Long-Acting Reversible Contraception: *Original Research*

Intrauterine Contraception Among Women Living With Human Immunodeficiency Virus

A Randomized Controlled Trial

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OBJECTIVE: To compare discontinuation rates of the levonorgestrel and copper intrauterine devices (IUDs) among women with human immunodeficiency virus.

METHODS: A double-masked randomized trial was conducted at Mulago Hospital, Uganda. Women received either a copper or levonorgestrel IUD. The primary outcome was discontinuation of intrauterine contraception within 1 year of placement. The secondary outcomes were incidence of side effects and severe adverse events. To discern a difference of 10% from a copper IUD discontinuation rate of 18%, power of 80%, and 95% confidence interval (CI), a sample size of 351 per arm was estimated. Analysis of the primary outcome was by intention-to-treat principle.

RESULTS: From September 2013 to December 2014, 979 were screened and 703 randomized as follows: 349 to the copper group and 354 to the levonorgestrel group. In total, 8.6% (29/338) women in the copper group com-pared with 8.1% (27/334) in the levonorgestrel group discontinued intrauterine conception within 1 year of placement (incidence rate ratio 1.1 [95% CI 0.64–1.96]). Overall, the incidence of heavy bleeding was higher in the copper group (37% [125/338]) than in the levonor-gestrel group (19.5% [65/334]). However, the incidence of amenorrhea, which occurred in 3.3% (11/338) of women, was lower in the copper group than the 19.8% (66/334) of women who reported amenorrhea in the levonorgestrel group.

CONCLUSION: There was no difference in discontinuation rates between the copper and levonorgestrel devices. Women in the levonorgestrel group had reduced incidence of heavy bleeding and a higher incidence of amenorrhea compared with those in the copper group.

CLINICAL TRIAL REGISTRATION: Pan African Clinical Trial Registry, www.pactr.org, PACTR 201308000561212.

LEVEL OF EVIDENCE: I

Contraceptive use is a public health strategy for the prevention of unintended pregnancies among women in human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) care.[1] Effective contraception is one of the pillars for prevention of pediatric HIV infection.[2] Despite the availability of contraceptives, unintended pregnancy among HIV-positive women remains a global problem.[3] In sub-Saharan Africa, HIV-positive women rely on short-acting hormonal contraceptive methods,[4] yet antiretroviral drugs reduce the effectiveness of hormonal contraceptives[5,6] and depot medroxyprogesterone acetate increases the risk of HIV transmission and acquisition.[7,8]

Intrauterine contraception does not require user compliance, is highly effective,[6,9] and does not interact with antiretroviral drugs. Despite these advantages,

intrauterine contraceptive devices (IUDs) are underutilized in sub-Saharan Africa. Available evidence shows that the copper IUD is a good option for HIV-positive women in low- and midincome countries.[10,11] It does not increase HIV viral shedding in the genitalia[12] and IUD-related complications are few.[10,11] It has been shown that HIV disease progresses faster among hormonal contraceptive than copper IUD users.[13] The levonorgestrel IUD has not been studied among HIV-positive women in low- to midincome countries, but available evidences show that it reduces the risk of pelvic inflammatory disease,[14] reduces menstrual bleeding,[15,16] and does not increase HIV viral shedding into the genital tract.[16]

The aim of this study was to compare the clinical performance of the copper and levonorgestrel IUDs among HIV-positive women. We hypothesized that the discontinuation rate of intrauterine contraception would be higher among copper than levonorgestrel IUD users.

MATERIALS AND METHODS

We report findings from a trial that compared discontinuation rates of copper and levonorgestrel IUDs. This was a parallel, double-masked randomized controlled trial done at Mulago Hospital, a national referral hospital for Uganda, and a university teaching hospital for Makerere University. The study protocol and trial followed the Consolidated Standards of Reporting Trials guidelines.[17] We included women who reported regular menstrual periods, desired long-acting reversible contraception, wanted to avoid pregnancy for at least 1 year, were between 18 and 49 years of age, were at least 4 weeks postpartum, and were not using contraceptives at the time of enrollment. We excluded women with known uterine or cervical anomaly, untreated cervical infection, pelvic infection within 3 months of the study, chronic disease (eg, malignancy, liver or kidney disease), genital bleeding of unknown etiology, or allergy to device ingredients and women with AIDS who were not on antiretroviral therapy.

Eligible women were approached as they awaited HIV care at the Makerere University Joint AIDS Program clinic. They were counseled on family planning in groups of three to four women by trained research assistants with more than 10 years' experience in counseling women for family planning services, and the study was introduced to them. Those who opted for intrauterine contraception and volunteered to participate were enrolled through an informed consent process. Before randomization syndromic[18] or laboratory screening for sexually transmitted infections, including a medical and demographic history and a pelvic examination.

Women free of sexually transmitted infections (STIs) had IUDs inserted by trained nurse midwives with more than 10 years of experience in IUD placement on the day of negative syndromic screening or after obtaining negative laboratory screening test results or completed treatment of an STI. Participants who were not menstruating underwent a pregnancy test to rule out pregnancy before enrollment into the study.

The investigators underwent training in good clinical practice, research assistants were trained in the study procedures, and the instruments pilot-tested before commencement of the study. The first month of the study was the run-in period in which the clinics set the routine for screening, enrollment, follow-up, and an audit trail for changes to the study database was kept. The principal investigators and the research team held weekly meetings during the run-in phase to ensure that the study team was well acquainted with the study procedures. We did not make any changes to the data collection method or the recruitment process and thus data collected during the run-in period were included in the analysis. The study was approved by the Makerere University College of Health Sciences Research and Ethics Committee (REC 2009-110) and the Uganda National Council for Science and Technology (HS 1335). The women gave written informed consent. This trial was registered at Pan African Clinical Trial, Registry PACTR201308000561212.

Participants were randomly allocated one to one to the copper or the levonorgestrel group. The randomization was done in blocks of six and eight, which were varied randomly. The women were randomized to the treatment groups at the time of device insertion. We used a computer random number generator to generate a list of codes from 1 to 703 and each code was linked to one of the two study groups. Sequentially numbered, opaque, sealed envelopes, each containing a random allocation, were prepared by an independent statistician at the School of Public Health, Makerere University. The envelopes were opened in consecutive order by the research assistants at the time of insertion. Questionnaires were collected and data double data-entry done using Epi data 3.1. Data validation was done by a statistician. The study was masked to the study participants, research team involved in the follow-up, and statistician.

Participants were followed up for 12 months and were scheduled for review at 1, 3, 6, and 12 months. Participants were contacted by telephone if they missed a scheduled visit by 2 weeks. Participants were

to report to the hospital if they developed any complications or health concerns. During the visits, participants were asked about their condition of health; if they had discontinued the intrauterine conception; if they had experienced any complications such as lower abdominal pain, purulent vaginal discharge, or fever; intrauterine contraception expulsion; or hormonal side effects. Physical examination to determine the presence of abdominal, cervical, or adnexal tenderness and adnexal masses was done. Speculum vaginal examination was carried out to check for presence of intrauterine contraception strings, purulent vaginal discharge, and inflammation of the vagina or cervix. The findings were recorded on standard clinical record forms. Women clinically diagnosed with pelvic inflammatory disease (PID) were managed according to the hospital protocol and those who had missing intrauterine contraception strings underwent pelvic ultrasonography to determine if the intrauterine contraception was still in position.

The primary outcome was discontinuation of IUD for any reason within 1 year of placement. We assigned the date the IUD was removed as the discontinuation date. The secondary outcomes were complete or partial IUD expulsion, heavy menstrual bleeding, and clinical PID within 1 year of IUD insertion. We defined heavy bleeding as prolonged menstrual flow of more than 7 days or passage of blood clots. Pelvic inflammatory disease was defined as described by the Centers for Disease Control and Prevention.[19] Under this classification, PID was defined as lower abdominal pain in the presence of cervical motion or adnexal tenderness, body temperature greater than 38°C, adnexal mass, and presence of purulent vaginal discharge. Expulsion was complete if the IUD was fully extruded through the cervical canal into the vagina and partial if the IUD was extruded from the uterine cavity into the cervical canal. Amenorrhea was defined as absence of menstrual periods for at least 90 days. The hormonal side effects included history of headaches, breast tenderness, weight changes, nausea, reduced libido, acne, bloating, loss of appetite, and backache. We performed one interim analysis when the accumulating follow-up data had accrued approximately half the estimated sample size according to O'Brien-Fleming boundaries (DeMets error-spending function) at a level $\alpha=0.05$ (two-sided); the significance level for the final analysis was $\alpha=0.0459$. A standardized test statistic was calculated for the rate of intrauterine contraception discontinuation and all adverse effects based on accrued data. The Data Safety and Monitoring Board recommended continuation of the study.

We calculated the sample size with the objective of showing that levonorgestrel was superior. Assuming a discontinuation rate for the copper IUD of 18%,[20] an absolute difference in discontinuation of 10%, a power of 80%, two-sided 95% confidence interval (CI), and 20% loss to follow-up, the sample size was 351 per group. We analyzed the data using Stata 12.

To compare baseline characteristics, continuous variables were assessed using a t test and χ^2 test or Fisher's exact t test for categorical variables as appropriate. Survival analysis was used to compare discontinuation rates of copper and levonorgestrel IUD groups. For women, time in analysis was censored at the earliest date the discontinuation was reported or the last contact date. One-year cumulative failure probabilities were estimated using the Kaplan-Meier method. To compare the primary and secondary outcomes, we estimated the relative risk ratios and the corresponding 95% CI. Analysis of the primary outcome was done by intention-to-treat principle. In the Poisson model, we evaluated a number of potential confounders that could be associated with IUD discontinuation including participant age, educational level, parity, fertility desire, history of STI treatment, disclosure of HIV status to the spouse, marital status, antiretroviral use, cotrimoxazole prophylaxis, HIV and CD4 count, and time-varying covariates such as heavy bleeding, pain, and amenorrhea. We present the incidence rate ratio for the primary outcome and secondary outcomes.

RESULTS

Between September 2013 and December 2014, we approached 1,500 women. A total of 979 were screened, and 703 consented to participate in the study (Fig. 1). We randomly assigned 349 women to receive copper and 354 to levonorgestrel IUDs. The participants were followed up for at least 1 year. At 1 year, the loss to follow-up was 31 of 703 (4.4%), 3.2% (11/349) in the copper group and 5.7% (20/354) in women in the levonorgestrel group. The randomization produced treatment groups that were similar in all important respects (Table 1). The overall mean age was 29.9±6.3 years, most (70%) had disclosed their HIV status to their spouses, 616 (88%) used condoms, on average participants had known their HIV serostatus for 4.8 years, and their mean age at sexual debut was 17 years. The mean number of living children was 3.0±1.6; nearly all 607 (86.3%) reported a single sexual partner over the past year. The majority (517 [73.7%]) had a CD4 count of more than 350 cells/mm³, most 618 (87.9%) were using antiretroviral drugs, 578 (82.2%) were using cotrimoxazole prophylaxis, and
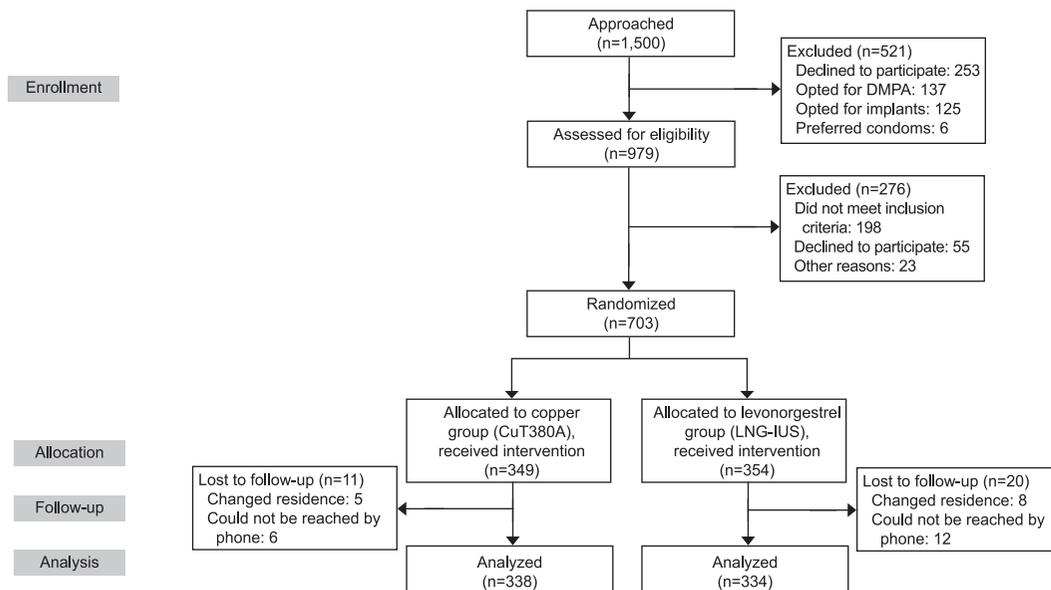
Fig. 1. Consolidated Standards of Reporting Trials flowchart. DMPA, depot medroxyprogesterone acetate; CuT380A, copper T 380A; LNG-IUS, levonorgestrel-releasing intrauterine system.

Kakaire. Copper vs Levonorgestrel IUD. Obstet Gynecol 2015.

438 (63%) had ever used a modern contraceptive. All participants met the eligibility criteria for intrauterine contraception.

Survival analysis was conducted and Kaplan-Meier survival curves are presented (Fig. 2). The total duration of follow-up was 328.5 years in the copper group and 340.8 years in the levonorgestrel group. The rate of discontinuation of intrauterine contraception within 1 year of placement was 8.6% (29/338) in the copper group and 8.1% (27/334) in the levonorgestrel group (incidence rate ratio 1.1 [95% CI 0.64–1.96]) (Table 2). The main reasons for IUD discontinuation were heavy bleeding, cramping, and vaginal discharge (Table 2). Heavy bleeding accounted for 1.5% (5/338) discontinuations in the copper group and 2.4% (8/334) discontinuations in the levonorgestrel group (incidence rate ratio 0.9 [95% CI 0.24–3.05]). There were 1.8% (6/338) discontinuations in the copper group and 1.5% (5/334) discontinuations in the levonorgestrel group attributed to cramping (incidence rate ratio 1.2 [95% CI 0.31–5.09]). Vaginal discharge was responsible for 1.8% (6/338) of discontinuations in the copper group and 1.8% (6/334) in the levonorgestrel group incidence rate ratio 1.4 (95% CI 0.39–5.72). The majority of the participants (88.5% [309/349] in the copper group and 86.7% [307/354] in the levonorgestrel group; incidence rate ratio 1.0 [95% CI 0.86–1.19]) chose to continue using intrauterine contraception at 1 year. The main side effects experienced by the participants were heavy bleeding, amenorrhea,

and cramping (Table 3). Heavy bleeding was more common in the copper group (37% [125/338]) than in the levonorgestrel group (19.5% [65/334]) (incidence rate ratio 2.0 [1.50–2.74]); amenorrhea was less in the copper group (3.3% [11/338]) than in the levonorgestrel group (19.8% [66/334]) (incidence rate ratio 0.2 [0.08–0.33]), although the rate of cramping of 19.5% (66/338) in the copper group was similar to the 15.3% (51/334) in the levonorgestrel group (incidence rate ratio 1.3 [95% CI 0.92–1.97]). The majority of the participants (56.8% [192/338] in the copper group and 55.4% [185/334] in the levonorgestrel group; incidence rate ratio 1.1 [0.88–1.33]) did not experience any complication. There were no differences in hormonal side effects between the groups.

There were three pregnancies (0.9% [3/338]) in the copper group and two pregnancies (0.6% [2/334]) in the levonorgestrel group (incidence rate ratio 1.5 [95% CI 0.18–18.64]). One woman in the copper group had the IUD removed from a clinic near her home as a result of her husband's threat of abandonment if she did not conceive. The IUD was removed after 2 months of placement, and she conceived 2 months later. The other two women presented with amenorrhea at 6 and 8 weeks, and pregnancies were confirmed by ultrasound scan 3 and 5 months after intrauterine contraception placement, respectively. The IUDs were in situ and were removed. The pregnancies progressed normally, and all had live births. Of the two women in the levonorgestrel group who

Table 1. Baseline Characteristics of Study Participants

Characteristic	Copper T 380A (n=349)	LNG-IUS (n=354)	P
Mean age (y)	30.3±6.2	29.4±6.3	.96
Married	260 (74.5)	254 (71.8)	.46
Disclosed HIV status to partner	233 (66.8)	236 (66.7)	.91
Duration of HIV infection (y)*	4.8±3.9	4.5±3.8	.99
Using cotrimoxazole prophylaxis	286 (82.0)	292 (82.5)	.85
Using antiretroviral treatment	308 (87.0)	310 (88.8)	.45
Condom use	190 (54.4)	199 (56.2)	.64
CD4 count higher than 350	265 (75.9)	253 (71.5)	.19
Parity category			
1	56 (16.1)	58 (16.4)	.26
2–4	174 (49.9)	195 (55.1)	
More than 4	119 (34.1)	101 (28.5)	
1 sexual partner in past year	302 (86.5)	304 (85.9)	.72
Previously used contraceptive	212 (60.7)	226 (63.8)	.97
Mean age at sexual debut (y)	17.0±2.5	17.1±2.4	1.0

LNG-IUS, levonorgestrel-releasing intrauterine system; HIV, human immunodeficiency virus.

Data are mean±standard deivation or n (%) unless otherwise specified.

* Years are computed from the time of HIV diagnosis.

conceived, one had the IUD expelled but came back to the clinic only with a 4-week history of amenorrhea, and her pregnancy test was positive. The other woman conceived with the levonorgestrel IUD in situ and presented 6 months after IUD placement with 7
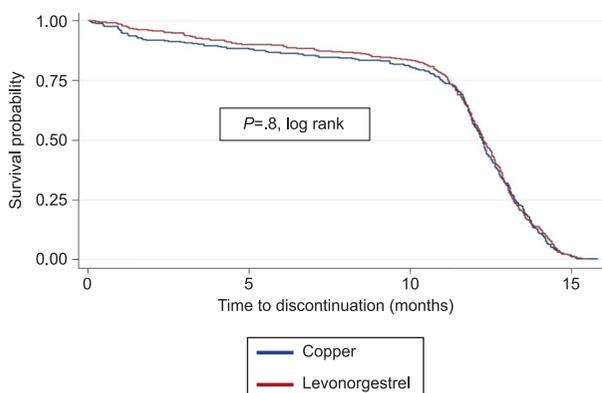

Fig. 2. Kaplan-Meier survival curve. Comparison of discontinuation of copper and levonorgestrel intrauterine devices among women with human immunodeficiency virus.

Kakaire. Copper vs Levonorgestrel IUD. Obstet Gynecol 2015.

weeks of amenorrhea. Ultrasound scan confirmed a 6-week pregnancy, and the IUD was removed. Both women had normal pregnancies and had live births at term. Only 0.6% (2/338) of women in the copper group and 0.9% (3/334) in the levonorgestrel group developed clinical (incidence rate ratio 0.7 [95% CI 0.06–6.04]). They were treated with oral antibiotics as per hospital protocol and had their intrauterine contraception removed after 48 hours of antibiotic treatment. They all fully recovered and switched to injection medroxyprogesterone acetate.

DISCUSSION

There rates of IUD discontinuation were low and there were no differences between the two groups. The majority of discontinuations occurred in the first 3 months. Participants' compliance with either copper or levonorgestrel IUD was high and expulsion rates low for both study groups. Both intrauterine methods were effective and well tolerated. Severe adverse events such as uterine perforations were not observed, few side effects were reported, and the majority of the participants did not experience any complications.

Similarly, recent cohort studies show that the discontinuation rates of copper and levonorgestrel IUDs are low.[20,21] However, older clinical trials reported higher discontinuation rates for levonorgestrel IUDs than for copper IUDs at 1 year[22,23]; more recent trials show that the copper IUD is poorly tolerated and has a higher discontinuation rate than the levonorgestrel IUD.[19] The low discontinuation rates in this study could be the result of the ongoing counseling women received during the follow-up. Counseling women about possible side effects reduces the rate of IUD discontinuation.[24]

Heavy menstrual bleeding, cramping, and vaginal discharge were the main reasons for discontinuation of IUD. Similar studies show that discontinuations resulting from menstrual bleeding are more common in copper IUD users than in levonorgestrel IUD users,[25] whereas amenorrhea accounts for more discontinuations among levonorgestrel IUD users than copper IUD users.[25] None of the participants discontinued levonorgestrel IUD use as a result of amenorrhea. Intrauterine contraception was very effective with only two and three pregnancies reported in the levonorgestrel and copper IUD groups, respectively. This is in agreement with the high efficacy of intrauterine contraception that has been well demonstrated in previous studies.[26,27] Additionally, the incidence of clinical PID was low. Similar studies have had mixed results with some reporting reduced PID risk among levonorgestrel IUD users,[14,25] whereas others find no significant differences compared with the copper IUD.[23,28]

Table 2. A Comparison of Reasons for Early Discontinuation of the Copper and Levonorgestrel Intrauterine Devices

Characteristic	Copper (n=338)	Levonorgestrel (n=334)	Crude IRR (CI)	P	Adjusted IRR (CI)	P
Heavy menstrual bleeding	6 (1.8)	8 (2.4)	0.8 (0.22–2.56)	.65	—	—
Pain	6 (1.8)	5 (1.5)	1.2 (0.32–5.15)	.73	—	—
Vaginal discharge	6 (1.8)	5 (1.5)	1.2 (0.32–5.15)	.73	—	—
Pregnancy	3 (0.9)	2 (0.6)	1.6 (0.18–18.62)	.66	—	—
PID	2 (0.6)	3 (0.9)	0.7 (0.06–6.03)	.72	—	—
Partner complaint	6 (1.8)	4 (1.2)	1.6 (0.37–7.49)	.51	—	—
Early discontinuation	29 (8.6)	27 (8.1)	1.1 (0.64–1.95)	.69	1.4 (0.69–2.81)	.35

IRR, incidence rate ratio; CI, confidence interval; PID, pelvic inflammatory disease.
Data are n (%) unless otherwise specified.

Intrauterine contraception in Africa south of the Sahara is still unpopular and most women utilize short-acting hormonal methods and condoms.[29] However, a recent study showed that continuation rates of copper IUD are high and similar to that of depot medroxyprogesterone acetate.[30] Condoms provide dual protection against both unintended pregnancy and horizontal transmission of STIs. However, the uptake and consistent use of condoms is low in sub-Saharan Africa[31] because they require negotiation with the male partner. Antiretroviral drugs interact with hormonal contraceptives including the implants,[5,6] reducing their effectives and leading to unintended pregnancies. Depot medroxyprogesterone acetate, the most commonly used contraceptive in sub-Saharan Africa, has been observed to increase HIV acquisition and transmission.[7,8] Thus, the need to expand access to women controlled contraceptive methods for women in HIV care that can be used concurrently with condoms to prevent pregnancy and HIV transmission.

The strength of this study is that we used a randomized, blinded, and controlled design, large sample size, and low rate of loss to follow-up at 12 months observed. The results of this study can be generalized to other women in settings of HIV care. There were, however, a number of limitations to this study. First, PID diagnosis was made basing on clinical assessment, which is known to overestimate the problem. Second, laboratory testing for genital HIV shedding was not conducted, although previous studies show no increase in genital HIV shedding during use of both copper and levonorgestrel IUDs. Third, laboratory markers for HIV disease progression including CD4 count, serum viral load, complete blood count, and hemoglobin estimation were not conducted; thus, the study lacks the power to report on the effect of IUDs on HIV disease progression.

Table 3. A Comparison of the Side Effects of the Copper and Levonorgestrel Intrauterine Devices

Side Effects or Complaints*	Copper (n=338)	Levonorgestrel (n=334)	IRR (CI)	P
Heavy menstrual bleeding	125 (37.0)	65 (19.5)	2.0 (1.47–2.73)	<.001
Amenorrhea	11 (3.3)	66 (19.8)	0.2 (0.08–0.33)	<.001
Abdominal pain	66 (19.5)	51 (15.3)	1.3 (0.92–1.97)	.12
Vaginal discharge	13 (3.8)	12 (3.6)	1.1 (0.47–2.69)	.78
Early expulsion	10 (3.0)	18 (5.4)	0.6 (0.24–1.32)	.16
Hormonal effects				
Backache	6 (1.8)	6 (1.8)	1.0 (0.28–3.88)	.95
Headache	0 (0.0)	2 (0.6)	0 (0–5.52)	.26
Acne	16 (4.7)	17 (5.1)	1.0 (0.46–2.06)	.95
Weight changes	1 (0.3)	2 (0.6)	0.5 (0.09–9.96)	.65
Bloating	1 (0.3)	1 (0.3)	1.1 (0.01–81.44)	.98
Loss appetite	11 (3.3)	19 (5.7)	0.6 (0.26–41.33)	.18
Loss of libido	15 (4.4)	15 (4.5)	1.0 (0.47–2.28)	.92
Reported no side effects	192 (56.8)	185 (55.4)	1.1 (0.88–1.33)	.47

IRR, incidence rate ratio; CI, confidence interval.
* Some participants had more than one side effect.

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