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Unintended Pregnancies Observed With Combined Use of the Levonorgestrel Contraceptive Implant and Efavirenz-based Antiretroviral Therapy: A Three-Arm Pharmacokinetic Evaluation Over 48 Weeks

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Background. Levonorgestrel subdermal implants are preferred contraceptives with an expected failure rate of <1% over 5 years. We assessed the effect of efavirenz- or nevirapine-based antiretroviral therapy (ART) coadministration on levonorgestrel pharmacokinetics.

Methods. This nonrandomized, parallel group, pharmacokinetic evaluation was conducted in three groups of human immunodeficiency virus–infected Ugandan women: ART-naive (n = 17), efavirenz-based ART (n = 20), and nevirapine-based ART (n = 20). Levonorgestrel implants were inserted at baseline in all women. Blood was collected at 1, 4, 12, 24, 36, and 48 weeks. The primary endpoint was week 24 levonorgestrel concentrations, compared between the ART-naive group and each ART group by geometric mean ratio (GMR) with 90% confidence interval (CI). Secondary endpoints included week 48 levonorgestrel concentrations and unintended pregnancies.

Results. Week 24 geometric mean levonorgestrel concentrations were 528, 280, and 710 pg/mL in the ART-naive, efavirenz, and nevirapine groups, respectively (efavirenz: ART-naive GMR, 0.53; 90% CI, .50, .55 and nevirapine: ART-naive GMR, 1.35; 90% CI, 1.29, 1.43). Week 48 levonorgestrel concentrations were 580, 247, and 664 pg/mL in the ART-naive, efavirenz, and nevirapine groups, respectively (efavirenz: ART-naive GMR, 0.43; 90% CI, .42, .44 and nevirapine: ART-naive GMR, 1.14; 90% CI, 1.14, 1.16). Three pregnancies (3/20, 15%) occurred in the efavirenz group between weeks 36 and 48. No pregnancies occurred in the ART-naive or nevirapine groups.

Conclusions. Within 1 year of combined use, levonorgestrel exposure was markedly reduced in participants who received efavirenz-based ART, accompanied by contraceptive failures. In contrast, nevirapine-based ART did not adversely affect levonorgestrel exposure or efficacy.

Clinical Trials Registration. NCT01789879.

Keywords. contraceptive implant; levonorgestrel; efavirenz; nevirapine; unintended pregnancy.

The integration of human immunodeficiency virus (HIV) care and family planning services is critical for more than 17.4 million HIV-infected women, of whom nearly 95% live in low- and middle-income countries (LMICs) [1, 2]. These women face an increased risk for complications following an unplanned pregnancy, including the risk of vertical transmission of HIV [3, 4]. Accordingly, the World Health Organization (WHO) recommends the use of long-acting, reversible contraceptive methods for family planning, including progestin-releasing subdermal implants [5], and the use of efavirenz-based antiretroviral therapy (ART) as preferred first-line treatment for HIV-1 [6, 7]. Nevirapine-based ART remains an alternative; however, its use is declining due to inferior virologic efficacy and a higher rate of toxicity compared with efavirenz [6, 8]. Despite the benefits of both implantable contraceptives and ART, drug–drug interactions between these recommended therapies represent a critical barrier to effective family planning methods for HIV-infected women.

The levonorgestrel-releasing subdermal implant is widely used in sub-Saharan Africa [9]. After insertion, the implant

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may remain in place for up to 5 years, with a low failure rate of 0.1 pregnancy per 100 woman-years during the first year [10]. Levonorgestrel is released from the implant initially at 100 μg/day, decreasing to 40 μg/day within 1 year and to 30 μg/day within 3 years, providing stable daily drug concentrations [10]. Levonorgestrel is metabolized via hepatic enzymes, and coadministration of medications that induce or inhibit the cytochrome P450 (CYP) enzyme system influences levonorgestrel exposure [10]. The risk for drug–drug interaction compromising contraception efficacy is greatest with antiretrovirals that induce CYP3A4, including efavirenz and nevirapine. Few data characterize the impact of the drug–drug interaction between ART and levonorgestrel. However, when oral levonorgestrel for emergency contraception was combined with efavirenz, levonorgestrel exposure decreased 56%, as measured by the area under the concentration time curve (AUC) in 12 healthy volunteers [11]. In contrast, 3 HIV-infected women who received nevirapine-based ART and oral contraceptive pills had higher levonorgestrel exposure compared with 3 HIV-infected participants who did not receive ART ($AUC_{0-24\ hours}$ 147 vs 114 ng h/mL) [12]. Further, a retrospective analysis among 570 HIV-infected women who used the levonorgestrel-releasing implant identified concomitant use of efavirenz as the only factor correlated with unintended pregnancy (15 of 16 observed pregnancies occurred in women receiving efavirenz; 12.4% pregnancy rate); no pregnancies occurred among 208 women who received nevirapine [13]. There is no known interaction between nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and levonorgestrel [14]. No evidence exists regarding the pharmacokinetic effect of ART on levonorgestrel-releasing implants.

Noting the absence of high-quality studies, recent WHO guidance states that women on efavirenz- or nevirapine-based ART can "generally use" subdermal implants, because the benefits of contraception generally outweigh the risks [5, 15]. Our primary objective in this study was to assess the effect of efavirenz- or nevirapine-based ART on the pharmacokinetic exposure of levonorgestrel released from a subdermal implant in HIV-infected women over 24 weeks. We hypothesized that levonorgestrel concentrations would be reduced but would remain effective. Secondary objectives were to assess levonorgestrel, efavirenz, and nevirapine concentrations; HIV-related outcomes; pregnancies; and levonorgestrel-related adverse events, each over 48 weeks.

METHODS

This was a nonrandomized, open-label, parallel group, pharmacokinetic study among HIV-infected Ugandan women. All study-related procedures occurred at the Infectious Diseases Institute (IDI), Makerere University College of Health Sciences, Uganda. All study procedures followed the Declaration of Helsinki and were approved by ethics boards at the Joint Clinical Research Centre Kampala, Uganda National Council for Science and Technology, and the University of Nebraska Medical Center.

Participants

All HIV-infected women who sought family planning services at the IDI received information about available family planning methods, including oral contraceptive pills, depo-medroxyprogesterone, intrauterine devices, condoms, and progestin-containing implants. Women aged >18 years who planned to receive the levonorgestrel implant and were judged medically eligible for the implant [16] were screened for study participation following informed consent. Women were included if they were receiving efavirenz-based ART (efavirenz 600 mg daily plus 2 NRTIs; efavirenz group), nevirapine-based ART (nevirapine 200 mg twice daily plus 2 NRTIs; nevirapine group), or were not receiving ART (ART-naive group). The ART-naive group included women with a CD4+ cell count >500 cells/mm^3 at screening who were not eligible for ART per Ugandan HIV guidelines at the time of enrollment [17]. Women in the efavirenz or nevirapine groups received efavirenz- or nevirapine-based ART for >30 days and had an HIV-RNA <400 copies/mL at screening. Participants were excluded if they were pregnant, were <30 days post-partum, or had abnormal laboratory parameters. Herbal products and medications expected to have significant interactions with study drugs were prohibited 30 days prior to entry and throughout the study [10, 14]. Additional hormonal contraception was prohibited.

Procedures

Participants who met enrollment criteria returned for an entry visit (day 0) within 30 days of screening. Participants self-reported parity and marital status. Blood was collected for measurement of plasma levonorgestrel concentrations prior to implant placement. After a negative urine pregnancy test and other entry procedures were complete, a standard-dose levonorgestrel implant system (2-rod, levonorgestrel 75 mg/rod; Jadelle, Bayer, New Zealand) was placed subdermally on the interior of the upper arm by a trained study team member [10].

Additional study visits occurred 1, 4, 12, 24, 36, and 48 weeks after implant placement. Blood was collected for measurement of plasma levonorgestrel, efavirenz, and nevirapine concentrations at each visit. Timing of the blood sampling for the ART groups was based on time since last ART dose: mid-efavirenz dosing interval (12–14 hours post-dose) or end of the nevirapine dosing interval (11–13 hours post-dose). If the participant missed an ART dose within the 3 prior days, the visit was rescheduled. A physical exam, documentation of new or changed medications, and a urine pregnancy test were performed at each visit. A questionnaire to detect adverse events was administered, and all adverse events were categorized by severity [18]. CD4+ cell counts were abstracted from the medical record for all participants. HIV-RNA was repeated at week 48 for participants in the ART arms. Family planning counseling was provided at each visit, emphasizing the uncertainty of implant contraceptive effectiveness in combination with ART and the provision of condoms.

Pharmacokinetic Analyses

Detailed methods for the levonorgestrel, efavirenz, and nevirapine assays are described in the Supplementary Materials. Briefly, plasma levonorgestrel concentrations were determined by reverse-phase high-performance liquid chromatography (HPLC) mass spectrometry (MS). The assay was validated over a calibration range of 49.6–1500 pg/mL. The interday precision was between 3.9% and 7.6%; accuracy was between −7.6% and 5.2%. Plasma concentrations of efavirenz and nevirapine were determined using HPLC assays with ultraviolet detection. The efavirenz assay was validated over a calibration range of 0.2–10.0 mg/L. The interday precision was between 2.8% and 5.3%; accuracy was between −6.4% and 7.0%. The nevirapine assay was validated over a calibration range of 0.05–16.1 mg/L. The interday precision was between 1.1% and 4.5%; accuracy was between 0.9% and 4.7%. All pharmacokinetic assays were validated in accordance with guidance from the US Food and Drug Administration (FDA) [19].

Statistical Analyses

To evaluate the primary outcome, 20 participants per group provided 95% power to detect a 45% difference in levonorgestrel concentrations, using an alpha level of 0.008 due to repeated measures and based on levonorgestrel interpatient variability (44% at 24 weeks) [20]. This sample size allowed for 20% attrition (leaving 16 participants per group), while maintaining 90% power. Participants were included in the analysis if they met the primary endpoint at week 24.

Levonorgestrel concentrations were summarized by study visit as the geometric mean with 90% confidence interval (CI). Levonorgestrel concentrations were compared between the ART-naive group and the efavirenz or nevirapine groups as a geometric mean ratio (GMR) and 90% CI and statistically assessed using Wilcoxon rank sum. Each participant's concentration–time curve was analyzed using noncompartmental methods (Phoenix WinNonlin, Certara). The levonorgestrel AUC from weeks 0–24 ($AUC_{0-24\ weeks}$) was determined using the trapezoidal rule. All safety and adverse event data were descriptively summarized. Descriptive data were compared using the Kruskal–Wallis or Wilcoxon rank sum tests for continuous data and a χ^2 test for discrete data. All statistical analyses were conducted using IBM SPSS Statistics.

RESULTS

Between June 2013 and December 2013, 72 women were screened and 60 women enrolled, 20 participants into each study group. All participants enrolled in the efavirenz and nevirapine groups reached the 24-week primary endpoint; 3 participants in the ART-naive group did not (Figure 1). Participants' baseline characteristics are described in Table 1. Overall, the median age of the study population was 31 years (interquartile

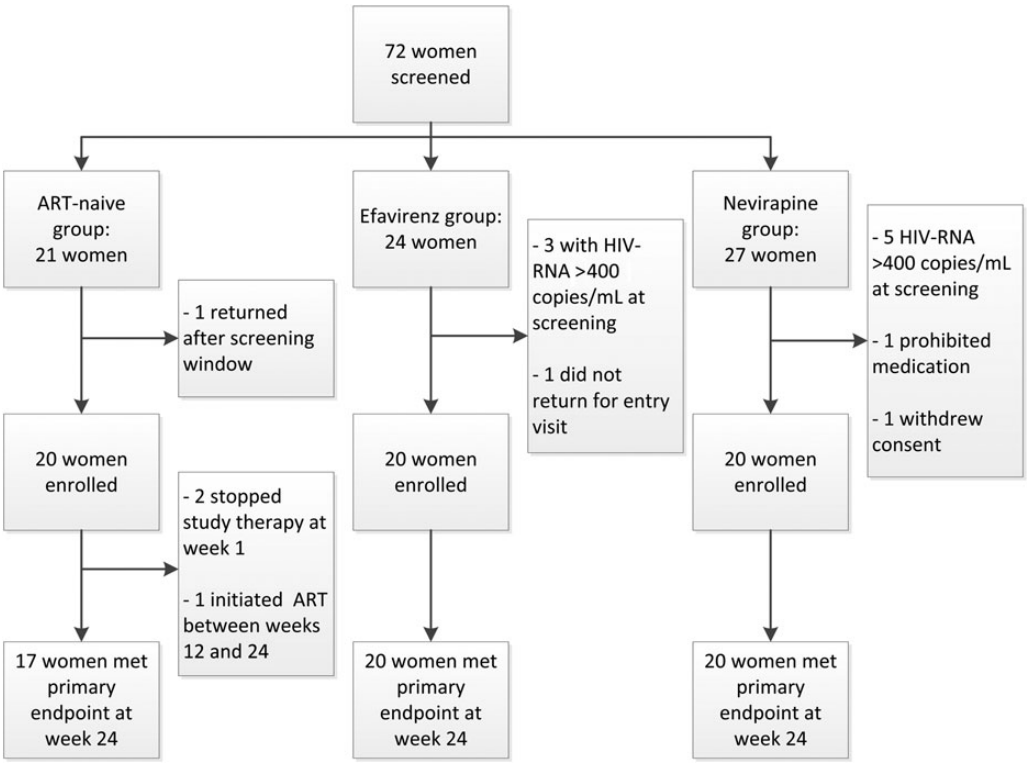

Figure 1. Flow diagram of screened and enrolled participants who reached the primary study endpoint at 24 weeks. Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus.

Table 1. Baseline Characteristics of Participants by Study Group

Characteristic	Antiretroviral Therapy–Naive Group, n = 17	Efavirenz Group, n = 20	Nevirapine Group, n = 20
Age (y)	29.0 (26.5–33.0)	31.0 (28.3–34.0)	32.5 (31.0–35.8)
Weight (kg)	69.0 (58.5–86.5)	59.5 (52.3–63.8)	59.5 (54.3–69.8)
Body mass index (kg/m^2)	29.5 (24.3–32.0)	23.5 (20.1–26.2)	24.4 (20.7–27.0)
Cohabitating or married, n (%)	11 (64.7)	16 (80.0)	13 (65.0)
Prior live births	3.0 (2.0–4.0)	3.0 (2.3–4.0)	3.0 (2.3–5.0)
CD4+ cell count (mm^3/mL)	663.0 (549.0–971.5)	556.5 (477.3–663.5)	626.0 (399.8–857.3)
Duration of time on current antiretroviral therapy regimen (months)	. . .	10.5 (6.3–37.8)	30.5 (13.5–80.3)

Data are presented as either n (%) or median (interquartile range), as appropriate.

range [IQR], 28.5–34.0), with 3 prior births (IQR, 2–4) and screening CD4+ cell count of 598 cells/mm^3 (IQR, 509–806).

Women on ART received the same regimen for a median of 17.5 months (IQR, 8.5–55.0) and all had an HIV-RNA <400 copies/mL at screening. In the efavirenz group, 13 (65%) of 20 participants received tenofovir–lamivudine 300/300 mg daily, the remaining 7 (35%) received zidovudine–lamivudine 300/150 mg twice daily. In the nevirapine group, 19 (95%) of 20 participants received zidovudine–lamivudine 300/150 mg twice daily and 1 (5%) participant received tenofovir–lamivudine 300/300 mg daily.

Primary Endpoint: 24-Week Levonorgestrel Concentrations

The levonorgestrel pharmacokinetic results are provided in Table 2 and Figure 2. In the efavirenz group, significantly lower levonorgestrel concentrations were observed by week 1 and persisted through week 24 compared with the ART-naive group (efavirenz: ART-naive 24-week GMR, 0.53; 90% CI, .50, .55). In contrast, we observed higher levonorgestrel concentrations in the nevirapine group by week 1, which persisted through week 24 compared with the ART-naive group (nevirapine: ART-naive 24-week GMR, 1.35; 90% CI, 1.29, 1.43). The $AUC_{0-24\ weeks}$ for the efavirenz and nevirapine groups (8053 and 19 643 pg wk/mL, respectively) relative to the ART-naive group (15 168 pg wk/mL) reflect the stable difference in levonorgestrel concentrations over the first 24 weeks of use (efavirenz: ART-naive $AUC_{0-24\ weeks}$ GMR, 0.53; 90% CI, .52, .54; $P < .001$ and nevirapine: ART-naive $AUC_{0-24\ weeks}$ GMR, 1.30; 90% CI, 1.25, 1.37; $P = .08$). Figure 3 presents the individual $AUC_{0-24\ weeks}$ values by group.

Secondary Endpoints: 48-Week Levonorgestrel Concentrations and Pregnancy Outcomes

The intended duration of study follow-up was 48 weeks. In the ART-naive and nevirapine groups, 19 participants in each group completed follow-up; 1 woman in the ART-naive group initiated ART and 1 woman in the nevirapine group changed ART, both occurred between week 36 and week 48. No pregnancies were identified in either the ART-naive or nevirapine groups. The week 48 nevirapine:ART-naive levonorgestrel GMR was 1.14 (90% CI, 1.14, 1.16; Table 2).

In the efavirenz group, 2 pregnancies were identified during the week 48 study visit (approximately 2 and 10 weeks post-conception). Following these serious events, the efavirenz group follow-up was halted, and all participants in the group returned for a study discontinuation visit. During these visits, a third pregnancy was identified at week 42 (approximately 2 weeks post-conception), bringing the total number of pregnancies to 3 (15%) of 20 participants in the efavirenz group. Levonorgestrel concentrations at the last study visit prior to each pregnancy (week 36 for all) were 122, 299, and 303 pg/mL. Levonorgestrel

Table 2. Levonorgestrel Plasma Concentrations Over 48 Weeks

Study Week	ART-Naive Group, n = 17 (pg/mL)[a]	Efavirenz Group, n = 20 (pg/mL)[a]	Nevirapine Group, n = 20 (pg/mL)[a]	Efavirenz: ART-Naive Geometric Mean Ratio[b]	*P* Value	Nevirapine: ART-Naive Geometric Mean Ratio[b]	*P* Value
1	1070 (783, 1356)	462 (370, 553)	1369 (1123, 1615)	0.43 (0.41, 0.47)	<.001	1.28 (1.19, 1.43)	.165
4	667 (541, 792)	359 (280, 437)	866 (737, 995)	0.54 (0.52, 0.55)	.001	1.30 (1.26, 1.36)	.104
12	590 (475, 704)	327 (268, 385)	778 (674, 881)	0.55 (0.55, 0.56)	.001	1.32 (1.25, 1.42)	.080
24	528 (423, 633)	280 (212, 348)	710 (603, 818)	0.53 (0.50, 0.55)	<.001	1.35 (1.29, 1.43)	.056
36	618 (520, 716)	279 (149, 409)	656 (536, 777)	0.45 (0.29, 0.57)	<.001	1.06 (1.03, 1.09)	.707
48[c]	580 (477, 684)	247 (209, 285)	664 (551, 777)	0.43 (0.42, 0.44)	.002	1.14 (1.14, 1.16)	.300

Abbreviation: ART, antiretroviral therapy.

All values were statistically compared using the Wilcoxon rank sum test.

[a] Data are presented as geometric mean with 90% confidence intervals.

[b] Data are presented as the geometric mean ratio with 90% confidence intervals.

[c] Week 48 participant numbers: ART-naive, n = 16; efavirenz, n = 11; nevirapine, n = 19.

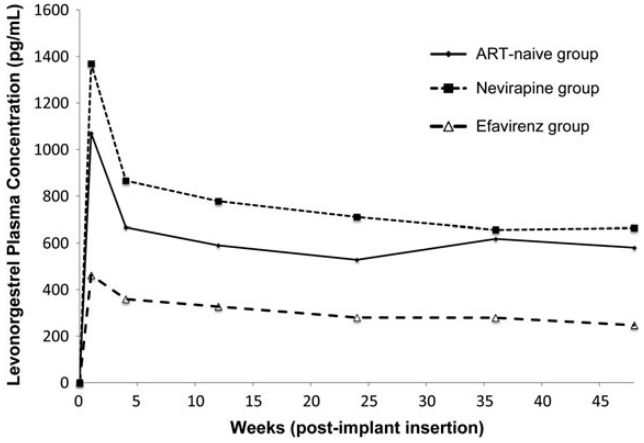

Figure 2. Geometric mean levonorgestrel concentration–time profiles over 48 weeks for each study group. A standard-dose levonorgestrel implant (2-rod, 75 mg/rod) was placed at time 0 for all participants. Values represent the geometric mean levonorgestrel plasma concentrations at each study visit for participants in the antiretroviral therapy (ART)–naive group (solid line with closed circle), efavirenz group (dashed line with open triangles), and nevirapine group (dashed line with closed squares).

concentrations at each study visit for these participants are presented in Supplementary Table 1. Eleven participants in the efavirenz group contributed results through week 48. The week 48 efavirenz:ART-naive levonorgestrel GMR was 0.43 (90% CI, .42, .44; Table 2). Of the remaining 9 participants, 3 were pregnant and 6 discontinued follow-up between study week 40 and week 44.

Post hoc, we evaluated the number of participants who had levonorgestrel concentrations below the highest levonorgestrel concentration at which a pregnancy occurred in our population (303 pg/mL). Eighteen (90%) of 20 participants in the efavirenz group, none (0%) of 20 participants in the nevirapine group, and 2 (11.8%) of 17 participants in the ART-naive group had a concentration below 303 pg/mL at least once ($P < .001$). For the 18 participants in the efavirenz group, levonorgestrel concentrations fell below 303 pg/mL by week 12 (IQR, 3.25–24.0) and remained below this threshold for the remainder of the study. In the ART-naive group, 1 participant had a concentration <303 pg/mL at week 24; however, subsequent concentrations were above this threshold (range, 420–529 pg/mL). The second participant had intermittent concentrations ≤303 pg/mL at weeks 1, 4, and 48 (remaining visits range, 327–487 pg/mL).

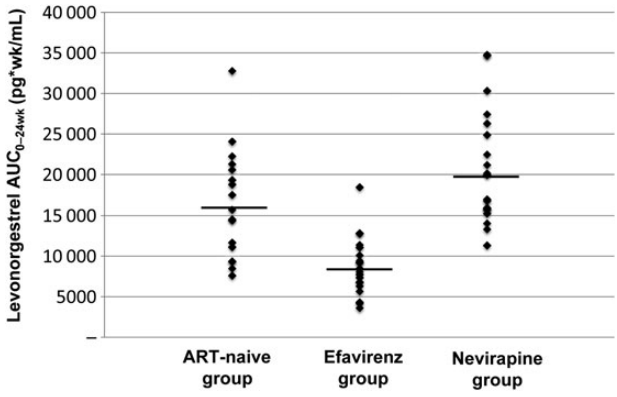

Figure 3. Individual levonorgestrel area under the concentration–time curve from week 0 through week 24 ($AUC_{0–24\ weeks}$) for each study group. Each participant's $AUC_{0–24\ weeks}$ is represented as a diamond; the median $AUC_{0–24\ weeks}$ by study group is shown (line). The interindividual $AUC_{0–24\ weeks}$ coefficient of variation (CV%) is as follows: antiretroviral therapy (ART)-naive group, 44.1%; efavirenz group, 43.7%; nevirapine group, 35.5%.

Antiretroviral Concentrations and HIV Outcomes

From week 1 through week 48, the geometric mean concentration of efavirenz was 2.7 mg/L (90% CI, 2.15, 3.30) and 6.5 mg/L for nevirapine (90% CI, 6.2, 6.9). Antiretroviral concentrations were not significantly different among individuals over the study period (data not shown).

No change was observed in the CD4+ cell count between baseline and week 48 (median week 48: ART-naive group, 698 cells/mm^3; efavirenz group, 588 cells/mm^3; nevirapine group, 598 cells/mm^3; all $P > .05$ within groups). In the efavirenz and nevirapine groups, HIV-RNA remained <400 copies/mL in 39 of 40 women through their final study visit. One woman had an HIV-RNA of 17 935 copies/mL at week 48, despite reported ART adherence and nevirapine concentrations above the suggested minimum trough concentration (3 mg/L) [21] at all study visits, except week 12.

Levonorgestrel-Related Adverse Events

Other than the pregnancies described above, adverse events that were possibly related to the implant are described in Table 3. Of those, 13 (7.5%) of 173 adverse events were of moderate intensity (grade 2) and were predominately related to menstrual changes. All other adverse events were grade 1, and no drug-related adverse event was severe or resulted in implant discontinuation.

DISCUSSION

We determined that women who use a levonorgestrel-releasing contraceptive implant in combination with efavirenz-based ART had 47% lower levonorgestrel concentrations after 24 weeks, decreasing to 57% at week 48, compared with ART-naive women. Critically, these pharmacokinetic changes were associated with 3 unintended pregnancies in the efavirenz group (15% pregnancy rate) during the 48-week study, which is in contrast to the implant's expected <1% failure rate over 5 years of use [10]. These results provide pharmacokinetic evidence and further support for the high unintended pregnancy rate (12.4%) that was observed retrospectively among 121 women in Swaziland who received efavirenz-based ART with a levonorgestrel-releasing implant [13]. In addition, our data are consistent with a pharmacokinetic study of ART with the only other progestin-releasing subdermal implant, etonogestrel,

Table 3. Adverse Events Reported Over 48 Weeks of Levonorgestrel Implant Therapy

Adverse Event	Antiretroviral Therapy–Naive Group, n = 17, n (%)	Efavirenz Group, n = 20, n (%)	Nevirapine Group, n = 20, n (%)
Headache	13 (76.5)	15 (75.0)	11 (55.0)
Menstrual changes	14 (82.4)	13 (65.0)	16 (80.0)
Mood changes	7 (41.2)	11 (55.0)	9 (45.0)
Breast tenderness	6 (35.3)	6 (30.0)	3 (15.0)
Acne	5 (29.4)	6 (30.0)	5 (25.0)
Nausea	4 (23.5)	11 (55.0)	5 (25.0)
Implant insertion site discomfort	2 (11.8)	3 (15.0)	5 (25.0)
Total adverse events	n = 51	n = 68	n = 54
Grade 1[a]	48 (94.1)	60 (88.2)	52 (96.3)
Grade 2[a]	3 (5.9)	8 (11.8)	2 (3.7)

Except where indicated, data are presented as n (%) of study group participants who reported the adverse event at least once over the entire study period. The frequency of adverse events in the antiretroviral therapy–naive group was compared to the frequency of events in either the efavirenz group or the nevirapine group using a χ^2 test of independence or Fisher exact test, as appropriate; all $P > .05$.

[a] Data are presented as n (%) of total adverse events reported per study group.

in that etonogestrel plasma concentrations were 63% lower among HIV-infected women who received efavirenz-based ART [22]. In a recent retrospective cohort from Kenya, a 3-fold higher pregnancy risk was observed in implant users (either levonorgestrel- or etonogestrel-containing) who received efavirenz-based ART compared with nevirapine-based ART (adjusted rate ratio, 3.0 [1.3–4.6]) [23]. Notably, the pregnancy rate in patients who received implants plus efavirenz-based ART in the Kenya cohort (unadjusted pregnancies, 3.3 per 100 person-years) was lower compared with both our results and those reported from Swaziland [13, 23]. Similarly, 6 published case reports describe etonogestrel implant failures in women who received efavirenz-based ART [24–27].

In contrast, women in our nevirapine group had 35% higher levonorgestrel concentrations after 24 weeks, and 14% higher after 48 weeks, compared with the ART-naive group. We observed no pregnancy or excess adverse events, supporting the effectiveness of levonorgestrel implants in combination with nevirapine-based ART. Although both are CYP3A enzyme inducers, differences in the drug–drug interaction potential of efavirenz and nevirapine have been observed [11, 12]. One possible explanation of higher levonorgestrel concentrations may be the study participants' body weight. Prior studies demonstrate an inverse association between levonorgestrel concentrations and body weight; women weighing <50 kg maintained levonorgestrel concentrations 43%–50% higher than women weighing >70 kg [20, 28, 29]. Although the difference in body weight between the nevirapine and ART-naive groups was not statistically different, the nevirapine group had more women with lower body weights (see Table 1).

We are the first to describe progestin concentrations prior to conception among women who became pregnant while using an implant due to a drug–drug interaction. One other study characterized levonorgestrel concentrations prior to pregnancy during an extended-use study of the implant over 7 years, 2 years beyond its intended duration of use [29]. Sivin and colleagues determined that no pregnancies occurred when levonorgestrel concentrations were maintained above 180 pg/mL [29]. In contrast, 2 pregnancies occurred in our participants at concentrations above this previously observed efficacy threshold, that is, 303 and 299 pg/mL, measured approximately 2 and 10 weeks prior to conception (Supplementary Table 1). The reason for this difference is unclear, but a potential explanation is differences in laboratory methods for quantitation of levonorgestrel: HPLC-MS vs radioimmunoassay [29].

Integrated guidelines for family planning and HIV suggest that contraceptive implants can be used for HIV-infected women receiving efavirenz-based ART [30]. However, our data suggest that efavirenz-based ART reduces the contraceptive efficacy of the levonorgestrel implant. Although both levonorgestrel implants and efavirenz have been available in LMICs over the past decade, the impact of this detrimental drug–drug interaction may not have been identified because, until recently, efavirenz was not widely prescribed among women of childbearing potential due to concerns for teratogenicity. Furthermore, because many HIV treatment centers do not have integrated family planning services, women may obtain levonorgestrel implants from other providers, and an unintended pregnancy could go unrecognized by HIV caregivers. This highlights the importance of integrated, comprehensive care of HIV-infected persons, as well as multidisciplinary collaboration to disseminate findings [31].

Our study has limitations related to its design. It was an open label, nonrandomized, clinical pharmacokinetic investigation of women already planning to receive the levonorgestrel implant. Therefore, baseline differences exist between study groups. We did not assess participants' sexual activity, and the study was not designed to evaluate the contraceptive effectiveness of the levonorgestrel implant in combination with ART. Therefore,

measures of contraceptive effectiveness such as detection of ovulation or changes in the cervical–vaginal lining were not included. Despite this, our results support an exposure–response relationship, and pharmacokinetic data are an FDA-accepted method to establish the impact of a drug–drug interaction [32]. Finally, we cannot compare our results with the contraception failure rate of other methods in combination with ART.

We describe suboptimal pharmacokinetic exposure when the levonorgestrel implant is combined with efavirenz-based ART, but not with nevirapine-based ART. The increased risk of unintended pregnancy in women who received the levonorgestrel implant and efavirenz-based ART is of critical public health importance, given the ongoing scale-up of both contraceptive implants [33] and efavirenz-based ART throughout LMICs and the resultant decreased use of nevirapine-based ART in many countries [6, 8]. Policymakers will need to assess the risk–benefit of the levonorgestrel implant combined with efavirenz-based ART in the context of alternative contraceptive failure rates and available ART options in LMICs. Given the increased risk of unintended pregnancy among HIV-infected women using the levonorgestrel implant with efavirenz-based ART, alternative strategies for long-acting contraceptive agents are urgently needed.

Supplementary Data

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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References

1. World Health Organization. Global summary of the AIDS epidemic, December 2014. Available at: http://www.who.int/hiv/data/epi_core_july2015.png?ua=1. Accessed 14 September 2015.
2. UNAIDS. How AIDS changed everything—MDG6: 15 years, 15 lessons of hope from the AIDS response. Available from: http://www.unaids.org/sites/default/files/media_asset/MDG6Report_en.pdf. Accessed 5 September 2015.
3. Reynolds HW, Janowitz B, Homan R, Johnson L. The value of contraception to prevent perinatal HIV transmission. Sex Transm Dis **2006**; 33:350–6.
4. 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.
5. World Health Organization. Medical eligibility criteria for contraceptive use, 5th edition 2015. Available at: http://apps.who.int/iris/bitstream/10665/181468/1/9789241549158_eng.pdf?ua=1 Accessed 15 September 2015.
6. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization, **2013**.
7. World Health Organization. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva: World Health Organization, **2015**.
8. World Health Organization Policy Brief. Transition to new HIV treatment regimens—procurement and supply chain management issues. Geneva: World Health Organization. **2014**.
9. Reproductive Health Supplies Coalition. Available at: http://rhsupplies.org. Accessed 12 September 15.
10. Jadelle [package insert]. Auckland, New Zealand: Bayer New Zealand Limited Company. August 2010.
11. Carten ML, Kiser JJ, Kwara A, Mawhinney S, Cu-Uvin S. Pharmacokinetic interactions between the hormonal emergency contraception, levonorgestrel (plan B), and efavirenz. Infect Dis Obstet Gynecol **2012**; 2012:137192.
12. Stuart GS, Moses A, Corbett A, et al. Combined oral contraceptives and antiretroviral PK/PD in Malawian women: pharmacokinetics and pharmacodynamics of a combined oral contraceptive and a generic combined formulation antiretroviral in Malawi. J Acquir Immune Defic Syndr **2011**; 58:e40–3.
13. 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.
14. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed 14 September 2015.
15. World Health Organization. WHO statement on progestogen-only implants. Geneva: World Health Organization. September 2015. Available at: http://apps.who.int/iris/bitstream/10665/190063/1/WHO_RHR_15.20_eng.pdf?ua=1. Accessed 23 November 2015.
16. World Health Organization. Medical eligibility criteria for contraceptive use, 4th ed. Geneva: World Health Organization, **2009**.
17. Uganda Ministry of Health. Addendum to the national antiretroviral treatment guidelines. Kampala: Uganda Ministry of Health, December 2013.
18. US Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0. **2014**. Available at: http://rsc.tech-res.com/Document/safetyandpharmacovigilance/DAIDS_AE_GRADING_TABLE_v2_NOV2014.pdf. Accessed 15 September 2015.
19. US Food and Drug Administration. Bioanalytical Method Validation. September 2013. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf. Accessed 5 September 2015.
20. Sivin I, Lahteenmaki P, Ranta S, et al. Levonorgestrel concentrations during use of levonorgestrel rod (LNG ROD) implants. Contraception **1997**; 55:81–5.
21. La Porte CJL, Back DJ, Blaschke T, et al. Updated guidelines to perform therapeutic drug monitoring for antiretroviral agents. Rev Antiviral Ther **2006**; 3:4–14.
22. Vieira CS, Bahamondes MV, de Souza RM, et al. Effect of antiretroviral therapy including lopinavir/ritonavir or efavirenz on etonogestrel-releasing implant pharmacokinetics in HIV-positive women. J Acquir Immune Defic Syndr **2014**; 66:378–85.
23. Patel RC, Onono M, Gandhi M, 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.
24. Leticee N, Viard JP, Yamgnane A, Karmochkine M, Benachi A. Contraceptive failure of etonogestrel implant in patients treated with antiretrovirals including efavirenz. Contraception **2012**; 85:425–7.
25. Matiluko AA, Soundararjan L, Hogston P. Early contraceptive failure of Implanon in an HIV-seropositive patient on triple antiretroviral therapy with zidovudine, lamivudine and efavirenz. J Fam Plann Reprod Health Care **2007**; 33:277–8.
26. McCarty EJ, Keane H, Quinn K, Quah S. Implanon failure in an HIV-positive woman on antiretroviral therapy resulting in two ectopic pregnancies. Int J STD AIDS **2011**; 22:413–4.
27. Lakhi N, Govind A. Implanon failure in patients on antiretroviral medication: the importance of disclosure. J Fam Plann Reprod Health Care **2010**; 36:181–2.
28. Sivin I, Lahteenmaki P, Mishell DR Jr, et al. First week drug concentrations in women with levonorgestrel rod or Norplant capsule implants. Contraception **1997**; 56:317–21.
29. Sivin I, Wan L, Ranta S, et al. Levonorgestrel concentrations during 7 years of continuous use of Jadelle contraceptive implants. Contraception **2001**; 64:43–9.

30. World Health Organization. Hormonal contraceptive methods for women at high risk of HIV and living with HIV: 2014 guidance statement. Geneva: World Health Organization.
31. World Health Organization. Strategic considerations for strengthening and linkages between family planning and HIV/AIDS policies, programs, and services. Available at: http://www.who.int/reproductivehealth/publications/linkages/fp_hiv_strategic_considerations.pdf. Accessed 21 December 2015.
32. Center for Drug Evaluation and Research (2003). Guidance for industry: bioavailability and bioequivalence studies for orally administered drug products—general considerations. US Food and Drug Administration. Available at: http://www.fda.gov/ohrms/dockets/ac/03/briefing/3995B1_07_GFI-BioAvail-BioEquiv.pdf. Accessed 21 December 2015.
33. Jacobstein R, Stanley H. Contraceptive implants: providing better choice to meet growing family planning demand. Global Health Sci Pract **2013**; 1:11–7.