RESEARCH ARTICLE

Contraceptive implant failures among women using antiretroviral therapy in western Kenya: a retrospective cohort study [version 1; peer review: 3 approved with reservations]

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Abstract

Background: Women living with HIV have the right to choose whether, when and how many children to have. Access to antiretroviral therapy (ART) and contraceptives, including implants, continues to increase due to a multitude of efforts. In Kenya, 4.8% of adults are living with HIV, and in 2017, 54% were receiving an efavirenz-based ART regimen. Meanwhile, 16.1% of all Kenyan married (and 10.4% of unmarried) women used implants. Studies have reported drug interactions leading to contraceptive failures among implant users on ART. This retrospective record review aimed to determine unintentional pregnancy rates among women 15-49 years of age, living with HIV and concurrently using implants and ART in western Kenya between 2011 and 2015.

Methods: We reviewed charts of women with more than three months of concurrent implant and ART use. Implant failure was defined as implant removal due to pregnancy or birth after implant placement, but prior to scheduled removal date. The incidence of unintended pregnancy was calculated by woman-years at risk, assuming a constant rate.

Results: Data from 1,152 charts were abstracted, resulting in 1,190 implant and ART combinations. We identified 115 pregnancies, yielding a pregnancy incidence rate of 6.32 (5.27–7.59), with 9.26 among ETG and 4.74 among LNG implant users, respectively. No pregnancies were recorded among women on non-NNRTI-based regimens, whereas pregnancy rates for efavirenz and nevirapine-containing regimens were similar, at 6.41 (4.70–8.73) and 6.44 (5.13–8.07), respectively.

Conclusions: Our findings highlight the implications of drug interaction on women’s choices for contraception.
Keywords
Drug interactions, contraceptive implants, contraception, ART, HIV

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Introduction

All women, regardless of HIV status, have the right to choose whether, when and how many children to have. For women living with HIV (WLHIV), the right to decide not only impacts maternal and infant morbidity and mortality but is a pillar of prevention of mother-to-child transmission (PMTCT) by decreasing unintended pregnancies.

Long-acting reversible contraceptives (LARCs), including progestin-only implants, are efficacious, cost-effective, and have high continuation rates. Implants are 99% effective in preventing pregnancy and are increasing in popularity worldwide1-3. Coupled with UNAIDS’s ambitious goal of reaching 90% of people living with HIV with antiretroviral therapy (ART) by 2020, a growing number of women are accessing contraceptives and ART concurrently. The WHO provides guidelines for this population4.

In Kenya, 5.9% of adults 15–49 years of age were living with HIV in 2015. Western counties had the highest HIV prevalence rates, ranging from 6.7% in Busia to 26.0% in Homa Bay5. HIV treatment became widely available in the public sector in 2005, consisting of a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse transcriptase inhibitor (NNRTI). In 2015, tenofovir (TDF) became the preferred NNRTI and efavirenz (EFV) replaced Nevirapine (NVP) as preferred NNRTI. As of 2017, approximately 54% of all people living with HIV (PLHIV) on ART in Kenya were taking an EFV-based regimen6.

Contraceptive prevalence, including implant use, has rapidly increased in Kenya7. An estimated 16.1% of married women and 10.4% of unmarried women use implants8. A study found that Kenyan WLHIV were more likely than their non-HIV affected peers to desire no more children and slightly more WLHIV used contraception9. Another study found high overall contraceptive use (91%) among women attending HIV care clinics, but low concurrent use of condoms10.

NVP and EFV are metabolized in the liver via cytochrome P450, as is hormonal contraception. Levonorgestrel (LNG, brand names: Jadelle® and Sino-implant/Levoplant®) and Etonogestrel (ETG, brand names: Implanon®, Nexplanon®) are metabolized by the CYP3A4 enzyme along this pathway11. Pharmacokinetic and retrospective clinical studies have described concomitant use of EFV with implants, although with small samples of women12-20. Three prospective studies have examined the pharmacokinetic effects of ART on hormone levels among implant users. A prospective nonrandomized pharmacokinetic study in Brazil found reduced ETG bioavailability among women on EFV19. Another prospective pharmacokinetic study in Brazil reported no pregnancies for the duration of the three years, six months study period among Implanon users on various ART regimens including EFV20. Similarly, a prospective pharmacokinetic study conducted in Uganda found that LNG levels were 32–39% higher among NVP users and 40–54% lower among EFV users compared to women not on ART. Three of the 20 women on EFV who were enrolled in the study had drug levels below the minimum recommended concentration for contraceptive efficacy and three pregnancies occurred within 48 weeks21. Secondary analyses of Swaziland clinical trial data by Perry et al. found that, in a sample of 570 women, 15 of 121 (12.4%) women using LNG implants and EFV became pregnant, with no pregnancies in women using NVP22. A large retrospective clinical record review by Patel et al. in Kenya revealed unadjusted pregnancy rates of 5.5 (ETG) and 7.1 (LNG) among 24,560 women using EFV23.

Clinicians serving WLHIV need guidance to appropriately counsel their clients, as misinformation is creating uncertainty about how to describe contraceptive choices to these women19,24. This study aimed to contribute to evidence related to contraceptive failures among women who are on ART and use implants and ultimately improve counseling for WLHIV. The primary aim of this retrospective record review is to determine unintentional pregnancy rates among WLHIV (15–49 years old) concurrently using contraceptive implants and ART in nine facilities in Western Kenya between January 2011 and December 2015. The secondary aim is to describe the characteristics of concurrent implant and ART users with and without implant failures and to explore alternative correlates of method failure.

Methods

We reviewed charts of all women of reproductive age (15–49 years) who had at least three months of concurrent use of any ART and a contraceptive implant, and who accessed services at a high-volume health facility7 offering comprehensive care for PLHIV. Prior to developing a protocol for the chart review, a feasibility assessment was conducted to: pretest data abstraction tools and processes; determine the degree of integration between HIV and FP services in high-volume facilities; establish whether linking HIV and FP client data was possible; and verify that there were cases of implant failure among ART clients. The investigators then prioritized nine health facilities in Western Kenya based on completeness of medical records, data management processes, local HIV prevalence, results from past programs and the lack of fees for family planning services. The investigators also excluded facilities in which a similar study was being conducted by Family AIDS Care and Education Services (FACES). To mitigate potential bias, we trained research assistants prior to the initiation of the study using standard operating procedures including a data abstraction form and we conducted a pilot test during this training. Data collection was monitored through supervision visits and calls throughout study implementation.

Data collection

Between January 2016 and March 2017, eleven research assistants (RAs) reviewed medical charts of all women receiving care at Comprehensive Care Clinics (CCC) for PLHIV in nine public-sector facilities in five counties. RAs retrieved medical records for all female clients who were seen at the CCCs between

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1 The nine facilities were: Awendo Sub-County Hospital, Busia County Referral Hospital, Kendu Seventh Day Adventist Hospital, Kendu Sub-County Hospital, Kisumu Sub-County Hospital, Migosi Health Centre, Nyalunya Health Centre, Railways Dispensary, and Siaya County Referral Hospital.
January 2011 and December 2015 and verified whether they were of reproductive age, on ART, and using a contraceptive implant. Women who did not meet these criteria were excluded from further data abstraction. Data abstracted from women’s medical records included: date of birth, implant type, date inserted, date removed, reason for removal, date of enrollment into HIV care, age at enrollment into care, date of ART start, date of stopping ART, ART regimen (multiple entries possible for start, end dates and type of ART regimen), date of transfer or death, notations of pregnancy in records, CD4 count, viral load results and date taken, number of liver function tests done and results, WHO stage, height and weight (to calculate BMI), tuberculosis (TB) status, and other concurrent chronic conditions (hepatitis, diabetes, hypertension) with dates of diagnosis and other medications used. The study was reviewed and approved by the Johns Hopkins School of Public Health review board (#6073) and the Kenya Medical Research Institute scientific and ethical review committee (#NON-SSC 510).

In cases where RAs were unable to complete full data abstraction from the client’s CCC medical record, they consulted other hospital records, including case notes from the consulting health care provider, Family Planning Register, PMTCT Register, Antenatal Care (ANC) Register, Logistics Management Information System, and laboratory records. For several clients in four Kisumu County facilities, the study team retrieved information on implant type from Marie Stopes Kenya’s database of family planning outreach events.

The investigators sought to identify possible pregnancies due to contraceptive implant failures from medical records: specifically, records of the client’s reason for implant removal as pregnancy or that the client gave birth after receiving an implant and before its removal date.

Each CCC client receives a unique identifier (eleven-digit, alpha-numeric code) at enrollment in HIV care and treatment services. The investigators only used this number to locate client records for data verification purposes. Client names were tallied but not included in data abstraction. De-identified data were entered into REDCap v6.14.0 (Research Electronic Data Capture), a web-based data management application, with limited, password-protected access. RAs were strictly instructed to properly store all paper and electronic copies of records with client-identifying information. Portable electronic devices did not contain identifiable information.

Data cleaning
The investigators abstracted 1,612 records from women concurrently using ART and an implant. Investigators excluded all 208 records from Busia County Referral Hospital due to inconsistencies in RAs’ adherence to standard operating procedures. Subsequently, investigators removed: 36 suspected duplicate records, 50 records with invalid ART or missing implant data, 81 records which indicated that there was fewer than three consecutive months of concurrent implant and ART use, and 85 records where the woman did not meet other inclusion criteria.

All observations without concurrence end dates were censored at December 31, 2015 or earlier if the end of approved implant effectiveness (3 years for Implanon/Nexplanon® and Levoplant® and 5 years for Jadelle®, per WHO prequalifications) preceded the end of the observation period. Records which listed emtricitabine (FTC) within the ART regimen were regrouped with 3TC due to pharmacokinetic similarity.

With exclusions, the dataset included 1,152 individual women (Table 1). The dataset was then expanded so that women who switched to a new ART and/or implant over the course of the study period were recoded as separate observations for each

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women N=1,152</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; ART regimen during concurrent use</td>
<td></td>
</tr>
<tr>
<td>NVP regimen</td>
<td>365</td>
</tr>
<tr>
<td>EFV regimen</td>
<td>769</td>
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<td>Non-NNRTI</td>
<td>18</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; ART regimen during concurrent use</td>
<td></td>
</tr>
<tr>
<td>NVP regimen</td>
<td>7</td>
</tr>
<tr>
<td>EFV regimen</td>
<td>16</td>
</tr>
<tr>
<td>Non-NNRTI</td>
<td>9</td>
</tr>
<tr>
<td>No 2nd ART regimen</td>
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</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; ART regimen during concurrent use</td>
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<td>NVP regimen</td>
<td>1</td>
</tr>
<tr>
<td>EFV regimen</td>
<td>0</td>
</tr>
<tr>
<td>Non-NNRTI</td>
<td>1</td>
</tr>
<tr>
<td>No 3rd ART regimen</td>
<td>1,150</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; Implant during concurrence</td>
<td></td>
</tr>
<tr>
<td>ETG</td>
<td>491</td>
</tr>
<tr>
<td>LNG</td>
<td>661</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Implant during concurrence</td>
<td></td>
</tr>
<tr>
<td>ETG</td>
<td>2</td>
</tr>
<tr>
<td>LNG</td>
<td>2</td>
</tr>
<tr>
<td>No 2nd implant</td>
<td>1,148</td>
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<tr>
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<td>Kendu Seventh Day Adventist Hospital</td>
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</tr>
<tr>
<td>Kendu Sub-County Hospital</td>
<td>185</td>
</tr>
<tr>
<td>Kisumu Sub-County Hospital</td>
<td>160</td>
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<tr>
<td>Migosi Health Centre</td>
<td>116</td>
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<tr>
<td>Nyalunya Health Centre</td>
<td>80</td>
</tr>
<tr>
<td>Railways Dispensary</td>
<td>133</td>
</tr>
<tr>
<td>Siaya County Referral Hospital</td>
<td>153</td>
</tr>
</tbody>
</table>

Table 1. Concurrent use of implants and antiretrovirals by women.

ART, antiretroviral therapy; NVP, Nevirapine; EFV, efavirenz; NNRTI, non-nucleoside reverse transcriptase inhibitor; ETG, Etonogestrel; LNG, Levonorgestrel.
Data analysis

We estimated contraception failure rates for LNG and ETG implants with concurrent ART regimens containing EFV, NVP, or a protease inhibitor (PI). We estimated the incidence of unintended pregnancy per 100-woman years at risk. We defined person years at risk as the start of concurrent implant and ART use (beginning from the start date of whichever was introduced second) to either pregnancy, date of implant removal, end of approved implant effectiveness, end of ART use, or end of the study period, whichever came first. Incidence of unintended pregnancy was calculated as number of pregnancies/number of woman-years at risk x100, assuming a constant rate of implant failure.

We used Poisson regression to calculate the incidence rate ratios (IRRs) of pregnancy by age, CD4 count, BMI, ART regimen, and implant type. We repeated this for all six possible combinations of concurrent ART and implant use. Data on TB symptom screening, TB diagnosis and viral load were missing for over 96% of women, precluding analysis of these variables. Differences were deemed statistically significant at the p<0.05 level (two-sided test of significance). IRRs were calculated after adjusting for potential clustering within HIV clinics, using cluster-adjusted standard errors\(^2^7,2^8\). To test for robustness of results, we reran analyses excluding women aged 35–49. Two separate investigators conducted analyses and cross-checked results; both used STATA with slightly different versions (14 and 15).

Kaplan-Meier failure curves were created to visualize time-to-implant failure for the different ART and implant combinations by using the date of unintended pregnancy as the failure date. We present duration of concurrent ART-implant use for interpretation of Kaplan-Meier results.

Results

Demographic and ART information

Table 2 provides age and clinical status of women at the start of each observation of each co-administration. Among the participants, the most common combination of implant and ART use was LNG-EFV (39.4%), followed by ETG-EFV (26.7%), LNG-NVP (16.7%), ETG-NVP (14.8%), LNG-PI (1.3%), and ETG-PI (1.0%).

In total, 32 of the 1,152 women included in the dataset switched ART regimens while using an implant during the study period; 30 women were exposed to two regimens and two women were exposed to three regimens. Four women used implants twice. Three women were exposed to three different combinations of implant and ART.

Pregnancy incidence

Table 3 presents pregnancy IRRs and incidence in person-years of observations broken down by clinical status of women at each observation of co-administration. There were 115 pregnancies in the 1,190 instances of co-administration, yielding a pregnancy incidence rate of 6.32 (95% CI: 5.27–7.59), with 9.26 (95% CI: 7.18–11.96) among ETG and 4.74 (95% CI: 3.65–6.16) among LNG implant users, respectively.

Analysis of incidence by ART and contraceptive use

The pregnancy IRRs did not differ between EFV- and NVP-based regimens (IRR = 1.00; 95% CI: 0.71–1.43). No pregnancies were recorded among women on non-NRTI-based regimens among both ETG and LNG implant users, which was

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<table>
<thead>
<tr>
<th>Variable</th>
<th>Co-administration</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at time of combination start</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 – 24</td>
<td>250</td>
<td>21.0</td>
</tr>
<tr>
<td>25 – 34</td>
<td>760</td>
<td>63.9</td>
</tr>
<tr>
<td>35 – 49</td>
<td>180</td>
<td>15.1</td>
</tr>
<tr>
<td>CD4 count within +/- 1 yr of combination start</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 – 349</td>
<td>326</td>
<td>27.4</td>
</tr>
<tr>
<td>&gt;=350</td>
<td>410</td>
<td>34.5</td>
</tr>
<tr>
<td>Missing</td>
<td>454</td>
<td>38.2</td>
</tr>
<tr>
<td>BMI within +/- 1 year of combination start</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>98</td>
<td>8.2</td>
</tr>
<tr>
<td>18.5 – 25</td>
<td>770</td>
<td>64.7</td>
</tr>
<tr>
<td>25 – 30</td>
<td>178</td>
<td>15.0</td>
</tr>
<tr>
<td>&gt;=30</td>
<td>46</td>
<td>3.9</td>
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<tr>
<td>Missing</td>
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<td>8.2</td>
</tr>
<tr>
<td>ART Regimen</td>
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<td></td>
</tr>
<tr>
<td>NVP regimen</td>
<td>375</td>
<td>31.5</td>
</tr>
<tr>
<td>EFV regimen</td>
<td>787</td>
<td>66.1</td>
</tr>
<tr>
<td>Non-NNRTI</td>
<td>28</td>
<td>2.4</td>
</tr>
<tr>
<td>Implant</td>
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<tr>
<td>ETG</td>
<td>506</td>
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<td>LNG</td>
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<td>57.5</td>
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<tr>
<td>Implant &amp; ART combination</td>
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<td>ETG-NVP</td>
<td>176</td>
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<tr>
<td>ETG-EFV</td>
<td>318</td>
<td>26.7</td>
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<tr>
<td>ETG-Non-NNRTI</td>
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<td>1.0</td>
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<td>LNG-NVP</td>
<td>199</td>
<td>16.7</td>
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<tr>
<td>LNG-EFV</td>
<td>469</td>
<td>39.4</td>
</tr>
<tr>
<td>LNG-Non-NNRTI</td>
<td>16</td>
<td>1.3</td>
</tr>
</tbody>
</table>

BMI: body mass index, ART: antiretroviral therapy, NVP: Nevirapine, EFV: efavirenz, NNRTI: non-nucleoside reverse transcriptase inhibitor, ETG: Etonogestrel, LNG: Levonorgestrel

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unique ART/implant co-administration, giving a final dataset of 1,190 observations.
statistically significant. There was also a statistically significant difference in pregnancy rates based on implant type. LNG implant users (Jadelle/Sino-plant) were 0.51 times as likely to become pregnant as ETG implant users (95% CI: 0.33–0.79, p<0.01). The likelihood of pregnancy decreased with increasing maternal age; the pregnancy IRRs were 0.61 (95% CI: 0.35–1.06) among 25–34 year-olds and 0.34 (95% CI: 0.18–0.62, p<0.01) among women >35 years of age, using 15–24 year-olds as the reference group.

Analysis of implant and ART combination showed that the pregnancy incidence rates among women using LNG implants with EFV and NVP or using a PI with either implant were significantly different from the reference population of ETG-EFV users.

Duration to failure curves (Figure 1) show that pregnancies began occurring within months of concurrent use, steadily accumulating thereafter. The shortest time to pregnancy was 94 days.
(16.5% and 48.7% within 6 and 12 months, respectively). ETG implant users had more early pregnancies than LNG implant users, but this is likely correlated with higher overall pregnancy incidence and shorter approved duration of use.

As shown in Figure 2, the distribution does show skewing of our sample towards shorter periods of co-administration, given that the rise in implant use in Kenya is a recent phenomenon. The median duration of implant and ART co-administration in our dataset is 1.33 years (not shown).

The sensitivity analysis among women aged 15–34 resulted in slightly higher pregnancy incidence (6.89 per 100 person-years [CI: 5.69–8.35]). Other results remained similar, except IRRs for LNG-NVP and LNG-EFV combinations compared to ETG-NVP were no longer statistically significant. This suggests a lack of robustness in differences across drug-drug combinations, a likely artifact of higher use of ETG implants by younger women.

Discussion
An increase in the incidence of pregnancy among implant users on ART may negatively impact acceptability and trust in implants as a contraceptive choice for all women and their partners, regardless of HIV status. Our findings confirm earlier reports of implant failures among women taking EFV-based ART. Pregnancy incidence ranged from 4.78 to 9.84 per 100-person years for women using an implant with an NNRTI, a rate considerably higher than found in the general population. Our results differ from previous studies in that NVP use was linked with higher incidence of pregnancies. Among NVP users, pregnancy incidence ranged from 4.85 to 8.68 per 100-person years with concurrent LNG and ETG users, respectively. This is the first report, to our knowledge, to present evidence that NVP-based ART regimens may also influence effectiveness of both ETG and LNG. While surprising, the higher incidence of pregnancies in this population is biologically plausible given the metabolic pathways in the liver for both NNRTIs and progestins.

Our exclusion of any pregnancy detected within three months of initiating co-administration minimizes accidental insertions of implants when conception has already occurred, which was a common problem in the Australia post-marketing study and could explain pregnancies in other studies. In our study, pregnancy incidence rates in women using EFV were higher for women using ETG implants than those using LNG implants, but this finding is not robust among younger women. This pattern was repeated among NVP users.

Limitations
Retrospective studies can be limited due to issues of reliability and completeness of medical charts. Prospective studies with more frequent and standardized timing of follow-up could address some of these limitations. Prospectively capturing data
could also allow for further analysis of drug-drug interactions with either ART or implants, such as rifampicin for TB or artemether-lumefantrine for malaria. However, the necessary financial investment and length of time would be substantial.

Our retrospective chart review had intended to measure multiple factors, including stage of HIV disease and other drug interactions; however, incompleteness of medical records did not allow for adequate analysis to answer these questions. We had also hoped to draw conclusions about timing of failure over time. However, because of recent expansion in use of implants in Western Kenya, most of the implant users in our data set had relatively a short duration of concurrent use with ART.

Biases may have also been introduced to the results because of variations in how RAs assessed abstracted records, due to the differing record management systems in the study facilities. Given the limitations in completeness of charts in the CCCs, the RAs diligently sought evidence of pregnancies in other units of the facilities, but it is difficult to do this systematically across diverse facilities.

Implications for practice

Women should be afforded choices when selecting FP and ART. However, women are generally unable to choose their ART. EFV is a safe, effective drug and will not be phased out soon as a first-line HIV treatment. Additionally, many countries still have a number of WLHIV using NVP, despite its continued phase out. In 2016, WHO included dolutegravir (DTG) as an alternative drug for first-line regimens, which became available in Kenya in 2017. Co-administration with implants has not been studied, although an interaction is unlikely, as DTG is not expected to significantly inhibit or induce CYP450 enzymes. Though DTG shows promise for women who wish to use contraceptive implants, concerns about potential birth defects has led to recommending that women of reproductive age be offered EFV instead. Results from a study in Botswana by Westhoff to assess change in ETG plasma levels among ETG implant users taking DTG are expected in late 2019.

It remains challenging to incorporate the results of this study into service delivery for WLHIV. It is premature to discourage women from adopting implants. However, women on NNRTIs need information, in simple, yet accurate language, about the drug interaction and possibility of method failure. Experiences in South Africa have demonstrated the difficulties in ensuring providers understand these drug interactions and are comfortable sharing information with clients. One option is to refer to the tier of effectiveness, but explain that for women on certain ART regimens, the implant falls somewhere in the middle tier of effectiveness: slightly better than pills or injectables, but less effective than IUDs or sterilization. Women should retain the right to make fully informed decisions about which contraceptive option works best for them and what level of method failure risk is acceptable, given that they cannot switch ART regimen based on their fertility preferences. Ideally, building a client-centered culture would allow WLHIV desiring control over their fertility to be offered DTG concurrently with an implant or other LARC.

At minimum, programs should encourage better documentation of all medications in medical charts. Health systems should establish mechanisms to track adverse events (pregnancies) in WLHIV using ART. Study facilities had ongoing efforts to

**Figure 2.** Years of concurrent implant and ART use. ART, antiretroviral therapy.
integrate FP within HIV care and treatments services. Fully integrating FP services by including LARCs within services for WLHIV may improve care. Health systems should also ensure that IUDs are as accessible as implants and remove barriers to sterilization services. Research into the benefits and costs of alternative service delivery models could inform national policies.

In conclusion, implants are highly effective; however, clients using a NNRTI-containing ART regimen need additional information about higher incidence of pregnancies when used in combination with ARVs to allow them to make informed decisions about contraceptive options.

Data availability

Underlying data

The dataset analyzed for this study was generated from client medical records under ownership of the Kenyan Ministry of Health. The authors’ permission to study this data does not extend to publically sharing the full dataset without prior permissions from the Kenyan Ministry of Health. Access to the de-identified dataset may be obtained by submitting a request to the Kenyan Medical Research Institute (KEMRI) (seru@kemri.org) and the Jhpiego Open Data Help team (OpenDataHelp@jhpiego.org), copied to anne.pfitzer@jhpiego.org, with a detailed description of the intended use and an IRB-approved protocol for secondary data analysis. Data will be provided under the condition that researchers have provided the required permissions from the Kenyan National AIDS Control Program and KEMRI.

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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The authors appreciate the Ministry of Health for their permission and support to the study. Specifically, thanks go to the Reproductive and Maternal Health Services Unit, the National AIDS and STI Control Program (NASCOP), and county and sub-county health officials from: Kisumu county – Nyalunya Dispensary, Migosi Health Centre, Kisumu sub-county hospital and Railways; Homabay County – Kendu Adventist, Kendu Sub county Hospital; Siaya County – Siaya County Referral Hospital and Migori County – Awendo Sub-county Hospital. The authors also thank the research assistants who spent many months abstracting data: Elizabeth Achieng, Tamimah Ajul Athimani, Jenifer Ayoji, Stephen Mang’eni Egesa, Esther Aluoch Obonyo, Samson Odoyo Okunu, Florence Awuor Ondek, Collins Otieno Oyoo, and Emily Anyango Sinoh. We also gratefully acknowledge Dr. Anthony Gichangi for his oversight and leadership of the Kenya Study team, Charles Waka for his support to managing the REDCap database and Rose Mulindi for her support during the feasibility phase of study preparation. We sincerely thank Jennifer Mason and Patricia MacDonald of USAID for their guidance and advice in the design and review of our results.

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Rena Patel
Department of Medicine, University of Washington, Seattle, WA, USA

Review

The authors present an important analysis related to possible higher contraceptive failures with specific concomitant antiretroviral therapies (ART). They undertook a retrospective chart review in their affiliated health facilities in western Kenya to help determine if contraceptive implants and efavirenz (EFV)-containing ART are implicated in possible higher failures, as has been shown by some prior data. Overall, the work is adequately presented though there are several clarifications, some more major than minor, that they could provide, especially in the methods and results sections (e.g. justification for choice of reference categories), to aid others in better replicating or interpreting their results. Another major concern is that the authors provide a very cursory interpretation of their findings, and given that they differ from the already published data to date, this is one of the key questions—why are your study findings different?—that should have been elucidated in their discussion. Another concern is that the authors make several statements, in the introduction and discussion sections (also these sections require some better organization and flow, more accurate citations, etc.), that are difficult to justify based on the leading PK data (my sense is that the authors would have benefited from including even a pharmacology expert in their authorship team, which could be considered even now). Detailed feedback is provided below.

Abstract

- Background line: technically these are considered drug-drug interactions, as the term “drug interactions” is non-specific

Introduction

- The last line in the 2nd paragraph is extremely vague; I don’t understand what the authors are trying to convey. It would be better to more explicitly elucidate their thinking.
- The first line in the 3rd paragraph should have a citation, and if it is the same citation as #6, then it should be cited with the first sentence with the assumption that the 2nd sentence is supported by the same citation (unless the citation standards for this journal indicate otherwise).
- Same paragraph: The 3rd sentence needs a bit of fine tuning, in that this combination is generally recommended as 1st line ART regimen. Also, the next line appears inaccurate on the year; if I am
not mistaken, single pill combination containing EFV, was the recommended 1st line ART regimen before 2015 in Kenya (maybe even before 2012?, and please provide your citation for this assertion if you disagree). Also, the next paragraph doesn’t make a lot of logical sense as written, and if the authors want to name the leading 1st line ART regimen, they should name all 3 components of it. The “n” in nevirapine should not be capitalized. For the last line, if they can cite specific number on how many women of reproductive potential were on EFV-containing regimen, the sentence would be more to the point.

- It seems like the paragraphs in the introduction could be organized better. For example, the first line in the 2nd paragraph discusses LARCs and implants and then discussion switches to ART for the rest of the paragraph. The 3rd paragraph then discusses more on ART and the 4th comes back to contraceptives. The 5th paragraph then goes into describing the potential pathway for any drug-drug interactions at play here, and the data to date on this topic. Strongly reconsider the organization of the intro section for more logical flow.

- 5th paragraph: 2nd line, technically 4 of the 6 citations are for case reports (which are not the same as retrospective clinical studies). The line discussing the Uganda PK study starts with “Similarly” which does not make any logic sense. It would greatly help readers if the authors only used either ETG/LNG acronyms or the brand names, but not both. Last sentence, technically this was not a record review, as is the current study, but rather a retrospective study of electronic medical record data, it would help to indicate the denominator for the rates i.e. “per 100 women-years of implant use,” and it appears that citation number #19 is mistakenly included here.

- 6th paragraph: it appears the first line mistakenly cites #13 (as that citation is not applicable to their statement). Arguably, the goal of the 2nd and 3rd lines are redundant, might consider combining by saying something along the lines of: “With the ultimate goal of improving counseling for WLHIV, the primary aim of this…”

Methods

- Data collection, 1st paragraph: how did you know who was seen between Jan 2011 and Dec 2015? When listing all the variables you extracted, it might make sense to name them all and indicate that the applicable dates were also extracted (instead of mentioning it twice, and presumably it is applicable to not only viral load results but also CD4 count results). It may help to discuss how pregnancies are detected generally in these facilities—i.e. was it detected with clinical presentation while being gravid or via routine biochemical testing (e.g. urine pregnancy tests)?

- 2nd paragraph: might consider saying “facilities” throughout the manuscript, unless you do literally mean “hospitals” in which case it would help to explain which hospitals you selected and why.

- Data cleaning paragraphs: There is a lot of detail here not usually included in publications, but the details do help. It appears only 38 women had a 2nd or 3rd observation in the dataset; it might help to state it as something along these lines. Given the organization of Table 1, you could consider including here or in the text, the median duration of observation time for 1st observation, 2nd observation, etc. Could you provide the justifications to censor observation time after the recommended use of implant durations, given that maintaining those times arguably provides even stronger evaluation for real-world effectiveness (if the woman is still using the implant past its recommended duration)?

- Data analysis: only clarification is on last line of first paragraph, as “x100” is not clear if it applies to numerator or denominator. Perhaps consider saying “per 100 women-years.”

- A couple questions: How did you arrive at your sample size? was there ever a determination of the required sample size to achieve power for detecting a difference between certain combinations? Or did you simply go with a convenience sample for what was feasible for the study duration? Could you also describe how you determined ascertainment of the incident pregnancy to a combination category? i.e. was it the combination category at the time of the pregnancy detection
or did you base it on date of likely conception (and if latter, please describe how you calculated the
date of likely conception)? Did you consider double entry for cases where a pregnancy was
detected (i.e. some cross-check or validation of your initial data entry), as data entry errors by RAs
could have also occurred?

**Results**

- Overall, the various comparisons are confusing and it is difficult for me to follow which comparison
  is being made when. It may help to use additional subheadings to clearly separate the findings,
  and it may also help to prioritize the main findings first
- Small note on Table 3, that the 3rd category of ART is “non-NNRTI” which does not necessarily
  equate to PI-containing ART (which is how the 3rd category is defined in the manuscript), so it
  would be better to clarify if PI-only. Of note, I would not recommend a non-specific non-NNRTI
  category as the drug-drug interaction implications vary markedly by not only ART family but
  individual antiretrovirals.
- Paragraph after Table 3 that starts with “Analysis of implant…”; Could you provide justification for
  why ETG-EFV combination was used as the referent group? It seems like picking a category where
  you don’t expect a drug-drug interaction, such as with NVP, is a better “control” group or the
  counterfactual. (Of note, when looking at Table 3, I see that you used ETG-NVP as your reference
  category—please rectify the difference.) More importantly, please justify why you would use
  ETG-EFV as the referent group for the LNG combinations? Wouldn’t you want to compare each
  implant type against itself, given the possible differences in hormone concentrations, affinity to
  receptors, recommended duration of use, number of rods, etc.? As a possible secondary analysis,
  you can compare the ETG to LNG implants. Also, the conjunctions of “EFV and NVP or using a PI”
  are confusing, please consider rephrasing for clarity.
- Figure 1: note use of PI here as opposed to NNRTI
- 2nd to last paragraph: it’s not clear the marked utility in Figure 2, however if you wish to keep it,
  please consider dividing or creating 3 separate figures for, for example, the ART type with then the
  breakdown of implant type within it. Also, when reporting median duration of co-administration
  time, please also report standard IQR or range, and consider doing this for your 3 or 6 combination
  categories.
- Several of the results paragraphs end in interpretation of the findings, which would be better
discussed in the discussion section.

**Discussion**

- The biggest missed opportunity in the discussion section is in better elucidating why no significant
  differences were found between EFV and NVP and respective implant combination groups. What
  are the possible reasons you did not detect a difference when several PK studies and other
  retrospective studies (namely Perry and Patel) have found differences? What are possible biases
  that arise from your chosen methodological approach? NVP’s DDI profile is markedly different from
  EFV, so grouping them together and suggesting that all NNRTIs have similar effects is not well
  supported by existing PK and clinical studies. To this point, etravirine and rilpivirine, other NNRTIs,
  also have very different DDI and PK profiles than EFV. Given the topic is deeply rooted in the PK
  world, greater clarity from the PK perspective on the study findings is a must.
- First paragraph: the use of “ranged” is likely not appropriate, as those are specific point estimates
  for certain combination categories, correct? So you might as well state that they are for x and y
  combinations, respectively. Also, generalizing to all NNRTIs is not appropriate as each NNRTI has
  a very different drug-drug interactions profile. Also, the first paragraph could use some
  rewording. It seems like in the middle of it, you are trying to highlight that, surprisingly, you found a
  higher rate of failures with NVP than you had hypothesized at the start of your study. Finally, in the
  latter half of the first paragraph, the interpretation of the authors for this finding comes across as
too definitive—isn’t it also possible that the nearly equivalent rate of implant failures among NVP
and EFV users you found may signal possibly a “baseline” rate of failures among implant users? Of course, it does not explain the higher than the “baseline” rate that has been described in other settings.

- First half of second paragraph: indeed, it is robust of you to censor pregnancies within the first 3 months of implant placement in cases where the implant may have been placed with a pregnancy already in place. However, shouldn’t that result in a bias towards a lower pregnancy rate compared to the post-marketing surveillance study from Australia that you are comparing to? It would be prudent to spend some space in the discussion section to offer thoughts on why the overall pregnancy rates are higher in your study that other, predominantly non-African, settings.

- The second half of second paragraph: this is a very interesting finding, and deserves discussion in a separate paragraph—why do you think this difference might exist? Why does it appear to diminish among younger women?

- Implications for practice: 1st paragraph, cite your basis for not anticipating DDIs with DTG and implants (i.e. the OC PK study by Song et al.1). 2nd paragraph, shouldn’t women also be offered the choice to pick an ART regimen that meets their values and preferences (e.g. DTG, knowing that there is currently an unknown and possible risk with adverse birth outcomes)? Given the great women-centered approach the intro and the first half of this paragraph takes, it seems like a missed opportunity to also not advocate for WLHIV to also be informed with best information available at the moment to make their own decisions.

Throughout

- Considering saying either “failure rates” or “unintended pregnancy” throughout the manuscript, as switching between the two, often in back to back sentences, is confusing for readers who may not be familiar with the “contraception world” where the two equate each other.

References

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly
**Competing Interests:** Yes, I have some minor competing interests in that I was asked to provide guidance to some of the authors in study design initially prior to data collection (though was not involved in study implementation at all) and was aware of their initial preliminary analyses. I have conducted very related analyses, and this group and mine held a joint study dissemination and stakeholder's meeting in Kisumu, Kenya in July of 2017 (some of our related analyses have been published to date, but not the primary results).

**Reviewer Expertise:** HIV and women's health; cohort studies; contraception; pharmacokinetic studies; resource-limited settings

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

15 July 2019
Reviewer Report 15 July 2019

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Kavita Nanda
Contraceptive Technology Innovation, Global Health, Population and Nutrition, FHI360, Durham, NC, USA

This is an important study that adds to the literature on the issue of contraceptive effectiveness for implants among women taking antiretroviral therapies. However, the study is limited by its retrospective nature, and by the existing limitations of databases designed for other purposes. Of most concern is the outcome ascertainment, as detailed in the specific comments below.

Introduction:
- The introduction is very long. Some of it could be moved to the discussion.

Methods:
1. How many research assistants abstracted data for each participant? How was data accuracy monitored?

2. The study inclusion criteria are not clear. Did they have to be currently using an implant to be included? Or were women included if they ever used an implant and ART concurrently?

3. For what proportion of women were the data incomplete? Did RAs consult other records for all women? Or only those on certain regimens? How were the MSI data matched to the ART data? How was the CCC number matched to other records?

4. How were data collected on reasons for removal? Were actual pregnancies verified if a woman said her implant was removed due to pregnancy? My concern is that a woman could be concerned about the risk of pregnancy and ask for her implant to be removed without actually being pregnant.
Also, how good were data on implant removal (for other reasons).

5. You state that the investigators abstracted 1,612 records from women concurrently using ART and an implant. However, earlier you stated that the RAs abstracted data. Please clarify. Also, are these all women who at any time used ART and an implant concurrently?

6. Please provide details on how you estimated the estimated fertilization date.

7. How good were data on type of implant? Was implant type always noted?

8. The exclusion of pregnancies within three months of implant insertion is important and appropriate.

9. In the discussion of limitations, the author should spend more time discussing the lack of information on other medications, as well as any uncertainties in outcome ascertainment. I am concerned that the way pregnancy was determined may not be accurate, as pregnancies were not clinically verified (just a desire for removal due to pregnancy). I'm also concerned that other co-administered medications are not adequately captured. Retrospective studies such as this, though hypothesis generating, are subject to bias and confounding. Were RAs as diligent in seeking out possible pregnancy in women not using ART?

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
No

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: HIV and contraception, systematic reviews/meta-analysis, clinical trials

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.
This is a retrospective cohort study of pregnancy rates among Kenyan women living with HIV on antiretroviral therapy and using the subdermal implantable contraceptive implant. The data is presented in a clear fashion, however some significant limitations of the study design precludes the reliability of the data.

Abstract: The background is too long and the conclusion is too short. For example, noting the percentage of women who are married in the cohort is too granular for the abstract. The background should focus on why ART might impact the contraceptive efficacy of the implant.

Introduction: The introduction is too long. Recommend giving only relevant background, such as why there might be a contraceptive-drug interaction and the number of women globally and in Kenya are using ART and implants together. What is the knowledge gap this study fills?

Introduction, paragraph 3, sentence 2: I do not understand the relevance of marital status in reporting the contraceptive implant use. More importantly would be how many Kenyan women use the contraceptive implant.

Introduction, paragraph 4, sentence 4: The interpretation of citation 20 is inaccurate, unless the authors have communicated directly with the authors of citation 20. In this study only 25 women were on NNRTIs, but they did not differentiate whether the NNRTI was EFV or NVP.

Introduction, paragraph 4: Recommend including PK study by Chappell et al. (2017) which showed ETG PK changes with EFV, but not NVP. Also Scarsi KK, et al., citation 21 has been published in CID. Please update the reference.

Methods: The section entitled “data cleaning” and Table 1 usually go into the results section.

Results, section “Analysis of incidence by ART and contraceptive use”, paragraph 1, sentence 4: This sentence is confusing because of the way it is written. I would recommend stating more clearly that LNG implant users were less likely to become pregnant than ETG implant users.

Results, section “Analysis of incidence by ART and contraceptive use”, paragraph 2: I believe in the table the reference population is ETG-NVP.

Results, last paragraph, sentence one: What pregnancy incidence is this referring to? The overall pregnancy incidence among women age 15-34? Or just those on NNRTIs?

Results, last paragraph, sentence 2: The findings are unclear. Could these data be placed into a table for clarity?
11. Discussion, limitations: The largest limiter is the lack of ability to know if any of these women were on medications for TB. My concern is that the women on NVP-based ART, had HIV longer and more likely had lower CD4 counts, and thus were more likely to get TB and be on rifampicin. Do you have any idea how many women had TB over the study period? How certain are you that the women on NVP were actually on NVP and had not been switched to EFV for some times depending on ART availability. The finding of the increased pregnancy rate among women on NVP using contraceptive implants is contradictory to all the published literature (though limited). In the limitation section, I recommend raising these concerns regarding the accuracy of the data and cautions readers on interpretation.

References

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Obstetrician-gynecologist with expertise in family planning and infectious diseases.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.