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Pre-exposure prophylaxis (PrEP) does not affect the fertility of HIV-1 uninfected men

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Abstract

Background—There is a paucity of data on the effect of antiretroviral medications on male fertility. Couples affected by HIV-1 often have fertility intentions, and antiretroviral medications, as both treatment of HIV-1 infected persons and pre-exposure prophylaxis (PrEP) for uninfected persons, are part of peri-conception risk reduction.

Methods—Within a randomized, placebo-controlled trial of daily oral tenofovir disoproxil fumarate (TDF) and combination emtricitabine (FTC)/TDF PrEP for HIV-1 prevention conducted among heterosexual HIV-1 serodiscordant couples, we assessed the impact of TDF and FTC/TDF use on male fertility, measured as incident pregnancy in female partners of men assigned to PrEP versus placebo.

Results—Of 2962 HIV-1 uninfected men partners, 986 were randomized to TDF, 1013 to FTC/TDF, and 963 to placebo. The overall pregnancy incidence in their HIV-1 infected female partners was 12.9 per 100 person-years and did not differ significantly across the study arms (13.2 TDF, 12.4 FTC/TDF, 13.2 placebo). The frequency of live births, pregnancy losses, and gestational age at birth or loss were also statistically similar in the three randomization groups.

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Author contributions

EOW and JMB conceived the study. RH performed the statistical analyses. EOW, RH, and JMB wrote the first draft of the manuscript. All authors contributed critical revisions to the analysis and interpretation and reviewed the final manuscript draft.

Conclusions—TDF and FTC/TDF, when used as PrEP by HIV-1 uninfected men, did not adversely affect male fertility or pregnancy outcomes.

Keywords

male fertility; HIV prevention; antiretroviral; Africa; pregnancy

Introduction

For heterosexual couples affected by HIV-1, a desire to have children is common, and strategies to reduce peri-conception HIV-1 transmission risk are needed [1, 2]. Antiretroviral medications, as antiretroviral therapy (ART) for HIV-1 infected persons and as pre-exposure prophylaxis (PrEP) for HIV-1 uninfected persons, are potential components of a risk-reduction package for peri-conception use.

Only limited data are available on the effect of use of antiretroviral medications on sperm health and male fertility. Seminal quality studies conducted among HIV-1 infected men have suggested potential detrimental effects of some antiretroviral agents on seminal volume, sperm motility, and abnormal sperm morphology [3]; however, HIV-1 infection itself has also been associated with reduced seminal quality, including leucocytospermia and decreased sperm motility [4, 5]. It is unclear if any potential effect of antiretroviral medications on seminal quality translates into a reduction in the capacity to father a child, as no studies have assessed the effect of antiretroviral medications directly on pregnancy incidence in female partners of men receiving versus not receiving antiretroviral medications.

The antiretroviral agents tenofovir disoproxil fumarate (TDF) and combination emtricitabine (FTC)/TDF are commonly used as components of ART regimens and have been demonstrated to have efficacy for HIV-1 prevention as PrEP in clinical trials in diverse geographic settings [6–8]. TDF and FTC achieve high concentrations in genital tract secretions [9], but their effects on male fertility are unknown. The safety of PrEP is a key concern to potential users and, for many potential PrEP users, would encompass noninterference with reproductive intentions. In a clinical trial of PrEP among heterosexual HIV-1 uninfected African men and their HIV-1 infected female partners, we assessed pregnancy rates among partners of men receiving TDF and FTC/TDF PrEP compared with partners of men receiving placebo.

Methods

Population and procedures

Between July 2008 and November 2010, 4747 heterosexual HIV-1 serodiscordant couples were enrolled from 9 sites in Kenya and Uganda in a phase III, randomized, double-blind, placebo-controlled trial of daily TDF and combination FTC/TDF PrEP for the prevention of HIV-1 acquisition (ClinicalTrials.gov number NCT00557245). The details of the study design, methods and primary results have been described elsewhere [6, 10]. In brief, couples were eligible if they were sexually active and planned to remain in their relationship for the

study period. HIV-1 uninfected members of the couple were required to have adequate renal, hepatic and hematological function and not be infected with hepatitis B virus. HIV-1 infected members of the couple were not yet eligible for initiation of ART, per the national guidelines at the time in Kenya and Uganda.

HIV-1 uninfected partners were assigned in a 1:1:1 ratio to one of three study arms: TDF (300 mg), FTC/TDF (200/300 mg), or placebo, taken once daily, and were followed monthly, with HIV-1 testing, provision of study medication, and adherence counseling. As reported previously, adherence was high, with >95% of dispensed pills estimated to have been taken, based on pill counts of returned unused study product, and >80% of a randomly-selected subset of participants in the trial's active PrEP arms having study medication detected in plasma samples. Women (both HIV-1 uninfected and HIV-1 infected) were provided with contraception counseling and offered contraception on-site at each study visit. HIV-1 infected partners were followed in parallel with their HIV-1 uninfected partners, with quarterly visits for clinical examinations and WHO staging, CD4 counts every six months, and active referral to nearby HIV-1 care providers to initiate ART for those who became eligible for ART under national guidelines during follow-up.

HIV-1 infected women were offered urine pregnancy testing as indicated clinically; those who became pregnant were referred for prevention of mother-to-child transmission (PMTCT) services. Pregnancy data were recorded on standardized case report forms, with outcomes of pregnancies occurring in HIV-1 infected women assessed by participant report; infants were not followed.

All couples received a comprehensive package of HIV-1 prevention services, including individual and couple risk-reduction counseling, free condoms, and screening and treatment for sexually transmitted infections. The study received ethical approval from Institutional Review Boards at the University of Washington and the collaborating institutions for each study site. All participants provided written informed consent.

Data analysis

The present analysis was limited to couples in which the HIV-1 uninfected partner was male. The primary outcome was incident pregnancy among the HIV-1 infected female study partners of HIV-1 uninfected men; the primary exposure was trial randomization group (TDF, FTC/TDF, or placebo), analyzed as intention-to-treat. Data through July 2011 were included, when the trial demonstrated efficacy of TDF and FTC/TDF PrEP for HIV-1 prevention and the placebo arm was discontinued. Pregnancy incidence rates across randomization arms were compared using Cox proportional hazards modeling. Chi-square tests were used to determine differences in pregnancy outcomes across study arms. Finally, a number of demographic, sexual behavior, and medical characteristics were considered as potential correlates of pregnancy using multivariate analysis. SAS 9.3 was used for all analysis.

Results

Of the 4747 HIV-1 serodiscordant couples enrolled and followed in the clinical trial, 2962 were couples in which the HIV-1 uninfected partner was male: 986 randomized to TDF, 1013 to FTC/TDF, and 963 to placebo (Table 1). The median age of the male HIV-1 uninfected partners was 34 years (interquartile range [IQR] 29–41) and 71.3% were less than 40 years of age. Nearly all (98.1%) were married to their HIV-1 infected partner, and 19.3% had an additional wife as enrollment. At enrollment, 31.6% of HIV-1 infected women reported using an effective contraceptive method and effective contraception was reported at 49.8% of follow-up visits. HIV-1 infected female partners had a median age of 29 years (IQR 24–35) and a median CD4 count of 527 cells/μL (IQR 395–704) at enrollment. Baseline characteristics were similar across the randomization arms.

Couples were followed for a median of 21 (IQR 15–27) months, with HIV-1 infected female partners contributing 4104 person-years of follow-up for assessment of incident pregnancy. A total of 583 pregnancies occurred during follow-up, for an overall pregnancy incidence of 12.9 (95% confidence interval [CI] 11.9–14.0) per 100 person-years (Table 2). Pregnancy incidence was similar across study arms: 13.2 for couples in which the male partner had been assigned TDF (hazard ratio [HR]=0.99, p=0.91 vs. placebo), 12.4 for FTC/TDF (HR=0.93, p=0.48 vs. placebo), and 13.2 for placebo. The majority (78.9%) of pregnancies resulted in a live birth. The gestational age at the end of the pregnancy, frequency of live births and pregnancy losses were similar across study arms, with a slightly greater proportion of pregnancies ending in live birth in the FTC/TDF arm compared to placebo.

In multivariate analysis, HIV-1 infected women were more likely to become pregnant if their male partner was younger (aHR=2.32 for men aged 18–24 years, aHR=1.76 for men aged 25–29 years, aHR=1.60 men aged 30–34 years vs. men ≥35 years). The likelihood of pregnancy was marginally lower for men reporting more than 1 alcoholic drink per week (aHR=0.74, 95% CI 0.57–0.97). Less than 100% condom use and non-use of effective contraception were associated with increased pregnancy likelihood.

Discussion

In this randomized, double-blind placebo-controlled trial which followed HIV-1 uninfected men receiving TDF and FTC/TDF as PrEP for HIV-1 prevention and their HIV-1 female partners, we found similar pregnancy incidence and outcomes for couples receiving PrEP versus placebo. These results suggest that the reproductive capacity of men was not attenuated by TDF-based PrEP. Importantly, in these HIV-1 serodiscordant couples who had access to effective contraception, pregnancy incidence (13% per year) was similar to the general population and to incidence seen in previous cohorts of HIV-1 serodiscordant couples. While contraception was used at approximately half of follow-up visits, fertility desires are strong and couples need to be counseled regarding risk-reduction strategies for peri-conception periods.

A limited number of studies among HIV-1 infected men have explored the potential impact of antiretroviral medications on male fertility, although these studies have assessed seminal

parameters rather than direct measures of fertility. Some of these studies suggested decreased seminal quality among HIV-1 infected men receiving ART, with speculation for multiple classes of antiretrovirals, including nucleoside/nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors to potentially reduce sperm quality. [4, 5] Our findings suggest that the antiretroviral agents TDF and FTC do not compromise male fertility.

In multivariate analysis, we found that incident pregnancy was associated with younger age, sexual behavior unprotected by condoms, and lack of contraception. These findings are not surprising and similar correlates of pregnancy have been documented in other studies [11].

As part of the growing repertoire of HIV-1 prevention interventions, PrEP has been proposed for use during “seasons” of high risk. One particular high risk period is when HIV-1 serodiscordant couples are trying to conceive, when condom use will necessarily be reduced. Our results add to accumulating data that PrEP could be a useful and safe strategy for couples to decrease transmission risk during peri-conception periods, along with ART if the infected partner is ready and eligible to initiate ART. Importantly, HIV-1 infected women who become pregnant should start and remain on ART for PMTCT of HIV-1 under the WHO-recommended Option B+ regimen that is being implemented in many settings.

Our study had important strengths. To our knowledge, this is the first analysis that has made a direct assessment of male fertility with a conception outcome in relation to use of an antiretroviral medication. In addition, we assessed antiretroviral exposure and male fertility within a randomized, placebo-controlled trial allowing us to accumulate high quality data under a study design that should substantially minimize bias. Another strength of our study is its large size: with the number of pregnancies that we observed, we had 90% power to detect a 20% reduction in pregnancy incidence due to PrEP use.

Our study had limitations. We did not collect information on seminal parameters, such as seminal volume, sperm count, morphology and motility, although it is known that conception is still possible with subtle changes or reduction in these parameters [12, 13]. Importantly, the ultimate demonstration of fertility is achieving conception, which was the primary outcome for this analysis. In addition, we did not have data on the couple’s fertility intentions, including the proportion trying to conceive. Furthermore, we did not have paternity data but women rarely reported partners other than the study partner [6, 10]. However, we would expect that differences in fertility intentions and instances of misclassified paternity would be balanced by randomization.

In conclusion, our findings suggest that TDF-based PrEP can prevent acquisition of HIV-1 infection in men without adverse effects on their fertility or the resultant pregnancy outcome. These reassuring findings are also relevant for HIV-1 infected men, as TDF is now part of first-line ART for HIV-1 infected persons in many settings.

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Table 1

Enrollment characteristics and associations with pregnancy incidence

	Prevalence at enrollment N (%)			Analysis of factors associated with pregnancy			
	TDF N=986	FTC/TDF N=1013	Placebo N=963	Unadjusted HR (95% CI)	p-value	Multivariate** HR (95% CI)	p-value
RANDOMIZATION ARM							
TDF				0.99 (0.80–1.22)	0.91		
FTC/TDF				0.93 (0.75–1.14)	0.48		
Placebo				1.00			
DEMOGRAPHIC CHARACTERISTICS							
Age, years							
18–24	98 (9.94)	108 (10.66)	95 (9.87)	2.11 (1.61–2.76)	<0.001	2.32 (1.73–3.11)	<0.001
25–29	209 (21.20)	197 (19.45)	175 (18.17)	1.77 (1.41–2.21)	<0.001	1.76 (1.37–2.27)	<0.001
30–34	240 (24.34)	239 (23.59)	223 (23.16)	1.52 (1.23–1.89)	<0.001	1.60 (1.27–2.01)	<0.001
35+	439 (44.52)	469 (46.30)	470 (48.81)	1.00		1.00	
Married							
Yes	968 (98.17)	991 (97.83)	948 (98.44)	1.69 (0.74–3.84)	0.21		
Not married	18 (1.83)	22 (2.17)	15 (1.56)	1.00			
Children with study partner							
0	262 (26.57)	280 (27.64)	249 (25.86)	1.54 (1.26–1.88)	<0.001	0.88 (0.71–1.10)	0.27
1	231 (23.43)	241 (23.79)	258 (26.79)	1.38 (1.12–1.70)	0.002	1.05 (0.84–1.33)	0.65
≥2	493 (50.00)	492 (48.57)	456 (47.35)	1.00		1.00	
Earns income							
Yes	842 (85.40)	848 (83.71)	838 (87.02)	0.88 (0.70–1.10)	0.26		
No	144 (14.60)	165 (16.29)	125 (12.98)	1.00			
Number of alcoholic drinks in 1 week							

	Prevalence at enrollment N (%)			Analysis of factors associated with pregnancy			
	TDF N=986	FTC/TDF N=1013	Placebo N=963	Unadjusted HR (95% CI)	p-value	Multivariate** HR (95% CI)	p-value
None	684 (69.37)	690 (68.11)	655 (68.02)	1.00		1.00	
1 drink	128 (12.98)	152 (15.00)	154 (15.99)	1.10 (0.87–1.37)	0.43	1.22 (0.97–1.54)	0.09
>1 drink	174 (17.65)	171 (16.88)	154 (15.99)	0.64 (0.49–0.83)	0.001	0.74 (0.57–0.97)	0.03
BEHAVIORAL CHARACTERISTICS							
Condom use with study partner, prior month *							
No sex	40 (4.06)	46 (4.54)	41 (4.26)	0.95 (0.73–1.26)	0.74	0.89 (0.68–1.18)	0.42
<100% condom use	301 (30.53)	295 (29.12)	265 (27.52)	3.26 (2.69–3.96)	<0.001	3.21 (2.63–3.92)	<0.001
100% condom use	645 (65.42)	672 (66.34)	657 (68.22)	1.00			
Sex with another partner, past month *							
Yes	146 (14.81)	134 (13.23)	118 (12.25)	0.99 (0.79–1.25)	0.96		
No	840 (85.19)	879 (86.77)	845 (87.75)	1.00			
CHARACTERISTICS OF HIV-1 INFECTED FEMALE PARTNER							
Age, years							
18–24	258 (26.17)	276 (27.25)	260 (27.00)	5.75 (4.21–7.86)	<0.001		
25–29	277 (28.09)	257 (25.37)	235 (24.40)	3.92 (2.84–5.41)	<0.001		
30–34	215 (21.81)	225 (22.21)	216 (22.43)	2.90 (2.07–4.06)	<0.001		
≥35	236 (23.94)	255 (25.17)	252 (26.17)	1.00			
Use of any effective contraception (oral, injectable, implant, IUD, diaphragm, surgical vs. none) *	290 (29.41)	324 (31.98)	321 (33.33)	0.18 (0.14–0.22)	<0.001	0.17 (0.13–0.22)	<0.001
ART use (vs. none) *†	0	0	0	0.74 (0.51–1.09)	0.13		
CD4 count, cells/μL *							
<250	0	0	0	1.21 (0.73–2.01)	0.45		

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	Prevalence at enrollment N (%)			Analysis of factors associated with pregnancy			
	TDF N=986	FTC/TDF N=1013	Placebo N=963	Unadjusted HR (95% CI)	p-value	Multivariate** HR (95% CI)	p-value
250–349	165 (16.73)	178 (17.57)	150 (15.58)	1.01 (0.68–1.51)	0.95		
350–500	299 (30.32)	278 (27.44)	277 (28.76)	1.18 (0.86–1.61)	0.31		
>500	522 (52.94)	557 (54.99)	536 (55.66)	1.00			
WHO stage *							
Stage 1–2	931 (94.42)	970 (95.76)	905 (93.98)	1.00			
Stage 3–4	55 (5.58)	43 (4.24)	58 (6.02)	1.08 (0.80–1.46)	0.60		

*Analyzed as a time-dependent factor in longitudinal analysis of factors associated with incident pregnancy. N (%) or median (IQR) are from the time of enrollment.

**The multivariate model includes all factors that were significantly associated with pregnancy (at a level of $p<0.05$) in unadjusted analysis and not co-linear with other factors.

†As part of trial eligibility criteria, women were not using ART at enrollment. 447 (15%) women initiated ART during study follow up.

Table 2

Pregnancy incidence and outcomes among HIV-1 infected female partners of HIV-1 uninfected men randomized to PrEP or placebo

	Total	TDF	FTC/TDF	Placebo	p-value vs. placebo
Number of pregnancies	583	192	193	198	
Number of women who became pregnant	541	181	177	183	
Pregnancy incidence (95% CI)	12.9 (11.9–14.0)	13.2 (11.4–15.1)	12.4 (10.7–14.1)	13.2 (11.4–15.0)	TDF: 0.91 FTC/TDF: 0.48
Outcome					
Live birth	460 (78.90)	152 (79.17)	162 (83.94)	146 (73.74)	TDF: 0.18 FTC/TDF: 0.039
Pregnancy loss	90 (15.44)	32 (16.67)	23 (11.92)	35 (17.68)	
Unknown	25 (4.29)	8 (4.17)	5 (2.59)	12 (6.06)	
Live births: gestational age at birth					
Term birth	425 (74.3)	142 (75.1)	148 (77.5)	135 (70.3)	TDF: 0.59 FTC/TDF: 0.63
Premature birth	22 (3.9)	7 (3.7)	9 (4.7)	6 (3.1)	
Unknown	4 (0.7)	0 (0.0)	3 (1.6)	1 (0.5)	
Pregnancy losses: gestational age at loss					
<20 weeks	60 (10.5)	20 (10.6)	15 (7.9)	25 (13.0)	TDF: 0.40 FTC/TDF: 0.45
20–36 weeks	23 (4.0)	10 (5.3)	7 (3.7)	6 (3.1)	
≥37 weeks	6 (1.1)	2 (1.1)	1 (0.5)	3 (1.6)	