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Effects of Hormonal Contraception on Anti-Retroviral Drug Metabolism, Pharmacokinetics and Pharmacodynamics

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Abstract

Among women, human immunodeficiency virus type 1 (HIV-1) infection is most prevalent in those of reproductive age. These women are also at risk of unintended or mistimed pregnancies. Hormonal contraceptives (HCs) are one of the most commonly used methods of family planning world-wide. Therefore concurrent use of HC among women on anti-retroviral medications (ARVs) is increasingly common. ARVs are being investigated and have been approved for pre-exposure prophylaxis (PrEP), and therefore drug-drug interactions must also be considered in HIV-1 negative women who want to prevent both unintended pregnancy and HIV-1 infection. This article will review four main interactions: (1) the effect of HCs on ARV pharmacokinetics (PK) and pharmacodynamics (PD) during therapy, (2) the effect of ARVs on HC PK and PD, (3) the role of drug transporters on drug-drug interactions and (4) ongoing research into the effect of HCs on pre-exposure prophylaxis PK and PD.

Keywords

Hormonal contraceptives; anti-retrovirals; drug-drug interactions; HIV mucosal acquisition

Introduction

Globally, 34 million people are currently infected with human immunodeficiency virus type 1 (HIV-1), and incident infections are more common in women than men, especially in sub-Saharan Africa¹. Recent data from the Microbicide Trials Network's Vaginal and Oral Interventions to Control the Epidemic (VOICE) study revealed HIV-1 incidence at clinical sites as high as 9%, especially in young, single women². The prevalence of HIV-1 in South Africa (SA) has increased from 10.6% in 2008 to 12.3% in 2012, according to data presented recently at the 6th SA Acquired Immunodeficiency Syndrome (AIDS) Conference in Durban. Condom use 'at last sex' has fallen in all age groups, most dramatically from 85.2% to 67.4% among men aged 15 to 24 and from 66.5% to 51% in women of the same age³.

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Almost half of all pregnancies worldwide, estimated to be over 100 million annually, are unintended⁴⁻⁶. Among women worldwide who reported using any contraceptive method at last intercourse, hormonal contraceptives (HCs), including the oral hormonal contraceptive pills, implants and injections were the second most common method used, after female sterilization⁷. Poverty, malnutrition, lack of education and gender inequality fuel both unplanned pregnancies and HIV-1 transmission. There are a significant number of women, especially in less developed countries, needing protection against sexually transmitted infections (STIs), in particular HIV/AIDS, and long-term, highly effective contraceptive methods to prevent unplanned or mistimed pregnancies and provide optimal birth spacing and family size.

The overlap between the goals of family planning, HIV-1 treatment and HIV-1 prevention is significant. For example, HIV-1 positive women now live longer, desire to have children and plan their families. Women at risk of acquiring HIV-1 increasingly seek highly effective methods of contraception. The interaction between antiretrovirals (ARVs) and HCs is therefore inevitable and must be studied in detail. For public health researchers, HCs are often used in HIV-1 prevention trials using investigational pre-exposure prophylaxis (PrEP) products. For example, in the CAPRISA 004 trial of tenofovir (TFV) 1% vaginal gel, 80% of participants were using injectable progestins, like depot medroxyprogesterone acetate (DMPA) for contraception⁸. In a trial of an efavirenz-based regimen in HIV-1 positive individuals, approximately 80% of the women were using HCs⁹. It is important for investigators to understand the potential pharmacodynamics (PD) and pharmacokinetic (PK) interactions between HCs and ARVs in order to interpret trial endpoints in HIV-1 prevention and treatment trials.

Biological Basis for Hormonal Contraceptive/Anti-Retroviral Interactions

The main biologic basis for the interactions between HCs and ARVs is based on the fact that HCs, protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are metabolized by the cytochrome P450 system. PIs and NNRTIs can both inhibit or induce the cytochrome P450 3A (CYP4503A) enzymes, which are the key enzymes involved in the metabolism of contraceptive steroid hormones^{10,11}. For example, ethinyl estradiol (EE), the estrogenic component in most oral contraceptive pills (OCPs), is hydroxylated by the hepatic enzymes CYP2C9 and CYP3A4¹². The CYP3A4 enzyme is crucial in the metabolism and clearance of DMPA¹⁰. Efavirenz, an NNRTI, is an inducer of CYP3A4¹³. These drug-drug interactions between ARVs and the cytochrome P450 system are utilized to increase concentrations of various ARVs, giving name to the term “PI boosted” regimens. For example, ritonavir, a PI, inhibits CYP3A4, an enzyme which normally metabolizes other PIs. Therefore, by including a low dose of ritonavir in highly active anti-retroviral treatment (HAART) regimens, this inhibition of CYP3A4 can increase the concentration of other PIs used in the combinations^{14,15}. Finally, although individual PK interactions between HCs and HAART or PrEP regimens can be modeled and tested, large studies are needed to determine if PK interactions result in changes in clinically significant outcomes, such as pregnancy, CD4 counts and HIV-1 viral load¹⁶.

Another possible mechanism contributing to PK and PD interactions involves the role of drug transporters. Many compounds are transported from the lumen (for example, gut) by uptake drug transporters for phase I and phase II enzyme metabolism (for example in the kidney or liver), and then transported out of the metabolizing site for elimination by efflux transporters¹¹. Both ARVs and HCs use drug transporters, to varying extent, for uptake, metabolism and elimination. In fact, nephrotoxicity from oral TFV has been modeled in mice, utilizing selective knock-out models of the uptake drug transporter OAT1 and the efflux transporter MRP4¹⁷. Although the function of drug transporters is well understood in the gut, kidney and liver, there is a paucity of data describing relevant drug transporters in the female reproductive tract¹⁸. However, there is modest to high mRNA expression in human and mouse cervicovaginal tissue of drug transporters involved in ARV efflux and uptake, which would be relevant for topically applied ARVs or for ARVs delivered vaginally¹⁸.

5'-nucleotidases are a group of cytosolic enzymes that regulate the pool of cellular nucleotide and nucleoside levels by catalyzing the dephosphorylation of nucleoside monophosphate¹⁹. The activation of nucleoside analogs, such as emtricitabine, can be inhibited by an increase in nucleotidase activity²⁰. The 5'-nucleotidases are regulators of nucleotide and drug metabolism²⁰. Studying the effect of TFV on immune cells isolated from peripheral blood mononuclear cells, it was observed that TFV altered expression of two of the seven 5'-nucleotidase genes, NT5E (CD73) and NT5M, but had no effect on any of the intracellular 5'-nucleotidases. TFV specifically increased NT5E and decreased NT5M gene expression in macrophages and DCs, with no changes in message observed in CD4⁺ T cells²¹. Estradiol, in turn, increased expression of cytosolic 5'-nucleotidase after 2 or 4 h in endometrial epithelial cells but not epithelial cells or fibroblasts from other female reproductive tract (FRT) sites. In studies using a modified 5'-nucleotidase biological assay for nucleotidases, estradiol increased nucleotidase activity in epithelial cells and fibroblasts from the FRT at 24 and 48 h²².

These examples suggest that interactions between HCs and ARVs can occur at different cellular and molecular levels. A description of the PK and PD effects of these interactions follows.

Effect of Hormonal Contraceptives on Anti-Retroviral Pharmacokinetics and Pharmacodynamics

In general, detailed PK studies support that concomitant use of HCs does not significantly alter the PK of NRTIs, PIs or NNRTIs. All currently recommended first-line HAART regimens for treatment-naïve HIV-1 positive patients include tenofovir disoproxil fumarate (TDF) marketed under the brand name Viread® (Gilead Sciences)²³. TDF alone or in combination with emtricitabine (FTC; brand name Truvada®; Gilead Sciences) is also a leading drug in PrEP regimens. Therefore, TDF is an essential drug in both HIV-1 prevention and treatment. Fortunately, TDF is a nucleotide analogue reverse transcriptase inhibitor (NRTI) and is not metabolized by cytochrome P450 enzymes. The only published drug-drug interaction study of TDF and combined OCPs was done with 20 women using a very popular 35 ug EE and triphasic norgestimate (NGM) (0.18/0.215/0.25 mg) regimen

(marketed as Ortho Tri Cyclen® and other generic brands)²⁴. These data support that concomitant administration of EE/NGM and TDF did not alter the levels of contraceptive steroids or TDF²⁴. The first FDA-approved drug to be used to treat patients with HIV-1 was zidovudine or azidothymidine (AZT), another NRTI. This drug is still widely used in HIV-1 treatment, particularly in less developed countries and is included in the World Health Organization's (WHO) Model List of Essential Medicines²⁵. The use of combined OCPs or injectable progestins does not significantly alter the PK of AZT²⁶.

Two of the four recommended first-line HAART regimens to initiate in treatment-naïve patients include ritonavir (brand name Norvir®), a PI, combined to boost drug levels of other PIs (atazanavir or daunavir)²³. Ritonavir is used to “boost” the levels of other PIs 2 – 5 fold by inhibiting cytochrome P450 3A4 and 2C9, while subsequently inducing glucuronidation to facilitate transport¹⁵. However, there was some concern that ritonavir, in addition to boosting PI levels, might also alter EE and progestin levels, with concurrent HC use¹⁵. Two studies examined the effect of combined EE/progestin OCPs on ritonavir boosted atazanavir¹⁵ and ritonavir boosted darunavir²⁷. Both studies support that concomitant administration of combined OCPs and ritonavir boosted PIs did not significantly alter the systemic levels of the PIs^{15,27}. Additional studies also support that combined OCP use does not alter the PK of saquinavir²⁸ or nelfinavir²⁹, both PIs.

Summarized data from the World Health Organization, compiled in the Medical Eligibility Criteria 2010 guidelines³⁰, indicate that, in comparison to historic controls, oral or injectable contraceptive steroids did not alter systemic levels of the NNRTI nevirapine^{29,31}, but increased systemic levels of efavirenz, another NNRTI³², without significant toxicities or side effects. DMPA use did not significantly change clearance of efavirenz²⁹. These data are important because efavirenz is included in combination with TDF and emtricitabine in a once daily pill called Atripla, with the hope of simplifying regimens for HIV-1 positive patients. There are no published data on the drug-drug interactions between Atripla and HCs.

Therefore, in general, detailed PK analyses indicate that HIV-1 positive women on ARVs can be assured that concomitant HC use will not alter their ARV levels. While these PK assessments provide reassurance that ARV levels are not significantly lowered, they do not provide insight on alterations in ARV efficacy or the risk of resistance as a result of HC use.

Effect of Hormonal Contraceptives on Anti-Retroviral Treatment Outcomes

Data regarding the effect of concomitant HC use on ARV PD generally take the form of observational, longitudinal studies which follow HIV-1 positive women using ARVs with or without concomitant HC use, and track clinically relevant endpoints such as CD4 count, viral load, incidence of opportunistic infections and pregnancy. A study which followed women on combined OCPs, DMPA or levonorgestrel (LNG) implants who initiated HAART and age, race, pre-HAART CD4 count and viral load matched controls (no HC use, initiating HAART) found no difference in CD4 counts and achievement of undetectable viral loads, even after controlling for race, hepatitis C status, illicit drug use, education, income and utilization of health care services³³. There is always a concern in this type of study for switching HC methods or discontinuing methods mid-study. Therefore, trials that

track long-acting HC use, such as with an intrauterine system (IUS) or a HC implant, avoid this issue. For example, a 2 year longitudinal study of HIV-1 positive women on HAART compared LNG implant users to age and CD4 count matched condom users, and found no difference in CD4 count, the incidence of opportunistic infections and pregnancy³⁴. Similarly, a small study of 15 HIV-1+ women using the LNG IUS and age matched controls found no difference in HAART outcomes, CD4 counts and viral load³⁵.

Therefore, not only do detailed PK studies support that HC use does not significantly affect ARV PK, but large, epidemiologic studies support that clinically relevant outcomes in women using HAART do not appear to be significantly affected in an adverse manner by concomitant HC use.

Effect of Hormonal Contraceptives on PrEP Pharmacokinetics and Pharmacodynamics

ARVs are typically used for treatment of HIV-1 infected individuals. TDF and emtricitabine are available as a combined NRTI with the brand name Truvada, which is a common drug used in HAART regimens. Oral TDF was approved by the FDA in July 2012 as oral PrEP³⁶ in at-risk individuals, based largely on data from the iPrEX study³⁷ and the Partners Prep study³⁸. Macaque data support that injectable progestins do not alter the efficacy of Truvada, used as PrEP in a SHIV challenge model³⁹.

Currently, ARVs are also being developed as topical formulations of vaginal gels, tablets, films and intravaginal rings (IVRs), to be dosed in either a peri-coital or daily regimen for the prevention of HIV-1 acquisition in women. The only topical ARV with proof-of-concept data is TFV 1% gel, dosed in a peri-coital regimen⁸. As mentioned above, in the sentinel CAPRISA 004 trial, 80% of participants were on injectable progestins for contraception⁸. There is renewed interest in how HCs, particularly systemic injectable progestins such as DMPA, affect ARV PK and PD, due to multiple longitudinal studies which show an increased odds of acquiring HIV-1 among women using DMPA, compared to matched controls (reviewed in⁴⁰). In order to further elucidate the biological mechanisms which mediate this interaction, CONRAD recently completed a clinical trial (CONRAD A10-114, ClinicalTrials.gov # NCT01421368) to investigate the PK and PD of TFV vaginal gel in DMPA versus combined OCP users. In this study, women undergo extensive sampling for PK and PD endpoints in various phases of the menstrual cycle at baseline and then after administration of combined OCPs or DMPA. Data are under analysis and will provide important information regarding the effect of endogenous and exogenous hormones on the PK and PD of one of the lead PrEP products.

Effect of ARVs on HC Pharmacokinetics and Pharmacodynamics

Unintended pregnancy and HIV-1 acquisition are linked by the same behavior: unprotected intercourse. For HIV-1 positive women on ARVs who want to space or prevent pregnancy, they must be assured that the efficacy of their HC will not be altered by concomitant use of ARVs. Effective contraception is a critical component in preventing mother-to-child HIV-1 transmission, with one mathematical model demonstrating that increasing access to contraception could prevent 29% more HIV-1 positive births than increasing the use of antepartum nevirapine⁴¹.

The WHO³⁰, Center for Disease Control (CDC)⁴² and the American College of Obstetricians and Gynecologists (ACOG)¹⁶ have published guidelines on the concurrent use of HCs and ARVs. In general, these three organizations note that both NRTIs and NNRTIs are unlikely to alter the PK or PD of HCs, including the combined OCP, and contraceptive patches, IVRs or injections^{16,30,42}. The recommendations for concomitant use of HCs and NRTIs or NNRTIs come from several small PK studies which show that overall, NRTI or NNRTI use does not change the PK of estrogen and progestins^{13,24,32}. However, there are reports of decreases in EE levels following administration of nevirapine³¹.

When examining the drug-drug interactions between HCs and ARVs, several aspects of contraceptive efficacy must be considered. The main mechanism of action of combined estrogen and progestin containing OCPs is progestin suppression of the luteinizing hormone (LH) surge^{43,44}. However, the minimum level of progestin needed for efficacy is not completely known and progestin PK may be influenced by participant weight, metabolism, diet etc. Increases in progestin levels should not have obvious clinical significance on OCP efficacy. In terms of the estrogen component, decreases in EE levels may lead to breakthrough bleeding⁴⁵. Finally, increases in estrogen levels have been correlated with venous thromboembolism, but the incremental increase in the odds of thromboembolism has not been accurately correlated to incremental increases in estrogen levels. Importantly, the overall risk of deep vein thrombosis with estrogen containing contraceptives is quite low, at approximately 3.5/10,000 users^{16,46,47}.

Decreases in EE levels may prompt contraceptive side effects, such as breakthrough bleeding, but should not affect contraceptive efficacy. Increases in EE levels, which have been shown with some ARV regimens¹⁵, have a theoretical risk of increasing thrombogenic side effects, but the absolute risk is likely still quite low, being outweighed by the benefits of effective contraception. Some of these small PK studies have found that concomitant NRTI or NNRTI use can decrease progestin levels, which would theoretically compromise contraceptive efficacy¹³; however most authors note that the PK data may not translate into alterations of overall contraceptive PD.

The WHO, CDC and ACOG all caution women using PIs that there are theoretical or proven risks of PIs which may decrease the efficacy of estrogen and progestin containing OCPs, patches, IVRs or injections^{16,30,42}. These recommendations are based on unpublished data from the GlaxoSmithKline Study APV10020⁴⁸, which found significant decreases in both estrogen and progestin when HCs were co-administered with PIs. The other studies cited by WHO (reviewed in³⁰), regarding the effect of PIs on HC PK include package insert data from Abbot Laboratories (lopinavir and ritonavir), Agouron Pharmaceuticals (nelfinavir) and Merck (indinavir) and other independent PK studies²⁷, all of which show no significant alterations of the progestin component with concomitant PI use.

A benefit of delivering contraceptive steroids transdermally or vaginally is the peaks and troughs of oral administration can be avoided, allowing for a more stable steady state drug concentration^{49,50}. Data support that in contraceptive patch users, HAART causes a slight decrease in EE levels, but significantly increases the contraceptive progestin component, primarily by interaction with hepatic metabolism⁵¹.

Use of injectable progestins, such as DMPA, is less complicated among HIV-1 positive women using HAART, as all three organizations grade the concomitant use of ARVs and injectable progestins either a category 1 (unrestricted use) or a category 2 (theoretical risks are outweighed by benefits)^{16,30,42}. These recommendations are based on large clinical trials, such as the AIDS Clinical Trials Group (ACTG) A5093 protocol, which found no difference in DMPA PK among nelfinavir, efavirenz or nevirapine users compared to DMPA controls not on ARVs^{29,52}.

There are some potential concerns with women using HAART taking LNG based emergency contraception (EC), with a very relevant study demonstrating potentially significant drug-drug interactions between EC and efavirenz⁵³. Neural tube defects (NTDs) were found after first trimester efavirenz exposure in animal models⁵⁴ and national registry information also suggests a higher than expected level of NTDs in infants whose mothers were exposed to efavirenz in the first trimester⁵⁵. Thus efavirenz users need to have effective contraception or would need to rely on EC if primary methods of contraception failed. A small study found a 56% decrease in EC LNG concentrations with concomitant use of efavirenz, which they attributed to induction of efavirenz metabolism by LNG⁵³. This study did not monitor ovulation, and the exact mechanisms of EC are unclear, with varying success rates based on time taken in the menstrual cycle, but these data raise concerns about drug-drug interactions between a known teratogen and LNG EC.

Although only case reports, other data note contraceptive failures in women using the etonogestrel implant (Nexplanon®) while on ARV regimens that included efavirenz⁵⁶⁻⁵⁹. In each circumstance, the women had been using a properly placed contraceptive implant for months to years prior to diagnosis of the pregnancy and their HIV disease was well controlled on the ARV regimens. More data are needed on the drug-drug interactions between this highly effective and safe method of contraception while using a known teratogen like efavirenz.

Effect of Anti-Retrovirals on Clinically Relevant Hormonal Contraceptive Endpoints

ACOG summarizes the results of several small PK studies examining drug-drug interactions between ARVs and HCs by stating that “in the absence of clinical outcome studies, the practical implications of these PK observations are unknown”¹⁶. There are some data to suggest that the pregnancy rates of women using HC and ARVs are not different than historic controls of women using HCs alone⁹. Condoms would obviously be an ideal non-hormonal method of contraception for HIV-1 positive women, which would also prevent transmission of the virus^{60,61}; however condom use is highly dependent on partner acceptance of the method and some condoms are lubricated with nonoxynol-9, a surfactant based spermicide which has been linked to increased efficiency of HIV-1 transmission and acquisition⁶²⁻⁶⁴. Copper intrauterine devices (IUDs) offer several benefits to HIV-1 positive women, based on the fact that they are discreet, non-hormonal, long-acting, reversible and highly effective. The WHO classifies IUD initiation and continuation as a category 2 for women with HIV-1 or women at high risk for HIV-1, and a category 3 for women with AIDS³⁰, due to a higher risk of infection in women with AIDS.

Conclusions

In summary, the goals of family planning and STI prevention often overlap in women of reproductive age, and importantly, highly effective, commonly used medications for each pose the potential for important drug-drug interactions. These interactions are based on mutual effects, for instance, on cytochrome P450, drug transporters such as OAT1 and MRP4, and 5'-nucleotidases. Detailed PK studies indicate that ARV administration alters systemic levels of HCs, and vice versa, but the clinical relevance of these alterations have not played out in large observational studies, utilizing the endpoints of pregnancy, CD4 count, viral load and the incidence of opportunistic infections. As the field of HIV PrEP advances, questions have emerged as to how HCs affect cervicovaginal and rectal concentrations of ARVs administered systemically or topically. This in turn requires a better understanding of the role of factors that modify the cellular uptake and metabolism of ARVs, e.g., drug transporters, in those tissues. Finally, it is important to recognize that many women need effective contraception, control of HIV-1 infection and/or effective HIV prevention, and therefore PK/PD interactions must be clearly established to support guidelines and recommendations for the safe and effective use of these products.

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