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Drug interactions between hormonal contraceptives and antiretrovirals

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Objective: To summarize published evidence on drug interactions between hormonal contraceptives and antiretrovirals.

Design: Systematic review of the published literature.

Methods: We searched PubMed, POPLINE, and EMBASE for peer-reviewed publications of studies (in any language) from inception to 21 September 2015. We included studies of women using hormonal contraceptives and antiretrovirals concurrently. Outcomes of interest were effectiveness of either therapy, toxicity, or pharmacokinetics. We used standard abstraction forms to summarize and assess strengths and weaknesses.

Results: Fifty reports from 46 studies were included. Most antiretrovirals whether used for therapy or prevention, have limited interactions with hormonal contraceptive methods, with the exception of efavirenz. Although depot medroxyprogesterone acetate is not affected, limited data on implants and combined oral contraceptive pills suggest that efavirenz-containing combination antiretroviral therapy may compromise contraceptive effectiveness of these methods. However, implants remain very effective despite such drug interactions. Antiretroviral plasma concentrations and effectiveness are generally not affected by hormonal contraceptives.

Conclusion: Women taking antiretrovirals, for treatment or prevention, should not be denied access to the full range of hormonal contraceptive options, but should be counseled on the expected rates of unplanned pregnancy associated with all contraceptive methods, in order to make their own informed choices.

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Introduction

Women living with HIV will likely take combination antiretroviral therapy (cART) for much of their lives [1]. Those at high risk for HIV may also use antiretrovirals for preexposure prophylaxis (PrEP). Contraceptive use among women living with HIV or using antiretrovirals for PrEP is critical, as unintended pregnancy and short interpregnancy intervals can be associated with negative health consequences for both mother and infant [2–4]. Decreasing unintended pregnancies also reduces vertical HIV transmission [5]. Hormonal contraceptives are highly used worldwide, including in areas of high HIV prevalence; they are also among the most effective contraceptive methods [6,7]. Evidence-based guidance for hormonal contraceptives use among women using cART or PrEP is needed to ensure access to a full range of the best contraceptive methods, and therefore increase the likelihood of achieving their reproductive life planning goals.

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Table 1. Steroids used in currently available contraceptive methods, their liver metabolism, and effects on liver enzymes.

Contraceptive steroid	Abbreviation	Contraceptive method type (s)	Metabolism
Estrogens			
Ethinyl estradiol	EE	COC, patch, ring	Inhibits CYP2C19, CYP3A4, and CYP2B6 Induces UGTs Metabolized by CYP3A4 and CYP 2C9 and UGT
Estradiol cypionate	E2C	CIC	Inhibits CYP2C19, CYP3A4, and CYP2B6 Induces UGTs Metabolized by CYP3A4 and CYP 2C9 and UGT
Estradiol valerate	E2V	COC	Inhibits CYP2C19, CYP3A4, and CYP2B6 Induces UGTs Metabolized by CYP3A4 and CYP 2C9 and UGT
Progestins			
Ethynodiol diacetate	EDA	COCs	Metabolized to norethindrone
Dienogest	DNG	COC	Metabolized by CYP3A4
Nomegestrol acetate	NOMAC	COC	Metabolized by CYP3A3, CYP3A4, and CYP2A6
Drospirenone	DRSP	COC	Metabolized only to a minor extent, by CYP3A4
Gestodene	GES	COC	Metabolized by CYP3A4
Norgestrel	NG	COC	Metabolized by CYP3A4
Norgestimate	NGM	COC	Metabolized by CYP3A4
Desogestrel	DSG	COC, POP	Metabolized by CYP2C9 and CYP3A4
Norethindrone, norethindrone acetate Norethisterone enanthate	NET	COC, POI, POP	Metabolized by CYP3A4
Levonorgestrel	LNG	COC, implant, IUD, ECP	Metabolized by CYP3A4
Norelgestromin	NGMN	Patch	Metabolized by CYP3A4
Etonogestrel	ENG	Ring, implant	Metabolized by CYP3A4
Medroxyprogesterone acetate	MPA	CIC, POI	Metabolized by CYP3A4

Data from USFDA prescribing information, and review articles summarizing published literature. CIC, combined injectable contraceptives; COC, combined oral contraceptive; CYP, cytochrome P450 isozyme; ECP, emergency contraceptive pill; IUD, intrauterine device; MPA, medroxyprogesterone acetate; POI, progestin-only injectable; POP, progestin-only pill; UGT, uridine diphosphate glucuronosyltransferase.

Concurrent use of hormonal contraceptives and antiretrovirals can lead to drug interactions, predominantly due to effects on liver metabolism (Tables 1 and 2). In the liver, cytochrome P450 (CYP) enzymes catalyze many important reactions, with the most significant for contraceptive metabolism being CYP3A4, which is also expressed in the intestines [8,9]. Antiretrovirals include different classes of drug (Table 2), including nonnucleoside reverse transcriptase inhibitors (NNRTIs), nucleoside analogue reverse transcriptase inhibitors or nucleotide analogue reverse transcriptase inhibitor (NRTIs), protease inhibitors, fusion inhibitors, and integrase inhibitors. The NNRTIs and integrase inhibitors are generally not substrates, inhibitors, nor inducers of cytochrome P450 enzymes [10]. In contrast, both protease inhibitors and NNRTIs are metabolized by CYP3A4 and also inhibit or induce this enzyme, resulting in increases or decreases in the concentration of concomitantly administered drugs [10].

Such interactions could lead to decreased contraceptive effectiveness (increasing risk of unintended pregnancy), decreased cART effectiveness (associated with resistance and/or HIV disease progression), decreased efficacy of PrEP (increasing risk of HIV acquisition), or increased antiretroviral or contraceptive toxicity. Based on theoretical concerns and limited data, women using cART are sometimes offered fewer contraceptive choices than their HIV-negative peers [11]. The objective of this review was to systematically examine published evidence on drug interactions between hormonal contraceptives and antiretrovirals, in order to contribute to improved clinical and policy decision-making.

Methods

We followed the PRISMA and MOOSE guidelines for conducting the review and reporting the results [12,13].

We searched PubMed, POPLINE, and EMBASE from database inception to 21 September 2015 for studies of hormonal contraceptive and antiretroviral drug interactions (Supplement 1, http://links.lww.com/QAD/B36). We also hand-searched reference lists of published studies, and contacted topic experts.

Study selection

We included published studies of women using hormonal contraceptives (Table 1), including combined oral contraceptives (COCs), progestin-only pills (POPs), emergency contraceptive pills (ECPs), injectables, vaginal rings, patches, or implants. Studies included women who were either HIV-positive, HIV-negative but at risk of HIV, or healthy, who concurrently used cART, PrEP, or single antiretrovirals and hormonal contraceptives. We included studies reporting on women taking oral contraceptives where the type of oral contraceptive was not specified. We excluded studies evaluating women on cART without comparisons by contraceptive use, those evaluating only genital HIV viral load, and those

Table 2. Antiretrovirals included in the review, their liver metabolism, and effects on liver enzymes.

Generic name	Liver metabolism
NNRTIs	
Efavirenz (EFV)	Induces CYP3A4, CYP2B6, and UGTs Metabolized by CYP2B6 and CYP3A
Etravirine (ETR)	Induces CYP3A and inhibits CYP2C9, CYP2C19 Metabolized by CYP3A, CYP2C9, and CYP2C19
Nevirapine (NVP)	Induces CYP3A and CYP2B6 Metabolized by CYP3A, CYP2B6, and UGTs
Rilpivirine (RPV)	At higher doses (>3× approved 25 mg dose), induces CYP3A4 Metabolized by CYP3A4, CYP2C19, CYP1A2, and CYP2C
Delavirdine (DLV)	Inhibits CYP3A, CYP3A4, CYP2C9, CYP2D6, and CYP2C19 Metabolized by CYP3A and CYP2D6
Fosdevirine/GSK GSK2248761[a]	Weak inhibitor of CYP3A4 and CYP2D6 Metabolized by CYP3A4?
NRTIs	
Zidovudine (ZDV) or azidothymidine (AZT)	Does not affect liver enzymes Metabolized by UGTs
Abacavir (ABC)	Does not affect liver enzymes Metabolized by alcohol dehydrogenase and UGTs
Tenofovir disoproxil fumarate (TDF)	Does not affect liver enzymes Minimal liver metabolism; mostly eliminated unchanged in urine
Emtricitabine (FTC)	Does not affect liver enzymes Minimal liver metabolism; mostly eliminated unchanged in urine
Didanosine (DDI)	Does not affect liver enzymes Minimal liver metabolism; mostly eliminated unchanged in urine
Lamivudine (3TC)	Does not affect liver enzymes Minimal liver metabolism; mostly eliminated unchanged in urine
Stavudine (d4T)	Does not affect liver enzymes Minimal liver metabolism; mostly eliminated unchanged in urine
PIs	
Ritonavir (RTV)	Induces and inhibits CYP3A Induces CYP1A2, CYP2C9, CYP2C19, CYP2B6, and UGTs Inhibits CYP2D6 Metabolized by CYP3A, CYP2D6
Atazanavir (ATV)	Inhibits CYP3A and UGT1A1, and weak inhibitor of CYP2C8 Mostly metabolized by CYP3A4; other pathways include UGTs
Darunavir (DRV)	Co-administered with ritonavir, inhibits CYP3A and CYP2D6 Mostly metabolized by CYP3A
Fosamprenavir (FOS-APV)	Amprenavir, the active metabolite, induces and inhibits CYP3A4 Metabolized by CYP3A4
Saquinavir (SQV)	Co-administered with ritonavir, inhibits CYP3A Metabolized by CYP3A
Tipranavir (TPV)	Co-administered with ritonavir, inhibits CYP3A and CYP2D6 Induces CYP1A2 and CYP2C19 at steady state Metabolized by CYP3A
Indinavir (IDV)	Inhibits CYP3A4 Weak inhibitor of CYP2D6 Metabolized by CYP3A4
Nelfinavir (NFV)	Inhibits CYP3A4 Metabolized by CYP3A, CYP2C19
CCR5 inhibitors	
Maraviroc (MVC)	Inhibits CYP2D6 at higher doses Metabolized by CYP3A
Vicriviroc (VCV)[a]	Does not affect liver enzymes Metabolized by CYP3A
Fusion inhibitors	
Enfuvirtide (ENF)	Does not affect liver enzymes Catabolized to constituent amino acids
Integrase inhibitors	
Dolutegravir (DTG)	Not an inducer or inhibitor of CYP enzymes Metabolized by UGTs and CYP3A
Elvitegravir (EVG)	Inducer of CYP2C9 Metabolized by CYP3A4
Raltegravir (RAL)	Not an inducer or inhibitor of CYP enzymes Metabolized by UGTs
Pharmacokinetic enhancers	
Cobicistat (COBI)	Inhibits CYP3A, CYP2D6 Metabolized by CYP3A

Data from prescribing information, http://medicine.iupui.edu/clinpharm/ddis/main-table, and https://aidsinfo.nih.gov/drugs. CYP, cytochrome P450 isozyme; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside or nucleotide reverse-transcriptase inhibitor; PI, protease inhibitor; UGT, uridine diphosphate glucuronosyltransferase.
[a]Development halted due to toxicity or lack of efficacy.

evaluating only hormonal intrauterine devices (IUDs). We also excluded case or case-series reports, cross-sectional studies, reviews, editorials, and letters.

Outcomes of interest were clinical and pharmacokinetic measures of the contraceptive and the antiretroviral. Clinical outcomes included measures of contraceptive, cART, or PrEP effectiveness, and combined toxicity. Contraceptive effectiveness measures of interest were pregnancy or surrogate measures of pregnancy risk, including ovulation, ovarian activity, or cervical mucus. Because no studies reported on true ovulation as documented by ultrasound, we included studies using serum progesterone alone as a marker of presumed ovulation. For cART effectiveness, we included studies that reported markers of HIV disease progression such as $CD4^+$ cell count or HIV viral load, need for change in cART regimen, or death; for PrEP effectiveness, the relevant outcome was HIV prevention. Pharmacokinetic endpoints were plasma drug concentrations over time, as well as the area under the concentration–time curve (AUC), half-life ($t_{1/2}$), minimum (C_{min}; trough) and maximum (C_{max}; peak) concentrations, for both contraceptive steroids and antiretrovirals.

Data abstraction and management

After screening and removal of duplicates, we abstracted relevant data from each included report using a predesigned form. Two authors independently reviewed selected manuscripts, with differences resolved by consensus.

We described strengths, weaknesses, and funding source for each included study (Tables 3 and 4) [14–65], but did not do formal quality assessment because no formal evidence grading system exists for pharmacokinetic studies.

Results

Our search identified 1570 records. Fifty published reports from 46 individual studies met the inclusion criteria (Fig. 1, Tables 3 and 4). Four reports were secondary analyses or subsets of the primary studies and are included with the primary study in the tables [14–17]. The results are presented by outcome assessed, focusing first on the most important clinical outcomes (contraceptive effectiveness, antiretroviral effectiveness, toxicity associated with combined administration), then the pharmacokinetic data (for contraceptives and antiretrovirals), in each case by antiretroviral class and by contraceptive method.

Contraceptive effectiveness

Although pregnancy is the most relevant outcome, few large studies were designed to investigate contraceptive effectiveness. Several secondary analyses helped fill this gap, particularly for women using nevirapine-containing or efavirenz-containing cART. Although some small pharmacokinetic studies of healthy women report on pregnancy, women were generally required to use additional contraception; these studies are included in Table 3 but not summarized here.

Nonnucleoside reverse transcriptase inhibitors

Fourteen reports from clinical trials and six secondary analyses described contraceptive effectiveness measures among women using NNRTIs and hormonal contraceptives (Table 3).

Oral contraceptives

Two clinical trials of women using cART and oral contraceptives [18,19], six secondary analyses [20–25] and five pharmacokinetic trials (mostly in healthy women using single antiretrovirals with COCs) [26–30], evaluated pregnancy or ovulation. No pregnancies were found to be associated with nevirapine or efavirenz in the prospective clinical trials.

Pregnancy rates and ovulation rates did not differ between HIV-positive women taking COCs and nevirapine-containing cART and those not yet taking cART [18]. In a small trial of women using COCs with efavirenz-containing cART, three women ovulated (out of 25) but no pregnancies were reported [19]. Five small pharmacokinetic trials of NNRTIs and COCs also demonstrated no ovulation among study participants [26–30].

In large cohort studies, pregnancy rates were slightly higher among women taking efavirenz-containing cART (11–15/100 woman-years) compared with women taking oral contraceptive and nevirapine-containing cART or no cART (pregnancy rates 6–11/100 woman-years) [24,25]. Notably the reported pregnancy rates in the large cohort studies are still lower than an expected pregnancy rate of 40 per 100 woman-years among women not using any modern contraceptive and trying to prevent pregnancy.

Other retrospective cohort studies reported pregnancy rates among oral contraceptive users ranging from 2.6 to 5.8 per 100 woman-years (most, but not all, women were using nevirapine) [20,21].

Depot medroxyprogesterone acetate

In two pharmacokinetic studies, women using depot medroxyprogesterone acetate (DMPA) remained anovulatory when using cART containing either efavirenz or nevirapine [14,31,32]. Five cohort studies also presented pregnancy rates with injectables among cART users. In the largest, pregnancy rates ranged from 8 to 10 per 100 woman-years for injectable users, with higher rates in efavirenz users and those not on cART compared with pregnancy rates in those using nevirapine [24]. Another

Table 3. Studies reporting clinical measures of contraceptive and/or antiretroviral effectiveness with co-administration of hormonal contraceptives and antiretrovirals.

Reference; location	Design objective (s)	Number of participants (*N*); population	Intervention/treatment	Results	Strengths; weaknesses; funding source
Scarsi *et al.* [35] Uganda	Prospective open-label pharmacokinetic study To assess the effect of EFV or NVP containing cART on pharmacokinetics of LNG implants in HIV+ women	Sixty HIV+ women >18 years (median age 31), medically eligible for LNG implant, not recently pregnant, and not using other potentially interacting drugs	LNG implant cART-containing NVP or EFV, or no cART	Study stopped early due to unintended pregnancies in EFV group: 3/20 (15%) women in EFV group were pregnant: two at week 48 visit and one at week 42 LNG concentrations at last visit before pregnancy (week 36) were 122, 299, and 303 pg/ml Zero pregnancies in either no-cART or NVP groups No change in $CD4^+$ cell count HIV-RNA in ART groups No difference in adverse events	Strengths: clearly described interventions and outcomes; pregnancy confirmed by urine test; HIV+ women Weaknesses: nonrandomized; not designed to evaluate contraceptive effectiveness; no measurement of progesterone Funded by government
Patel *et al.* [24] Kenya	Retrospective cohort To compare pregnancy rates among women using different contraceptives and EFV and NVP containing cart	Twenty-four thousand, five hundred and sixty HIV+ women aged 15–45 years	2% ENG implant 5% LNG implant 17% DMPA 3% COCs/oral contraceptives 3% IUDs/permanent 49% NVP-containing cART 14% EFV-containing 4% LPV/r-containing 32% no cART	3337 incident pregnancies: overall pregnancy rate of 8.9/100 woman-years Unadjusted pregnancy rates by method and antiretroviral type (per 100 woman-years) COCs/oral contraceptives NVP 10.9 EFV 15.4 LPV 15.4 no cART 11.1 DMPA NVP 8.4 EFV 9.4 LPV 7.2 no cART 9.8 ENG implant NVP 2.3 EFV 5.5 LPV 1.3 no cART 3.4 LNG implant NVP 1.9 EFV 7.1 LPV 0 pregnancies no cART 3.3	Strengths: very large sample size; HIV+; good data on cART use; comparisons made to no contraception; able to separate implant type; pregnancy as main outcome Weaknesses: retrospective; self-reported pregnancy; high pregnancy rates even with no cART; self-reported contraceptive use; oral contraceptive use included progestin-only pills; no information on contraceptive method insertion/timing; different visit schedule for those on cART and those not on cart Funded by government
Pyra *et al.* [25] Kenya, Uganda	Secondary analysis of HIV prevention trials To understand the effect of cART on contraceptive effectiveness	Five thousand, one hundred and fifty-three HIV+ women <50 years; not sterilized and not using IUDs	9% implants 40% injectables 14% oral contraceptives 31% used cART: 23% NVP-containing regimen 5% EFV-containing	Pregnancy rates (per 100 woman-years) Implant no cART 1.4 NVP 0 EFV 6.0 Injectable no cART 5.3 NVP 3.3 EFV 3.8 oral contraceptives no cART 11.0 NVP 6.4 EFV 12.9	Strengths: large sample size; prospective data collection; pregnancy diagnosed by urine pregnancy test Weaknesses: self-reported contraceptive and cART use; no information on contraceptive method timing or implant type; few women using EFV-containing regimens Funded by government

Table 3 (*continued*)

Reference; location	Design objective (s)	Number of participants (*N*); population	Intervention/treatment	Results	Strengths; weaknesses; funding source
Callahan *et al*. [41] Kenya, South Africa	Secondary analysis of HIV prevention trial To describe contraceptive effectiveness and predictors of pregnancy; and relationship between TDF/FTC and contraceptive effectiveness	Two thousand, one hundred and twenty sexually active women at risk of HIV enrolled in PrEP trial; median age 23; median BMI 23; use of effective contraceptive required at enrollment	~50% not using any method or using condoms alone at screening At enrollment: 55% injectables 43% COCs 2% implants, IUDs, or sterilization TDF/FTC or placebo	Pregnancy rates (per 100 woman-years) Overall 9.6 TDF/FTC 11.4 placebo 7.7 Implant 0 Injectable: TDF/FTC 2.2 placebo 1.1 COCs: TDF/FTC 34.9 placebo 27.9 new users 35.1 prior users 20.7 TDF/FTC had no effect on contraceptive effectiveness of COCs in final model Women on TDF/FTC and COCs had more nausea or vomiting (8.1%) vs. COC + placebo group (1.4%)	Strengths: large cohort over long period; pregnancy confirmed by urine tests; contraceptive methods dispensed at study clinic; TDF/FTC use verified by blood levels; low loss to follow-up Weaknesses: poor adherence to TDF/FTC; self-reported COC use Funded by government
Whiteman *et al*. [43] Russia	Prospective cohort To examine the associations between hormonal contraceptive use and HIV progression and cART effectiveness	Seven hundred and nine sexually active HIV+ women; age 16–45 years; not pregnant or breast-feeding; no hysterectomy, infertility, or recent hormonal contraceptive or IUD use	At enrollment: 183 COCs 87 DMPA 156 nonhormonal methods cART-containing either PI or NNRTI	545 not on cART 161 on cART Three women discontinued due to unrecognized pregnancy at enrollment Five pregnancies during study but contraceptive method or cART use not reported No significant change in $CD4^+$ cell count or viral suppression between COC or DMPA and nonhormonal users Two deaths; no report of which contraceptive method used	Strengths: cART and contraceptive use verified; pregnancy by urine test or medical records; death verified by records Weaknesses: very high loss to follow-up; unclear if women becoming pregnant were using contraceptives; limited information on cART regimen Funded by government
Song *et al*. [42] USA	Randomized; double-blind; placebo-controlled; crossover study To examine the effect of DTG on pharmacokinetics and pharmacodynamics of EE and NGMN in COC users	Sixteen healthy women; age 18–40; mean age 31 years; 94% white; BMI 19–30 (mean 24.7); normal liver function; women had to use a second nonhormonal contraceptive	COC-containing NGM DTG 50 mg or placebo twice daily for 11 days	Fifteen women completed study Serum pregnancy test 7–14 days after last dose; zero pregnancies No difference in LH, FSH Progesterone data not reported No participants discontinued due to adverse events; no grade 3 or 4 or serious adverse events	Strengths: randomized; clearly described population and methods; progesterone measured several times during cycle Weaknesses: small sample size; healthy women; single antiretroviral; single cycle; ovulation data not reported and unclear from figure Funded by industry

Table 3 (*continued*)

Reference; location	Design objective (s)	Number of participants (*N*); population	Intervention/treatment	Results	Strengths; weaknesses; funding source
Kasonde *et al*. [51] Botswana	Secondary analysis of RCT To investigate the effect of TDF and the interaction of TDF and hormonal contraception on BMD among HIV-uninfected African men and women	One hundred and fourteen sexually active women at risk of HIV, from HIV prevention trial; 18–39 years; nonpregnant and nonbreast-feeding	Injectable or implant oral contraceptives TDF TDF/FTC placebo	Data not separated for women vs. men Bone mineral density with DEXA at distal and ultradistal forearm; lumbar spine; hip 3/114 (2.6%) had a low baseline bone mineral density; Changes in bone mineral density for women on either oral or injectable vs. no contraception not significant except for a positive effect of oral contraceptives on spine bone mineral density for women on TDF/FTC	Strengths: used DEXA to measure bone mineral density Weaknesses: some results not separated by gender or HIV status; no mention of pregnancy or lactation or other medication use; few data on contraceptive use; low adherence to TDF/FTC; unclear if injectable group also included implant users Funded by government
Luque *et al*. [39] USA	Open-label; multicenter; nonrandomized; steady-state pharmacokinetic study To assess the effect of LPV/r on DMPA pharmacokinetics and vice versa; and to assess safety and tolerance of DMPA given concurrent with LPV/r	Twenty nonpregnant; premenopausal HIV+ women; on stable LPV/r for at least 14 days; no DMPA within 180 days Median BMI 28	DMPA cART-containing LPV/r	No pregnancies Progesterone >5 ng/ml considered presumptive ovulation; zero ovulations noted No serious adverse events; one grade 3 adverse event (prolonged bleeding). No changes in $CD4^+$ cell count or HIV RNA through week 8 At week 12–3/24 women in LPV/r group had detectable HIV RNA; two due to antiretroviral noncompliance	Strengths: clearly described population and methods; HIV+ women; assessed ovulation at several time points Weaknesses: small sample size; short duration Funded by government
Todd *et al*. [59] Kenya	Secondary analysis of PrEP HIV prevention trial To examine PK of LNG with concurrent use of TDF-FTC as PrEP	Twenty-nine sexually active women at risk of HIV, who elected to received LNG implant; ages 18–35 TDF/FTC group: $N = 17$ Placebo group: $N = 12$ Mean BMI 22.6	LNG implant TDF/FTC or placebo	Follow-up 36 weeks No pregnancies and one implant discontinuation at 7 months, with reason for discontinuation not recorded	Strengths: TDF levels measured to assess for adherence Weaknesses: Small sample size; percentage retention not stated Funded by government

Table 3 (*continued*)

Reference; location	Design objective (s)	Number of participants (*N*); population	Intervention/treatment	Results	Strengths; weaknesses; funding source
Heffron *et al*. [50] Kenya, Uganda	Secondary analysis of PrEP RCT To evaluate TDF/FTC and TDF efficacy among women using DMPA compared with nonhormonal users	One thousand, seven hundred and eighty-five women at risk of HIV; median age 33 years	At enrollment: 486 DMPA users In follow-up: additional 415 DMPA users TDF/FTC, TDF, or placebo	Efficacy of PrEP not different for women using DMPA compared with women using no hormonal contraception Among DMPA users: efficacy 64.7% (PrEP vs. placebo) Among nonhormonal users: efficacy 75.5% (PrEP vs. placebo) *P* interaction = 0.65 No data about pregnancy reported	Strengths: large sample size; high adherence Weaknesses: secondary analysis; self-reported contraceptive use; adjustment for unprotected sex but unclear whether or how condom use was collected Funded by government
Day *et al*. [44] Kenya	Prospective cohort To test the hypothesis that DMPA would be associated with increased detection of HIV-1 RNA in women initiating and continuing cart	One hundred and two HIV+ women starting cART; median age 36; median $CD4^+$ cell count 122 cells/μl	At baseline: 18 (18%) DMPA 5 (5%) implants; 5 (5%) oral contraceptives cART-containing ZDV; d4T; 3TC; and NVP	Seventy two completed ≥33 months follow-up DMPA did not increase plasma HIV RNA	Strengths: long follow-up; adjusted for antiretroviral adherence and $CD4^+$ cell count Weaknesses: self-reported contraceptive and antiretroviral use; large loss to follow-up; 14% changed cART regimen; small number of women using DMPA Funded by government
Atrio *et al*. [16], Atrio *et al*. [56], Dubois *et al*. [17] USA	Nonrandomized clinical trial To evaluate the effect of protease inhibitors on cervical mucus of POP users	Thirty-five HIV+ women, age 18–44 years; no changes in medications; no recent hormonal contraceptives; no immunocompromise; no liver or renal disease; normal ovulation; BMI <40; >30 days postpartum	POPs containing NET In PI group: 11 taking cART containing ATV (10/11 on ATV/r); 3 DRV/r; 2 LPV/r In control group: four women not taking cART; 13 taking combinations including ETR, RPV, TDF, FTC, and RAL	Baseline mucus scores similar Cervical mucus scores in PI and non-PI groups similar after POPs: median score 3.5 for PI group and four for controls score <10 (unfavorable to sperm penetration): 81% of study group; 60% of comparison group	Strengths: prospective design; blinded assessments Weaknesses: no baseline of periovulatory mucus for all women; small sample size; nonrandomized; cART use self-reported; results not separated by antiretroviral Funded by government

Table 3 (*continued*)

Reference; location	Design objective (s)	Number of participants (*N*); population	Intervention/treatment	Results	Strengths; weaknesses; funding source
Murnane *et al*. [40] Kenya, Uganda	Secondary analysis of PrEP HIV prevention trial To assess the impact of TDF and TDF/FTC on hormonal contraceptive effectiveness	One thousand, seven hundred and eighty-five sexually active women at risk of HIV, enrolled in HIV prevention trial; median age 33	At enrollment: 27% injectables During follow-up: 14% initiated oral contraceptives 20% injectables 6% implants TDF/FTC; TDF; or placebo	Two hundred and eighty eight pregnancies in 267 women (179 TDF or TDF/FTC and 88 placebo); no difference across arms Pregnancy rates per 100 women-years Oral contraceptives TDF or TDF/FTC 17.7 placebo 10.0; no significant difference Injectables TDF or TDF/FTC 5.1 placebo 5.3 Implants <1% per year in both arms	Strengths: large sample size; verified contraceptive use; good adherence to study product; Weaknesses: nonrandomized; oral contraceptive, implant, and injectable type not specified; contraceptive use and adherence self-reported Funded by government
Perry *et al*. [36] Switzerland	Retrospective cohort To evaluate risk of pregnancy in implant users using cART	Five hundred and seventy HIV+ women who had LNG implant	LNG implants 347 (61%) using cART at implant insertion: 208 on NVP-containing regimens; 121 on EFV-containing regimens; 18 on LPV/r-containing regimens	Sixteen pregnancies in 570 women 15/121 (12.4%) of women on EFV became pregnant; mean time between implant insertion and pregnancy was 16.4 months No women conceived while using NVP or LPV/r, one pregnancy occurred before cART was started Age, condom use, inserting provider, $CD4^+$ cell count had no association with pregnancy	Strengths: large sample size; HIV+; verified contraceptive use, implant insertion date known Weaknesses: retrospective study; self-reported cART use; 3/16 women who became pregnant had received antituberculosis treatment; no BMI information Funded by hospital
Vieira *et al*. [34] Brazil	Prospective cohort with pharmacokinetic analysis To evaluate the effects of EFV-containing or LPV/r-containing cART on ENG implant pharmacokinetics and to determine the impact of cART on luteal activity	Forty five HIV+ women with regular menstrual cycles, BMI 18–30; excluded women with recent pregnancy or hormonal contraceptive use, acute infections or other opportunistic illnesses, drug or alcohol addiction, use of other potentially interacting drug, chronic diarrhea or malabsorption or noncompliance with cART	ENG implant LPV/r-containing or EFV-containing cART, or no cART	Progesterone measured every 2 weeks; >4.7 ng/ml considered presumptive ovulation; progesterone >3 ng/ml considered luteal activity 2.8% of the P samples in EFV group had presumptive ovulation; and 5% had luteal activity No women in LPV/r or no cART groups had evidence of any luteal activity VL <50 copies/ml in LPV/r and EFV groups	Strengths: clearly described population and methods; frequent progesterone measurements Weaknesses: Small sample size; nonrandomized Funded by government

Table 3 (*continued*)

Reference; location	Design objective (s)	Number of participants (*N*); population	Intervention/treatment	Results	Strengths; weaknesses; funding source
Hubacher *et al*. [45] Kenya	Prospective cohort To examine how concurrent use of hormonal contraceptive implants and cART might lessen the effectiveness of both medications	Ninty-three sexually active HIV+ nonpregnant women, age 18–44 years; $CD4^+$ cell count ≥ 200 cells/μl; without recent hormonal contraceptive or rifampin use, desire for pregnancy, or contraindications to implant use	LNG implant or nonhormonal contraception NVP-containing cart	LNG implant users (60 recruited; 48 analyzed) matched to women not using hormonal contraception (36 recruited; 33 analyzed) $CD4^+$ cell counts for both groups rose slightly but did not differ between groups No participants died; six participants (two implant users, four controls) diagnosed with opportunistic infections Zero pregnancies in implant users	Strengths: large sample size; implant inserted at study site Weaknesses: method of pregnancy ascertainment not stated; observational study; no non-cART users; six women (10%) of implant group had implant removed within 12 months; cART self-reported Funded by government
Landolt *et al*. [15,19] Thailand	Prospective; open-label; nonrandomized steady-state clinical trial To assess risk of ovulation and safety in women taking COCs with cart	Forty-nine HIV+ nonpregnant, nonlactating women; 18–45 years, with regular menses, on EFV-containing or NVP-containing cART; nonsmoking, no recent injectable contraceptive use, no contraindications to COCs Fourteen HIV− controls	COC containing DSG for two cycles NVP-containing or EFV-containing cART	Forty-eight completed study, 15 discontinued, including 13 due to protocol adherence issues Ovulation by serum progesterone: NVP group: All women had progesterone <1.0 ng/ml EFV group: three women had progesterone >3.0 ng/ml More women in EFV group reported adverse events than NVP group	Strengths: prospective clinical trial; HIV+ women Weaknesses: nonrandomized; small sample size; single progesterone measurement; no adherence information; high dropout rate Funded by government

Table 3 (*continued*)

Reference; location	Design objective (s)	Number of participants (*N*); population	Intervention/treatment	Results	Strengths; weaknesses; funding source
Nanda *et al.* [18] Uganda, South Africa	Prospective open-label nonrandomized clinical trial To compare ovulation and pregnancy rates between two groups of women: those taking COCs concurrently with NVP-containing cART and those taking COCs alone	Four hundred and two sexually active HIV+ women 18–35 years, with regular menses and no contraindications to COC use; median age 29 and median $CD4^+$ cell count 486 cells/μl	COC-containing NG cART group included women on NVP-containing cART; $n=196$ Control group included women not yet eligible for cART; $n=206$	Ovulation by serum progesterone (>3 ng/ml) cART group: 43/168 (26%) ovulated in cycle 1; 30/163 (18%) in cycle 2; 18/163 (11%) in both cycles Non-cART group: 26/168 (15%) ovulated in cycle 1; 31/165 (19%) in cycle 2; and 20/165 (12%) in both cycles No significant difference in ovulation rates between groups Pregnancy rates (per 100 woman-years): 10. in cART group and 10.1 in non-cART group Adverse events similar; five serious adverse events, all in non-cART group	Strengths: prospective clinical trial; COCs and antiretrovirals at steady state; multiple progesterone measurements; large sample size; HIV+ women; information on COC adherence Weaknesses: nonrandomized, self-reported cART and COC adherence; no pharmacokinetic measures Funded by government
Crauwels *et al.* [27] UK	Open-label, three period pharmacokinetic study To evaluate the effect of RPV on COC pharmacokinetics and vice versa, and assess effects on sex hormones and safety of co-administration	Eighteen healthy nonsmoking women, 18–45 years; BMI 18–30 (median 24.6); 67% white; excluded pregnant, breast-feeding, or menopausal women, those with history of drug/alcohol abuse, skin disease, or any significant medical problems; use of concomitant medication	COC-containing NET In third cycle; RPV 25 mg daily days 1–15	Thirteen completed trial Progesterone; LH; and FSH on day 1 and 14; 0 ovulations; no effect on FSH; LH No difference in adverse events	Strengths: clearly described population and methods; directly observed therapy Weaknesses: healthy women; short-term dosing; single antiretroviral; high discontinuation rate Funded by industry

Table 3 (*continued*)

Reference; location	Design objective (s)	Number of participants (*N*); population	Intervention/treatment	Results	Strengths; weaknesses; funding source
Polis *et al*. [46] Uganda	Retrospective cohort To assess the effect of injectable contraceptive use on cART effectiveness and adherence to cart	Four hundred and eighteen pregnant and nonpregnant sexually active HIV+ women initiating cART, without tuberculosis, with information on baseline viral load	51/418 (12%) used unspecified injectables at baseline cART (not specified)	Failure defined as failure to achieve virologic suppression at 12 months, switch to second-line therapy, or death within 12 months of cART initiation No difference in treatment failure at 12 months between injectable users and nonusers (11 vs. 12%) Injectables not associated with cART failure in sensitivity analysis restricted to women with complete information who never used pills or implants No differences in cART adherence at 6 and 12 months for injectable users and nonusers	Strengths: large sample size Weaknesses: retrospective; observational database analysis; self-reported contraceptive use; inconsistent injectable use over time; type of injectable and cART not specified Funded by government
Carten *et al*. [52] USA	Open-label two period pharmacokinetic study To determine the effect of EFV on the pharmacokinetics of LNG EC and vice versa, and assess safety	Twenty-four healthy women; 18–45; normal BMI (mean BMI 27) with no recent use of hormonal contraceptives or other interacting medications; women were either sterilized or used two nonhormonal contraceptive methods	LNG ECPs (0.75 mg) at 0 and 12 h on days 0 and 17 EFV 600 mg 72 h after day 0, for 14 days	Twenty-one women completed study Follow-up pregnancy test at visit 3 (study day not specified) Pregnancy test results not given No grade 3 or 4 treatment-related toxicities.	Strengths: clearly described population and methods Weaknesses: small sample size; healthy women; single antiretroviral; ovulation not tested; single follow-up pregnancy test but timing and results not given Funded by industry
Piscitelli *et al*. [29] UK	Randomized crossover pharmacokinetic study To examine if GSK2248761 (fosdevirine) interacts with CYP450 substrates, including COCs	Ten healthy women, without hepatitis and not taking any medications	COC containing DRSP GSK228761 200 mg or placebo days 1–11	No differences in LH/FSH No serious adverse events or treatment due to adverse events, and no significant laboratory abnormalities	Strengths: randomized Weaknesses: short term administration; healthy women; single antiretroviral; small sample size; very few study details provided; trials of fosdevirine on hold due to other safety concerns; study terminated early for unknown reasons Funded by industry

Table 3 (*continued*)

Reference; location	Design objective (s)	Number of participants (*N*); population	Intervention/treatment	Results	Strengths; weaknesses; funding source
Schwartz *et al*. [21] South Africa	Prospective cohort To determine the incidence of unplanned pregnancies in HIV+ women on cART; to assess contraceptive use and associations with unplanned pregnancy	Eight hundred and fifty HIV+ women; ages 18–35; on/starting cART; not pregnant, recently pregnant, or breast-feeding; no known infertility	243 (29%) using HC: Injectables (DMPA + NET-EN; 192); COCs (46); implants (type not stated 4); IUD (1) Multiple antiretrovirals: 52% NVP-containing regimens; 42% EFV-containing	One hundred and seventy pregnancies in 161 women; 105 (62%) unplanned (incidence rate: 16.1/100 woman-years Nine of 105 unplanned pregnancies were potentially hormonal contraceptive failures; seven on NVP and one on EFV; incidence of unplanned pregnancy 4.4 per 100 woman-years One failure not related to adherence in COC user (5.8/100 woman-years) Seven injectable failures (two DMPA; five NET-EN; (incidence rate 4.2/100 woman-years); 5/7 in last 2 weeks of injection cycle	Strengths: pregnancy by urine hCG; cART confirmed by pharmacy records; contraceptive failures confirmed through records review Weaknesses: observational study; contraceptive use self-reported; reported only at baseline; did not report which HC failures were using which antiretroviral Funded by government
Kreitchmann *et al*. [33] Brazil	Prospective cohort To evaluate the safety and efficacy of ENG implants among HIV+ women	Seventy nine HIV+ women with comorbidities and poor adherence to other contraceptive methods; mean age 29; mean weight 59 kg (range 42–104)	ENG implant At baseline: 47 used cART; nine began cART during follow-up (PI containing-regimen 31; NNRTI-containing 25)	Women followed up every 6 months over 3 years and 0 pregnancies noted Four women had elevated liver enzymes: all coinfected with hepatitis C ENG implant removed in five women: two had tubal ligation; one hysterectomy; two because of excessive bleeding Menstrual irregularity most common adverse event; two unrelated deaths: one of AIDS, and one of cardiac arrest (baseline cardiomyopathy)	Strengths: verified contraceptive use; prospective study; HIV+ women Weaknesses: self-reported pregnancy; did not specify cART type Funding source not specified

Table 3 (*continued*)

Reference; location	Design objective (s)	Number of participants (*N*); population	Intervention/treatment	Results	Strengths; weaknesses; funding source
Johnson *et al*. [47] USA	Retrospective cohort To examine how use of hormonal contraceptives affects response to cART	One hundred and seven HIV+ adolescent women reporting consistent cART; median age 17 years	Seventy-two percent oral contraceptives Twenty eight percent DMPA cART regimens included ZDV and ZDV/3TC	No difference in $CD4^+$ cell counts over time Viral load decreased over time in hormonal users and nonusers; but an interaction was noted: decrease in viral load was slightly slower (1.2×10^{-3}; 95% CI: 6.2×10^{-5} to 2.4×10^{-3} copies/ml log viral load per day; $P = 0.03$) among hormonal contraceptive users	Strengths: HIV+ women Weaknesses: retrospective; changes in viral load of questionable clinical significance; contraceptive use self-reported; not separate type of contraceptives Funded by government
Stuart *et al*. [30] Malawi	Prospective nonrandomized clinical trial To assess the feasibility of measuring anovulation in a pharmacokinetic study of COCs and antiretrovirals	Nine women ages 21–35 (3/group) with similar age and BMI: group 1 included HIV+ women on cART; group 2 included HIV+ women not on cART; and group 3 included HIV− women	COC with NG NVP-containing cART or no cART	Ovulation by serum progesterone (>3.0 ng/ml) on day 14; 0 ovulations	Strengths: Clearly described population and methods; valid assays; included HIV+ women Weaknesses: very small sample size; nonrandomized; progesterone measured only once Funding source not reported
Sevinsky *et al*. [26] USA	Open-label 3-period pharmacokinetic study To examine effect of EFV on pharmacokinetics of EE and NGMN and vice versa	Twenty-eight healthy women; 18–45 years (median 26); BMI 20–32 (median 25); on COCs for at least 2 months and no baseline safety issues or breakthrough bleeding	COC-containing NGM EFV 600 mg daily for 14 days during third cycle	Nineteen women completed study Pregnancy test day 108; results not reported Progesterone levels similar and all <1.25 ng/ml No discontinuations for adverse events; three severe adverse events: headache; anhedonia; and depression; one serious adverse event – suicide attempt after treatment in a woman with prior undisclosed depression	Strengths: clearly described population and methods Weaknesses: small sample size; single progesterone measurement per cycle; pregnancy testing results not reported; healthy women; single antiretroviral; high discontinuation rate Funded by industry

Table 3 (*continued*)

Reference; location	Design objective (s)	Number of participants (*N*); population	Intervention/treatment	Results	Strengths; weaknesses; funding source
Vogler *et al*. [37] USA	Open-label; 4-week; nonrandomized; comparative clinical trial To evaluate pharmacokinetics interactions between LPV/r and contraceptive patch and COCs	Thirty two nonpregnant; premenopausal HIV+ women >13 years either on stable LPV/r-containing regimens for at least 14 days ($n=8$) or not on cART or taking NRTIs only ($n=24$); nonsmoking; median weight 72 kg; no recent use of injectables or COCs; <198 lb; not taking enzyme inducers	EE/NGMN contraceptive patch Single-dose COC containing NET LPV/r (400 mg/100 mg twice a day) or no cART/NRTIs only	Zero ovulations by serum progesterone HIV-1 RNA and $CD4^+$ cell counts measured at 30–45 days prior to entry; at entry and 4 weeks Median $CD4^+$ ↑15% (LPV group) with maintenance of viral suppression Treatment arm: single possibly related grade-3 adverse event (generalized aches and pains); 3 patients with 7 w/grade 1–2 adverse events; 14 control pts w/ grade 1–2 adverse events; No significant changes in weight; chemical or lab values	Strengths: clearly described population and methods; HIV+ Weaknesses: study stopped due to slow accrual; small sample size; single progesterone measurement; single dose COC; high loss to follow-up; not randomised Funded by government
Myer *et al*. [20] Cote d'Ivoire, Kenya, Rwanda, South Africa, Uganda, Zambia	Secondary analysis of MTCT-Plus Initiative cohort To examine whether improved health from cART affects pregnancy rates	Four thousand, five hundred and thirty-one HIV+ women who had received PMTCT services; median age = 27	At baseline 1; 755 (39%) reported contraceptive use: Injectables (15%) oral contraceptives (4%) IUDs (1%) Among women who started cART; 90% used NVP-containing regimens	Five hundred and eighty-nine pregnancies in 4531 women (7.8/100 woman-years) Higher pregnancy rate in women taking cART (9.0/100 woman-years) compared with women not on cART (6.5/100 woman-years) In injectable users pregnancy rates (per 100 woman-years) 1.1 before cART and 2.0 after cart In oral contraceptive users pregnancy rates (per 100 woman-years) 3.1 before cART and 5.4 after cart	Strengths: large sample size; prospective data collection; long follow-up; HIV+ Weaknesses: unclear whether women were actually using contraceptives when pregnancy occurred; study not designed to look at pregnancy; self-reported pregnancy and contraceptive use Funded by private foundation
Schöller-Gyüre *et al*. [28] USA	Open-label three period pharmacokinetic study To assess the effect of ETR on COC pharmacokinetics	Twenty-four healthy women; 18–45 years (median 24); BMI 18–30; 97% white; nonsmoking; not pregnant or breast-feeding; no contraindications to hormonal contraceptives; not taking enzyme inducers	COC-containing NET In cycle 3; 200 mg ETR twice daily from day 1–15	Serum progesterone; LH; FSH on days 1 and 14 of cycles 2 and 3 Zero ovulations; no difference in LH; FSH Nine adverse events led to discontinuation: seven grade 2 rashes; one grade 2 pyrexia	Strengths: clearly described population and methods; valid assays Weaknesses: healthy women; small sample size; few progesterone measurements; single antiretroviral Funded by industry

Table 3 (*continued*)

Reference; location	Design objective (s)	Number of participants (*N*); population	Intervention/treatment	Results	Strengths; weaknesses; funding source
Nanda *et al.* [32] Brazil	Nonrandomized, controlled, open-label pharmacokinetic study To evaluate the effect of EFV-containing cART on pharmacokinetics of MPA, and to evaluate suppression of ovulation and bleeding patterns	Thirty-three HIV+ women aged 19–40 years; with regular menstrual cycles and BMI 18–30 kg/m^2; not recently pregnant or breast-feeding	DMPA EFV-containing cART vs. no cart	Progesterone measured every 2 weeks; >3 ng/ml considered evidence of ovulation: one ovulation in non-cART group at 12 weeks No differences in bleeding patterns between groups No serious adverse events	Strengths: Clearly described population and methods; HIV+ women; frequent progesterone measurements Weaknesses: small sample size, no progesterone levels beyond 12 weeks Funded by government
Sekar *et al.* [38] Belgium	Randomized crossover pharmacokinetic study To investigate the effect of DRV/r on COC pharmacokinetics and to examine safety	Twenty-two nonsmoking healthy women, 18–45 years; BMI 18–30; using a second nonhormonal contraceptive method	COC-containing NET DRV/r 600/100 mg twice daily days 1–14 or no treatment	Progesterone; LH; FSH on days 1 and 14 of each cycle No significant changes in LH or FSH with co-administration No serious adverse events or grade 3 or 4 adverse events; five women discontinued due to grade 2 cutaneous reactions with combined treatment	Strengths: clearly described population and methods; randomized Weaknesses: 17-OH progesterone levels presented instead of progesterone levels; small sample size; healthy women; single antiretroviral; high discontinuation rate Funded by industry
Cohn *et al.*, Watts *et al.* [14,31] USA	Nonrandomized open-label pharmacokinetic study To evaluate the effect of various antiretrovirals on pharmacokinetics of MPA and vice versa; and to determine effects on suppression of ovulation and adverse events	Seventy-two HIV+ nonpregnant; premenopausal women, 22–46 years (median 35); median weight 71 kg; with no recent potentially interacting drugs; women required to use second nonhormonal method of contraception	DMPA Sixteen on no PI or NNRTI (control) 21 on nelfinavir and NRTIs 17 on EFV and NRTIs 16 on NVP and NRTIs	Zero pregnancies Progesterone every 2 weeks; >5 ng/ml considered presumed ovulation; zero ovulations No changes in median CD4$^+$ cell count or proportion with viral load <400 copies/ml No grade 3 or 4 related adverse events.	Strengths: Clearly described population and methods; HIV+ women; frequent progesterone measurements Weaknesses: nonrandomized; small sample size; progesterone only measure up to 12 weeks Funded by government
Danel *et al.* [22] Cote d'Ivoire	Prospective cohort To evaluate the efficacy and tolerance of ZDV; 3TC; and EFV in West African women and men	Five hundred and forty-eight HIV+ women <18 years (median age 23), naive to cART, CD4$^+$ cell count 150–350 cells/ml	Approx. 80 reported using contraceptives: 65% 'intramuscular progesterone' 35% COCs EFV-containing cart	Seven pregnancies; incidence 2.6/100 person-years (95% CI 0.67–4.51)	Strengths: HIV+ women; large sample size; prospective Weaknesses: study not designed to measure pregnancy; unclear whether women were actually using contraceptives when conception occurred; did not separate injectables from oral contraceptives Funded by government

Table 3 (*continued*)

Reference; location	Design objective (s)	Number of participants (*N*); population	Intervention/treatment	Results	Strengths; weaknesses; funding source
Chu *et al.* [48] USA	Retrospective cohort To determine the effects of hormonal contraceptives on response to cart	Seventy-seven hormonal contraceptive users matched with 77 nonusers from the Women's Interagency HIV Study; all women took cART	Seventy-seven hormonal contraceptive users: 64% COC 27% DMPA 4% LNG implant 4% COCs and DMPA Seventy-seven women not using hormonal contraceptives cART containing NRTIs + PI or NNRTI; or NRTIs alone	By fourth visit; 65% stopped hormonal contraceptives No significant difference in $CD4^+$ cell count and HIV viral load by hormone use after antiretroviral initiation except in viral load at the third visit after initiation Time-dependent hormonal contraceptive use not associated with changes in $CD4^+$ cell count or undetectable viral load after cART initiation	Strengths: matched comparison group, HIV+ women Weaknesses: retrospective; low overall use of hormonal methods contraceptive information obtained retrospectively and mainly at baseline (before cART); did not separate COCs from progestin-only methods; high method discontinuation rate Funded by government
Clark and Theall [23] USA	Retrospective cohort To determine the frequency of oral contraceptive failure among HIV+ women on cART	Two thousand and fifty-three women	86 (4.2%) taking oral contraceptives cART containing various antiretrovirals	Forty one women were pregnant with records showing hormonal contraceptive during the same 6-month period Eleven of 41 women apparently conceived while using hormonal contraceptives (DMPA = 1 or oral contraceptives = 10) Women on NFV-containing regimens more likely to experience oral contraceptive failure	Strengths: large sample size, HIV^+ women Weaknesses: retrospective chart review; unclear whether women actually taking contraceptives at time of pregnancy; difficult to interpret findings; no data on cART use or adherence; no details about pregnancy; very small numbers of cases; timing of HC and cART use not clear Funding source not specified
Frohlich *et al.* [64] Germany	Open-label single period pharmacokinetic study To investigate the influence of COCs on SQV pharmacokinetic and to assess the potential contribution of CYP3A4 and P-gp	Eight healthy nonsmoking nonpregnant women with regular menses; mean age 24 years and mean BMI 21; not using any potentially interacting drugs	COC containing GES days 4–25	Estradiol; progesterone; LH; FSH on days 1 and 22 COC use resulted in decreased plasma estradiol levels; progesterone; FSH; and LH; and increased SHBG	Strengths: Clearly described population and methods Weaknesses: did not evaluate the effect of SQV use on ovarian suppression; not randomized; very small sample size; short course of COCs; healthy women; single antiretroviral only given twice Funded by government

Table 3 (*continued*)

Reference; location	Design objective (s)	Number of participants (*N*); population	Intervention/treatment	Results	Strengths; weaknesses; funding source
Cejtin *et al*. [49] USA	Retrospective cohort To compare HIV-1-RNA and $CD4^+$ cell counts from users and nonusers of hormonal contraception	Premenopausal HIV+ women <50 years of age	One hundred and seventy-seven users of hormonal contraception: 87 oral contraceptives 77 DMPA 13 LNG implant One thousand, five hundred and forty-four nonusers of hormones 40.7% of users and 32.9% of nonusers on cART; most on monotherapy	Hormonal contraceptive use not associated with significant changes in viral load or $CD4^+$ cell count	Strengths: Some longitudinal data and large study size Weaknesses: no disaggregation by type of cART or contraceptive method; difficult to interpret findings; self-reported contraceptive use Funded by government
Mildvan *et al*. [53] USA	Open-label, single dose, two period pharmacokinetic study To determine the effects of NVP on COC pharmacokinetics and vice versa	Fourteen HIV+ nonpregnant, nonlactating, nonsmoking women; age 18–65 (mean age 37); viral load <400; $CD4^+$ cell count >100; normal renal and hepatic function; no RTV or DLV use	Single dose of COC containing NET on cycle days 1 and 30 NVP 200-mg daily on days 2–15; then 200-mg twice daily days 16–29; single dose on day 30 cART regimens included IDV; NFV; SQV/RTV	Ten women completed the study Pregnancy test on day 30 HIV RNA and T cells measured at screening, day 0, day 30 No change in HIV RNA concentration or $CD4^+$ cell count on day 30 compared with baseline Eight of 14 had at least one adverse event; no adverse event considered related to COC	Strengths: HIV+ women, well described population Weaknesses: small study; only single dose COC; NVP added to current cART regiment; included postmenopausal women Funded by industry

Abbreviations for antiretrovirals and contraceptive steroids defined in Tables 1 and 2. cART, combination antiretroviral therapy; COC, combined oral contraceptive; DEXA, dual energy x-ray absorptiometry; DMPA, depot medroxyprogesterone acetate; ECP, emergency contraceptive pill; FSH, follicle stimulation hormone; HC, hormonal contraceptive; LH, luteinizing hormone; MPA, medroxyprogesterone acetate; NET-EN, norethisterone enanthate; POP, progestin-only pill; PrEP, preexposure prophylaxis; SHBG, sex hormone binding globulin.

Table 4. Studies reporting pharmacokinetic outcomes with co-administration of hormonal contraceptives and antiretrovirals.

Reference; location	Design objective (s)	Number of participants (*N*); Population	Intervention/treatment	Results	Strengths, weaknesses; funding
Scarsi *et al.* [35] Uganda	Prospective open-label pharmacokinetic study To assess the effect of EFV-containing or NVP-containing cART on pharmacokinetics of LNG implants in women living with HIV	Sixty HIV+ women >18 years (median age 31), medically eligible for LNG implant, not recently pregnant, and not using other potentially interacting drugs	LNG implant cART-containing NVP or EFV or no cART	Primary endpoint: LNG levels at 24 weeks (compared with no cART group) EFV group ↓47% NVP group ↑35% Secondary: LNG levels at 48 weeks EFV group ↓57% NVP group ↑14% EFV and NVP levels not affected by LNG	Strengths: clearly described interventions and outcomes; valid assays; HIV+ women Weaknesses: nonrandomized; open label; LNG levels much higher than previously seen in other studies Funded by government
Song *et al.* [42] USA	Randomized; double-blind; placebo-controlled; crossover study To examine the effect of DTG on pharmacokinetic and pharmacodynamic of EE and NGMN in COC users	Sixteen healthy women; age 18–40; mean age 31 years; 94% white; BMI 19–30 (mean 24.7); normal liver function; women had to use a second nonhormonal contraceptive	COC-containing NGM DTG 50 mg or placebo twice daily for 11 days	EE levels unchanged NGMN AUC; C_{min}; C_{max} unchanged DTG levels similar to historical controls	Strengths: randomized; clearly described methods; valid assays Weaknesses: healthy women only; single cycle Funded by industry
Luque *et al.* [39] USA	Open-label nonrandomized pharmacokinetic study To assess the effect of LPV/r on DMPA pharmacokinetics and vice versa; and to assess safety and tolerability	Twenty-four nonpregnant premenopausal HIV+ women with no recent DMPA; median BMI 28; HIV RNA <400 copies/ml	DMPA; LPV/r containing cART cART-containing LPV/r	MPA levels compared with historical controls: AUC↑ 46% C_{max} ↑66% No changes in LPV or RTV levels after DMPA	Strengths: clearly described population and methods; valid assays; HIV+ women Weaknesses: small sample size; historical controls; levels only assessed through 12 weeks Funded by government
Todd *et al.* [59] Kenya	Secondary analysis of PrEP HIV prevention trial To examine pharmacokinetic of LNG with concurrent use of TDF/FTC as PrEP	Twenty-nine healthy women who elected to received LNG implant; ages 18–35 TDF/FTC group: $N = 17$ Placebo group: $N = 12$ Mean BMI 22.6	LNG implant TDF/FTC or placebo	Follow-up 36 weeks LNG levels all above 400 pg/ml; mean LNG levels 469–660 pg/ml LNG levels lower for women randomized to the TDF/FTC arm, but in multivariable analysis TDF/FTC use not associated with changes in LNG levels compared with placebo	Strengths: TDF levels measured to assess for adherence Weaknesses: Small sample size; percentage retention not stated; LNG concentration measures were missing for 42 time points Funded by government

Table 4 (*continued*)

Reference; location	Design objective (s)	Number of participants (*N*); Population	Intervention/treatment	Results	Strengths, weaknesses; funding
Landolt *et al*. [15,19] Thailand	Open-label; nonrandomized clinical trial To evaluate EE and ENG levels in women taking EFV-containing and NVP-containing cART and COCs	Forty-eight HIV+ nonpregnant, nonlactating women; 18–45 years, with regular menses, on EFV-containing or NVP-containing cART; no smoking, recent injectable contraceptive use, or contraindications to COCs Forteen HIV− controls	COC-containing DSG for two cycles NVP-containing or EFV-containing cART or no cART	NVP group: EE C_{min} ↓58% ENG C_{min}↓22% EFV group: EE C_{min} ↓9% ENG C_{min}↓61% One woman (6%) had NVP level below therapeutic level of 3.1 mg/l Three women had EFV level below therapeutic level of 1.0 mg/l	Strengths: prospective clinical trial; COCs and antiretrovirals at steady state; HIV+ women Weaknesses: nonrandomized; small sample size; single measurement of ENG levels; high drop out/loss to follow-up rate; unable to measure ENG in 8/16 due to assay interference Funded by government
Vieira 2014 [34] Brazil	Prospective cohort with pharmacokinetic analysis To evaluate the effects of EFV-containing or LPV/r-containing cART on ENG implant pharmacokinetics and to determine the impact of cART on luteal activity	Forty-five HIV+ women with regular menstrual cycles, BMI 18–30; excluded women with recent pregnancy or hormonal contraceptive use, acute infections or other opportunistic illnesses, drug or alcohol addiction, use of other potentially interacting drug, chronic diarrhea or malabsorption or noncompliance with cART	ENG implant LPV/r-containing or EFV-containing cART or no cART	ENG levels through 24 weeks EFV group: ENG AUC↓63% C_{max}↓54% C_{min} ↓70% LPV/r group: ENG AUC↑52% C_{max} ↑61% C_{min} ↑ 34%	Strengths: Clearly described population and methods; valid assays, HIV+ Weaknesses: Small sample size; nonrandomized Funded by government
Atrio *et al*. [16] Atrio *et al*. [56] Dubois *et al*. [17] USA	Open-label; nonrandomized; clinical trial To compare NET pharmacokinetic in women taking cART with PIs compared with women receiving other cART regimens	Thirty-five HIV+ women age 18–44 years; no changes in medications; no recent hormonal contraceptives; no immunocompromise; no liver or renal disease; normal ovulation; BMI <40; >30 days postpartum;	POPs containing NET In PI-containing cART group: 11 taking ATV (10/11 on ATV/r); 3 DRV/r; 2 LPV/r In control group: four women not taking PI-containing cART; 13 taking combinations including ETR, RPV, TDF, FTC, and RAL	PI group: NET AUC ↑50% NET C_{max} ↑33% NET C_{min} ↑26% In subanalysis limited to women on ATV/r; NETAUC ↑35% NET C_{min} ↑39% NET C24 ↑67%	Strengths: clearly described population and methods; valid assays; HIV+ women Weaknesses: nonrandomized; small sample size; cART use self-reported Funded by government

Table 4 (*continued*)

Reference; location	Design objective (s)	Number of participants (*N*); Population	Intervention/treatment	Results	Strengths, weaknesses; funding
Crauwels *et al*. [27] UK	Open-label, three period pharmacokinetic study To evaluate the effect of RPV on COC pharmacokinetics and vice versa, and assess effects on sex hormones and safety of co-administration	Eighteen healthy nonsmoking women, 18–45 years; BMI 18–30 (median 24.6); 67% white; excluded pregnant, breast-feeding, or menopausal women, those with history of drug/alcohol abuse, skin disease, or any significant medical problems; use of concomitant medication	COC-containing NET In third cycle; RPV 25 mg daily days 1–15	Thirteen completed trial EE C_{min} and AUC unchanged EE C_{max} ↑17% NET AUC; C_{min}; C_{max} unchanged RPV pharmacokinetic unchanged from historical controls	Strengths: clearly described population and methods; valid assays; directly observed therapy Weaknesses: healthy women; short-term dosing; single antiretroviral; high discontinuation rate Funded by industry
Carten *et al*. [52] USA	Open-label two period pharmacokinetic study To determine the effect of EFV on the pharmacokinetics of LNG EC and vice versa, and assess safety	Twenty-four healthy women; 18–45; normal BMI (mean BMI 27) with no recent use of hormonal contraceptives or other interacting medications; women were either sterilized or used two nonhormonal contraceptive methods	LNG ECPs (0.75 mg) at 0 and 12 h on days 0 and 17 EFV 600 mg 72 h after day 0, for 14 days.	Twenty-one women completed study LNG AUC ↓58% LNG C_{max} ↓45% LNG C_{min} ↓69%	Strengths: clearly described population and methods; valid assays Weaknesses: small sample size; healthy women; single antiretroviral Funded by industry
Piscitelli *et al*. [29] UK	Randomized crossover pharmacokinetic study To examine if GSK2248761 (fosdevirine) interacts with CYP450 substrates, including COCs	Ten healthy women, without hepatitis and not taking any medications	COC-containing DRSP GSK228761 200 mg or placebo days 1–11	EE levels unchanged DRSP AUC, C_{max}, C_{min} ↑18–22%	Strengths: randomized Weaknesses: short term administration; healthy women; single antiretroviral; small sample size; very few study details provided; trials of fosdevirine on hold due to other safety concerns; study terminated early for unknown reasons Funded by industry
Kasserra *et al*. [57] USA	Randomized crossover pharmacokinetic study To determine the effect of vicriviroc alone or with RTV on COC pharmacokinetics and evaluate safety	Twenty-seven healthy nonpregnant women, 18–40 years; no recent medication use other than acetaminophen or oral contraceptives; BMI 19–32 (median 24.5)	COC-containing NET Vicriviroc 75 mg BID for 10 days then vicriviroc 30 mg plus RTV 100 mg daily for next 11 days; group 2: RTV 100 mg daily for first 10 days then plus vicriviroc 30 mg daily for next 11 days	VCV alone: EE AUC and C_{max} unchanged NET AUC and C_{max} unchanged RTV alone: EE C_{max} ↓11% EE AUC ↓29% NET C_{max} ↓11% NET AUC ↓7% VCV+RTV: EE C_{max} ↓24%% EEAUC ↓29% NET: C_{max} ↓11% NET AUC ↓17% No severe or serious AEs	Strengths: randomized; valid assays Weaknesses: healthy women; small sample size; single antiretroviral Funded by industry

Table 4 (*continued*)

Reference; location	Design objective (s)	Number of participants (*N*); Population	Intervention/treatment	Results	Strengths, weaknesses; funding
Anderson *et al*. [61] USA	Randomized crossover pharmacokinetic study To assess the effect of RAL on COC pharmacokinetic	Twenty healthy nonobese nonpregnant women 18–45 years (mean age 27) using additional barrier contraceptive	COC-containing NGM Raltegravir 400 mg twice daily or placebo days 1–21	Nineteen women completed the trial EE levels unchanged NGMN AUC ↑ 14% NGMN C_{max} ↑29%. No serious clinical or laboratory AEs	Strengths: Randomized; placebo-controlled; clearly described population and methods; valid assays Weaknesses: evening dose of RAL on day 21 of both periods missed; small sample size; healthy women; single antiretroviral Funded by industry
Zhang *et al*. [55] USA	Open-label three period pharmacokinetic study To assess the impact of RTV-boosted ATV on COC pharmacokinetic	Twenty healthy nonpregnant nonbreast-feeding women, 18–45 years (mean age 28); BMI 18–32 (mean 25)	COC containing NGM In third cycle; ATV/r 300 mg/100 mg daily days 1–14	EE AUC ↓19% C_{max} ↓16% C_{min} ↓37% NGMN C_{max} ↑ 68% AUC ↑85% C_{min} ↑102% Dose normalization estimate magnitude of reduction with lower dose EE ATV AUC ↑20% than historical controls More AEs with co-administration than with COCs alone (vomiting; headache and abdominal pain); no deaths or SAEs	Strengths: Clearly described population and methods; valid assays Weaknesses: small sample size; healthy women; single antiretroviral Funded by industry
Stuart *et al*. [30] Malawi	Open label; nonrandomized clinical trial To assess the feasibility of measuring anovulation in a pharmacokinetic study of COCs and antiretrovirals	Nine women ages 21–35 (3/group) with similar age and BMI: group 1 included HIV+ women on cART; group 2 included HIV+ women not on cART; and group 3 included HIV− women	COC with NG NVP-containing cART or no cART	LNG and EE levels measured by radioimmunoassay LNG AUC 147 in NVP group; 114 no cART group; and 38 in HIV− women EE AUC; 1384, 1457, 1144, respectively Antiretroviral pharmacokinetic similar to historical controls	Strengths: Clearly described population and methods; valid assays; included HIV+ women Weaknesses: small sample size; nonrandomized; progesterone measured only 1 day Funding source not reported

Table 4 (*continued*)

Reference; location	Design objective (s)	Number of participants (*N*); Population	Intervention/treatment	Results	Strengths, weaknesses; funding
Sevinsky *et al*. [26] USA	Open-label three period pharmacokinetic study To examine effect of EFV on pharmacokinetics of EE and NGMN and vice versa	Twenty-eight healthy women; 18–45 years (median 26); BMI 20–32 (median 25); on COCs for at least 2 months and no baseline safety issues or breakthrough bleeding	COC-containing NGM EFV 600 mg daily for 14 days during third cycle	Nineteen women completed study EE AUC, C_{max}, C_{min} unchanged NGMN C_{max} ↓46%; AUC ↓64% C_{min} ↓82% Posthoc LNG C_{max}; AUC; and C_{min} ↓80–86% EFV levels comparable to historical controls	Strengths: clearly described population and methods; valid assays Weaknesses: small sample size; healthy women; single antiretroviral; high discontinuation rate Funded by industry
Vogler *et al*. [37] USA	Open-label; nonrandomized; clinical trial To evaluate pharmacokinetic interactions between LPV/r and contraceptive patch and COCs	Thirty-two nonpregnant; premenopausal HIV+ women >13 years either on stable LPV/r regimens for at least 14 days ($n = 8$) or not on cART or taking NRTIs only ($n = 24$); nonsmoking; median weight 72 kg; no recent use of injectables or COCs; <198 lb; not taking enzyme inducers	EE/NGMN contraceptive patch Single-dose COC-containing NET LPV/r (400 mg/100 mg twice a day) or no cART/NRTIs only	Patch EE AUC ↓45% C_{min} ↓25% NGMN AUC ↑83% C_{min} ↑134% COC EE AUC ↓55% LPV AUC ↓19% C_{min} ↓27% C_{max} ↓22% RTV AUC↓24% C_{min} ↓14% C_{max} ↓8%	Strengths: clearly described population and methods; valid assays; HIV infected Weaknesses: study closed prematurely due to slow accrual; small sample size; single dose COC; high loss to follow-up; not randomized Funded by government
Schöller-Gyüre *et al*. [28] USA	Open-label three period pharmacokinetic study To assess the effect of ETR on COC pharmacokinetics	Twenty-four healthy women; 18–45 years (median 24); BMI 18–30; 97% white; nonsmoking; not pregnant or breast-feeding; no contraindications to hormonal contraceptives; not taking enzyme inducers	COC containing NET In cycle 3; 200 mg ETR twice daily from day 1 to 15	EE AUC ↑ 22% C_{max} ↑33% C_{min} ↑9% NET C_{max}; AUC unchanged C_{min} ↓22% ETR levels higher than historical controls	Strengths: Clearly described population and methods; valid assays Weaknesses: small sample size; healthy women; single antiretroviral; not randomized Funded by industry
Kearney and Mathias [58] USA	Open-label; two period pharmacokinetic study To evaluate the effect of TDF on the pharmacokinetic of COCs	Twenty healthy nonpregnant; nonlactating women; 19–45 years taking study COC for at least 3 months; without recent medication use or active alcohol or drug use; mean age 25 years; mean weight 64 kg	COC NGM TDF 300 mg/day on days 15–21 of contraceptive cycle 2	No change in NGMN and EE pharmacokinetic TFV levels similar to historical data No serious AEs and no discontinuations due to AEs; AEs reported by 10 participants; most commonly headache; rash; dysmenorrhea; nausea; and rhinitis AEs reported by 10 participants; most commonly headache; rash; dysmenorrhea; nausea; and rhinitis	Strengths: clearly described population and methods; valid assays Weaknesses: healthy women; single antiretroviral; small sample size Funded by industry

Table 4 (*continued*)

Reference; location	Design objective (s)	Number of participants (*N*); Population	Intervention/treatment	Results	Strengths, weaknesses; funding
Abel *et al*. [60] USA	Randomized controlled; crossover pharmacokinetic study To evaluate the effect of MVC on COC pharmacokinetic and to assess pharmacokinetic and safety of MVC in women	Fifteen healthy sterilized white women; age 32–45; between 7 and 76 kg (mean 65 kg) and BMI 18–30	COC LNG MVC 100 mg twice daily or placebo days 1–10 and am of day 11	EE AUC; C_{max} unchanged LNG AUC; C_{max} unchanged MVC pharmacokinetic within the range seen in healthy males in previous studies No clinically significant abnormalities or severe or serious AEs	Strengths: randomized; placebo controlled; clearly described population and methods; valid assays; 100% retention Weaknesses: small sample size; healthy women; single antiretroviral; COC only given days 2–8 Funded by industry
Nanda *et al*. [32] Brazil	Open-label; nonrandomized; pharmacokinetic study To evaluate the effect of EFV-containing cART on pharmacokinetics of MPA and to determine effects on suppression of ovulation and bleeding patterns	Thirty-three HIV+ women aged 19–40 years; with regular menstrual cycles and BMI 18–30 kg/m^2; not recently pregnant or breast-feeding	DMPA 150 mg given at enrollment EFV-containing cART	No difference in MPA levels between groups through 12 weeks	Strengths: Clearly described population and methods; valid assays; HIV+ women Weaknesses: small sample size; no EFV levels; no MPA levels beyond 12 weeks Funded by government
Sekar *et al*. [38] Belgium	Randomized crossover pharmacokinetic study To investigate the effect of DRV/r on COC pharmacokinetics and to examine safety	Twenty-two nonsmoking healthy women, 18–45 years; BMI 18–30; using a second nonhormonal contraceptive method	COC containing NET DRV/r 600/100 mg twice daily days 1–14 or no treatment	Eleven women completed study EE AUC ↓44% C_{min} ↓62% C_{max} ↓32% NET AUC ↓14% C_{min} ↓30% C_{max} ↓10% DRV and RTV levels comparable to historical controls	Strengths: clearly described population and methods; valid assays; randomized Weaknesses: small sample size; healthy women; single antiretroviral; high discontinuation rate Funded by industry
Cohn *et al*., Watts *et al*. [14,31] USA	Nonrandomized open-label pharmacokinetic study To evaluate the effect of various antiretrovirals on pharmacokinetics of MPA and vice versa; and to determine effects on suppression of ovulation and adverse events	Seventy-two HIV+ nonpregnant; premenopausal women, 22–46 years (median 35); median weight 71 kg; with no recent potentially interacting drugs; women required to use second nonhormonal method of contraception	DMPA Antiretrovirals regimens containing NFV; EFV; NVP; or no antiretroviral/ NRTI only	No difference in MPA AUC; C_{max}; C_{min}; clearance half-life between groups NVP AUC slightly higher after DMPA. No changes in EFV; nelfinavir pharmacokinetic	Strengths: clearly described population and methods; valid assays; HIV+ women Weaknesses: nonrandomized; small sample size Funded by government

Table 4 (*continued*)

Reference; location	Design objective (s)	Number of participants (*N*); Population	Intervention/treatment	Results	Strengths, weaknesses; funding
Aweeka *et al*. [65] USA	Open-label two-period pharmacokinetic time series study To investigate the effects of sex and contraceptives on ZDV pharmacokinetic and HIV viral load; to evaluate the effect of COCs and DMPA on plasma and genital HIV load among women on stable cART	HIV+: 18 men and 20 women; 22–52 years; on stable ZDV-containing cART	COC containing NET or DMPA begun at second cycle and continued through third cycle Participants randomized to oral or intravenous ZDV (200 mg) Antiretrovirals included indinavir; nelfinavir; or any NRTI except d4T or tenofovir	Fourteen women (eight DMPA; six COC) provided pharmacokinetic data No effect on plasma or cervical HIV viral load ZDV levels and levels of by radioimmunoassay and liquid chromatography/ mass spectrometry No change in ZDV pharmacokinetic after contraceptive use No differences between COC and DMPA on ZDV pharmacokinetic	Strengths: HIV+; prospective pharmacokinetic study; both PO and IV dosing of ZDV Weaknesses: open-label; nonrandomized; small sample; study stopped early due to slow enrollment; ZDV levels analyzed by two different methods due to discontinuation of reagents; no disaggregation of data for oral contraceptive vs. DMPA Funded by government
Burger *et al*. [62] Netherlands	Single time point retrospective pharmacokinetic analysis To characterize factors that influence interpatient variability in EFV concentrations	Sixty-six HIV+ women	Eight hormonal contraceptive users containing EFV-containing cART	EFV concentration: No HC: 5.0 mg/l HC: 2.7 mg/l	Strengths: HIV+ women Weaknesses: Study not designed to look at contraceptive effects; retrospective; single time point; very few hormonal users; population not well described; self-reported hormonal contraceptive use, type not specified Funding source not specified
Muro *et al*. [63] Netherlands	Open-label; single-period pharmacokinetic study To evaluate factors that influence interpatient variability in single dose NVP half-life	Forty-four healthy nonpregnant women age 18–40 (median 26 years); without hepatitis infection; median weight 64 kg	Seventeen oral contraceptive users 27 nonusers Single dose of 200 mg of NVP	Seventeen women reported COCs; median time to first undetectable NVP plasma level was 21 days; longer than in 27 women not reporting COC use (14 days; $P < 0.001$) Median half-life of NVP in COC users versus nonusers not significantly different (69.7 vs. 52.8 h; $P = 0.053$).	Strengths: clearly described population and methods; valid assays Weaknesses: study not designed to look at contraceptive effects; few hormonal users; healthy women; single dose of single antiretroviral; self-reported hormonal contraceptive use Funding source not specified

Table 4 (*continued*)

Reference; location	Design objective (s)	Number of participants (*N*); Population	Intervention/treatment	Results	Strengths, weaknesses; funding
Frohlich *et al.* [64] Germany	Open-label; two period pharmacokinetic study To investigate the influence of COCs on SQV pharmacokinetic and to assess the potential contribution of CYP3A4 and P-glycoprotein	Eight healthy nonsmoking nonpregnant women with regular menses; mean age 24 years and mean BMI 21; not using any potentially interacting drugs	COC containing GES days 4-25 600 mg SQV on days 1 and 22	No effect of COCs on SQV pharmacokinetics	Strengths: Clearly described population and methods; valid assays Weaknesses: not randomized; very small sample size; short course of COCs; healthy women; single antiretroviral only given twice Funded by government
Mildvan *et al.* [53] USA	Open-label, single dose, two period pharmacokinetic study To determine the effects of NVP on COC pharmacokinetics and vice versa	Fourteen HIV+ nonpregnant, nonlactating, nonsmoking women; age18–65 (mean age 37); viral load <400; $CD4^+$ cell count > 100 cells/μl; normal renal and hepatic function; no RTV or DLV use	Single dose of COC containing NET on cycle day 1 and 30 NVP 200-mg daily on days 2–15; then 200-mg twice daily days 16–29; single dose on day 30 cART regimens included IDV; NFV; SQV/RTV	Ten women completed the study EE AUC ↓29% C_{max} unchanged NET AUC ↓18% C_{max} unchanged NVP levels similar to historical controls	Strengths: HIV+ clearly described population and methods; valid assays Weaknesses: small study; only single dose COC; NVP added to current cART regiment; included postmenopausal women Funded by industry
Ouellet *et al.* [54] Canada	Single dose, single period pharmacokinetic study To assess the effects of RTV on EE pharmacokinetics	Twenty-three healthy nonpregnant nonlactating women, 18–45, close to ideal weight; women were postmenopausal, sterilized, practiced abstinence, or had a vasectomized partner	Single dose of COC with 50 μg EE + 1 mg ethynodiol diacetate given on cycle days 1 and 29 RTV oral solution from day 15–30, 300 mg q12h on Day 15, 400 mg q12h on Day 16, and 500 mg q12h thereafter	EE C_{max} ↓32% AUC ↓41%	Strengths: valid assays Weaknesses: no progestin levels; nonrandomized; single dose COC; postmenopausal healthy women; nonstandard RTV doses Funded by industry

Abbreviations for antiretrovirals and contraceptive steroids defined in Tables 1 and 2. AUC, area under the curve; C_{max}, Peak concentration; C_{min}, rough concentration; COC, combined oral contraceptive; DMPA, depot medroxyprogesterone acetate; ECP, emergency contraceptive pill; MPA, medroxyprogesterone acetate; POP, progestin-only pill.

found women using DMPA had pregnancy rates from 3 to 5 per 100 woman-years, with lower rates among users of nevirapine and efavirenz compared with no cART [25]. Two additional studies reported pregnancy rates from 1.8 to 4.2 per 100 woman-years among DMPA users taking various antiretrovirals (primarily nevirapine) [20,21].

Implants

Pregnancy rates among users of cART and contraceptive implants differed by whether the implant contained levonorgestrel or etonogestrel, and whether women were taking efavirenz or nevirapine. Pregnancy rates were higher among women using the levonorgestrel implant concomitantly with efavirenz. Two prospective studies ($N = 79$ and $N = 45$) reported no pregnancies through 3 years and 6 months, respectively, among women using etonogestrel implants and NNRTI-containing cART [33,34], although the second study found that women taking efavirenz-containing cART had a 2.8% presumed ovulation rate over 6 months. In a small pharmacokinetic study of women using levonorgestrel implants and cART containing efavirenz or nevirapine, three pregnancies (3/20; 15%) occurred within 48 weeks, all in women taking efavirenz [35]. Similar findings were seen in a large retrospective study, where 15 of 121 (12.4%) women using levonorgestrel implants and efavirenz-containing cART became pregnant, at a mean duration of 16.4 months; no pregnancies occurred among women taking nevirapine-containing cART [36].

Two secondary analyses described pregnancy rates with implant use in women using efavirenz-containing or nevirapine-containing cART [24,25]. In the first, pregnancy rates for users of efavirenz, nevirapine, and no cART were 5.5, 2.3, and 3.4 per 100 woman-years for etonogestrel implant users, and 7.1, 1.9, and 3.3 per 100 woman-years for levonorgestrel implant users, respectively [24]. In the second, pregnancy rates per 100 woman-years were 1.4 for unspecified implant users not taking cART, 0 for nevirapine users, and 6 for women taking efavirenz [25].

Protease inhibitors

Seven small pharmacokinetic trials described contraceptive effectiveness measures among women using protease inhibitors and hormonal contraceptives (Table 3) [14,16,31,34,37–39].

Combined oral contraceptives/patches

Co-administration of darunavir/ritonavir with COCs resulted in no ovulation [38]. Similarly, coadministration of lopinavir/ritonavir containing cART in women using a contraceptive patch also found no ovulations [37].

Progestin-only pills

One report showed that oral norethindrone thickened cervical mucus and led to similar mucus scores in women using protease inhibitor-containing cART compared with those taking NRTIs alone [16].

Depot medroxyprogesterone acetate

Reports of women using lopinavir/ritonavir-containing or nelfinavir-containing cART with DMPA found that no women ovulated [14,31,39].

Implants

No ovulations nor pregnancies were reported in a pharmacokinetic study of etonogestrel implant users taking lopinavir/ritonavir-containing cART [34].

Nucleoside/nucleotide reverse transcriptase inhibitors

Analyses of two large trials of hormonal contraceptives and NRTIs used for PrEP found that use of tenofovir/emtricitabine did not affect pregnancy rates among users of COCs, injectables, or implants [40,41].

Integrase inhibitors

A small pharmacokinetic study of dolutegravir with COCs resulted in no ovulations [42].

Antiretroviral effectiveness

Eight reports evaluated the effects of hormonal contraceptive use on the effectiveness of NNRTI-containing or protease inhibitor-containing cART, and found no effects on death, $CD4^+$ cell count, or plasma viral load with concurrent use of DMPA, levonorgestrel implants, or oral contraceptives [14,43–49]. Use of DMPA also did not affect the efficacy of PrEP [50].

Toxicity of combined administration

Studies among healthy women using hormonal contraceptives concurrently with single antiretrovirals, or HIV-positive women using cART, generally reported no difference in adverse events of concurrent treatment compared with use of either hormonal contraceptives or antiretrovirals alone (Table 3). One HIV prevention trial evaluated pharmacodynamic interactions between tenofovir-containing PrEP with oral contraceptives or DMPA, and found that bone mineral density was not significantly decreased [51].

Contraceptive pharmacokinetics

Thirty-two reports include contraceptive pharmacokinetic measures among women using antiretrovirals and hormonal contraceptives (Table 4).

Nonnucleoside reverse transcriptase inhibitors

Contraceptive pharmacokinetics among women using NNRTIs and hormonal contraceptives were described in 11 studies (Table 4) [15,26–32,34,52,53].

Combined oral contraceptives

Two studies evaluated efavirenz with COCs: one in women taking only efavirenz, and one in women taking

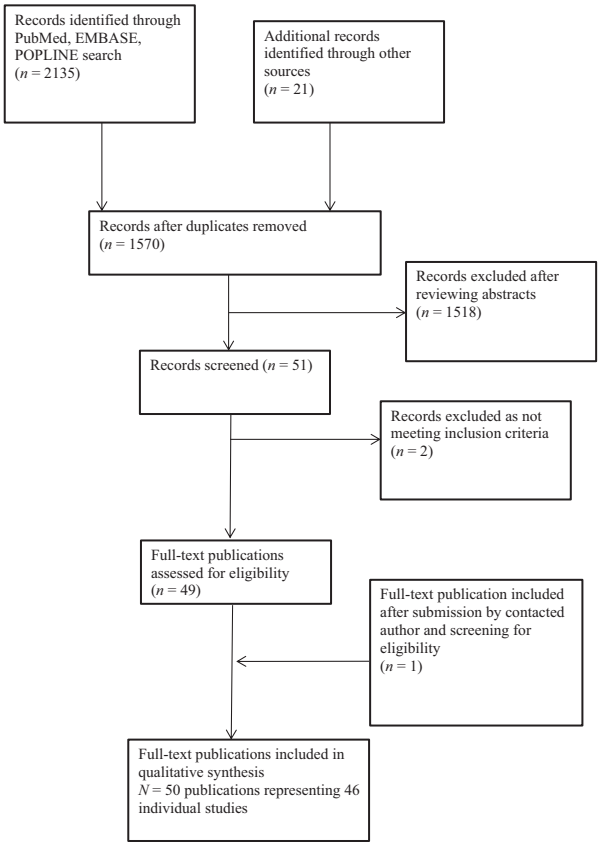

Fig. 1. Flow diagram of publication selection for inclusion into the review.

efavirenz-containing cART [15,26]. Ethinyl estradiol concentrations were not significantly changed, but progestin levels decreased by approximately 60%.

Three studies reported the effect of nevirapine on COC pharmacokinetics. Ethinyl estradiol levels varied from being unchanged to being approximately 30–60% lower [15,30,53]. Progestin levels were not significantly affected.

Studies of etravirine and rilpivirine in women taking COCs found minimal effects [27,28]. Similarly, a study of fosdevirine (the development of which was discontinued due to toxicity) found no effect on hormone levels in COC users [29].

Depot medroxyprogesterone acetate

Two studies evaluated the effect of NNRTIs on DMPA, and found no difference in medroxyprogesterone acetate pharmacokinetics through 12 weeks with concurrent use of either efavirenz-containing or nevirapine-containing cART [31,32].

Implants

A study of women using etonogestrel implants found 54–70% lower etonogestrel levels among women taking efavirenz-containing cART compared with women taking no cART [34].

Emergency contraceptive pills

One study in healthy women showed that levonorgestrel levels were 56% lower in ECP users after use of efavirenz [52].

Protease Inhibitors

Ten reports described contraceptive pharmacokinetics among women using protease inhibitors and hormonal contraceptives (Table 3) [17,31,34,37–39,54–57].

Combined oral contraceptives/Patch

Two studies examining concurrent use of ritonavir and COCs found decreased ethinyl estradiol levels, whereas progestin levels were unaffected [54,57]. Another study showed decreased ethinyl estradiol levels, but increased progestin levels, when COCs were used with atazanavir/ritonavir [55]. Similar findings were reported with lopinavir/ritonavir-containing cART and the contraceptive patch [37]. This study also reported lower ethinyl estradiol levels with concurrent use of a single COC pill, but progestin levels were not evaluated. Only darunavir/ritonavir was associated with significantly lower ethinyl estradiol levels as well as slightly lower norethindrone levels [38].

Progestin-only pills

In women receiving protease inhibitor-containing cART, norethindrone levels were higher compared with controls [56]. A subanalysis restricted to women using ritonavir-boosted atazanavir confirmed this finding [17].

Depot medroxyprogesterone acetate

One study showed significantly increased medroxyprogesterone acetate concentrations, compared with historical controls, in women using DMPA and lopinavir/ritonavir-containing cART [39].

Implants

A study evaluating the effect of cART on the pharmacokinetics of the etonogestrel implant found women using lopinavir/ritonavir-containing cART had etonogestrel levels approximately 50% higher than women not taking cART [34].

Nucleoside/nucleotide reverse transcriptase inhibitors

Two studies evaluating NRTIs used for PrEP with COCs or levonorgestrel implants showed no change in hormone levels [58,59].

Chemokine receptor 5 antagonists

Two studies showed that neither maraviroc nor vicriviroc impacted hormone levels when used concurrently with COCs [57,60].

Integrase inhibitors

In two studies, concurrent use of COCs and raltegravir led to small increases in progestin exposure [61], but dolutegravir had no impact on hormone levels [42].

Antiretroviral pharmacokinetics

Fifteen studies described antiretroviral pharmacokinetics among women using antiretrovirals and hormonal contraceptives; most were among healthy women and compared drug concentrations to historical controls (Table 4) [19,26,27,31,37–39,53–55,60,62–65].

Nonnucleoside reverse transcriptase inhibitors

Three studies evaluated the impact of COCs on the pharmacokinetics of efavirenz [19,26,62]. Among women using COCs and efavirenz alone, concentrations were similar to historical controls [26]. However, in a trial of women on efavirenz-containing cART, use of COCs led to efavirenz concentrations lower than historical controls [19]. Another analysis of women taking efavirenz-containing cART found no difference in efavirenz concentrations between hormonal contraceptive users and nonusers [62].

Three studies evaluated the impact of COCs on nevirapine levels. In two reports of women using nevirapine-containing cART, nevirapine levels were not significantly different in women using COCs [19,53]. Time to undetectable nevirapine levels was longer in women receiving single-dose nevirapine and using COCs [63]. Another study found rilpivirine levels in COC users to be similar to historical controls [27].

Among women on various cART regimens, nevirapine levels were slightly higher after administration of DMPA, but no changes in efavirenz levels were noted [31].

Protease inhibitors

Four studies investigated the effects of COCs on the pharmacokinetics of protease inhibitors [38,54,55,64]. Levels of saquinavir were not affected by COC use, but atazanavir levels were slightly increased [55,64]. Co-administration with COCs resulted in darunavir and ritonavir levels comparable to those in historical controls [38,54].

Co-administration of the contraceptive patch with lopinavir/ritonavir-containing cART resulted in slightly decreased levels of both protease inhibitors compared with historical controls [37], whereas DMPA had no effect on protease inhibitor levels in women taking such regimens [39].

Nucleoside/nucleotide reverse transcriptase inhibitors

One study found no effect of hormonal contraceptives (COCs and DMPA) on zidovudine plasma or intracellular pharmacokinetics [65].

Chemokine receptor 5 antagonists

When maraviroc was taken with COCs, levels were similar to those seen in historical controls [60].

Discussion

Few of the 50 reports included in this review provided relevant data that can be applied to clinical practice with certainty (Table 5). The most significant interactions with hormonal contraceptives occurred in women using cART-containing NNRTIs, particularly efavirenz. However, even in these studies, the outcomes reported were often pharmacokinetic rather than clinical, involved small populations, which limited study power, or were derived retrospectively from secondary analyses of existing cohorts.

The most important outcome for contraceptive drug interactions is method failure resulting in pregnancy, but few studies reported this outcome (Table 5). Changes in contraceptive hormone levels do not necessarily translate into reduced efficacy or increased toxicity, as levels vary greatly within and between individuals and populations [66,67]. Further, the contraceptive threshold, or minimum steroid hormone level required to maintain contraceptive effectiveness, is difficult to determine [68,69]. However, when pharmacokinetic data show no or minimal changes, clinical effects are unlikely. Ovulation is used in many drug–drug interaction studies to indicate risk of pregnancy, but ovulation is also a surrogate marker. The occurrence of ovulation does not always result in pregnancy. For example, many women ovulate during levonorgestrel implant use, yet contraceptive effectiveness remains high [70]. Additionally, no included studies evaluated true ovulation; rather, ovulation was presumed based on serum progesterone measurements alone, which can be inaccurate [70].

The most clinically significant drug–drug interactions identified in our systematic review were reported in women using efavirenz-containing cART and COCs or progestin-containing subdermal implants. Although studies show DMPA is not impacted by efavirenz use, studies of women using efavirenz and contraceptive implants reported pregnancy rates ranging from 5 to 15 per 100 woman-years, and COC users taking efavirenz had pregnancy rates ranging from 13 to 15 per 100 woman-years [24,25,35]. For COCs, because contraceptive effectiveness relies on user adherence, potential additional reductions in effectiveness from a drug interaction, if confirmed, are concerning. Conversely, studies that reported on women using contraceptives with nevirapine-containing cART were generally reassuring. None of the studies that enrolled women using a number of different hormonal contraceptives with nevirapine

Table 5. Summary of included clinical and pharmacokinetic data on HC-antiretroviral drug interactions; PK differences <30% considered no change (↔), blank cells indicate absence of data.

Antiretroviral	Ethinyl estradiol pharmacokinetics	Progestin pharmacokinetics	Antiretroviral pharmacokinetics	Contraceptive effectiveness (pregnancy rates per 100 woman-years or ovulation %)	Antiretroviral effectiveness	Reported adverse events/toxicity
NNRTIs						
Efavirenz						
COCs	AUC↔	ENG AUC ENG C24↓61% NGM AUC↓64%	EFV levels <1.0 mg/l in 3/16	Pregnancy rates 13–15		Bleeding, nausea, mood change, dizziness
	C24↔	NGM C_{max}↓46% NGM C_{min}↓82%		Ovulation rates 0–19		
ECPs		LNG AUC ↓58% LNG C_{max} ↓45% LNG C_{min} ↓69%				
Injectables	NA	MPA ↔	↔	Pregnancy rates 4–9 Ovulation rate 0	No effect on time to virologic suppression, $CD4^+$ cell count, death, viral load, treatment failure	No grade3/4 AEs
LNG implants		LNG AUC ↓47%		Pregnancy rates 6–15	No change in $CD4^+$ cell count or HIV viral load	Bleeding
ENG implants		ENG AUC↓63% ENG C_{max}↓54% ENG C_{min} ↓70% in		Pregnancy rate 5 Ovulation rate 3		
Nevirapine						
COCs	EE AUC↔	NET AUC↔	↔	Pregnancy rates 6–10		Nausea, headache, breast tenderness, mood changes
	EE C_{max} ↔ EE C24 ↓58%	NET C_{max}↔ LNG AUC↔ LNG C_{min}↔ ENG C24↔		Ovulation rates 0–30		
Injectables			↔	Pregnancy rates 3–8		No grade 3 or 4 AEs
LNG implants				Pregnancy rate 0–2		
ENG implants				Pregnancy rate 2		
Etravirine						
COCs	AUC↔	NET C_{max}↔	↔	Ovulation rate 0		Nine discontinued due to AEs (rash in 7)
	EE C_{max} ↑ 33%, C_{min}↔	NET AUC↔ NET C_{min}↔				
Rilpivirine						
COCs	C_{max} ↔ C_{min} ↔ AUC ↔	NET C_{max}↔ NET C_{min}↔ NET AUC↔	↔	Ovulation rate 0		No grade 3 or 4 AEs
Ritonavir-boosted PIs						
Lopinavir/ ritonavir						

Table 5 (*continued*)

Antiretroviral	Ethinyl estradiol pharmacokinetics	Progestin pharmacokinetics	Antiretroviral pharmacokinetics	Contraceptive effectiveness (pregnancy rates per 100 woman-years or ovulation %)	Antiretroviral effectiveness	Reported adverse events/toxicity
COCs, patch	EE AUC ↓55% Patch: EE AUC ↓ 45% EE C_{min} ↔	Patch: NGMN AUC ↑ 83%, NGMN C_{min} ↑ 134%	↔	COC pregnancy rate 15 Patch ovulation rate 0		One grade 3 AE
Injectables		MPA AUC ↑46% MPA C_{max} ↑66%	↔	Pregnancy rate 5–7 Ovulation rate 0	No difference in $CD4^+$ cell count or HIV RNA	Menstrual irregularities in 25%, only one considered grade 3 due to persistent bleeding
LNG implants				Pregnancy rate 0		
ENG implants		AUC ↑ 52% C_{max} ↑ 61% C_{min} ↑ 34%		Pregnancy rate 1 Ovulation rate 0		
Atazanavir/ ritonavir						
COCs	AUC ↔ C_{max} ↔ C_{min} ↓37%	NGM C_{max} ↑ 68%, NGM AUC ↑ 85%, NGM C_{min} ↑ 102%,	↔			incr side-effects
POPs		NET C_{max} ↑ 39% NET C24 ↑ 67%, NET AUC ↑ 50%		Cervical mucus remained thickened		
Darunavir/ ritonavir						
COCs	C_{min} ↓62% C_{max} ↓32% AUC ↓44%;	NET C_{min} ↓30% NET C_{max} ↔ NET AUC ↔	DRV and RTV ↔			26% discontinued due to grade two AEs
SQV/ritonavir						
COCs			↔			
PIs without ritonavir						
Indinavir						
COCs				Zero pregnancies		
Nelfinavir						
COCs				Higher failure rate with NFV than other PIs		
Injectables		MPA ↔	AUC ↔ C_{max} ↔ C_{min} ↓46%	Zero pregnancies Ovulation rate 0	No change in $CD4^+$ cell count or HIV RNA	No grade 3 or 4 AEs

Table 5 (*continued*)

Antiretroviral	Ethinyl estradiol pharmacokinetics	Progestin pharmacokinetics	Antiretroviral pharmacokinetics	Contraceptive effectiveness (pregnancy rates per 100 woman-years or ovulation %)	Antiretroviral effectiveness	Reported adverse events/toxicity
CCR5 antagonists						
Maraviroc						
COCs	↔	LNG ↔				No serious AEs
Integrase inhibitors						
Dolutegravir						
COCs	↔	↔				
Raltegravir						
COCs	↔	↔				
NRTIs						
Tenofovir disaproxil fumarate, emtricitabine						
COCs	↔	↔		Pregnancy rate 18–35		
Injectables				Pregnancy rate 2–5	No difference	
LNG implants				Pregnancy rate <1		
Zidovudine						
COCs		↔			No change in plasma and cervical HIV viral load	
Injectables		↔			No change in plasma and cervical HIV viral load	

Abbreviations for antiretrovirals and contraceptive steroids defined in Tables 1 and 2. COC, combined oral contraceptive; DMPA, depot medroxyprogesterone acetate; ECP, emergency contraceptive pill; POP, progestin-only pill. AUC, area under the curve; C_{max}, peak concentration; C_{min}, trough concentration.

reported increases in pregnancy or ovulation rates [18,19,21,24,25,30,35,36,45].

The many other studies included in this review that evaluated hormonal contraceptives and antiretrovirals other than efavirenz reported no results that should change clinical practice. Antiretrovirals used in PrEP do not affect hormonal contraceptive effectiveness. Concurrent use of protease inhibitors with COCs does not alter contraceptive effectiveness despite the observed decreased ethinyl estradiol plasma levels found, as the progestin component is primarily responsible for contraceptive effectiveness. Minimal to no changes in progestin levels were reported in multiple studies of concurrent protease inhibitor and hormonal contraceptive use. Although concomitant use of a few protease inhibitors led to increased progestin levels in some studies, these changes are unlikely to impact safety given the variable doses and wide safety margin of contraceptive progestins.

Despite the small number of reports in our review, studies were also reassuring with regard to the effect of hormonal contraceptives on cART or PrEP effectiveness, or antiretroviral pharmacokinetics. Pharmacokinetic studies were limited because they either only reported antiretroviral pharmacokinetics compared with historical controls or presented data from healthy women taking single antiretrovirals.

Concurrent antiretroviral and hormonal contraceptive use also does not appear to lead to increased toxicity, though most studies were of short duration (1–28 days). Short-term pharmacokinetic studies may not accurately reflect adverse effects that may occur during use of long-term cART or PrEP with hormonal contraceptives. The only study to evaluate long-term toxicity showed little impact of concurrent use of DMPA and tenofovir on bone mineral density over 1 year [51]. Pharmacokinetic effects may also be time-dependent, further limiting the utility of short-term evaluations.

Strengths of our review included a comprehensive search strategy, systematic review of study inclusion by all authors, and dual data abstraction. Limitations are generally due to lack of studies evaluating relevant clinical outcomes. In addition, few studies are available regarding whether implants containing levonorgestrel or etonogestrel have different contraceptive effectiveness when used with efavirenz. Furthermore, with both implants, it is possible that interactions with enzyme inducers such as efavirenz are time-dependent, because hormone levels decrease over time after implantation [71]. Other data gaps are whether injectable contraceptives other than intramuscular DMPA, such as the lower-dose subcutaneous DMPA or injectable norethisterone enanthate, might be susceptible to drug interactions. Questions also remain regarding any impact of lower-dose efavirenz regimens [72] on hormonal contraceptive effectiveness, which cannot be predicted. Another limitation is that intracellular antiretroviral concentrations are likely a better predictor of clinical effectiveness than plasma levels, but pharmacokinetic studies only reported the latter. Finally, women on cART may also take other drugs that can alter liver metabolism, such as rifampin, and the combined effect of multiple enzyme-inducing medications on contraceptive hormone levels remains poorly characterized.

Our review highlights the dearth of studies designed to provide meaningful clinical data to guide contraceptive choices for HIV-positive women taking cART. Studies should be designed to report clinical outcomes such as pregnancy and HIV disease progression during long-term administration. Currently, incomplete data are being used to limit contraceptive choices for HIV-positive women. In the absence of well conducted prospective clinical trials, data from pharmacokinetic studies and secondary analyses have been used to make clinical judgments on medication effectiveness and inform contraceptive policy. For example, in October 2014 the South African authorities recommended that women using efavirenz or other enzyme-inducing drugs should not use etonogestrel implants [11]. In May 2016, the European Medicines Agency recommended that women taking hepatic enzyme inducing drugs, including efavirenz, be offered double doses of oral levonorgestrel for postcoital emergency contraception [73]. When such guidance is developed, the absolute risk of pregnancy should be considered and addressed in the guidance publications, as well as other considerations such as availability and contraceptive effectiveness of the alternatives proposed. Even if a particular contraceptive method is potentially less effective than usual in a woman using a concomitant antiretroviral, it may still be more effective than many alternative contraceptive methods [74]. Although non-hormonal methods such as copper IUDs are not affected by drug interactions, their use remains very low in many settings worldwide, and efforts to increase IUD use have had limited success [7]. If access to implants is restricted, in many settings DMPA would be the primary option available to women, virtually eliminating woman-centered decision making.

In summary, current published data do not support limiting women's access to any hormonal contraceptives. Women taking antiretrovirals for HIV treatment (in the form of cART) or prevention (in the form of PrEP) should have access to the full range of hormonal contraceptive options, and be enabled to make informed decisions about their options. Contraceptive efficacy is only one of many factors that an individual may consider when choosing a contraceptive method, and some women who are motivated to use the etonogestrel implant may wish to do so even if there is concern for decreased efficacy when used with efavirenz. National or regional restrictions on contraceptive method access,

while well intentioned, supersede women's personal decisions, which may actually increase risk of unintended pregnancy if remaining contraceptive options are unacceptable or inaccessible. More well designed prospective studies are needed to examine potential drug interactions between antiretrovirals and all contraceptive methods, to better inform guidelines and counseling for the more than 16 million women living with HIV.

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Disclaimer: The contents are the responsibility of the authors and do not necessarily reflect represent the official positions of FHI360, USAID, the Centers for Disease Control and Prevention, the WHO, or other institutions with which the authors are affiliated.

Conflicts of interest

There are no conflicts of interest.

References

1. Gunthard HF, Saag MS, Benson CA, del Rio C, Eron JJ, Gallant JE, *et al*. **Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2016 recommendations of the International Antiviral Society – USA panel.** *JAMA* 2016; **316**:191–210.
2. Obare F, van der Kwaak A, Birungi H. **Factors associated with unintended pregnancy, poor birth outcomes and postpartum contraceptive use among HIV-positive female adolescents in Kenya.** *BMC Womens Health* 2012; **12**:34.
3. DeFranco EA, Seske LM, Greenberg JM, Muglia LJ. **Influence of interpregnancy interval on neonatal morbidity.** *Am J Obstet Gynecol* 2015; **212**:386.e381–386.389.
4. Ngo AD, Roberts CL, Figtree G. **Association between interpregnancy interval and future risk of maternal cardiovascular disease – a population-based record linkage study.** *BJOG* 2016; **123**:1311–1318.
5. Wilcher R, Petruney T, Cates W. **The role of family planning in elimination of new pediatric HIV infection.** *Curr Opin HIV AIDS* 2013; **8**:490–497.
6. Trussell J. **Contraceptive failure in the United States.** *Contraception* 2011; **83**:397–404.
7. United Nations Department of Social and Economic Affairs, Population Division. World Contraceptive Use; 2015. http://www.un.org/en/development/desa/population/publications/dataset/contraception/wcu2015.shtml. [Accessed 1 December 2016].
8. Shen DD, Kunze KL, Thummel KE. **Enzyme-catalyzed processes of first-pass hepatic and intestinal drug extraction.** *Adv Drug Deliv Rev* 1997; **27**:99–127.
9. Edelman AB, Cherala G, Stanczyk FZ. **Metabolism and pharmacokinetics of contraceptive steroids in obese women: a review.** *Contraception* 2010; **82**:314–323.
10. Tseng A, Hills-Nieminen C. **Drug interactions between antiretrovirals and hormonal contraceptives.** *Expert Opin Drug Metab Toxicol* 2013; **9**:559–572.
11. Department of Health, Republic of South Africa. Circular: changes in the prescription of progestin subdermal implants (Implanon) in women who are taking enzyme inducing drugs such as efavirenz for HIV, rifampicin for TB, and certain drugs used for epilepsy (carbamazepine, phenytoin, and phenobarbital); 2014. Available at: http://www.sahivsoc.org/upload/documents/Circular – Changes in the Prescription of Progestin Subdermal Implants.pdf. [Accessed 1 December 2016].
12. Moher D, Liberati A, Tetzlaff J, Altman DG. **Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.** *BMJ* 2009; **339**:b2535.
13. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, *et al*. **Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group.** *JAMA* 2000; **283**:2008–2012.
14. Watts DH, Park JG, Cohn SE, Yu S, Hitti J, Stek A, *et al*. **Safety and tolerability of depot medroxyprogesterone acetate among HIV-infected women on antiretroviral therapy: ACTG A5093.** *Contraception* 2008; **77**:84–90.
15. Landolt NK, Phanuphak N, Ubolyam S, Pinyakorn S, Kerr S, Ahluwalia J, *et al*. **Significant decrease of ethinylestradiol with nevirapine, and of etonogestrel with efavirenz in HIV-positive women.** *J Acquir Immune Defic Syndr* 2014; **66**:e50–e52.
16. Atrio J, Stek A, Vora H, Sanchez-Keeland L, Zannat F, Natavio M. **The effect of protease inhibitors on the cervical mucus of HIV-positive women taking norethindrone contraception.** *Eur J Contracept Reprod Healthcare* 2015; **20**:149–153.
17. DuBois BN, Atrio J, Stanczyk FZ, Cherala G. **Increased exposure of norethindrone in HIV+ women treated with ritonavir-boosted atazanavir therapy.** *Contraception* 2015; **91**:71–75.
18. Nanda K, Delany-Moretlwe S, Dube K, Lendvay A, Kwok C, Molife L, *et al*. **Nevirapine-based antiretroviral therapy does not reduce oral contraceptive effectiveness.** *AIDS* 2013; **27 (Suppl 1)**:S17–S25.
19. Landolt NK, Phanuphak N, Ubolyam S, Pinyakorn S, Kriengsinyot R, Ahluwalia J, *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**:534–539.
20. Myer L, Carter RJ, Katyal M, Toro P, El-Sadr WM, Abrams EJ. **Impact of antiretroviral therapy on incidence of pregnancy among HIV-infected women in Sub-Saharan Africa: a cohort study.** *PLoS Med* 2010; **7**:e1000229.
21. Schwartz SR, Rees H, Mehta S, Venter WD, Taha TE, Black V. **High incidence of unplanned pregnancy after antiretroviral therapy initiation: findings from a prospective cohort study in South Africa.** *PLoS One* 2012; **7**:e36039.

22. Danel C, Moh R, Anzian A, Abo Y, Chenal H, Guehi C, *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**:29–35.
23. Clark RA, Theall K. **Population-based study evaluating association between selected antiretroviral therapies and potential oral contraceptive failure.** *J Acquir Immune Defic Syndr* 2004; **37**:1219–1220.
24. Patel RC, Onono M, Gandhi M, Blat C, Hagey J, Shade SB, *et al*. **Pregnancy rates in HIV-positive women using contraceptives and efavirenz-based or nevirapine-based antiretroviral therapy in Kenya: a retrospective cohort study.** *Lancet HIV* 2015; **2**:e474–e482.
25. Pyra M, Heffron R, Mugo NR, Nanda K, Thomas KK, Celum C, *et al*. **Effectiveness of hormonal contraception in HIV-infected women using antiretroviral therapy.** *AIDS* 2015; **29**:2353–2359.
26. Sevinsky H, Eley T, Persson A, Garner D, Yones C, Nettles R, *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**:149–156.
27. Crauwels HM, Van Heeswijk RPG, Buelens A, Stevens M, Hoetelmans RMW. **Lack of an effect of rilpivirine on the pharmacokinetics of ethinylestradiol and norethindrone in healthy volunteers.** *Int J Clin Pharmacol Ther* 2014; **52**:118–128.
28. Scholler-Gyure M, Kakuda TN, Woodfall B, Aharchi F, Peeters M, Vandermeulen K, *et al*. **Effect of steady-state etravirine on the pharmacokinetics and pharmacodynamics of ethinylestradiol and norethindrone.** *Contraception* 2009; **80**:44–52.
29. Piscitelli S, Kim J, Gould E, Lou Y, White S, de Serres M, *et al*. **Drug interaction profile for GSK2248761, a next generation nonnucleoside reverse transcriptase inhibitor.** *Br J Clin Pharmacol* 2012; **74**:336–345.
30. Stuart GS, Moses A, Corbett A, Phiri G, Kumwenda W, Mkandawire N, *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**:e40–e43.
31. Cohn SE, Park JG, Watts DH, Stek A, Hitti J, Clax PA, *et al*. **Depo-medroxyprogesterone in women on antiretroviral therapy: effective contraception and lack of clinically significant interactions.** *Clin Pharmacol Ther* 2007; **81**:222–227.
32. Nanda K, Amaral E, Hays M, Viscola MA, Mehta N. **Pharmacokinetic interactions between depot medroxyprogesterone acetate and combination antiretroviral therapy.** *Fertil Steril* 2008; **90**:965–971.
33. 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**:81–82.
34. Vieira C, Bahamondes MV, Souza R, Brito M, Prandini T, Amaral E, *et al*. **Effect of antiretroviral therapy including lopinavir/ritonavir or efavirenz on the etonogestrel-releasing implant pharmacokinetics in HIV-infected women.** *Eur J Contracept Reprod Healthcare* 2014; **19**:S72–S73.
35. Scarsi KK, Darin KM, Nakalema S, Back DJ, Byakika-Kibwika P, Else LJ, *et al*. **Unintended pregnancies observed with combined use of the levonorgestrel contraceptive implant and efavirenz-based antiretroviral therapy: a three-arm pharmacokinetic evaluation over 48 weeks.** *Clin Infect Dis* 2016; **62**:675–682.
36. 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**:791–793.
37. Vogler MA, Patterson K, Kamemoto L, Park JG, Watts H, Aweeka F, *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**:473–482.
38. Sekar VJ, Lefebvre E, Guzman SS, Felicione E, De Pauw M, Vangeneugden T, *et al*. **Pharmacokinetic interaction between ethinyl estradiol, norethindrone and darunavir with low-dose ritonavir in healthy women.** *Antivir Ther* 2008; **13**:563–569.
39. Luque AE, Cohn SE, Park JG, Cramer Y, Weinberg A, Livingston E, *et al*. **Depot medroxyprogesterone acetate in combination with a twice-daily lopinavir-ritonavir-based regimen in HIV-infected women showed effective contraception and a lack of clinically significant interactions, with good safety and tolerability: results of the ACTG 5283 study.** *Antimicrob Agents Chemother* 2015; **59**:2094–2101.
40. Murnane PM, Heffron R, Ronald A, Bukusi EA, Donnell D, Mugo NR, *et al*. **Preexposure prophylaxis for HIV-1 prevention does not diminish the pregnancy prevention effectiveness of hormonal contraception.** *AIDS* 2014; **28**:1825–1830.
41. Callahan R, Nanda K, Kapiga S, Malahleha M, Mandala J, Ogada T, *et al*. **Pregnancy and contraceptive use among women participating in the FEM-PrEP trial.** *J Acquir Immune Defic Syndr* 2015; **68**:196–203.
42. Song IH, Borland J, Chen S, Wajima T, Peppercorn AF, Piscitelli SC. **Dolutegravir has no effect on the pharmacokinetics of oral contraceptives with norgestimate and ethinyl estradiol.** *Ann Pharmacother* 2015; **49**:784–789.
43. Whiteman MK, Jeng G, Samarina A, Akatova N, Martirosyan M, Kissin DM, *et al*. **Associations of hormonal contraceptive use with measures of HIV disease progression and antiretroviral therapy effectiveness.** *Contraception* 2015; **93**:17–24.
44. Day S, Graham SM, Masese LN, Richardson BA, Kiarie JN, Jaoko W, *et al*. **A prospective cohort study of the effect of depot medroxyprogesterone acetate on detection of plasma and cervical HIV-1 in women initiating and continuing antiretroviral therapy.** *J Acquir Immune Defic Syndr* 2014; **66**:452–456.
45. Hubacher D, Liku J, Kiarie J, Rakwar J, Muiruri P, Omwenga 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.
46. Polis CB, Nakigozi G, Ssempijja V, Makumbi FE, Boaz I, Reynolds SJ, *et al*. **Effect of injectable contraceptive use on response to antiretroviral therapy among women in Rakai, Uganda.** *Contraception* 2012; **86**:725–730.
47. Johnson D, Kempf MC, Wilson CM, Shrestha S. **Hormonal contraceptive use and response to antiretroviral therapy among adolescent females.** *HIV AIDS Rev* 2011; **10**:65–69.
48. Chu JH, Gange SJ, Anastos K, Minkoff H, Cejtin H, Bacon M, *et al*. **Hormonal contraceptive use and the effectiveness of highly active antiretroviral therapy.** *Am J Epidemiol* 2005; **161**:881–890.
49. Cejtin HE, Jacobson L, Springer G, Watts DH, Levine A, Greenblatt R, *et al*. **Effect of hormonal contraceptive use on plasma HIV-1-RNA levels among HIV-infected women.** *AIDS* 2003; **17**:1702–1704.
50. Heffron R, Mugo N, Were E, Kiarie J, Bukusi E, Mujugira A, *et al*. **PrEP is efficacious for HIV prevention among women using DMPA for contraception.** *Topics Antivir Med* 2014; **22**:498.
51. Kasonde M, Niska RW, Rose C, Henderson FL, Segolodi TM, Turner K, *et al*. **Bone mineral density changes among HIV-uninfected young adults in a randomised trial of preexposure prophylaxis with tenofovir-emtricitabine or placebo in Botswana.** *PLoS One* 2014; **9**:e90111.
52. 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.
53. Mildvan D, Yarrish R, Marshak A, Hutman HW, McDonough M, Lamson M, *et al*. **Pharmacokinetic interaction between nevirapine and ethinyl estradiol/norethindrone when administered concurrently to HIV-infected women.** *J Acquir Immune Defic Syndr* 2002; **29**:471–477.
54. Ouellet D, Hsu A, Qian J, Locke CS, Eason CJ, Cavanaugh JH, *et al*. **Effect of ritonavir on the pharmacokinetics of ethinyl oestradiol in healthy female volunteers.** *Br J Clin Pharmacol* 1998; **46**:111–116.
55. Zhang J, Chung E, Yones C, Persson A, Mahnke L, Eley T, *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**:157–164.
56. Atrio J, Stanczyk FZ, Neely M, Cherala G, Kovacs A, Mishell DR Jr. **Effect of protease inhibitors on steady state pharmacokinetics of oral norethindrone contraception in HIV infected women.** *J Acquir Immune Defic Syndr* 2014; **65**:72–77.

57. 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**:1503–1514.
58. Kearney BP, Mathias A. **Lack of effect of tenofovir disoproxil fumarate on pharmacokinetics of hormonal contraceptives.** *Pharmacotherapy* 2009; **29**:924–929.
59. Todd CS, Deese J, Wang M, Hubacher D, Steiner MJ, Otunga S, *et al*. **Sino-implant (II)(R) continuation and effect of concomitant tenofovir disoproxil fumarate-emtricitabine use on plasma levonorgestrel concentrations among women in Bondo, Kenya.** *Contraception* 2015; **91**:248–252.
60. 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.
61. Anderson MS, Hanley WD, Moreau AR, Jin B, Bieberdorf FA, Kost JT, *et al*. **Effect of raltegravir on estradiol and norgestimate plasma pharmacokinetics following oral contraceptive administration in healthy women.** *Br J Clin Pharmacol* 2011; **71**:616–620.
62. Burger D, van der Heiden I, la Porte C, van der Ende M, Groeneveld P, Richter C, *et al*. **Interpatient variability in the pharmacokinetics of the HIV nonnucleoside reverse transcriptase inhibitor efavirenz: the effect of gender, race, and CYP2B6 polymorphism.** *Br J Clin Pharmacol* 2006; **61**:148–154.
63. Muro E, Droste JA, Hofstede HT, Bosch M, Dolmans W, Burger DM. **Nevirapine plasma concentrations are still detectable after more than 2 weeks in the majority of women receiving single-dose nevirapine: implications for intervention studies.** *J Acquir Immune Defic Syndr* 2005; **39**:419–421.
64. Frohlich M, Burhenne J, Martin-Facklam M, Weiss J, von Wolff M, Strowitzki T, *et al*. **Oral contraception does not alter single dose saquinavir pharmacokinetics in women.** *Br J Clin Pharmacol* 2004; **57**:244–252.
65. Aweeka FT, Rosenkranz SL, Segal Y, Coombs RW, Bardeguez A, Thevanayagam L, *et al*. **The impact of sex and contraceptive therapy on the plasma and intracellular pharmacokinetics of zidovudine.** *Aids* 2006; **20**:1833–1841.
66. Fotherby K, Akpoviroro J, Abdel-Rahman HA, Toppozada HK, de Souza JC, Coutinho EM, *et al*. **Pharmacokinetics of ethynyloestradiol in women for different populations.** *Contraception* 1981; **23**:487–496.
67. Fotherby K. **Variability of pharmacokinetic parameters for contraceptive steroids.** *J Steroid Biochem* 1983; **19**:817–820.
68. Lobo RA, Stanczyk FZ. **New knowledge in the physiology of hormonal contraceptives.** *Am J Obstet Gynecol* 1994; **170**:1499–1507.
69. Cherala G, Edelman A, Dorflinger L, Stanczyk FZ. **The elusive minimum threshold concentration of levonorgestrel for contraceptive efficacy.** *Contraception* 2016; **94**:104–108.
70. Alvarez F, Brache V, Faundes A, Tejada AS, Thevenin F. **Ultrasonographic and endocrine evaluation of ovarian function among Norplant implants users with regular menses.** *Contraception* 1996; **54**:275–279.
71. Sivin I, Wan L, Ranta S, Alvarez F, Brache V, Mishell DR Jr, *et al*. **Levonorgestrel concentrations during 7 years of continuous use of Jadelle contraceptive implants.** *Contraception* 2001; **64**:43–49.
72. Carey D, Puls R, Amin J, Losso M, Phanupak P, Foulkes S, *et al*. **Efficacy and safety of efavirenz 400 mg daily versus 600 mg daily: 96-week data from the randomised, double-blind, placebo-controlled, noninferiority ENCORE1 study.** *Lancet Infect Dis* 2015; **15**:793–802.
73. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). CHMP assessment report: Levonelle 1500 mcg tablets and associated names; 26 May 2016. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Levonelle_13/WC500211776.pdf. [Accessed 1 December 2016].
74. Steiner MJ, Kwok C, Dominik R, Byamugisha JK, Chipato T, Magwali T, *et al*. **Pregnancy risk among oral contraceptive pill, injectable contraceptive, and condom users in Uganda, zimbabwe, and Thailand.** *Obstet Gynecol* 2007; **110**:1003–1009.