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REVIEW

Hormonal contraceptive use in HIV-infected women using antiretroviral therapy: a systematic review

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Background: While extensive research has explored pharmacokinetic interactions between antiretroviral therapy (ART) and hormonal contraception, few studies have examined whether these interactions affect clinical outcomes. To address this gap, we conducted a systematic review of the literature that describes hormonal contraceptive use among HIV-infected women who also use ART, focusing on papers that address clinically important outcomes such as pregnancy or ovulation.

Methods/design: An electronic literature search was conducted of PubMed and Ovid to identify all articles that addressed hormonal contraception co-administered with ART published in English between January 1, 1990 and October 30, 2014. In addition, manual reference checks of all articles of interest were conducted to identify articles not captured in the electronic search. Our search criteria identified 405 records. The title and abstract of data reports retrieved via the search were reviewed to identify potential articles of interest. Those with any indication of the main outcomes of interest were considered for inclusion (N=162). Abstracts were then reviewed to identify those manuscripts that would merit a review of the full-text version (N=64). Eight articles that addressed the outcomes of interest were identified. The Newcastle-Ottawa Scale was used to assess the quality of these articles.

Results: The studies reviewed were limited in a number of ways that precluded their providing a rigorous assessment of the efficacy of contraception when co-administered with ART.

Discussion: None of the studies were of adequate quality to provide the guidance that providers and HIV-infected women need when considering contraceptive options. High-quality, well-powered studies are required to address the efficacy of hormonal contraception when co-administered with ART.

Keywords: hormonal contraception, HIV, antiretroviral therapy, systematic review

Introduction

More than half of HIV-infected individuals worldwide are women, the majority of whom are of reproductive age.[1] In 2013, 3.2 million children under the age of 15 were living with HIV, representing 9.1% of all individuals living with HIV worldwide. Most of these children were infected perinatally.[1] Given that perinatal transmission is preventable with antiretroviral therapy (ART), access to ART is a World Health Organization priority.[2] Furthermore, as unintended pregnancies among HIV-infected women are more likely than planned pregnancies to result in HIV transmission to the infant,[1] there is also growing interest in the role of contraception as an additional tool to prevent maternal/child HIV transmission.[3,4]

However, if HIV-infected women are to benefit from effective contraception, and if new infections in children are to be prevented by encouraging women to plan

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their pregnancies, women and providers need to know that hormonal contraceptives will be effective in preventing pregnancy when co-administered with ART. Pharmacokinetic interactions between hormonal contraceptives and ART, primarily those that affect area under the concentration–time curve (drug bioavailability) and half-life, have been extensively documented. A number of case studies have also been published that suggest that these pharmacokinetic interactions may have clinical implications.[5–8] Whether the concerns raised in these studies translate into clinically significant alterations in contraceptive efficacy is not known.

This paper presents the results of a systematic review of the literature that explores the clinical efficacy of hormonal contraception when co-administered with ART. Prior to presenting these findings, we will review what is known from pharmacokinetic and case studies. We will briefly describe hormonal contraceptive methods, mechanisms of action, and metabolic pathways. We will also provide a similar review of ART. We will conclude by discussing clinical implications and areas for future research.

Background

Hormonal contraception

Overview of hormonal contraception

Hormonal contraceptives are among the most effective and most commonly used forms of contraception worldwide (Table 1).[9] All methods of hormonal contraception include a progestin (synthetic progesterone), and some also contain estrogen (usually ethinyl estradiol). The most commonly used methods are the following: 1) oral contraceptive pills that are taken daily and can contain either a progestin alone or combined estrogen and progestin, 2) hormonal patch containing estrogen and progestin that is applied weekly, 3) vaginal ring containing estrogen and progestin that is changed monthly, 4) injection of depot medroxyprogesterone acetate (DMPA) that is given every 3 months, 5) subcutaneous implants containing progestin (etonogestrel implant, one rod; levonorgestrel implant, two rods) that are effective for either 3 years or 5 years, and 6) intrauterine devices that contain progestin (levonorgestrel) and are effective for 3 years or 5 years.

Mechanism of action of hormonal contraception

Hormonal contraceptives prevent conception through several mechanisms, although the relative contributions of these different mechanisms are controversial.[10–13] A number of authors suggest that prevention of ovulation is the primary mechanism.[10] Combined hormonal contraceptives that include ethinyl estradiol and a progestin inhibit follicular development, ovulation, and thus the formation of the corpus luteum. These effects are driven by the inhibitory action of contraceptives on the production and secretion of both follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Either estrogen or progestin alone can inhibit FSH and LH sufficiently to prevent ovulation, but when used

Table 1 Hormonal contraceptives and efficacy

Contraceptive	Hormone(s)	Ideal use failure	Typical use failure	% of contraceptive users in the US	% of contraceptive users worldwide (estimated 661 million)
Combined oral contraceptive pills	Estrogen: ethinyl estradiol Progestins: gestodene, norethindrone, levonorgestrel, desogestrel, drospirenone, norgestrel, dienogest, norgestimate, ethynodiol diacetate	0.3%	9%	27.5%	16%
Progestin-only pills	Norethindrone, ethynodiol diacetate, levonorgestrel, desogestrel	0.3%	9%	–	Included in estimates of COCs
Combined contraceptive patch	Ethinyl estradiol + norelgestromin	0.3%	9%	0.7%	*
Combined contraceptive vaginal ring	Ethinyl estradiol + etonogestrel	0.3%	9%	2.2%	*
DMPA (or other injectables)	Medroxyprogesterone acetate	0.2%	6%	3.8%	6%
Levonorgestrel IUD	Levonorgestrel	0.2%	0.2%	5.6% (IUDs in general)	25% (IUDs in general)
Implants		0.05%	0.05%	0.5%	*
Single rod	Etonogestrel				
Double rod	Levonorgestrel				

Notes: *Other modern methods constitute 1% of contraceptive use worldwide. Data from Guttmacher Institute, Contraceptive use in the United States, Fact Sheet, 2014, http://www.guttmacher.org/pubs/fb_contr_use.pdf, accessed January 20, 2015.[69] Adapted from Reading BF. Growth in world contraceptive use stalling; 215 million women's needs still unmet [webpage on the Internet]. Washington, DC: Earth Policy Institute; 2012 [cited March 27, 2012]. Available from: http://www.earth-policy.org/data_highlights/2012/highlights26. Accessed October 27, 2014.[70]

Abbreviations: COCs, combined oral contraceptives; DMPA, depot medroxyprogesterone acetate; IUD, intrauterine device.

in combination, it is thought that the progestin component drives ovulation inhibition by blocking the midcycle LH rise, while the estrogen component acts primarily to potentiate the antiovulatory effects of progestins and to stabilize the endometrium to prevent irregular bleeding.[10]

However, other authors suggest that at the doses of estrogen and progestin that are used in modern oral contraceptives, low-dose progestins prevent pregnancy primarily by mechanisms other than suppression of ovulation.[13–15] The most important of these is thickening of the cervical mucus, leading to inhibition of spinnbarkeit and prevention of sperm penetration. Effects of progestins on the endometrium that result in atrophic changes, and possibly inhibition of follicular development and follicular atresia, may also play a role. Higher doses of estrogen and progestin than are used in hormonal contraceptives are required for an anovulatory effect.[13]

Metabolism and pharmacokinetics of hormonal contraceptives

The major enzyme system that determines an individual's ability to metabolize drugs and chemicals is the cytochrome P450 enzyme system. Cytochrome P450 occurs in different isoforms that vary in terms of chemical and immunological properties as well as substrate affinities.[16] Cytochrome P450 3A (CYP3A) is one of the most important of these isoforms, as it is found in metabolically active tissues such as the gastrointestinal tract and liver, and because it is the primary metabolic pathway for numerous medications.[17] Other enzyme systems include dehydrogenases, oxidases, esterases, reductases, as well as a number of conjugating enzyme systems such as the glucuronosyltransferases.[16] Ethinyl estradiol is metabolized through the cytochrome P450 liver enzyme system. Specifically, hydroxylation of ethinyl estradiol is catalyzed by CYP3A4 and CYP2C9.[18] Relatively little is known about the metabolism of progestins, but their metabolic pathways are more varied than those for ethinyl estradiol.[19]

Drug interactions and significance of alterations in the pharmacokinetic parameters of hormonal contraceptives

Because so many medications are metabolized by the cytochrome P450 enzyme system, drug–drug interactions are a common occurrence, with varying severity and clinical importance. Hormonal contraceptives interact with a number of different medications including ART, antibiotics, and antiepileptic medications.[20–22] These interactions are a source of concern, at least in theory, because decreased exposure to contraceptive hormones, either because of decreased bioavailability or because of more rapid clearance, could lead to decreased contraceptive efficacy. If, in contrast, bioavailability of the contraceptive hormones increases or clearance is reduced, significant side effects could result.

Antiretroviral therapy

Overview of ART

ART is recommended for all individuals diagnosed with HIV, regardless of CD4 count, to prevent both disease progression and transmission of HIV.[23] There are several classes of antiretroviral medications (Table 2), including nucleoside reverse transcriptase inhibitors (NRTIs) that form the backbone of most ART regimens, protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase inhibitors (ISTIs), CCR5 inhibitors, and fusion inhibitors. Each class of antiretrovirals attacks the virus at a different point in its life cycle. For example, NRTIs function as faulty DNA-building blocks. When one of these blocks is integrated into a growing HIV-DNA chain, further DNA synthesis is blocked. PIs act later in the viral life cycle by

Table 2 Antiretroviral therapy

Drug class	Generic name	Brand name	FDA approval year
NRTIs	Abacavir	Ziagen	1998
	Didanosine (ddI)	Videx	1991
	Emtricitabine (FTC)	Emtriva	2003
	Lamivudine (3TC)	Epivir	1995
	Stavudine (d4T)	Zerit	1994
	Tenofovir disoproxil fumarate (TDF)	Viread	2001
	Zidovudine (AZT, ZDV)	Retrovir	1987
NNRTIs	Delavirdine (DLV)	Rescriptor	1997
	Efavirenz (EFV)	Sustiva	1998
	Etravirine (ETR)	Intelence	2008
	Nevirapine (NVP)	Viramune	1996
	Rilpivirine (RPV)	Edurant	2011
PIs	Atazanavir (ATV)	Reyataz	2003
	Darunavir (DRV)	Prezista	2006
	Fosamprenavir (FOS-APV, FPV)	Lexiva	2003
	Indinavir (IDV)	Crixivan	1996
	Lopinavir/ritonavir (LPV/r)	Kaletra	2000
	Nelfinavir (NFV)	Viracept	1997
	Ritonavir (RTV)	Norvir	1996
	Saquinavir (SQV)	Invirase	1995
	Tipranavir (TPV)	Aptivus	2005
Fusion inhibitors	Enfuvirtide (T-20)	Fuzeon	2003
Entry inhibitors	Maraviroc (MVC)	Selzentry	2007
Integrase inhibitors	Dolutegravir (DTG)	Tivicay	2013
	Raltegravir (RAL)	Isentress	2007

Note: Data from AIDSInfo, accessed November 29, 2014.[23]
Abbreviations: FDA, US Food and Drug Administration; NRTIs, nucleoside reverse transcriptase inhibitors; NNRTIs, non-nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors.

interfering with the HIV enzyme called "protease". This enzyme typically cuts long chains of HIV proteins into functional, smaller proteins. When protease does not work properly, new virus particles cannot be correctly assembled. New individual antiretroviral medications as well as new drug classes have increased ART potency and activity against multidrug-resistant HIV.

Optimal treatment for a patient who has never been exposed to ART typically consists of two NRTIs in combination with a third active drug from one of three drug classes: an NNRTI, a PI boosted with ritonavir (a PI taken with low-dose ritonavir that boosts the serum concentration of the primary PI), or an ISTI. The goal of therapy is to suppress plasma HIV-RNA (viral load) to below detectable levels.[23]

Pharmacokinetics and drug interactions of ART

Most antiretroviral medications, like hormonal contraceptives, are metabolized through the cytochrome P450 liver enzyme system, and thus, they interact with a number of other medications.[24,25] NRTIs are an exception and are metabolized through other pathways.[26,27] PIs and NNRTIs can be inhibitors and/or inducers of the cytochrome P450 enzyme systems, making it difficult to anticipate outcomes of drug interactions with these classes of ART.

Interactions between ART and hormonal contraceptives

Pharmacokinetic interactions between hormonal contraceptives and ART are complex and depend on the antiretroviral medications used, the specific contraceptive hormones involved, and the mode of delivery of these hormones. Antiretroviral medications can interact with hormonal contraceptives, leading to changes in the pharmacokinetic parameters of these hormones (Table 3).[28–47] Specifics of these interactions are summarized in detail in Table S1. A brief summary of these studies is presented here.

Effect of ART on hormonal contraceptive efficacy

Efavirenz appears to interact with most contraceptives.[28,33–35] While it does not seem to alter the pharmacokinetics of

Table 3 Summary table of the impact of antiretroviral therapy on hormonal contraceptive area under the plasma concentration–time curve and half-life

	EE oral	EE patch	NET	DSG	NGM	NGMN patch	LNG oral	LNG implant	DMPA	ETG implant
NRTI										
TDF	↔[27]				↔[27]					
NNRTI										
NVP	↓[29]		AUC ↓[29] $T_{1/2}$ ↔[29]	↔[28]					↔[31,32]	
EFV	↔[33]			↓[28]	↓[33]		↓[34]		↔[32]	↓[35]
ETV	↑[37]		↓[37]							
RPV	↔[38]		↔[38]							
PI										
RTV	↓[40]									
NFV									↔[31,32]	
LPV/r	↓[50]	↓[42]	↓[50]			↑[42]				↑[35]
ATV	↑[71]		↑[71]							
ATV/r	↓[43]		↑[39]		↑[43]					
DRV/r	↓[44]		↓[44]							
TPV/r	↔[72]		↔[72]							
FPV	↓[73]									
FPV/r	↓[73]		↓[73]							
ISTI										
RAL	↔[45]				↔[45]					
DTG	↔[49]				↔[49]					
CCR5 inhibitor										
MVC	↔[46]						↔[74]			
VCV	↔[47]		↔[47]							
Cobicistat	↓[75]				↑[75]					

Abbreviations: AUC, area under the concentration-time curve; $T_{1/2}$, half-life; EE, ethinyl estradiol; NET, norethindrone; DSG, desogestrel; NGM, norgestimate; NGMN, norelgestromin; LNG, levonorgestrel; DMPA, depot medroxyprogesterone acetate; ETG, etonogestrel; NRTI, nucleoside reverse transcriptase inhibitor; TDF, tenofovir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NVP, nevirapine, EFV, efavirenz; ETV, etravirine; RPV, rilpivirine; PI, protease inhibitor; RTV, ritonavir; NFV, nelfinavir; LPV/r, lopinavir/ritonavir; ATV, atazanavir; ATV/r, atazanavir/ritonavir; DRV/r, darunavir/ritonavir; TPV/r, tipranavir/ritonavir; FPV, fosamprenavir; FPV/r, fosamprenavir/ritonavir; ISTI, integrase inhibitor; RAL, raltegravir; DTG, dolutegravir; MVC, maraviroc, VCV, vicriviroc; ↑, increase; ↓, decrease; ↔, unchanged.

ethinyl estradiol, it consistently decreases the bioavailability and half-life of progestins when co-administered. The only exception to this is DMPA, which does not appear to interact with any of the antiretrovirals with which it has been tested.[31,32,36] In contrast, nevirapine primarily interacts with ethinyl estradiol, causing a decrease in the area under the concentration–time curve and half-life,[28,29] although Stuart et al[30] reported that ethinyl estradiol area under the concentration-time curve was higher among HIV-infected compared with uninfected women. It also decreases the area under the concentration-time curve of norethindrone[29] but has minimal effect on desogestrel.[28]

Lopinavir/ritonavir has also received a lot of attention from researchers. It decreases pharmacokinetic parameters of ethinyl estradiol, both in oral and patch formulations, and norethindrone taken orally but increases those of norelgestromin when administered as part of the contraceptive patch.[42] Pharmacokinetic parameters of etonogestrel when administered as an implant also increase when co-administered with lopinavir/ritonavir.[35] ISTIs do not appear to interact significantly with ethinyl estradiol or norgestimate.[48,49]

Effect of hormonal contraception on ART efficacy

The effect of drug–drug interactions on ART efficacy has received far less attention than the impact of drug–drug interactions on hormonal contraceptive efficacy (Table 4). Oral contraceptive pills containing ethinyl estradiol and desogestrel decrease pharmacokinetic parameters of nevirapine[30] but increase that of efavirenz slightly.[28] Nevirapine area under the concentration-time curve also increased when co-administered with DMPA, as did that of etravirine when co-administered with ethinyl estradiol/norethindrone.[37] The contraceptive patch seems to cause a mild decrease in pharmacokinetic parameters of lopinavir but a more dramatic decrease in the ritonavir component when taken as the combined formulation, Kaletra (AbbVie, Inc., Worcester, MA, USA).[50]

Clinical impact of pharmacokinetic interactions between hormonal contraception and ART

Changes in the pharmacokinetic parameters of ethinyl estradiol and progestins, such as area under the concentration–time curve and half-life, do not necessarily result in clinically important outcomes, such as pregnancy. There is substantial inter- and intraindividual variation in the area under the concentration–time curve and/or half-life of ethinyl estradiol and the progestins even in the absence of major drug–drug interactions.[51,52] In part, because of this variation, target levels for serum concentrations of ethinyl estradiol or the progestins, or acceptable ranges for the half-life and bioavailability of these medications, have not been established.[53] Therefore, it is difficult to come to any conclusion about the clinical importance of changes in the pharmacokinetic parameters of hormonal contraceptives.

Heightening concern about the clinical implications of these interactions are a number of case studies that document the occurrence of pregnancies when the single-rod implant that contains etonogestrel and efavirenz is used concurrently.[5–8] Table S2 provides detailed information on these four case studies.

In addition, interactions between hormonal contraception and ART could also result in increased serum concentrations of either ART or the hormonal contraceptives, resulting in potentially significant side effects. For example, increased progestin concentrations – that may occur when atazanavir, ritonavir-boosted atazanavir, or lopinavir/ritonavir are co-administered with subcutaneous implants or the patch[35,39,42,43] – may make women more at risk for metabolic complications such as insulin resistance, metabolic syndrome,

Table 4 Summary table of the impact of hormonal contraceptives on antiretroviral therapy

	TDF	NVP	EFV	ETV	RPV	SQV	LPV/r	FPV	FPV/r
EE/NGM	↔[27]		↔[33] ↓[76]						
EE/DSG		↓[76]	Slt ↑[76]						
EE/NET		↔[29]		↑[37]	↔[38]			↓[73]	↔[73]
DMPA		↑[32]	↔[32]						
LNG oral			↔[34]						
EE/GSD						↔[41]			
EE/NGMN patch							LPV ↓[42] (NS) RTV ↓[42]		

Abbreviations: TDF, tenofovir; NVP, nevirapine; EFV, efavirenz; ETV, etravirine; RPV, rilpivirine; SQV, saquinavir; LPV/r, lopinavir/ritonavir; FPV, fosamprenavir; FPV/r, fosamprenavir/ritonavir; EE, ethinyl estradiol; NGM, norgestimate; DSG, desogestrel; NET, norethindrone; DMPA, depot medroxyprogesterone acetate; LNG, levonorgestrel; GSD, gestodene; NGMN, norelgestromin; LPV, lopinavir; RTV, ritonavir; Slt, slight; NS, not significant; ↑, increase; ↓, decrease; ↔, unchanged.

or venous thromboembolic disorders.[54] Those that decrease serum estradiol concentrations[28,29,40,42] may increase the risk of irregular spotting between periods. Such side effects may make women less likely to continue with these regimens.

While all of these studies highlight potential areas of concern, none provide information about the impact that these pharmacokinetic interactions have on clinical outcomes such as pregnancy. The purpose of this manuscript, therefore, is to identify and explore clinical outcomes occurring in HIV-infected women using both ART and hormonal contraception.

Methods/design

Design and scope

We conducted a systematic review of the efficacy of hormonal contraception when used by HIV-infected women on ART. Our goal was to review clinically relevant outcomes and assess the quality of evidence so as to provide a foundation for understanding the consequences of co-administration, and ultimately for developing management strategies for HIV-infected women using both hormonal contraception and ART.

Criteria for considering studies

Inclusion and exclusion criteria

Published reports were included in this analysis if they were written in English and published between January 1, 1990 and October 30, 2014. To be included, articles had to address contraceptive efficacy in women using ART. They could, but did not have to, address ART efficacy in women using hormonal contraception, or side effects that could be related to pharmacokinetic interactions.

Outcome measures

The primary outcome of interest was evidence of the efficacy or lack thereof of hormonal contraception when co-administered with ART. Pregnancy was the primary outcome, but evidence of ovarian function, including ovulation, was also acceptable.

Exposure measures

The exposures of interest were ART and hormonal contraceptive use. ART use was defined as use of any of the US Food and Drug Administration-approved antiretroviral medications. Hormonal contraceptive use included use of any contraceptive that contains a progestin, either alone or with estrogen.

Search strategy

We searched PubMed and Ovid for pertinent articles (Figure 1). The search terms were related to hormonal contraception and ART use among HIV-infected women and included hormonal contraception, or birth control, or family planning, or contraception, or contraceptives, or hormonal contraceptives, in combination with the terms HIV, or antiretroviral therapy, or ART, or cART, or HAART. All of these terms were entered together into the search engine. We also reviewed the references from all studies included in the analysis to be sure that we had not missed any pertinent references.

Screening and data collection

Our search criteria identified 405 records. As an initial screening step, the title and abstract of data reports retrieved via the search were reviewed. Titles or abstracts with any indication of the main outcomes of interest were considered for inclusion (N=162). Full-text versions of 64 of these articles were retrieved and reviewed. For studies that were excluded (n=56), reasons for the exclusion were noted. The remaining full-text articles (n=8) were read in-depth, and data were entered onto grids developed for the purposes of this study. The information collected included sample size and descriptors of the sample, ART and hormonal contraception regimens, primary and secondary study outcomes, measures of adherence, duration of follow-up, results, and the country where the subjects were recruited.

Newcastle-Ottawa Scale: study quality and critical appraisal

To assess the quality of the studies reviewed, we used the Newcastle-Ottawa Scale (NOS)[55] which assigns quality ratings to studies based on threats to internal validity. In particular, the NOS assesses the presence of selection bias: the likelihood that the process of assigning or recruiting subjects has resulted in unidentified differences between exposed and nonexposed subjects. The NOS employs separate rating scales for cohort studies and case–control studies. For cohort studies, there are three categories in the NOS: Selection, Comparability, and Outcome. For case–control studies, the categories are Selection, Comparability, and Exposure.

Categories

Selection

To determine selection bias in cohort studies, raters evaluate the following items: 1) the representativeness of the exposed cohort, 2) selection of the nonexposed cohort, 3) ascertainment of the exposure (self-report versus a more reliable method such as documentation in the health record or a laboratory test result), and 4) demonstration that the outcome

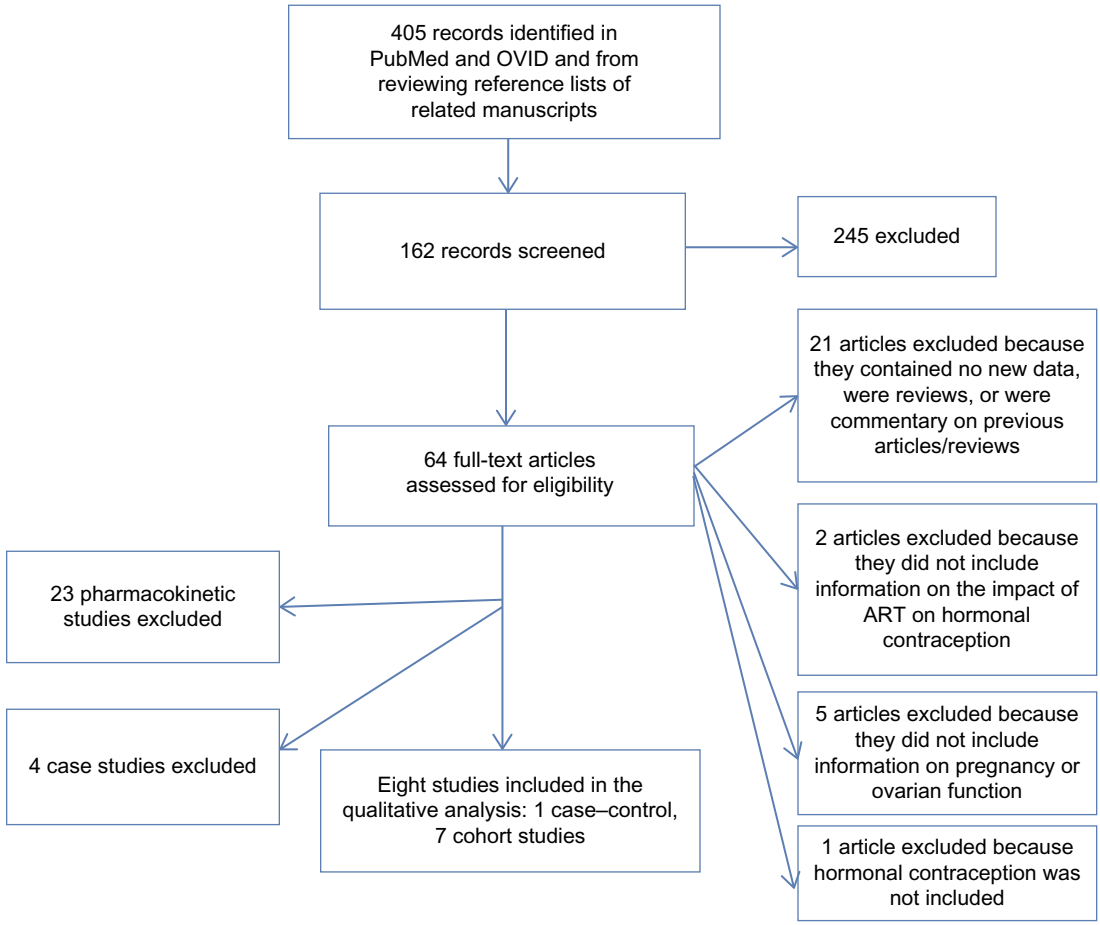

Figure 1 Flow diagram for study selection.
Abbreviation: ART, antiretroviral therapy.

of interest was not present at study initiation. In case–control studies, the focus is on the following items: 1) adequacy of case definition, 2) the representativeness of the cases, and 3) the selection and definition of controls.

Comparability

To assess for confounding due to noncomparability of groups, reviewers must evaluate whether the study authors matched their groups on important confounders, or whether confounders were included in the statistical analyses.

Outcome/exposure

For cohort studies, the outcome must also be assessed in a reliable manner. For example, self-reported outcomes may be less reliable than documentation in the medical record. Adequacy of follow-up is also important to ensure that enough time has elapsed for the outcome to have occurred. Of equal importance is verifying that comparable follow-up is provided by those with the exposure and those without. Finally, in cohort studies, reviewers assess how the study authors address subject attrition and follow-up. No attrition is ideal, but if it occurs, minimal numbers (<5%) are preferable, and descriptions of those subjects who were lost to follow-up are imperative so that they can be compared to those who remained in the study.

For case–control studies, the final area of interest is exposure: how it was ascertained, and whether it was ascertained in the same way in both cases and controls. A full description of those who did not respond must also be provided.

Scoring

Studies are awarded points for each of the categories as follows: a maximum of one point is awarded for each of the four items within the Selection category, up to two points can be awarded for Comparability, and one point can be awarded for each of the three items in the Outcome or Exposure categories. The highest possible total score is nine points. For the current manuscript, each study was reviewed and scored by two of the authors (JAW and GN). When ratings differed between reviewers, discussion achieved consensus.

Results

We identified eight studies with clinically significant outcomes (Table 5). Seven were cohort studies, and one was case–control. No randomized controlled trials met our search criteria.

Results of individual studies

Contraceptive efficacy

Out of the eight studies reviewed, two had findings that suggested that ART use was associated with an increased risk of pregnancy among women using hormonal contraception. Clark and Theall[56] found that among women taking combined oral contraceptive pills, seven of the eight contraceptive failures experienced by women using PI-based regimens occurred among women using nelfinavir. One instance of failure occurred in women using saquinavir. No pregnancies were identified among the women using indinavir or ritonavir. Among women using NNRTI-based regimens, two pregnancies occurred in women using efavirenz. None of the six women taking nevirapine became pregnant. Perry et al[57] found that the ART regimen was the only factor associated with risk of pregnancy in a cohort of women using the levonorgestrel implant: 15 of the 16 pregnancies occurred in women using efavirenz.

Danel et al[58] identified seven pregnancies in a cohort of women who used efavirenz-based ART, and either DMPA or combined oral contraceptives. The association between

Table 5 Cohort and case–control studies

Authors	Sample	Controls	Study design	Primary outcomes	ART regimens
Clark and Theall[56]	11 HIV+ women who may have conceived while on oral contraceptive pills. From urban clinic, New Orleans	86 women on COCs who did not conceive from same clinic	Retrospective case–control EHR-based	Determine frequency of potential COC failure among women on ART and COC	PI-based: NFV, SQV, IDV, RTV NNRTI-based: EFV, NVP Neither PI nor NNRTI
Nanda et al[36]	172 HIV+ women on NVP. Clinics in South Africa and Uganda	178 HIV+ women not yet eligible for ART	Nonrandomized prospective clinical trial	Compare ovulation rates between women taking COCs concurrently with NVP-containing ART, and those taking COCs alone. Secondary objective: comparing pregnancy rates	NVP-containing ART versus no ART
Danel et al[58]	740 total, 548 HIV+ women Clinics in Abijan, Cote d'Ivoire	None	Cohort	6-month efficacy and tolerance of AZT/3TC/EFV in adults in Abidjan, Cote d'Ivoire	AZT/3TC EFV
Kreitchmann et al[59]	79 HIV+ implant users in Porto Alegre, Brazil	None	Cohort	Evaluate safety and efficacy of Implanon	71% on ART (NNRTI- and PI-based regimens)
Heikinheimo et al[60]	12 HIV+ LNG-IUS users from clinic, Helsinki, Finland	None	Cohort	Assess effects of LNG-IUS on bleeding patterns, iron stores, ovarian function, and genital shedding of HIV	Various – 10/12 on ART, either PI- or NNRTI-based
Heikinheimo et al[61]	15 HIV+ LNG-IUS users from clinic, Helsinki, Finland	25 age and CD4 count matched controls	Retrospective cohort	Assess the effects of long-term use and safety of LNG-IUS among HIV+ women	No description of ART
Perry et al[57]	570 HIV+ implant users, Swaziland	Groups on different antiretrovirals	EHR-based retrospective cohort	Efficacy of 5-year implant among HIV+ women on ART	NVP EFV LPV/r
Hubacher et al[62]	48 implant users from hospital clinic, Kenya	33 nonhormonal contraceptive users matched on age, CD4 count, same ART as cohort	Prospective cohort	Examine impact of concurrent use of ART and 5-year implant on efficacy of both medications	D4T or AZT and 3TC/NVP

Note: *This is an exposure rather than an outcome point.

Abbreviations: ART, antiretroviral therapy; COCs, combined oral contraceptives; PI, protease inhibitor; NFV, nelfinavir; SQV, saquinavir; IDV, indinavir; RTV, ritonavir; EHR, electronic health record; NNRTI, non-nucleoside reverse transcriptase inhibitor; EFV, efavirenz; NVP, nevirapine; EE, ethinyl estradiol; NG, norgestrel; AZT, azidothymidine; 3TC, epivir; DMPA, depot medroxyprogesterone acetate; LNG-IUS, levonorgestrel intrauterine system; LPV/r, lopinavir/ritonavir; OI, opportunistic infection; CD, cluster of differentiation; D4T, stavudine.

the different contraceptives and pregnancy, however, was not assessed.

No pregnancies occurred among HIV-infected women on ART in four of the studies.[59–62] Hubacher et al[62] explored the use of levonorgestrel implants among women using nevirapine-based ART regimens. In the other studies, ART use was not well described. Heikinheimo et al explored the use of the levonorgestrel intrauterine system (LNG-IUS) among HIV-infected women most of whom were on PI/NRTI combinations, with no further information provided on the specific antiretrovirals used.[60,61] Kreitchmann et al[59] studied a group of HIV-infected women using Implanon and ART. Only the categories of ART were provided (PI- and NNRTI-based therapies), so understanding the impact of specific medications was not possible.

Nanda et al[36] explored the association between nevirapine-based therapy and combined oral contraceptive use on pregnancy and ovulation. Pregnancy incidence at 6 months of follow-up was similar for women using nevirapine (4.8% [95% confidence interval 1.2, 8.4%]) and for those not on ART (5.0% [95% confidence interval 1.2, 8.9%]). Rates of ovulation also did not differ by ART status.

ART efficacy

While most of these analyses were primarily focused on the efficacy of hormonal contraception when co-administered

HC regimens	Adherence	Duration of follow-up	Results	Study quality		
				Selection points	Comparability points	Outcome points
Cases: COC (formulation not specified): 10 Controls: COC: 86	Not described	Not described	32% of those on PI-based regimens became pregnant, 10% of those on NNRTI-based regimens, 0% on other regimens	2	0	1*
COCs EE (30 μg)/NG	Self-report	6 cycles – 24 weeks	ART use was not significantly associated with ovulation or pregnancy Pregnancy incidence at 6 months: 4.8% (ART), 5.0% (non-ART) No difference in adverse events	0	2	1
65% DMPA, 35% COC (formulation not specified)	Self-report	6 months	Incidence of serious side effects of 0.9/100 person months. Contraceptive use increased over the 6 months: 58%–80%. 7 pregnancies occurred (2.6/100 person years) – not assessed by COC status	2	0	1
Implanon	Pharmacy records	3 years	No pregnancies	3	0	1
LNG-IUS	Not described	1 year	No pregnancies. Levels of LNG were similar in all subjects. Estrogen remained in the follicular-phase range in all subjects. No change in CD4 count	2	0	2
LNG-IUS	Not described	5 years	No pregnancies, no adverse events	1	2	3
Jadelle	Not described	Not described	All bivariate associations. 15 of the 16 women who became pregnant were on EFV	3	0	1
Jadelle	Not described	2 years	None of the implant users and 1 of the nonusers became pregnant. No difference in CD4 count/increase. OI rates did not differ	2	2	0

with ART, Hubacher et al[62] were also interested in implications for the efficacy of ART when co-administered with the levonorgestrel implant. They found that there were no differences in CD4 count recovery among women using the levonorgestrel implant compared with those who did not, nor did opportunistic infection rates differ between the two groups, suggesting that the implant did not adversely affect ART efficacy.

Side effects potentially related to drug–drug interactions

Three studies also examined the occurrence of side effects that could be related to pharmacokinetic interactions between ART and hormonal contraceptives. Hubacher et al[62] identified no serious side effects in women using both nevirapine-based ART and the levonogestrel implant. Heikinheimo et al[60,61] were also interested in the safety of the LNG-IUS among HIV-infected women on various ART regimens in both of their studies and found no serious side effects.

Assessment of study quality

The risk of bias in these studies was significant (Table 5). Out of nine possible points, the average number of points given to the studies we reviewed was four. The point range for individual studies was three to six.

Risk of bias within cohort and case–control studies based on the NOS

Cohort studies

Selection: In the cohort studies, the average score for Selection was two out of four possible points (Table 6). Points were typically lost because recruitment procedures were not described, making it difficult to assess whether or not the exposed cohort was truly representative of the population of interest. Authors reported that women were recruited from certain clinics, but details about the recruitment process were not provided. The two articles that were scored favorably for representativeness of the exposed cohort used electronic health record (EHR)-based cohorts; they were able to identify and include all of the women from the clinics of interest who met inclusion criteria. The nonexposed cohorts in these studies were from the same clinics as the exposed groups and were also identified using the EHR.[57,59] All but one study used reliable methods for ascertaining exposure (secure records such as documentation in the EHR and structured interviews) and thus received full points. The one study that did not receive points for this item did not describe how

Table 6 Newcastle-Ottawa Scale: components and rating scale

Cohort studies			**Case–control studies**		
Selection	**Comparability**	**Outcome**	**Selection**	**Comparability**	**Exposure**
4 points possible	**2 points possible**	**3 points possible**	**4 points possible**	**2 points possible**	**3 points possible**
• Is the exposed cohort representative of the population of interest? • How was the nonexposed cohort selected, and was this process similar to that used for the exposed cohort? • How was the exposure ascertained? • Does the study demonstrate that the outcome of interest was not present at study initiation?	• Are groups matched on important confounders? OR • Are important confounders included in the statistical analysis?	• Were the outcomes assessed in a reliable manner? • Was the duration of follow-up in both groups adequate • Was there attrition in the study, and if so, are the numbers of those who left the study low, and/or are the subjects who left the study well described?	• Is the case definition adequate? • Are the cases representative of the exposed population? • How were the controls selected? • Is there clear evidence that the controls have no history of the exposure?	• Are groups matched on important confounders? OR • Are important confounders included in the statistical analysis?	• How was the exposure ascertained? • Was exposure ascertained in the same way for both cases and controls? • Is a full description of those who did not respond provided?

exposure was ascertained.[36] Demonstration that the outcome of interest was not present at the start of the study was also an item where many of the studies lost points. Only one study demonstrated that the outcome of interest (pregnancy) was not present at baseline.[60] For the others, while pregnancy was typically mentioned in the exclusion criteria, there was no description provided for how pregnancy was identified or ruled out.

Comparability: The average score for Comparability was 0.75 out of two possible points. Points were not awarded primarily because the exposed and nonexposed participants were neither matched on important confounders, nor were statistical tests used that would allow for confounders to be included in the models; only bivariate statistics were used by a number of authors. Not controlling for confounders made it impossible to assess the association between the predictor (ART and hormonal contraceptive use) and outcome (pregnancy) variables. Of the studies that used more complex statistical analyses and controlled for a number of confounders,[36,61,62] none controlled for adherence to ART. Including measures of contraceptive adherence is important when studying combined oral contraceptives, the contraceptive patch, the vaginal ring, and DMPA. For long-term contraceptives such as implants or intrauterine devices, adherence is less of an issue.

Outcome: The average score for Outcome was 1.25 out of three possible points. For the first item, assessment of the outcome, four of the seven cohort studies identified the outcome through laboratory results or documentation in the medical record, both reliable methods, and were thus positively scored.[36,57,60,61] Among studies that were not awarded points for this item, one relied on self-report of outcomes by participants,[58] and the other two did not document how the outcomes of interest were determined.[59,62] Points were also lost because follow-up was inadequate or incompletely described. Follow-up was not long enough to determine outcomes,[60] or studies lacked information regarding duration of follow-up in the exposed versus unexposed groups.[36,57–59,62] For example, Perry et al[57] reported that participants were followed through pregnancy, transfer out of clinic, implant removal, or death. It is unlikely that follow-up times were identical for both exposed and unexposed groups, and yet the time contributed to follow-up by each group was not reported. Four of the seven studies adequately reported on follow-up of the cohorts: none of the participants were lost to follow-up in three of the studies,[59–61] and only very few in one study,[58] and these studies received a point for this item. In the remaining three studies, either no statement was provided regarding those lost to follow-up[57] or the lost to follow-up rate was greater than 5% and no description of these individuals was provided.[36,62]

Case–control studies

There was only one case–control study included in this review.[56] It garnered three of nine possible points on the NOS: two for Selection, none for Comparability, and one for Exposure.

Selection: A real strength of this study was the selection process. Using the EHR, the authors identified all women who were seen in a specific clinic over a 2-year period. All of these women were HIV infected. All of those who were pregnant and on hormonal contraception within the same 6-month period were then identified, and these subjects' charts were reviewed to identify women who were likely to have become pregnant while taking hormonal contraception. Of the eleven women identified, ten were taking oral contraceptive pills when they became pregnant. Controls were those women who attended the clinic in the same time period and who took combined oral contraceptive pills but who did not become pregnant. Thus, cases and controls came from the same population, and there was no bias in how they were selected. Pregnancy was identified in the medical record, although how it was identified (self-report, urine pregnancy test, blood pregnancy test) was not described, nor was there any assessment of the validity or reliability of this approach to identifying pregnancy. Thus, the requirements for case definition and the evidence of the exposure were not fulfilled.

Comparability and exposure: Comparability was weak as bivariate statistics alone were used, which did not allow for control of important confounders. Ascertainment of the exposure (hormonal contraception and ART) was identified by the medical record, and the same method was used for both cases and controls. Follow-up, however, was not well described. For example, women included in the study could have presented only once for care.

Additional critiques

In addition to the threats to validity assessed using the NOS, our review identified other limitations to these studies. As noted earlier, pregnancy is an uncommon outcome among women using highly effective forms of birth control who have also been told to use condoms. Thus, adequate sample

size to assure power to detect meaningful differences in outcomes, in addition to adequate duration of follow-up, is key. For example, Heikinheimo et al[61] explored the effects of long-term use and safety of the LNG-IUS among 15 HIV-infected women compared with 25 women who did not use the LNG-IUS. These women were followed for 5 years. As failure rates of LNG-IUS are less than 0.1% in the general population, the fact that none of these participants became pregnant during the study period may reflect the small sample size rather than there truly being no evidence of reduced contraceptive efficacy.

Many of the studies reviewed were also limited by threats to external validity. Most of the studies had small samples, and the study populations were recruited from a single clinic or geographic area, thus limiting the ability to translate results to HIV-infected women from different clinics or geographic locations. In addition, some of the studies used strict inclusion and exclusion criteria, limiting generalizability.

Discussion

The goals of this manuscript were to review what is known about clinically meaningful outcomes when HIV-infected women use both hormonal contraceptives and ART, and to recommend a framework for guidelines that would help clinicians and HIV-infected women make appropriate choices about the use of hormonal contraceptives when co-administered with ART. We identified eight studies that explored clinical outcomes (pregnancy or ovulation) in HIV-infected women using both hormonal contraception and ART. It is important to understand and evaluate these studies because they indicate the growing interest in translating the concerns that have been raised by pharmacokinetic studies into studies with clinically meaningful outcomes. Unfortunately, given the limited number and quality of the studies published to date, we do not have sufficient evidence on which to base clinical guidelines that will help clinicians and HIV-infected women make informed decisions about contraceptive options.

Of the studies that met our search criteria, four explored the use of long-acting reversible contraception (LARC), specifically Jadelle (levonogestrel implant), Implanon (etonogestrel implant), and the LNG-IUS, among HIV-infected women. The emphasis on LARC is interesting given that, with the exception of DMPA, these are not the most commonly used contraceptives among HIV-infected women; combined oral contraceptive pills and DMPA are far more common.[9] Three studies explored clinical outcomes in women using oral contraceptive pills, and one included women using DMPA. This lack of attention to DMPA use may be because pharmacokinetic studies have not demonstrated an interaction between DMPA and ART, and thus, researchers may feel that clinically focused trials are unnecessary. It is also possible that more recent concerns about an increased risk of transmission of HIV among women using DMPA,[63] as well as concern regarding more rapid HIV disease progression among women using DMPA, have made researchers more hesitant to study DMPA until these concerns have been fully addressed.[64] That LARC methods were more researched than combined oral contraceptives may be related to the problem of assessing adherence. However, in studying concerns of medication efficacy, an understanding of adherence to both contraceptives and ART is important.

Implications for clinical practice

Most of the existing guidelines for the management of contraception in HIV-infected women who use ART state that all contraceptive methods are or should be available to HIV-infected women.[3,65,66] The research reviewed herein does not provide evidence to either support or refute these guidelines. However, that being said, clinicians can provide counseling that clearly presents the potential risks and benefits of the different contraceptive methods, including the risk of unintended pregnancy, and particularly if a woman has not been pregnant before, the signs of pregnancy so that she can seek care in a timely fashion. Clinicians should also discuss appropriate follow-up if pregnancy is suspected, particularly for women taking efavirenz, as an association between efavirenz and birth defects in nonhuman populations has been identified.[67] Clinicians can reinforce the importance of condom use, even though most clinicians and women recognize that this may be out of the woman's control and may also be something that neither she nor her partner desire. In addition, clinicians can reinforce the importance of ART adherence, primarily for the woman's health, but also as an additional way to decrease the risk of transmission to her partner and to her baby, should she become pregnant.

Future research

Researchers have suggested that randomized controlled trials be designed to evaluate contraceptive efficacy when hormonal contraception is co-administered with ART. We would suggest that randomized controlled trials may not be the most useful approach. Individuals who enroll in

clinical trials are often not representative of most patients in clinical care. Thus, there are often important differences between what is found in clinical trials and what providers and patients experience in clinical practice. Furthermore, the cost of a randomized clinical trial that would be large enough and of sufficient duration to fully evaluate outcomes (pregnancy) would be prohibitively expensive.

We suggest that large collaborations that include a number of observational cohorts might be better suited for this research. There are a number of cohorts in North America, Europe, and Africa, all of which should be encouraged to collect data on contraception and adherence to both ART and contraception. When designing large cohort studies, researchers should collect information on the efficacy of ART (HIV-RNA, time to viral suppression, recovery of CD4 count), and on contraceptive- and ART-related side effects, as well as on contraceptive efficacy. Most of the pharmacokinetic studies did not identify serious adverse events when hormonal contraceptives and ART were co-administered, but it is possible that the negative results reflect small sample sizes, brief follow-up, and the infrequency of the outcomes rather than the absence of adverse events. Studies involving combined oral contraceptives should also include information about the hormones used as results from pharmacokinetic studies suggest that interactions with ART may differ by progestin,[28,29] and about adherence, a key confounder when studying possible drug interactions.

In addition, any future studies should avoid the potential sources of bias identified in the studies described. For example, reliable methods for ascertaining exposure and outcomes should be used. EHR-based cohorts are ideal for these analyses. Pharmacy fill/refill data can identify those taking contraceptives and ART (exposure), and laboratory data can identify pregnancy (outcome). In addition, if patients are prescribed these medications in other health care settings, or if they report the result of a home pregnancy test to their provider, information retrieval can identify these exposures and outcomes through provider documentation in clinical progress notes.[68] Important confounders for these analyses should also be identified and used either for matching or as covariates in the statistical analyses. Finally, follow-up should be similar between the exposed and unexposed groups, or duration of follow-up should be included as a variable in the analyses.

These larger studies should also be designed with pregnancy as the outcome of interest. Ovulation is not an appropriate outcome because hormonal contraception likely works through multiple modes of action, not just suppression of ovulation.

Limitations

This study has a number of limitations. We did not include abstracts from conferences because we felt that the best abstracts would be published as manuscripts and would include more detailed and useful information than is possible in an abstract. It is possible that manuscripts based on abstracts from more recent conferences have not yet been published. In addition, we did not include specific drug names in our search criteria. Brand names differ from one country to the next, and the generic name is not consistently used. We wanted to access results from all countries where this research might be conducted and did not want to limit ourselves to only those countries using the terminology that we included in the search criteria. We believe that we significantly strengthened our search algorithm, however, by hand-searching all of the references for the articles initially identified by the search algorithm. It is still possible, however, that we could have excluded some articles inadvertently.

The NOS is a set of validated criteria for evaluating observational cohorts. There is, however, no validated threshold score that distinguishes between "good"- and "poor"-quality studies. We therefore made the decision that studies that were awarded less than two-thirds the number of possible points would be considered lower quality studies. This assumption, however, has not been validated.

Conclusion

The studies reviewed constitute an important first step in moving from pharmacokinetic studies of the interactions between hormonal contraception and ART, toward larger studies focusing on clinically relevant outcomes. However, these studies still do not provide women and clinicians with the information that they need to select appropriate contraceptives when considering women's ART regimens, and to manage these contraceptives over the course of HIV-infected women's reproductive years. Researchers must continue to pursue this topic to improve the health and well-being of HIV-infected women and to decrease rates of unintended pregnancy and maternal–child transmission of HIV.

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The authors report no conflicts of interest in this work.

References

1. UNAIDS/WHO. *The Gap Report. Children and Pregnant Women Living with HIV*; 2014:20. Available from: http://www.unaids.org/sites/default/files/media_asset/09_ChildrenandpregnantwomenlivingwithHIV.pdf. Accessed December 7, 2014.
2. UNAIDS/WHO. *AIDS Epidemic Update*; 2007. Available from: http://data.unaids.org/pub/EpiReport/2006/2006_EpiUpdate_en.pdf. Accessed January 2, 2007.
3. Tepper NK, Curtis KM, Jamieson DJ, Marchbanks PA. Update to CDC's U.lS. *MMWR Morb Mortal Wkly Rep*. 2012;61(24):449–452. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6124a4.htm. Accessed November 15, 2014.
4. Delvaux T, Nostlinger C. Reproductive choice for women and men living with HIV: contraception, abortion and fertility. *Reprod Health Matters*. 2007;15(29 Suppl):46–66.
5. Leticee N, Viard JP, Yamgnane A, Karmochkine M, Benachi A. Contraceptive failure of etonogestrel implant in patients treated with antiretrovirals including efavirenz. *Contraception*. 2012;85(4):425–427.
6. Lakhi N, Govind A. Implanon failure in patients on antiretroviral medication: the importance of disclosure. *J Fam Plann Reprod Health Care*. 2010;36(3):181–182.
7. Matiluko AA, Soundararjan L, Hogston P. Early contraceptive failure of implanon in an HIV-seropositive patient on triple antiretroviral therapy with zidovudine, lamivudine and efavirenz. *J Fam Plann Reprod Health Care*. 2007;33(4):277–278.
8. McCarty EJ, Keane H, Quinn K, Quah S. Implanon(R) failure in an HIV-positive woman on antiretroviral therapy resulting in two ectopic pregnancies. *Int J STD AIDS*. 2011;22(7):413–414.
9. Massad LS, Evans CT, Wilson TE, et al. Contraceptive use among US women with HIV. *J Womens Health (Larchmt)*. 2007;16(5):657–666.
10. Rivera R, Yacobson I, Grimes D. The mechanism of action of hormonal contraceptives and intrauterine contraceptive devices. *Am J Obstet Gynecol*. 1999;181(5 pt 1):1263–1269.
11. Frye CA. An overview of oral contraceptives: mechanism of action and clinical use. *Neurology*. 2006;66(6 Suppl 3):S29–S36.
12. Fleischman DS, Navarrete CD, Fessler DM. Oral contraceptives suppress ovarian hormone production. *Psychol Sci*. 2010;21(5):750–752. [author reply 753].
13. Lobo RA, Stanczyk FZ. New knowledge in the physiology of hormonal contraceptives. *Am J Obstet Gynecol*. 1994;170(5 pt 2):1499–1507.
14. Croxatto HB. Mechanisms that explain the contraceptive action of progestin implants for women. *Contraception*. 2002;65(1):21–27.
15. Bronson RA. Oral contraception: mechanism of action. *Clin Obstet Gynecol*. 1981;24(3):869–877.
16. Meyer UA. Overview of enzymes of drug metabolism. *J Pharmacokinet Biopharm*. 1996;24(5):449–459.
17. Wilkinson GR. Cytochrome P4503A (CYP3A) metabolism: prediction of in vivo activity in humans. *J Pharmacokinet Biopharm*. 1996;24(5):475–490.
18. Wang B, Sanchez RI, Franklin RB, Evans DC, Huskey SE. The involvement of CYP3A4 and CYP2C9 in the metabolism of 17 alpha-ethinylestradiol. *Drug Metab Dispos*. 2004;32(11):1209–1212.
19. Stanczyk FZ. All progestins are not created equal. *Steroids*. 2003;68(10–13):879–890.
20. Dickinson BD, Altman RD, Nielsen NH, Sterling ML. Council on scientific affairs AMA. Drug interactions between oral contraceptives and antibiotics. *Obstet Gynecol*. 2001;98(5 pt 1):853–860.
21. Reddy DS. Clinical pharmacokinetic interactions between antiepileptic drugs and hormonal contraceptives. *Expert Rev Clin Pharmacol*. 2010;3(2):183–192.
22. Robinson JA, Jamshidi R, Burke AE. Contraception for the HIV-positive woman: a review of interactions between hormonal contraception and antiretroviral therapy. *Infect Dis Obstet Gynecol*. 2012;2012:890160.
23. AIDSInfo. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*; 2014. Available from: http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0. Accessed November 29, 2014.
24. Flexner C. HIV-protease inhibitors. *N Engl J Med*. 1998;338(18):1281–1292.
25. Smith PF, DiCenzo R, Morse GD. Clinical pharmacokinetics of non-nucleoside reverse transcriptase inhibitors. *Clin Pharmacokinet*. 2001;40(12):893–905.
26. Piliero PJ. Pharmacokinetic properties of nucleoside/nucleotide reverse transcriptase inhibitors. *J Acquir Immune Defic Syndr*. 2004;37(Suppl 1):S2–S12.
27. Kearney BP, Mathias A. Lack of effect of tenofovir disoproxil fumarate on pharmacokinetics of hormonal contraceptives. *Pharmacotherapy*. 2009;29(8):924–929.
28. Landolt NK, Phanuphak N, Ubolyam S, et al. Significant decrease of ethinylestradiol with nevirapine, and of etonogestrel with efavirenz in HIV-positive women. *J Acquir Immune Defic Syndr*. 2014;66(2):e50–e52.
29. Mildvan D, Yarrish R, Marshak A, et al. Pharmacokinetic interaction between nevirapine and ethinyl estradiol/norethindrone when administered concurrently to HIV-infected women. *J Acquir Immune Defic Syndr*. 2002;29(5):471–477.
30. Stuart GS, Moses A, Corbett A, et al. Combined oral contraceptives and antiretroviral PK/PD in Malawian women: pharmacokinetics and pharmacodynamics of a combined oral contraceptive and a generic combined formulation antiretroviral in Malawi. *J Acquir Immune Defic Syndr*. 2011;58(2):e40–e43.
31. Watts DH, Park JG, Cohn SE, et al. Safety and tolerability of depot medroxyprogesterone acetate among HIV-infected women on antiretroviral therapy: ACTG A5093. *Contraception*. 2008;77(2):84–90.
32. Cohn SE, Park JG, Watts DH, et al; ACTG A5093 Protocol Team. Depo-medroxyprogesterone in women on antiretroviral therapy: effective contraception and lack of clinically significant interactions. *Clin Pharmacol Ther*. 2007;81(2):222–227.
33. Sevinsky H, Eley T, Persson A, et al. The effect of efavirenz on the pharmacokinetics of an oral contraceptive containing ethinyl estradiol and norgestimate in healthy HIV-negative women. *Antivir Ther*. 2011;16(2):149–156.
34. Carten ML, Kiser JJ, Kwara A, Mawhinney S, Cu-Uvin S. Pharmacokinetic interactions between the hormonal emergency contraception, levonorgestrel (Plan B), and Efavirenz. *Infect Dis Obstet Gynecol*. 2012;2012:137192.
35. Vieira CS, Bahamondes MV, de Souza RM, et al. Effect of antiretroviral therapy including lopinavir/ritonavir or efavirenz on etonogestrel-releasing implant pharmacokinetics in HIV-positive women. *J Acquir Immune Defic Syndr*. 2014;66(4):378–385.
36. Nanda K, Delany-Moretlwe S, Dubé K, et al. Nevirapine-based antiretroviral therapy does not reduce oral contraceptive effectiveness. *AIDS*. 2013;27(Suppl 1):S17–S25.
37. Scholler-Gyure M, Kakuda TN, Raoof A, De Smedt G, Hoetelmans RM. Clinical pharmacokinetics and pharmacodynamics of etravirine. *Clin Pharmacokinet*. 2009;48(9):561–574.
38. Crauwels HM, van Heeswijk RP, Vandevoorde A, Buelens A, Stevens M, Hoetelmans RM. The effect of rilpivirine on the pharmacokinetics of methadone in HIV-negative volunteers. *J Clin Pharmacol*. 2014;54(2):133–140.

39. DuBois BN, Atrio J, Stanczyk FZ, Cherala G. Increased exposure of norethindrone in HIV+ women treated with ritonavir-boosted atazanavir therapy. *Contraception*. 2015;91(1):71–75.
40. Ouellet D, Hsu A, Qian J, et al. Effect of ritonavir on the pharmacokinetics of ethinyl oestradiol in healthy female volunteers. *Br J Clin Pharmacol*. 1998;46(2):111–116.
41. Frohlich M, Burhenne J, Martin-Facklam M, et al. Oral contraception does not alter single dose saquinavir pharmacokinetics in women. *Br J Clin Pharmacol*. 2004;57(3):244–252.
42. Vogler MA, Patterson K, Kamemoto L, et al. Contraceptive efficacy of oral and transdermal hormones when co-administered with protease inhibitors in HIV-1-infected women: pharmacokinetic results of ACTG trial A5188. *J Acquir Immune Defic Syndr*. 2010;55(4):473–482.
43. Zhang J, Chung E, Yones C, et al. The effect of atazanavir/ritonavir on the pharmacokinetics of an oral contraceptive containing ethinyl estradiol and norgestimate in healthy women. *Antivir Ther*. 2011;16(2):157–164.
44. Sekar VJ, Lefebvre E, Guzman SS, et al. Pharmacokinetic interaction between ethinyl estradiol, norethindrone and darunavir with low-dose ritonavir in healthy women. *Antivir Ther*. 2008;13(4):563–569.
45. Anderson MS, Hanley WD, Moreau AR, et al. Effect of raltegravir on estradiol and norgestimate plasma pharmacokinetics following oral contraceptive administration in healthy women. *Br J Clin Pharmacol*. 2011;71(4):616–620.
46. Abel S, Russell D, Whitlock LA, Ridgway CE, Muirhead GJ. Effect of maraviroc on the pharmacokinetics of midazolam, lamivudine/zidovudine, and ethinyloestradiol/levonorgestrel in healthy volunteers. *Br J Clin Pharmacol*. 2008;65(Suppl 1):19–26.
47. Kasserra C, Li J, March B, O'Mara E. Effect of vicriviroc with or without ritonavir on oral contraceptive pharmacokinetics: a randomized, open-label, parallel-group, fixed-sequence crossover trial in healthy women. *Clin Ther*. 2011;33(10):1503–1514.
48. Benson CA, Hua L, Andersen JW, et al. ZOSTAVAX is generally safe and immunogenic in HIV-Infected adults with CD4 counts > 200 cells/microliter virologically suppressed on antiretroviral therapy: results of a phase 2, randomized, double-blind, placebo-controlled trial (A5247). Paper presented at: Conference on Retroviruses and Opportunistic Infections; March 5–8, 2012; Seattle, WA.
49. ViiV Healthcare. *Tivicay (Dolutegravir) Package Label*. Research Triangle Park, NC: ViiV Healthcare; 2013. Accessed October 14, 2014.
50. AbbVie I. *Kaletra (Lopinavir/Ritonavir) Package Label*. Chicago, IL: AbbVie Inc; 2013. Accessed October 11, 2014.
51. Fotherby K, Akpoviroro J, Abdel-Rahman HA, et al. Pharmacokinetics of ethynyloestradiol in women for different populations. *Contraception*. 1981;23(5):487–496.
52. Goldzieher JW. Selected aspects of the pharmacokinetics and metabolism of ethinyl estrogens and their clinical implications. *Am J Obstet Gynecol*. 1990;163(1 pt 2):318–322.
53. Goldzieher JW, Stanczyk FZ. Oral contraceptives and individual variability of circulating levels of ethinyl estradiol and progestins. *Contraception*. 2008;78(1):4–9.
54. Womack J, Richman S, Tien PC, Grey M, Williams A. Hormonal contraception and HIV-positive women: metabolic concerns and management strategies. *J Midwifery Womens Health*. 2008;53(4):362–375.
55. Wells GH, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. 2014. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed October 15, 2014.
56. Clark RA, Theall KP. Trends and correlates of hormonal contraception use among HIV-infected women. *J Acquir Immune Defic Syndr*. 2004;36(4):986–988.
57. Perry SH, Swamy P, Preidis GA, Mwanyumba A, Motsa N, Sarero HN. Implementing the Jadelle implant for women living with HIV in a resource-limited setting: concerns for drug interactions leading to unintended pregnancies. *AIDS*. 2014;28(5):791–793.
58. Danel C, Moh R, Anzian A, et al. Tolerance and acceptability of an efavirenz-based regimen in 740 adults (predominantly women) in West Africa. *J Acquir Immune Defic Syndr*. 2006;42(1):29–35.
59. Kreitchmann R, Innocente AP, Preussler GM. Safety and efficacy of contraceptive implants for HIV-infected women in Porto Alegre, Brazil. *Int J Gynaecol Obstet*. 2012;117(1):81–82.
60. Heikinheimo O, Lehtovirta P, Suni J, Paavonen J. The levonorgestrel-releasing intrauterine system (LNG-IUS) in HIV-infected women – effects on bleeding patterns, ovarian function and genital shedding of HIV. *Hum Reprod*. 2006;21(11):2857–2861.
61. Heikinheimo O, Lehtovirta P, Aho I, Ristola M, Paavonen J. The levonorgestrel-releasing intrauterine system in human immunodeficiency virus-infected women: a 5-year follow-up study. *Am J Obstet Gynecol*. 2011;204(2):126. e1–e4.
62. Hubacher D, Liku J, Kiarie J, et al. Effect of concurrent use of antiretroviral therapy and levonorgestrel sub-dermal implant for contraception on CD4 counts: a prospective cohort study in Kenya. *J Int AIDS Soc*. 2013;16:18448.
63. Heffron R, Mugo N, Ngure K, et al; Partners in Prevention HSVHIV Transmission Study Team. Hormonal contraceptive use and risk of HIV-1 disease progression. *AIDS*. 2013;27(2):261–267.
64. Stringer E, Antonsen E. Hormonal contraception and HIV disease progression. *Clin Infect Dis*. 2008;47(7):945–951.
65. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. *Considerations for Antiretroviral Use in Special Patient Populations: HIV-Infected Women*; 2013. Available from: http://aidsinfo.nih.gov/contentfiles/lvguidelines/glchunk/glchunk_23.pdf. Accessed November 15, 2014.
66. WHO. *Hormonal Contraceptive Methods for Women at High Risk of HIV and Living with HIV: 2014 Guidance Statement*; 2014. Available from: http://apps.who.int/iris/bitstream/10665/128537/1/WHO_RHR_14.24_eng.pdf. Accessed November 15, 2014.
67. Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy. *Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*; 2007. Available from: http://www.aidsinfo.nih.gov/contentfiles/PerinatalGLSafetyTox_Sup.pdf. Accessed December 7, 2014.
68. Womack JA, Scotch M, Leung SN, et al. Use of structured and unstructured data to identify contraceptive use in women veterans. *Perspect Health Inf Manag*. 2013;10:1e.
69. Guttmacher Institute. *Fact Sheet: Contraceptive use in the United States*. New York, NY: Guttmacher Institute; 2014. Accessed October 21, 2014.
70. Growth in World Contraceptive Use Stalling; 215 Million Women's Needs Still Unmet [webpage on the Internet]. Washington, DC: Earth Policy Institute; 2012 [cited March 27, 2012]. Available from: http://www.earth-policy.org/data_highlights/2012/highlights26. Accessed October 27, 2014.
71. Bristol-Myers Squibb. *Reyataz (Atazanavir) Package Label*. New York, NY: Bristol-Myers Squibb; 2014. Accessed October 12, 2014.
72. Boehringer-Ingelheim Pharmaceuticals I. *Aptivus (Tipranavir) Package Label*. Ingelheim am Rhein, Germany: Boehringer-Ingelheim; 2014. Accessed October 27, 2014.
73. GlaxoSmithKline. *Lexiva (Fosamprenavir) Package Label*. Brentford, UK: GlaxoSmithKline; 2009. Accessed October 24, 2014.
74. Pfizer. *Selzentry (Maraviroc) Package Label*. New York, NY: Pfizer; 2009. Accessed October 11, 2014.
75. Gilead Sciences I. *Stribild Package Label*. Foster City, CA: Gilead Sciences; 2012. Accessed October 27, 2014.
76. Landolt NK, Phanuphak N, Ubolyam S, et al. Efavirenz, in contrast to nevirapine, is associated with unfavorable progesterone and antiretroviral levels when coadministered with combined oral contraceptives. *J Acquir Immune Defic Syndr*. 2013;62(5):534–539.