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

Kimberly K. Scarsi,1 Kristin M. Darin,2,3 Shadia Nakalema,4 David J. Back,2 Pauline Byakika-Kibwika,4 Laura J. Else,5 Sujan Dilly Penchala,5 Allan Buzibye,4 Susan E. Cohn,2 Concepta Merry,2,5 and Mohammed Lamorde4

1Department of Pharmacy Practice, College of Pharmacy, University of Nebraska Medical Center, Omaha; 2Center for Global Health, and 3Division of Infectious Diseases, Feinberg School of Medicine, Northwestern University, Chicago, Illinois; 4Infectious Diseases Institute, Makerere University College of Health Sciences, Kampala, Uganda; 5Department of Molecular and Clinical Pharmacology, University of Liverpool, United Kingdom; and 6Department of Medicine, Trinity College Dublin, Ireland

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.
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 co-administration 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 antiretroviral 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 (AUC0–24 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.
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 (AUC0–24 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 χ² 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](image-url). 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/m²)             | 29.5 (24.3–32.0)                         | 23.5 (20.1–26.2)       | 24.4 (20.7–27.0)        |
| Cohabiting 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 (mm³/mL)            | 663.0 (549.0–971.5)                      | 556.5 (477.3–663.5)    | 626.0 (399.8–857.3)     |
| Duration of time on current ARV 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/mm³ (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, .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 a woman in the nevirapine group changed ART, both of whom 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) | Efavirenz Group, n = 20 (pg/mL) | Nevirapine Group, n = 20 (pg/mL) | Efavirenz: ART-Naive Geometric Mean Ratio⁺ | P Value | Nevirapine: ART-Naive Geometric Mean Ratio⁺ | 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 (0.56, 0.56)                         | .001    | 1.33 (1.25, 1.42)                         | .080    |
| 24         | 528 (423, 633)                 | 258 (201, 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⁺        | 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.

⁺ Data are presented as geometric mean with 90% confidence intervals.

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

⁺ Week 48 participant numbers: ART-naive, n = 16; efavirenz, n = 11; nevirapine, n = 19.
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).

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/mm³; efavirenz group, 588 cells/mm³; nevirapine group, 598 cells/mm³; 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 progestin-releasing subdermal implant, etonogestrel,
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,

### 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 = 64                          |
| Grade 1*                               | 48 (94.1)                                       | 60 (88.2)                      | 52 (96.3)                       |
| Grade 2*                               | 3 (5.9)                                         | 8 (11.8)                       | 2 (3.7)                         |

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

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 χ² test of independence or Fisher exact test, as appropriate; all P > .05.
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 copyrighted and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes
Acknowledgments. We thank the study participants and members of the clinical study team, Angela Kusiima and Hope Mackline, for their commitment and dedication to this project. We gratefully acknowledge the contribution of the National Institutes of Health (NIH) Clinical Center Bioethics Consultation Service for their expert guidance related to the closure of the efavirenz study arm (Seema K. Shah, Attending Consultant; Marion Danis, Chief of Service).

Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Financial support. This project was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development at the NIH (grant number 5R21HD074462).

Potential conflicts of interest. D. J. B. received personal fees from Gilead, and his institution received grants from Gilead and Bristol-Myers Squibb outside of the submitted work. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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, Janowitw B, Homan R, Johnson L. The value of contraception to prevent perinatal HIV transmission. Sex Transm Dis 2006; 33:550–6.
4. Reynolds HW, Janowitw 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):i49–53.
5. World Health Organization. Medical eligibility criteria for contraceptive use, 5th edition 2015. Available at: http://apps.who.int/iris/bitstream/10665/181468/1/978924159158_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 2015.
10. Jaddelle [package insert]. Auckland, New Zealand: Bayer New Zealand Limited Company. August 2010.
11. Carter ML, Kiser JF, Kwara A, Mawhinney S, Cu-Uvin S. Pharmacokinetic interactions between the hormonal emergency contraception, levonorgestrel (plan B), and efavirenz. Infect Dis Obstet Gynecol 2012; 2013:179.
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, Soapy P, Predisi GA, Mwanjamba A, Motsa N, Saremo FN. Implementing the Jaddell 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. Available at: http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed 14 September 2015.
15. World Health Organization. WHO statement on progesterone-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://srctech-res.com/Document/SafetyandPharmacovigilance/DAIDS_AF_GRADING_TABLE_v2_NOV2014.pdf. Accessed 15 September 2015.
19. US Food and Drug Administration. Bioanalytical Method Validation. September 2015. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/InformationGuidances/UCM3468107.pdf. Accessed 5 September 2015.
20. Sivin I, Lheteenmaki 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; 68:378–85.
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, Yamgnae A, Karmochkine M, Benachi A. Contraceptive failure of etonogestrel implant in patients treated with antiretrovirals including efavirenz. Contraception 2012; 85:422–7.
25. Matulko AA, Soudarazarjan I, 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 patient resulting in two ectopic pregnancies. Int J STD AIDS 2011; 22:413–4.
27. Lakhni 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, Lahteemaki 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.