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Potential risk of drug–drug interactions with hormonal contraceptives and antiretrovirals: prevalence in women living with HIV

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Abstract

Background: Family planning services are vital for women living with HIV (WLH); however, the use of concomitant antiretroviral therapy (ART) and hormonal contraceptives (HCs) may pose challenges due to the risk of potential drug–drug interactions (DDIs). The objectives of this study were to assess ART and HC use among WLH and quantify the frequency of potential DDIs between ART and HCs.

Methods: This was a retrospective, observational, cohort study of WLH aged 18–55 years, prescribed ART, with at least one clinic visit from January 1, 2010 to April 30, 2014. Potential DDIs between HCs and ART were assessed using the University of Liverpool HIV Drug Interactions website (www.hiv-druginteractions.org) and categorized as 'weak potential interaction,' 'potential interaction,' or 'do not co-administer.'

Results: Overall, a contraceptive method was reported in 167 (54%) of the 309 women included in the study. Of those using contraception, 73 (43.7%) reported using HCs, which was most frequently a progestin intrauterine device (*n*=43), progestin injection (*n*=17), or combination oral contraceptive pills (*n*=9). Out of a total of 449 ART regimens, a potential DDI was identified in 21 of 115 (18.3%) ART–HC combinations from 19 women using ART and HCs. Atazanavir/ritonavir was the most common potentially interacting ART (10, 47.6%); for HCs, these were combination oral contraceptive pills (16, 76.2%) and progestin implants (2, 9.5%).

Conclusion: In this cohort, one-quarter of WLH on ART–HCs had a potential DDI. Future studies should investigate the impact of DDIs on unintended pregnancies, the side effects of DDIs, and the effects of HC DDIs on ART concentrations.

Keywords: AIDS, antiretroviral agents, cisgender women, drug interactions, HIV, hormonal contraception, reproductive health, women.

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Introduction

It is imperative for women living with HIV (WLH) to be aware of the full range of contraception options and for healthcare providers to address the reproductive health needs of WLH, including contraception use, on an ongoing basis.[1] Data suggest that the desire for children and pregnancy rates are now similar among both WLH and women not living with HIV.[2,3]

Overall, a lower proportion of WLH use prescription contraceptive methods when compared to women not living with HIV.[2] Family planning barriers exist due to the potential for drug–drug interactions (DDIs) between hormonal contraceptives (HCs) and antiretroviral therapy (ART), with DDIs having the potential to jeopardize HC effectiveness, resulting in unintended pregnancies.[4] Mitigating DDIs to reduce unintended pregnancies may also help decrease mother-to-child transmission of the virus.[5] Given recent concerns with some integrase strand transfer inhibitors (INSTIs) and risk of teratogenicity, the prevalence of DDIs in all ART drug classes becomes relevant.[1]

As hormonal contraception is one of the most common methods of family planning,[6] this study sought to quantify the risk of potential DDIs between HCs and ART in an outpatient hospital-based infectious diseases clinic to inform clinicians who prescribe ART and/or contraception. The objectives of this

study were to assess ART and HC use among WLH and quantify the frequency of potential DDIs between ART and HCs.

Methods

This was a retrospective, observational, cohort study of WLH aged 18–55 years, receiving ART, who had at least one clinic visit from January 1, 2010, to April 30, 2014. Data collection included patient age, race/ethnicity, baseline CD4 T-lymphocyte count and HIV RNA level, ART and contraceptive use at each visit, and the number of clinic visits during the study period. An undetectable HIV RNA was defined as being below the lower limit of the assay used at the time it was drawn. All laboratory values were recorded from the date closest to the first clinic visit. Contraceptives were grouped into hormonal *versus* non-hormonal methods. Permanent contraception (e.g. sterilization, tubal ligation), the non-hormonal intrauterine device, and condom use alone were considered non-hormonal contraception. This study was reviewed and approved by the Institutional Review Boards of Northwestern University (July 2014; Chicago, IL, USA) and Midwestern University (May 2015; Downers Grove, IL, USA) and granted a waiver of informed consent.

ART use was recorded over time, with each ART regimen being evaluated separately due to their individual risk for a DDI. Therefore, there were more ART regimens assessed for DDIs than the total number of patients in the study. Potential DDIs between HC and ART were assessed using the University of Liverpool HIV Drug Interactions website (www.hiv-druginteractions.org) and categorized as 'weak potential interaction,' 'potential interaction,' or 'do not co-administer.' Weak potential interactions were predicted to be of weak intensity (less than twofold increase of area under the curve [AUC] or <50% decrease of AUC) or unlikely to impair contraceptive or ART efficacy. A potential interaction may require a dosage adjustment or close monitoring. A 'do not co-administer' interaction stated that the drugs should not be co-administered.

Statistical analysis

The primary outcome was the percentage of women with an identified potential DDI between ART and HCs. For assessment of age, the cohort was split into two groups based upon the median age in the study. Descriptive analyses were conducted using Intercooled Stata, version 15 (Statacorp, College Station, TX, USA).

Results

A total of 309 women met the criteria for study inclusion. The median age on entry was 37 years (interquartile range 28–45 years; range 16–55; 33 patients were aged >50 years) and the median number of clinic visits was 8 (interquartile range 5–13; Table 1). The majority of WLH were African American (*n*=162, 53.1%) and Caucasian (*n*=60, 19.7%). There were 449 total ART regimens used among the 309 women during the study period. The most commonly used ART regimens were based on ritonavir-boosted protease inhibitors (PIs) (*n*=288, 64.1%), followed by those based on non-nucleoside reverse transcriptase inhibitors (*n*=82, 18.3%) and on INSTIs (*n*=32, 7.1%).

Overall, a contraceptive method was reported in 167 (54%) of the 309 women included in the study. Of these methods, 92 (55.1%) were non-hormonal methods and 75 (44.9%) were HCs

Table 1. Socio-demographic variables of women living with HIV, *n*=309.

Baseline age, years (median, IQR)	37 (28–45)
Race/Ethnicity, *n* (%)	
Black (African American)	162 (52.4)
Caucasian	60 (19.4)
Black (African-born)	38 (12.3)
Hispanic (Not Black)	36 (11.7)
Other	9 (2.9)
Missing	4 (1.3)
Baseline CD4 T lymphocyte, cells/mm^3 (median, IQR)	402 (256–600)
Baseline HIV RNA undetectable[a], *n* (%)	158 (51.5)
Number of clinic visits (median, IQR)	8 (5–13)
Antiretroviral regimens during the study period (*N*=449 regimens), *n* (%)	
Ritonavir-boosted protease inhibitors	288 (64.1)
Non-nucleoside reverse transcriptase inhibitors	82 (18.3)
Integrase strand transfer inhibitors	32 (7.1)
Other	47 (10.5)

[a]Based upon the lower limit of lab sensitivity when drawn.

(of note, two women used two different HC methods during the study period). Non-hormonal methods included condoms alone (51, 55.4%), tubal ligation (30, 32.6%), non-hormonal intrauterine device (7, 7.6%), and hysterectomy (4, 4.3%). HC use included the progestin intrauterine device (43, 58.9%), progestin injection (17, 23.3%), combination oral contraceptive pills (OCPs) (9, 12.3%), progestin subdermal implant (3, 4.1%), vaginal ring (2, 2.7%), and the estrogen patch (1, 1.4%).

Of the reported contraceptive methods, condoms alone were the most commonly reported method for Caucasian and Black African-born WLH (*n*=9 for each). For African American WLH, the most commonly reported methods were the progestin intrauterine device (*n*=27), tubal ligation (*n*=23), and condoms (*n*=21). WLH equal to or older than the median age in the study (37 years) most commonly reported the use of condoms (*n*=28), tubal ligation (*n*=20), and the progestin intrauterine device (*n*=7). WLH younger than the median age most commonly reported the use of a progestin intrauterine device (*n*=36), condoms alone (*n*=23), and the progestin injection (*n*=15).

There were a total of 73 women on concurrent HCs and ART, with 115 unique regimens being checked for DDIs among these 73 women. A potential DDI was identified for 21 of 115 (18.3%) ART–HC combinations from 19 (26%) women using ART and HCs. Potential HC-ART DDIs were higher in African American WLH (*n*=11) and those under the median age of 37 years (*n*=11).

The ART regimens most likely to interact with HCs were atazanavir/ritonavir (10, 47.6%) and lopinavir/ritonavir (3, 14.3%), followed by darunavir/ritonavir (2, 9.5%), efavirenz (2, 9.5%), fosamprenavir/ritonavir (2, 9.5%), elvitegravir boosted with cobicistat (1, 4.8%), and etravirine (1, 4.8%). The interacting HCs used were combination OCPs (16, 76.2%), progestin implant (2, 9.5%), vaginal ring (2, 9.5%), and estrogen patch (1, 4.8%). Overall, in this cohort, there were 2 (9.5%) 'do not co-administer' interactions, 17 (81%) 'potential interactions,' and 2 (9.5%) 'potential weak interactions.' The use of combination OCPs and efavirenz was classified as having a 'do not co-administer' interaction. The use of combination OCPs with boosted PI-based regimens was classified as having a 'potential interaction.' Cobicistat (with elvitegravir) and combination OCPs was also classified as having a 'potential interaction.' The combination of a vaginal ring and atazanavir/ritonavir was classified as having a 'potential interaction.' The estrogen patch with fosamprenavir/ritonavir was classified as having a 'potential interaction.' Etonogestrel subdermal implants with atazanavir/ritonavir or darunavir/ritonavir were classified as having 'potential weak interactions.' Combination OCPs and etravirine was classified as having a 'potential weak interaction.' There were no DDIs identified with the progestin intrauterine device.

Discussion

In this study, 54% of WLH on ART were using a contraceptive method, and 44.9% of those were using HCs. Approximately one-quarter of WLH on HCs were taking an ART regimen with a risk for a DDI. Of these DDIs, the most common were with combination OCPs. The effect of DDIs may lead to contraception failure, thus reinforcing the need to assess reproductive health choices with each patient on an ongoing basis. A previous study noted that, between 2008 and 2014, the number of WLH using HCs significantly increased when compared to women not living with HIV.[2] The increase in the number of WLH using HCs further underscores the need for an ongoing discussion regarding family planning and DDIs.

Altered levels of hormones have implications for adverse effects in addition to concerns for contraceptive efficacy.[7] Ethinyl estradiol helps stabilize the uterine lining, and increased vaginal bleeding may occur if ethinyl estradiol levels decrease due to a DDI. The progesterone component of an HC needs to be high enough to prevent the endogenous hormonal surge (lutenizing hormone and follicle-stimulating hormone) that leads to ovulation. Thus, HC–ART DDIs that result in decreased progesterone levels may lead to unplanned pregnancies.[7] Other concerns of HC–ART DDIs include increases in hormone levels that can result in adverse effects, such as nausea, hypertension, or thromboembolism. In contrast to the effect of ART on HCs, HCs do not generally affect ART plasma concentrations and effectiveness.[7,8]

The World Health Organization,[9] the Centers for Disease Control,[10,11] the American College of Obstetricians and Gynecologists,[12] and the US Department of Health and Human Services[1,4] have all published guidelines regarding the concurrent use of HCs and ART. Overall, these organizations note that nucleoside reverse transcriptase inhibitors are unlikely to alter the pharmacokinetics or pharmacodynamics of HCs, including combination OCPs, contraceptive patches, intravaginal rings, or injections. However, there have been several publications noting the occurrence of unintended pregnancies with efavirenz and HCs.[13–18] Recent evidence recommends a dose reduction of efavirenz in women who are slow metabolizers of CYP 2B6 to reduce DDIs, although the clinical applicability of this is not yet known.[19] In contrast, there is a general lack of DDIs and no additional contraceptive protection needed when depot medroxyprogesterone acetate is used with ART due to the relatively high levels of medroxyprogesterone, the active component.[4,20] Of note, the Department of Health and Human Services guidelines state that the contraceptive effectiveness of the levonorgestrel intrauterine device is largely through local (i.e. intrauterine) release of levonorgestrel and not through systemic absorption, thus decreasing the potential for DDIs with ART.[4]

Many WLH using HCs may initiate ART or switch to ART with a low DDI potential such as an INSTI-based regimen.[1] Bictegravir, dolutegravir, and raltegravir do not have any clinically relevant effects on oral contraceptives and no dose adjustments are recommended.[1,7,21] As elvitegravir is coformulated with cobicistat, this INSTI has several DDIs of potential concern. Taking elvitegravir/cobicistat with drospirenone, a progestin, may lead to a potential for hyperkalemia, and monitoring

is recommended; norgestimate AUC and maximum and minimum concentrations increased by twofold and ethinyl estradiol AUC and minimum concentration decreased by 25 and 44%, respectively.[1] Due to these DDIs, an alternative contraceptive method or alternative ART is recommended. Present evidence suggests no clinically significant interactions with cabotegravir, currently an investigational INSTI, and HCs; however, further research is needed as oral formulations of contraceptives followed by cabotegravir in cisgender women not living with HIV have been associated with lower peak cabotegravir concentrations.[22,23]

Other DDIs with ART and HCs should be considered. When etravirine and OCPs are taken together, there is a potential decrease in ethinyl estradiol AUC but, as the progestin component is unchanged, contraceptive efficacy is unlikely to be impaired.[24] The dose of ethinyl estradiol in combination OCPs should be at least 35 mg if used concomitantly with atazanavir/ritonavir.[1] Previous studies found a 44% decrease in the AUC of ethinyl estradiol when used with darunavir/ritonavir,[25] a 55% decrease with lopinavir/ritonavir,[26] and a 37% decrease with fosamprenavir/ritonavir.[4] Ethinyl estradiol AUC was decreased by 25% with a minimum concentration decrease by 44% when taken with elvitegravir/cobicistat.[1,27] Levonorgestrel (oral) AUC decreases by 83% and norelgestromin AUC decreases by 64% when administered with efavirenz, and the interaction may be associated with levels of progesterone that fall below those needed to prevent ovulation.[1,28,29] An alternative contraceptive method or a reliable method of barrier contraception should be used when combination OCPs are taken with efavirenz.[4]

The etonogestrel subdermal implant may be used with atazanavir/ritonavir without the need for additional contraceptive protection whereas an alternative contraceptive method (or reliable barrier method) is warranted with darunavir/ritonavir.[4] Efavirenz use with the etonogestrel and levonorgestrel subdermal implants has been associated with lower progesterone levels, threatening contraception efficacy.[30–32] When the hormonal vaginal ring is used with ritonavir-boosted atazanavir, etonogestrel levels increase by 71% and ethinyl estradiol levels drop by 38%, suggesting that there is no associated drop in contraception efficacy.[33] When the vaginal ring was used with efavirenz-based ART, there were 79% lower etonogestrel levels and 59% lower ethinyl estradiol levels, threatening contraception efficacy.[33] The combination of an estrogen patch and fosamprenavir/ritonavir decreases the AUC of ethinyl estradiol by 37%,[4] which should not affect contraception efficacy. In our cohort study, there were no WLH on concurrent HC and PIs boosted with cobicistat; this combination has been noted to present a potential issue, especially with drospirenone-associated hyperkalemia.[34]

The limitations of this study should be considered when interpreting the reported results. All contraception use in our population may not have been systematically included in the electronic medical records. Furthermore, sterilization may not have been uniformly included into the electronic medical records and records were not assessed to confirm this method of contraception. Given the small number of potential DDIs, these results may not be generalizable to all WLH or to all possible HC–ART combinations such as the more concerning DDIs with HCs and efavirenz. There were also few INSTI-based regimens to assess given that the study was conducted in 2010–2014, and national guidelines for first-line treatment recommendations differed at this time; however, most of these regimens have fewer potential DDIs.[4] Additionally, this study did not record the intention of the cohort to become pregnant. As this was a retrospective study, the causality of the potential DDIs on any unintended pregnancies cannot be determined. Finally, this study assessed for potential DDIs and was unable to assess the actual effects of any DDIs if they had occurred.

Conclusion

The findings of this study emphasize the need for HIV providers to discuss family planning intentions with all patients at each visit, considering any potential HC–ART DDIs and adjusting ART as indicated. Further research should explore pregnancies that occur among WLH using HCs and the specific role of potential DDIs in those pregnancies. Future studies should also focus on the effects of HCs on newer ART concentrations such as INSTIs.

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