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Pharmacokinetic and Clinical Associations Between Doravirine-Containing Antiretroviral Therapy and Injectable and Implantable Hormonal Contraceptive Methods Among Women Living With Human Immunodeficiency Virus in South Africa

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Background. Drug resistance and intolerance of dolutegravir-containing antiretroviral therapy (ART) are rising in low- and middle-income countries, resulting in a potentially increased use of doravirine-containing ART use. There are knowledge gaps regarding doravirine and hormonal contraceptive drug–drug interactions among women living with human immunodeficiency virus (HIV).

Methods. We conducted a 5-parallel-group, prospective pharmacokinetic study among women living with HIV aged 18–45 years in Johannesburg, South Africa, between November 2021 and February 2024. We included a sixth, historical comparator group from a Kenyan study. After a ≥6-week lead-in period with doravirine-containing ART, participants initiated injectable medroxyprogesterone acetate (MPA), implantable etonogestrel (ENG), or nonhormonal intrauterine device contraception and were observed every 2–4 weeks for an additional 12 or 24 weeks. We analyzed serum MPA and ENG and plasma doravirine or dolutegravir concentrations per visit, using validated liquid chromatography–mass spectrometry assays. We assessed log-transformed concentrations of each drug with geometric mean ratios (90% confidence intervals) and a multivariate model adjusted for age and body mass index. We described safety, tolerability, and effectiveness (HIV RNA <40 copies/mL) of doravirine-containing ART.

Results. A total of 128 participants are included in this analysis. There were no significant reductions in the MPA, ENG, or doravirine concentrations. A total of 8 (3%) adverse events grade ≥2 were considered attributable to doravirine-containing ART and 22 (8%) to the contraceptive method. ART satisfaction was 100%, and viral suppression at study exit ranged from 86% to 96%.

Conclusions. We found no detrimental bidirectional drug–drug interactions and few adverse events between doravirine and hormonal contraceptives.

Keywords. drug–drug interactions; pharmacokinetic study; hormonal contraception; doravirine-containing ART; South Africa.

Globally, women make up more than half of all persons on antiretroviral therapy (ART) and are most at risk for human immunodeficiency virus (HIV) acquisition [1]. Despite this prevalence, women's unique needs in both the HIV treatment and prevention spheres are often underserved, particularly concerning sexual and reproductive health. Unintended pregnancy among women living with HIV is estimated to be as high as 40% globally [2], which can have significant consequences for maternal mortality, morbidity, and vertical transmission of HIV. Contraception, especially highly effective hormonal contraception, may be the most cost-effective tool to reduce rates of these consequences [3]. It is therefore imperative to optimize the concurrent use of contraceptives and ART to avoid unintended pregnancies. However, critical gaps exist regarding the effective concomitant use of ART and frequently used hormonal contraceptive methods in global HIV treatment guidelines [4, 5], especially for low- and middle-income countries (LMICs) where access to either sets of these options may often be limited [6].

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The critical gaps in guidelines are due to insufficient data concerning HIV treatment, prevention, and women's sexual reproductive health, spanning the spectrum of preventing to having safe pregnancies. For instance, a drug–drug interaction (DDI) between efavirenz and contraceptive implants only emerged after real-world reports and cohort studies, followed by pharmacokinetic (PK) studies corroborating this DDI [7]. All of this was in the postmarketing surveillance phase, not only after the drug was approved for use but also once the drug was scaled up worldwide [8, 9]. More recently, integrase inhibitor–containing ART with dolutegravir is the recommended first-line ART for use worldwide [10]. However, enthusiasm for its use among women of reproductive age was initially dampened by its possible association with neural tube defects [11, 12], and despite reversal of initiation limitations in using dolutegravir-containing ART among women living with HIV, its rollout among women was slow [13].

Furthermore, with growing drug resistance to dolutegravir being reported, additional ART options among all people living with HIV are needed [14, 15]. Doravirine, one of the newest nonnucleoside reverse transcriptase inhibitors (NNRTIs), has a relatively high barrier to resistance and favorable side effect profile compared to previously used NNRTIs such as nevirapine and efavirenz [16, 17]. Doravirine-containing ART may be a leading alternative ART recommendation in LMICs. Thus, eliciting any DDIs with a range of hormonal contraceptives *early* is critical as a significant majority of women living with HIV use hormonal contraceptives at some point in their lives [18].

The leading cause of DDIs between hormonal contraceptives and ART is related to hepatic metabolism, particularly by cytochrome P450 (CYP) enzymes (eg, CYP3A4), which are often inhibited or induced by some antiretrovirals (ARVs) [19]. Doravirine is largely metabolized by CYP3A enzymes [19]. Contraceptive progestins, including medroxyprogesterone acetate (MPA) and etonogestrel (ENG) hormones, are also known substrates of CYP3A. While an initial, crossover PK study among healthy individuals suggests that doravirine should not have any detrimental DDIs on oral contraceptive effectiveness [20], a greater profiling of the concomitant use of doravirine-containing ART and common hormonal contraceptive methods is urgently needed.

Furthermore, women are often underrepresented in HIV treatment trials, and have, until recently, been underrepresented in HIV prevention trials as well [21]. For instance, in 2 efficacy trials of doravirine-containing ART, only 16%–17% of the study participants were women and only 6%–10% of them were African [22, 23]. To help address some gaps in knowledge regarding doravirine's use among women living with HIV of reproductive age, we conducted a PK study, called EPIC (Evaluation of Pharmacokinetic Drug–Drug Interactions between Hormonal Contraceptives and Doravirine-Containing ART in South Africa), investigating bidirectional DDIs between doravirine-containing ART and leading hormonal contraceptive methods used in LMICs. We also included assessments, such as safety, satisfaction, and effectiveness, to explore the clinical implications of concomitant use.

METHODS

Overall Study Design

We conducted a prospective observational, parallel group, single-site PK study among women living with HIV on first-line ART, who were virally suppressed and between the ages of 18 and 45 years at the Wits RHI Research Centre, University of the Witwatersrand, in Johannesburg, South Africa.

Study Setting

The study was conducted in Johannesburg, Gauteng province, South Africa. The estimated HIV prevalence in Gauteng in 2022 was 15% and an estimated 67% of people living with HIV receiving care in the province are women [24]. At the time of the study design, efavirenz-containing ART was the recommended first-line ART in South Africa but by the time of study implementation, the South African guidelines recommended optimization of first-line ART from efavirenz- to dolutegravir-containing ART [25].

Ethics Review

The study was reviewed and received ethical approval from the University of the Witwatersrand Human Research Ethics Committee, in South Africa (#201010), and the University of Washington Human Subjects Division, in the United States (#11487). The study also received approval from the South African Health Product Regulatory Agency, as at the time of initial review, doravirine was not yet a registered drug in South Africa. The study was registered with ClinicalTrials.gov (NCT04669678) and the South African National Clinical Trials Registry (DOH-27-062022-5454) [26, 27].

Study Groups

The 5 groups enrolled in EPIC were (1) doravirine + intramuscular (IM) depot medroxyprogesterone acetate (DMPA); (2) doravirine + subcutaneous (SC) MPA; (3) doravirine + subdermal ENG implant; (4) doravirine + nonhormonal intrauterine device (IUD); and (5) dolutegravir + IM DMPA. The sixth group, a historical comparator group, consisted of women living with HIV of similar age on dolutegravir + ENG implant from a Kenyan PK study called "PK of ARVs and Implant" (PARVI) [28]. Since the manufacturer of doravirine already conducted the industry standard PK study with doravirine and a combined oral contraceptive method, containing ethinyl estradiol and levonorgestrel [29], which did not demonstrate any bidirectional DDIs, we chose to exclude an oral contraceptive pill method in EPIC. We chose to not randomize assignments to contraceptive groups but to allow women to choose

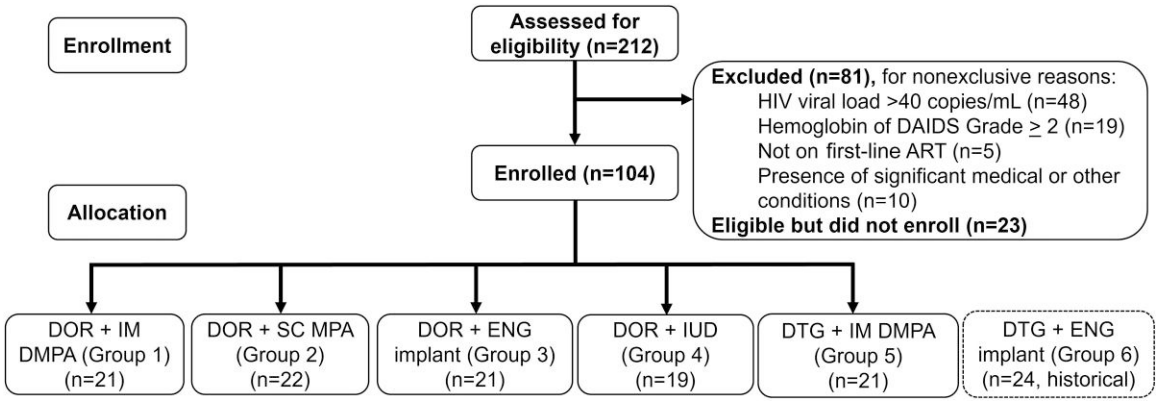

Figure 1. Flow diagram of study participants. Reasons for noncompletion of study leading to exclusion from analysis were as follows: In group 2, 2 participants experienced an incident pregnancy after starting doravirine-containing antiretroviral therapy but prior to starting their contraceptive method; in group 3, one participant reported husband's opposition to their chosen contraceptive method, requiring discontinuation of etonogestrel (ENG) implant, and a second participant was terminated due to no longer desiring continuing the ENG implant; and in group 4, 2 participants were discontinued after the third visit due to being lost to follow-up. The sixth group, a historical comparator group, consisted of women living with human immunodeficiency virus on dolutegravir + ENG implant from another pharmacokinetic study in Kenya ("PK of ARVs and Implant" [PARVI]). Abbreviations: ART, antiretroviral therapy; DAIDS, Division of AIDS; DMPA, depot medroxyprogesterone acetate; DOR, doravirine; DTG, dolutegravir; ENG, etonogestrel; HIV, human immunodeficiency virus; IM, intramuscular; IUD, intrauterine device; MPA, medroxyprogesterone acetate; SC, subcutaneous.

a method that best suited their preferences and allowed for enough persistence to the method for us to complete study follow-up, noting that women choosing one contraceptive method over another may have some differences [30].

Once enrolled, participants underwent a 6-week "lead-in" period with oral doravirine-containing ART to ensure that any hepatic induction with prior ARVs, especially efavirenz, was minimized before beginning contraception [26]. After the lead-in period, once participants initiated their chosen contraceptive method, they were followed every 2–4 weeks for an additional 12 or 24 weeks (primary endpoint), depending on the contraceptive method chosen (12 weeks for the IM DMPA or SC MPA groups and 24 weeks for the ENG implant and nonhormonal IUD groups). Additional details regarding eligibility, recruitment, retention, procedures, historical comparator group, and sample size calculations can be found in the Supplementary Text.

Exposures

We considered the study groups the primary exposures. Groups 1–4 received doravirine in a single-pill combination of doravirine/lamivudine/tenofovir disoproxil fumarate (100 mg/300 mg/300 mg) taken orally once a day through the study. Groups 5 and 6 received dolutegravir/lamivudine/tenofovir disoproxil fumarate (50 mg/300 mg/300 mg) taken orally once a day through routine care, not from the study. At study exit, women in groups 1–4 were asked to resume their ART from routine care and their providers were notified of cessation of doravirine-containing ART.

Groups 1–4 received the IM DMPA, SC MPA, ENG implant, and nonhormonal IUD, respectively, while group 5 received IM DMPA and group 6 was on ENG implant. The study team administered IM DMPA (150 mg/mL) and SC MPA (104 mg/mL) every 3 months and placed the ENG implant (68 mg single rod) and nonhormonal IUD (T-shaped polyethylene frame wound with a copper wire) once. At study exit, IM DMPA and SC MPA group women were offered additional doses, while women on the ENG implant and nonhormonal IUD were offered removals if desired.

Outcomes

The co-primary outcomes were (1) the hormonal contraceptive concentrations and (2) doravirine concentrations, ideally timed at 24 hours since last dose to approximate concentration at 24 hours or minimum concentration (C_{min}), at each study visit. For the serum hormonal contraceptive concentrations, we utilized a validated, liquid chromatography–heated electrospray ionization–tandem triple quadrupole mass spectrometry (LC-MS/MS) technique, with the lower limit of quantification (LLOQ) of 10 pg/mL for ENG or MPA [27]. For the plasma doravirine concentrations, we also utilized LC-MS/MS techniques, with an LLOQ of 20 ng/mL.

Our secondary outcomes included (1) safety of ART (ascertained via solicited self-reports of frequency and severity of adverse events [AEs] at every study visit); (2) satisfaction of both ART and contraception (ascertained via self-reports at every study visit); and (3) doravirine-containing ART's effectiveness (measured via HIV-1 RNA <40 copies/mL, via GeneXpert quantification) at study exit.

Statistical Analysis

We present baseline characteristics by group descriptively. We calculated the geometric mean and ratios (GMR) for the log-transformed contraceptive hormone concentrations at each

Table 1. Study Follow-up Characteristics of Women Living With Human Immunodeficiency Virus Among EPIC Participants (N = 104), November 2021–February 2024

Characteristic	All EPIC Study Participants (Groups 1–5; n = 104)	Group 1: DOR + IM DMPA (n = 21)	Group 2: DOR + SC MPA (n = 22)	Group 3: DOR + ENG Implant (n = 21)	Group 4: DOR + IUD (n = 19)	Group 5: DTG + IM DPMA (n = 21)	Group 6: DTG + ENG Implant[a] (Historical Comparator Group, n = 24)
Baseline characteristics							
Age, y, median (IQR)	37 (29–40)	35 (28–38)	37 (28.2–40)	37 (28–40)	37 (31–42)	39 (35–41)	35 (33–37)
Parity, median (IQR)	2 (2–3)	2 (1–3)	2 (2–3)	2.5 (2–3)	2.5 (2–4)	2 (1–3)	3 (2–3)
Married	8 (8.4)	2 (10)	0	2 (10)	2 (12.5)	2 (9.5)	11 (45.8)
Educational level							
Primary	1 (1)	0	1 (4.5)	0	0	0	14 (58.3)
Secondary	98 (94.2)	20 (95.2)	20 (91)	18 (85.7)	19 (100)	21 (100)	9 (37.5)
Higher	5 (4.8)	1 (4.8)	1 (4.5)	3 (14.3)	0	0	1 (4.2)
Ethnicity							
Zulu	37 (35.6)	6 (28.6)	12 (54.5)	8 (38)	5 (26)	6 (28.6)	0
Sotho	25 (24.0)	5(23.8)	3 (13.6)	6 (29)	4 (21)	7 (33.3)	0
Xhosa	12 (11.5)	2 (9.5)	3 (13.6)	3 (14)	3 (16)	1 (4.8)	0
Ndebele	1 (1.0)	1 (4.8)	0	0	0	0	0
Shona	1 (1.0)	0	0	0	0	1 (4.8)	0
Luo	0	0	0	0	0	0	23 (96)
Luhya	0	0	0	0	0	0	1 (4)
Other	28 (26.9)	7 (33.3)	4 (18.2)	4 (19)	7 (37)	6 (28.6)	0
BMI, kg/m^2, median (IQR)	24 (20.7–26.9)	25 (21–27.5)	24.1 (22–26.2)	22.5 (20.0–24.7)	25.6 (24.6–27.5)	22.1 (19.8–25.3)	23.5 (20.0–26.0)
Most recent ART regimen prior to study enrollment							
DTG-containing ART	65 (62.5)	6 (28.6)	20 (90.9)	9 (42.9)	10 (52.6)	21 (100)	24 (100)
EFV-containing ART	39 (37.5)	15 (71.4)	2 (9.1)	12 (57.1)	9 (47.4)	0	0
Duration on ART before study enrollment, y, median (IQR)	7 (3–11)	5 (2–12)	10 (4–14)	9 (6–10)	4 (3–6)	7 (4.5–11.2)	9 (8–11.2)
No. of days since enrollment to study exit, median (IQR)	141 (131.8–217)	141 (136–142)	135 (131.5–137.5)	218 (217–223)	219 (216–227)	89 (87–92)	168 (168–169)
Study follow-up characteristics							
Total participants with at least 1 visit where DOR/DTG is missing when expected	42 (40.4)	12 (57.1)	8 (36.4)	10 (47.6)	9 (47.4)	3 (14.3)	1 (4.2)
No. of participants with missing DOR/DTG for 1 visit	14 (13.5)	5 (23.8)	3 (13.6)	3 (14.3)	2 (10.5)	1 (4.8)	1 (4.2)
No. of participants with missing DOR/DTG for 2 visits	9 (8.7)	1 (4.8)	3 (13.6)	2 (9.5)	2 (10.5)	1 (4.8)	0
No. of participants with missing DOR/DTG for 3 visits	1 (1.0)	0	0	1 (4.8)	0	0	0
No. of participants with missing DOR/DTG for ≥4 visits	18 (17.3)	6 (28.6)	2 (9.1)	4 (19)	5 (26.3)	1 (4.8)	0

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; DMPA, depot medroxyprogesterone acetate; DOR, doravirine; DTG, dolutegravir; EFV, efavirenz; ENG, etonogestrel; EPIC, Evaluation of Pharmacokinetic Drug–Drug Interactions between Hormonal Contraceptives and Doravirine-Containing ART in South Africa; IM, intramuscular; IQR, interquartile range; IUD, intrauterine device; MPA, medroxyprogesterone acetate; SC, subcutaneous.

[a]A historical control group consisted of women living with human immunodeficiency virus on DTG + ENG implant from a Kenyan pharmacokinetics study called "PK of ARVs and Implant" (PARVI).

study visit by group, with 90% confidence intervals (CIs), comparing doravirine + IM DMPA (group 1) and doravirine + ENG implant (group 3) to its respective dolutegravir groups (ie, groups 5 and 6, respectively). Post hoc, in a sensitivity analysis, we censored visit concentrations for the contraceptive hormones when the ARV concentrations were below the LLOQ

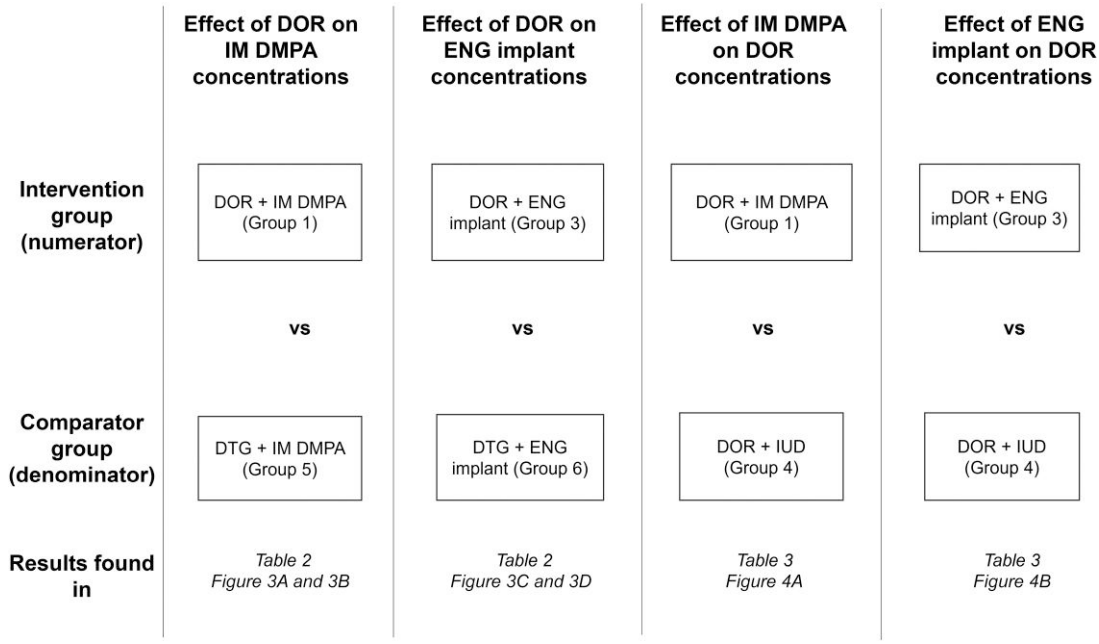

Figure 2. Study comparator groups for bidirectional effects of doravirine-containing antiretroviral therapy and hormonal contraception in EPIC participants (N = 104), November 2021–February 2024. Abbreviations: DMPA, depot medroxyprogesterone acetate; DOR, doravirine; DTG, dolutegravir; ENG, etonogestrel; IM, intramuscular; IUD, intrauterine device.

when expected (eg, doravirine concentration was <20 ng/mL when the participant was supposed to be taking doravirine-containing ART). Thus, for the contraceptive hormones, we presented both the primary outcomes as planned (regardless of detecting doravirine concentrations), termed "original sample," and in the sensitivity analysis, termed "censored sample." Similarly, when comparing each contraceptive method (ie, groups 1 and 3) to the IUD group (group 4) to examine differences in doravirine concentrations, post hoc, we censored visits when doravirine concentrations were below the LLOQ; this is the only doravirine concentration analysis presented. We calculated GMRs with linear mixed models per study visit. To account for any potential baseline differences by participant characteristics of women self-selecting which study group they would join, we utilized *a priori* multivariate models that helped account for potential confounding by age and body mass index (BMI), both measured at study start and treated as a continuous variable. In this analysis, we exclude planned comparisons between the IM DMPA and SC MPA groups.

RESULTS

Baseline Characteristics

This analysis includes 104 participants from the EPIC study and 24 from the PARVI study (Figure 1). The median age for all EPIC participants was 37 years (interquartile range [IQR], 29–40 years); among them, 8.4% were married, median parity was 2 (IQR, 2–3), median BMI was 24 (IQR, 20.7–26.9) kg/m^2, and median duration on ART prior to study start was 7 (IQR, 3–11) years (Table 1). Many of these characteristics were comparable between EPIC and PARVI participants, and across each group, though noting ethnic differences between South African and Kenyan participants.

Study Follow-up

There were a total of 6 participants who had initially enrolled but did not complete the study, 2 were terminated early from the study due to incident pregnancies prior to initiation of the contraceptive method, 2 discontinued their ENG implant, and 2 were considered lost to follow-up (Figure 1). Three participants, including the 2 already mentioned, became pregnant with varying amounts of exposure to doravirine; all 3 exited the study at pregnancy detection, stopped using doravirine, and were followed for pregnancy outcomes. One participant in group 4 was detected pregnant at study exit visit (with IUD strings visible on examination), estimated at 3 weeks of gestation, and was referred for IUD removal; her data are included in this analysis. This participant had twin gestation and went into labor preterm, with one fetus delivered stillbirth and the second infant born alive but deceased the next day; none of these adverse outcomes were deemed related to study or study product. The other 2 participants had uneventful pregnancies and normal vaginal deliveries, with infants well soon after birth.

During study follow-up, the total number of participants who did not have ARV concentrations detected above the LLOQ on at

Table 2. Medroxyprogesterone Acetate or Etonogestrel Plasma Concentrations (pg/mL)[a] Among Doravirine- Versus Dolutegravir-Containing Groups at Each Study Visit, EPIC Study, November 2021–February 2024

Study Visit Week	Original vs Censored Sample[b]	Doravirine-Containing ART, Median (Range), No. of Samples	Dolutegravir-Containing ART, Median (Range), No. of Samples	Unadjusted Contraceptive + DOR: Contraceptive + DTG GMR[c] (90% CI)	*P* Value	Adjusted Contraceptive + DOR: Contraceptive + DTG GMR[d] (90% CI)	*P* Value
Medroxyprogesterone acetate group comparisons							
2	Original sample	1246.0 (2.0–2852.0), n = 20	1761.0 (577–3610.0), n = 20	.76 (.59–.97)	.069	.85 (.65–1.11)	.306
	Censored sample	1196.0 (2.0–2642.0), n = 16	1769.0 (577.0–3610.0), n = 18	.71 (.53–.95)	.054	0.81 (.60–1.09)	.249
4	Original sample	1046.5 (514.0–3913.0), n = 21	1283.0 (384.0–4098.0), n = 21	.95 (.83–1.08)	.517	.99 (.86–1.13)	.874
	Censored sample	1025.0 (514.0–1969.0), n = 15	1350.0 (384.0–4098.0), n = 20	.92 (.80–1.05)	.316	.95 (.82–1.10)	.544
8	Original sample	805.0 (222.0–2310.0), n = 20	984.0 (148.0–2136.0), n = 21	.96 (.84–1.11)	.663	1.04 (.91–1.19)	.646
	Censored sample	805.0 (222.0–2276.0), n = 15	1009.0 (148.0–2136.0), n = 19	.96 (.82–1.13)	.708	1.04 (.89–1.22)	.650
12	Original sample	535.0 (295.0–1439.0), n = 21	601.5 (13.0–3569.0), n = 20	1.01 (.82–1.24)	.943	1.02 (.82–1.28)	.869
	Censored sample	542.0 (318.0–1439.0), n = 11	631 (13.0–3569.0), n = 18	.99 (.75–1.32)	.972	1.02 (.75–1.41)	.904
Etonogestrel group comparisons							
2	Original sample	589.0 (193.0–954.0), n = 17	435.5 (93.0–600.0), n = 22	1.15 (1.09–1.21)	<.001	1.16 (1.07–1.26)	.004
	Censored sample	644.0 (444.0–954.0), n = 15	435.5 (93.0–600.0), n = 22	1.19 (1.14–1.24)	<.001	1.19 (1.09–1.29)	.001
4	Original sample	550.0 (157.0–4014.0), n = 21	355.0 (256.0–788.0), n = 23	1.19 (1.10–1.29)	.001	1.21 (1.11–1.34)	.001
	Censored sample	557.0 (302.0–4014.0), n = 20	355.0 (256.0–788.0), n = 23	1.22 (1.18–1.26)	<.001	1.23 (1.13–1.34)	<.001
8	Original sample	518.5 (163.0–2827.0), n = 20	306.5 (226.0–518.0), n = 22	1.19 (1.12–1.25)	<.001	1.20 (1.09–1.32)	.002
	Censored sample	529.0 (308.0–2827.0), n = 16	306.5 (226.0–518.0), n = 22	1.26 (1.26–1.26)	<.001	1.26 (1.16–1.38)	<.001
12	Original sample	475.0 (85.0–953.0), n = 19	258.0 (183.0–563.0), n = 23	1.18 (1.10–1.26)	<.001	1.18 (1.07–1.31)	.006
	Censored sample	551.0 (325.0–953.0), n = 15	258.0 (183.0–563.0), n = 23	1.28 (1.20–1.34)	<.001	1.28 (1.19–1.38)	<.001
20	Original sample	390.0 (196.0–819.0), n = 19	240.5 (138.0–562.0), n = 20	1.21 (1.20–1.21)	<.001	1.22 (1.13–1.31)	<.001
	Censored sample	373.5 (231.0–819.0), n = 12	240.5 (138.0–562.0), n = 20	1.22 (1.12–1.34)	<.001	1.24 (1.13–1.35)	<.001
24	Original sample	378.0 (111.0–521.0), n = 21	221.0 (91.0–456.0), n = 23	1.20 (1.19–1.20)	<.001	1.21 (1.12–1.31)	<.001
	Censored sample	392.0 (179.0–521.0), n = 14	221.0 (91.0–456.0), n = 23	1.22 (1.12–1.34)	<.001	1.24 (1.13–1.35)	<.001

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; DOR, doravirine; DTG, dolutegravir; GMR, geometric mean ratio.

[a]Lower limit of quantification (LLOQ) of medroxyprogesterone acetate and etonogestrel is 20 pg/mL.

[b]Sensitivity analysis censors or excludes hormone concentration data from visits when the antiretroviral concentrations for the respective group were not detected above the LLOQ for that assay (20 ng/mL).

[c]Calculated with a linear mixed model per study visit.

[d]Calculated with a linear mixed model per study visit adjusting for age and body mass index.

least one study visit were 12 in group 1 (doravirine + IM DMPA), 8 in group 2 (doravirine + SC MPA), 10 in group 3 (doravirine + ENG implant), 9 in group 4 (doravirine + nonhormonal IUD), and 3 in group 5 (dolutegravir + IM DMPA) (Table 1).

Primary Outcome Measures

Comparator groups are delineated in Figure 2. Comparing IM DMPA hormonal contraceptive concentrations between doravirine- and dolutegravir-containing ART groups, the GMRs at each study visit ranged from 0.85 (90% CI, .65–1.11) to 1.04 (.91–1.19) in the original sample (most *P* values >.10; Table 2, Figure 3*A*). Comparing ENG implant hormonal contraceptive concentrations between doravirine- and dolutegravir-containing ART groups, the GMRs at each study visit ranged from 1.16 (95% CI, 1.07–1.26) to 1.22 (95% CI, 1.13–1.31) in the original sample (all *P* values <.10; Table 2, Figure 3*C*). For the above comparisons, no significant differences were detected between the original and censored samples (Table 2, Figure 3*B* and 3*D*).

Comparing doravirine concentrations between IM DMPA and nonhormonal IUD groups, the GMRs at each study visit ranged from 1.25 (95% CI, .57–2.74; *P* = .64) to 2.23 (95% CI, 1.23–4.06; *P* = .027) (Table 3, Figure 4*A*). Similarly, comparing doravirine concentrations between ENG and IUD groups, the GMRs at each study visit ranged from 0.78 (95% CI, .46–1.34; *P* = .46) to 2.61 (95% CI, 1.57–4.33; *P* = .002) (Table 3, Figure 4*B*).

Secondary Outcome Measures

A total of 264 solicited AEs were recorded from 104 EPIC participants, with 2 being at grade 3 or higher from 2 separate participants (Supplementary Tables 1 and 2). A total of 8 (3%) AEs grade 2 or higher were considered attributable to doravirine-containing ART and 22 (8%) to the contraceptive method.

Regarding satisfaction with their ART regimen, all participants indicated being satisfied or very satisfied with their ART during the study period (Supplementary Table 1). However, 22 (21%) participants indicated being somewhat or very dissatisfied with their contraceptive method ever during the study period.

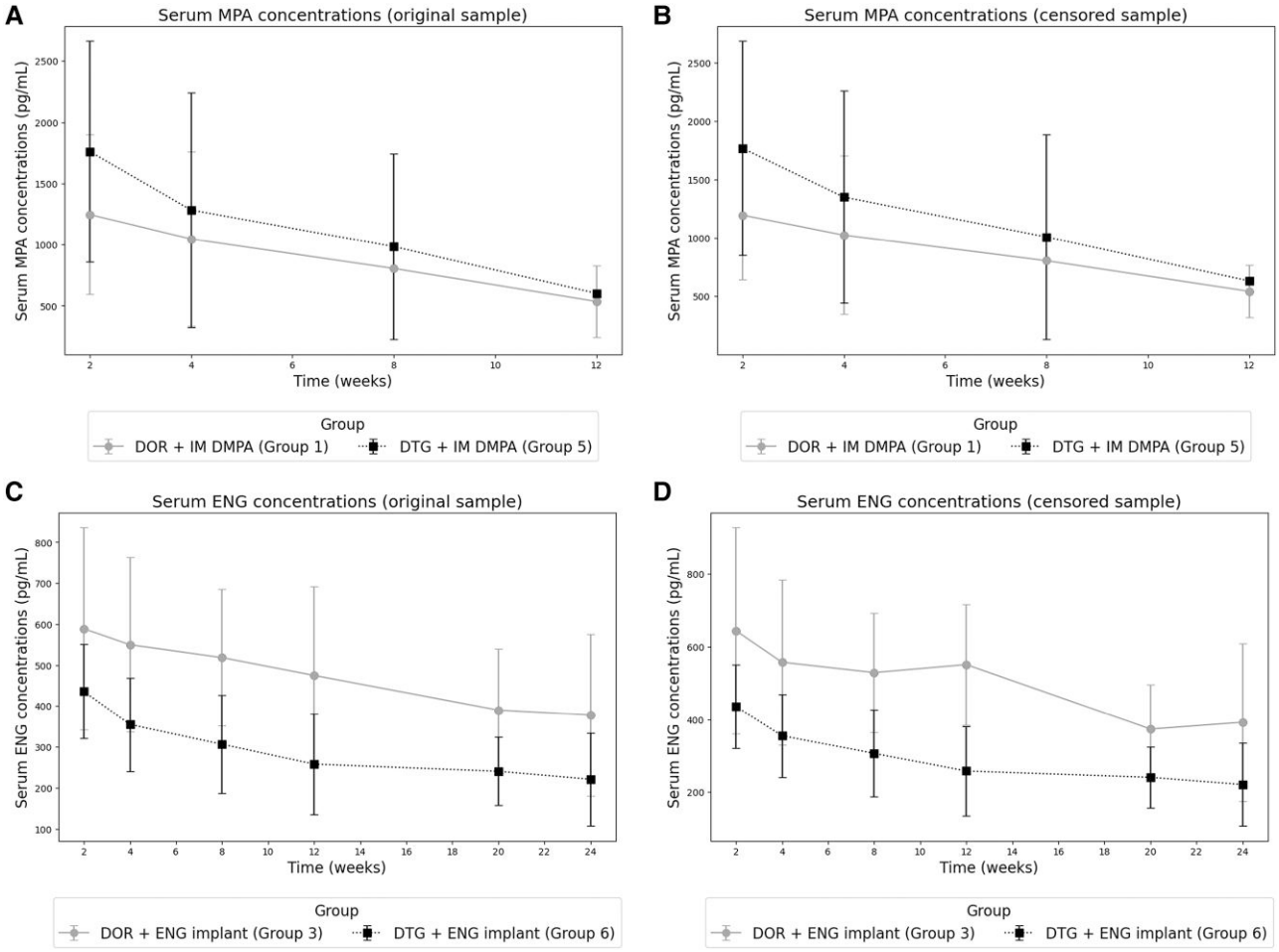

Figure 3. Median and interquartile ranges of medroxyprogesterone acetate (MPA) and etonogestrel (ENG) serum concentrations among doravirine (DOR)- vs dolutegravir (DTG)-containing antiretroviral therapy groups, in original and censored samples, among EPIC participants (N = 104), November 2021–February 2024. *A–D*, MPA serum concentrations (pg/mL) among DOR- vs DTG-containing groups at each study visit for the original sample (*A*) and the censored sample (*B*); and ENG serum concentrations (pg/mL) among DOR- vs DTG-containing groups at each study visit for the original sample (*C*) and the censored sample (*D*). Abbreviations: DMPA, depot medroxyprogesterone acetate; DOR, doravirine; DTG, dolutegravir; ENG, etonogestrel; IM, intramuscular; MPA, medroxyprogesterone acetate.

Adherence to ART by pill count ≥80% per study visit was generally low (range, 35%–41%; Supplementary Table 1). ARV concentrations detected above the LLOQ per study visit were modest and variable (range, 66%–91%).

Viral suppression (<40 copies/mL) at study exit ranged from 86% to 96% between groups (Supplementary Table 1).

DISCUSSION

We found no significant bidirectional DDIs in this PK study among South African women concomitantly using doravirine-containing ART and IM DMPA, ENG implant, and nonhormonal IUD. Women living with HIV neither had significantly lower MPA and ENG nor lower doravirine concentrations when concomitantly using hormonal contraception and doravirine-containing ART. Although doravirine concentrations were occasionally higher at certain visits, these differences in concentrations are unlikely to be clinically significant as doravirine-containing ART appears to be well tolerated at various doses [20]. A recent PK study of bidirectional effects among doravirine and feminizing hormones, admittedly of different drugs, doses, and metabolism, among transgender women also found no detrimental DDIs [24]. An early PK study of doravirine and oral contraceptives was also reassuring [25]. Our findings align with existing data and expand our understanding of potential DDIs between doravirine-containing ART and commonly used contraceptive methods. This is timely as newer ART regimens, such as those containing doravirine, might have a role to play in LMICs. Yet, our work comes well after initial approvals for use of doravirine-containing ART, stressing the need to more fully profile potential DDIs between newer ARVs and common hormonal contraceptives before scale-up worldwide.

While participants in EPIC reported many low-grade, solicited AEs, very few were attributable to doravirine. This is consistent

Table 3. Doravirine Concentrations (ng/mL)[a] Among Medroxyprogesterone Acetate– or Etonogestrel-Containing Versus Intrauterine Device Groups at Each Study Visit, EPIC Study, November 2021–February 2024

Study Visit Week	MPA-Containing Group, Median (Range)	Self-reported Time Since Last Dose[b], h, Median (Range)	IUD-Containing Group, Median (Range)	Self-reported Time Since Last Dose, h, Median (Range)	Unadjusted MPA + DOR: IUD + DOR GMR[c] (90% CI)	*P* Value	Adjusted MPA + DOR: IUD + DOR GMR[d] (90% CI)	*P* Value
Medroxyprogesterone acetate group comparisons								
2	609.1 (29.6–1752.0) n = 16	14.7 (12.0–17.4)	413.7 (24.4–1472.0) n = 13	14.4 (12.4–19.8)	1.50 (.70–3.20)	.379	1.25 (.57–2.74)	.641
4	906.2 (100.8–1500.0) n = 15	14.2 (12.42–17.8)	784.7 (33.5–1381.0) n = 12	14.3 (12.4–18.5)	1.54 (.85–2.79)	.228	1.57 (.87–2.80)	.204
8	778.0 (213.1–1167.0) n = 15	14.6 (12.9–17.7)	894.4 (60.8–1168.0) n = 9	13.9 (12.3–16.7)	1.21 (.77–1.91)	.489	1.29 (.77–2.15)	.415
12	1068.0 (475.8–1513.0) n = 11	14.4 (12.6–17.3)	650.4 (48.7–983.9) n = 12	13.9 (12.7–16.2)	2.25 (1.63–3.11)	<.001	2.23 (1.23–4.06)	.027
Etonogestrel group comparisons								
2	705.5 (25.6–2852.0) n = 14	14.8 (13.5–21.3)	413.7 (24.4–1472.0) n = 13	14.4 (12.4–19.8)	1.94 (1.04–3.61)	.078	1.86 (.73–4.73)	.274
4	897.4 (267.5–1773.0) n = 20	14.2 (11.9–37.9)	784.7 (33.5–1381.0) n = 12	14.3 (12.4–18.5)	1.78 (1.29–2.46)	.003	1.83 (1.07–3.13)	.065
8	916.1 (36.3–2769.0) n = 15	14.5 (13.2–18.2)	894.4 (60.8–1168.0) n = 9	13.9 (12.3–16.7)	1.22 (.76–1.94)	.491	1.72 (.79–3.75)	.252
12	975.4 (545.9–2853.0) n = 17	14.4 (12.6–18.6)	650.4 (48.7–983.9) n = 12	13.9 (12.7–16.2)	2.47 (2.06–2.97)	<.001	2.61 (1.57–4.33)	.002
20	919.2 (83.5–1522.0) n = 11	13.7 (12.1–15.7)	947.6 (183.4–1756.0) n = 13	14.4 (12.2–16.8)	.79 (.55–1.14)	.296	.78 (.46–1.34)	.460
24	1147.0 (187.6–1916.0) n = 13	14.3 (13.1–16.4)	766.3 (261.8–1006.0) n = 14	14.3 (12.9–15.6)	1.48 (1.18–1.85)	.004	1.59 (1.15–2.20)	.019

Abbreviations: CI, confidence interval; DOR, doravirine; GMR, geometric mean ratio, IUD, intrauterine device.

[a]Only calculated from visits when the DOR concentrations were equal to or above the lower limit of quantification for that assay (20 ng/mL).

[b]Calculated from visits when participant self-reported time was ≥0 hours; 3 total observations where time <0 were dropped from analysis.

[c]Calculated with a linear mixed model per study visit.

[d]Calculated with a linear mixed model per study visit adjusting for age, body mass index, and time since last dose in hours.

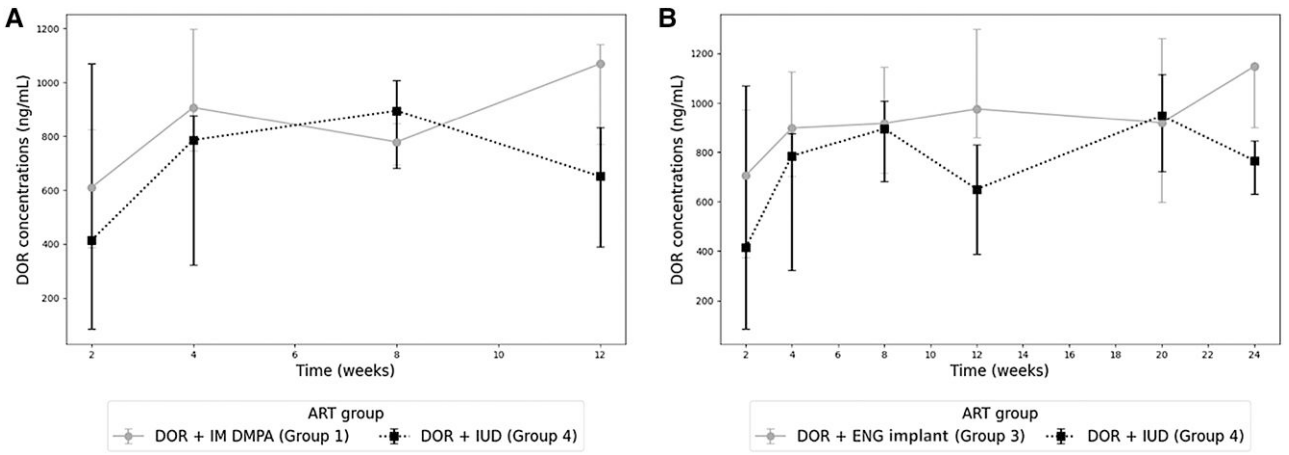

Figure 4. Median and interquartile ranges of doravirine (DOR) plasma concentrations among medroxyprogesterone acetate (MPA) vs etonogestrel (ENG) contraceptive method groups, among EPIC participants (N = 104), November 2021–February 2024. DOR concentrations (ng/mL) among MPA- vs intrauterine device (IUD)–containing groups (*A*) and among ENG- vs IUD-containing groups (*B*) at each study visit. Abbreviations: DMPA, depot medroxyprogesterone acetate; DOR, doravirine; ENG, etonogestrel; IM, intramuscular; IDU, intrauterine device.

with the overall favorable side-effect profile of doravirine-containing ART. Participants followed for 192 weeks in the open-label extension of efficacy trials had minimal (<1%) serious AEs or events leading to discontinuation, and renal and lipid profiles were generally better on doravirine-containing versus other ART [31]; real-world effectiveness data corroborate this favorable profile as well [22]. Effectiveness of doravirine-containing ART was reported around 80% in extension studies [31], with viral

suppression generally equivalent to other regimens in real-world effectiveness [29]. As HIV drug resistance and patient intolerance of dolutegravir-containing ART increase in LMICs [30], it may be reasonable to consider doravirine-containing ART as an alternative first-line ART option. Furthermore, doravirine combinations with other ARVs that do not use any nucleoside reverse transcriptase inhibitors (NRTIs) may be attractive in LMICs due to the increasing NRTI resistance and side effects, particularly weight gain, associated with them [32].

In a PK study where drawing associations with drug exposures is key, having some participants not take their ART consistently in our study despite adherence counseling, and though surprising, is not unusual in this setting. Some participants who did not have detectable doravirine concentrations when expected had dolutegravir concentrations detected above the LLOQ (data not shown) [33]. Since our study inclusion criteria required viral suppression on their current ART from routine care, participants switching to the study ART may have been hesitant to switch from a known, trusted, and reliable ART regimen. Women in sub-Saharan Africa face a host of social and contextual barriers that impact their ability to effectively use HIV treatment options [34–36]. We have planned analyses to investigate this issue further, using both the quantitative and qualitative data collected in the study. Nonuse of study HIV prevention options has long been recognized [37], and novel tools, from pill bottle openings to tenofovir detection in point-of-care urine assays [38], to detect and provide real-time feedback have been shown to increase adherence to biomedical prevention, including in real-world scale-up of oral preexposure prophylaxis [39]. Similar technologies may have a role in HIV treatment. In high-income settings, checking a viral load or an HIV drug resistance profile often serves as a proxy for ART adherence. Given the complexity of measuring real-time blood ARV concentrations on a routine basis, and the expense of HIV viral load and drug resistance testing in LMICs, novel tools, such as urine ARV testing, could play a role in ART adherence monitoring [38]. Ultimately, we think the less than ideal uptake of study ART was not intrinsically due to the specific regimen; once used in routine care, we anticipate people who initiate doravirine-containing ART will be just as adherent to it as they are to other regimens.

Limitations

Despite being one of the most comprehensive PK studies to profile DDIs regarding concomitant use of doravirine-containing ART and hormonal contraceptives, our study faces several limitations. First, that not all participants adhered to their ART optimally limits exposure–outcome relationship ascertainment; nonetheless, our sensitivity analysis excluding ARV samples below limits of quantification did not alter the overall findings of no detrimental associations. Second, our historical comparator group was from a different country; our sociodemographic characteristics highlight some differences, and pharmacogenetic differences may play a role in PK associations for DDIs [25]. Third, our implementation of the timing of blood collection to truly generate ARV C_{min} outside of an intensive 24-hour sampling strategy were suboptimal. Thus, our analyses of doravirine concentrations resemble "random" time sampling; assuming this sampling is nondifferential between the groups, which we believe it is, our estimates will be biased toward the null. Therefore, future studies should better account for timing of blood collection, working carefully with study participants, to ensure the samples collected better represent the C_{min} time windows or conduct observed therapy with intensive 24-hour sampling.

CONCLUSIONS

In this PK study examining bidirectional DDIs between concomitant doravirine-containing ART among South African women living with HIV using injectable or implantable hormonal contraception, we found no detrimental associations. Doravirine-containing ART may have an increasing role to play in LMICs, and we hope these data provide further reassurance to patients, providers, and policymakers for the use of this regimen with common hormonal contraceptive methods. Both the HIV treatment and prevention fields need to conduct relevant studies earlier, before real-world use, that cover the nuances of sexual and reproductive health, spanning the pregnancy spectrum from prevention to having safe pregnancies.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Author contributions. Conceptualization: R. C. P., T. P.-P., K. K. S., N. N., and K. R. Data curation: P. M. and N. Y. Formal analysis: P. M. and R. C. P. Funding acquisition: R. C. P., T. P.-P., and K. R. Investigation: R. C. P., K. K. S., T. P.-P., N. N., R. K., L. K., L. K., K. R., M. G., N. M., N. S., M. S., and L. S. Methodology: R. C. P., K. K. S., T. P.-P., and D. W. E. Project administration: R. C. P., T. P.-P., K. R., N. N., L. K., and T. W. Resources: P. M., N. Y., R. C. P., D. W. E., and K. K. S. Software: P. M. and N. Y. Supervision: R. C. P., T. P.-P., N. N., K. R., and L. K. Visualization: P. M. Writing–original draft preparation: R. C. P. and P. M. Writing–review and editing: All coauthors.

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Data availability. Data are not publicly available but can be requested from the corresponding author with appropriate ethics review and data sharing agreements.

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