

Contraceptive Use and Pregnancy Incidence Among Women Participating in an HIV Prevention Trial

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Abstract

Background: Recent HIV prevention trials required use of effective contraceptive methods to fulfill eligibility for enrollment. We compared pregnancy rates in a subset of participants enrolled in the Microbicide Trials Network protocol (MTN-003), a randomized trial of chemoprophylaxis to prevent HIV acquisition among women aged 18–45 years who initiated depot medroxyprogesterone acetate (DMPA) or combined oral contraceptives (COCs) at enrollment, relative to those already using DMPA or COCs.

Methods: Data were analyzed from MTN-003 participants from Uganda. Before enrollment, information on contraceptive type and initiation date was obtained. Urine pregnancy tests were performed at monthly follow-up visits. Cox proportional hazards models were used to compare pregnancy incidence among new users (initiated ≤ 60 days before enrollment) and established users (initiated >60 days before enrollment).

Results: Of 322 women enrolled, 296 were COC or DMPA users, 82 (28%) were new users, and 214 (72%) were established users. Pregnancy incidence was higher among new contraceptive users compared to established users (20.70% vs. 10.55%; adjusted hazard ratio [HR]=1.66; 95% confidence interval [95% CI] 0.93–2.96). Among DMPA users, pregnancy incidence was 10.20% in new users versus 3.48% in established users (HR=2.56; 95% CI 0.86–7.65). Among new COC users, pregnancy incidence was 42.67% in new users versus 23.67% in established COC users (adjusted HR=1.74; 95% CI 0.87–3.48).

Conclusions: New contraceptive users, regardless of method, at the Uganda MTN-003 site had an increased pregnancy risk compared to established users, which may be due to contraceptive initiation primarily for trial eligibility. New users may benefit from intensive contraceptive counseling and additional contraceptive options, including longer acting reversible contraceptives.

Keywords: hormonal contraception, contraceptive initiation, DMPA, oral contraception, Uganda, HIV prevention

Introduction

THE INCIDENCE OF HIV remains alarmingly high among young women in sub-Saharan Africa.¹ Despite recent advances in HIV prevention,^{2–5} additional novel prevention strategies are needed to curb the epidemic.^{5,6} HIV prevention trials evaluating biomedical strategies such as

vaginal microbicides and oral pre-exposure prophylaxis (PrEP) typically enroll sexually active, reproductive-age women.^{7–11} The majority of these trials have been conducted in sub-Saharan Africa, where fertility rates are high and there is an unmet need for highly effective contraceptive methods.¹² In particular, Uganda continues to have a high HIV prevalence (7.2%) while also having the second

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highest total fertility rate in the world, with 6.2 children per woman and a high unmet contraceptive need (41%).^{1,13,14}

HIV prevention trials typically include follow-up over several years; therefore, it is possible that trial participants may become pregnant during study participation. In biomedical HIV prevention trials, women who become pregnant are often required to discontinue study product to minimize fetal exposure to a product in which safety and effectiveness is being evaluated. This requirement results in less time on study product and impacts the ability to adequately assess safety and effectiveness by reducing study power.^{15–17} Consequently, many HIV prevention trials have implemented programs to increase uptake of highly effective contraceptive methods and reduce pregnancy incidence during the trial^{7,15,18–21}; however, in some studies, the pregnancy incidence was high despite regular contraceptive counseling and access to contraceptive methods.²²

Several recent biomedical HIV prevention trials required the use of a highly effective contraceptive method as a criterion for study enrollment.^{7,10,11,21–23} As a result, women interested in trial participation who were not using family planning (FP) were asked to initiate a highly effective contraceptive method, in addition to condoms, to be eligible. To assess the impact of this enrollment requirement in a population with a high fertility rate and unmet contraceptive needs, we compared the pregnancy incidence of those who may have initiated contraceptive use as a study requirement compared to those already using a contraceptive method among Ugandan women enrolled in the Vaginal and Oral Interventions to Control the Epidemic (VOICE) study/Microbicide Trials Network protocol 003 (MTN-003), a safety and effectiveness trial of tenofovir-based prophylaxis for HIV-1 prevention in women. We hypothesized that the incidence of pregnancy would be higher among women who initiated contraception as part of trial participation requirements compared to women who were established users.

Methods

We conducted a secondary analysis of data from Ugandan women enrolled in VOICE/MTN-003, a multisite, randomized, double-blinded, placebo-controlled trial that assessed the safety and effectiveness of daily tenofovir 1% gel, tenofovir disoproxil fumarate (TDF) 300 mg tablet, and emtricitabine/TDF 200/300 mg tablet compared to placebo to prevent HIV acquisition in women (Clinicaltrials.gov number NCT00705679). Detailed methods for the trial have been described previously.²² In brief, between September 2009 and June 2011, 5029 HIV-uninfected, nonpregnant, sexually active women aged 18–45 years from three countries (Uganda, South Africa, and Zimbabwe) were enrolled and followed monthly for a planned follow-up duration of 12 months at minimum and a maximum of 33 months of study product use.

At enrollment, eligible women were required to be using an effective method of contraception (oral or injectable hormonal contraception, hormonal implants, intrauterine device [IUD], or tubal ligation) and agree to continued use throughout study participation. In addition, an eligibility requirement was for women to report no intention of becoming pregnant during the next 24 months. Information on contraceptive type and initiation date was obtained for women who

reported using contraception at screening. For those not using an effective contraceptive method, women underwent contraception counseling, which was standardized across all study counselors, and were encouraged to choose among available methods. Hormonal contraceptives (HC), including injectable depot medroxyprogesterone acetate (DMPA) and combined oral contraceptive (COC) pills, were provided on site at no cost. Long-acting reversible contraceptions (LARCs) were provided from the FP clinics, which were some distance away from the study clinic. Women who elected to use implants or IUD and women who opted to pursue a tubal ligation were referred to the nearest FP clinic. Contraceptive choice was recorded on an FP card and on a contraceptive log kept in each participant's file; the log was updated when the participant switched to another method. Participants who received contraception from an external FP clinic were instructed to bring their FP cards as evidence that contraception was provided. Individualized contraceptive counseling was provided by trained clinical staff at each study visit. Contraceptive dispensing was scheduled to coincide with scheduled study visits as much as possible to ensure continual contraceptive supply. Participants were allowed to continue study participation even if they stopped using a highly effective contraceptive method.

At enrollment and monthly follow-up visits, information on demographic characteristics, medical history, contraceptive use, and sexual behaviors was collected using standardized case report forms (CRFs) and audio computerized-assisted self-interview. Urine pregnancy testing was conducted monthly and whenever clinically indicated. Male condoms were provided at each visit. This study was approved by the U.S. National Institutes of Health Division of AIDS Prevention Science Review Committee and locally by the National AIDS Research Committee, Uganda National Council for Science and Technology, National Drug Authority, and Johns Hopkins Medicine Institutional Review Boards. All participants provided written informed consent before enrollment.

Statistical analysis

The objective of this analysis was to compare pregnancy incidence among participants who reported being new HC users at enrollment versus those who were established HC users. Participants were considered new users if they initiated COCs or DMPA in the 60 days before study enrollment (which reflects the maximum interval between screening and enrollment). Participants using other forms of reversible contraception (implants, IUD) were excluded due to low numbers. Participants not at risk for pregnancy due to tubal ligation or total abdominal hysterectomy were also excluded. For this analysis, data on new versus established HC user status were abstracted from participant charts using a standardized data abstraction tool. Other relevant data were collected using standardized CRFs. The primary outcome was first positive pregnancy test during follow-up. Descriptive statistics were used to summarize participant characteristics at enrollment. Chi-squared and Fisher's exact tests (when appropriate) for categorical data and Wilcoxon rank-sum tests for continuous data were used to compare baseline characteristics of new and established HC users. These methods were also used to compare baseline characteristics by HC method reported at enrollment.

Pregnancy incidence and 95% confidence intervals (95% CIs) were computed for new and established HC users overall and stratified by HC method reported at enrollment (COCs vs. DMPA). Separate Cox proportional hazard models were used to assess associations between baseline factors and pregnancy incidence, including new versus established HC use, by baseline HC method. Factors were considered for inclusion in multivariable models if they trended toward an association ($p < 0.10$) with both the exposure (HC user status) and the outcome (pregnancy). Effect modification by contraceptive methods was assessed using a likelihood ratio test.

We also hypothesized that as women in the community learned of the contraceptive requirement for VOICE enrollment, they may have initiated HC before screening for this study. To assess the impact of possible misclassification of new HC user status, we conducted a sensitivity analysis that defined being a new user as having started DMPA or COCs within 120 days of enrollment (rather than 60 days) and repeated the above analyses. All tests used a two-sided α of 0.05. Analyses were conducted using Stata version 12.0 (StataCorp, Inc., College Station, TX) and R (R Foundation for Statistical Computing, Vienna, Austria).

Results

Of 322 women enrolled in Uganda, 26 reported using contraceptive implants, IUD, or having had a tubal ligation or hysterectomy and were excluded from the analysis. Among 296 women included in this analysis, 179 (60.5%) reported using DMPA and 117 (39.5%) using COCs at enrollment. Baseline characteristics by contraceptive initiation status (new vs. established HC users) are presented in Table 1. Overall, new HC users did not differ from established HC users with regard to age, education, being married or living with a partner, reproductive history or self-reported condom use at the last sex act. However, number of live births differed between established and new users ($p = 0.03$).

Participants who reported DMPA use at enrollment were similar to those who reported COC use with regard to age <25 years (27.4% vs. 24.6%; $p = 0.29$), having some secondary education or higher (38.5% vs. 43.6%; $p = 0.39$), being married (50.8% vs. 57.3%; $p = 0.28$), history of miscarriage or termination (15.6% vs. 23.9%; $p = 0.08$), and reported condom use at the last sex act (57.0% vs. 54.7%; $p = 0.70$). Among baseline DMPA users, 133 (74%) continued to use DMPA throughout study follow-up (62% of new users; 82%

TABLE 1. BASELINE CHARACTERISTICS BY HORMONAL CONTRACEPTIVE INITIATION STATUS

Characteristic	All women, n = 296	New HC users, n = 82	Established HC users, n = 214	p ¹
Demographics				
Age (median years, IQR)	28 (24–31)	30 (24–32)	28 (24–31)	0.11
Age category				0.56
18–24	76 (25.7)	21 (25.6)	55 (25.7)	
25–34	186 (62.8)	49 (59.8)	137 (64.0)	
35–45	34 (11.5)	12 (14.6)	22 (10.3)	
Education status				0.55
None or primary	176 (59.5)	51 (62.2)	125 (58.4)	
Secondary or higher	120 (40.5)	31 (37.8)	89 (41.6)	
Married	158 (53.4)	46 (56.1)	112 (52.3)	0.56
Lives with partner	153 (51.7)	43 (52.4)	110 (51.4)	0.87
Reproductive history				
Number of live births (median, IQR)	3 (2–4)	3 (2–4)	3 (2–4)	0.27
Number of live births (category)				0.03
0–1	62 (21.0)	20 (24.4)	42 (19.6)	
2–3	144 (48.6)	30 (36.6)	114 (53.3)	
4 or more	90 (30.4)	32 (39.0)	58 (27.1)	
Age of last born (years) ²				0.17
<2	30 (10.5)	6 (7.9)	24 (11.3)	
2 to <3	71 (24.7)	21 (27.6)	50 (23.7)	
3 to <4	62 (21.6)	22 (29.0)	40 (19.0)	
4 or older	124 (43.2)	27 (35.5)	97 (46.0)	
Baseline contraceptive use				0.91
DMPA	179 (60.5)	50 (61.0)	129 (60.3)	
COCs	117 (39.5)	32 (39.0)	85 (39.7)	
Previous miscarriage or termination	56 (18.9)	20 (22.7)	45 (19.2)	0.47
Condom use at last sex act (before enrollment)	166 (56.1)	42 (51.2)	124 (57.9)	0.30

Data presented as *n* (%) or median (IQR). New HC user defined as a participant who initiated hormonal contraceptive ≤ 60 days before enrollment into Vaginal and Oral Interventions to Control the Epidemic; established HC user defined as a participant who initiated hormonal contraceptive more than 60 days before enrollment.

¹Pearson's chi-squared test used for categorical data and Wilcoxon rank-sum test was used for continuous data.

²Among participants with history of a live birth, nine participants did not have information for age of last born child.

COCs, combined oral contraceptives; DMPA, depot medroxyprogesterone acetate; HC, hormonal contraceptives; IQR, interquartile range.

of established users), while 105 (90%) COC users continued with COC use throughout follow-up (97% of new users; 87% of established users).

Participants contributed a total of 367 person-years of follow-up, with the majority of participants contributing more than 1 year (197 [67%]). There were a total of 49 incident first pregnancies resulting in a pregnancy incidence of 13.4 per 100 person-years. Pregnancy incidence by contraceptive initiation status and select baseline characteristics are presented in Table 2. Among new users, the pregnancy incidence was 20.7 per 100 person-years (95% CI 13.5–31.8) compared to 10.5 per 100 person-years (95% CI 7.3–15.3) among established users (hazard ratio [HR]= 1.91; 95% CI 1.08–3.37). This association attenuated after adjustment for potential confounders (Table 2).

The overall pregnancy incidence among DMPA users was 5.4 per 100 person-years (13/241 person-years; 95% CI 2.46–8.32) compared to 28.6 per 100 person-years (36/126 person-years; 95% CI 19.28–37.98) among COC users. Of 13 pregnancies reported among baseline DMPA users, at the time pregnancy was detected three participants reported using DMPA, eight participants reported having changed to COCs, and two reported using condoms only. Of the 36 pregnancies detected among baseline COC users, all but one participant reported using COCs consistently at the time pregnancy was first detected (one participant reported having changed to DMPA). Among participants who reported DMPA use at baseline, the pregnancy incidence among new users was 10.2 per 100 person-years (95% CI 4.9–21.4) compared to 3.5 per 100 person-years (95% CI 1.6–7.7) among established users (hazard ratio [HR]= 2.56; 95% CI 0.86–7.65) (Table 3).

Given that no factors were significantly associated with both new user status and pregnancy among women using DMPA only, the results from unadjusted models are presented in Table 3. Among women who reported COC use at baseline, the pregnancy incidence among new users was 42.7

per 100 person-years (95% CI 25.3–72.1) compared to 23.7 per 100 person-years (95% CI 15.6–36.0) among established users (HR = 1.83; 95% CI 0.93–3.60) (Table 3). The association between new COC user status and incident pregnancy was similar after adjustment for age and education. Despite differences in pregnancy incidence by HC method, a test for effect modification by contraceptive method at baseline was not statistically significant ($p=0.63$). In addition, results for DMPA and COC users were similar in sensitivity analyses, in which a new HC user was defined as initiating an HC method within 120 days before enrollment. New DMPA and COC users had higher, but not statistically significant, pregnancy incidences compared to established users (data not shown).

Discussion

In this analysis of Ugandan women participating in a biomedical HIV prevention trial, pregnancy incidence was higher among new HC users who may have initiated contraception to fulfill trial eligibility criteria compared to established users of both COC and DMPA. Independent of contraceptive initiation timing, COC users had a fivefold higher pregnancy incidence compared to DMPA users. Given that COCs require daily use to effectively prevent pregnancy, the higher pregnancy incidence observed among COC users in this study is not surprising and is consistent with previous studies.^{7,8,10,16,24,25} We and others have found that incident pregnancy was more common among women who were younger, had fewer live births, or had a history of a miscarriage or termination, although these associations were not statistically significant in our analysis.^{26–28}

The overall pregnancy rate in this cohort was 13.35 per 100 person-years and similar to the pregnancy rate in other HIV prevention studies,^{24,27–31} including the FEM-PrEP trial that also reported a higher pregnancy incidence among new COC users.^{10,24} The VOICE study, FEM-PrEP, and CAPRISA 004

TABLE 2. SELECT BASELINE CORRELATES OF INCIDENT PREGNANCY

	<i>Number of pregnancies/woman years</i>	<i>Pregnancy incidence¹</i>	<i>Unadjusted HR (95% CI)</i>	<i>Adjusted HR² (95% CI)</i>
Contraception initiation status				
Established users	28/265.49	10.55	—	—
New users	21/101.43	20.70	1.91 (1.08–3.37)	1.66 (0.93–2.96)
Age (years)²				
18–24	20/88.97	22.48	—	—
25–45	29/277.95	10.43	0.47 (0.26–0.82)	0.45 (0.21–0.93)
Parity				
0–1	15/69.29	21.65	—	—
2–3	19/183.35	10.36	0.47 (0.24–0.92)	0.60 (0.29–1.27)
4 or more	15/114.29	13.12	0.59 (0.29–1.20)	0.83 (0.33–2.06)
Previous miscarriage/termination				
No	32/302.60	10.58	—	—
Yes	17/64.33	26.43	2.55 (1.41–4.60)	2.86 (1.56–5.25)
Condom user at last sex act (before enrollment)				
No	23/163.50	14.07	—	—
Yes	26/203.43	25.82	2.55 (1.41–4.60)	0.76 (0.43–1.35)

¹Per 100 woman-years.

²Age categories 25–34 and 35–45 were combined as there were no pregnancies in the highest age category (35–45 years). 95% CI, confidence interval; HR, hazard ratio.

TABLE 3. SELECT CORRELATES OF INCIDENT PREGNANCY BY CONTRACEPTIVE METHOD AT BASELINE

	<i>Number of pregnancies/woman years</i>	<i>Pregnancy incidence¹ (95% CI)</i>	<i>Unadjusted HR (95% CI)</i>	<i>Adjusted HR (95% CI)</i>
Participants reporting DMPA use at baseline (<i>n</i> = 179)				
Contraception initiation status				
Established users	6/172.56	3.48 (1.56–7.74)	Ref.	—
New users	7/68.62	10.20 (4.86–21.40)	2.56 (0.86–7.65)	—
Age (years) ²				
18–24	6/64.38	9.32 (4.19–20.75)	Ref.	—
25–45	7/176.8	3.96 (1.89–8.30)	0.46 (0.15–1.37)	—
Education status				
None or primary	8/144.78	5.53 (2.76–11.05)	Ref.	—
Secondary or higher	5/96.4	5.19 (2.16–12.46)	0.91 (0.30–2.81)	—
Lives with partner				
No	10/123.31	8.11 (4.36–15.07)	Ref.	—
Yes	3/117.87	2.55 (0.80–7.65)	0.32 (0.09–1.19)	—
Parity				
0–1	5/42.67	11.72 (4.88–28.15)	Ref.	—
2–3	4/119.79	3.34 (1.25–8.90)	0.30 (0.08–1.11)	—
4 or more	4/78.72	5.08 (1.91–13.54)	0.46 (0.12–1.71)	—
Prior miscarriage or termination				
No	10/206.61	4.84 (2.60–9.00)	Ref.	—
Yes	3/34.57	8.68 (2.80–26.90)	2.10 (0.58–7.71)	—
Participants reporting COC use at baseline (<i>n</i> = 117)				
Contraception initiation status				
Established users	22/92.94	23.67 (15.59–35.95)	Ref.	Ref.
New users	14/32.81	42.67 (25.27–72.05)	1.83 (0.93–3.60)	1.74 (0.87–3.48)
Age (years)				
18–24	14/24.6	56.91 (33.71–96.09)	Ref.	Ref.
25–34	19/78.89	24.08 (15.36–37.76)	0.41 (0.21–0.83)	0.54 (0.25–1.15)
34–45	3/22.26	13.48 (4.35–41.78)	0.22 (0.06–0.77)	0.25 (0.07–0.88)
Education status				
None or primary	16/76.5	20.92 (12.81–34.14)	Ref.	Ref.
Secondary or higher	20/49.25	40.61 (26.20–62.95)	2.06 (1.05–4.01)	1.60 (0.88–3.48)
Lives with partner				
No	12/60.22	19.93 (11.32–35.09)	Ref.	—
Yes	24/65.52	36.63 (24.55–54.65)	1.81 (0.90–3.62)	—
Parity				
0–1	10/26.63	37.55 (20.21–69.80)	Ref.	—
2–3	15/63.56	23.60 (14.23–39.14)	0.60 (0.29–1.37)	—
4 or more	11/35.56	30.93 (17.13–55.85)	0.77 (0.32–1.83)	—
Prior miscarriage or termination				
No	22/95.99	22.92 (15.09–34.80)	Ref.	—
Yes	14/29.76	47.04 (27.86–79.44)	2.11 (0.58–7.71)	—

¹Per 100 woman-years.

²Age categories 25–34 and 35–45 were combined as no pregnancies occurred in the highest age category (35–45 years).

all required continued use or initiation of an effective contraceptive method as a criterion for study participation. However, the pregnancy rates in FEM-PrEP and our analysis using data from VOICE were higher than in the CAPRISA 004 trial (3.95 per 100 woman years). CAPRISA 004 enrolled women from South Africa, where the total fertility rate is low compared to Uganda.¹² Also, more than 80% of women in CAPRISA 004 reported using an injectable contraceptive at enrollment and only 15% reported using COCs. Given that more women reported use of injectable HC, this may also have contributed to the lower pregnancy incidence. In VOICE/MTN-003, LARCs were not provided at study clinic, and hence, women opted for the readily accessible COCs and DMPA. In countries such as Uganda with poor access to and acceptability of LARCs, provision of these methods should be promoted at the study clinic for ease of access.

We observed minimal switching between DMPA and COCs; however, among eight participants who switched from DMPA to COCs, all became pregnant. Unfortunately, data were not available concerning the motivation for changing contraceptive methods. It is possible that fertility intentions changed during study participation and participants may have chosen to switch to COCs with the intention of getting pregnant. Alternatively, participants who switched from a more user-independent method (DMPA) may have experienced challenges with successful uptake of a highly user-dependent method (COCs). Regardless of the motivation for switching, contraceptive counseling is highly beneficial when initiating new methods, even among experienced HC users.³²

Some participants may have been motivated to participate in VOICE/MTN-003 for the benefits that accompany trial

participation and may not have been fully engaged in the protocol.³³ As with many HIV prevention studies, participants in VOICE/MTN-003 received care for routine health needs, regular HIV testing, FP services, and a per visit travel stipend (equivalent to 11USD). In most sub-Saharan African settings, there is limited health infrastructure with highly inequitable and inefficient healthcare in the public health sector. Access to the services provided at the study clinic may drive enrollment into clinical trials, which may explain why study requirements, such as using an effective FP method during the study duration, may not have been adhered to resulting in the high pregnancy incidence seen among new HC users, in particular COC users. Alternatively, adherence to COCs has been recognized as a challenge for new COC users in multiple settings.^{34,35} Additional contraceptive counseling should be considered for new users of any contraceptive method to ensure optimal adherence and protection against unintended pregnancy.

This study had a number of strengths, including the use of data collected in the course of a clinical trial that had excellent retention and monthly pregnancy assessment. In addition, detailed contraceptive use data were systematically collected in real time. Nonetheless, our results should be interpreted in the context of several limitations. First, this is a secondary analysis that included all pregnancies detected by monthly testing. Frequent testing may have inflated the overall pregnancy rate compared to studies with longer intervals between pregnancy testing or those that only test following missed menses.^{15,36} Second, our definition of user status was informed by the design of the parent trial and may not be generalizable to other populations. Some participants may have initiated more than 60 days before study enrollment when they learned of the eligibility requirements in the community. A sensitivity analysis was performed, which showed similar results when the definition of “new user” was extended to 120 days. Third, few participants reported LARC use; therefore, our comparison was necessarily limited to COC and DMPA users. Fourth, the number of pregnancies among DMPA users was low, which limited statistical power when assessing correlates of incident pregnancy among women using DMPA. Other VOICE/MTN-003 sites were not included in this analysis as data on contraceptive use before enrollment in VOICE/MTN-003 were abstracted and entered locally at the Uganda site. This was not feasible at other sites. Finally, information was not available on pregnancy intentions, disclosure of contraceptive use to partners, and partner engagement in FP decision-making as these data were not systematically collected as part of the parent study. Future studies should consider assessments of partnership factors, as they are likely to influence FP uptake.

Conclusions

In summary, among women who agreed to use a highly effective method of contraception as a condition for enrolling in an HIV prevention trial, pregnancies occurred with higher frequency among new contraceptive users. In particular, the pregnancy rate among new COC users was well above the estimated COC failure rate with typical use (9 per 100 person-years) and is more similar to pregnancy rates observed with condoms (18 per 100 person-years).²⁵ New users, especially those choosing to initiate COCs may benefit from

adherence counseling or targeted counseling about other highly effective contraceptive methods that do not require daily use. In addition, future clinical trials should support efforts to diversify the contraceptive method mix available at sites so that barriers to uptake of longer acting reversible contraceptives might be reduced. The implementation of pregnancy prevention programs that include access to multiple forms of highly effective HC is an important component of biomedical HIV prevention research and other clinical trials of investigational products seeking to minimize time off study product due to pregnancy or exposure during pregnancy.

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