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Pre-exposure prophylaxis for HIV-1 prevention does not diminish the pregnancy prevention effectiveness of hormonal contraception

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Abstract

Background—For women at risk of HIV-1, effective contraception and effective HIV-1 prevention are global priorities.

Methodology—In a clinical trial of pre-exposure prophylaxis (PrEP) for HIV-1 prevention in HIV-1 serodiscordant couples, we estimated the effectiveness of hormonal contraceptives (oral contraceptive pills, injectable depot medroxyprogesterone acetate, and hormonal implants) for pregnancy prevention relative to no contraception among 1785 HIV-1 uninfected women followed up to 36 months. We compared the effectiveness of each method among women assigned PrEP versus placebo. Contraception was not required for participation but was offered on-site and was recorded monthly; incident pregnancy was determined by monthly urine testing.

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Results—For women using no contraception, overall pregnancy incidence was 15.4% per year. Women reporting oral contraceptive use had comparable pregnancy incidence to women using no contraception, and this lack of contraceptive effectiveness was similar for those assigned PrEP and placebo (17.7% and 10.0% incidence per year respectively; p-value for difference in effect by PrEP use=0.24). Women reporting injectable contraception had reduced pregnancy incidence compared to those reporting no contraception, which did not differ by arm (PrEP 5.1%, placebo 5.3% per year; p-value for difference=0.47). Contraceptive effectiveness was highest among women using implants (pregnancy incidence <1% per year in both arms).

Conclusions—PrEP had no adverse impact on hormonal contraceptive effectiveness for pregnancy prevention. As seen previously in similar populations, women reporting contraceptive pill use had little protection from pregnancy, possibly due to poor adherence. Injectable or implantable hormonal contraception plus PrEP provides effective prevention for pregnancy and HIV-1.

INTRODUCTION

Women account for nearly one-half of new HIV-1 infections worldwide and the majority of new infections in Africa. For women at risk of HIV-1, effective contraception and effective methods of HIV-1 prevention are public health imperatives. Hormonal forms of contraception are highly effective for the prevention of unintended pregnancy, although some observational studies suggest hormonal contraceptive use may increase susceptibility to HIV-1 [1, 2], further necessitating effective HIV-1 prevention strategies for women. Antiretroviral pre-exposure prophylaxis (PrEP) is a promising new HIV-1 prevention strategy, and joint use of hormonal contraception and PrEP could offer dual protection. However, in a recent clinical trial of PrEP conducted among women in sub-Saharan Africa, more pregnancies were observed among women randomized to daily oral emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) PrEP compared to placebo [3], raising a concern that PrEP potentially reduces the pregnancy-prevention effectiveness of hormonal contraception [4]. The few published pharmacokinetic studies of TDF and hormonal contraception have shown mixed results, with one study finding no evidence of reduced plasma oral contraceptive concentrations when the products were used together [5], while another found use of oral and injectable hormonal contraceptives reduced cellular levels of TDF metabolites [6]. Data directly measuring pregnancy incidence among women using both PrEP medications and hormonal contraceptives are very limited [7], and further evidence is needed to ensure there are no adverse interactions between PrEP and hormonal contraceptives. We assessed the impact of TDF-based PrEP on hormonal contraceptive effectiveness in a large clinical trial of PrEP for HIV-1 prevention.

METHODS

Study population and procedures

Between July 2008 and November 2010, 4747 heterosexual HIV-1 serodiscordant couples (1785 in which the HIV-1 uninfected partner was female) from Kenya and Uganda were enrolled in the Partners PrEP Study, a randomized, placebo-controlled trial of PrEP [8]. HIV-1 uninfected partners were randomized 1:1:1 to daily oral TDF, co-formulated FTC/

TDF, or placebo and followed monthly up to 36 months. Women who were pregnant or intending to become pregnant were not eligible for enrollment. Contraceptive use was not required for study participation but monthly study visits included contraceptive counseling and provision of contraception on-site free of charge, if desired. Direct monitoring of contraceptive use was not conducted. Sexual behavior in the prior month and contraceptive use were recorded monthly on standardized interviewer-administered questionnaires; condom use was recorded in the sexual behavior assessment, not as contraception. At each study visit, women were screened for incident pregnancy with urine testing and for HIV-1 seroconversion with rapid HIV-1 antibody tests. Women with positive pregnancy tests were referred to antenatal care and study drug was withheld until the end of pregnancy and breastfeeding. HIV-1 infected male partners were not eligible for antiretroviral therapy (ART) under the national guidelines of Kenya and Uganda at enrollment; they were followed quarterly, with clinical and CD4 count monitoring, and were actively referred for ART initiation during follow-up.

Statistical analysis

To estimate the effectiveness of hormonal contraceptive methods for pregnancy prevention, we used the Andersen-Gill extension of Cox proportional hazards regression to account for repeated events [9]. Pregnancy start was estimated by the last menstrual period prior to the first positive pregnancy test. Follow-up time was measured by study visit months, therefore the first study visit during pregnancy was classified as the incident visit, and all subsequent visits during pregnancy were censored. Women re-entered the risk set when no longer pregnant. Contraceptive method was included as a time-dependent variable with no contraceptive use as the reference group. Whether PrEP modified the effect of each hormonal contraceptive method was tested with interaction terms on the log scale. Because both active PrEP arms contained TDF, they were analyzed as a single PrEP-exposed group. Covariates were selected *a priori*, including, at enrollment, age, number of children, partnership duration, and sexually transmitted infections, and, during follow-up, any unprotected sex, sexual frequency with the study partner, any sex with additional partners, and ART initiation by the HIV-1 infected partner. Women who acquired HIV-1 were censored at seroconversion.

Follow-up time when women reported non-hormonal contraceptive methods (tubal ligation, hysterectomy, IUD, diaphragm, or “other”) was excluded from the analysis. Because injectable contraceptive efficacy increases after initiation, we also estimated effectiveness for each of the first three months after initiation and for longer duration of use, and assessed whether PrEP modified these effects. As a sensitivity analysis, all analyses were repeated excluding visits when PrEP/placebo study drug was withheld according to protocol-defined indications and when PrEP adherence was estimated to be low, classified by pill counts of returned study medication <80% or >104%, as excess doses potentially represent non-use (e.g. “pill dumping”) [10]. Analyses were conducted in SAS 9.3.

RESULTS

Among the 1785 HIV-1 uninfected women enrolled in the Partners PrEP Study, the median age was 33 (interquartile range [IQR] 28–38) and median partnership duration with their HIV-1 infected partner was 12 years (IQR 6–18) (Table 1). Women reported an average of 3 (IQR 1–5) children with their study partner, with 15% having no children. Curable sexually transmitted infections were identified in 10%, and unprotected sex in the past month was reported by 23%.

Approximately half of the study population reported contraceptive use at enrollment, with injectable hormones the most common method reported (27% of all women). During follow up, 14% of women initiated oral pills, 20% initiated injectable hormones, and 6% received implants. In total, hormonal contraceptives were used during 51% of all non-pregnant follow-up time: oral contraceptives 11%, injectables 31%, and implants 8%. No contraception was reported during 35% of non-pregnant follow-up time and other forms of contraception were reported for the remaining 14%.

A total of 288 pregnancies were observed in 267 women (179 assigned PrEP and 88 assigned placebo). Pregnancy incidence and outcomes did not differ across study arms [11]. Among women reporting no contraceptive use, pregnancy incidence was 15.4% per year: 14.6% and 17.4% for women assigned PrEP and placebo, respectively (Table 2). Women reporting oral contraceptive use had similar pregnancy incidence compared to women reporting no contraception; oral contraceptive effectiveness did not differ significantly for women assigned PrEP (adjusted hazard ratio [aHR] 0.96) compared to placebo (aHR 0.55, p-value for difference in aHRs=0.24). Women reporting injectable contraception had 75–80% reduction in pregnancy incidence compared to women not using contraception, and this did not differ by randomization arm (PrEP: aHR 0.26, $p<0.001$; placebo: aHR 0.19, $p<0.001$; p-value for difference=0.47). Further, effectiveness during the first three months after injectable contraception initiation and after longer duration use did not differ by randomization arm (data not shown). Implantable contraception was highly effective for pregnancy prevention (incidence <1% per year) in both PrEP and placebo arms. In sensitivity analyses, excluding follow-up time when the PrEP study drug was withheld and when adherence to PrEP/placebo was estimated to be poor (16% of non-pregnant follow-up time), the results for all contraceptive methods were essentially the same (data not shown).

DISCUSSION

In this randomized, placebo-controlled trial of FTC/TDF and TDF PrEP among 1785 HIV-1 uninfected women, we found no evidence that PrEP reduced the effectiveness of hormonal contraception for pregnancy prevention. Our study population provided a unique opportunity to evaluate the question of a potential adverse interaction between PrEP and contraception for several reasons: contraception was not required for participation, allowing for a comparison group of women not using hormonal contraception to estimate contraceptive effectiveness; PrEP was randomly assigned, providing a placebo comparison; and PrEP was used with high adherence [8], thus permitting a robust assessment of whether PrEP modified contraceptive effectiveness.

In FEM-PrEP [3], another clinical trial of FTC/TDF PrEP among African women, more pregnancies occurred among those assigned PrEP (incidence 11.2% per year) versus placebo (7.5% per year). Because contraception was required for participation in that trial and over 95% of women selected a hormonal method, this difference in pregnancy incidence raised concern that PrEP might negatively affect hormonal contraception effectiveness. Both biologic and behavioral hypotheses were offered to potentially explain this observed difference. Little evidence supports an adverse biologic interaction between TDF and contraception, as tenofovir is not a substrate, inducer, or inhibitor of human cytochrome P450 enzymes, does not interact with selected drugs that are metabolized similarly to hormonal contraceptives, and was not found to affect plasma concentrations of oral contraceptives [5]. Instead, behavioral factors could explain the FEM-PrEP findings: adherence to PrEP was low overall in FEM-PrEP (~30%), and pregnancy incidence was 29% per year among women reporting oral contraceptive use, suggesting poor adherence to oral contraception as well. In addition, the proportion using oral contraception was slightly higher among women assigned PrEP (32%) compared to placebo (28%), and thus the difference in pregnancy incidence between arms was likely confounded by this imbalance. In our study, we found no adverse effect of PrEP on contraceptive effectiveness, although, as in FEM-PrEP, we found high pregnancy incidence in women reporting oral contraceptive use.

Hormonal contraception in the form of implants was nearly perfectly efficacious in our study; notably this method requires minimal user dependence as implants remain effective up to five years. Adherence is likely the primary reason for the lack of oral contraceptive effectiveness we observed. Other prospective studies among women at risk for HIV-1 have reported high pregnancy incidence in oral contraceptive users, suggesting low real-world effectiveness in this important population [12, 13]. In our study, family planning counseling was provided at study sites by trained counselors and at family planning clinics for those who sought contraception elsewhere. It is notable that PrEP adherence in our population was high, in contrast to the suggestion that oral contraceptive adherence was not. Women at risk of HIV-1 require increased access to long-acting reversible contraception, and development of long-acting HIV-1 prevention methods is needed. Pre-clinical studies of longer-acting PrEP report promising results [14, 15] and further study is underway in humans [16]. Ongoing PrEP trials are not limited to TDF-based PrEP, therefore continued study of potential interactions between hormonal contraceptives and new PrEP formulations is necessary. Further examination of whether hormonal contraception diminishes PrEP efficacy is also needed [6]. Co-formulated PrEP and hormonal contraceptives in development are of particular interest, including intravaginal rings and injectables; these products promise further reduction in user dependence while offering dual protection [17].

A potential limitation of our study is that contraceptive use was self-reported which could result in misclassification, though monthly reporting minimizes the likelihood of recall bias. Also, unmeasured or imperfectly measured confounders of contraceptive effectiveness are possible. Nonetheless, we do not expect these potential limitations to be differential by randomization arm and therefore they would not bias our primary analysis, which was to evaluate the effect of PrEP on contraceptive effectiveness.

In conclusion, our results suggest that TDF-based PrEP can be used together with hormonal contraception as a dual prevention strategy with no reduction in protection from unintended pregnancy. Future development of co-formulated long-acting PrEP and contraception is an important public health goal.

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Table 1

Participant characteristics at enrollment and contraceptive use during follow up

	PrEP (N=1164)	Placebo (N=621)
Participant enrollment characteristics	Median (IQR) or Number (%)	
Age, years	33 (28, 38)	33 (28, 39)
Number of children with study partner	3 (1, 5)	3 (1, 5)
No children with study partner	169 (15%)	93 (15%)
Partnership duration, years	12 (6, 19)	12 (6, 18)
Number of sex acts with study partner in prior month	4 (2, 7)	4 (2, 8)
Any unprotected sex with study partner in prior month	262 (23%)	144 (23%)
Any sex with additional partner in prior month	4 (0%)	4 (1%)
Infection with *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, or *Trichomonas vaginalis*	94 (8%)	76 (12%)
Contraceptive use		
At enrollment		
None	600 (52%)	310 (50%)
Oral pills	83 (7%)	40 (7%)
Injectable depot medroxyprogesterone acetate	318 (27%)	168 (27%)
Implants*	56 (5%)	32 (5%)
Other**	107 (9%)	71 (11%)
Initiated during follow-up^		
Oral pills	168 (14%)	84 (14%)
Injectable depot medroxyprogesterone acetate	225 (19%)	127 (20%)
Implants*	75 (6%)	37 (6%)
Other**	116 (10%)	65 (10%)
Percent of total non-pregnant follow-up time		
None	37%	32%
Oral pills	11%	11%
Injectable depot medroxyprogesterone acetate	30%	33%
Implants*	8%	8%
Other**	14%	16%

* During the study, 200 women ever reported using a contraceptive implant: 70 (35%) levonorgestrel, 71 (36%) etonogestrel, 59 (30%) unknown.

** Other contraceptive methods included: intrauterine device, tubal ligation, hysterectomy, diaphragm, traditional herbs or methods, being peri- or post-menopausal, and the calendar method.

^ Initiation during follow up included participants who started each method after reporting no contraception at enrollment as well as those who switched to each method.

Table 2

Contraceptive effectiveness, compared to no contraception, by PrEP randomization arm.

Contraceptive method	PrEP* or placebo	# pregnancies**	Person-years	Incidence rate	Adjusted HR***, p-value versus no contraception	p-value for difference in HRs by arm
No contraception	PrEP	100	687.2	14.6		
	Placebo	53	303.8	17.4		
Oral pills	PrEP	37	209.3	17.7	0.96 (0.58–1.58), p=0.87	0.24
	Placebo	11	108.7	10.1	0.55 (0.26–1.19), p=0.13	
Injectables	PrEP	29	564.3	5.1	0.26 (0.16–0.41), p<0.001	0.47
	Placebo	17	319.7	5.3	0.19 (0.10–0.37), p<0.001	
Implants	PrEP	1	150.6	0.7	unable to model****	
	Placebo	0	79.7	0.0	unable to model****	

HR=hazard ratio

* Both active PrEP arms, TDF and TDF/FTC, were combined in this analysis.

** 25 additional pregnancies occurred in the PrEP arms and 15 in the placebo arm when contraception method was reported as IUD, diaphragm, other, or was not reported.

*** HRs are adjusted for, at enrollment: age, number of children, partnership duration, and sexually transmitted infections, and, during follow-up: any unprotected sex and sexual frequency with the study partner, any sex with additional partners, and ART initiation by the HIV-1 infected partner.

**** For implantable contraception, too few pregnancies occurred for the Cox model to reliably estimate hazard ratios and confidence intervals. The unadjusted incidence rate ratio (IRR) for implants among women on PrEP was 0.05 (95% CI: 0.00–0.26, p<0.001) and on placebo was 0.00 (95% CI: 0.00–0.27, p<0.001). Exact confidence intervals were estimated in Stata 12 assuming a poisson probability distribution of pregnancy events.