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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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Introduction: Pre-exposure prophylaxis (PrEP) may be an important safer conception strategy for HIV-1–uninfected women with HIV-1–infected partners. Understanding medication adherence in this population may inform whether PrEP is a feasible safer conception strategy.

Methods: We evaluated predictors of pregnancy and adherence to study medication among HIV-1–uninfected women enrolled in a randomized placebo-controlled trial of PrEP among African HIV-1–serodiscordant couples. Participants were counseled on HIV-1 risk reduction, contraception, and adherence and tested for pregnancy at monthly study visits. Pill counts of dispensed drug were performed and, at a subset of visits, plasma was collected to measure active drug concentration.

Results: Among 1785 women, pregnancy incidence was 10.2 per 100 person-years. Younger age, not using contraception, having an additional sexual partner, and reporting unprotected sex were associated with increased likelihood of pregnancy. Monthly clinic pill counts estimated that women experiencing pregnancy took 97% of prescribed doses overall, with at least 80% pill adherence for 98% of study months, and no difference in adherence in the periconception period compared with previous periods ($P = 0.98$). Tenofovir was detected in plasma at 71% of visits where pregnancy was discovered. By multiple measures, adherence was similar for women experiencing and not experiencing pregnancy ($P \geq 0.1$).

Conclusions: In this clinical trial of PrEP, pregnancy incidence was 10% per year despite excellent access to effective contraception. Women experiencing pregnancy had high medication adherence, suggesting that PrEP may be an acceptable and feasible safer conception strategy for HIV-1–uninfected women with HIV-1–serodiscordant partners.

Key Words: pregnancy, HIV-1 prevention, pre-exposure prophylaxis, adherence, safer conception, serodiscordant couples, sub-Saharan Africa

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Members of the Partners PrEP Study Team are listed in Appendix.

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INTRODUCTION

For women in sub-Saharan Africa, having biologic children is important to secure a relationship, prove suitability as a spouse, maintain marriage, expand family lineage, and demonstrate health.^{1,2} For women at risk for HIV-1 acquisition, including women in HIV-1–serodiscordant relationships (where 1 partner is HIV-1 infected and the other is not), pregnancy desires are common^{3–6} but conception attempts risk sexual HIV-1 acquisition. HIV-1–uninfected women who attempt to conceive with an HIV-1–infected partner or a partner of unknown HIV-1 status need safe, feasible, and effective strategies to reduce HIV-1 acquisition risk.

Antiretroviral pre-exposure prophylaxis (PrEP) could be a key component of safer conception strategies for women in HIV-1–serodiscordant couples, particularly when the infected partner is not eligible, willing, or able to take antiretroviral treatment (ART).^{7–13} Oral tenofovir (TDF) and co-formulated emtricitabine (FTC)/TDF, the antiretrovirals

studied in PrEP efficacy trials conducted to date, have an excellent safety profile among pregnant and breastfeeding women^{14,15}; however, clinical trials of PrEP, like most trials of novel pharmacologic therapies, encouraged delaying pregnancy and withheld study drug during pregnancy to minimize fetal exposure. Nevertheless, pregnancy incidence has been high among HIV-1–uninfected women in trials of biomedical HIV-1 prevention interventions, including trials of PrEP.^{16–20} Given high pregnancy incidence and associated risks of HIV-1 acquisition, understanding correlates of pregnancy among women in HIV-1 prevention trials may inform safer conception programs.

PrEP effectiveness is highly dependent on adherence,^{7,8,21–23} and PrEP efficacy trials offer an early opportunity to identify populations for whom medication adherence may be challenging. Women who desire children might adhere to prevention strategies to protect a potential child from acquiring HIV-1^{4,24–26} or, alternatively, may not adhere out of fear of side effects, including effects on the fetus. Understanding PrEP adherence in the context of conception is important given the potential of periconception PrEP as an HIV-1 risk-reduction strategy.^{10–12,27}

We evaluated predictors of pregnancy and adherence to study medication before and during periconception among African HIV-1–uninfected women in serodiscordant partnerships enrolled in a randomized placebo-controlled trial of oral PrEP.

METHODS

Study Population and Procedures

The Partners PrEP Study was a phase III, randomized, double-blind, placebo-controlled, 3-arm clinical trial of daily oral TDF and FTC/TDF PrEP or placebo provided to HIV-1–uninfected members of HIV-1–serodiscordant couples. Beginning in July 2008, 4747 HIV-1–serodiscordant couples were enrolled and followed at 9 research sites in Kenya and Uganda. Eligible couples were sexually active and planned to remain in the relationship for the duration of the study. HIV-1–uninfected participants had normal renal function and were not infected with Hepatitis B virus. HIV-1–uninfected women were neither pregnant nor immediately 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. HIV-1–infected partners were not receiving and did not meet Kenyan or Ugandan guidelines for initiation of ART at enrollment and were monitored and actively referred for ART initiation if they became eligible during study follow-up. At each study visit, couples received a package of HIV-1 prevention services, including risk-reduction counseling, couples counseling, and condoms.^{8,28}

At monthly follow-up visits for up to 36 months, HIV-1–uninfected partners underwent rapid HIV-1 testing, dispensation of study medication, and adherence counseling. For HIV-1–uninfected women, monthly visits included pregnancy testing with urine β -HCG and contraceptive counseling and provision; pregnant women were referred to local antenatal clinics, and study drug was held during pregnancy and

breastfeeding. Testing for sexually transmitted infections (*Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Trichomonas vaginalis*) was conducted at baseline and annually. Interviewer-administered questionnaires captured demographic, partnership characteristics, sexual behavior, contraceptive use, and medical history data.

In July 2011, the trial's independent Data and Safety Monitoring Board recommended discontinuation of the trial placebo arm and public report of the results due to demonstration of PrEP efficacy for HIV-1 protection.⁸

The study protocol was reviewed by human subjects committees at the University of Washington and all study sites. Participants provided written informed consent.

Statistical Methods

This analysis includes data collected up to July 2011, when primary efficacy results were disseminated and the placebo arm was discontinued, and is limited to 1785 couples with HIV-1–uninfected female partners. Follow-up time from women who seroconverted to HIV-1 was censored at the time of seroconversion.

Pregnancy Incidence and Correlates

Pregnancy incidence was calculated as the number of new pregnancies divided by the total person-years of follow-up (excluding pregnant follow-up time). Baseline and time-dependent factors associated with incident pregnancy were examined using an Andersen–Gill²⁹ extension to the Cox proportional hazards model to allow for multiple pregnancies per woman. Adjusted models included all factors associated with incident pregnancy in univariate analysis at $P < 0.05$.

Study Medication Adherence Among Women With and Without Pregnancy

We used several approaches to assess adherence to study medication. Pill count adherence was calculated from monthly clinic counts of dispensed and returned study pills, based on date of study dispensation and days since last visit. Missed visits were assigned an adherence value of zero because a missed visit corresponded with no pills dispensed. Previous work conducted in a subset of Partner PrEP Study participants showed high correlation between clinic-based pill counts, unannounced home pill counts, and electronic monitoring of pill bottle opening.³⁰

We used log-binomial regression with generalized estimating equations to compare 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.³¹ High adherence was defined as taking at least 80% of doses based on biologic plausibility,³² prior definitions of low and high adherence to antiretroviral PrEP,⁷ and prior adherence data from this study.³⁰ A priori specified covariates included age, unprotected sex, sex with an additional partner, use of an effective contraceptive method, and time in the study.

To examine the relationship between periconception periods of follow-up and adherence to study drug restricted to women who became pregnant (thus removing differences between women who did and did not experience pregnancy), we evaluated adherence during the periconception period, defined as the 3 months before the visit at which the first pregnancy was discovered, compared with follow-up before the periconception period. To minimize confounding by enrollment characteristics that could be associated with both adherence and becoming pregnant, we used conditional logistic regression³³ with adjustment for time-dependent confounders (any unprotected sex, sex with an additional partner, use of an effective contraceptive method, and time in the study), selected a priori based on factors with strong associations with pregnancy.

Finally, for women randomized to the trial's active arms (TDF or FTC/TDF), stored plasma from selected study visits was tested for tenofovir drug concentrations, using methods previously described (assay limit of quantitation = 0.3 ng/mL).⁸ For the present analysis, we tested samples from the visit at which pregnancy was first discovered among women who became pregnant and had a sample available from this study visit. Detection of tenofovir was compared between these samples and specimens from a randomly selected cohort of women who did not become pregnant; samples from the random cohort were tested from across the study follow-up (months 1, 3, 6, 12, 18, 24, and 36, as available depending on the length of follow-up). For this analysis, a priori specified covariates included age, any unprotected sex, sex with an additional partner, use of an effective contraceptive method, and time in the study. This analysis was conducted in R version 2.12.2 using the Lumley survey package (version 3.26 <http://faculty.washington.edu/tlumley/survey/>).³⁴ All other analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Participant Characteristics

The median age of the 1785 HIV-1-uninfected women included in this analysis was 33 years [interquartile range (IQR), 28–38], median partnership duration was 12 years (IQR, 6–19), and median number of children was 4 (2–5) with 5% of women reporting no children (Table 1). Twenty-three percent of women reported sex without condoms in the month before enrollment and 53% were not using effective contraception.

Pregnancy Incidence and Predictors

During 2827.5 person-years of follow-up, 267 women had 288 pregnancies for an incidence of 10.2 pregnancies per 100 person-years of follow-up [95% confidence interval (CI): 9.1 to 11.3]. Of the 267 women who became pregnant, 247 had 1 pregnancy and 20 had 2 pregnancies. Pregnancies occurred steadily throughout the follow-up period (data not shown). In multivariate analysis, multiple factors were independently associated with increased likelihood of

pregnancy (Table 1): unprotected sex with the study partner [adjusted hazard ratio (aHR), 3.04; 95% CI: 2.28 to 4.05], having an additional sexual partner during follow-up (aHR, 2.57; 95% CI: 1.44 to 4.56), younger age (aHR, 11.12, 95% CI: 5.23 to 23.63, for age 18–29 and aHR 5.78, 95% CI: 2.86 to 11.70, for age 30–39, each compared with age \geq 40 years), and not using effective contraception (aHR 3.89, 95% CI: 2.93 to 5.16). Effective contraceptive use was reported at 57.6% of follow-up visits, a proportion that was relatively consistent throughout follow-up (ranging from 54.1% to 62.2%).

Pregnancy and Adherence to Study Drug

Clinic-based pill count adherence was high, with 97.0% (SD, 6.9) of dispensed pills taken by women who experienced a pregnancy and 97.9% (SD, 6.0) taken by women without pregnancies. High adherence (defined as \geq 80% of dispensed pills taken) was present at 97.7% of visits among women who became pregnant, which was not statistically different than among women who did not become pregnant, for whom \geq 80% adherence was present for 98.7% of visits [adjusted relative risk (aRR), 0.99; 95% CI: 0.99 to 1.0; Table 2].

To discern whether adherence differed relative to the time of pregnancy, we conducted an analysis of adherence among the subset of women who became pregnant. In these women, the likelihood of adhering to at least 80% of pills dispensed during the 3-month periconception period was similar to other time points before pregnancy in unadjusted analysis (odds ratio, 0.88; 95% CI: 0.50 to 1.55) and after adjustment for effective contraceptive use, unprotected sex, additional partners, and time in study (adjusted odds ratio = 1.01; 95% CI: 0.50 to 2.04; $P = 0.98$) (Fig. 1 and Table 2).

We also evaluated tenofovir concentrations among pregnant and nonpregnant follow-up periods. Tenofovir plasma concentrations were available from 76 women who became pregnant at the visit when their pregnancy was first discovered (77 specimens, with 1 woman having 2 pregnancies) and 103 women who did not become pregnant (329 specimens across their follow-up, with a median of 4 samples per woman). Tenofovir was detectable (consistent with dosing in the previous week) in 71% (55/77) of specimens from women who became pregnant and 81% (252/313) of specimens from women not experiencing pregnancy (aHR, 0.81; 95% CI: 0.43 to 1.52). There was also no statistically significant difference when a higher concentration cutoff was used (\geq 40 ng/mL of tenofovir, suggesting steady-state dosing, data not shown).

DISCUSSION

As in many clinical trials of biomedical interventions, women were eligible for enrollment into the Partners PrEP Study if they were not pregnant and reported no plans for pregnancy. The trial protocol included counseling to avoid pregnancy, contraceptive counseling, and provision of free contraception, without a requirement for contraception. In these circumstances, just over half of women used effective contraception, and pregnancy incidence was 10% per year

TABLE 1. Participant Characteristics and Associations With Incident Pregnancy

| | Prevalence/Frequency at Baseline | Factors Associated With Incident Pregnancy | | | |
|---|----------------------------------|--|--------|-----------------------|------------|
| | N (%) or Median (IQR) | Unadjusted HR (95% CI) | P | Adjusted HR (95% CI) | Adjusted P |
| Demographic characteristics | | | | | |
| Active PrEP arm (ref. placebo) | 1164 (65) | 1.00 (0.77 to 1.29) | 1.0 | | |
| Age (yrs) | 33 (28–38) | — | — | — | — |
| 18–29 | 586 (33) | 13.17 (6.73 to 25.79) | <0.001 | 11.12 (5.23 to 23.63) | <0.001 |
| 30–39 | 832 (47) | 6.08 (3.09 to 11.96) | <0.001 | 5.78 (2.86 to 11.70) | <0.001 |
| ≥40 | 367 (21) | Reference | — | Reference | — |
| Partnership duration (yrs) | 12 (6–19) | 0.93 (0.91 to 0.94) | <0.001 | 0.98 (0.96 to 1.01) | 0.1 |
| Number of children | 4 (2–5) | — | — | — | — |
| 0 | 81 (5) | Reference | — | — | — |
| 1 child | 183 (10) | 1.73 (0.89 to 3.35) | 0.1 | — | — |
| 2–3 children | 553 (31) | 1.27 (0.68 to 2.40) | 0.5 | — | — |
| >4 children | 968 (54) | 0.83 (0.44 to 1.55) | 0.6 | — | — |
| Any income (ref. none) | 1242 (69) | 0.83 (0.65 to 1.08) | 0.2 | — | — |
| Sexual behavior | | | | | |
| Coital frequency* | 4 (2–8) | 1.02 (1.00 to 1.05) | 0.05 | — | — |
| Any unprotected sex with study partner (ref. none)* | 406 (23) | 2.93 (2.24 to 3.83) | <0.001 | 3.04 (2.28 to 4.05) | <0.001 |
| Any sex with additional partner(s) (ref. none)* | 8 (0.5) | 3.28 (1.96 to 5.49) | <0.001 | 2.57 (1.44 to 4.56) | 0.001 |
| Clinical characteristics | | | | | |
| BMI (kg/m ²) | 23 (21–26) | — | — | — | — |
| <18.5 | 100 (6) | 1.21 (0.77 to 1.90) | 0.4 | — | — |
| 18.5–24.9 | 1160 (65) | Reference | — | — | — |
| 25–29.9 | 389 (22) | 0.95 (0.70 to 1.29) | 0.7 | — | — |
| ≥30 | 136 (8) | 0.75 (0.46 to 1.22) | 0.2 | — | — |
| No effective contraception† (ref. any contraception)* | 948 (53) | 2.80 (2.16 to 3.63) | <0.001 | 3.89 (2.93 to 5.16) | <0.001 |
| Sexually transmitted infection‡ | 144 (8) | 1.53 (1.02 to 2.28) | 0.04 | 1.35 (0.90 to 2.02) | 0.2 |
| Male partner characteristics | | | | | |
| Age of male partner (yrs) | 39 (33–44) | — | — | — | — |
| 18–29 | 182 (10) | 3.64 (2.53 to 5.25) | <0.001 | 1.25 (0.80 to 1.93) | 0.3 |
| 30–39 | 788 (44) | 2.48 (1.86 to 3.31) | <0.001 | 1.35 (0.98 to 1.86) | 0.06 |
| ≥40 | 815 (46) | Reference | — | — | — |
| Male partner ART use* | — | 0.56 (0.31 to 1.01) | 0.06 | — | — |
| Male partner CD4 cell count (cells/mm ³)* | 457 (354–596) | — | — | — | — |
| <250 | 0 (0) | 0.75 (0.53 to 1.06) | 0.1 | — | — |
| 250–349 | 420 (24) | 0.90 (0.69 to 1.18) | 0.5 | — | — |
| 350–500 | 649 (36) | 1.02 (0.62 to 1.67) | 0.9 | — | — |
| >500 | 716 (40) | Reference | — | — | — |

*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.

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

‡Sexually transmitted infections including *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Trichomonas vaginalis*.

among HIV-1–uninfected women with HIV-1–infected partners. By multiple measures, adherence to study drug (blinded PrEP or placebo) was high among women experiencing pregnancy.

Medication adherence has been low in some studies of PrEP for women.^{22,23} However, in the Partners PrEP Study, adherence was high, by multiple measures.^{8,30} In the present analysis, we found that women with and without pregnancies had high adherence to study drug, as measured both by pill counts and detection of tenofovir in plasma. Because women

in PrEP trials have been encouraged to delay pregnancy and counseled about unclear safety data for tenofovir use in early pregnancy, we explored whether women with pregnancy were less likely to take study drug during the periconception period, but found no difference. These 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.

In contrast to these results, among women with pregnancy in CAPRISA 004, a median of 50% of sex acts

TABLE 2. Adherence to Study Medication (PrEP/Placebo), by Multiple Measures

| | % of Visit Months With ≥80% Adherence | RR of ≥80% Adherence (95% CI); P | Adjusted RR of ≥80% Adherence (95% CI); P |
|---|---------------------------------------|--|---|
| Clinic-based pill count adherence, women experiencing pregnancy vs. women not experiencing pregnancy* | | | |
| Ever pregnant during follow-up | 97.7 | 0.99 (0.98 to 0.99); 0.01 | 0.99 (0.98 to 1.00); 0.12 |
| Never pregnant during follow-up | 98.7 | Reference | Reference |
| | % of Visit Months With ≥80% Adherence | OR of ≥80% Adherence (95% CI); P | Adjusted OR of ≥80% Adherence (95% CI); P |
| Clinic-based pill count adherence, limited to women experiencing pregnancy† | | | |
| Periconception period | 94.4 | 0.88 (0.50 to 1.55); 0.65 | 1.01 (0.50 to 2.04); 0.98 |
| Visits before periconception period | 97.1 | Reference | Reference |
| | % Visits With Detectable Tenofovir | HR of Detectable Tenofovir (95% CI); P | Adjusted HR of Detectable Tenofovir (95% CI); P |
| Tenofovir detection in plasma, women assigned to active PrEP (TDF or FTC/TDF)‡ | | | |
| Visits when pregnancy discovered (cases) | 71.4 | 0.59 (0.34 to 1.03); 0.06 | 0.81 (0.43 to 1.52); 0.51 |
| Visits from nonpregnant women (cohort) | 80.5 | Reference | Reference |

*Population: all women. Analysis: log-binomial regression with generalized estimating equations; adjusted analysis controls for age, unprotected sex, sex with an additional partner, use of an effective contraceptive method, and time in the study.

†Population: women experiencing pregnancy. Analysis: conditional logistic regression; adjusted analysis controls for unprotected sex, sex with an additional partner, use of an effective contraceptive method, and time in the study.

‡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 use a Cox proportional hazards regression; adjusted analysis controls for age, unprotected sex, sex with an additional partner, use of an effective contraceptive method, and time in the study.

HR, hazard ratio; OR, odds ratio; RR, relative risk.

were protected according to the dosing schedule of 2 gel applications per sex act. Women with pregnancy were about half as likely to adhere to at least 80% of study gel doses compared with women without pregnancy.³⁵ Several differences in study populations may explain these differences. The CAPRISA 004 study required participants to start contraception at trial entry—use was 100% at baseline and 97% at

18 months³⁶; thus, women with pregnancies in that study may have been less likely to adhere to study gel because pregnancies also likely reflected nonadherence to contraception. In addition, CAPRISA 004 enrolled individual younger women (median age 22) at high risk for HIV-1 acquisition, whereas the Partners PrEP Study enrolled older women (median age, 33) in known HIV-1-serodiscordant couples.

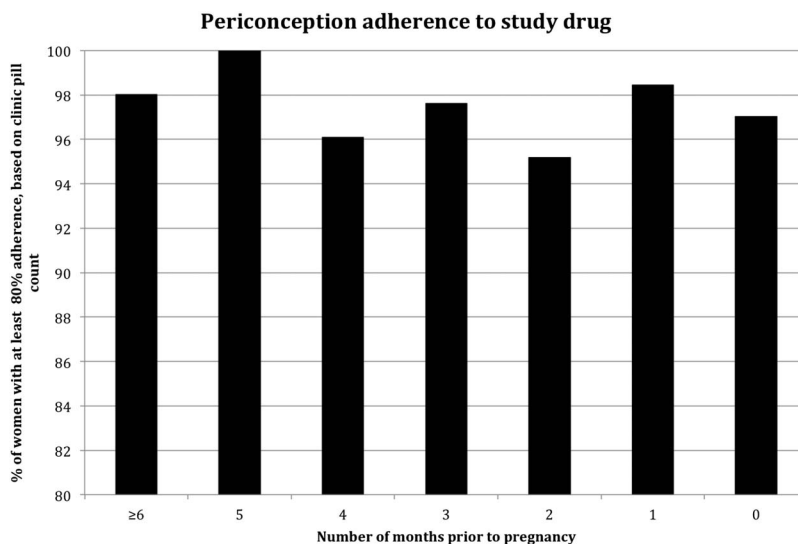


FIGURE 1. Adherence relative to pregnancy among 267 women with pregnancies. Percentage of women taking at least 80% of pills prescribed (by clinic-based pill count) is graphed on the y axis. Number of months before pregnancy is on the x axis, month 0 is the month where pregnancy was first detected. The percentage of women with high adherence did not differ by month.

Qualitative data suggest that higher medication adherence in the Partners PrEP Study may have been partially because of partner involvement.³⁷ In addition, although neither trial reported prospective pregnancy intention data, qualitative interviews with 36 couples experiencing pregnancy while enrolled in the Partners PrEP Study suggested that most intended to become pregnant or were pleased when they discovered they were pregnant.³⁸ Thus, it is possible that most of the pregnancies in the Partners PrEP Study were intended or planned.

HIV-1 prevention studies enrolling women from sub-Saharan Africa have reported pregnancy incidence ranging from 3.95/100 person-years in the CAPRISA 004 trial of tenofovir vaginal gel in South Africa³⁶ to 52/100 person-years in a phase 2 trial of oral tenofovir in West Africa.¹⁹ 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 an infected or high-risk partner.^{39,40} Factors associated with incident pregnancy in this study included younger age, unprotected sex, having an outside partner, and not being on effective contraception. These associations are intuitive and consistent with previous reports of pregnancy predictors among women enrolled in HIV-1 prevention trials.^{16–18,41} Interestingly, 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 markers of HIV-1 transmission risk from their partners. Our results do not point to a specific group to target in safer conception interventions but highlight that 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 given her goals. Women who enroll in a clinical trial without plans for pregnancy merit ongoing counseling sensitive to the fact that her goals may change over time.⁴⁰

Limitations to this study include interpreting pregnancy incidence without prospective data around fertility intention. Second, studying adherence to an intervention with unknown efficacy (at the time of the study) with blinded randomization to placebo makes both the measure of adherence and the significance of the findings an imperfect reflection of what delivery of effective PrEP might find. Although this analysis focuses on the periconception period, women having children within serodiscordant partnerships remain at risk after conception. Couples who achieve pregnancy are at particular risk for transmitting and acquiring HIV with associated risks of perinatal transmission.^{42–44} Risk-reduction interventions, including PrEP, should continue to be evaluated for women during pregnancy and postpartum periods.

In conclusion, these data show that women at risk for HIV-1 acquisition within stable, mutually disclosed, HIV-1-serodiscordant partnerships, with understanding of that risk,⁴⁵ and with 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 and recommended for use as oral PrEP^{46–48} and there is enthusiasm for PrEP as a safer conception strategy,^{10–12} implementation and demonstration projects should

include women with pregnancy and/or plans for pregnancy to understand the risks, the benefits, and challenges to biomedical prevention in this high priority group.

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APPENDIX. Partners PrEP Study Team

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