**Title**:

Etonogestrel concentrations among contraceptive implant users in Botswana using and not using dolutegravir-based antiretroviral therapy

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CLW receives honoraria from Bayer AG and Merck for serving on the DSMB of several phase 4 safety studies. CLW is an advisor to Mithra and AbbVie, and through Columbia University receives research support from Sebela and Chemo Exeltis. AA is an advisor to ViiV Healthcare and receives research support. CM has received a separate investigator-initiated research grant from ViiV Healthcare outside of the submitted work. The other authors have no disclosures.

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**ABSTRACT**

**Objectives:**

To evaluate whether etonogestrel concentrations are reduced to a level that could potentially reduce contraceptive efficacy when the etonogestrel contraceptive implant is used concomitantly with dolutegravir-based antiretroviral therapy (ART).

**Study Design:**

We conducted a non-randomized, open-label, cross-sectional pharmacokinetic study among women using single-rod etonogestrel contraceptive implants in Botswana. We compared plasma etonogestrel concentrations, sampled at a single time-point between 3 and 12 months from implant insertion, among implant users living with HIV and receiving dolutegravir-based ART with HIV-negative implant users. We also assessed concentrations among implant users living with HIV and receiving efavirenz-based ART. We compared geometric mean etonogestrel concentrations analyzing data from 142 participants: 97 HIV-negative, 30 using dolutegravir, and 15 using efavirenz.

**Results:**

The groups were similar. Duration of implant use was between 3 and 12 months (median=5). Geometric mean etonogestrel plasma concentrations and 90% confidence intervals of the mean were 227.5(212.4-243.8), 289.6(251.8-333.0) and 76.4(63.9-91.4) pg/mL among the HIV-negative, dolutegravir- and efavirenz-based ART groups, respectively. All women in the HIV-negative and dolutegravir-based ART groups had etonogestrel concentrations above 90pg/mL; 9/15 women (60%) using efavirenz-based ART had concentrations below 90 pg/mL. On average, etonogestrel levels were lower among individuals who had implants inserted for longer durations.

**Conclusions:**

Implant users receiving dolutegravir-based ART had a higher mean etonogestrel concentration compared to HIV-negative women, and none had etonogestrel concentrations below the posited threshold for ovulation suppression. In contrast, women in the efavirenz-group had much lower etonogestrel concentrations. Overall, these data provide evidence that the etonogestrel implant may be effectively combined with dolutegravir-based ART regimens.

**Keywords:**

Antiretroviral therapy, contraceptive implant, drug–drug interaction, dolutegravir, efavirenz, etonogestrel

**Implications**

The etonogestrel implant remains a highly effective contraceptive option for women living with HIV who use dolutegravir-based ART.

**1. INTRODUCTION**

Among women living with HIV in low- and middle- income countries (LMICs), over half of the 1.5 million annual pregnancies are unintended [1–3]. Preventing unintended pregnancy is essential to improving the health and well-being of the 19.6 million girls and women living with HIV [4] and to avoiding maternal-to-child HIV transmission [5–7].

Rapidly increasing availability and use of both etonogestrel and levonorgestrel progestin-only contraceptive implants has the potential to markedly decrease unmet contraceptive need and reduce unintended pregnancy in LMICs [8,9]. Implants now account for 25-50% of all use of modern contraception in diverse African settings [9]. The circulating progestin hormone concentration among implant users is relatively close to the level postulated as required for ovulatory suppression, making this method potentially more vulnerable to contraceptive failure in the presence of any drug–drug interactions. Pharmacokinetic data show that cytochrome P450 (CYP) enzyme-system-mediated drug–drug interactions lead to markedly reduced etonogestrel and levonorgestrel contraceptive implant hormone concentrations among women using efavirenz-based antiretroviral therapy (ART) for HIV treatment (50-80%) [10,11], and clinical reports of contraceptive failures with concomitant implant-efavirenz use are concerning [12–14]. Until recently, efavirenz was the WHO-recommended first-line HIV treatment regimen for all adults living with HIV [15], so this drug-drug interaction has complicated contraceptive policy and clinical care, and created a critical barrier to implant uptake and successful use in women living with HIV [10–14]. In the WHO 2019-updated recommendations for HIV treatment, dolutegravir is now the preferred antiretroviral drug in first- and second-line regimens, including among women of reproductive age [16].

The introduction of dolutegravir-based ART treatment across Africa, which began in 2016-2017, has the potential to markedly improve HIV outcomes [17]. Unlike efavirenz, dolutegravir is metabolized mostly by UGT pathways (primarily UGT1A1 glucuronidation), and dolutegravir is not a potent inducer of CYP450 enzymes. Dolutegravir is, thus, less likely than efavirenz to interfere with the pharmacokinetics or effectiveness of the contraceptive implants and other hormonal contraceptives [18,19]. Pharmacokinetic and clinical data on concomitant use of dolutegravir and hormonal contraceptives have been lacking, despite the clinical and public health importance of such data, as dolutegravir-based ART is rolled-out to millions of women of reproductive age. In 2018 a potential signal of increased risk of neural tube defects in the offspring of women using dolutegravir at the time of conception [20] made the need to evaluate dolutegravir-hormonal contraceptive interactions even more urgent.

This study aimed to evaluate whether dolutegravir-based ART and the etonogestrel contraceptive implant have an interaction that could potentially reduce contraceptive efficacy. We hypothesized that there would be no such detrimental drug-drug interaction. The primary outcome of this study is whether concomitant dolutegravir-based ART during etonogestrel implant use in women living with HIV decreases plasma etonogestrel concentrations, relative to those concentrations in HIV-negative women. Women living with HIV and their healthcare providers need evidence-based reassurance that their treatment with dolutegravir will not decrease the efficacy of their etonogestrel contraceptive implant. Information from this study will assist in developing evidence-based contraceptive guidance for women living with HIV.

**2. METHODS**

We conducted a non-randomized, open-label, cross-sectional pharmacokinetic study among women using the single-rod etonogestrel contraceptive implant in Botswana. All study procedures took place at the Botswana-Harvard Partnership and Botswana-UPenn Partnership in Gaborone, Botswana. The University of Botswana, the Health Research and Development Division of the Botswana Ministry of Health and Wellness (MoHW), the Princess Marina Hospital Research and Ethics Committee and Columbia University Medical Center approved the study. This study followed the Declaration of Helsinki and was registered at clinicaltrials.gov (NCT03336346).

The primary aim was to compare plasma etonogestrel concentrations, sampled at a single time-point between 3 and 12 months from implant insertion, among HIV positive implant-users receiving dolutegravir-based ART with etonogestrel concentrations among HIV-negative implant users. A secondary objective was to compare etonogestrel concentrations, sampled at a single time-point between 3 and 12 months from implant insertion, among HIV-negative implant users to concentrations among those receiving efavirenz-based ART. We also describe the proportion of women in each study group with plasma etonogestrel concentrations below the posited ovulation suppression threshold (90pg/mL) [21].

**2.1 Participants**

Eligible women were between the ages of 18 and 45 years, using the etonogestrel implant for at least three but no more than 12 months, and were either 1) HIV-negative (taking no ART; ART-naïve), or 2) living with HIV and receiving dolutegravir-based ART (dolutegravir 50 mg once daily along with two nucleoside reverse transcriptase inhibitors [NRTIs]), or 3) living with HIV and receiving efavirenz-based ART (efavirenz 600 mg once daily along with two NRTIs). Women in the two ART groups had received stable ART regimens for at least 2-months prior to enrollment. Botswana introduced universal ART in 2016, thus the study did not include an HIV-infected, non-ART, comparison group; the study comparison group was HIV-negative and, thus, ART-naïve implant users. This comparison enabled us to answer the key question of whether the etonogestrel implant, when used simultaneously with dolutegravir, provides plasma etonogestrel levels comparable to a group in which it has established contraceptive efficacy (i.e. HIV-negative women of reproductive age).

We excluded women who were pregnant or less than 30-days postpartum, and those who were taking other medications with CYP-inducing (e.g. rifampin, carbamazepine) or inhibiting potential. We also excluded women who reported using other hormonal contraceptives or who were not virally suppressed (<400 copies/ml) (among women living with HIV). No participants were using HIV pre-exposure prophylaxis (PrEP).

**2.2 Study procedures**

The Botswana Ministry of Health and Wellness maintains clinic registries to track contraceptive implant insertions across MoHW and non-governmental clinical sites in Gaborone, Botswana. We used these registries to identify potentially eligible women as the registries include implant insertion date, HIV status, ART regimen, and patient contact information. Study staff contacted women using a standardized telephone script to assess interest in participation, eligibility, and to schedule an enrollment visit. To confirm eligibility, we ascertained type and duration of implant use and type and duration of ART use from medical records, and we confirmed implant location by palpation at the enrollment visit, which was the only study visit.

After providing written informed consent, participants completed a demographic and medical history questionnaire, which included questions on ART adherence, underwent height and weight measurements, and provided a single blood sample from the arm contralateral to their implant. We abstracted their most recent CD4 cell count and HIV viral load information from medical records, if one was recorded in the past six months. We used the blood sample to measure etonogestrel concentrations for all participants and CD4 cell count and HIV viral load for participants living with HIV who did not have a recorded CD4 cell count and HIV viral load in the past six months.

According to the local standard of care, study staff encouraged all participants to use condoms as a second form of contraception and to prevent sexually transmitted infections. Participants using efavirenz-based ART received information about the accumulating data on observed pregnancies in women using contraceptive implants along with efavirenz-based ART, in line with Botswana MoHW guidance on the issue. Participants received 50 Botswana Pula (approximately five USD) for participation.

**2.3 Laboratory and pharmacokinetic assessments**

Blood samples were collected into K-EDTA plasma tubes, stored on ice (4°C) and transported to the laboratory at the University of Botswana, where they were centrifuged at 3400 revolutions/minute for 10 minutes to separate plasma, within 24 hours of collection. Plasma aliquots were stored at -80°C and shipped on dry ice to the Biomarkers Core Laboratory of the Irving Institute of Clinical and Translational Research at Columbia University Medical Center in New York, USA. The analysis used a validated etonogestrel assay with liquid chromatography-mass spectrometry (LC-MS/MS). The laboratory measured etonogestrel in plasma by LC-MS/MS after liquid/liquid extraction using D-8 Progesterone as the internal standard [22].

**2.4 Statistical analysis**

A sample size of 90 participants in the HIV-negative group and 30 in the dolutegravir-based ART group provided greater than 90% power to detect a 20% difference between the groups (two-sided alpha of 0.05). This calculation is based on an expected etonogestrel concentration (without ART use) of 338 pg/mL (standard deviation 77 pg/mL) at three months post-insertion, when the etonogestrel contraceptive implant first reaches a relative steady state [23]. We also included a small number of women receiving efavirenz, a medication known to reduce etonogestrel concentrations, to evaluate whether our results would be consistent with previously published data [10].

We calculated the median etonogestrel concentration with interquartile range (IQR) for each of the three groups. We also calculated an etonogestrel geometric mean concentration for each of the three groups, and then compared the geometric mean concentration between the dolutegravir group and the HIV-negative group as a geometric mean ratio (GMR) with a 90% confidence interval (CI). We calculated the same outcomes for users of efavirenz-based ART. We also calculated the proportion of participants in each group with an etonogestrel concentration below 90 pg/mL, the level posited for ovulation suppression [21]. We had recorded the duration of implant use in each individual and adjusted for this using multivariate linear regression in our comparisons. All statistical analyses were conducted using STATA 16 (Stata Corporation, College Station, Texas).

**2.5 Participant follow-up**

We contacted participants by telephone to report their etonogestrel level and HIV viral load results, and then counselled, referred, or provided a visit by our study team for contraceptive or HIV care, as appropriate.

**3. RESULTS**

**3.1 Demographic characteristics**

Between February 2018 to October 2019, we identified 494 potentially eligible women from the clinic registries (Figure 1). We were able to contact 323 (65%) of these women in the clinic or by telephone for initial study screening (of those not contacted, the vast majority was due to a non-working telephone number in the registry, n=171). Of the 323 contacted, 134 declined participation and 29 were no longer eligible. We enrolled 160 women. Of those enrolled, we excluded 18 after blood sample collection: nine who were using levonorgestrel implants, four who had an etonogestrel implant duration of less than three months (due to miscalculation of implant duration at the time of enrollment), one who was using nevirapine-based ART, two with detectable HIV viral loads who, on further enquiry, reported poor ART adherence, and two in whom the samples had been collected from the ipsilateral arm. We thus included 142 participants in this analysis: 97 HIV-negative women, 30 using dolutegravir-based ART, and 15 using efavirenz-based ART. Demographic characteristics, as well as duration of implant use and body mass index (BMI) were similar across the groups (Table 1). The median duration of implant use was 147 days (IQR 119.5-271), 182 days (IQR 119-247.5) and 152 days (IQR 130-272) in the HIV-negative, dolutegravir, and efavirenz groups, respectively.

**3.2 Etonogestrel pharmacokinetics**

Table 2 and Figure 2 summarize the etonogestrel pharmacokinetic data. The median etonogestrel concentrations were 235.9 pg/mL (IQR 171.7-298.3), 303.0 pg/mL (IQR 207.2- 406.1) and 71.9 pg/mL (IQR 57.7-104.9) in the HIV-negative, dolutegravir-, and efavirenz-based ART groups, respectively. Geometric mean etonogestrel plasma concentrations and 90% CIs of the mean were 227.5 (212.4-243.8), 289.6 (251.8-333.0) and 76.4 (63.9-91.4) pg/mL among the HIV-negative, dolutegravir-, and efavirenz-based ART groups, respectively. In the efavirenz group, the etonogestrel concentration was substantially lower compared to the HIV-negative group [GMR: 0.58 (90% CI 0.53-0.64)]. In contrast, the etonogestrel concentration in the dolutegravir group was higher compared to the HIV-negative group [GMR: 1.27 (90% CI 1.10-1.47)]. Adjusting for duration of implant use did not make any notable difference to the GMR comparisons. The adjusted GMR comparing the efavirenz group with the HIV-negative group was 0.60 (90% CI 0.55-0.66), and the adjusted GMR comparing the dolutegravir group with the HIV-negative group was 1.28 (90% CI 1.13-1.46). All women in the HIV-negative and dolutegravir-based ART groups had etonogestrel concentrations above 90 pg/mL, while 60% (9/15) of women on efavirenz-based ART had concentrations below 90 pg/mL. On average, etonogestrel levels were lower in individuals who had implants inserted for longer durations in all groups (Figure 2).

**4. DISCUSSION**

Women living with HIV who were using the etonogestrel contraceptive implant in combination with dolutegravir-based ART had a higher mean etonogestrel plasma concentration compared to HIV-negative women. No participant in the dolutegravir-based ART or HIV-negative groups of our study had etonogestrel concentrations below the presumed threshold for ovulation suppression of 90 pg/mL [21] after up to 12 months of contraceptive implant use. In contrast, women in the efavirenz-group had much lower etonogestrel concentrations. We found no evidence of detrimental drug-drug interactions between etonogestrel implants and dolutegravir-based ART. Overall, these data provide evidence that the etonogestrel implant may be effectively combined with dolutegravir-based ART regimens.

One published study has reported on hormonal contraception concentrations during dolutegravir use. This single site, cross-over study of a combined oral pill (norelgestromin/ethinyl estradiol) in 16 healthy women in the U.S. found no significant differences in pharmacokinetic parameters of the hormones under study with or without dolutegravir [24]. Our findings of a decreased mean etonogestrel level among women using efavirenz-based ART (66% lower) are similar to a Brazilian study [11] that reported 63% lower serum etonogestrel area-under-the-curve (AUC) over 24 weeks for women using the etonogestrel implant along with efavirenz compared to those not using ART. Similarly, a Ugandan study of the etonogestrel implant reported that 24 weeks after implant insertion, etonogestrel exposure was 82% lower in women using efavirenz-based ART compared to ART-naïve women [10]. Another Ugandan study of the levonorgestrel implant reported 47% lower levonorgestrel concentrations for women using efavirenz-based ART when compared with those that were ART-naïve [14]. Unlike our study, these three studies enrolled HIV-infected but ART-naïve control participants; a comparison that is no longer permissible in the era of universal ART.

The reason for the slightly higher mean etonogestrel concentration in the dolutegravir group as compared to the HIV-negative group is not known but is corroborated by preliminary data recently presented by Patel et al [25]. This finding requires replication in other studies and further investigation into the underlying mechanisms. Even if replicated, this slightly greater concentration should not lead to safety concerns about concomitant implant and dolutegravir use [26].

Collecting just a single specimen from each woman could have presented a problem if the women in the different groups had markedly different durations of implant use. Fortunately, the groups had similar durations of implant use. In addition, we carried out an adjusted analysis accounting for duration of use, which did not change the findings. ART non-adherence would result in underestimation of the effects of dolutegravir or efavirenz on etonogestrel concentrations.Self-reported adherence to ART is a weak measure; so the study also evaluated HIV viral load for all of the women reported taking ART; and only included those who had viral load suppression in analysis. This provides a reassuring, objective measure of ART adherence.

The etonogestrel implant is a highly effective contraceptive option for women living with HIV who use dolutegravir-based ART.

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**REFERENCES**

[1] Feyissa TR, Harris ML, Melka AS, Loxton D. Unintended Pregnancy in Women Living with HIV in Sub-Saharan Africa: A Systematic Review and Meta-analysis. AIDS Behav 2019;23:1431–51.

[2] Adeniyi OV, Ajayi AI, Moyaki MG, Goon D Ter, Avramovic G, Lambert J. High rate of unplanned pregnancy in the context of integrated family planning and HIV care services in South Africa. BMC Health Serv Res 2018;18:140.

[3] Sutton MY, Zhou W, Frazier EL. Unplanned pregnancies and contraceptive use among HIV- positive women in care. PLoS One 2018;13:e0197216.

[4] UNAIDS. 19.6 million girls and women living with HIV 2019. https://www.unaids.org/en/resources/infographics/girls-and-women-living-with-HIV (accessed March 16, 2020).

[5] Reynolds HW, Janowitz B, Homan R, Johnson L. The value of contraception to prevent perinatal HIV transmission. Sex Transm Dis 2006;33:350–6.

[6] Reynolds HW, Janowitz B, Wilcher R, Cates W. Contraception to prevent HIV-positive births: current contribution and potential cost savings in PEPFAR countries. Sex Transm Infect 2008;84 Suppl 2:ii49-53.

[7] IATT M&E WG. Global Monitoring Framework and Strategy for the Global Plan towards elimination of new HIV infections among children by 2015 and keeping their mothers alive (EMTCT) 2012. http://srhhivlinkages.org/wp-content/uploads/2013/04/global\_plan\_me\_frame\_en.pdf (accessed March 16, 2020).

[8] Duvall S, Thurston S, Weinberger M, Nuccio O, Fuchs-Montgomery N. Scaling up delivery of contraceptive implants in sub-Saharan Africa: operational experiences of Marie Stopes International. Glob Heal Sci Pract 2014;2:72–92.

[9] Jacobstein R. Liftoff: The Blossoming of Contraceptive Implant Use in Africa. Glob Heal Sci Pract 2018;6:17–39.

[10] Chappell CA, Lamorde M, Nakalema S, Chen BA, Mackline H, Riddler SA, et al. Efavirenz decreases etonogestrel exposure: a pharmacokinetic evaluation of implantable contraception with antiretroviral therapy. AIDS 2017;31:1965–72.

[11] Vieira CS, Bahamondes M V, de Souza RM, Brito MB, Rocha Prandini TR, Amaral E, et al. Effect of antiretroviral therapy including lopinavir/ritonavir or efavirenz on etonogestrel-releasing implant pharmacokinetics in HIV-positive women. J Acquir Immune Defic Syndr 2014;66:378–85.

[12] 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;28:791–3.

[13] 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:e474-82.

[14] 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;62:675–82.

[15] WHO. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infections. Recommendations for a Public Health Approach n.d. https://apps.who.int/iris/bitstream/handle/10665/208825/9789241549684\_eng.pdf?sequence=1 (accessed March 16, 2020).

[16] WHO. Update of recommendations on first- and second-line antiretroviral regimens. 2019 n.d. https://apps.who.int/iris/bitstream/handle/10665/325892/WHO-CDS-HIV-19.15-eng.pdf?ua=1 (accessed March 16, 2020).

[17] Phillips AN, Bansi-Matharu L, Venter F, Havlir D, Pozniak A, Kuritzkes DR, et al. Updated assessment of risks and benefits of dolutegravir versus efavirenz in new antiretroviral treatment initiators in sub-Saharan Africa: modelling to inform treatment guidelines. Lancet HIV 2020;7:e193–200. https://doi.org/10.1016/S2352-3018(19)30400-X.

[18] Reese MJ, Savina PM, Generaux GT, Tracey H, Humphreys JE, Kanaoka E, et al. In vitro investigations into the roles of drug transporters and metabolizing enzymes in the disposition and drug interactions of dolutegravir, a HIV integrase inhibitor. Drug Metab Dispos 2013;41:353–61.

[19] Scarsi KK, Darin KM, Chappell CA, Nitz SM, Lamorde M. Drug-Drug Interactions, Effectiveness, and Safety of Hormonal Contraceptives in Women Living with HIV. Drug Saf 2016;39:1053–72.

[20] Zash R, Makhema J, Shapiro RL. Neural-Tube Defects with Dolutegravir Treatment from the Time of Conception. N Engl J Med 2018;379:979–81.

[21] Diaz S, Pavez M, Moo-Young AJ, Bardin CW, Croxatto HB. Clinical trial with 3-keto-desogestrel subdermal implants. Contraception 1991;44:393–408.

[22] Thomas T, Petrie K, Shim J, Abildskov KM, Westhoff CL, Cremers S. A UPLC-MS/MS method for therapeutic drug monitoring of etonogestrel. Ther Drug Monit 2013;35:844–8.

[23] Coelingh-Bennink HJ. The pharmacokinetics and pharmacodynamics of Implanon, a single-rod etonogestrel contraceptive implant. Eur J Contracept Reprod Health Care 2000;5 Suppl 2:12–20.

[24] 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;49:784–9.

[25] Patel RC, Stalter R, Onono M, Brown E, Adeojo LW, Kidiga Adhu C, Bukusi EA, Scarsi KK. Dolutegravir-containing ART does not reduce etonogestrel implant concentrations. Boston, USA: Conference on Retroviruses and Opportunistic Infections (CROI); 8-11 March 2020.

[26] Scarsi KK, Cramer YS, Rosenkranz SL, Aweeka F, Berzins B, Coombs RW, et al. Antiretroviral therapy and vaginally administered contraceptive hormones: a three-arm, pharmacokinetic study. Lancet HIV 2019;6:e601–12.

**Table 1:** Characteristics of participants among women using the etonogestrel implant in Botswana, stratified by antiretroviral therapy group

|  |  |  |  |
| --- | --- | --- | --- |
|  | **HIV-negative group (n=97)** | **DTG group (n=30)** | **EFV group (n=15)** |
| Age, in years  | 28.0 (24-33) | 29.5 (24-35.5) | 28 (26-37) |
| Weight, kg  | 67.1 (58.1-75.7) | 65.9 (55.4-77.0) | 63 (58.5-75.0) |
| BMI, kg/m2  | 25.65 (21.9-29.2) | 24.41 (20.2-28.3) | 24.9 (20.7-27.5) |
| Ethnicity black African, n (%) | 97 (100) | 30 (100) | 15 (100) |
| Married, n (%) | 14 (14.4) | 3 (10.0) | 2 (13.3) |
| Live births  | 2 (1-2) | 2 (1-3) | 2 (1-4) |
| CD4 cell count (cells/ml) | -- | 653.5 (497.8-887.3) | 620 (580-803) |
| Current ART regimen | -- | DTG/TDF/FTC28 (93.3)DTG/TDF/3TC2 (6.7) | EFV/TDF/FTC15 (100) |
| Duration on current ART regimen (months)\* | -- | 13.5 (7.3-25.7) | 39.1 (16.7-63.7) |
| HIV viral load <400 copies/ml, n (%) | -- | 30 (100) | 15 (100) |
| Duration of implant use (days) | 147 (119.5-271) | 182 (119-247.5) | 152 (130-272) |

ART, antiretroviral therapy; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; 3TC, lamivudine

Data are represented either as n (%) or median (interquartile range), as appropriate. \*Note: This difference in duration on current ART regimen reflects the fact that efavirenz has been the first-line ART and available for many years, while dolutegravir is being newly introduced across African settings, including Botswana, since 2016. This difference in duration on current ART regimen does not impact our study findings as the eligibility criteria for the study included the following: “Women in the two ART groups had received stable ART regimens for at least 2-months prior to enrolment”.

**Table 2.** Etonogestrel plasma concentrations (pg/mL) by study group among women using the etonogestrel implant in Botswana

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Geometric mean with 90% confidence intervals | GMR with 90% CI | Adjusted\* GMR with 90% CI | Proportion of ENG plasma concentrations below 90 pg/ml, n(%) |
| HIV-negative group (N=97) | 227.5 (212.4- 243.8) | Reference group | Reference group | 0/97 (0) |
| DTG group (N=30) | 289.6 (251.8-333.0) | 1.27 (1.10-1.47) | 1.28 (1.13-1.46) | 0/30 (0) |
| EFV group (N=15) | 76.4 (63.9-91.4) | 0.58 (0.53-0.64) | 0.60 (0.55-0.66) | 9/15 (60) |

ART, antiretroviral therapy; DTG, dolutegravir; EFV, efavirenz; CI, confidence interval; GMR, geometric mean ratio

\*Adjusted for duration of implant use (days)

**Figure Legend**

**Figure 1:** Participants in a study of contraceptive implant use in HIV-negative women, women using dolutegravir-based ART, and women using efavirenz-based ART in Botswana. ART, antiretroviral therapy; ENG, etonogestrel; LNG, levonorgestrel; DTG, dolutegravir; EFV, efavirenz.

**Figure 2:** Etonogestrel plasma concentrations (pg/mL) by study groups over duration of implant use in days. Locally weighted scatterplot smoothing was used to visualize the trends. The grey line shows plasma etonogestrel concentrations over time in pg/mL in the dolutegravir-based ART group; the black line shows plasma etonogestrel concentrations over time in pg/mL in the HIV-negative group; the dotted line shows plasma etonogestrel concentrations over time in pg/mL in the efavirenz-based ART group. Individual data points are shown by grey circles for the dolutegravir-based ART group; by black circles for the HIV-negative group; and by hollow triangles for the efavirenz-based ART group.

**Figure 1.**

**Figure 2.**