High medication adherence during periconception periods among HIV-1-uninfected women participating in a clinical trial of antiretroviral pre-exposure prophylaxis

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Background

- For women at risk for HIV-1 acquisition, pregnancy desires are common.
- Pregnancy incidence has been high among HIV-1 uninfected women in biomedical HIV-1 prevention trials, including trials of pre-exposure prophylaxis (PrEP).
- Understanding PrEP adherence in the context of conception is important given the potential of periconception PrEP as a component of safer conception strategies for HIV-1-uninfected women (Matthews *AIDS* 2010, Vernazza *AIDS* 2011, Lampe *Am J Obst Gyn* 2011).
- This study evaluated predictors of pregnancy and adherence to study medication before and during periconception periods among HIV-1-uninfected women in serodiscordant partnerships enrolled in a randomized, placebo-controlled trial of oral PrEP (Baeten *NEJM* 2012).

Methods

Study Setting & Participants

The Partners PrEP Study was a phase III, randomized, double-blind, placebo-controlled clinical trial of

- daily oral TDF,
- daily oral FTC/TDF,
- or placebo provided to HIV-1 uninfected members of 4747 HIV-1 serodiscordant couples from 9 research sites in Kenya and Uganda.

HIV-1 uninfected women were neither pregnant nor planning pregnancy at the time of enrollment, counseled to delay pregnancy until the end of the study, and offered contraception, provided at no cost on-site. Study drug was held during pregnancy and breastfeeding.

Monthly visits included rapid HIV-1 testing, dispensation of study medication, adherence counseling, pregnancy testing with urine β-hCG, counseling about and provision of contraception.

Measures

Interviewer-administered questionnaires captured demographic, partnership characteristics, sexual behavior, contraceptive use, and medical history data.

Urine β-hCG testing at monthly study visits was used to detect pregnancy

Adherence was measured with

- Clinic-based pill counts. Adherence was calculated from monthly clinic counts of dispensed and returned study pills, based on date of study dispensation and days since last visit.
- Stored plasma from selected study visits was tested for tenofovir drug concentrations.

Analysis

This analysis includes data collected up to July 2011 and is limited to 1785 couples with HIV-1 uninfected female partners.

- **Pregnancy incidence:** Number of new pregnancies divided by the total person-years of follow up
- **Factors associated with pregnancy:** Baseline and time-dependent factors associated with pregnancy were examined using an Andersen-Gill extension to the Cox proportional hazards model.
- **Adherence to study drug was analyzed in three ways:**
  1. We compared the relative risk of adhering to at least 80% of study drug doses among HIV-1 uninfected women who experienced pregnancy compared with women who did not experience pregnancy using log-binomial regression with GEE.
  2. For women who became pregnant, we evaluated adherence during the periconception period (3 months prior to the visit at which pregnancy was discovered), compared with follow-up prior to the periconception period using conditional logistic regression.
  3. Tenofovir plasma concentrations were available from
     - 76 women who became pregnant at the visit when their pregnancy was first discovered (77 specimens, with one woman having two pregnancies), **case samples**
     - 103 women who did not become pregnant (329 specimens across their follow-up), **cohort samples.**

     We used a case-cohort design and Cox proportional hazards regression to compare the likelihood of having detectable tenofovir at pregnancy visits versus non-pregnancy visits.

Results

Table 1. Participant characteristics at enrollment

	Prevalence or Frequency
	N (%) or median (IQR)
Active PrEP arm	1164 (65%)
Age	33 (28 - 38)
18-29 years	586 (33%)
30-39 years	832 (47%)
40+ years	367 (21%)
Partnership duration (years)	12 (6 - 19)
Number of children	4 (2 - 5)
Any income (ref. none)	1242 (69)
Coital frequency	4 (2 - 8)
Any unprotected sex with study partner	406 (23%)
Any sex with additional partner(s)	8 (0.5%)
BMI (kg/m2)	23 (21 – 26)
No effective contraception†	948 (53%)
Sexually transmitted infection *	144 (8%)
Age of male partner (years)	39 (33 - 44)
18-29 years	182 (10%)
30-39 years	788 (44%)
40+ years	815 (46%)
Male partner ART use	--
Male partner CD4 cell count (cells/mm3)	457 (354-596)
<250	0 (0%)
250-349	420 (24%)
350-500	649 (36%)
> 500	716 (40%)

† Effective contraception defined as use of oral, injectable, implant, or IUD; women having undergone a hysterectomy were excluded from the analysis.

* Sexually-transmitted infections including Neisseria gonorrheae, Chlamydia trachomatis, and Trichomonas vaginalis

Pregnancy incidence & associated factors

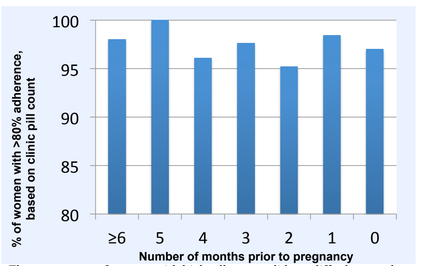
- During 2827.5 person-years of follow-up, 267 women had 288 pregnancies:
  10.2 pregnancies per 100 person-years of follow-up (95% CI 9.1 – 11.3)
- Factors associated with incident pregnancy are shown in Table 3.

Table 3. Factors associated with incident pregnancy

Variable	aHR (95% CI)
Age (years) 18-29 30-39 ≥ 40	 11.12 (5.23-23.63) 5.78 (2.86-11.70) Ref.
Unprotected sex with study partner	3.04 (2.28-4.05)
Additional partners during follow-up	2.57 (1.44-4.56)
Not using effective contraception	3.89 (2.93-5.16)

Adjusted for factors significant in unadjusted analysis including partnership duration, STI, age of male partner.

Figure 1. Adherence relative to pregnancy among 267 women with pregnancies.



The percentage of women with high adherence did not differ by month.

Tables 2A-C. Adherence to study medication (PrEP/placebo)

2A. Clinic-based pill count adherence, women experiencing pregnancy vs. women not experiencing pregnancy

	% of visit months with ≥ 80% adherence	RR (95% CI) p-value	Adjusted RR (95% CI) p-value
Ever pregnant during follow-up	97.7	0.99 (0.98-0.99) p=0.01	0.99 (0.98-1.00) p=0.12
Never pregnant during follow-up	98.7	Ref.	Ref.

Population: all women. Analysis: log binomial regression with GEE
Adjusted analysis controls for age, unprotected sex, sex with an additional partner, use of an effective contraceptive method, and time in the study.

2B. Clinic-based pill count adherence, limited to women experiencing pregnancy

	% of visit months with ≥ 80% adherence	OR (95% CI) p-value	Adjusted OR (95% CI) p-value
Periconception period	94.4	0.88 (0.50-1.55) p=0.65	1.01 (0.50-2.04) p=0.98
Visits before periconception period	97.1	Reference	Reference

Population: women experiencing pregnancy. Analysis: conditional logistic regression. Adjusted analysis as per 2A.

2C. Tenofovir detection in plasma, women assigned to active PrEP

	% visits with detectable tenofovir	HR (95% CI) p-value	Adjusted HR (95% CI) p-value
Visits when pregnancy discovered (cases)	71.4	0.59 (0.34-1.03) p=0.06	0.81 (0.43-1.52) p = 0.51
Visits from non-pregnant women (cohort)	80.5	Reference	Reference

Population: women in the active PrEP arms, including women who experienced pregnancy and a random selection of women without pregnancy.
Analysis: case-cohort design to up-weight data from women in the random sample and Cox proportional hazards regression. Adjusted analysis as per 2A.

Discussion

In this study, just over half of women used effective contraception and pregnancy incidence was 10% per year among HIV-1 uninfected women with HIV-1 infected partners.

- Our data did not show an association with partner CD4 cell count or ART use, suggesting that women were not making decisions to conceive based on clinical markers of HIV-1 transmission risk from their partners.
- High pregnancy incidence in studies providing access to and counseling about contraception highlights the importance of HIV-1 prevention for women who may want to conceive with a high-risk partner.
- Sexually-active women of reproductive age who are not on contraception may benefit from routine discussions of fertility goals and counseling for the best HIV-1 risk reduction strategies.

By multiple measures, adherence to study drug was high among women experiencing pregnancy.

- Women with and without pregnancies had high adherence to study drug, as measured both by pill counts and detection of tenofovir in plasma.
- Women with pregnancy were adherent to study drug, including during the periconception period.
- Data suggest that women were willing to use PrEP around the time of conception, even in the absence of data regarding the safety and efficacy of PrEP for HIV-1 prevention.

Conclusions

Our study shows that women at risk for HIV-1 acquisition within stable, mutually-disclosed, HIV-1-serodiscordant partnerships, with understanding of that risk, and ready access to condoms, contraception, and counseling still have a high pregnancy rate.

In addition, they remained highly adherent to PrEP, both overall and around the time of conception. Now that FTC/TDF is approved for use as oral PrEP and there is enthusiasm for PrEP as a safer conception strategy, implementation and demonstration projects should include women with pregnancy or plans for pregnancy in order to understand the risks, benefits, and challenges to biomedical prevention in this high priority group.

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