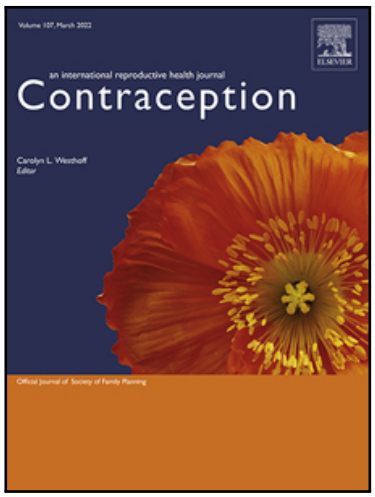

Pharmacokinetics of dose-adjusted levonorgestrel emergency contraception combined with efavirenz-based antiretroviral therapy or rifampicin-containing tuberculosis regimens

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Pharmacokinetics of dose-adjusted levonorgestrel emergency contraception combined with efavirenz-based antiretroviral therapy or rifampicin-containing tuberculosis regimens

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ABSTRACT

Objectives: To determine if double-dose levonorgestrel emergency contraception (EC) in combination with efavirenz or rifampicin, two drugs known to decrease levonorgestrel exposure, resulted in similar pharmacokinetics compared to standard-dose levonorgestrel EC without drug-drug interactions.

Study Design: We conducted a phase 2, open-label, multicenter, partially randomized, four parallel group trial in pre-menopausal females ≥16 years old without an indication for EC and not on hormonal contraception. Participants on dolutegravir-based antiretroviral therapy (ART) received levonorgestrel 1.5mg (control group); those on rifampicin-containing tuberculosis therapy received levonorgestrel 3mg; those on efavirenz-based ART were randomized 1:2 to levonorgestrel 1.5mg or 3mg. Plasma was collected through 48h post-dose to assess levonorgestrel pharmacokinetics. Area under the concentration-time curve (AUC) over 8 hours was the primary outcome. Levonorgestrel pharmacokinetic parameters were compared between groups using geometric mean ratios (GMR) with 90% confidence intervals.

Results: The median (Q1, Q3) age for all participants (n=118) was 34 (27, 41) years and BMI was 23.2 (20, 26.3) kg/m^2. Participants receiving levonorgestrel 1.5mg plus efavirenz (n=17) had 50% lower $AUC_{0\text{-}8h}$ compared to the control group (n=32) [0.50 (0.40, 0.62)]. Participants receiving levonorgestrel 3mg had a similar $AUC_{0\text{-}8h}$ when receiving either efavirenz (n=35) [0.99 (0.81, 1.20)] or rifampicin (n=34) [1.16 (0.99, 1.36)] compared to control. Levonorgestrel 3mg resulted in similar or higher maximum concentration with either efavirenz [1.17 (0.96, 1.41)] or rifampicin [1.27 (1.09, 1.49)] compared to the control group.

Conclusions: Doubling the dose of levonorgestrel EC successfully increased levonorgestrel exposure over the first 8 hours in participants receiving either efavirenz-based ART or rifampicin-containing tuberculosis therapy.

Key words: Emergency contraception; efavirenz; rifampicin; pharmacokinetics; drug interaction

Implications: Adjusting levonorgestrel emergency contraception from 1.5mg to 3mg improves levonorgestrel pharmacokinetic exposure in participants receiving either efavirenz-based antiretroviral regimens or rifampicin-containing tuberculosis therapy. These data support guideline recommendations to double the dose of levonorgestrel

emergency contraception in persons on medications that decrease levonorgestrel exposure by inducing levonorgestrel metabolism.

1.0 INTRODUCTION

Women account for over 50% of people living with HIV. In addition, tuberculosis (TB) remains one of the greatest threats to public health. For women living with either HIV or TB, unintended pregnancies are associated with poor maternal and neonatal outcomes [1, 2]. Emergency contraception (EC) is a safe and effective form of birth control when used intermittently after sex that could lead to pregnancy in the absence of other effective contraception [3].

Levonorgestrel EC is given as a single 1.5mg dose within 72 hours after unprotected sex that could lead to pregnancy. An inverse relationship between levonorgestrel pharmacokinetics (PK) and body mass index (BMI) has been reported [4-6]. Further, levonorgestrel is metabolized via the cytochrome P450 3A4 (CYP3A4) isoenzyme. Co-administration of medications that induce CYP3A4 decrease levonorgestrel concentrations. When combined with efavirenz or rifampicin in healthy volunteers, the levonorgestrel area under the concentration-time curve (AUC) was reduced by more than 50% [7, 8]. Based on these data, European Medicines Authority and United Kingdom guidelines advise that women receiving CYP inducers receive double-dose levonorgestrel EC (3mg instead of 1.5mg) [9, 10]. However, there are no data to confirm this strategy restores levonorgestrel exposure in the presence of these drug-drug interactions (DDIs) without excess adverse events, nor are there data demonstrating the effectiveness of this strategy.

AIDS Clinical Trial Group (ACTG) trial A5375 was designed to evaluate the PK and safety of dose-adjusted levonorgestrel EC in combination with efavirenz-based antiretroviral therapy (ART) or rifampicin-containing TB therapy. We hypothesized that doubling the dose of levonorgestrel EC in combination with either efavirenz or rifampicin would result in similar PK exposure and rate of adverse events compared with participants receiving standard-dose levonorgestrel EC in the absence of a DDI. We also evaluated the change in exposure that occurred when doubling the dose of levonorgestrel EC in participants receiving efavirenz-based ART.

2.0 MATERIAL AND METHODS

2.1 Study design

A5375 was a phase 2, open-label, multicenter, partially randomized, four parallel group trial that enrolled participants at 18 ACTG sites in Botswana, Brazil, Kenya, Malawi, South Africa, Thailand, and the United States. Based on group assignment, levonorgestrel was administered as either 1.5mg or 3mg given once with food at entry.

Participants with HIV who were receiving dolutegravir-based ART received levonorgestrel 1.5mg (**control group**). Participants with HIV who were taking efavirenz-based ART were randomized on a 1:2 basis to receive either levonorgestrel 1.5mg (**efavirenz-levonorgestrel 1.5mg group**) or 3mg (**efavirenz-levonorgestrel 3mg group**), utilizing centrally coordinated, computerized implementation of permuted blocks randomization (block size of 6) without stratification, and dynamic balancing within each institution (maximum allowed imbalance of 2). Participants without HIV in the continuation phase of rifampicin-containing TB therapy received levonorgestrel 3mg (**rifampicin group**). Because levonorgestrel PK is affected by body weight [4-6], we limited enrollment of participants with a body mass index (BMI) ≥30 kg/m^2 to no more than 18% per group.

Intensive PK sampling occurred over 48 hours around the levonorgestrel dose. The visit was not timed according to the menstrual cycle. Adverse events were assessed at each in-person visit, and by phone 7, 14, and 28 days after the levonorgestrel dose. The study was conducted in accordance with the Declaration of Helsinki and registered at ClinicalTrials.gov (NCT03819114). The study was approved by an institutional review board at each study site and written informed consent was obtained from each participant.

2.2 Participants

Detailed inclusion and exclusion criteria are provided in **Supplementary Material**. Participants were non-pregnant volunteers who did not require EC at entry (i.e., no unprotected sex that could lead to pregnancy in the previous 14 days). Participants were required to be at least 16 years of age, post-menarchal, pre-menopausal, assigned female sex at birth, without a history of bilateral oophorectomy or hysterectomy, and not breastfeeding an infant under six months of age. All participants agreed to use a non-hormonal method of contraception during the study and could not have recent exposure to hormones or drugs known to interact with levonorgestrel based on self-report.

Participants with HIV could not be on treatment for active TB and were taking either efavirenz 600mg daily or dolutegravir 50mg daily plus two nucleoside-reverse transcriptase inhibitors for at least 30 days prior to enrollment. Participants with TB had a recent negative HIV test and were receiving daily rifampicin plus isoniazid, with or without ethambutol. Rifampicin was dosed by weight (10mg/kg/day) in accordance with local standard of care.

2.3 PK assessment and analyses

At the entry visit, blood samples were collected before the levonorgestrel dose, and then 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24, and 48-hours post-dose. Participants were allowed to leave the clinical research site after 8-hours and returned for 24- and 48-hour sampling. Participants who reported missing an ART or rifampicin dose in previous three days had the visit rescheduled. From each participant, one sample was identified for additional analysis of efavirenz, (12-20h post-dose), dolutegravir, (20-28h post-dose), or rifampicin and desacetyl-rifampicin (1-16h post-dose). These timeframes were selected to correspond with previously defined PK-pharmacodynamic relationships for efavirenz and dolutegravir [11, 12], and the most recent sample post-reported dose for rifampicin, because of its short half-life. Plasma was separated within one hour of blood collection and stored at ≤-70°C until analysis. Drug concentrations were quantified by validated, quality-controlled, liquid chromatography-tandem mass spectroscopy methods [13-15]. The coefficient of variation of each analyte was less than 15%, and the assays met Food and Drug Administration guidance on bioanalytical method validation criteria [16].

Non-compartmental analysis of levonorgestrel was performed with WinNonLin (Certara®, Princeton, NJ, USA) software using the linear up/log down trapezoidal rule to estimate AUCs, apparent oral clearance (Cl/F), apparent volume of distribution (Vd/F), and elimination half-life ($T_{1/2}$). The maximum concentration (C_{max}), time to C_{max} (T_{max}), and last concentration (C_{last}) were directly observed. Any concentrations below the limit of quantification and occurring post-dose were set to half the lower limit of quantification. All levonorgestrel concentrations were used to calculate individual PK parameters with no additional adjustments or exclusions. To avoid potential loss of power or introduction of bias due to participants who did not return for the 24- and 48-hour sampling, the primary outcome was specified *a priori* as AUC from 0-8 hours; the AUCs from 0-24h, 0-48h, and to infinity were calculated to provide a comparison with published levonorgestrel EC evaluations.

2.4 Safety assessments

We evaluated safety in all participants and reported adverse events by dose received: 1.5mg versus 3mg. Participants had a targeted physical exam at entry and when indicated. Participants were asked about their typical menstrual cycle at study entry (reflecting the past 6 months) and again at each study visit, including their perception of the usual frequency of cycles, duration of bleeding, and spotting. Study related menstrual changes had to be either new in onset or aggravated in severity or frequency from baseline. Severity of adverse events were assessed using

the Division of AIDS Adverse Event Grading Table and the Female Genital Grading Table for Use in Microbicide Studies [17, 18]. All adverse events were assessed by site investigators; only the following required reporting to case report forms: pregnancy, serious adverse events [19], Grade ≥3 adverse event, or Grade ≥2 nausea, diarrhea, or menstrual abnormalities potentially related to levonorgestrel.

2.5 Statistical analysis

For primary objectives, the target sample size was 30 in the control, efavirenz-levonorgestrel 3mg, and rifampicin groups. Assumptions included the levonorgestrel $AUC_{0\text{-}8hr}$ coefficient of variation of 0.45, and 10% significance, corresponding to inverting two 5% one-sided tests (TOST). Assuming equivalence, there was 88% statistical power for declaring similarity in $AUC_{0\text{-}8hr}$ between either 3mg levonorgestrel group versus control, using reference interval of (0.7, 1.43) [20, 21]. Target sample size of 15 participants in the efavirenz-levonorgestrel 1.5mg group, provided 80% statistical power that the true 1.5mg versus 3mg levonorgestrel $AUC_{0\text{-}8hr}$ geometric mean ratio (GMR) was ≤0.67.

Inclusion in the primary PK analysis required sufficient samples to calculate levonorgestrel $AUC_{0\text{-}8hr}$. In a PK sensitivity analysis, we excluded participants with inadequate companion drug levels: efavirenz <650 ng/mL (the lower 95% prediction bound 20 hours post dose), dolutegravir <398 ng/mL (lower 95% bound of the trough), or rifampicin below the limit of quantitation (<75 ng/mL for rifampicin, <37.5 ng/mL for desacetyl-rifampicin) [22, 23].

The 90% confidence interval (CI) on the GMR was calculated using pooled variance of the difference and log-transformation of PK parameters; CI of 90% matches TOST each at 5%. The anti-log of GMRs and confidence bounds are reported. Since weight is prognostic for levonorgestrel exposure [4-6], GMRs were adjusted for BMI via inclusion in a linear model.

A historical group verified absence of DDI between levonorgestrel and dolutegravir-based ART [6]. Within BMI subgroups, $AUC_{0\text{-}24h}$ GMRs and 90% CIs (using Satterthwaite standard error) reflected control versus historical group comparisons.

Imbalances between non-randomized groups in *a priori* selected baseline characteristics were tested using Fisher's exact tests and Wilcoxon Rank Sum tests, using 5% significance. Statistical analyses used SAS (v9.4, SAS Institute, Cary, NC).

3.0 RESULTS

We enrolled 122 participants between May 2019 and November 2020; four did not meet criteria for the primary PK analysis (**Figure 1**), leaving 32 participants in the control group, 17 in the efavirenz-levonorgestrel 1.5mg group, 35 in the efavirenz-levonorgestrel 3mg group, and 34 in the rifampicin group. Baseline characteristics are described in **Table 1**. The median BMI across all groups was 23.2 kg/m^2. The country of enrollment and participant race/ethnicity differed by group; age and BMI was statistically different between the rifampicin and control groups.

3.1 Pharmacokinetic outcomes

Using our designated historical comparator [6], we first confirmed there was no evidence of a DDI between dolutegravir-based ART and levonorgestrel (**Supplementary Table 1**). The levonorgestrel $AUC_{0\text{-}24h}$ were similar among both normal BMI [GMR 0.97, 90% CI (0.73, 1.29)] and obese BMI [0.81 (0.58, 1.14)], thus affirming participants receiving dolutegravir-based ART were an appropriate control group.

To assess the primary objectives of evaluating the double-dose groups compared to standard dose in the absence of a DDI, we compared each levonorgestrel 3mg group to the control group. In the efavirenz-levonorgestrel 3mg group, C_{max} and $AUC_{0\text{-}8h}$ were similar to the control group (**Figure 2C; Table 2**). The levonorgestrel half-life was 46% shorter (median: 11.8 hours vs. 24.0 hours), resulting in 76% lower C_{last}, 30% lower $AUC_{0\text{-}24h}$, and 42% lower $AUC_{0\text{-}48h}$ compared to control. In the rifampicin group, the AUCs over the first 8 and 24 hours were similar to the control group (**Figure 2D; Table 2**). The C_{max} was 27% higher, while the half-life was 57% shorter in the rifampicin group, resulting in 82% lower C_{last} and 21% lower AUC_{48h}. While the primary results were adjusted for BMI, unadjusted results are presented in **Supplemental Table 3**.

Compared to the control group, the efavirenz-levonorgestrel 1.5mg group had 50% lower $AUC_{0\text{-}8h}$ [0.50 (0.40, 0.62)] (**Figure 2A; Supplementary Table 2**). The half-life was nearly two-fold shorter, which resulted in 64-70% lower exposure over 24 and 48 hours compared to the control group. Comparing levonorgestrel 1.5mg vs. 3mg in participants receiving efavirenz-based ART (**Figure 2B; Supplementary Table 2)**, those taking levonorgestrel 3mg had higher $AUC_{0\text{-}8h}$ [1.81 (1.42, 2.30)], which remained 88-90% higher over 24- and 48-hours post-dose. The C_{max} was 61% higher in the 3mg vs. 1.5mg efavirenz groups [24.9 (16.2, 29.6) vs. 15.1 (11.2, 24) ng/mL] and C_{last}

was 126% higher [0.61 (1.45, 3.67) vs. 0.32 (0.2, 0.38) ng/mL]. Other PK parameters were similar between the two efavirenz groups.

In the PK sensitivity analyses, nine participants with inadequate companion drug concentrations were excluded, four in the control group, one in the efavirenz-levonorgestrel 3mg group, and four in the rifampicin group. Results were similar to the primary analyses (**Supplementary Tables 2 and 3**).

3.2 Safety outcomes

Of the 122 participants enrolled, two participants (4%) receiving levonorgestrel 1.5mg and two participants (3%) receiving levonorgestrel 3mg experienced reportable adverse events. In the 1.5mg dosing groups, one participant had Grade 2 nausea after the levonorgestrel dose on day 0 and one participant experienced Grade 2 heavy menstrual bleeding on day 26. In the 3mg dosing groups, one participant had Grade 2 nausea on day 0, and another participant had Grade 2 nausea on day 0, Grade 2 intermenstrual bleeding on day 4, and Grade 3 headache and menstrual discomfort in the final week of follow-up. No pregnancies were reported during follow-up.

4.0 DISCUSSION

This trial demonstrated that adjusting levonorgestrel EC from 1.5mg to 3mg in participants receiving either efavirenz-based ART or rifampicin-containing TB therapy resulted in similar levonorgestrel exposure in the first 8 hours post-dose. Both efavirenz and rifampicin induced the metabolism of levonorgestrel, resulting in a shorter half-life and lower levonorgestrel exposure at the end of the 48-hour PK sampling interval. Although there are no data directly evaluating the PK:pharmacodynamic relationship of levonorgestrel EC, an adequate C_{max} is desired to prevent or delay ovulation [4]. Doubling the dose of levonorgestrel resulted in similar, or higher, C_{max} in both 3mg study groups. While these data support guideline recommendations to increase the dose of levonorgestrel to improve PK, without increasing adverse effects of levonorgestrel in people requiring EC plus efavirenz or rifampicin [9, 10], it is unknown if this correction of exposure over the first 8 hours is sufficient to maintain EC effectiveness.

Consistent with prior evaluations of standard dose levonorgestrel with efavirenz in healthy volunteers [7], the administration of levonorgestrel 1.5mg plus efavirenz-based ART resulted in 50% lower exposure over 8 hours compared to the control group. Over 48 hours, the AUC was 70% lower, and the C_{last} was 90% lower than the control group. This reflects a shorter half-life of levonorgestrel, consistent with efavirenz inducing levonorgestrel

metabolism. Levonorgestrel exposure was not proportionally increased when participants on efavirenz received double-dose levonorgestrel. While the C_{last} was two-fold higher in the 3mg vs 1.5mg efavirenz-levonorgestrel groups, the C_{max} and AUCs were only 51-80% higher. These findings are consistent with levonorgestrel contraceptive implants in combination with efavirenz-based ART, where proportionally higher plasma exposure was not observed with double-dose levonorgestrel implants over 48 weeks [24].

In contrast, Edelman and colleagues evaluated dose escalation to overcome decreased levonorgestrel exposure in obesity and reported similar C_{max} and AUC over 2.5 hours post-dose in obese individuals receiving levonorgestrel 3mg compared to individuals with normal BMI receiving standard dose [4], consistent with our findings over 8 hours post-dose. In a follow-up, randomized, controlled trial, Edelman and colleagues found no difference in ovulation delay in obese individuals despite dose escalation (follicle rupture: 1.5mg, 17/35 (48.6%); 3mg, 11/35, (31.4%), p=0.14], nor in the time to follicle rupture (p=0.21) [25]. The authors propose that levonorgestrel PK:pharmacodynamic changes may be due to changes in protein binding or differences in the hypothalamus-pituitary-ovulation relationship related to obesity. While it is unclear if these results would be similar in the setting of a DDI which enhances drug clearance rather than physiologic changes related to obesity, the findings highlight that alternative options for EC may be preferred. Unfortunately, the alternative oral EC, ulipristal, is also metabolized by CYP3A4 enzymes, resulting in similar DDI concerns, and the copper intrauterine device is not consistently available or accessible in areas where HIV and TB are most prevalent.

Pharmacogenetics may contribute to the extent of the DDI observed. Prior evaluations of progestin DDIs with efavirenz found that individuals who have CYP2B6 polymorphisms, which result in slower efavirenz metabolism (thus higher overall efavirenz concentrations), had lower progestin concentrations when combined with efavirenz than those without these polymorphisms [26-28]. In addition, all participants in the rifampicin group were receiving isoniazid. Recent data suggest individuals who are NAT2 slow acetylators have higher concentrations of isoniazid, a mechanistic CYP inhibitor, resulting in higher concentrations of CYP3A4 metabolized medications [29]. Planned future work will evaluate if pharmacogenetic characteristics influenced the levonorgestrel exposure in trial participants.

This trial has limitations to consider when interpreting the findings. First, participants did not require EC for prevention of pregnancy at entry and was not designed to evaluate contraceptive effectiveness. Second, we observed differences in age, BMI, country of enrollment, and race between groups, and there is the potential for

residual confounding due to lack of randomization between some groups. While BMI was adjusted for in our comparisons, we did not adjust for other differences between groups. Without daily menstrual cycle diaries, we may not have adequately captured menstrual cycle abnormalities. Finally, if adherence to efavirenz or rifampicin were suboptimal prior to entry, we may have observed higher levonorgestrel exposure in the 3mg arms, which may overestimate the effect of levonorgestrel dose-adjustment compared to the control group. Reassuringly, the results of the PK sensitivity analysis were similar to our primary estimates.

Unintended pregnancy rates are high worldwide. This is especially true in areas of limited resources where both HIV and TB infections are a significant public health burden, and women are less empowered to control their reproductive health. Gender based violence against women, including sexual violence, is linked to HIV acquisition, and may be associated with poorer treatment outcomes [30, 31]. Therefore, providing effective contraception and understanding DDIs between antimicrobials and contraceptives in people living with either HIV or TB are of paramount importance. In the absence of options without concern for DDIs (i.e., copper intrauterine device) or based on patient preference for levonorgestrel EC, double-dose levonorgestrel should be offered to those receiving either efavirenz or rifampicin.

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DATA STATEMENT

The authors confirm that all data underlying the findings are fully available without restriction. Due to ethical restrictions, study data are available upon request from sdac.data@sdac.harvard.edu with the written agreement of the AIDS Clinical Trials Group

DECLARATIONS OF INTEREST

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Table 1. Baseline demographics and clinical characteristics.

Characteristics	**Control group:** LNG 1.5mg + DTG-based ART (n=32)	**EFV-LNG 1.5mg group:** LNG 1.5mg + EFV-based ART (n=17)	**EFV-LNG 3mg group:** LNG 3mg + EFV-based ART (n=35)	**RIF group:** LNG 3mg + RIF-containing TB therapy (n=34)	Total (n=118)
Age in years, median (Q1, Q3)[a]	34 (29, 40)	42 (35, 45)	36 (29, 42)	25 (21, 35)	34 (27, 41)
Cis-gender females, n (%)	32 (100%)	17 (100%)	35 (100%)	34 (100%)	118 (100%)
Country, n (%)[b]					
Botswana	0 (0%)	0 (0%)	0 (0%)	2 (6%)	2 (2%)
Brazil	4 (13%)	1 (6%)	3 (9%)	2 (6%)	10 (8%)
Kenya	0 (0%)	0 (0%)	0 (0%)	4 (12%)	4 (3%)
Malawi	10 (31%)	0 (0%)	0 (0%)	6 (18%)	16 (14%)
South Africa	2 (6%)	7 (41%)	12 (34%)	18 (53%)	39 (33%)
Thailand	2 (6%)	9 (53%)	20 (57%)	2 (6%)	33 (28%)
United States	14 (44%)	0 (0%)	0 (0%)	0 (0%)	14 (12%)
Race/Ethnicity, n (%)[c]					
Asian	2 (6%)	9 (53%)	20 (57%)	2 (6%)	33 (28%)
Black	24 (75%)	7 (41%)	12 (34%)	30 (88%)	73 (62%)
Multiple races	1 (3%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
White	1 (3%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Hispanic or Latino	4 (13%)	1 (6%)	3 (9%)	2 (6%0	10 (8%)
Body weight, median (Q1, Q3), kg	62.2 (54.5, 74.3)	52.3 (46.5, 68.9)	58.5 (50.3, 74.0)	54.6 (48.0, 61.9)	58.4 (50.2, 68.9)
BMI, median (Q1, Q3), kg/m^{2} [d]	25.3 (21.6, 28.1)	20.3 (18.3, 26.0)	23.5 (20.5, 26.6)	21.5 (19.7, 24.5)	23.2 (20.0, 26.3)
BMI category, n (%)[e]					
Underweight <18.5 kg/m^2	3 (9%)	5 (29%)	2 (6%)	7 (21%)	17 (14%)
Normal weight 18.5 – 24.9 kg/m^2	12 (38%)	7 (41%)	21 (60%)	20 (59%)	60 (51%)
Overweight 25.0 – 29.9 kg/m^2	12 (38%)	2 (12%)	7 (20%)	4 (12%)	25 (21%)

Obese ≥30 kg/m^2	5 (16%)	3 (18%)	5 (14%)	3 (9%)	16 (14%)
Time on efavirenz, dolutegravir, or rifampicin (months), median (Q1, Q3)	12.4 (3.0, 27.0)	38.8 (32.3, 69.7)	32.4 (23.7, 58.9)	3.8 (3.2, 5.1)	…
HIV group characteristics					Total (n=84)
HIV-1 RNA <40 copies/mL, n (%)	27 (84%)	14 (82%)	35 (100%)	…	76 (90%)
HIV-1 RNA, median (Q1, Q3), copies/mL[a,f]	314 (223, 6238) (n=5)	642 (163, 770) (n=3)	…	…	478 (193, 3504) (n=8)
CD4+, median (Q1, Q3), cells/mm^3	599 (389, 864)	548 (426, 611)	676 (520, 834)	…	629 (427, 815)
Co-administered ARV medications, n (%)					
Lamivudine/ tenofovir DF	15 (47%)	1 (6%)	2 (6%)	…	…
Abacavir/lamivudine	6 (19%)	0 (0%)	1 (3%)	…	…
Emtricitabine/ tenofovir DF	3 (9%)	16 (94%)	32 (91%)	…	…
Emtricitabine/ tenofovir AF	8 (25%)	0 (0%)	0 (0%)	…	…

Abbreviations: AF, alafenamide; ARV, antiretroviral; ART, antiretroviral therapy; BMI, body mass index; DF, disoproxil fumarate; DTG, dolutegravir; EFV, efavirenz; LNG, levonorgestrel; TB, tuberculosis

[a] Comparisons of age among non-randomized groups: EFV-LNG 1.5mg vs control (p=0.008); EFV-LNG 3mg vs control (p=0.4); RIF vs control (0.002) [p-values from Wilcoxon Rank Sum Tests]

[b] Comparisons of country among non-randomized groups: EFV-LNG 1.5mg vs control; EFV-LNG 3mg vs control; RIF vs control all p < 0.001 [p-values from Fisher's exact Tests]

[c] Comparisons of race/ethnicity among non-randomized groups: EFV-LNG 1.5mg vs control (p=0.002); EFV-LNG 3mg vs control (p<0.001.); RIF vs control (0.56) [p-values from Fisher's exact Tests]

[d] Comparisons of BMI among non-randomized groups: EFV-LNG 1.5mg vs control (p=0.06); EFV-LNG 3mg vs control (p=0.31); RIF vs control (0.01) [p-values from Wilcoxon Rank Sum Tests]

[e] Comparisons of BMI category among non-randomized groups: EFV-LNG 1.5mg vs control (p=0.14); EFV-LNG 3mg vs control (p=0.26); RIF vs control (0.048) [p-values from Fisher's exact Tests]

[f] Among those with HIV-1 RNA ≥40 copies/mL

Table 2. Levonorgestrel plasma pharmacokinetic parameters over 48-hours after a single dose of emergency contraception.

Pharmacokinetic parameters	Median (Q1, Q3)				GMR (90% Confidence Interval) Adjusted for BMI	
	Control group: LNG 1.5mg + DTG-based ART (n=32)	**EFV-LNG 1.5mg group:** LNG 1.5mg + EFV-based ART (n=17)[a]	**EFV-LNG 3mg group:** LNG 3mg + EFV-based ART (n=35)	**RIF group:** LNG 3mg + RIF-containing TB therapy (n=34)	EFV-LNG 3mg group vs. Control group	RIF group vs. Control group
C_{max} (ng/mL)	18.7 (14.1, 26.2)	15.1 (11.2, 24.0)	24.9 (16.2, 29.6)	28.0 (23.0, 39.6)	1.10 (0.93, 1.31)	1.27 (1.09, 1.49)
T_{max} (h)	2.0 (1.5, 3.0)	1.5 (1.5, 2.1)	2.0 (1.5, 3.0)	2.0 (1.5, 3.0)	…	…
C_{last} (ng/mL)[b]	2.8 (1.5, 3.7)	0.3 (0.2, 0.4)	0.6 (0.3, 1.1)	0.5 (0.2, 1.0)	0.24 (0.17, 0.34)	0.18 (0.11, 0.27)
Vd/F (L)	169.1 (93.8, 215.2)	276.7 (118.3, 411.8)	294.9 (208.7, 489.5)	156.3 (105.3, 247.2)	2.28 (1.87, 2.78)	1.36 (1.13, 1.65)
Cl/F (L/h)	4.4 (2.9, 6.6)	12.6 (10.4, 21.1)	15.2 (12.6, 27.7)	12.1 (9.0, 16.3)	4.22 (3.35, 5.33)	3.18 (2.53, 4.00)
$T_{1/2}$ (h)	24.0 (20.0, 28.0)	12.1 (8.6, 13.7)	11.8 (10.6, 13.8)	9.0 (6.7, 11.9)	0.54 (0.49, 0.60)	0.43 (0.39, 0.48)
$AUC_{0\text{-}8h}$ (h*ng/mL)[c]	80.5 (66.6, 125.0)	52.1 (36.7, 88.3)	102.1 (64.5, 114.8)	124.4 (87.1, 168.8)	0.92 (0.78, 1.10)	1.16 (0.99, 1.36)
$AUC_{0\text{-}24h}$ (h*ng/mL)	157.6 (132.3, 282.3)	81.6 (56.1, 128.5)	153.4 (100.1, 190.5)	213.7 (148.6, 283.2)	0.70 (0.57, 0.85)	0.96 (0.79, 1.17)
$AUC_{0\text{-}48h}$ (h*ng/mL)	224.8 (178.3, 400.9)	99.0 (66.4, 141.3)	180.3 (106.9, 216.8)	242.7 (181.6, 322.0)	0.58 (0.47, 0.72)	0.79 (0.63, 0.97)
AUC_{inf} (h*ng/mL)	345.8 (227.8, 518.7)	118.7 (71.2, 143.7)	196.8 (108.5, 238.2)	249.0 (183.9, 333.0)	0.47 (0.38, 0.60)	0.63 (0.50, 0.79)

Abbreviations: AUC, area under the concentration-time curve; BMI, body mass index; Clast, last observed concentration; Cl/F, apparent clearance; Cmax, maximum concentration; DTG, dolutegravir; EFV, efavirenz; GMR, geometric mean ratio; LNG, levonorgestrel; RIF, rifampicin; Tmax, time of maximum concentration; Vd/F, apparent volume of distribution; $T_{1/2}$, apparent half-life.

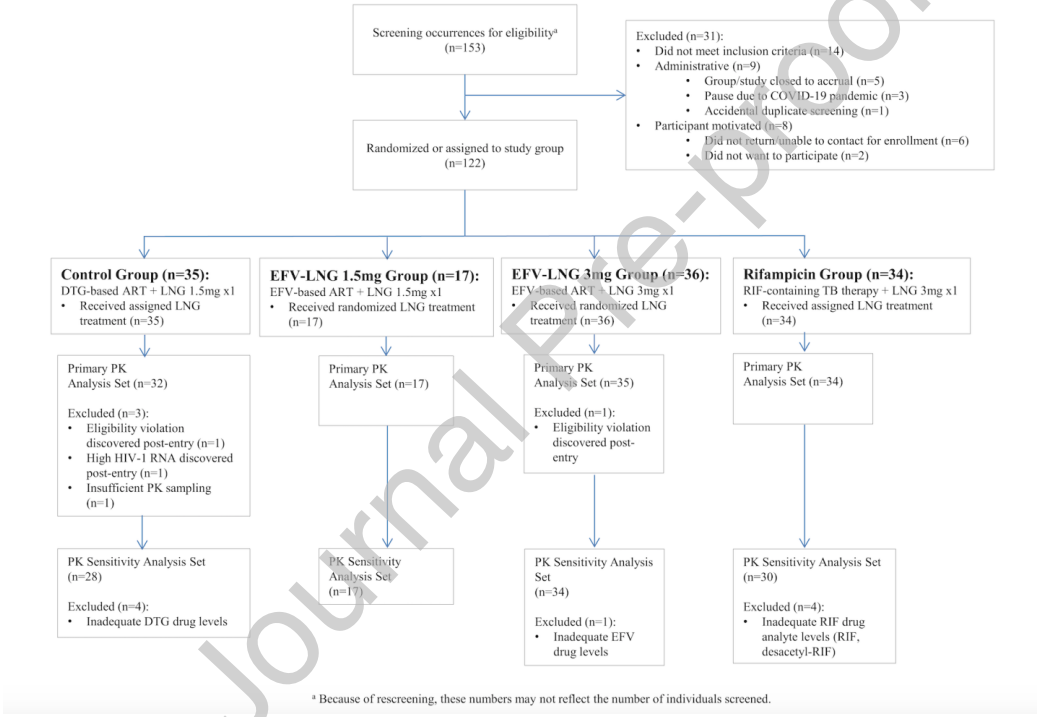
[a] See supplementary material for GMR and 90% confidence interval comparisons with the standard dose efavirenz group and the control group.

[b] All C_{last} concentrations were drawn 48 hours after the levonorgestrel dose, except one participant in the control group, which was drawn 24 hours post-dose.

[c] $AUC_{0\text{-}8h}$ was the primary outcome.

FIGURES

Figure 1. Participant disposition. Primary PK analysis set includes all participants included in the analysis. PK sensitivity analysis set excludes participants with suboptimal dolutegravir, efavirenz, or rifampicin concentrations.



Abbreviations: ART, antiretroviral therapy; DTG, dolutegravir; EFV, efavirenz; LNG, levonorgestrel; PK, pharmacokinetic; RIF, rifampicin.

Figure 2. Levonorgestrel concentration-time curve (median, 25% and 75% quartile) in plasma over 48 hours after a single dose of emergency contraception. Figure 2a illustrates the control group (solid line, triangle) compared to efavirenz-levonorgestrel 1.5mg group (dotted-line, squares). Figure 2b illustrates the efavirenz-levonorgestrel 1.5mg group (dotted-line, squares) and the efavirenz-levonorgestrel 3mg group (dashed line, circles). Figure 2c illustrates the control group (solid line, triangle) compared to the efavirenz-levonorgestrel 3mg group (dashed line, circles). Figure 2d illustrates control group (solid line, triangle) compared to the rifampicin group (dashed line, squares). The control group participants were on dolutegravir-based ART and received levonorgestrel 1.5mg. The efavirenz-levonorgestrel 1.5mg group participants were on efavirenz-based ART and received levonorgestrel 1.5mg. The efavirenz-levonorgestrel 3mg group participants were on efavirenz-based ART and received levonorgestrel 3mg. The rifampicin group participants were on rifampicin-containing tuberculosis therapy in the continuation phase and received levonorgestrel 3mg. Levonorgestrel was administered as a single dose with food at time 0.