.html and 2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host) including against influenza, pneumococcus, HBV, and tetanus. All women, including those with HIV infection, should receive Tdap vaccination during each pregnancy.

Offer all women who do not currently desire pregnancy effective and appropriate contraceptive methods to reduce the likelihood of unintended pregnancy. Women living with HIV can use all available contraceptive methods, including hormonal contraception (e.g., pill, patch, ring, injection, implant) and intrauterine devices (IUDs).²² Providers should be aware of potential interactions between ARV drugs and hormonal contraceptives that could lower contraceptive efficacy (see Table 3 below).

Offer emergency contraception as appropriate, including emergency contraceptive pills and the copper IUD (see ACOG Guidelines for emergency contraception). Concerns about drug interactions between ARV drugs and emergency contraceptive pills containing estrogen and a progestin, or containing levonorgestrel only, may be similar to concerns when those formulations are used for regular contraception.²³ There are no data on potential interactions between ARV drugs and ulipristal acetate, a progesterone receptor modulator; however, ulipristal acetate is predominantly metabolized by CYP3A4, so interactions can be expected (see http://www.hiv-druginteractions.org/ checker).
• Optimize the woman’s health prior to conception (e.g., ensure appropriate folate intake, test for all sexually transmitted infections and treat as indicated, consider the teratogenic potential of all prescribed medications, consider the option of switching to safer medications).

Drug-drug interactions between hormonal contraceptives and ART should be considered (see Table 3).

Data on drug interactions between ARV agents and hormonal contraceptives primarily come from drug labels and limited studies.\textsuperscript{23-39} The contraceptive effectiveness of the levonorgestrel IUD (Mirena) is largely through local (i.e., intrauterine) release of levonorgestrel, not through systemic absorption. The CDC’s U.S. Medical Eligibility Criteria for Contraceptive Use list the levonorgestrel IUD (Mirena) as category 1 (no restrictions) in drug interactions with all ARVs listed in women who already have IUD and category 1/2 (benefits outweigh risk) for those initiating use of an IUD.

Newer data provide some understanding as to the magnitude of changes in contraceptive drug levels that may reduce contraceptive efficacy. In a study of 570 women with HIV in Swaziland using levonorgestrel implants (Jadelle), none of the women on nevirapine or lopinavir/ritonavir-based regimens (n = 208 and 13, respectively) became pregnant, whereas 15 women on efavirenz (n = 121; 12.4%) became pregnant.\textsuperscript{35} In a study using data from 5,153 women with HIV followed prospectively for 1 to 3 years, 9% of women ever used implants (mostly levonorgestrel), 40% used injectables, and 14% used oral contraceptives; 31% of women ever used ART, mostly nevirapine (75%) or EFV (15%). Among women not using contraception, pregnancy rates were 13.2 and 22.5 per 100 person-years for those on and not on ART, respectively. Implants greatly reduced the incidence of pregnancy among women on ART (aHR 0.06, 95% CI, 0.01–0.45) and not on ART (aHR 0.05,95% CI, 0.02–0.11). Injectable and oral contraceptives also reduced pregnancy risk, though by lesser degrees. ART use did not significantly diminish contraceptive effectiveness, although all methods showed nonstatistically significant reduced contraceptive effectiveness when concurrently using efavirenz.\textsuperscript{40} Scarsi et al. reported on 3 groups of Ugandan women living with HIV (not on ART [17 women], nevirapine-based ART [20 women], and efavirenz-based ART [20 women]) who had levonorgestrel implants placed, and had levonorgestrel pharmacokinetic (PK) levels assessed at 1, 4, 12, 24, 36, and 48 weeks post-insertion. The geometric mean ratio of levonorgestrel (efavirenz-based vs. ART-naive patients) was 0.53 at 24 weeks and 0.43 at 48 weeks. Three pregnancies (3/20, 15%) occurred in the efavirenz group between weeks 36 and 48, whereas no pregnancies occurred in the ART-naive or nevirapine groups.\textsuperscript{39}

Hormonal contraceptives can be used with ART in women without other contraindications. Additional or alternative methods of contraception may be recommended when drug interactions are known. For women using ritonavir-boosted protease inhibitors who are on combination hormonal contraceptives (e.g., pills, patches, rings) or progestin-only pills, use of an alternative or additional method of contraception can be considered since the area under the curve of hormones may be decreased (see Table 3). Implants (etonogestrel/levonorgestrel) generally can be used, but providers can consider use of an alternative method or recommend the additional use of a reliable barrier method with efavirenz-based regimens.\textsuperscript{35,41,42} Depot medroxyprogesterone acetate (DMPA) can be used without restriction because of its relatively higher dose and limited studies that have shown no significant interaction between DMPA and ARV drugs.\textsuperscript{25,27,37,43} Nucleoside reverse transcriptase inhibitors have no effect on hormonal contraceptive doses.

Because no high-quality, definitive studies exist on pregnancy rates among women on different hormonal contraceptives and ARV drugs, the dosing recommendations in Table 3 are based on consensus expert opinion. Whenever possible, the recommendations are based on available data regarding PK interactions between ARV drugs and combined hormonal methods, DMPA, levonorgestrel and etonogestrel implants. The smallest decreases in PK for which an alternative method was recommended were 14% in norethindrone (with darunavir/ritonavir) and 19% in ethinyl estradiol (with atazanavir/ritonavir). For women using atazanavir without ritonavir boosting (ethinyl estradiol increase 48%, norethindrone increase 110%), the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) recommends use of oral contraceptives containing ≤30 µg ethinyl estradiol. The Panel does not recommend any change in ethinyl estradiol dose for etravirine (ethinyl estradiol increase 22%), rilpivirine (ethinyl estradiol increase 14%), or indinavir (ethinyl estradiol increase 25%, norethindrone increase 26%).

\textit{Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States}  
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**Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives** (page 1 of 8)

<table>
<thead>
<tr>
<th>ARV Drug</th>
<th>Effect on Contraceptive Drug Levels and Contraceptive’s Effects on ART and HIV</th>
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<th>Dosing Recommendation/ Clinical Comment for COC/P/R</th>
<th>Dosing Recommendation/ Clinical Comment for POPs</th>
<th>Dosing Recommendation/ Clinical Comment for DMPA</th>
<th>Dosing Recommendation/ Clinical Comment for Etonogestrel Implants</th>
<th>Justification/Evidence for Recommendation</th>
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<td><strong>NNRTIs</strong></td>
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<td>EFV COC:</td>
<td>• No effect on EE concentrations • ↓ active metabolites of norgestimate LN AUC ↓ 83%; norelgestromin AUC ↓ 64%28 • Etonogestrel (in COC) C24 ↓ 61%34</td>
<td></td>
<td>Consider an alternative method (or a reliable method of barrier contraception) in addition to this method.</td>
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<tr>
<td>DMPA:</td>
<td>• No effect on DMPA levels25,27</td>
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<tr>
<td>Etonogestrel Implant:</td>
<td>• Etonogestrel AUC ↓ 63% to 82%44,45</td>
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<td>No additional contraceptive protection is needed.</td>
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<tr>
<td>LN Implant:</td>
<td>• LN AUC ↓ 47%30 • LN (emergency contraception) AUC ↓ 58%25</td>
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<tr>
<td>Changes in ARV Levels and/or Effects on HIV:</td>
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<tr>
<td>COC:</td>
<td>• No effect on EFV concentrations28 • EFV C12 ↓ 22%; was under therapeutic threshold in 3/16 subjects34</td>
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<tr>
<td>DMPA:</td>
<td>• No effect on HIV disease progression25,46,47 • No effect on EFV concentrations25</td>
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<tr>
<td>LN Implant:</td>
<td>• No effect on HIV disease progression39</td>
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<tr>
<td><strong>Consider an alternative method (or a reliable method of barrier contraception) in addition to this method.</strong></td>
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**Note:** All recommendations in the following table are based on consensus expert opinion. More details can be found in the CDC’s U.S. Medical Eligibility Criteria for Contraceptive Use, 2016.

For COCs, some studies suggest higher pregnancy rate and ovulation and decreased progestin levels. EFV may decrease, but clinical significance unclear.

For DMPA, evidence does not show effects on pregnancy rate, ovulation, or DMPA levels. Also, no effect on HIV disease progression or EFV levels.

For implants, some studies suggest higher pregnancy rate and decreased hormone levels.
Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 2 of 8)

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<th>Dosing Recommendation/ Clinical Comment for POPs</th>
<th>Dosing Recommendation/ Clinical Comment for DMPA</th>
<th>Justification/Evidence for Recommendation</th>
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<tr>
<td>NNRTIs, continued</td>
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<tr>
<td>ETR</td>
<td>EE AUC ↑ 22%&lt;sup&gt;50&lt;/sup&gt;</td>
<td>COC:</td>
<td>No additional contraceptive protection is needed.</td>
<td>No additional contraceptive protection is needed.</td>
<td>No additional contraceptive protection is needed.</td>
<td>For COCs, 1 study found no ovulations and no significant change in progestin levels. No evidence on POPs.</td>
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<td></td>
<td>NE:</td>
<td>• No significant effect&lt;sup&gt;60&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>DMPA:</td>
<td>• No significant change&lt;sup&gt;29&lt;/sup&gt;</td>
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<td></td>
<td>Etonogestrel (in COC)</td>
<td>C24</td>
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<td></td>
<td>Decreased 22%&lt;sup&gt;34&lt;/sup&gt;</td>
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<td></td>
<td>LN Implant:</td>
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<tr>
<td></td>
<td>• LN AUC ↑ 35%&lt;sup&gt;39&lt;/sup&gt;</td>
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<td>Changes in ARV Levels and/or Effects on HIV</td>
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<td></td>
<td>COC:</td>
<td>• NVP no significant effect&lt;sup&gt;49,51,53&lt;/sup&gt;</td>
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<td></td>
<td>DMPA:</td>
<td>• No effect on HIV disease progression&lt;sup&gt;25,41,47,54&lt;/sup&gt;</td>
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<td></td>
<td>LN Implant:</td>
<td>• No effect on HIV disease progression&lt;sup&gt;39,55&lt;/sup&gt;</td>
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<tr>
<td>NVP</td>
<td>EE AUC ↓ 29%&lt;sup&gt;51&lt;/sup&gt; EE AUC no change&lt;sup&gt;52&lt;/sup&gt;</td>
<td>COC:</td>
<td>No additional contraceptive protection is needed.</td>
<td>No additional contraceptive protection is needed.</td>
<td>No additional contraceptive protection is needed.</td>
<td>For COCs, evidence does not show effects on pregnancy rate or ovulations and demonstrated small decrease in progestin levels. Also, no effect on NVP levels.</td>
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<td>NE AUC ↓ 18%&lt;sup&gt;51&lt;/sup&gt;</td>
<td>• No ovulations&lt;sup&gt;50&lt;/sup&gt;</td>
<td>• No increase in pregnancy rate&lt;sup&gt;40,42,48,56,57&lt;/sup&gt;</td>
<td>• No increase in pregnancy rate&lt;sup&gt;40,42,47,56&lt;/sup&gt;</td>
<td>• No increase in pregnancy rate&lt;sup&gt;42&lt;/sup&gt;</td>
<td>For DMPA, evidence does not show effects on pregnancy rate, ovulation, or DMPA levels. Also, no effect on HIV disease progression.</td>
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<td></td>
<td>Etonogestrel (in COC)</td>
<td>C24</td>
<td>• No ovulations&lt;sup&gt;59,52,57&lt;/sup&gt;</td>
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<td>For implants, evidence does not show effects on pregnancy rate or HIV disease progression.</td>
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<td></td>
<td>Decreased 22%&lt;sup&gt;34&lt;/sup&gt;</td>
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<td></td>
<td>LN Implant:</td>
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<td></td>
<td>• LN AUC ↑ 35%&lt;sup&gt;39&lt;/sup&gt;</td>
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<td>Changes in ARV Levels and/or Effects on HIV</td>
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<tr>
<td></td>
<td>COC:</td>
<td>• NVP no significant effect&lt;sup&gt;49,51,53&lt;/sup&gt;</td>
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<td></td>
<td>DMPA:</td>
<td>• No effect on HIV disease progression&lt;sup&gt;25,41,47,54&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>LN Implant:</td>
<td>• No effect on HIV disease progression&lt;sup&gt;39,55&lt;/sup&gt;</td>
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<th>Dosing Recommendation/ Clinical Comment for DMPA&lt;sup&gt;a&lt;/sup&gt;</th>
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| RPV | EE AUC ↑ 14%<sup>33</sup>  
NE:  
• No significant change<sup>33</sup>  
Changes in ARV Levels and/or Effects on HIV  
COC:  
• No change in RPV levels compared to historical controls<sup>33</sup> | COC:  
• No change in progesterone<sup>33</sup> | No additional contraceptive protection is needed. | No additional contraceptive protection is needed. | No additional contraceptive protection is needed. | No additional contraceptive protection is needed. | For COCs, evidence does not show effects on ovulation or progesterin levels. Also, no change in RPV levels. No evidence on POPs. |
| **RTV-Boosted PIs** |
| ATV/r | EE AUC ↓ 19%<sup>58</sup>  
Norgestimate AUC ↑ 85%<sup>58</sup>  
POP:  
• NE AUC ↑ 50%<sup>59</sup> | N/A | No additional contraceptive protection is needed. | No additional contraceptive protection is needed. | No additional contraceptive protection is needed. | No additional contraceptive protection is needed. | For COCs, increase in progestin levels but only 1 study. For POPs, increase in progestin levels but only 1 study. RTV inhibits CYP3A4 which may increase contraceptive hormone levels. |
| DRV/r | EE AUC ↓ 44%<sup>60</sup>  
NE AUC ↓ 14%<sup>60</sup> | N/A | Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method. | Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method. | No additional contraceptive protection is needed. | Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method. | For COCs, small decrease in progestin levels. No evidence on POPs. |
Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 4 of 8)

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<th>Dosing Recommendation/ Clinical Comment for POPs</th>
<th>Dosing Recommendation/ Clinical Comment for DMPA*</th>
<th>Dosing Recommendation/ Clinical Comment for Etonogestrel Implants</th>
<th>Justification/Evidence for Recommendation</th>
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<tr>
<td>RTV-Boosted PIs, continued</td>
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| FPV/r | EE AUC ↓ 37%<sup>61</sup>  
NE AUC ↓ 34%<sup>61</sup>  
FPV/r level: no change<sup>61</sup> | N/A | Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method. | Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method. | No additional contraceptive protection is needed. | Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method. | For COCs, decrease in progestin levels.  
No evidence on POPs. |
| LPV/r | EE AUC ↓ 55<sup>24</sup>%  
NE AUC ↓ 17%  
Patch:  
• EE AUC ↓ 45%<sup>24</sup>  
• Norelgestromin AUC ↑ 83<sup>26</sup>%  
DMPA:  
• DMPA AUC ↑ 46<sup>37</sup>%  
Etonogestrel Implant:  
• Etonogestrel AUC ↑ 52<sup>44</sup>%  
Changes in ARV Levels and/or Effects on HIV  
Patch:  
• LPV/r level ↓ 19<sup>24</sup>%  
DMPA:  
• No effect on HIV disease progression<sup>37</sup>  
• LPV/r no change<sup>37</sup> | COC:  
• Increased pregnancy rate, but CIs overlap<sup>42</sup>  
Patch:  
• No ovulations<sup>24</sup>  
DMPA:  
• No pregnancies, no ovulations<sup>37</sup>  
• Increased pregnancy rate, but CIs overlap<sup>42</sup>  
Etonogestrel Implant:  
• No increase in pregnancy rate<sup>42</sup>  
LN Implant:  
• No increase in pregnancy rate<sup>35,42</sup> | No additional contraceptive protection is needed. | No additional contraceptive protection is needed. | No additional contraceptive protection is needed. | No additional contraceptive protection is needed. | For COCs, nonsignificant increase in pregnancy rate. Small decrease in progestin level.  
For patch, no ovulations and progestin levels increase.  
For DMPA, evidence shows no effect on pregnancy rate or ovulations and progestin levels increased.  
For implants, evidence shows no effect on pregnancy rate and progestin levels increased. |
Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 5 of 8)

<table>
<thead>
<tr>
<th>ARV Drug</th>
<th>Effect on Contraceptive Drug Levels and Contraceptive’s Effects on ART and HIV</th>
<th>Clinical Studies</th>
<th>Dosing Recommendation/ Clinical Comment for COC/P/R</th>
<th>Dosing Recommendation/ Clinical Comment for POPs</th>
<th>Dosing Recommendation/ Clinical Comment for DMPA³</th>
<th>Dosing Recommendation/ Clinical Comment for Etonogestrel Implants</th>
<th>Justification/Evidence for Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RTV-Boosted PIs, continued</strong></td>
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</tbody>
</table>
| SQV/r | ↓ EE⁵²  
Changes in ARV Levels and/or Effects on HIV:  
COC:  
• SQV/r no change⁶³ | N/A | Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method. | Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method. | No additional contraceptive protection is needed. | Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method. | No information on progestin levels for CHCs or POPs.  
RTV inhibits CYP3A4 which may increase contraceptive hormone levels. However, some PI/r cause decreases in progestin levels, so there are theoretical concerns about contraceptive effectiveness. |
| TPV/r | EE AUC ↓ 48%⁶⁴  
NE:  
• No significant change⁶⁴  
Changes in ARV Levels and/or Effects on HIV  
• TPV no change⁶⁴ | N/A | Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method. | Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method. | No additional contraceptive protection is needed. | Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method. | For COCs, no significant change in progestin levels but only from product label.  
No evidence on POPs.  
RTV inhibits CYP3A4 which may increase contraceptive hormone levels. However, some PI/r cause decreases in progestin levels, so there are theoretical concerns about contraceptive effectiveness. |
Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 6 of 8)

<table>
<thead>
<tr>
<th>ARV Drug</th>
<th>Effect on Contraceptive Drug Levels and Contraceptive’s Effects on ART and HIV</th>
<th>Clinical Studies</th>
<th>Dosing Recommendation/ Clinical Comment for COC/P/R</th>
<th>Dosing Recommendation/ Clinical Comment for POPs</th>
<th>Dosing Recommendation/ Clinical Comment for DMPA*</th>
<th>Dosing Recommendation/ Clinical Comment for Etonogestrel Implants</th>
<th>Justification/Evidence for Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PIs without RTV</strong></td>
<td></td>
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</tr>
</tbody>
</table>
| **ATV** | COC:  
• EE AUC ↑ 48%<sup>65</sup>  
• NE AUC ↑ 110%<sup>65</sup> | N/A | Prescribe oral contraceptive that contains no more than 30 mcg of EE, or recommend alternative contraceptive method. | No additional contraceptive protection is needed. | No additional contraceptive protection is needed. | No additional contraceptive protection is needed. | For COCs, increased concentrations of estrogen and progestin, but only data available are from the product label.  
No evidence on POPs. |
| **ATV/c** | Drospirenone AUC ↑ 2.3-fold; EE AUC ↓ 22%<sup>66</sup> | N/A | Contraindicated with drospirenone-containing hormonal contraceptive due to potential for hyperkalemia.  
Consider alternative or additional contraceptive method. | Can consider an alternative method based on safety concerns. | Can consider an alternative method based on safety concerns. | Can consider an alternative method based on safety concerns. | No evidence on POPs. |
| **DRV/c** | Drospirenone AUC ↑ 1.6-fold; EE AUC ↓ 30%<sup>67</sup> | N/A | In combination with drospirenone-containing COCs, clinical monitoring is recommended due to the potential for hyperkalemia.  
Consider alternative or additional contraceptive method. | Can consider an alternative method based on safety concerns. | Can consider an alternative method based on safety concerns. | Can consider an alternative method based on safety concerns. | No evidence on POPs. |
### Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 7 of 8)

<table>
<thead>
<tr>
<th>ARV Drug</th>
<th>Effect on Contraceptive Drug Levels and Contraceptive’s Effects on ART and HIV</th>
<th>Clinical Studies</th>
<th>Dosing Recommendation/ Clinical Comment for COC/P/R</th>
<th>Dosing Recommendation/ Clinical Comment for POPs</th>
<th>Dosing Recommendation/ Clinical Comment for DMPA</th>
<th>Justification/Evidence for Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PIs without RTV, continued</strong></td>
<td></td>
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</tr>
</tbody>
</table>
| FPV | COC:  
• EE AUC no change, C_{min} ↑ 32%  
• NE AUC ↑ 18%, C_{min} ↑ 45%61  
FPV with EE/Norethindrone:  
• ↓ APV (AUC 22%, C_{min} 20%)61 | N/A | Use alternative contraceptive method. | Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method. | Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method. | Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method. | Use of FPV alone with ethinyl estradiol/norethindrone may lead to loss of virologic response.  
No evidence on POPs. |
| IDV | COC:  
• EE AUC ↑ 22%  
• NE AUC ↑ 26%67 | COCs:  
• No pregnancies among women taking IDV and COCs66 | No additional contraceptive protection is needed. | No additional contraceptive protection is needed. | No additional contraceptive protection is needed. | No additional contraceptive protection is needed. | For COCs, small increases in EE and progestin, and 1 clinical study did not suggest any efficacy concerns.  
No evidence on POPs. |
| NFV | COC:  
• EE AUC ↓ 47%  
• NE AUC ↓ 18%66  
DMPA:  
• No change25  
NFV:  
• AUC ↓ 18% | COCs:  
• 1 small study suggested that women using COCs and NFV may have had higher pregnancy rates than those using COCs alone49  
DMPA:  
• No pregnancies, no ovulations25,47  
• CD4 count/HIV RNA: no change25,47 | Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method. | Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method. | No additional contraceptive protection is needed. | Can consider an alternative method (or a reliable method of barrier contraception) in addition to this method. | For COCs, small decrease in progestin and decrease in estrogen; 1 small clinical study suggests possible higher pregnancy rate with COC and NFV use.  
DMPA, PK, and clinical data demonstrate no change. However, NFV AUC slightly decreased.  
No evidence on POPs or implants. |
| **CCR5 Antagonist** | | | | | | |
| MVC | COC:  
• No significant effect on EE or LN66 | N/A | No additional contraceptive protection is needed. | No additional contraceptive protection is needed. | No additional contraceptive protection is needed. | No additional contraceptive protection is needed. | For COCs, no change in EE or progestin. No clinical data.  
No evidence on POPs. |

*Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States*
### Table 3. Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (page 8 of 8)

<table>
<thead>
<tr>
<th>ARV Drug</th>
<th>Effect on Contraceptive Drug Levels and Contraceptive’s Effects on ART and HIV</th>
<th>Clinical Studies</th>
<th>Dosing Recommendation/ Clinical Comment for COC/P/R</th>
<th>Dosing Recommendation/ Clinical Comment for POPs</th>
<th>Dosing Recommendation/ Clinical Comment for DMPA&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Justification/Evidence for Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Integrase Inhibitors</strong></td>
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<tr>
<td>RAL</td>
<td>COC:</td>
<td>• EE no change</td>
<td>N/A</td>
<td>No additional contraceptive protection is needed.</td>
<td>No additional contraceptive protection is needed.</td>
<td>No additional contraceptive protection is needed.</td>
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<tr>
<td></td>
<td>• Norgestimate AUC ↑ 14%&lt;sup&gt;70&lt;/sup&gt;</td>
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</tr>
<tr>
<td>DTG</td>
<td>COC:</td>
<td>• No significant effect on norgestimate or EE</td>
<td>N/A</td>
<td>No additional contraceptive protection is needed.</td>
<td>No additional contraceptive protection is needed.</td>
<td>No additional contraceptive protection is needed.</td>
</tr>
<tr>
<td></td>
<td>• DTG AUC no change&lt;sup&gt;38&lt;/sup&gt;</td>
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<td></td>
</tr>
<tr>
<td>EVG/c</td>
<td>EVG/COBI/FTC/TDF</td>
<td>COC:</td>
<td>No additional contraceptive protection is needed.</td>
<td>No additional contraceptive protection is needed.</td>
<td>No additional contraceptive protection is needed.</td>
<td>For COCs, no change in EE and small increase in progestin. No clinical data.</td>
</tr>
<tr>
<td></td>
<td>• Norgestimate AUC ↑ 126%</td>
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<tr>
<td></td>
<td>• EE AUC ↓ 25%&lt;sup&gt;9&lt;/sup&gt;</td>
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</tbody>
</table>

<sup>a</sup> Because the hormonal levels achieved with DMPA are substantially higher than are required for contraception, any small reduction in hormonal level due to ARVs is unlikely to reduce contraceptive effectiveness.

**Key to Acronyms:** ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; AUC = area under the curve; CHC = combination hormonal contraceptives; CI = confidence interval; C<sub>min</sub> = minimum plasma concentration; COBI = cobicistat; COC/P/R = combined oral contraceptives/patch/implant; DMPA = depot medroxyprogesterone acetate; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; e = estrogen; EE = ethinyl estradiol; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; IDV = indinavir; LN = levonorgestrel; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NE = norethindrone; NFV = nelfinavir; NVP = nevirapine; P = progestin; PI = protease inhibitor; PI/r = ritonavir boosted-protease inhibitor; PK = pharmacokinetic; POP = progesterone-only oral contraceptive pills; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV/r = saquinavir/ritonavir; TDF = tenofovir disoproxil fumarate; TPV/r = tipranavir/ritonavir

References


66. Majeed SR, West SK, Jiang S, et al. Confirmation of the drug-drug interaction (DDI) potential between cobicistat-boosted antiretroviral regimens and hormonal contraceptives. 18th International Workshop on Clinical Pharmacology of Antiviral Therapy; 2017; Chicago, IL.


