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A retrospective cohort analysis comparing pregnancy rates among HIV-positive women using contraceptives and efavirenz- or nevirapine-based antiretroviral therapy in Kenya

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SUMMARY

Background—Given recent concerns of efavirenz reducing the efficacy of contraceptive implants, we sought to determine if pregnancy rates differ among HIV-positive women using various contraceptive methods and efavirenz- or nevirapine-based antiretroviral therapy (ART) regimens.

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Declaration of interests

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Contributors

RCP, MO, CB, SBS, SJN, and CRC designed the study. CB constructed the dataset, SBS and EV provided biostatistical expertise, and RCP led the analysis. MO, MG, JH, EAB, and CRC reviewed the analysis and supported the development of the manuscript. RCP, MG, and CRC prepared the first full draft of the manuscript, and all authors contributed to subsequent drafts. All authors approved the final draft of the manuscript.

Methods—We conducted a retrospective cohort analysis of HIV-positive women aged 15–45 years enrolled in HIV care facilities in western Kenya from January 2011 to December 2013. Pregnancy was diagnosed clinically and the primary exposure was a combination of contraceptive method and ART regimen. We used Poisson models, adjusting for repeated measures, as well as demographic, behavioral and clinical factors, to compare pregnancy rates among women on different contraceptive/ART combinations.

Findings—24,560 women contributed 37,635 years of follow-up with 3,337 incident pregnancies. Among women using implants, adjusted pregnancy incidence for nevirapine- and efavirenz-based ART users were 1·1 (95% CI 0·72–1·5) and 3·3 (95% CI 1·8–4·8) per 100 women-years (w-y), respectively (adjusted incidence rate ratio (aIRR) 3·0, 95% CI 1·3–4·6). Among women using depomedroxyprogesterone acetate (DMPA), adjusted pregnancy incidence for nevirapine- and efavirenz-based ART users were 4·5 (95% CI 3·7–5·2) and 5·4 (95% CI 4·0–6·8) per 100 w-y, respectively (aIRR 1·2, 95% CI 0·91–1·5). Women using other contraceptive methods, except for intrauterine devices and permanent methods, experienced 3·1–4·1 higher rates of pregnancy than women using implants, with 1·6–2·8 higher rates specifically among women using efavirenz-based ART.

Interpretation—While HIV-positive women using implants on efavirenz-based ART faced three times higher risk of contraceptive failure than those on nevirapine-based ART, these women still experienced lower contraceptive failure rates than women on all other contraceptive methods, except for intrauterine devices and permanent methods. Guidelines for contraceptive and ART combinations should balance the failure rates for each contraceptive method and ART regimen combination against the high effectiveness of implants.

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INTRODUCTION

Unintended pregnancies among HIV-positive women may have significant consequences for HIV-related maternal morbidity[1] and vertical transmission of HIV.[2] Effective contraception can prevent unintended pregnancies, but potential interactions between antiretroviral therapy (ART) and hormonal contraception, particularly between efavirenz-based ART and subdermal implants, may compromise a contraceptive's efficacy. This issue is particularly important to the nearly 13 million women living with HIV in sub-Saharan Africa.[3] First, there is increasing use of efavirenz-based ART as the first-line regimen, facilitated by its availability as a fixed dose combination pill.[4] Second, there is increasing access over time to hormonal contraceptives for family planning in sub-Saharan Africa, including implants, which are used by up to 14% of HIV-positive women in the region.[5–7] Implants prevent pregnancies by gradually releasing synthetic forms of progesterone, etonogestrel or levonorgestrel, into the serum, thereby suppressing ovulation, increasing cervical mucus viscosity, and altering the endometrium. The two types of implants commonly used in sub-Saharan Africa are Implanon® (68 mg etonogestrel/rod) and Jadelle® or Sino Implant (II)® (75 mg levonorgestrel/rod x 2 rods). The contraceptive failure rate with implants is reported below 1%,[8,9] making them the most effective reversible contraceptive method available.

Because of pharmacokinetic data regarding potential drug-drug interactions between ART and certain hormonal contraceptives, current national guidelines often advise dual use of condoms or alternative contraceptive methods.[10–12] Hormonal contraceptives, including etonogestrel and levonorgestrel, are metabolized by hepatic cytochrome P450 (CYP450) enzymes, specifically by CYP3A4.[13] Antiretrovirals, including protease inhibitors, non-nucleoside reverse transcriptase inhibitors (NNRTIs), such as nevirapine and efavirenz, and cobicistat-boosted agents, influence the activity of CYP3A4 and 2B6 enzymes; NNRTIs are specifically implicated in CYP3A4 induction.[13] Recently, two pharmacokinetic studies found reduced etonogestrel or levonorgestrel concentrations in women on implants and efavirenz-based ART.[14,15]

The ultimate significance of any drug-drug interaction remains unclear as few studies have examined contraceptive failure rates with efavirenz and implant use. Some case reports,[16–19] two retrospective studies,[20,21] and a pharmacokinetic study from Uganda[22] document contraceptive failures among women using efavirenz-based ART and implants, though another study from Brazil found no pregnancies among its implant and ART users.[23] In light of the limited existing literature and on-going debate regarding implant use among women on efavirenz-based ART, we sought to determine if pregnancy rates differ among HIV-positive women enrolled in care in Kenya using various combinations of contraceptive methods and ART regimens. We hypothesized that there would not be a significant difference in the pregnancy rates among women using implants and nevirapine- vs. efavirenz-based ART.

METHODS

Overview of study design, site and population

We conducted a retrospective, longitudinal cohort analysis of 24,560 HIV-positive women from 15 to 45 years of age enrolled at HIV health facilities in Kisumu, Homabay, and Migori counties in western Kenya supported by Family AIDS Care & Education Services (FACES). FACES is a President's Emergency Plan for AIDS Relief-sponsored program jointly managed by the University of California San Francisco (UCSF) and the Kenya Medical Research Institute (KEMRI).[24] See supplemental text for additional background information on the services FACES provides. The Committee on Human Research at UCSF, the Ethical Review Committee at KEMRI, and the U.S. Centers for Disease Control and Prevention approved the use of de-identified patient information for research purposes.

Participant information was extracted from the FACES electronic medical record system, OpenMRS, from clinical visits from all women HIV-positive aged 15–45 years dating between January 1, 2011 and December 31, 2013 from the 19 FACES-supported HIV health facilities with OpenMRS. No exclusion criteria were applied. These facilities follow the Kenya Ministry of Health guidelines for frequency of visits, which is generally every 1–3 months for patients on ART and every 6 months for those not on ART.[25] Women contributed observation time starting with a visit after January 1, 2011 until their last documented visit or end of the study period. An observation in the cohort was defined by a change in exposure categories; therefore, more than one clinical visit may have contributed

data to the same observation. See supplemental text for additional information on data collection and quality control measures utilized by FACES.

Definitions of variables

Primary Exposures—Contraceptive method was documented at each clinic visit and then categorized as: 1) implants, which included information on specific types, such as Implanon® or Jadelle®; 2) depomedroxyprogesterone acetate (DMPA); 3) combined oral contraceptives (COCs) or oral contraceptive pills (OCPs); 4) other more effective contraceptive methods (MEC; intrauterine devices (IUDs) and permanent methods); 5) less effective contraceptive methods (LEC; male and female condoms and "natural" contraceptive methods, such as withdrawal and rhythm); or 6) no contraceptive method. When multiple methods were documented at the same visit, the contraceptive method was assigned according to the following hierarchy: MEC over implants over DMPA over COCs or OCPs over LEC.

ART regimen was documented at each clinic visit and then categorized as: 1) efavirenz-based ART; 2) nevirapine-based ART; 3) lopinavir/ritonavir-based ART; or 4) no ART. We defined an "ART regimen" as at least a three-drug combination of antiretrovirals; women exposed to single-dose nevirapine or zidovudine monotherapy for prevention of mother-to-child transmission were categorized as being on "no ART."

Since we were interested in the interaction of contraceptive method and ART regimen on pregnancy rates, we captured exposure based on a combination of one of six contraceptive and four ART categories, resulting in 24 total combination categories. This categorization could be time-dependent, with women switching categories when they changed contraceptive method, ART regimen, or both. Duration on a combined category was calculated in days from the earliest record until the participant switched a category, became pregnant, or was censored at her last visit during the study period. If missing, contraceptive method and ART regimen were imputed from the most recent previous documented record. Of note, implant removal dates were not recorded in OpenMRS so when a participant was recorded to be on a different contraceptive method, except for condoms, we assumed implant discontinuation.

Outcome—Our primary outcome was incident pregnancy diagnosed clinically, through self-reports or presenting while gravid; biochemical tests are not routinely used to confirm clinically suspected pregnancies in this setting. We estimated the date of incident pregnancy as the date of likely conception based on reports of last menstrual period or estimated delivery date. For 303 of 3337 (9.1%) pregnancies we could not determine the date of likely conception based on these two criteria. For these observations, we used the median time of documented clinical pregnancy to the date of likely conception derived from the remainder of the cohort (4·2 months) and imputed this value for those missing the date of likely conception. We tracked reported pregnancies until nine months after the end of our observation period, to capture pregnancies that may have occurred within our study period.

Women were censored: 1) for the duration of a full-term pregnancy (38 weeks) plus the subsequent 12 weeks for lactational amenorrhea (50 weeks total), after which they were able

to re-enter the cohort; or 2) at last visit during the study period. We allowed for multiple pregnancies to occur. For 8,847 of 94,162 (9.4%) observations that were missing pregnancy status, we assumed these women were not pregnant.

Covariates—Based on previously identified factors associated with the exposures, outcome, or both,[26–28] we considered the following covariates for inclusion in the multivariable models: baseline age, educational attainment, marital status, number of living children, HIV-positive status disclosure to partner, and time-dependent percent use of condoms, body mass index (BMI), World Health Organization (WHO) stage of HIV disease, CD4 cell count, self-reported ART adherence, and use of anti-tuberculosis medications during the observation period (see supplemental text for definitions of each covariate).

Statistical analysis

Frequencies and proportions are presented for categorical variables, mean and standard deviation (SD) for normally distributed variables, and median and interquartile range (IQR) for non-normally distributed continuous variables. We used multiple imputation by iterative chained equations to account for missing information. We used unadjusted and adjusted Poisson models with robust standard errors to estimate incident pregnancy rates per 100 woman-years (w-y) for each exposure combination category. Adjusted incident rates and rate ratios (aIRR) are conditional and evaluated at the mean of all the covariates. We selected covariates on *a priori* grounds and included them in the final model regardless of the *p*-values in the bivariate analysis; however, due to lack of variation, self-reported ART adherence was excluded from the final model. To reduce skewness, we used $\log_{10}$ and square root transformations of BMI and CD4 cell count, respectively. To better meet the assumptions of linearity in our adjusted models, we added quadratic terms of all continuous variables.

We conducted three sensitivity analyses on the original dataset by placing more stringent criteria on both the definitions of contraceptive and ART exposure and pregnancy. If a woman was recorded being on a long-acting contraceptive method (implants, IUDs, or permanent methods), followed by another contraceptive method or no method for one observation, and then back on the prior long-acting contraceptive method, we considered the recording of the intermediate contraceptive method an error and replaced it with the first contraceptive method. If a woman was noted to switch from another contraceptive method or no method to a long-acting contraceptive method, we required two consecutive visits documenting its use to consider it a true switch. Similarly, if another ART regimen was "sandwiched" between two identical ART regimens, we considered it an error and replaced it with the first ART regimen. Pregnancies were verified through the use of two data points, either through two visit dates recording a pregnancy or one visit date where both a pregnancy as well as an estimated delivery date were noted. Finally, we conducted a fourth sensitivity analysis by dropping the 8,847 of 94,162 (9.4%) observations missing pregnancy status. Data were prepared using SAS version 9·3 (Cary, North Carolina, USA) and analyses were conducted using STATA version 12·1 (College Station, Texas, USA).

Role of funding source

The funders had no involvement in the study design, data collection and analysis, interpretation of results, and writing or publication of this report other than obtaining clearance from the Centers for Disease Control and Prevention-Kenya officials prior to manuscript submission.

RESULTS

General characteristics of overall cohort

24,560 women contributed 94,162 observations to the analysis, representing 37,635 w-y of observation. The women contributed a median of 11 (IQR 5–17) visits, 3 (IQR 2–5) observations, and 18 (IQR 5–30) months of person-time during the study period. Women had a median age of 31 (IQR 26–36) years, 18% had completed primary schooling or a higher level of education, 44% were married or co-habiting, and participants had a median of two living children (IQR 1–3). The mean participant BMI was 22 kg/m^2 (SD ±4), 66% of the women were in WHO clinical stages 1 or 2, and 44% had CD4 counts ≥500 $cells/mm^3$ proximal to the start of the observation period (table 1).

In this cohort, implants were used in 6,232 (6·6%), DMPA in 16,363 (17·4%), COC/OCPs in 2,495 (2·7%), other more effective contraception in 2,811 (3·0%), less effective contraception in 34,444 (36·6%), and no contraceptive method in 30,934 (32·9%) of the observations. Nevirapine-based ART was used in 46,132 (49·0%), efavirenz-based ART in 13,573 (14·4%), lopinavir/ritonavir-based ART in 3,649 (3·9%), and no ART in 30,494 (32·4%) of the observations (table 1 and supplemental table 1).

Pregnancy incidence

Overall, 3,337 incident pregnancies occurred, including 157 multiple pregnancies, resulting in a pregnancy rate of 8·9 per 100 w-y (95% CI 8·6–9·2). Among implant users, adjusted pregnancy incidence was 1·4 (95% CI 1·1–1·8) per 100 w-y. Stratified by ART regimen, adjusted rates for nevirapine- and efavirenz-based ART users were 1·1 (95% CI 0·72–1·5) and 3·3 (95% CI 1·8–4·8) per 100 w-y, respectively (aIRR 3·0, 95% CI 1·3–4·6; table 2).

Adjusted pregnancy incidence for etonogestrel and levonorgestrel implant users were 1·4 (95% CI 1·0–1·8) and 1·4 (95% CI 0·82–2·0) per 100 w-y, respectively. Among etonogestrel implant users, pregnancy incidence for nevirapine- and efavirenz-based ART users were 1·2 (95% CI 0·67–1·6) and 3·0 (95% CI 1·4–4·7) per 100 w-y, respectively (aIRR 2·6, 95% CI 0·89–4·3). Among levonorgestrel implant users, pregnancy incidence for nevirapine- and efavirenz-based ART users were 1·0 (95% CI 0·38–1·7) and 4·2 (95% CI 0·84–7·5) per 100 w-y, respectively (aIRR 4·1, 95% CI 0–8·2; supplemental table 2).

Among the overall cohort, adjusted pregnancy rates for women on all other contraceptive methods, except for IUDs and permanent methods, were 3·1–4·1 times higher than with implants. Among efavirenz-based ART users, adjusted pregnancy rates on all other contraceptive methods, except for IUDs and permanent methods, were 1·6–2·8 times higher than with implants (tables 2 and 3). For example, among DMPA users, pregnancy rates for

those on nevirapine- and efavirenz-based ART were 4·5 (95% CI 3·7–5·2) and 5·4 (95% CI 4·0–6·8) per 100 w-y, respectively, and among COC/OCPs users, pregnancy rates for women on nevirapine- and efavirenz-based ART were 5·8 (95% CI 4·0–7·6) and 9·3 (95% CI 4·6–14·0) per 100 w-y, respectively (table 2). However, among IUD and permanent methods users, pregnancy rates for those on nevirapine- and efavirenz-based ART were 0·92 (95% CI 0·28–1·6) and 0·93 (0–2·2) per 100 w-y. Supplemental table 3 contains the unadjusted and adjusted pregnancy rates ratios for the covariates. The sensitivity analyses did not significantly alter our original adjusted rate ratios for incident pregnancy (supplemental tables 4–7).

DISCUSSION

In the largest study to date to examine incident pregnancies in nearly 25,000 HIV-positive women from western Kenya using various combinations of contraceptive methods and ART, we found that among women using either etonogestrel or levnorgestrel implants, adjusted pregnancy rates were three times higher among those on efavirenz- versus nevirapine-based ART. However, implant use was associated with substantially lower pregnancy rates than use of alternative contraceptive methods other than IUDs and permanent methods, even among women on efavirenz-based ART.

Implants are among the most effective forms of contraception available,[29] and the most readily available, reversible, and effective form of contraception in western Kenya. Due to the implant's high effectiveness, despite likely drug-drug interactions reducing its efficacy in women on efavirenz, women using implants and efavirenz-based ART still experienced lower pregnancy rates than women on other readily-available contraceptives in our study. For example, among women using efavirenz-based ART, those reporting use of DMPA had 1·6 times higher incident pregnancies compared to those using implants. Contraceptive failure with DMPA is more common than with implants since proper DMPA use requires repeat injections on a timely basis, and, therefore, DMPA is more user dependent than maintaining a subdermal implant. As such, some women and their providers are likely to still choose implants for contraception while on efavirenz-based ART. HIV programs and providers need to actively engage women in conversations regarding potential risks and benefits of each contraceptive method, as greater choice exists with options for contraceptives than ART regimens in resource-limited settings. Counseling and messaging around implant and efavirenz use needs to be comprehensive and include effectiveness data regarding implants compared to other contraceptive methods. Certainly, further research on strategies to optimize the implant's efficacy, such as shortening the duration of the implant use, is urgently needed. However, until additional effective contraceptive or ART alternatives are widely available to HIV-positive women, we caution against policies excluding implants as a choice for women using efavirenz-based ART.

Few contraceptives as efficacious as implants exist in resource-limited settings for women prescribed efavirenz-based ART, the currently recommended first-line therapy in sub-Saharan Africa.[4] Our data show that, even among women using efavirenz-based ART, those using other hormonal contraceptives face up to three times higher pregnancy rates than women using implants. Permanent methods are not viable options for women desiring

reversible contraception. Though IUDs, particularly non-hormonal IUDs, are a compelling long-acting reversible alternative to implants, they are seldom used in sub-Saharan Africa, for reasons that include patient and provider preferences and misconceptions[30] and lack of provider training, sufficient space, or privacy for insertion. In settings such as western Kenya, DMPA is the leading alternative to implants for more effective contraception, which requires the user to return every three months for repeat injections. Given this high level of user action requirement, HIV-positive women on DMPA may face higher risks of non-compliance and, hence, incident pregnancies. Oral contraceptives need to be taken daily, are therefore limited by adherence issues, and may be liable to similar drug-drug interactions as implants and efavirenz.[13]

Efavirenz-based ART is not only the WHO recommended first-line therapy for resource-limited countries, it is also the first single-pill combination available in these settings, which has marked advantages in facilitating adherence.[31] Nevirapine-based ART has a less favorable side effect and resistance profile and has more limited virological efficacy than efavirenz.[32,33] We observed lower incident pregnancies among women on implants in the lopinavir/ritonavir- vs. efavirenz-based ART or no ART groups, a finding that appears consistent with a pharmacokinetic study where etonogestrel concentrations among implant users were higher in women using lopinavir/ritonavir-based ART vs. no ART.[14] However, with too few women contributing person-time to the lopinavir/ritonavir-based ART categories in our analysis, we cannot draw strong conclusions. Lopinavir/ritonavir-based ART is also a less attractive alternative than newer generation protease inhibitors due to its side effect profile, virological efficacy, and pill burden.[34,35] Atazanavir/ritonavir-based ART is now approved as second line therapy in some resource-limited settings such as Kenya,[36] and may be a better alternative to efavirenz-based ART for women wishing to use implants. Integrase-inhibitors, such as raltegravir, are becoming available in the private sector in resource-limited settings and may be viable alternatives as well. However, further clinical and pharmacokinetic studies need to evaluate these newer ART regimens in combination with implants.

Although our study's sample size is large and we followed women for up to three years, our study has several limitations. First, we were limited in our accounting of contraceptive use to the electronic records available from clinic visits, where it is possible that clinicians did not accurately document contraceptive initiation, continuation, or discontinuation. Second, since we were unable to determine contraceptive initiation dates, we could not ensure that the pregnancies fell within the efficacy periods of each contraceptive method nor determine at which point in the life of the implant women became pregnant. Third, the rates of pregnancy with more effective contraceptive methods in our study are slightly higher than those published in the literature,[29] though our overall incident pregnancy rate of 8.9 pregnancies per 100 w-y is within the range of rates reported previously among women with or at high risk for HIV.[37–39] Some women may have falsely reported using a contraceptive method given the social desirability of using contraception and difficulties in discussing fertility intentions with providers.[40] This difference may also be due to data quality issues with programmatic data, such as misclassification of contraceptive methods or pregnancies due to data entry errors; however, our sensitivity analyses, attempting to correct for data entry errors, did not uncover differential biases by contraceptive method or ART regimen.

Fourth, we do not know pregnancy intention, though one can safely assume that women using long-acting contraception intend to avoid pregnancy. Fifth, we were not able to account for certain covariates, such as measures of sexual activity or ART adherence.

In conclusion, our study supports the growing evidence that efavirenz-based ART may reduce the effectiveness of contraceptive implants, though implants continue to remain one of the most effective forms of reversible contraception, even in combination with efavirenz-based ART. As such, we advocate for offering HIV-positive women all currently available contraceptive methods, including implants, and counseling them on the failure rates when used in combination with efavirenz-based ART. More prospective and pharmacokinetic studies, which better account for contraceptive and ART adherence and pregnancy ascertainment, are urgently needed to further explore the interactions between hormonal contraceptives and ART and guide the use and availability of newer single-pill combination ART regimens that are effective, well tolerated, and do not reduce contraceptive effectiveness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Panel: Research in context

Evidence before this study

We searched PubMed for articles published in English between January 1, 1950 and August 18, 2015 with a combination of the following terms: “efavirenz”, “antiretrovirals”, “antiretroviral therapy”, “contraceptive implants”, “implants”, and “contraceptive failure.” We also included pertinent published abstracts from leading HIV conferences. We found four case reports, two pharmacokinetic studies, and three clinical studies. The four case reports noted six women who were on contraceptive implants and then initiated efavirenz-based ART and experienced unintended pregnancies. In the two pharmacokinetic studies, the implant hormone serum concentrations were approximately 40–60% lower in women using efavirenz-based ART versus no ART. In one of the two studies, three women became pregnant within the first 48 weeks of follow-up while using efavirenz-based ART and implants. The first clinical study from Brazil inserted Implanon® in 79 HIV-positive women and followed them for three years and found no pregnancies in the group. The second clinical study from Swaziland conducted a retrospective chart review of 332 Jadelle® and ART users and found that all 15 (12·4%) of the pregnancies were among those using efavirenz-based ART. The last clinical study combined data from three longitudinal studies in Africa and found that among women using implants, no pregnancies occurred among those on nevirapine-based ART, one pregnancy among those on efavirenz-based ART (6·0 pregnancies/100 w-y), and seven pregnancies among those on no ART (1·4 pregnancies/100 w-y).

Added value of this study

In this large cohort analysis, we found that among women using implants, those using efavirenz-based ART faced three times higher pregnancy rates than women using nevirapine-based ART. However, among women using efavirenz-based ART, those using other contraceptive methods, except for IUDs and permanent methods, faced up to three times higher pregnancy rates than women using implants.

Implications of all the available evidence

While our study supports the growing evidence that efavirenz-based ART may reduce the effectiveness of contraceptive implants, implants continue to remain the most effective and readily available form of reversible contraception in resource-limited settings, including in combination with efavirenz-based ART. HIV programs, providers, and ministries of health should continue to offer HIV-positive women the choice of selecting concomitant implants and efavirenz-based ART until better contraceptive and ART alternatives are shown to be more effective and readily available.

Table 1

Baseline characteristics of cohort (n=94,162 observations)

Variable	N (%)
Contraceptive method	
Implant	6,232 (6.6%)
Etonogestrel implants (e.g. Implanon®)	1,512 (24.3%)
Levonorgestrel implants (e.g. Jadelle®)	4,704 (75.5%)
Depomedroxyprogesterone acetate (DMPA)	16,363 (17.4%)
Combined oral contraceptives or oral contraceptive pills (COCs or OCPs)	2,495 (2.7%)
Other more effective contraception	2,811 (3.0%)
Intrauterine devices (IUDs)	720 (25.6%)
Permanent methods	2,079 (74.0%)
Less effective contraception (condoms, “natural” methods)	34,444 (36.6%)
No contraceptive method	30,934 (32.9%)
Missing	883 (0.94%)
Antiretroviral therapy (ART) regimen	
Nevirapine-based ART	46,132 (49.0%)
Efavirenz-based ART	13,573 (14.4%)
Lopinavir/ritonavir-based ART	3,649 (3.9%)
No ART	30,494 (32.4%)
Missing	314 (0.33%)
Age at start of observation period, median	31 (IQR 26–36)
Education level*	
None	247 (1.0%)
Some primary school	8,943 (36.4%)
Completed primary school	742 (3.0%)
Some secondary school	2,912 (11.9%)
Completed secondary school	191 (0.78%)
Some college or university	592 (2.4%)
Missing	10,933 (44.5%)
Marital Status*	
Married or cohabitating	10,702 (43.6%)
Single, widowed, or divorced	6,870 (28.0%)
Missing	6,988 (28.5%)
Number of living children (≤14 years of age), median*	2 (IQR 1–3)
Had disclosed HIV status to main sexual partner at the time of enrollment in care*	
Yes	10,298 (41.9%)
No	7,402 (30.1%)
Missing	6,860 (27.9%)

Variable	N (%)
Self-reported ART adherence closest to start of observation period	
"Good"	59,366 (93.2%)
"Fair" or "Poor"	1,073 (1.7%)
Missing	3,229 (5.1%)
Percent usage of male or female condoms used noted at each visit out of total visits during observation period, median	33% (IQR 0–100%)
Duration in care, since enrollment to start of observation period (in years), median	1.2 (IQR 0.25–2.7)
Total number of visits, median*	11 (IQR 5–17)
Total number of observations, median*	3 (IQR 2–5)
Total woman-time contributed to cohort (in months), median*	18 (IQR 5–30)
BMI, mean (kg/m^2)	22.3 (SD 4.0)
WHO stage closest to start of observation period (within +/− one year)	
1	28,959 (30.8%)
2	33,495 (35.6%)
3	25,949 (27.6%)
4	5,646 (6.0%)
Missing	113 (0.12%)
CD4 cell count closest to start of observation period (within +/− one year), median (cells/mm^3)	463 (IQR 305–657)
CD4 cell count category closest to start of observation period (within +/− one year, cells/mm^3)	
0–49	2,486 (2.6%)
50–199	9,051 (9.6%)
200–349	17,963 (19.1%)
350–499	21,346 (22.7%)
≥500	40,918 (43.5%)
Missing	2,398 (2.6%)
Use of anti-tuberculosis drugs during observation period	3,453 (3.7%)
Active tuberculosis treatment	2,744 (79.5%)
Latent tuberculosis treatment	709 (20.5%)

* These characteristics are calculated by number of women, instead of observations (n=24,560 women)

Table 2

Pregnancy incidence per 100 women-years, grouped by contraceptive method and antiretroviral therapy (ART) regimen combinations

Contraceptive method and ART regimen combinations	Number of pregnancies	Women-years of follow-up	Unadjusted pregnancy rate[§] per 100 women-years (95% CI)	Adjusted pregnancy rate[#] per 100 women-years (95% CI)	Adjusted pregnancy rate ratios[#] per 100 women-years (95% CI)
Implant	86	3047	3.0 (2.3–3.6)*	1.4 (1.1–1.8)**	
Nevirapine-based ART	34	1648	2.2 (1.4–2.9)	1.1 (0.72–1.5)	Ref.
Efavirenz-based ART	21	375	5.8 (3.3–8.4)	3.3 (1.8–4.8)	3.0 (1.3–4.6)
Lopinavir/ritonavir-based ART	2	126	1.7 (0–4.1)	0.95 (0–2.3)	0.86 (0–2.1)
No ART	29	897	3.4 (2.1–4.6)	1.3 (0.82–1.8)	1.2 (0.60–1.8)
Depomedroxyprogesterone acetate (DMPA)	631	7406	8.9 (8.2–9.6)*	4.3 (3.7–4.9)**	
Nevirapine-based ART	320	3983	8.4 (7.5–9.3)	4.5 (3.7–5.2)	Ref.
Efavirenz-based ART	76	842	9.4 (7.3–11.5)	5.4 (4.0–6.8)	1.2 (0.91–1.5)
Lopinavir/ritonavir-based ART	20	299	7.2 (4.1–10.3)	4.5 (2.5–6.5)	1.0 (0.56–1.5)
No ART	215	2275	9.8 (8.5–11.0)	3.9 (3.2–4.6)	0.87 (0.72–1.0)
Combined oral contraceptives or oral contraceptive pills (COCs or OCPs)	95	850	11.7 (9.4–14.1)*	5.8 (4.5–7.2)**	
Nevirapine-based ART	46	443	10.9 (7.8–14.0)	5.8 (4.0–7.6)	Ref.
Efavirenz-based ART	17	115	15.4 (8.2–22.6)	9.3 (4.6–14.0)	1.6 (0.69–2.5)
Lopinavir/ritonavir-based ART	4	32	15.4 (0.54–30.2)	7.6 (0.18–14.9)	1.3 (0–2.6)
No ART	28	260	11.1 (6.9–15.3)	4.7 (2.9–6.6)	0.81 (0.43–1.2)
Other more effective contraception (IUDs, permanent)	17	1327	1.3 (0.69–1.9)*	1.1 (0.56–1.6)**	
Nevirapine-based ART	8	767	1.1 (0.33–1.8)	0.92 (0.28–1.6)	Ref.
Efavirenz-based ART	2	217	0.93 (0–2.2)	0.93 (0–2.2)	1.0 (0–2.6)
Lopinavir/ritonavir-based ART	1	68	1.6 (0–4.6)	1.7 (0–5.1)	1.9 (0–5.8)
No ART	6	273	2.3 (0.47–4.1)	1.5 (0.29–2.7)	1.6 (0–3.3)
Less effective contraception (condoms, "natural" methods)	1739	14028	13.1 (12.5–13.7)*	5.6 (4.6–6.6)**	
Nevirapine-based ART	957	8113	12.5 (11.7–13.3)	5.7 (4.7–6.8)	Ref.
Efavirenz-based ART	202	2077	10.1 (8.7–11.5)	5.4 (4.2–6.5)	0.94 (0.79–1.1)

Contraceptive method and ART regimen combinations	Number of pregnancies	Women-years of follow-up	Unadjusted pregnancy rate[§] per 100 women-years (95% CI)	Adjusted pregnancy rate[#] per 100 women-years (95% CI)	Adjusted pregnancy rate ratios[#] per 100 women-years (95% CI)
Lopinavir/ritonavir-based ART	67	570	12.7 (9.7–15.7)	6.6 (4.7–8.5)	1.2 (0.87–1.4)
No ART	513	3262	16.6 (15.1–18.0)	5.4 (4.4–6.5)	0.95 (0.84–1.1)
No contraceptive method	762	10837	7.4 (6.8–7.9)[*]	4.8 (3.9–5.8)[**]	
Nevirapine-based ART	351	5681	6.5 (5.8–7.2)	4.7 (3.7–5.6)	Ref.
Efavirenz-based ART	98	2111	4.8 (3.8–5.7)	4.0 (3.0–5.1)	0.86 (0.67–1.1)
Lopinavir/ritonavir-based ART	29	480	6.4 (4.0–8.8)	5.2 (3.0–7.4)	1.1 (0.68–1.6)
No ART	284	2555	11.6 (10.2–13.0)	5.3 (4.2–6.5)	1.1 (0.96–1.3)
Overall	**3,330**[¶]	**37,495**	**8.9 (8.6–9.2)**		

[§]Stratified rates by ART regimen calculated with an unadjusted Poisson model that included an interaction term between contraceptive method and ART regimen.

[#]Stratified rates by ART regimen calculated with an adjusted Poisson model that included an interaction term between contraceptive method and ART regimen and covariates adjusted for included age, educational attainment, marital status, number of living children, HIV-positive status disclosure to partner, and time-dependent covariates of percent use of condoms, body mass index (BMI), World Health Organization (WHO) stage, CD4 cell count, and use of anti-tuberculosis medications during the observation period.

[*]Unadjusted rates by contraceptive method calculated with an unadjusted Poisson model without ART regimen or an interaction term between contraceptive method and ART regimen.

[**]Adjusted rates by contraceptive method calculated with ART regimen (but not an interaction term between contraceptive method and ART regimen) and covariates adjusted for included age, educational attainment, marital status, number of living children, HIV-positive status disclosure to partner, and time-dependent covariates of percent use of condoms, body mass index (BMI), World Health Organization (WHO) stage, CD4 cell count, and use of anti-tuberculosis medications during the observation period.

[¶]Seven pregnancies occurred in observations where the contraceptive method was missing (in seven different women).

Table 3

Pregnancy incidence per 100 women-years for each contraceptive method and antiretroviral therapy (ART) regimen

Variable	Unadjusted pregnancy rate[§] per 100 women-years (95% CI)	Adjusted pregnancy rate[#] per 100 women-years (95% CI)	Adjusted pregnancy rate ratios[#] per 100 women-years (95% CI) (model without an interaction term)	Adjusted pregnancy rate ratios[¶] per 100 women-years (95% CI) (model with an interaction term)
Contraceptive method				
Implant	3.0 (2.3–3.6)	1.4 (1.1–1.8)	Ref.	Ref.
Depomedroxyprogesterone acetate (DMPA)	8.9 (8.2–9.6)	4.3 (3.7–4.9)	3.1 (2.4–3.8)	1.6 (0.83–2.5)
Combined oral contraceptives or oral contraceptive pills (COCs or OCPs)	11.7 (9.4–14.1)	5.8 (4.5–7.2)	4.1 (2.9–5.4)	2.8 (0.97–4.7)
Other more effective contraception (IUDs, permanent)	1.3 (0.69–1.9)	1.1 (0.56–1.6)	0.78 (0.37–1.2)	0.29 (0–0.71)
Less effective contraception (condoms, “natural” methods)	13.1 (12.5–13.7)	5.6 (4.6–6.6)	4.0 (3.0–4.9)	1.6 (0.86–2.4)
No contraceptive method	7.4 (6.8–7.9)	4.8 (3.9–5.8)	3.4 (2.6–4.3)	1.2 (0.62–1.8)
Antiretroviral therapy (ART) regimen				
Nevirapine-based ART	8.8 (8.3–9.2)	4.4 (3.8–5.1)	Ref.	Ref.
Efavirenz-based ART	7.5 (6.8–8.2)	4.5 (3.7–5.3)	1.0 (0.90–1.1)	3.0 (1.3–4.6)
Lopinavir/ritonavir-based ART	8.4 (6.9–9.9)	5.0 (3.8–6.1)	1.1 (0.91–1.3)	0.86 (0–2.1)
No ART	11.8 (11.1–12.5)	4.3 (3.6–5.0)	0.97 (0.89–1.1)	1.2 (0.60–1.8)

[§]Calculated with an unadjusted Poisson model that included ART regimen for contraceptive method and contraceptive method for ART regimen (but not an interaction term).

[#]Calculated with an adjusted Poisson model that included contraceptive method and ART regimen (but not an interaction term between contraceptive method and ART regimen) and covariates adjusted for included age, educational attainment, marital status, number of living children, HIV-positive status disclosure to partner, and time-dependent covariates of percent use of condoms, body mass index (BMI), World Health Organization (WHO) stage, CD4 cell count, and use of anti-tuberculosis medications during the observation period.

[¶]Calculated with an adjusted Poisson model that included an interaction term between contraceptive method and ART regimen and covariates adjusted for included age, educational attainment, marital status, number of living children, HIV-positive status disclosure to partner, and time-dependent covariates of percent use of condoms, body mass index (BMI), World Health Organization (WHO) stage, CD4 cell count, and use of anti-tuberculosis medications during the observation period. The reference group for ART regimen is efavirenz-based ART when generating the rate ratios for the contraceptive methods. The reference group for contraceptive method is implants when generating the rate ratios for the ART regimens.