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FAMILY PLANNING (A BURKE, SECTION EDITOR)

Interactions Between Hormonal Contraception and Anti-Retroviral Therapy: an Updated Review

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Abstract

Purpose of Review Hormonal contraception provides women living with HIV the ability to control their fertility and avoid pregnancy-related morbidity. Due to shared metabolic pathways, there has been concern over drug-drug interactions between hormonal contraception and anti-retroviral therapy, which may affect the drugs' safety and efficacy. This article aims to provide an updated review of the most recent data around hormonal contraceptives and anti-retroviral therapy.

Recent Findings Prior data have suggested possible pharmacologic interactions between certain hormonal contraceptives and anti-retroviral therapy. The most significant interactions implicated include those between progestin-based contraceptive implants and efavirenz as well as between combined hormonal contraceptives and protease inhibitors. Most past studies, however, feature small sample sizes with few clinical outcomes reported.

Summary Recent data since 2017 have largely affirmed prior studies on this topic, showing possible pharmacokinetic relationships between certain contraceptives and anti-retrovirals. Notably, while the effectiveness of progestin-based contraceptives, specifically the implant, appears reduced with efavirenz use, the overall effectiveness may remain higher than most other contraceptive methods. Larger studies are needed to provide further guidance before contraceptive-prescribing recommendations can be changed.

Keywords HIV · Anti-retroviral therapy · Contraception · Hormonal contraception

Introduction

As of 2018, approximately 37.9 million people globally are living with HIV [1]. Women share a significant burden of the disease, making up nearly half of all adults living with HIV and 61% of all persons 15–24 years old living with HIV [2]. For these women, unintended pregnancy remains a major concern as it is estimated that up to 78% of pregnancies are unintended [3]. Beyond the adverse outcomes associated with unintended pregnancy for all women, such as low birth weight and preterm birth, unintended pregnancy among women living with HIV (WLHIV) has been associated with worse virologic control and increased perinatal HIV transmission [4–6]. Hormonal contraception is a central component in preventing unintended pregnancy.

Anti-retroviral therapy (ART) has vastly reduced rates of mortality and complications from HIV as well as transmission risk of HIV to uninfected partners. First line combination therapy usually consists of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse transcriptase inhibitor (NNRTIs), an integrase strand transfer inhibitor (INSTIs), or a protease inhibitor (PI) [7]. As the use of both ART and hormonal contraception expands globally, there has been increasing concern over drug-drug interactions. After first pass metabolism in the intestines or liver, hormonal contraceptives are then metabolized through cytochrome (CYP) P450 enzymes in the liver [8]. ART can affect this metabolism by altering gut metabolism, inducing or inhibiting the effects of the CYP pathways, as well as affecting glucuronidation [8]. This can alter levels of hormone and/or anti-retroviral drugs. Concerning interactions are those that may either increase the side effects or failure rates for the contraceptive or reduce the efficacy or increase side effects associated with the anti-retroviral regimen.

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This article aims to review the available literature on interactions between hormonal contraception and ART, with a specific focus on recent data on this topic.

Methods

We performed a literature review using PubMed and EMBASE, identifying English-language peer-reviewed articles published from January 2017 to January 2020. This time frame was selected given a recent systematic review published in 2017 that included studies up until December 2016 [9••]. Search terms used included HIV, contraception, hormonal contraception, birth control, anti-retroviral, as well as generic names of ART and contraceptive components (Tables 1 and 2). We included studies that analyzed interactions between hormonal contraceptives and ART with a focus on efficacy and safety of the hormonal contraceptive method and/or the ART studied. We considered studies that evaluated both clinical outcomes as well as pharmacologic measures of drug or hormone concentrations. We excluded studies discussing PrEP and ones that discussed contraceptive methods and HIV without mentioning ART use. We synergized these results with those from the prior 2017 systematic review [9••].

Results

The results of our literature review, combined with those from prior systematic reviews, are summarized by contraceptive method (Table 3).

Table 1 Anti-retroviral therapies by drug class

Drug Class	
NRTIs Inhibits reverse transcriptase	Abacavir Emtricitabine Lamivudine Tenofovir disoproxil fumarate Zidovudine
NNRTIs Binds reverse transcriptase and alters function	Doravirine Efavirenz Etravirine Nevirapine Rilpivirine
PI Inhibits HIV protease	Atazanavir Darunavir Fosamprenavir Ritonavir Saquinavir Tipranavir
Fusion inhibitors Inhibits fusion of virus with CD4 cell membrane	Enfuvirtide
CCR5 antagonists Inhibits CCR5 coreceptors to prevent HIV viral entry	Maraviroc
Integrase inhibitors Prevents integration of viral DNA into human DNA	Dolutegravir Raltegravir
Post-attachment inhibitor Block CD4 receptors used for HIV entry	Ibalizumab-uiyk
Pharmacokinetic enhancers Boost effectiveness of other anti-retrovirals	Cobicistat

NRTIs, nucleoside reverse transcriptase inhibitors; *NNRTIs*, non-nucloeside reverse transcriptase inhibitors; *PI*, protease inhibitors

Table 2 Hormones used in contraceptive methods

Contraceptive method	Estrogen	Progestin
Oral contraception	Ethinyl estradiol	Drospirenone Levonorgestrel Norethindrone acetate Desogestrel Norgestrel Ethynodiol diacetate Norethindrone Norgestimate Cyproterone Nomegestrol Acetate
Patch	Ethinyl estradiol	Norelgestromin
Ring	Ethinyl estradiol	Etonogestrel
Injectable	None	Depot Medroxyprogesterone acetate (DMPA)
Implant	None	Etonogestrel Levonorgestrel
Intrauterine device	None	Levonorgestrel
Emergency contraception	None	Ulipristal acetate Levonorgestrel

Combined Hormonal Contraceptives

Combined hormonal contraceptives (CHC) are formulated by a combination of estrogen, most commonly ethinyl estradiol, and a progestin. CHC can come in the form of a daily oral pill, a weekly patch, or a monthly vaginal ring. The CDC Medical Eligibility Criteria for Contraceptive Use (MEC) Use (MEC) lists CHCs as category 1 or 2 for most ART (no restrictions/advantages generally outweigh risks) [23]. The protease inhibitor fosamprenavir (FPV), however, is listed as category 3 (theoretical or proven risks outweigh advantages). This is due to concern over

Table 3 Summary of interactions between hormonal contraceptives and anti-retroviral therapy

ART drug class	CHC	POP	Implant	DMPA	LNG-IUD	EC
NRTIs	No effect [9••]	-	No effect [9••]	No effect [9••]	-	-
NNRTIs Efavirenz	↓ Progestin [9••, 10] ↓ Ethinyl Estradiol [10]	-	↓ Progestin [11–14] ↑ Pregnancy rate [11, 15••, 16]	↓ Progestin vs. no change [9••, 17]	-	↓ Progestin [18]
Nevirapine	↓ Progestin vs. no change [9••] ↓ Ethinyl Estradiol vs. no change [9••]	-	↓ Progestin [9••]	↓ Progestin vs. no change [9••, 15••]	-	-
PI	↑ Progestin [9••, 10, 19, 20] ↓ Ethinyl Estradiol [9••, 10, 20]	↑ Progestin [21]	↑ Progestin [9••]	↑ Progestin [9••, 22]	-	-
CCR5 Antagonists	No effect [9••]	-	-	-	-	-
Integrase Inhibitors	↑ Progestin vs. no change [9••]	-	-	-	-	-

NRTIs, nucleoside reverse transcriptase inhibitors; *NNRTIs*, non-nucleoside reverse transcriptase inhibitors; *PI*, protease inhibitors; *CHC*, combined hormonal contraception; *POP*, progestin-only pills; *DMPA*, depot medroxyprogesterone acetate; *LNG-IUD*, levonorgestrel intrauterine device; *EC*, emergency contraception

decreased levels of FPV with CHC use, although this recommendation is based on scant data, largely from small studies published by the manufacturer [23, 24].

The 2017 systematic review showed little clinical significance in the interactions between combined oral contraceptives (COCs) and ART evaluated at that time, although some pharmacokinetic changes, such as decreased ethinyl estradiol levels, were noted with use of COCs and PI or NNRTIs [9••]. A 2019 prospective cohort study further assessed pharmacokinetics of COCs in fifteen HIV-positive women using ritonavir-boosted PI over a single cycle of COC use. Study findings were notable for significantly higher levonorgestrel exposure than the control group with increased AUC_{last}, C_{min}, and C_{max} [19]. The authors attributed this to CYP inhibition by ritonavir, resulting in increased levels of levonorgestrel. The study, however, did not detect a difference in ethinyl estradiol pharmacokinetics, in contrast to some prior studies finding decreased ethinyl estradiol levels associated with ritonavir use [9••]. Lastly, progesterone levels through the COC cycle were noted to be uniformly low, indicating effective ovulation suppression; however, clinical data on adverse effects or contraceptive failure were not available. Overall, these findings were consistent with prior data on COC use in those taking ritonavir [25].

Fewer data are available on the effects of the contraceptive patch and ring. The 2010 AIDS Clinical Trial Group Protocol A5188 study investigated the interactions between PI (lopinavir/ritonavir) and the contraceptive patch (ethinyl estradiol/norelgestromin) [20]. Women using the patch were found to have a 45% decrease in the AUC of ethinyl estradiol, similar to effects on ethinyl estradiol AUC seen with COCs, and an 83% increase in norelgestromin. Decreased progesterone levels were noted on both arms, suggesting ovulation suppression; however, pregnancy rates were not reported. The sample size for this study was small, with only eight women in the PI arm.

More recently, a 2019 *Lancet* article explored the pharmacokinetics between ART and the contraceptive ring (ethinyl estradiol/etonogestrel) [10]. Eighty-four HIV-positive women were non-randomly assigned to a control group (not yet using ART), an efavirenz group, and an atazanavir-ritonavir group. Weekly serum hormone and HIV NAAT levels were measured over a 21-day ring cycle. The efavirenz arm had 79% lower etonogestrel and 59% lower ethinyl estradiol concentrations compared with control groups ($p < 0.0001$), while the ritonavir-boosted atazanavir group had 71% higher etonogestrel and 38% lower ethinyl estradiol concentrations. Despite the lower hormone concentrations noted in the efavirenz arm, adverse effects were similar among the three arms, and undetectable levels of progesterone on day 21 were noted in the efavirenz group. Similarly, the efavirenz C_{min} was 36% lower during hormone use, but remained above the concentration level threshold believed to be needed for drug effectiveness.

Progestin-Only Methods

The progestin-only methods encompass a wide variety of medications including progestin-only pills (POPs), intramuscular depo medroxyprogesterone acetate (DMPA), the contraceptive implant, the levonorgestrel intrauterine device (IUD), and emergency contraception (EC).

The CDC MEC considers DMPA to be category 1/2 for all ART regimens [23]. Per a 2012 review article, most existing evidence had not yet demonstrated significant clinical implications between DMPA and ART use; however, the 2017 review did show increased medroxyprogesterone concentrations with concurrent use of PI in certain pharmacokinetic studies [9, 22]. One recent retrospective cohort study of 24,560 women in Kenya found slightly higher pregnancy incidence for nevirapine-based ART compared with efavirenz-based regimen, although this difference was not statistically significant [15••].

Given that efavirenz and nevirapine are known CYP inducers, a secondary analysis of a randomized controlled trial published in 2019 investigated medroxyprogesterone acetate (MPA) concentrations in women taking NNRTIs [17]. MPA concentrations were found to be significantly lower in HIV-positive women on these NNRTI-based ART compared with HIV-negative women on DMPA at 4 and 13 weeks after injection initiations. Notably, two HIV-positive women had MPA concentrations below 100 pg/mL, the presumed contraceptive threshold of efficacy, although no pregnancies were observed over the 26-week study period. No clinically significant findings were noted in the study.

The contraceptive implant, composed of either etonogestrel or levonorgestrel, is among the most effective methods of long-term pregnancy prevention. The current CDC MEC lists the implant as category 1/2 for all ART [23]. There has been concern, however, of contraceptive failure with the implant when used with certain ART. A 2016 pharmacokinetic study of women taking efavirenz who were using levonorgestrel implants reported three pregnancies among 20 women (15%) over the 48 weeks of observation [11], substantially higher than the rate anticipated with a method with a reported pregnancy rate of less than 1 in 100. The study also found significantly lower levonorgestrel levels in efavirenz users. Another notable study implicating drug-drug interactions between contraceptive implants and efavirenz was a 2015 retrospective cohort study by Patel et al. in Kenya [15••]. Among women using both levonorgestrel and etonogestrel implants, adjusted pregnancy incidence was significantly higher in the efavirenz-based ART groups when compared with nevirapine-based ART groups (3.3 vs. 1.1 per 100 women-years). It is important to note, however, that rates of pregnancy with use of the implant were still substantially lower than with other non-long-acting and non-permanent

methods of contraception, even among women using efavirenz-containing ART regimens.

Newer data continue to support these initial findings. A retrospective observational study of 148 women using contraceptive implants at an HIV clinic in Uganda found a 6.1% pregnancy incidence, all which were conceived while on an efavirenz-based ART regimen [16]. No pregnancies were noted in the non-efavirenz-based groups. A 2019 pharmacokinetic study of contraceptive implant concentrations in HIV-positive women on efavirenz-based therapy found significantly reduced levels of both levonorgestrel and etonogestrel by 49%, respectively [12]. One woman in the efavirenz-containing study group was found to be pregnant. These results were similar to a 2017 pharmacokinetic study of etonogestrel levels between patients receiving efavirenz or nevirapine-based contraception compared with ART-naïve patients [13]. After 24 weeks, etonogestrel exposure was 82% lower in those on efavirenz-based regimens, whereas drug levels were not significantly impacted by nevirapine-based regimens. A recent study of Ugandan women using efavirenz-based therapy also implicated potential pharmacogenetic variations in CYP2B6 enzymes that were associated with lower levonorgestrel C_{max} and AUC in this population [14].

While these recent data have brought into question the effects of ART on hormone safety and efficacy, other studies have shown less concerning effects of progestin-based contraception on ART efficacy. A 2017 prospective cohort study of 1079 HIV-positive women using injectables, implants, or oral hormonal contraception and initiating ART did not find significant differences between self-reported hormonal contraception use and rates of plasma viral suppression or genital viral shedding [26]. More recently, a 2018 randomized controlled trial of 68 HIV-positive women assessed HIV genital tract shedding in women on ART randomized to either DMPA or levonorgestrel implant [27]. Of note, approximately 80% of women receiving ART were on efavirenz-based regimens. The study found that initiation of DMPA or levonorgestrel implant was not associated with increased genital shedding of HIV during the first 6 months of use.

Levonorgestrel-containing intrauterine devices (LNG-IUD) are another long acting, highly effective, and reversible method of contraception. CDC MEC categorizes LNG-IUD as category 1/2 for ART use [23]. A 2012 review did not note any changes in serum LNG levels in women taking ART or differences in HIV viral loads or pregnancy rates while using the LNG-IUD [22]. Thus, the LNG-IUD remains a viable and effective option for those seeking long-acting contraception.

There are limited data on the effects of ART on progestin-only pills (POP) and EC. POPs are listed as category 1/2 under CDC MEC recommendations [23]. A 2015 prospective study of women taking norethindrone and PI compared with other ART regimens or no ART demonstrated no significant changes in cervical mucous score, suggesting comparable contraceptive efficacy between these groups [28]. A pharmacokinetic study in 2015 of HIV-positive women taking norethindrone while on ritonavir-boosted PI regimens, however, showed increased $AUC_{0–24}$ and maximum serum concentration of norethindrone suggesting that POPs exhibit greater drug exposure when taken with PI [21].

Hormonal EC can consist of levonorgestrel or ulipristal acetate, a progesterone receptor modulator. A 2012 prospective study followed pharmacokinetics of HIV-negative patients following single dose of levonorgestrel while taking efavirenz [18]. Levonorgestrel AUC_{12} and C_{max} were noted to be significantly reduced by 56% and 41%, respectively. More recent data on POPs and EC were not available as of this review.

Discussion

The pharmacology around anti-retroviral therapy and hormonal contraception is complex. Most data available are from pharmacokinetic and pharmacodynamic studies with short study periods and small sample sizes. The most notable interactions seen in the literature thus far implicate decreased efficacy of progestin-based contraceptive implants with efavirenz-based regimens, with higher pregnancy rates compared with those using non-efavirenz-containing methods. Importantly, the pregnancy rates among these implant users are still lower than those using most other methods of contraception. Of note, many of these studies had small sample sizes and were not powered to assess contraceptive effectiveness and pregnancy rates, and thus, the clinical implications of these pharmacokinetic hormonal changes require further study. Additionally, many study periods were short, only assessing single menstrual cycles of contraceptive use and not long-term effects of contraceptive or ARV efficacy.

There are also pharmacologic data implicating drug-drug interactions between CHC and efavirenz; however, clinical consequences are still unknown. Ultimately, larger studies are required to assess the full clinical implications of these pharmacologic studies to assess if changes in hormone levels result in contraceptive failure (i.e., unintended pregnancy) or in supratherapeutic side effects ranging from breakthrough bleeding to venous thromboembolism.

While data is overall limited on the effects of hormonal contraception on ARV efficacy, recent randomized controlled trials have shown no effect between HC and genital tract shedding or plasma HIV concentrations [26, 27]. Further studies are needed to better understand this relationship given small sample size [26] in one randomized controlled trial. These results, however, are

in line with past studies on cervicovaginal shedding with concomitant use of both contraception and anti-retrovirals [29, 30].

A recent pharmacokinetic modeling study has suggested some strategies to help overcome this drug-drug interaction [31••]. Physiologically-based simulated pharmokinetic models utilized virtual individuals with placement of two 75 mg levonorgestrel implants (150 mg total dose) and four 75 mg implants (300 mg total dose). Models showed that low plasma levels of levonorgestrel persisted despite dose decreases in efavirenz; however, increased dosing of levonorgestrel (300 mg from 150 mg) restored levonorgestrel concentrations to levels similar to no ART controls receiving a 150 mg levonorgestrel dose. While these findings suggest important pharmacokinetic adjustments, further clinical research is needed to provide better recommendations and guidelines for dose modifications of hormonal contraception.

Women living with HIV should still be offered comprehensive contraception counseling to prevent perinatal complications from unintended pregnancy. Public health efforts have explored integrating family planning and ART services, with some studies showing increase in contraceptive use from 28% to 62% and a 66% decrease in unintended pregnancy rates [32]. A patient-centered counseling approach about potential risks of combining contraception methods with ART medications balanced with the benefits of family planning and pregnancy prevention will allow patients to make the best decision for themselves and their families.

Conclusions

Hormonal contraception can provide HIV-positive patients the ability to plan pregnancy and fertility in a safe fashion. While current evidence does implicate some potential drug-drug interactions between certain anti-retroviral therapy and hormonal contraceptives, the clinical implications of these interactions are still unclear. Furthermore, hormonal contraception does not appear to significantly alter the efficacy of anti-retrovirals. While further data are being studied, HIV-positive patients should still be counseled on the existing data on these drug-drug interactions and the ambiguities of this data. Patients should still be offered the full spectrum of family planning options, and contraceptive counseling should continue to be integrated into routine care for these patients.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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