



Original research article

Increasing body mass index or weight does not appear to influence the association between efavirenz-based antiretroviral therapy and implant effectiveness among HIV-positive women in western Kenya

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ABSTRACT

Objective: Our objective was to evaluate if increasing body mass index (BMI) or weight influences the association between efavirenz-based antiretroviral therapy (ART) and implant effectiveness.

Study design: We conducted a secondary cohort analysis of HIV-positive women aged 15 to 45 years enrolled in HIV care in western Kenya using an implant from January 2011 to December 2015. Implant use, ART regimen and weight were documented at each clinic visit and height at enrollment. We categorized BMI as underweight, normal weight, overweight or obese, and weight as <70 kg or ≥70 kg. Our primary outcome was incident pregnancy diagnosed clinically. We used crude and adjusted Poisson models with robust standard errors to account for covariates and repeated observations to estimate adjusted incident rate ratios (aIRRs).

Results: In this analysis, 12,960 women contributed a total of 11,285 woman-years of observation time while using an implant, with a median of 6.6 months. The aIRRs comparing efavirenz- to nevirapine-based ART groups did not increase as BMI increased; the aIRRs were 2.0 (1.1–3.6) for underweight, 1.9 (1.5–2.5) for normal, 3.1 (1.6–6.0) for overweight and 2.1 (0.6–6.9) for obese women. The aIRRs comparing efavirenz- to nevirapine-based ART groups did not increase as weight increased; the aIRRs were 2.0 (1.6–2.6) for weight <70 kg and 2.1 (1.0–4.5) for weight ≥70 kg.

Conclusion: Higher BMI or weight did not appear to modify the relationship between efavirenz use and implant effectiveness.

Implications: Programs should not recommend differential counseling for women with higher BMI or weight who concomitantly use implants and efavirenz.

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1. Introduction

Women of reproductive age in sub-Saharan Africa, including the 13 million women living with HIV, have increasing access to hormonal contraceptives [1–4]. The World Health Organization (WHO) now recommends initiation of life-long antiretroviral therapy (ART) for HIV treatment, and efavirenz-based ART is the recommended first-line regimen [5]. Thus, the concomitant use of hormonal contraceptives and ART is common for HIV-positive women in sub-Saharan Africa.

Concomitant use of hormonal contraceptives and ART may, however, increase contraceptive failures. Drug–drug interactions between specific hormonal contraceptives and ART regimens may reduce the effectiveness of the hormonal contraceptive [6,7]. Specifically, increasing observational data now suggest that the effectiveness of contraceptive implants may be reduced by efavirenz-based ART [8,9]. These clinical studies are supported by pharmacokinetic data demonstrating reduced plasma levonorgestrel and etonogestrel concentrations in women concomitantly using implants and efavirenz-based ART [10–13].

Conflicting findings exist among studies examining a reduction in certain hormonal contraceptive method effectiveness with increasing body mass index (BMI) or weight [14,15]. Obesity may influence

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contraceptive efficacy in several ways, including influencing behavior as well as pharmacokinetics of steroid hormones [16]. For example, obesity results in a higher volume of distribution of steroid hormones, potentially lowering the hormone plasma concentrations. While it largely appears that higher BMI or weight does not significantly influence implant effectiveness in the general population, higher BMI or weight could potentially influence efavirenz-based ART's impact on implant effectiveness. Therefore, we aimed to determine if increasing BMI or weight modifies the association between efavirenz use and incident pregnancies among implant users.

2. Methods

2.1. Study site and population

We conducted a secondary analysis of a longitudinal cohort of HIV-positive women from 15 to 45 years of age followed at two HIV treatment programs in western Kenya affiliated with the East Africa International Epidemiology Databases to Evaluate AIDS (EA-IeDEA). Specifically, two President's Emergency Plan for AIDS Relief-sponsored HIV treatment programs, Academic Model Providing Access to Healthcare (AMPATH) and Family AIDS Care & Education Services (FACES), which support care for approximately 65,000 and 43,000 HIV-positive individuals in western Kenya, respectively, contributed data to this analysis.

Clinical and demographic data were collected at baseline and follow-up visits utilizing standardized, paper instruments, which trained data clerks transcribed into an electronic medical record system supported by an OpenMRS platform. Only data from visits with clinician notes of implant, whether levonorgestrel or etonogestrel, use between January 1, 2011, and December 31, 2015, were included in this analysis. The first observation period for a woman began on the date of the woman's first visit documenting use of an implant on or after January 1, 2011 (which may not necessarily be at the time of implant insertion or at the time of enrollment in HIV care). An observation period ended when the woman changed her ART regimen category, stopped using an implant (or was noted to be using another contraceptive method), was noted to be pregnant or reached the end of the study period. Thus, each observation could span multiple clinical visits. A woman with only one documented visit during our study period would not contribute data to this analysis. For periods not covered by clinical visits in our analysis, we assume that the data are missing at random. Our study made no efforts to track women lost to follow-up in clinical care.

The Human Subjects Division at University of Washington, Indiana University Institutional Review Board, Committee on Human Research at University of California, San Francisco, Institutional Research and Ethics Committee at Moi University, Ethical Review Committee at Kenya Medical Research Institute, and U.S. Centers for Disease Control and Prevention approved this research.

2.2. Variable definitions

2.2.1. Exposures

The ART regimen was documented at each visit and was categorized as: (1) efavirenz-based ART; (2) nevirapine-based ART; (3) protease inhibitor-based ART; (4) nucleos(t)ide reverse transcriptase inhibitors; (5) a combination ART regimen containing two or more of efavirenz, nevirapine, or protease inhibitors; or (6) no ART. We defined an "ART regimen" as at least a three-drug combination of antiretrovirals. Due to few person-years in ART regimen categories 3 through 5, observations in these categories were dropped before conducting this analysis. We chose the use of nevirapine-based ART as the reference category for ART comparisons, as the alternative option of no ART is not clinically meaningful in the era of universal ART use.

Weight was documented at each visit and the value closest to the start of observation period was used, and height was documented at least during enrollment in care. BMI was calculated using weight in kilograms divided by height in meters² at the start of each observation period. BMI was categorized according to the WHO classification as (1) underweight for BMI <18.5, (2) normal weight for BMI ≥18.5 but <25, (3) overweight for BMI ≥25 and <30 or (4) obese BMI ≥30. Weight was categorized as (1) <70 kg or (2) ≥70 kg, and for a sensitivity analysis, we categorized weight as (1) <50 kg, (2) 50–59 kg, (3) 60–69 kg or (4) ≥70 kg. If weight was <30 kg or height was <100 cm, we replaced the value with a backward and then forward imputation when such values were available. If the adjacent values were not available, we conducted multiple imputations to replace values of weight <30 kg or height <100 cm.

ART regimen, BMI and weight were all considered time-varying.

Table 1

General characteristics of women using implants and enrolled in HIV care in western Kenya, aged 15–45 years, 2011–2015

	N (%) of all woman-years or median (IQR) (n=11,285 w-y, among 12,960 women)
Age ^a (years), median (IQR)	30 (26–35)
Woman-months contributed while being on an implant, median (IQR)	6.6 (2.0–15.2)
ART regimen	
Nevirapine-based	5651 (50.1%)
Efavirenz-based	3270 (29.0%)
No ART	2364 (20.9%)
WHO clinical stage ^a	
1	5142 (45.6%)
2	3464 (30.7%)
3	2272 (20.1%)
4	400 (3.5%)
Missing	6 (<0.1%)
CD4 cell count ^a	
<50	88 (0.8%)
50–199	482 (4.3%)
200–349	1598 (14.2%)
350–499	2278 (20.2%)
≥500	5283 (46.8%)
Missing	1557 (13.8%)
Weight (kg) ^a	
<50	1766 (15.7%)
50–59	4919 (43.6%)
60–69	3387 (30.0%)
≥70	1212 (10.7%)
BMI (kg/cm ²) ^a	
<18.5 (underweight)	1238 (11.0%)
18.5–25 (normal weight)	7654 (67.8%)
25–30 (overweight)	1671 (14.8%)
≥30 (obese)	357 (3.2%)
Missing	365 (3.2%)
Use of anti-TB medications ^b	
None	10,537 (93.4%)
Active TB treatment	193 (1.7%)
Latent TB treatment	554 (4.9%)
Education level ^c	
Completed secondary	597 (5.3%)
Completed primary	2417 (21.4%)
Less	4624 (40.9%)
Missing	3647 (32.3%)
Marital status ^c	
Married or cohabitating	6768 (60.0%)
Other	2576 (22.8%)
Missing	1941 (17.2%)
Number of living children ^c	
0	871 (7.7%)
1	2576 (22.8%)
2	2436 (21.6%)
3	1478 (13.0%)
4 or more	1192 (10.6%)
Missing	2732 (24.2%)

^a At the start of the observation period.

^b At any point during the observation period.

^c At enrollment in care, except for marital status which varied over time only at AMPATH.

2.2.2. Outcome

Our primary outcome was incident pregnancy documented by a clinical diagnosis, through self-reports or presenting while gravid. Neither urine nor serum tests are routinely used to confirm clinically suspected pregnancies nor to rule out a pregnancy prior to implant placement 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 gestational age. Our dataset lacked the ability to confirm that an implant was in place at the time of pregnancy detection. In the overall cohort of all women followed in our dataset regardless of contraceptive method, for 3614 (29.3%) of 12,350 and 903 (8.7%) of 10,401 pregnancies at AMPATH and FACES, respectively, the data needed to calculate the date of likely conception were unavailable. For these pregnancies, we used the median time from the date of likely conception to the initial detection of the pregnancy derived from the remainder of the cohort (5.3 and 4.3 months at AMPATH and FACES, respectively) to impute the date of likely conception. In order to identify pregnancies that may have been conceived towards the end of our study period but not yet clinically detected, we tracked reported pregnancies for another 9 months past December 2015.

In the AMPATH dataset, women were censored for the duration of a pregnancy as indicated by the pregnancy outcome records (miscarriage, abortion, or preterm or term delivery). In the FACES dataset, however, such information was unavailable, and therefore, women who became pregnant were censored for 38 weeks from the date of likely conception. After the pregnancy, the women were considered to be at risk again and could contribute multiple pregnancies to our dataset. For the overall cohort of all women, there were 31,291 (12.3%) of 254,605 and 8847 (9.4%) of 94,162 observation periods at AMPATH and FACES, respectively, that had a missing pregnancy status. We assumed that the women were not pregnant during these periods.

2.2.3. Covariates

We a priori included age, marital status, number of living children under 14 years of age, education level, CD4 cell count, WHO clinical stage of HIV disease, use of anti-tuberculosis (TB) medications, calendar time and program (AMPATH or FACES) as adjusting variables. The number of living children, marital status and education level were documented at enrollment in care, though marital status was time-varying at AMPATH. Age, CD4 cell count, WHO clinical stage, use of TB medications and calendar time were time-varying, with average age calculated for each observation period, CD4 cell count and WHO clinical stage documented closest to the start of each period, and use of TB medications documented at any point during the period.

See publication of related analysis for greater information on the various variables [8].

2.3. Statistical analysis

We present frequencies and proportions for categorical variables and median and interquartile range (IQR) for continuous variables. We imputed missing data using multiple imputation by iterative chained equations, with all model covariates as predictors and, for time-varying variables, next and preceding nonmissing values as well. Crude incident pregnancy rates with exact confidence intervals (CIs) were calculated for each combination of ART and BMI or weight category. Adjusted incident rate ratios (aIRRs) were calculated using Poisson models with interaction terms between ART and BMI or weight categories, and cluster-robust standard errors to account for repeated observations. We conducted secondary analyses stratified by implant type when known and duration of implant use. Data were prepared using SAS version 9.3 (Cary, NC, USA), and analyses were conducted using STATA version 12.1 (College Station, TX, USA).

3. Results

3.1. General characteristics of all implant users

In this analysis, 12,960 women (6018 from AMPATH and 6942 from FACES) using an implant contributed a total of 11,285 woman-years (w-y) of observation time with a median of 6.6 months per woman (IQR 2.0–15.2; Table 1). The distribution of time contributed by each BMI category was as follows: 11.0% underweight, 67.8% normal weight, 14.8% overweight, 3.2% obese and 3.2% unknown; and 10.7% of the time women weighed ≥ 70 kg.

3.2. BMI or weight and pregnancy incidence (regardless of ART)

The overall crude or adjusted pregnancy rates did not vary significantly among women with differing BMI or weight (Table 2), and the unstratified results were similar to those when stratified by duration of implant use (Supplemental Tables 1a and 1b).

3.3. ART and pregnancy incidence

The crude pregnancy rate among women using implants and efavirenz- or nevirapine-based ART, or no ART were 6.0 (95% CI 5.2–6.9), 2.7 (2.3–3.2) and 4.7 (3.8–5.6) per 100 w-y, respectively (Table 3). Compared to while using nevirapine-based ART, the aIRRs were 2.1

Table 2

Pregnancy rates and rate ratios for overall effect of BMI or weight among women using implants and enrolled in HIV care in western Kenya, 2011–2015

	Pregnancies/person-years	Pregnancy rate ^a (95% CI)	Crude IRR ^b (95% CI)	Adjusted IRR ^c (95% CI)	p value
BMI (kg/cm ²)					.39
Underweight	57/1238	4.6 (3.5–6.0)	1.1 (0.8–1.4)	1.1 (0.8–1.4)	
Normal weight	328/7654	4.3 (3.8–4.8)	Reference	Reference	
Overweight	51/1671	3.1 (2.3–4.0)	0.7 (0.5–0.9)	0.8 (0.6–1.1)	
Obese	13/357	3.6 (1.9–6.2)	0.8 (0.5–1.4)	1.0 (0.6–1.7)	
missing	11/365	3.0 (1.5–5.4)	--	--	
Weight (kg)					.22
<70	426/10072	4.2 (3.8–4.7)	Reference	Reference	
≥ 70	34/1212	2.8 (1.9–3.9)	0.7 (0.5–0.9)	0.8 (0.6–1.1)	
Weight (kg)					.47
<50	80/1766	4.5 (3.6–5.6)	1.1 (0.8–1.4)	1.1 (0.8–1.4)	
50–59	202/4919	4.1 (3.6–4.7)	Reference	Reference	
60–69	144/3387	4.3 (3.6–5.0)	1.0 (0.8–1.3)	1.1 (0.9–1.4)	
≥ 70	34/1212	2.8 (1.9–3.9)	0.7 (0.5–1.0)	0.8 (0.6–1.2)	

BMI categories are: underweight, BMI <18.5; normal weight, 18.5–24.9; overweight, 25–29.9; obese, ≥ 30 .

^a Per 100 w-y.

^b All crude models included BMI or weight categories and program (AMPATH or FACES).

^c All adjusted models included the BMI or weight categories and the following covariates: average age during observation period (categorized into 5-year intervals), marital status, number of living children, education level, CD4 cell count, WHO clinical stage, use of anti-TB medications, calendar time and program (AMPATH or FACES).

Table 3
Pregnancy rates and rate ratios for ART group by BMI or weight among women using implants and enrolled in HIV care in western Kenya, 2011–2015.

	Nevirapine-based ART (reference group)		Efavirenz-based ART					No ART use						
	Pregnancies/Woman-Years	Pregnancy Rate ^a (95% CI)	Pregnancies/Woman-Years	Pregnancy Rate ^a (95% CI)	Crude IRR ^b (95% CI)	Adjusted IRR ^c (95% CI)	<i>p</i> for interaction term or ratio of adjusted IRRs (95% CI) ^d	Forest plot of adjusted IRRs	Pregnancies/Woman-Years	Pregnancy Rate ^a (95% CI)	Crude IRR ^b (95% CI)	Adjusted IRR ^c (95% CI)	<i>p</i> for interaction term or ratio of adjusted IRRs (95% CI) ^e	Forest plot of adjusted IRRs
Overall	154/5651	2.7 (2.3, 3.2)	196/3270	6.0 (5.2, 6.9)	2.4 (1.9, 3.0)	2.1 (1.6, 2.6)			110/2364	4.7 (3.8, 5.6)	1.7 (1.3, 2.2)	1.4 (1.0, 1.8)		
BMI (kg/cm²)							0.67						0.46	
Underweight	18/608	3.0 (1.8, 4.7)	25/437	5.7 (3.7, 8.4)	2.1 (1.2, 3.8)	2.0 (1.1, 3.6)	1.0 (0.5, 1.9)		14/193	7.2 (4.0, 12.2)	2.4 (1.2, 4.8)	2.0 (1.0, 4.0)	1.6 (0.8, 3.4)	
Normal weight	116/3891	3.0 (2.5, 3.6)	137/2164	6.3 (5.3, 7.5)	2.3 (1.8, 3.0)	1.9 (1.5, 2.5)	Ref.		75/1599	4.7 (3.7, 5.9)	1.6 (1.2, 2.1)	1.3 (0.9, 1.7)	Ref.	
Overweight	14/845	1.7 (0.9, 2.8)	23/423	5.4 (3.4, 8.1)	3.5 (1.8, 6.8)	3.1 (1.6, 6.0)	1.6 (0.8, 3.2)		14/403	3.5 (1.9, 5.8)	2.1 (1.0, 4.5)	1.7 (0.8, 3.6)	1.4 (0.6, 3.0)	
Obese	5/172	2.9 (0.9, 6.8)	5/80	6.3 (2.0, 14.7)	2.3 (0.7, 7.9)	2.1 (0.6, 6.9)	1.1 (0.3, 3.6)		3/105	2.9 (0.6, 8.3)	1.0 (0.2, 4.0)	0.8 (0.2, 3.3)	0.7 (0.2, 2.7)	
missing	1/135	0.7 (0.0, 4.1)	6/166	3.6 (1.3, 7.9)	--	--	--		4/63	6.3 (1.7, 16.1)	--	--	--	
Weight (kg)							0.91						0.25	
<70	141/5048	2.8 (2.4, 3.3)	181/2957	6.1 (5.3, 7.1)	2.4 (1.9, 3.0)	2.0 (1.6, 2.6)	Ref.		104/2068	5.0 (4.1, 6.1)	1.8 (1.4, 2.3)	1.4 (1.1, 1.9)	Ref.	
≥70	13/603	2.2 (1.1, 3.7)	15/314	4.8 (2.7, 7.9)	2.4 (1.1, 4.9)	2.1 (1.0, 4.5)	1.0 (0.5, 2.2)		6/296	2.0 (0.7, 4.4)	0.9 (0.4, 2.5)	0.8 (0.3, 2.1)	0.6 (0.2, 1.5)	
Weight (kg)							0.70						0.44	
<50	26/836	3.1 (2.0, 4.6)	33/599	5.5 (3.8, 7.7)	1.9 (1.2, 3.2)	1.7 (1.0, 2.8)	0.9 (0.5, 1.6)		21/331	6.3 (3.9, 9.7)	2.0 (1.1, 3.5)	1.6 (0.9, 2.8)	1.3 (0.7, 2.6)	
50–59	70/2459	2.8 (2.2, 3.6)	87/1447	6.0 (4.8, 7.4)	2.3 (1.7, 3.2)	2.0 (1.4, 2.7)	Ref.		45/1014	4.4 (3.2, 5.9)	1.6 (1.1, 2.3)	1.2 (0.8, 1.8)	Ref.	
60–69	45/1753	2.6 (1.9, 3.4)	61/911	6.7 (5.1, 8.6)	2.8 (1.9, 4.2)	2.4 (1.6, 3.6)	1.2 (0.8, 2.0)		38/723	5.3 (3.7, 7.2)	2.0 (1.3, 3.1)	1.6 (1.1, 2.6)	1.4 (0.8, 2.4)	
≥70	13/603	2.2 (1.1, 3.7)	15/314	4.8 (2.7, 7.9)	2.4 (1.1, 4.9)	2.1 (1.0, 4.5)	1.1 (0.5, 2.4)		6/296	2.0 (0.7, 4.4)	0.9 (0.4, 2.5)	0.8 (0.3, 2.1)	0.7 (0.2, 1.8)	

BMI categories are: Underweight, BMI < 18.5; Normal weight, 18.5–24.9; Overweight, 25–29.9; Obese, ≥30.

^a Per 100 woman-years.

^b All crude models included the BMI or weight categories, ART group, an interaction term between BMI or weight and ART group, and program (AMPATH or FACES).

^c All adjusted models included the BMI or weight categories and the following covariates: average age during observation period (categorized into 5-year intervals), marital status, number of living children, education level, CD4 cell count, WHO clinical stage, use of anti-TB medications, calendar time, and program (AMPATH or FACES).

^d *p* value for interaction term between ART group and BMI or weight, which tests whether the effect of efavirenz-based ART group, vs. nevirapine-based ART group as reference group, on pregnancy differs by BMI or weight.

^e *p* value for interaction term between ART group and BMI or weight, which tests whether the effect of no ART use group, vs. nevirapine-based ART group as reference group, on pregnancy differs by BMI or weight.

(1.6–2.6) while using efavirenz-based ART and 1.4 (1.0–1.8) while not on ART. The aRRs stratified by implant types (Table 4) or by duration of implant use (Supplemental Tables 2a and 2b) are similar to the unstratified results.

3.4. BMI, ART and pregnancy incidence

Compared to while using nevirapine-based ART, the aRRs while using efavirenz-based ART were 2.0 (1.1–3.6) for underweight, 1.9 (1.5–2.5) for normal, 3.1 (1.6–6.0) for overweight and 2.1 (0.6–6.9) for obese women (Table 3). Similarly, the aRRs stratified by implant types (Table 4) or by duration of implant use (Supplemental Tables 2a and 2b) did not vary significantly by BMI category.

3.5. Weight, ART and pregnancy incidence

Compared to while using nevirapine-based ART, the aRRs while using efavirenz-based ART were 2.0 (1.6–2.6) for weight <70 kg and 2.1 (1.0–4.5) for weight ≥70 kg (Table 3). In a sensitivity analysis, the aRRs were 1.7 (1.0–2.8) for weight <50 kg, 2.0 (1.4–2.7) for 50–59 kg, 2.4 (1.6–3.6) for 60–69 kg and 2.1 (1.0–4.5) for weight ≥70 kg (Table 3). Similarly, the aRRs stratified by implant types (Table 4) or by duration of implant use (Supplemental Tables 2a and 2b) did not vary significantly by weight category.

4. Discussion

In this large cohort analysis conducted in western Kenya, we did not find a statistically significant association between higher BMI or weight and implant effectiveness among HIV-positive women, including among women on efavirenz-based ART.

Despite ongoing debate regarding potential dosing adjustments for hormonal contraceptives in women with higher BMI or weight, based on our study findings, we concur with the current US CDC and WHO guidelines that continue to recommend implants for women regardless of BMI or weight [17,18]. Our study findings do not demonstrate significantly higher pregnancy rates as BMI or weight increases in HIV-positive women concomitantly using implants and efavirenz-based ART. However, our confidence intervals are large, and it is possible that the true estimates may be up to threefold higher among women with higher BMI or weight; relatively short duration of implant use, large portion of unknown implant type and lack of precision on implant insertion relative to pregnancies further limit definitive interpretation of our findings. Future studies with greater observation periods and pregnancies should shed additional light on this topic.

When specifically considering levonorgestrel implant use, our data did not suggest higher pregnancy incidence with greater BMI or weight. Of note, early studies informing the initial approval of levonorgestrel implants in the United States showed higher contraceptive failure rates in women with greater weight. For example, the 5-year cumulative pregnancy rate per 100 women in Jadelle® users was 0.5 in women weighing 50–59 kg but 1.4 or higher in women weighing 60 kg or more [19,20]. Serum levonorgestrel concentrations in women weighing 70 kg or more were approximately half of those in women weighing less than 50 kg [20], corroborating the higher failure rates in women with greater weight.

As for etonogestrel implant use in our study, we also did not observe higher pregnancy incidence with greater BMI or weight. The suggestion of possibly higher pregnancy incidence among women not using ART with lower BMI is likely spurious given the multiple comparisons we made with this dataset ($p=.06$ for rate ratios differing by BMI), as the same trend was not observed across weight categories. Other clinical studies have concluded no significant decrease in etonogestrel implant effectiveness in overweight or obese women [21,22].

We found that concomitant use of efavirenz reduces implant effectiveness when compared to nevirapine-based ART (adjusted pregnancy

rate ratio of 1.9), consistent with our prior publication based on some of the same data [8]. However, it is important to note that this reduced effectiveness still translates to relatively high effectiveness of implants, likely due to the overall high effectiveness of the implants, when compared to other more readily available contraceptive options, such as injectables (e.g., depot medroxyprogesterone acetate) in these settings [8]. Thus, HIV-positive women should be counseled about the potential increased risk of implant failure with concomitant use of efavirenz but still be offered all available contraceptive options and allowed to choose contraceptive methods that best meet their needs. Policies or programs — as well intentioned as they may be — that remove any contraceptive options, including implants, from the method mix for HIV-positive women should be immediately reversed.

We observed higher absolute pregnancy incidence with implant use in this secondary analysis of programmatic data than what has been reported elsewhere, which generally is either derived from postmarketing surveillance or life table calculations excluding this study population [23–26]. First, only analyzing person-time in between documented clinical visits, as opposed to from the time of implant insertion, likely reduces the denominators in our analysis. Second, women living with HIV who become pregnant are likely to seek medical care more often than uninfected or nonpregnant women, which likely increases our numerators. Together, these two factors may lead to our reported higher pregnancy incidence. In addition, implant placement may have occurred during early pregnancies, and our dataset lacks confirmation of implant use, e.g., via palpation, at the time of pregnancy detection, both leading to potential misclassification of a pregnancy while on an implant. Therefore, we advise caution in interpreting the crude incident rates as definitive findings. Nonetheless, we do not anticipate any differential bias affecting specific exposure categories and thus significantly influencing our incident rate ratios as our sensitivity analyses on a similar dataset have upheld the primary results [8].

Although our study followed a relatively large cohort, it has additional limitations. First, our data include few women who were obese or weighed >70 kg, thereby limiting definitive inferences regarding the relationship between BMI or weight and implant/efavirenz failures. Second, the median time women contributed to the analysis while using an implant was 6.6 months, a period much shorter than the life of these implants. Additionally, if the observations in our analysis are biased towards initial implant use, we may be underestimating failures occurring with longer duration of implant use. Third, 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 or patients did not accurately report contraceptive initiation, continuation or discontinuation or data entry errors occurred when transferring the information in the paper records to the electronic medical records.

5. Conclusion

In this large cohort analysis from western Kenya, we did not find any significant association between higher BMI or weight and implant effectiveness among HIV-positive women, including among women on efavirenz-based ART. Our study findings support current contraceptive guidelines that recommend the use of implants for women regardless of BMI or weight. While family planning and HIV programs and policies should counsel women on the potential increased risk of implant failures with concomitant efavirenz use, they should not recommend differential counseling depending on higher BMI or weight. HIV-positive women should continue to be counseled on and offered all available contraceptive options.

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Table 4
Pregnancy rates and rate ratios for ART group by BMI or weight and implant type among women enrolled in HIV care in western Kenya, 2011–2015

	Nevirapine-based ART (reference group)		Efavirenz-based ART				No ART use					
	Pregnancies/ person-years	Pregnancy rate ^a (95% CI)	Pregnancies/ person-years	Pregnancy rate ^a (95% CI)	Crude IRR ^b (95% CI)	Adjusted IRR ^c (95% CI)	p for interaction term or ratio of adjusted IRRs (95% CI) ^d	Pregnancies/ person-years	Pregnancy rate ^a (95% CI)	Crude IRR ^b (95% CI)	Adjusted IRR ^c (95% CI)	p for interaction term or ratio of adjusted IRRs (95% CI) ^e
Etonogestrel- containing BMI (kg/cm²)	100/3210	3.1 (2.5–3.8)	103/1469	7.0 (5.7–8.5)	2.3 (1.7–3.0)	1.9 (1.5–2.6)		77/1430	5.4 (4.2–6.7)	1.7 (1.3–2.3)	1.3 (1.0–1.9)	
							.72					.06
Underweight	11/330	3.3 (1.7–6.0)	13/194	6.7 (3.6–11.5)	2.0 (0.9–4.4)	2.0 (0.9–4.4)	1.1 (0.5–2.6)	14/101	13.9 (7.6–23.3)	4.2 (1.9–9.0)	3.5 (1.6–7.5)	3.1 (1.3–7.0)
Normal weight	77/2254	3.4 (2.7–4.3)	73/982	7.4 (5.8–9.3)	2.2 (1.6–3.0)	1.8 (1.3–2.5)	Ref	51/1013	5.0 (3.7–6.6)	1.5 (1.0–2.1)	1.1 (0.8–1.7)	Ref
Overweight	8/507	1.6 (0.7–3.1)	14/247	5.7 (3.1–9.5)	3.6 (1.5–8.8)	3.1 (1.3–7.6)	1.7 (0.7–4.4)	9/253	3.6 (1.6–6.8)	2.3 (0.9–5.9)	1.7 (0.6–4.5)	1.5 (0.5–4.2)
Obese	4/117	3.4 (0.9–8.8)	3/45	6.7 (1.4–19.6)	2.0 (0.5–8.5)	1.8 (0.4–7.7)	1.0 (0.2–4.4)	3/62	4.8 (1.0–14.1)	1.4 (0.3–6.0)	1.1 (0.3–4.6)	1.0 (0.2–4.2)
Missing	0/2	0.0 (0.0–199.3)	0/2	0.0 (0.0–225.7)	--	--		0/1	0.0 (0.0–438.9)	--	--	
Weight (kg)							.97					.27
<70	89/2835	3.1 (2.5–3.9)	92/1292	7.1 (5.7–8.7)	2.3 (1.7–3.0)	1.9 (1.4–2.6)	Ref	72/1249	5.8 (4.5–7.3)	1.8 (1.3–2.5)	1.4 (1.0–2.0)	Ref
≥70	11/375	2.9 (1.5–5.2)	11/177	6.2 (3.1–11.1)	2.1 (0.9–4.8)	1.9 (0.8–4.4)	1.0 (0.4–2.4)	5/181	2.8 (0.9–6.4)	0.9 (0.3–2.7)	0.8 (0.3–2.2)	0.5 (0.2–1.6)
Weight (kg)							.87					.54
<50	16/430	3.7 (2.1–6.0)	16/253	6.3 (3.6–10.3)	1.7 (0.9–3.4)	1.5 (0.8–3.0)	0.7 (0.3–1.6)	15/195	7.7 (4.3–12.7)	2.1 (1.0–4.1)	1.7 (0.8–3.5)	1.4 (0.6–3.2)
50–59	44/1379	3.2 (2.3–4.3)	46/608	7.6 (5.5–10.1)	2.4 (1.6–3.6)	2.0 (1.3–3.1)	Ref	31/594	5.2 (3.5–7.4)	1.6 (1.0–2.6)	1.2 (0.8–2.0)	Ref
60–69	29/1025	2.8 (1.9–4.1)	30/431	7.0 (4.7–9.9)	2.5 (1.5–4.1)	2.1 (1.3–3.6)	1.1 (0.5–2.1)	26/460	5.7 (3.7–8.3)	2.0 (1.2–3.4)	1.6 (0.9–2.7)	1.3 (0.7–2.6)
≥70	11/375	2.4 (1.5–5.2)	11/177	6.2 (3.1–11.1)	2.1 (0.9–4.8)	1.9 (0.8–4.4)	1.0 (0.4–2.4)	5/181	2.8 (0.9–6.4)	0.9 (0.3–2.7)	0.8 (0.3–2.2)	0.6 (0.2–2.0)
Levonorgestrel- containing BMI (kg/cm²)	19/727	2.6 (1.6–4.1)	10/100	10.0 (4.8–18.5)	3.8 (1.8–8.1)	3.5 (1.7–7.2)		14/287	4.9 (2.7–8.2)	1.9 (0.9–3.7)	1.1 (0.5–2.5)	
							--					--
Underweight	2/81	2.5 (0.3–8.9)	1/6	15.8 (0.4–88.1)	6.4 (0.5–80.0)	12.0 (0.7–218.8)	3.8 (0.2–69.2)	0/27	0.0 (0.0–13.8)	--	--	--
Normal weight	15/494	3.0 (1.7–5.0)	9/77	11.6 (5.3–22.1)	3.9 (1.7–8.6)	3.5 (1.5–8.6)	Ref	11/175	6.3 (3.1–11.2)	2.1 (1.0–4.4)	1.1 (0.5–2.8)	Ref
Overweight	2/128	1.6 (0.2–5.7)	0/13	0.0 (0.0–29.0)	--	--		3/62	4.8 (1.0–14.1)	3.1 (0.5–18.2)	2.4 (0.4–13.8)	2.1 (0.3–14.4)
Obese	0/17	0.0 (0.0–21.5)	0/3	0.0 (0.0–128.7)	--	--		0/21	0.0 (0.0–17.6)	--	--	
Missing	0/6	0.0 (0.0–58.1)	0/0	--	--	--		0/2	0.0 (0.0–167.0)	--	--	

Weight (kg)							.65					.46
<70	19/660	2.9 (1.7–4.5)	10/93	10.8 (5.2–19.8)	3.7 (1.8–7.9)	3.4 (1.7–7.1)		14/250	5.6 (3.1–9.4)	1.9 (1.0–3.8)	1.2 (0.5–2.6)	
≥70	0/67	0.0 (0.0–5.5)	0/7	0.0 (0.0–53.9)	--	--		0/37	0.0 (0.0–9.9)	--	--	
Weight (kg)							.96					.83
<50	3/110	2.7 (0.6–8.0)	2/15	13.2 (1.6–47.8)	4.8 (0.8–31.1)	4.8 (0.6–37.4)	1.4 (0.2–12.9)	3/43	7.0 (1.4–20.4)	2.6 (0.6–11.8)	1.0 (0.2–4.4)	0.7 (0.1–3.9)
50–59	10/331	3.0 (1.4–5.6)	7/48	14.7 (5.9–30.2)	4.9 (2.0–12.1)	3.4 (1.3–9.0)	Ref	7/121	5.8 (2.3–11.9)	1.9 (0.7–5.0)	1.5 (0.5–4.3)	Ref
60–69	6/219	2.7 (1.0–6.0)	1/30	3.3 (0.1–18.6)	1.2 (0.1–10.5)	2.3 (0.3–20.0)	0.7 (0.1–9.0)	4/86	4.7 (1.3–12.0)	1.7 (0.5–5.9)	1.0 (0.3–3.4)	0.7 (0.1–3.3)
≥70	0/67	0.0 (0.0–5.5)	0/7	0.0 (0.0–53.9)	--	--	-	0/37	0.0 (0.0–9.9)	--	--	
Unknown type	35/1714	2.0 (1.4–2.8)	83/1702	4.9 (3.9–6.0)	2.4 (1.6–3.5)	2.1 (1.4–3.1)		19/647	2.9 (1.8–4.6)	1.4 (0.8–2.5)	1.3 (0.7–2.3)	
BMI (kg/cm²)							.96					.02
Underweight	5/197	2.5 (0.9–5.9)	11/237	4.6 (2.3–8.3)	1.8 (0.7–5.1)	1.7 (0.6–4.6)	0.8 (0.3–2.4)	0/66	0.0 (0.0–5.6)	--	--	
Normal weight	24/1142	2.1 (1.3–3.1)	55/1105	5.0 (3.7–6.5)	2.4 (1.5–3.9)	2.2 (1.3–3.5)	Ref	13/411	3.2 (1.7–5.4)	1.8 (0.9–3.4)	1.6 (0.8–3.2)	Ref
Overweight	4/211	1.9 (0.5–4.9)	9/164	5.5 (2.5–10.4)	3.0 (0.9–9.5)	2.5 (0.8–7.8)	1.1 (0.3–4.0)	2/88	2.3 (0.3–8.2)	1.5 (0.3–7.7)	1.3 (0.3–6.7)	0.8 (0.1–4.8)
Obese	1/38	2.6 (0.1–14.6)	2/32	6.3 (0.8–22.6)	2.5 (0.2–26.6)	1.7 (0.2–18.7)	0.8 (0.1–9.1)	0/22	0.0 (0.6–0.17)	--	--	
Missing	1/127	0.8 (0.0–4.4)	6/164	3.7 (1.3–8.0)	--	--		4/60	6.6 (1.8–17.0)	--	--	
Weight (kg)							.97					.77
<70	33/1553	2.1 (1.5–3.0)	79/1572	5.0 (4.0–6.3)	2.4 (1.6–3.6)	2.1 (1.4–3.2)	Ref	18/570	3.2 (1.9–5.0)	1.5 (0.8–2.6)	1.3 (0.7–2.4)	Ref
≥70	2/161	1.2 (0.2–4.5)	4/129	3.1 (0.8–7.9)	2.5 (0.5–13.6)	2.2 (0.4–11.7)	1.0 (0.2–5.9)	1/77	1.3 (0.0–7.2)	1.0 (0.1–11.5)	0.9 (0.1–10.1)	0.7 (0.1–8.2)
Weight (kg)							.76					.61
<50	7/296	2.4 (1.0–4.9)	15/331	4.5 (2.5–7.5)	1.9 (0.8–4.7)	1.9 (0.8–4.5)	1.1 (0.4–3.1)	3/93	3.2 (0.7–9.4)	1.4 (0.4–5.2)	1.2 (0.3–4.5)	1.3 (0.3–6.2)
50–59	16/749	2.1 (1.2–3.5)	34/791	4.3 (3.0–6.0)	2.0 (1.1–3.6)	1.7 (1.0–3.1)	Ref	7/299	2.3 (0.9–4.8)	1.1 (0.4–2.6)	1.0 (0.4–2.4)	Ref
60–69	10/508	2.0 (0.9–3.6)	30/450	6.7 (4.5–9.5)	3.4 (1.7–7.1)	2.9 (1.4–6.1)	1.7 (0.6–4.2)	8/178	4.5 (1.9–8.9)	2.3 (0.9–5.9)	2.2 (0.9–5.7)	2.3 (0.6–8.5)
≥70	2/161	1.2 (0.2–4.5)	4/129	3.1 (0.8–7.9)	2.5 (0.5–13.7)	2.2 (0.4–11.7)	1.2 (0.2–7.5)	1/77	1.3 (0.0–7.2)	1.0 (0.1–11.5)	0.9 (0.1–10.1)	1.0 (0.1–12.5)

BMI categories are underweight, BMI <18.5; normal weight, 18.5–24.9; overweight, 25–29.9; obese, ≥30.

^a Per 100 w-y.

^b All crude models included the BMI or weight categories, ART group, an interaction term between BMI or weight and ART group, and program (AMPATH or FACES).

^c All adjusted models included the BMI or weight categories and the following covariates: average age during observation period (categorized into 5-year intervals), marital status, number of living children, education level, CD4 cell count, WHO clinical stage, use of anti-TB medications, calendar time and program (AMPATH or FACES).

^d p value for interaction term between ART group and BMI or weight, which tests whether the effect of efavirenz-based ART group, vs. nevirapine-based ART group as reference group, on pregnancy differs by BMI or weight.

^e p value for interaction term between ART group and BMI or weight, which tests whether the effect of no ART use group, vs. nevirapine-based ART group as reference group, on pregnancy differs by BMI or weight.

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Appendix A. Supplementary data

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