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Drug-Drug Interactions, Effectiveness, and Safety of Hormonal Contraceptives in Women Living with HIV

Kimberly K. Scarsi[1,*], **Kristin M. Darin**[2], **Catherine A. Chappell**[3], **Stephanie M. Nitz**[1], and **Mohammed Lamorde**[4]

[1]Department of Pharmacy Practice, College of Pharmacy, University of Nebraska Medical Center, Omaha, NE [2]Center for Global Health, Northwestern University Feinberg School of Medicine, Chicago, IL [3]Department of Obstetrics, Gynecology, and Reproductive Sciences, Magee-Womens Hospital, University of Pittsburgh Medical Center, Pittsburgh, PA [4]Infectious Diseases Institute, Makerere University College of Health Sciences, Kampala, Uganda

Abstract

Family planning options, including hormonal contraceptives, are essential for improving reproductive health among the more than 17 million women living with human immunodeficiency virus (HIV) worldwide. For these women, prevention of unintended pregnancy decreases maternal and child mortality, as well as reduces the risk of perinatal HIV transmission. Similarly, treatment of HIV with antiretroviral therapy (ART) is essential for reducing morbidity and mortality among HIV-positive individuals, as well as preventing HIV transmission between sexual partners or from mother to child. Importantly, despite the benefits of hormonal contraceptives, barriers to effective family planning methods exist for HIV-positive women. Specifically, drug-drug interactions can occur between some antiretroviral medications and some hormonal contraceptives, which may influence both contraceptive efficacy and tolerability. In addition, safety concerns have been raised about the impact of hormonal contraceptives on HIV disease progression, tolerability and the risk of female-to-male HIV transmission. This review article summarizes the potential for drug-drug interactions, tolerability, and contraceptive effectiveness when hormonal contraceptives are combined with ART. In addition, the evidence surrounding the influence of hormonal contraceptives on HIV transmission and HIV disease progression in women living with HIV are summarized.

1. Introduction

Effective antiretroviral therapy (ART) has transformed human immunodeficiency virus (HIV) infection into a medically manageable, chronic condition that requires life-long medication therapy. For those living with HIV, modern ART significantly reduces morbidity

[*]**Corresponding Author:** Kimberly K. Scarsi, PharmD, MS, Associate Professor, University of Nebraska Medical Center, College of Pharmacy, 986145 Nebraska Medical Center, Omaha, NE 68198-6145, Ph. +1.402.559.9916, Fax +1.402.559.5673, kim.scarsi@unmc.edu.

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and mortality with fewer adverse effects than older combinations [1, 2]. As a result, ART is now recommended for all HIV-positive patients worldwide and remains a particularly important intervention for women of reproductive age to prevent perinatal HIV transmission [2–4]. Family planning options, including hormonal contraceptives, are also vital among HIV-positive women of reproductive age, and are an essential component of a comprehensive HIV care program. Important for the over 17 million women living with HIV worldwide [5], contraceptives decrease the risk of perinatal HIV transmission, maternal mortality, and maternal economic disparity [6–10]. Despite the importance of family planning methods and ART for HIV-positive women, the use of some hormonal contraceptives presents challenges. Specifically, changes in hormone pharmacokinetic exposure during coadministration with ART may influence contraceptive effectiveness and safety. In addition, safety concerns exist about the effect of hormonal contraceptives on HIV disease progression and HIV transmissibility [11]. This review summarizes the available literature on the effectiveness and safety of hormonal contraceptives in HIV-positive women, with an emphasis on the impact of drug-drug interactions on these clinical outcomes.

2. Methods

The corresponding author searched EMBASE and PubMed to identify peer-reviewed publications related to HIV infection and hormonal contraception through January 6, 2016. Articles were identified from EMBASE using the search criteria: ‘human immunodeficiency virus infection’/exp AND ‘antivirus agent’/exp/mj AND ‘contraceptive agent’/exp/mj AND [humans]/lim. Pubmed was searched using the following terms: ((“Contraceptive Agents” [Mesh] OR “Contraceptive Agents” [Pharmacological Action]) AND (“Anti-HIV Agents” [Mesh] OR “HIV Infections”[Mesh])). Publications were excluded if the content was not relevant to this manuscript or not available in English. Further review of search results yielded additional relevant publications and abstracts for inclusion.

3. Overview of antiretroviral therapy and hormonal contraceptives

3.1. Antiretroviral therapy options

Recommended regimens for ART-naïve individuals include two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with a third active drug from another antiretroviral drug class, the choice of which varies by global region, but most commonly includes an integrase-strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI) [2, 12]. Less commonly, antiretrovirals in the entry inhibitor class (maraviroc and enfuvirtide) are used. In the US, the recommended first-line regimens include an INSTI or PI as the third drug [2]. Directed mostly towards low- and middle-income countries, the World Health Organization (WHO) recommends efavirenz, an NNRTI, as the third drug for all adults receiving first-line ART; nevirapine, another NNRTI, or dolutegravir, an INSTI, are alternative options [12]. Also per the WHO guidelines, PI-based regimens are reserved for second-line therapy. Given these guidelines, efavirenz-based ART is the most widely used regimen where the majority of women living with HIV reside.

3.1.1 Pharmacokinetic considerations of antiretroviral agents—With the exception of most NRTIs and enfuvirtide, antiretrovirals are common victims and perpetrators of drug-drug interactions. These interactions are typically mediated by drug metabolizing enzymes, including cytochrome P450 (CYP) enzymes and glucuronidation via uridine 5′-diphospho-glucuronosyltransferase (UGT), and drug transporters, including p-glycoprotein and organic anion transporter (OAT). With regard to drug-drug interactions between antiretroviral and hormonal contraceptives specifically, CYP enzymes are most often implicated and UGT occasionally plays a role. The impact of drug transporters on hormone disposition has not been clearly elucidated and will not be addressed in detail by this review. The role of CYP enzymes in antiretroviral drug metabolism (as substrates for CYP enzymes), and the effect of antiretrovirals on CYP enzyme expression (as inducers and/or inhibitors of CYP enzymes), is summarized in Table 1.

3.2 Hormonal contraceptive options

Hormonal contraceptives are offered in a wide range of formulations, including oral pills, a transdermal patch, a vaginal ring, injectables, implants, and intrauterine devices (IUD). Hormonal contraceptives may include either a progestin alone or a combination of estrogen and progestin. The progestin provides most of the contraceptive effect by preventing the luteinizing hormone surge, which prevents ovulation. Progestin therapy also thickens the cervical mucus, which slows tubal mobility, and induces endometrial atrophy. Exogenous estrogen suppresses follicle stimulating hormone release, also contributing to ovulation suppression. However, the primary role of exogenous estrogen is to improve tolerability of hormonal contraceptives by stabilizing the endometrial lining and preventing unpredictable bleeding [13]. Guidelines on contraceptive use recommend long-acting, reversible contraceptive methods as first-line options [14], either a progestin-containing subdermal implant or an IUD [8, 15]. This recommendation is due to their high efficacy (<1% contraceptive failure rate) and ease of use. However, patients and providers are encouraged to review all contraceptive options to select a method that is best suited for the individual.

Oral contraceptive pills, which are available as a combination of progestin and estrogen (COC) or progestin alone (POP), are typically administered daily for 28 days per package. The 28-day cycle includes three weeks of a daily, hormone-containing tablet, followed by three to seven days of a placebo tablet to allow for menses. A 21-day cycle is also available, in which the placebo week is omitted to avoid menstruation [13]. There is currently one transdermal patch marketed as a contraceptive, which contains ethinyl estradiol/norelgestromin; as well as one contraceptive vaginal ring, which contains ethinyl estradiol/etonogestrel. Similar to oral pills, both the patch and vaginal ring are generally applied or inserted for three weeks and then removed for one week to allow for menses, but can also be used continuously to avoid menstruation. Injectable hormonal contraceptives include medroxyprogesterone acetate, norethisterone enanthate, and combined ethinyl estradiol and medroxyprogestone acetate. These injectables are administered every three months, every two months, or every one month, respectively. Medroxyprogesterone remains the most common injectable used worldwide, most often as an intramuscular injection; however, it is also available as a subcutaneous injection. Subdermal implants vary by the progestin (levonorgestrel or etonogestrel) released and the duration of use after placement (3 to 5

years). Following subdermal insertion into the upper arm, progestin is released from the implant at a steady, daily dose throughout the period of intended use. Lastly, the IUD is the most commonly used form of long-acting reversible contraception worldwide; however, the frequency and type of IUD used varies significantly across and within global regions [16]. There are currently two types of IUDs available for contraception, the non-hormonal copper-bearing IUD and the levonorgestrel-releasing IUD. Each is a very small, often T-shaped, device that is inserted into the uterus to prevent pregnancy [17]. Depending on product and manufacturer, the IUD is approved for 3 to 10 years of use [18], though extended use in select populations has demonstrated effectiveness [19].

3.2.1 Pharmacokinetic considerations of hormonal contraceptives—The metabolism of hormonal contraceptives is complex and varied depending on the drug used and the route of administration. Through these metabolic pathways, hormones can be both victims and perpetrators of drug-drug interactions, which may influence hormone effectiveness and safety. Orally administered forms of estrogen and most progestins undergo extensive first-pass metabolism in the gut or liver by phase I enzymatic pathways, such as oxidation, reduction, and hydrolysis; followed by phase II metabolism via glucuronide and/or sulfate conjugation [20]. These routes of pre-systemic clearance, which can be further altered as a result of drug-drug interactions, may significantly impact the oral bioavailability of some hormones. The impact of first-pass metabolism varies widely by hormone and formulation. For example, ethinyl estradiol undergoes extensive first-pass metabolism with a reported oral bioavailability of 38–83% [21, 22]. For the progestins, oral bioavailability varies from 64% for norethindrone [23]; to 84% for desogestrel, the prodrug for etonogestrel [21]; to as high as 100% for levonorgestrel [22]. Non-oral routes of hormonal contraceptive delivery effectively bypass first-pass metabolism and drug-drug interactions occurring at the pre-systemic stage. Once in systemic circulation, hormones undergo further hepatic metabolism, mostly by phase I pathways mediated by CYP enzymes or other minor routes. Hormonal contraceptives may induce and inhibit CYP enzymes, either through direct competition for metabolism or by modulation of nuclear receptors that govern enzyme expression [24–27]. Table 2 describes the metabolic pathways for hormonal contraceptives that are most likely to be implicated in drug-drug interactions with antiretrovirals.

3.2.2 Effectiveness of hormonal contraceptives—A recent evaluation of contraceptive effectiveness during typical use (i.e. outside of the clinical trial environment) was conducted using demographic survey data from 43 developing countries [28]. Table 3 describes the results after 12, 24, and 36 months of use for various methods of contraception. These data support that long-acting reversible contraceptives have the highest rate of effectiveness, followed by injectable methods, and finally contraceptive pills. All methods were more effective than traditional family planning methods, such as withdrawal.

Studies evaluating hormonal contraceptive effectiveness in women living with HIV describe similar trends irrespective of ART use; that is, long-acting, reversible contraceptives are the most effective, followed by injectable, and then contraceptive pills [29, 30]. When considering type of ART used, studies to date are appropriately powered to evaluate only NNRTI-based ART regimens containing either efavirenz or nevirapine. A large,

retrospective cohort from Kenya identified 3337 incident pregnancies among 24,560 women; pregnancy rates were 3.1 to 4.1 times higher in women using forms of hormonal contraceptives other than progestin-containing implants (excluding IUDs) [29]. Notably, adjusted pregnancy rates were three-fold higher in efavirenz users compared to nevirapine users [Adjusted Rate Ratio (aRR) (95% confidence interval [CI]): 3.0 (1.3–4.6)]. Differences in contraceptive effectiveness among women receiving efavirenz or nevirapine were not observed for other forms of hormonal contraceptives in this study (primarily injectables and COCs). A smaller prospective cohort evaluation of women receiving efavirenz- or nevirapine-based ART also found that implants reduced incident pregnancies the most compared to no hormonal contraceptive use [adjusted hazard ratio (HR) (95% CI): 0.06 (0.01–0.45)], followed by injectables [0.18 (0.10–0.35)], and then COC [0.37 (0.15–0.91)] [30]. Notably, the majority of women in this cohort were receiving nevirapine-based ART.

These studies provide clinical evidence that the use of efavirenz-based ART may impair the effectiveness of some hormonal contraceptive methods; see Section 4.0 for further discussion of the proposed mechanism for this change and the type of hormonal contraceptives most significantly impacted by efavirenz. Despite the decreased contraceptive effectiveness reported in women receiving efavirenz-based ART, the rate of unintended pregnancy remained lower in these women than compared to women not using contraception [29, 30]. Therefore, careful consideration of family planning desires, local ART and contraceptive availability, and the potential risk of reduced contraceptive effectiveness for some ART-contraceptive combinations is needed when choosing contraception among HIV-positive women.

3.2.3 Tolerability of hormonal contraceptives—There are no reported differences in the side effect profile of hormonal contraceptives in HIV-positive women compared to HIV-negative women [8]. In general, adverse effects of hormonal contraceptives depend on the progestin and/or estrogen component, along with the dose and route of administration that determines the amount of systemic exposure. Higher progestin exposure is usually well tolerated, while lower systemic progestin exposure may impact the bleeding profile of the contraceptive; specifically, decreases in progestin exposure could increase the number of days or amount of vaginal bleeding. The addition of ethinyl estradiol to progestins in COCs improves the bleeding profile, making it similar to monthly menstruation. Accordingly, lower systemic exposure of ethinyl estradiol may cause irregular bleeding and impact adherence to the contraceptive method. The side effects of estrogen exposure include breast tenderness, headache and nausea, which could also worsen contraceptive adherence [31]. The most concerning health risk of increased estrogen exposure is related to estrogen-induced hepatic production of clotting factors and subsequent thrombosis-related complications, such as venous thromboembolism, myocardial infarction, and cerebrovascular accident. Additionally, estrogen increases circulating levels of angiotensinogen and could lead to an increase in blood pressure [32]. Therefore, the side effect profile and health risks (other than contraceptive failures, as discussed in Section 3.2.2) of systemic hormonal contraceptives are more dependent on the systemic estrogen rather than progestin exposure.

New IUD users can expect to have irregular bleeding for the first three to six months after insertion; thereafter, levonorgestrel IUD users might have lighter menstrual cycles or amenorrhea [33]. Historically, there were concerns for increased risk of pelvic infection and resultant complications following IUD use among immunocompromised women; however, studies that utilized modern forms of IUDs have not shown an increased risk among women living with versus without HIV [34]. Risk of pelvic inflammatory disease attributable to an IUD occurs in the first 20 days after insertion [35]. After this time period, the rate of pelvic inflammatory disease in IUD-users decreases to the baseline level (1.4/1,000 women) for women without IUDs. Accordingly, the Centers for Disease Control and Prevention and WHO include IUDs as a recommended form of contraception, generally acceptable for use in HIV-positive women who are asymptomatic or with mild clinical disease (WHO stage 1 or 2) [17, 36]. Given the theoretical risk of an increased rate of infection following IUD insertion, caution is advised for women with severe or advanced HIV clinical disease (WHO HIV stage 3 or 4) who want to initiate contraception with an IUD, though continued use of an already inserted IUD is acceptable with close monitoring for pelvic infection [17, 36].

4.0 Drug-drug interactions between hormonal contraceptives and antiretroviral therapy

Given the overlapping metabolic pathways for hormonal contraceptives and antiretrovirals (Tables 1 and 2), there is significant concern that coadministration may influence hormone exposure. Considering the mechanism of action of the estrogen and progestin components of hormonal contraceptives, drug-drug interactions that decrease progestin exposure may influence contraceptive effectiveness to a greater extent than those that decrease estrogen exposure. In contrast, drug-drug interactions which increase either progestin or estrogen exposure may influence the potential for drug exposure-related adverse events. Table 4 summarizes the published pharmacokinetic studies that evaluate drug-drug interactions between hormonal contraceptives and ART, as well as the original authors' clinical conclusions based on study results.

Some pharmacokinetic studies include a pharmacodynamic component by evaluating luteal activity, a surrogate marker of the ability to become pregnant, as a measure of contraceptive efficacy in the presence of changing hormone exposure. Luteal activity is assessed by endogenous progesterone concentrations, repeatedly measured during the study period. Herein, these pharmacodynamic data are presented in conjunction with the pharmacokinetic data, when available, as a measure of effectiveness.

4.1 Antiretroviral agents with no known or anticipated drug-drug interactions with hormonal contraceptives

Antiretrovirals in the NRTI, INSTI, and entry inhibitor classes are not known to induce or inhibit the drug metabolizing enzymes that often influence hormone pharmacokinetics (Table 2). Given this, significant drug-drug interactions with these agents are not expected. Studies to date have found no effect of NRTIs or maraviroc on hormone exposure (Table 4) [37–40]. Specific to INSTIs, raltegravir and dolutegravir were each evaluated in healthy volunteers receiving COC and no change in hormone exposure was observed (Table 4) [41,

42]. In contrast, elvitegravir, also an INSTI, must be coadministered with a pharmacokinetic-enhancing agent such as ritonavir or cobicistat, which influences its drug-drug interaction potential. The published literature available to describe the potential interactions between hormone contraceptives and pharmacokinetically-enhanced elvitegravir, as well as antiretrovirals in the NNRTI and PI classes, are described below.

4.2 Oral contraceptive methods

A large number of oral contraceptive products are commercially available, with variable dosing of the estrogen component, most commonly ethinyl estradiol, as well as variable progestin type and dose. Individual drug-drug interaction studies between ART and oral contraceptives evaluate only one specific COC product; therefore, careful interpretation of the results, in the context of overlapping metabolic pathways (Table 2), is needed before extrapolating the results to other COC products that were not evaluated.

4.2.1 Integrase strand transfer inhibitor: elvitegravir—One drug-drug interaction study with elvitegravir and hormonal contraceptives has been conducted. In this healthy volunteer study, elvitegravir, pharmacokinetically-enhanced with cobicistat, was evaluated with ethinyl estradiol/norethindrone [43]. In combination, the ethinyl estradiol exposure was significantly reduced 25%, while the norethindrone exposure significantly increased 126%. While the increase in norethindrone exposure may be explained by cobicistat-mediated CYP inhibition, the decrease in ethinyl estradiol exposure is unexplained by the known induction or inhibition of enzymes and transporters by cobicistat or elvitegravir (Table 1). No data are available when elvitegravir is coadministered with ritonavir as the pharmacokinetic-enhancer, and product labeling suggests that alternative, non-hormonal methods of contraception should be considered in the absence of available evidence [2].

4.2.2 Non-nucleoside reverse transcriptase inhibitors (NNRTIs)—The potential for drug-drug interactions between COC and individual NNRTI agents is variable. Nevirapine, the first available NNRTI, remains widely used in low- and middle-income countries. In a small case-series, three HIV-positive women receiving nevirapine 200mg twice daily plus ethinyl estradiol/norgestrel had higher exposure of ethinyl estradiol and levonorgestrel (the active metabolite of norgestrel) than three HIV-negative women [44]. Notably, HIV-positive women, with or without ART, had higher hormone exposure than the three HIV-negative women. Landolt et al. compared the pharmacokinetics of ethinyl estradiol/desogestrel in HIV-positive women receiving ART to HIV-negative women. In that study, women receiving nevirapine-based ART had etonogestrel (the active metabolite of desogestrel) concentrations 22% lower and ethinyl estradiol concentrations 58% lower than HIV-negative individuals [45]. However, no participant receiving nevirapine-based ART had luteal activity, despite the decrease in etonogestrel and ethinyl estradiol exposure [46].

In the same ethinyl estradiol/desogestrel COC study, Landolt et al. described 61% lower etonogestrel exposure, but no significant difference in ethinyl estradiol exposure, when the COC was combined with efavirenz [45]. In an effort to describe the clinical significance of lower progestin exposure, the authors found a statistically higher number of women with luteal activity in the efavirenz group compared to the nevirapine group (25% vs. 0%;

p=0.04), raising concern for reduced contraceptive efficacy when this COC is coadministered with efavirenz [46]. Another crossover study of ethinyl estradiol/norgestimate in healthy volunteers with and without efavirenz monotherapy found no significant change in ethinyl estradiol exposure, while concentrations of norgestimate and its active metabolite, levonorgestrel, decreased 46–86% during efavirenz coadministration [47]. Despite this marked decrease in progestin exposure, no luteal activity was noted in the efavirenz group. The impact of efavirenz on progestin-only emergency contraception was also evaluated in one study of healthy volunteers [48]. Consistent with the results when combined with a COC, levonorgestrel exposure was decreased 58% in combination with efavirenz.

The impact of the newer NNRTIs, etravirine and rilpivirine, on COCs were separately evaluated in healthy volunteer crossover studies of women receiving ethinyl estradiol/norethindrone with or without etravirine or rilpivirine monotherapy. When coadministered with etravirine, ethinyl estradiol and norethindrone exposure remained within the defined limits of bioequivalence (least squares mean ratio 0.8–1.25) [49], with the exception of the minimum concentration (Cmin) of norethindrone, which was 22% lower during etravirine coadministration [50]. Despite this, no difference in the laboratory markers of ovulation were observed, leading the authors to conclude that this decrease in progestin exposure was not clinically significant. Rilpivirine demonstrated minimal potential for drug-drug interaction with COCs; all pharmacokinetic parameters were unchanged and there was no laboratory signal for ovulation [51].

4.2.3 Protease inhibitors (PIs)—Currently used PIs are coadministered with either ritonavir or cobicistat to pharmacokinetically enhance PI exposure. As a pharmacokinetic enhancer, ritonavir 100mg is given once or twice daily, which is in contrast to 400–600 mg twice daily used historically when ritonavir was given as an active drug for the treatment of HIV. One study reported a significant decrease in ethinyl estradiol exposure when administered with high dose ritonavir [52], likely mediated by UGT induction. A decrease in ethinyl estradiol exposure was also observed when ritonavir was given as a pharmacokinetic enhancer in combination with atazanavir, darunavir and lopinavir [53–56]. In contrast to the consistent results with ethinyl estradiol, the impact of ritonavir-boosted PIs on progestin exposure is variable. In one study of ethinyl estradiol/norethindrone combined with darunavir/ritonavir, norethindrone exposure was non-significantly reduced 14% [54]. Also, no significant change in the progestin Cmin was observed after coadministration of lopinavir/ritonavir with ethinyl estradiol/desogestrel [55]. In contrast, norgestimate exposure increased 85% when combined with atazanavir/ritonavir [56]. Similarly, in two studies of a POP in women predominately receiving atazanavir/ritonavir-based ART, the norethindrone exposure was 50% higher in combination with the PIs [57, 58]. Only one study evaluated luteal activity and no participant had evidence of luteal activity, regardless of receipt of lopinavir/ritonavir-based ART [55]. This result is consistent with the expectation that the progestin exposure is primarily responsible for ovulation.

Co-formulated products of cobicistat-boosted atazanavir and darunavir, are recently available. However, no drug-drug interaction studies have been completed with these

combination products. Therefore, coadministration of hormonal contraceptives with cobicistat-enhanced PIs is not currently recommended [2].

4.3 Transdermal contraceptive methods

One study evaluated the effect of lopinavir/ritonavir-based ART on the pharmacokinetics of ethinyl estradiol/norelgestromin released from a transdermal patch [53]. Consistent with studies evaluating lopinavir/ritonavir coadministered with COCs, ethinyl estradiol exposure was 45% lower, while progestin exposure was 83% higher in women receiving lopinavir/ritonavir-based ART plus the contraceptive patch. The decreased exposure to ethinyl estradiol did not influence luteal activity. In this same study, ethinyl estradiol exposure after a single dose of a COC was measured and was similar ethinyl estradiol exposure when given transdermally in combination with ART, signaling that avoidance of oral first-pass effect did not mitigate the ART-hormone drug-drug interaction.

4.4 Injectable contraceptive methods

To date, data regarding the effect of ART on injectable contraceptives are limited to the progestin depot-medroxyprogesterone acetate (DMPA) administered by the intramuscular route. Studies evaluating the pharmacokinetics of medroxyprogesterone have not identified a clinically significant effect of ART on DMPA [59–61]. Specifically, clinical studies on efavirenz-, nelfinavir-, and nevirapine-based ART found no influence of ART on medroxyprogesterone exposure [59, 61]. One recent study compared women receiving lopinavir/ritonavir-based ART to women not receiving ART and found that medroxyprogesterone exposure was 46% higher with lopinavir/ritonavir-based ART, but remained well tolerated [60].

4.5 Long-acting, reversible contraceptive methods

4.5.1 Progestin-releasing subdermal implants—The pharmacokinetics of etonogestrel released from an implant have been assessed in one study [62]. An etonogestrel implant was placed at entry in HIV-positive women either receiving lopinavir/ritonavir-based ART, efavirenz-based ART, or not yet on ART (control group). Pharmacokinetic samples were collected over 24 weeks, at which time the minimum etonogestrel concentration was 33% higher in the lopinavir/ritonavir group, but 70% lower in the efavirenz group, each compared to control subjects. Luteal activity was observed in 2.8% to 5% of participants receiving efavirenz, depending on the progesterone level threshold applied, compared to no luteal activity in subjects in the control group ($p<0.05$).

The pharmacokinetics of levonorgestrel released from an implant were also characterized in HIV-positive women receiving ART [63]. Specifically, a levonorgestrel implant was placed at entry and pharmacokinetic samples were collected over 48 weeks in women receiving nevirapine-based ART, efavirenz-based ART, and a control group not yet on ART. At week 48, the levonorgestrel Cmin was 57% lower in the efavirenz group compared to control subjects, but was not significantly different in the nevirapine group compared to the control group. No differences were observed between the three groups related to contraceptive-associated adverse events over 48 weeks. During this pharmacokinetic evaluation, three women became pregnant in the efavirenz group between weeks 36 and 48 post-implant

placement (3 of 20, 15%). No pregnancy occurred in the nevirapine or control groups, highlighting the clinical significance of the lower levonorgestrel exposure when used in combination with efavirenz.

4.5.2 Levonorgestrel-releasing intrauterine devices—Although pharmacokinetic data are lacking, limited observational data suggest the contraceptive effectiveness of the levonorgestrel-releasing IUD is not compromised when used in women receiving ART [4, 64–66]. Given the localized delivery and action of levonorgestrel released from IUDs, systemic ART is not expected to significantly affect hormone concentrations in the genital tract [18, 67]. In addition, the IUD provides contraceptive effectiveness primarily by preventing fertilization via thickening of the cervical mucus and reducing sperm motility and function, irrespective of local hormone exposure.

5.0 Hormonal contraceptive use and HIV disease progression

There is now international consensus that ART should be initiated in all adults living with HIV [12, 2], making the concern about HIV disease progression with contraceptives in the absence of ART less relevant. Historically, concerns existed that the use of some hormonal contraceptives negatively impacted HIV disease progression in the absence of ART. Several biological mechanisms were proposed to explain this effect. First, exogenous progestin administration can induce immunosuppression. Progestins have a varying affinity to the progestin receptor, as well as to other steroid receptors, such as the androgen, glucocorticoid and mineralocorticoid receptors [68, 69]. For example, the hormonal contraceptive medroxyprogesterone acetate binds to the glucocorticoid receptor at a much higher affinity than endogenous progesterone or other exogenous progestins used for contraception, and activity at the glucocorticoid receptor may lead to immunosuppression [69]. A recent ex-vivo study of human primary T lymphocytes showed that medroxyprogesterone acetate inhibited the activation of T lymphocytes and peripheral dendritic cell response; whereas, norethisterone and levonorgestrel did not have any detectable immunosuppressive activity [70]. This study indicates that exogenous progestins have varying effects on immune function via interactions with the glucocorticoid receptor.

Another potential mechanism by which contraceptives could increase the risk of HIV disease progression is by a drug-drug interaction between the hormonal contraceptive and the antiretroviral drugs, resulting in a decrease in systemic ART exposure. A few pharmacokinetic studies have found that exogenous hormone exposure influenced ART exposure. One study found statistically lower efavirenz concentrations when given with an oral contraceptive pill containing ethinyl estradiol/desogestrel (efavirenze concentrations: 3.3 vs. 2.7 mg/L; p=0.03) [46]. Another study of the contraceptive transdermal patch (ethinyl estradiol/norelgestromin) plus lopinavir/ritonavir-based ART identified significantly lower ritonavir area under the concentration-time curve and maximum concentration when combined with the patch (24% and 8% lower, respectively, both p=0.031) [53]. Also, one study observed 18% lower nelfinavir and 17% higher nevirapine exposure, which were both statistically significant by 90% confidence intervals, when combined with DMPA [59]. Despite these statistically significant changes, the antiretroviral drug exposure still meets the FDA definition of bioequivalence (least squares mean ratio 0.80–1.25) [49], and are unlikely

to be clinically significant. In addition, most studies have not identified significant changes in antiretroviral concentrations when used with hormonal contraceptives. For oral contraceptives, a significant impact on antiretroviral pharmacokinetics was not observed when given with lamivudine/stavudine [44], zidovudine [37], emtricitabine [38], tenofovir [38, 39], efavirenz [48], etravirine [50], nevirapine [45, 44], rilpivirine [51], darunavir/ritonavir [54], lopinavir/ritonavir [55], and elvitegravir/cobicistat [43]. For non-oral routes of hormonal contraception, DMPA did not impact the pharmacokinetic exposure of lopinavir/ritonavir [60], efavirenz or nevirapine [59]. Similarly, the levonorgestrel implant did not impact efavirenz or nevirapine systemic exposure over 48 weeks of combined use [63]. Based on these data, the impact of hormonal contraceptives on ART exposure, if any, is small and unlikely to be clinically significant.

Two recent systematic reviews identified 13 high quality studies that evaluated the risk of HIV disease progression and hormonal contraception [11, 71]. A secondary analysis from a randomized trial of 595 women showed an increased risk of declining CD4+ count (a marker of immune system function and predictor of HIV disease progression) among the 302 women randomized to hormonal contraceptives [DMPA or COC] when compared with the 293 women randomized to the copper IUD (HR [95% CI]: 1.56 [1.08–2.26] for DMPA and 1.69 [1.09–2.64] for COC) [72]. However, loss to follow-up and contraceptive method switching were common; therefore, the intent-to-treat analysis failed to show an association between hormonal contraception and HIV disease progression. Conversely, a prospective cohort of 2269 HIV-positive women in sub-Saharan Africa found that the use of injectable contraceptives (DMPA and norethisterone enanthate), but not COCs, was associated with a lower likelihood of disease progression, defined as a composite measure of ART initiation, CD4+ count falling below 200 cells/mL, or atraumatic death (adjusted HR: 0.74, p=0.04 for injectable users and adjusted HR: 0.83, p=0.5 for COC users) [73]. Similarly, other studies have not observed a change in plasma HIV-RNA levels (a measure of ART effectiveness) and none have observed a negative impact on CD4+ cell count [11, 71, 74–76].

Overall, only one outlying study with the methodologic limitations described above has indicated concern for HIV disease progression with use of hormonal contraception [72], but others show either no effect or reduced disease progression with use of hormonal contraception [11]. Therefore, the available data indicate that hormonal contraceptives do not impact the rate of disease progression for women living with HIV.

6.0 Hormonal contraceptive use and HIV transmission

Similar to hormonal contraceptive influence on HIV progression, concerns regarding an increased risk of HIV transmission from HIV-positive women using hormonal contraceptives to HIV-negative male partners are less relevant following the worldwide recommendation for ART initiation in all adults living with HIV [12, 2]. This is because treatment of HIV infection with ART is perhaps the most effective method to reduce HIV transmission between serodiscordant couples; (HIV transmission in ART vs. no ART: HR [95% CI], 0.04 [0.01–0.27]) [77]. However, this has been an area of significant concern for patients without access to ART. Several biological mechanisms suggesting an increased risk of HIV transmission with some hormonal contraceptives were proposed, including the potential for

increased genital HIV viral shedding [78] and increased plasma HIV-RNA [79]. Increased HIV genital shedding may be the result of direct immunosuppressive effects of the hormonal contraceptives on HIV replication in the genital tract [70] or indirectly by increasing genital tract inflammation [69], the latter of which increases susceptibility to sexually transmitted infection [80] or results in the thinning of the genital tract mucosa [81, 82].

There are 20 high quality studies evaluating the effect of hormonal contraception on HIV infectiousness, summarized in recent systematic reviews [11, 83]. These studies evaluated the effect of hormonal contraceptives on HIV transmission risk by direct evidence (incident cases of new HIV infection in the male partner) and by indirect evidence (genital or plasma HIV-RNA levels in HIV-positive women). Direct evidence of incident HIV cases among the male partners is difficult to interpret considering potentially significant methodological limitations, such as behavioral confounders, presence of other sexually transmitted infections, and dependence on self-report for hormonal or barrier contraceptive use. However, a recent study in a Ugandan community cohort of 159 serodiscordant couples found no significant difference in HIV transmission among women using hormonal contraception and those not using hormonal contraception [84]. Long intervals between follow-up (6–12 months) made misclassification of contraceptive use at the time of HIV transmissions more likely in this study. Another secondary data analysis of 3790 serodiscordant couples in African countries found that hormonal contraceptives were associated with increased female-to-male HIV transmission (adjusted HR [95%CI]: 1.97 [1.12–3.45]); however, only injectable hormonal contraceptives were associated with a significant increase in transmission (adjusted HR [95%CI]: 1.95 [1.06–3.58]) while an association with oral contraceptives was not observed (adjusted HR [95%CI]: 1.09 [0.75–5.84]) [85]. The strengths of this study were that seroconversions were genetically linked between partners and there was frequent follow-up (every three months) during the study period.

There are thirteen studies summarized in recent reviews that examine the influence of hormonal contraceptive use on genital HIV-DNA or RNA shedding [11, 73]. There is significant heterogeneity among these studies due to differences in study design; methods of sample collection; methods of detection and quantification of HIV; and type and classification of hormonal contraceptive use, which makes comparison and interpretation of these studies difficult. Notably, of these 13 studies, 10 found no change in HIV genital shedding when comparing women using hormonal contraceptives to those not using hormones, after controlling for covariates [11, 73]. One study of 97 women at a sexually transmitted infection (STI) clinic in Kenya found COCs to increase the odds of detecting cervical HIV-DNA (adjusted odds ratio (OR) [95% CI]: 11.6 [1.7–77.6]) when compared to women not using hormonal contraception, but did not change the odds of detecting vaginal HIV-DNA [86]. Another study of 318 Kenyan women in a STI clinic found increased odds of detecting both cervical and vaginal HIV-DNA in women using COCs (adjusted OR [95% CI]: cervical 4.9 [2.1–11.8]; vaginal 2.4 [1.0–5.7]); and cervical, but not vaginal, HIV-DNA in women using DMPA (adjusted OR [95% CI]: 2.9 [1.5–5.7]) when compared to women not using hormonal contraception [87]. Most compelling is the Heffron et al. study that, in addition to providing direct evidence of transmission, reported that women using injectable hormonal contraceptives, but not COCs, were more likely to have a detectable HIV-RNA in

the genital tract (adjusted OR [95% CI]: 1.67 [1.21–2.31]) [85]. In addition to cervical and vaginal viral detection, eight of the reported studies described the impact of hormonal contraceptives on plasma HIV-RNA [11, 73]. Only one of these studies, after adjusting for covariates, reported an association between DMPA use and a higher plasma HIV-RNA set point in 161 commercial sex workers who became infected with HIV over the study period compared to women not using hormonal contraception (p=0.03). However, the rate of HIV-RNA increase in plasma was not greater with DMPA compared to no hormonal contraception [88]. This indicates that women using DMPA at the time of HIV acquisition had higher HIV-RNA at baseline, and thus higher HIV-RNA during the follow-up period. DMPA did not affect the rate of plasma HIV-RNA change over time in these women who were acutely infected with HIV and not yet on ART.

Only four studies have evaluated a long-acting, reversible contraceptive. Two included women using subdermal implants, one evaluated genital HIV shedding [89] and the other evaluated plasma HIV-RNA levels [88]); neither found a significant association between contraceptive implants and these markers of HIV transmission or progression. Additionally, there have been two prospective studies of HIV-1 genital shedding in women using either the copper IUD or the levonorgestrel IUD that showed no increased HIV-1 shedding after IUD placement [90, 91].

It should be highlighted that most studies have been conducted in HIV-positive women not yet on ART or those initiating ART. More recently, studies evaluating HIV-positive women receiving ART over several years did not identify an association between the risk of HIV transmission and hormonal contraceptive use [92, 93]. In summary, although some studies indicate there may be an increased risk of female-to-male HIV transmission with some hormonal contraception in the absence of ART, the widespread use of potent ART regimens likely mitigates this risk.

7.0 Conclusions

For the ART-hormone combinations evaluated to date, the effectiveness of most hormonal contraceptives in combination with most antiretrovirals is not significantly influenced by pharmacokinetic drug-drug interactions, with a critical exception and some gaps in information. A notable gap in evidence exists regarding effective hormonal contraceptive options for women receiving elvitegravir, pharmacokinetically enhanced with either ritonavir or cobicistat, which has only been evaluated in a single, healthy-volunteer study, despite predicted drug-drug interactions given overlapping metabolic pathways. Perhaps most importantly, when some hormonal contraceptives are combined with efavirenz-based ART, significant reductions in progestin pharmacokinetic exposure occur, irrespective of the progestin route of administration. This decrease in drug exposure has been correlated with decreased contraceptive effectiveness, as measured by either observed unintended pregnancies or observed luteal activity, for subdermal implants and some oral contraceptive pills. Data suggests that DMPA is an exception to this detrimental ART-contraceptive interaction, as it appears to retain contraceptive effectiveness in combination with efavirenz-based ART [59]. Globally, the drug-drug interactions between efavirenz and hormonal contraceptives have high clinical significance because the WHO recommends efavirenz-

based ART as the only preferred first-line regimen for HIV-positive adults [12]. For these women, effective hormonal contraceptive options in addition to DMPA are critically needed in combination with widely available ART options.

In general, tolerability of hormonal contraceptives was not influenced in these studies by coadministration of ART, even when hormone exposure was increased due to drug-drug interactions. Therefore, hormonal contraceptive tolerability in HIV-positive women is expected to be similar to other populations. Providers may wish to monitor patients who are receiving ART that is known to increase hormone exposure for excess hormone-related toxicities, including thrombosis and hypertension.

Overall, hormonal contraceptives are safe and critically important for use among HIV-positive women. Direct evidence indicates there may be a slight increased risk of HIV infectiousness with DMPA; but data with other methods of hormonal contraception do not support this, though the limited representation of modern, long-acting reversible contraceptives, such as progestin-containing contraceptive implants, from these studies is noted. Because HIV transmission between serodiscordant partners is dramatically decreased when plasma HIV-RNA is below the limit of detection, any small increase in infectiousness due to hormonal contraceptives is likely to be eliminated by the use of ART resulting in suppressed plasma HIV-RNA. Given the recent WHO recommendations for universal use of ART irrespective of CD4+ cell counts [94], remaining concerns regarding the influence of hormonal contraceptives on HIV progression or transmission will also be eliminated.

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Key Points

- Efavirenz-based antiretroviral therapy is demonstrated to decrease contraceptive effectiveness when combined with subdermal contraceptive implants and some oral contraceptive pills. This negative impact on contraceptive effectiveness has not been observed with other antiretroviral medications.
- Hormonal contraceptive tolerability is similar between women living with or without HIV; however, providers should monitor patients receiving antiretroviral therapy known to increase hormone exposure for possible excess contraceptive-related toxicity.
- Data from systematic reviews indicate that hormonal contraceptive use is not associated with HIV disease progression and some data suggest that depot-medroxyprogesterone use may increase the risk of HIV transmission in the absence of antiretroviral therapy. Widespread access to effective antiretroviral therapy is the most important factor for reducing the risk of HIV disease progression and HIV transmission, minimizing the potential influence of hormonal contraceptives.

Table 1

Mechanisms of antiretroviral-associated drug metabolizing enzyme mediated drug-drug interactions. Adapted from the Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents, Table 17 [2].

Antiretroviral[a]	CYP Substrate	CYP Inhibitor	CYP Inducer	UGT1A1
Entry Inhibitors				
Maraviroc	3A4	…	…	…
Integrase Strand Transfer Inhibitors (INSTIs)				
Dolutegravir	3A4 (minor)	…	…	Substrate
Elvitegravir	3A4	…	2C9	Substrate
Raltegravir	…	…	…	Substrate
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)				
Efavirenz	2B6 (primary), 2A6, 3A4	2C9, 2C19, 3A4	3A4, 2B6	…
Etravirine	3A4, 2C9, 2C19	2C9, 2C19	3A4	…
Nevirapine	3A4, 2B6	…	3A4, 2B6	…
Rilpivirine	3A4	…	…	…
Pharmacokinetic (PK) Enhancers (Boosters)				
Cobicistat	3A4	3A4, 2D6	…	…
Ritonavir	3A4, 2D6	3A4 (potent), 2D6 (lesser extent)	1A2, 2C8, 2C9, 2C19	Inducer
Protease Inhibitors (PIs)				
Atazanavir	3A4	3A4, 2C8 (weak)	…	Inhibitor
Darunavir	3A4	3A4	2C9	…
Fosamprenavir	3A4	3A4	3A4 (weak)	…
Lopinavir	3A4	3A4	…	…
Saquinavir	3A4	3A4	…	…
Tipranavir	3A4	2D6	3A4, 1A2, 2C19	…

Abbreviations: CYP; cytochrome P450; UGT1A1; uridine diphosphate glucuronosyltransferase.

[a]None of the currently marketed nucleos(t)ide reverse transcriptase inhibitors (NRTIs) or the entry inhibitor, enfuvirtide, are known to be metabolized by or inhibit or induce CYP or UGT enzymes. Therefore, they are not included in this summary table.

Table 2

Available hormonal contraceptive products and potential routes of drug-drug interactions.

		Enzymes that metabolize and/or are inhibited or induced by contraceptive hormones				
Contraceptive Hormone	**Available Delivery Routes**	**CYP substrate**	**CYP inhibitor**	**CYP inducer**	**UGT1A1**	**Other major routes of metabolism**
Estrogen						
Ethinyl estradiol [95–98] **Estradiol valerate** [99]	COC Transdermal patch Vaginal ring	3A4 (61%) 2C9 (23%) Minor (<20% total): 1A2, 2C19, 3A5	In vitro: 2B6, 2C19, 3A4	2A6 (proposed)	Substrate Inducer	Sulfate conjugation
Progestins						
1st Generation *– derived from 17-hydroxyprogesterone or from testosterone*						
Medroxyprogesterone acetate [98, 100–102]	IM injection SC injection	3A4	…	3A4 (by 25%)	None	…
Norethindrone (U.S.)/**Norethisterone** (international) [103, 104]	COC POP	3A4	In vitro: 2C9 (weak)	…	Substrate	Sulfate conjugation
2nd Generation *– derived from testosterone*						
Levonorgestrel [22, 24, 98]	COC POP (emergency) IUD Subdermal implant	3A4	In-vitro: 3A4 (weak)	…	Substrate (minor)	Sulfate conjugation
Norgestrel [98] *Includes levonorgestrel and its inactive isomer, dextronorgestrel*	COC	3A4	…	…	…	…
3rd Generation *– derived from levonorgestrel*						
Desogestrel [20, 105, 106] *Prodrug, rapidly and extensively converted to etonogestrel*	COC	In-vitro: 2C9 (not supported by in-vivo data)	…	…	Substrate	…
Etonogestrel [24]	Vaginal ring Subdermal implant	3A4	In-vitro: 3A4 (weak)	…	Substrate	…
Gestodene [20, 24]	COC	3A4	In-vitro: 3A4(potent), not clinically significant at low doses	…	…	…
Norgestimate [20, 24] *Prodrug, rapidly and extensively converted to norelgestromin and norgestrel*	COC	3A4	In-vitro: 3A4 (weak)	…	…	…
Norelgestromin [107] *Metabolized to norgestrel*	Transdermal patch	…	…	…	…	Undergoes hepatic metabolism to norgestrel

		Enzymes that metabolize and/or are inhibited or induced by contraceptive hormones				
Contraceptive Hormone	**Available Delivery Routes**	**CYP substrate**	**CYP inhibitor**	**CYP inducer**	**UGT1A1**	**Other major routes of metabolism**
4th Generation						
Drospirenone [98, 108]	COC	3A4 (minor)	In-vivo: inhibition of 2C19 and 3A4 were not significant			Reduction, then sulfate conjugation

Abbreviations: CYP, cytochrome P450; COC, combination (estrogen/progestin) oral contraceptive; IM: intramuscular; SC: subcutaneous; POP, progestin-only oral contraceptive; IUD, intrauterine device.

Table 3

Contraceptive failure rates by method across 43 countries at 12, 24, and 36 months. Adapted from Polis CB, et al. [28], Supplemental Table 8. Data are presented as pooled rate per 100 episodes of typical use (95% confidence intervals).

Contraceptive method	12 months	24 months	36 months
Implant	0.6 (0.3, 0.9)	0.8 (0.4, 1.1)	1.1 (0.5, 1.6)
Intrauterine Device	1.5 (1.2, 1.8)	3.0 (2.5, 3.4)	3.9 (3.4, 4.4)
Injectable	2.3 (2.0, 2.5)	4.1 (3.8, 4.4)	6.0 (5.5, 6.5)
Oral Pill	5.7 (5.4, 6.0)	11.0 (10.5, 11.5)	15.1 (14.4, 15.7)
Male Condom	6.8 (6.3, 7.3)	12.6 (11.8, 13.4)	17.6 (16.4, 18.8)
Withdrawal	14.9 (14.1, 15.6)	27.5 (26.5, 28.5)	35.7 (34.5, 37.0)

Table 4

Summary of pharmacokinetic studies between hormonal contraceptives and antiretroviral therapy. Hormone pharmacokinetic parameters are presented as a ratio measure or summary value. The p value represents a comparison between antiretroviral treatment groups compared to a control, if available.

ART evaluated	Hormones evaluated	Study groups	Study design	Hormone AUC Ratio ART:Control	Hormone Cmax Ratio ART:Control	Hormone Cmin Ratio ART:Control	Clinical conclusions by study authors
Combined Oral Contraceptives (COC)							
Atazanavir/ritonavir [56][a]	Ethinyl estradiol	Atazanavir/ritonavir monotherapy, HIV-negative (n=18)	Prospective, randomized, crossover study; hormone PK evaluated mid-cycle of COC alone and in combination with atazanavir/ ritonavir monotherapy.	0.81 (0.75, 0.87)	0.84 (0.74, 0.95)	0.63 (0.55, 0.71)	An oral contraceptive agent containing ≥30 mcg of ethinyl estradiol may minimize breakthrough bleeding due to the reduced ethinyl estradiol exposure when combined with atazanavir/ ritonavir. Contraceptive effectiveness of COC is unlikely to decrease given the increase in progestin exposure.
	Norgestimate			1.85 (1.67, 2.05)	1.68 (1.51, 1.88)	2.02 (1.77, 2.31)	
Darunavir/ritonavir [54][b]	Ethinyl estradiol	Darunavir/ritonavir monotherapy, HIV-negative (n=13)	Prospective, randomized, crossover study; hormone PK evaluated mid-cycle of COC alone and in combination with darunavir/ ritonavir monotherapy.	0.56 (0.50, 0.63)	0.68 (0.61, 0.74)	0.38 (0.27, 0.53)	Darunavir/ ritonavir significantly reduced ethinyl estradiol exposure, which the authors concluded were clinically relevant, while the progestin exposure was non-significantly decreased.
	Norethindrone			0.86 (0.75, 0.98)	0.90 (0.83, 0.97)	0.70 (0.51–0.97)	
Dolutegravir [42][b]	Ethinyl estradiol	Dolutegravir monotherapy, HIV-negative (n=16)	Prospective, randomized, double-blind, placebo-controlled, cross-over study;	1.03 (0.96, 1.11)	0.99 (0.91, 1.08)	1.02 (0.93, 1.11)	Coadministration of dolutegravir and COC does not affect hormone PK.
	Norgestimate			0.98 (0.91, 1.04)	0.89 (0.82, 0.97)	0.93 (0.85, 1.03)	

ART evaluated	Hormones evaluated	Study groups	Study design	Hormone AUC Ratio ART:Control	Hormone Cmax Ratio ART:Control	Hormone Cmin Ratio ART:Control	Clinical conclusions by study authors
			hormone PK evaluated on days 10 and 21 of COC in combination with dolutegravir or placebo.				
Efavirenz [47][a]	Ethinyl estradiol	Efavirenz monotherapy, HIV-negative (n=28)	Prospective, non-randomized, cross-over study; hormone PK evaluated mid-cycle of COC alone and in combination with efavirenz monotherapy; post-hoc analysis of efavirenz impact on levonorgestrel PK.	0.90 (0.80, 1.01)	1.06 (0.95, 1.19)	0.92 (0.75, 1.14)	Given the significant decrease in progestin exposure, a second form of barrier contraception is recommended when efavirenz is combined with COCs.
	Norgestimate			0.36 (0.33, 0.38)	0.54 (0.48, 0.61)	0.18 (0.15, 0.21)	
	Levonorgestrel (active metabolite of norgestimate)			0.17 (0.13, 0.21)	0.20 (0.17, 0.23)	0.14 (0.10, 0.20)	
Efavirenz and Nevirapine [45][c]	Ethinyl estradiol	Efavirenz-based ART, HIV-positive (n=16) Nevirapine-based ART, HIV-positive (n=18) HIV-negative (n=14)	Prospective, non-randomized, parallel group study; hormone PK evaluated on day 16 of the second cycle of COC.	…	…	EFV: 0.91 (0.74, 1.11) NVP: 0.42 (0.30, 0.57)	Caution against the use of this COC in HIV-positive women on efavirenz-based ART due to possible contraceptive failure. Hormone PK changes in the nevirapine-based ART group did not affect the contraceptive efficacy of the COC.
	Etonogestrel (active metabolite of desogestrel)			…	…	EFV: 0.39 (0.30, 0.51) NVP: 0.78 (0.53, 1.15)	
Elvitegravir/cobicistat [43][b]	Ethinyl estradiol	Elvitegravir/cobicistat, HIV-negative, (n=13)	Prospective, non-randomized, cross-over study; hormone PK evaluated	0.75 (0.69, 0.81)	0.94 (0.86, 1.04)	0.56 (0.52, 0.61)	Elvitegravir/ cobicistat-based ART significantly reduced ethinyl estradiol exposure, while
	Norgestromin (active metabolite of norgestimate)			2.26 (2.15, 2.37)	2.08 (2.00, 2.17)	2.67 (2.43, 2.92)	

ART evaluated	Hormones evaluated	Study groups	Study design	Hormone AUC Ratio ART:Control	Hormone Cmax Ratio ART:Control	Hormone Cmin Ratio ART:Control	Clinical conclusions by study authors
			mid-cycle of COC alone and in combination with elvitegravir/ cobicistat-based ART.				the progestin exposure was significantly increased. Contraceptive effectiveness of COC is unlikely to decrease given the increase in progestin exposure.
Etravirine [50][b]	Ethinyl estradiol	Etravirine monotherapy, HIV-negative (n=30)	Prospective, non-randomized, cross-over study; hormone PK evaluated on day 15 of COC alone (second cycle) and in combination with etravirine monotherapy (third cycle).	1.22 (1.13, 1.31)	1.33 (1.21, 1.46)	1.09 (1.01, 1.18)	No loss in contraceptive efficacy is expected when COC is coadministered with etravirine.
	Norethindrone			0.95 (0.90, 0.99)	1.05 (0.98, 1.12)	0.78 (0.68, 0.90)	
Lopinavir/ritonavir [55][c]	Ethinyl estradiol	Lopinavir/ritonavir-based ART, HIV-positive (n=16) Historical control, HIV-negative (n=14)	Prospective, non-randomized, intervention group compared to historical control patients; hormone PK evaluated on day16 of the second cycle of COC.	…	…	0.68 (0.42, 1.08)	High variability in hormone Cmin values were observed, but no clinically significant effect was observed based on measures of ovulation.
	Etonogestrel (active metabolite of desogestrel)			…	…	1.08 (0.73, 1.60)	
Lopinavir/ritonavir [53][d]	Ethinyl estradiol (given as COC with norethindrone)	Lopinavir/ritonavir-based ART, HIV-positive (n=8) HIV-positive controls (n=24)	Prospective, non-randomized, parallel group study; ethinyl estradiol PK evaluated after a single dose. Norethindrone	LPV/r: 344.67 (310.43, 476.52) pg•h/mL No ART: 765.38	…	LPV/r: 1.00 (1.00, 2.13) pg/mL No ART: 4.15 (3.11, 5.81) pg/mL *	Lopinavir/ ritonavir significantly decreased ethinyl estradiol exposure.

ART evaluated	Hormones evaluated	Study groups	Study design	Hormone AUC Ratio ART:Control	Hormone Cmax Ratio ART:Control	Hormone Cmin Ratio ART:Control	Clinical conclusions by study authors
			PK not evaluated.	(680.48, 890.69) pg•h/mL **			
Nevirapine [44][d]	Ethinyl estradiol	Nevirapine-based ART, HIV-positive (n=3) No ART, HIV-positive control (n=3) HIV-negative control (n=3)	Prospective, non-randomized, parallel group study; hormone PK evaluated on day 14 of the second cycle of COC.	NVP: 1384 (1130, 1425) pg•h/mL No ART: 1457 (1371, 1610) pg•h/mL Control: 1144 (1111, 1583) pg•h/mL	…	NVP: 57.3 (40.8, 60.7) pg/mL No ART: 82.2 (67.1, 98.2) pg/mL Control: 47.0 (39.3, 81.7) pg/mL	Hormone concentrations were higher in women with HIV compared to uninfected women, irrespective of combined use with ART.
	Levonorgestrel (active metabolite of norgestrel)			NVP: 147 (112, 177) ng•h/mL No ART: 114 (105, 139) ng•h/mL Control: 37.9 (36.9, 107) ng•h/mL	…	NVP: 6.11 (3.50, 7.02) ng/mL No ART: 4.72 (4.03, 7.36) ng/mL Control: 1.41 (1.04, 4.03) ng/mL	
Raltegravir [41][a]	Ethinyl estradiol	Raltegravir monotherapy, HIV-negative (n=19)	Prospective, randomized, placebo-controlled, cross-over study; hormone PK evaluated day 21 of COC and placebo and COC in combination with raltegravir monotherapy.	0.99 (0.94, 1.04)	1.06 (0.98, 1.14)	…	Coadministration of raltegravir with COC does not have a clinically meaningful effect on hormone PK.
	Norelgestromin (active metabolite of norgestimate)			1.16 (1.09, 1.22)	1.29 (1.23, 1.37)	…	
Rilpivirine [51][b]	Ethinyl estradiol	Rilpivirine monotherapy, HIV-negative (n=18)	Prospective, non-randomized, sequential design study; hormone PK evaluated day 15 of COC alone (second cycle) and in combination with rilpivirine	1.14 (1.10, 1.19)	1.17 (1.06, 1.30)	1.09 (1.03, 1.16)	Coadministration of rilpivirine with COC does not affect hormone PK.
	Norethindrone			0.89 (0.84, 0.94)	0.94 (0.83, 1.06)	0.99 (0.90, 1.08)	

ART evaluated	Hormones evaluated	Study groups	Study design	Hormone AUC Ratio ART:Control	Hormone Cmax Ratio ART:Control	Hormone Cmin Ratio ART:Control	Clinical conclusions by study authors
			monotherapy (third cycle).				
Ritonavir [52][c]	Ethinyl estradiol (given as COC with ethynodiol diacetate)	Ritonavir monotherapy, HIV-negative (n=23)	Prospective, non-randomized, sequential design study; ethinyl estradiol PK evaluated after a single dose alone (day 1) and in combination with ritonavir monotherapy (day 29).	0.60 (0.51, 0.70)	0.68 (0.61, 0.76)	…	High dose, steady-state ritonavir (500mg twice daily) significantly decreased ethinyl estradiol exposure.
Tenofovir [39][a]	Ethinyl estradiol	Tenofovir monotherapy, HIV-negative (n=20)	Prospective, non-randomized, sequential design study; hormone PK evaluated on day 21 of COC alone (second cycle) and in combination with tenofovir monotherapy (third cycle)	0.96 (0.91, 1.01)	0.94 (0.88, 1.00)	0.98 (0.91, 1.06)	Coadministration of tenofovir with COC does not influence hormone exposure.
	Norelgestromin (active metabolite of norgestimate)			0.95 (0.91, 0.99)	0.94 (0.87, 1.01)	0.96 (0.92, 1.01)	
Progestin Only Oral Contraceptive Pill (POP)							
Atazanavir/ritonavir [58][e]	Norethindrone	Atazanavir/riton avir-based ART, HIV-positive (n=10) Non-interacting ART, HIV-positive controls (n=17)	Prospective, non-randomized, parallel group study; hormone PK evaluated on day 22 of POP with either atazanavir/ ritonavir-based or a non-interacting ART regimen.	ATV/r: 25.20 (17.94, 32.73) ng•h/mL Control: 16.69 (13.28, 20.55) ng•h/mL *	ATV/r: 3.19 (2.19, 4.79) ng/mL Control: 2.09 (1.49, 3.06) ng/mL *	ATV/r: 0.45 (0.32, 0.59) ng/mL Control: 0.27 (0.19, 0.37) ng/mL	Progestin-only contraceptives benefit from protease inhibitor-based drug-drug interactions by achieving higher levels of progestin exposure.

ART evaluated	Hormones evaluated	Study groups	Study design	Hormone AUC Ratio ART:Control	Hormone Cmax Ratio ART:Control	Hormone Cmin Ratio ART:Control	Clinical conclusions by study authors
Efavirenz [48][a]	Levonorgestrel emergency contraception	Efavirenz monotherapy, HIV-negative (n=21)	Prospective, non-randomized, cross-over study; hormone PK evaluated after a single dose of emergency contraception alone and in combination with steady-state efavirenz monotherapy.	0.42 (0.36, 0.48)	0.55 (0.49, 0.63)	0.31 (0.26, 0.36)	Efavirenz significantly reduced exposure to levonorgestrel for emergency contraception.
Protease inhibitor-based ART (various) [57][c]	Norethindrone	Protease inhibitor-based therapy (total n=16: • Atazanavir/ritonavir (n=10) • Atazanavir(n=1) • Darunavir/ritonavir (n=3) • Lopinavir/ritonavir (n=2) No or non-interacting ART, HIV-positive controls (n=17)	Prospective, non-randomized, parallel group study; hormone PK evaluated on day 22 of POP in combination with protease inhibitor-based ART or with a non-interacting or no ART	1.50 (1.21, 1.86)	1.33 (0.93, 1.88)	1.26 (1.05, 1.51)	Progestin concentrations were higher in women receiving protease-inhibitor-based ART; this increase is not expected to result in clinically significant adverse events.
Transdermal combined contraceptives							
Lopinavir/ritonavir [53][d]	Ethinyl estradiol	Lopinavir/ritonavir-based ART (n=8) No or non-interacting ART, HIV-positive controls (n=24)	Prospective, non-randomized, parallel group study; hormone PK evaluated during the third weekly patch cycle.	LPV/r: 6010.36 (5140.83, 7388.01) pg•h/mL No ART: 10911.42 (7548.36, 15667.44) pg•h/mL	…	LPV/r: 32.10 (28.60, 39.15) pg/mL No ART: 44.40 (4.59, 67.60) pg/mL	Lopinavir/ritonavir non-significantly decreased ethinyl estradiol exposure, while significantly increasing progestin exposure. The contraceptive efficacy of the patch is likely to be maintained.
	Norelgestromin			LPV/r: 138.39 (106.44, 234.75) ng•h/mL	…	LPV/r: 0.63 (0.51, 0.89) ng/mL No ART: 0.27	

ART evaluated	Hormones evaluated	Study groups	Study design	Hormone AUC Ratio ART:Control	Hormone Cmax Ratio ART:Control	Hormone Cmin Ratio ART:Control	Clinical conclusions by study authors
				No ART: 75.63 (59.20, 121.13) ng•h/mL *		(0.22, 0.43) ng/mL	
Injectable contraceptives							
Efavirenz [61][a]	Depot medroxyprogesterone	Efavirenz-based ART (n=15) No ART, HIV-positive controls (n=15)	Prospective, non-randomized, parallel group study; hormone PK evaluated every 2 weeks over 12 weeks post-injection.	1.01 (0.85, 1.20)	1.01 (0.84, 1.22)	0.90 (0.77, 1.06)	Efavirenz-based ART did not influence hormone PK, suggesting contraceptive effectiveness will be maintained.
Efavirenz, Nelfinavir, and Nevirapine [59][a]	Depot medroxyprogesterone	Efavirenz-based ART (n=17) Nelfinavir-based ART (n=21) Nevirapine-based ART (n=16) No or non-interacting ART, HIV-positive controls (n=16)	Prospective, non-randomized, parallel group study; progesterone levels were evaluated every 2 weeks over 12 weeks post-injection.	…	…	…	Raw hormone PK parameters were not reported, but authors report no statistically significant differences between groups; all progesterone levels remained below the level indicative of ovulation.
Lopinavir/ritonavir [60][d]	Depot medroxy-progesterone	Lopinavir/ritonavir-based ART (n=24) No or non-interacting ART, HIV-positive controls (n=14)	Prospective, non-randomized, single-arm study compared to historical controls; hormone PK evaluated every 2 weeks over 12 weeks post-injection	LPV/r: 18.08 (16.22, 24.10) ng•wk/mL No ART: 12.38 (8.88, 13.88) ng•wk/mL **	LPV/r: 2.88 (2.28, 4.04) ng/mL No ART: 1.74 (1.02, 2.09) ng/mL **	LPV/r: 0.47 (0.35, 0.74) ng/mL No ART: 0.43 (0.29, 0.60) ng/mL	Although hormone exposure increased during LPV/r-based ART, the authors concluded this is not likely clinically significant.
Implantable Progestin-only Contraceptives							
Efavirenz and Lopinavir/ ritonavir [62][a]	Etonogestrel	Efavirenz-based ART, HIV-positive (n=14) Lopinavir/ritonavir-based ART, HIV-positive (n=15) HIV-positive controls (n=15)	Prospective, non-randomized, parallel group	EFV: 0.34 (0.28, 0.42) LPV/r: 1.5 (1.2, 1.8)	EFV: 0.38 (0.30, 0.50) LPV/r: 1.6 (1.2, 2.1)	EFV: 0.30 (0.25, 0.36) LPV/r: 1.3 (1.1, 1.6)	Efavirenz significantly decreased the etonogestrel

ART evaluated	Hormones evaluated	Study groups	Study design	Hormone AUC Ratio ART:Control	Hormone Cmax Ratio ART:Control	Hormone Cmin Ratio ART:Control	Clinical conclusions by study authors
			study; hormone PK evaluated over 24 weeks of combined use.				exposure, while lopinavir/ ritonavir significantly increased exposure. Efavirenz may reduce the effectiveness of etonogestrel implants.
Efavirenz and Nevirapine [63][a]	Levonorgestrel	Efavirenz-based ART (n=20) Nevirapine based ART (n=20) HIV-positive controls (n=17)	Prospective, non-randomized, parallel group study; hormone PK evaluated over 48 weeks of combined use.	EFV: 0.53 (0.52, 0.54) NVP: 1.30 (1.25, 1.37)	EFV: 0.43 (0.41, 0.47) NVP: 1.28 (1.19, 1.43)	EFV: 0.43 (0.42, 0.44) NVP: 1.14 (1.14, 1.16)	Efavirenz significantly decreased levonorgestrel, paired with observed, unintended pregnancies during the study (3 of 20; 15%). In contrast, nevirapine did not significantly impact levonorgestrel exposure.
Tenofovir/Emtricitabine [38]	Levonorgestrel	Tenofovir/emtricitabine (n=17) Placebo (n=12)	Prospective, randomized, placebo-controlled study of TDF/FTC for PrEP; hormone PK evaluated over 36 weeks of combined use.	…	…	…	Average exposure was not different between groups, measured via linear mixed modeling. (TDF/FTC group estimate= − 67.3 pg/mL, 95% CI: − 194.7, 60.0)

Abbreviations: ART, antiretroviral therapy; ATV/r, atazanavir/ritonavir; AUC, area under the concentration time curve; Cmax, maximum concentration; Cmin, minimum concentration; COC, combined oral contraceptive; EE, ethinyl estradiol; EFV, efavirenz; ENG, etonogestrel; HIV, human immunodeficiency virus; LNG, levonorgestrel; LPV/r, lopinavir/ritonavir; PK, pharmacokinetic; POP, progestin-only oral contraceptive; PrEP, pre-exposure prophylaxis

*p<0.05

**p<0.01

[a]Data presented as Geometric Mean Ratio (90% Confidence Interval)

[b]Data presented as Least Squares Mean Ratio (90% Confidence Interval)

[c] Data presented as Geometric Mean Ratio (95% Confidence Interval)

[d] Data presented as Median (Interquartile Range)

[e] Data presented as Geometric Mean (Interquartile Range)