



RESEARCH ARTICLE

REVISED Pre-exposure prophylaxis for HIV-negative persons with partners living with HIV: uptake, use, and effectiveness in an open-label demonstration project in East Africa [version 2; peer review: 2 approved]

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Abstract

Background: Pre-exposure prophylaxis (PrEP) can provide high protection against HIV infection and is a recommended intervention for HIV-negative persons with substantial HIV risk. Demonstration projects conducted in diverse settings worldwide illustrate practical examples of how PrEP can be delivered. This manuscript presents estimates of effectiveness and patterns

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Invited Reviewers

of PrEP use within a two-year demonstration project of PrEP for HIV-negative members of heterosexual HIV serodiscordant couples in East Africa.

Methods: The PrEP delivery model integrated PrEP into HIV treatment services, prioritizing PrEP use for HIV-negative partners within serodiscordant couples before and during the first 6 months after the partner living with HIV initiated antiretroviral therapy (ART). We measured PrEP uptake through pharmacy records and adherence to PrEP through medication event monitoring system (MEMS) bottle caps and quantification of tenofovir in plasma among a random sample of participants. We estimated HIV infections prevented using a counterfactual cohort simulated from the placebo arm of a previous PrEP clinical trial.

Results: We enrolled 1,010 HIV serodiscordant couples that were naïve to ART and PrEP. Ninety-seven percent of HIV-negative partners initiated PrEP. Objective measures suggest high adherence: 71% of HIV-negative participants took $\geq 80\%$ of expected doses, as recorded via MEMS, and 81% of plasma samples had tenofovir detected. Four incident HIV infections were observed (incidence rate=0.24 per 100 person-years), a 95% reduction (95% CI 86-98%, $p < 0.0001$) in HIV incidence, relative to estimated HIV incidence for the population in the absence of PrEP integrated into HIV treatment services.

Conclusions: PrEP uptake and adherence were high and incident HIV was rare in this PrEP demonstration project for African HIV-negative individuals whose partners were known to be living with HIV. Delivery of PrEP to HIV-negative partners within HIV serodiscordant couples was feasible and should be prioritized for wide-scale implementation.

Keywords

HIV prevention, HIV serodiscordant couples, PrEP, ART

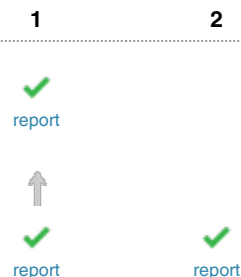
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version 1

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Competing interests: Gilead Sciences donated the PrEP medication but had no role in data collection or analysis. The authors disclosed no competing interests.

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REVISED Amendments from Version 1

We have made minor revisions to the manuscript text and Figures based on suggestions from Reviewers #1 and #2. Revisions were made to provide details about PrEP dosing and dispensing, how HIV RNA testing was incorporated in to the project, to add disaggregated data on men and women's use of PrEP, and to add details about participant sexual behavior. Figure 2 and Figure 3 were revised to improve clarity and add a legend.

See referee reports

Introduction

Pre-exposure prophylaxis (PrEP) is a new intervention to contribute to control of the global HIV epidemic¹⁻⁴. Delivery systems for PrEP that maximize impact and sustainability, while minimizing cost are ideal, especially in settings with limited resources and large numbers of people with substantial risk for HIV. Approaches that synergize with existing health programs – including HIV treatment, family planning, HIV testing and counseling, and antenatal care – can capitalize on opportunities that come with existing infrastructure and community health-seeking behavior, easing the process for introducing PrEP.

Demonstration projects are needed to introduce PrEP in different settings, target individuals with different levels of HIV risk, and pilot PrEP integration into different public health programs. Through demonstration projects, implementers can gauge the infrastructure needed to provide and scale up an intervention and how individuals incorporate a new intervention into their life⁵. They can also identify populations which will easily adopt a new intervention and which populations need targeted demand creation tools. For PrEP, demonstration projects were initiated immediately following clinical trials and continue to identify models that maximize adherence and create demand among people who are the best candidates⁶.

Partnerships between HIV-negative persons and people living with HIV, i.e. serodiscordant couples, have a high risk for transmission in the absence of HIV prevention interventions and are thus a priority population for delivery of novel HIV prevention tools. Because HIV transmission risk is greatest prior to initiation of antiretroviral therapy (ART) and consequent viral suppression in the partner living with HIV, PrEP can be a time-limited intervention for periods without ART use and/or viral suppression. Furthermore, when PrEP and ART are offered together as components of combination HIV prevention programs, couples have multiple options and can be encouraged to adopt strategies based on their preferences and true risk factors, in addition to continuous encouragement for sustained ART use by the partner living with HIV.

We conducted a demonstration project of PrEP for HIV prevention among HIV serodiscordant couples attending four HIV care clinics in East Africa. Interim results, focusing on HIV incidence reduction from this project, were previously reported⁷. Here, we present the final results from two years of follow up, including estimates of intervention effectiveness and patterns of PrEP uptake and use.

Methods

Study design. The Partners Demonstration Project (clinicaltrials.gov #NCT02775929) was an open-label evaluation of integrated delivery of PrEP and ART for high risk HIV serodiscordant couples. Four clinics located in Kampala and Kabwohe in Uganda and Thika and Kisumu in Kenya were engaged to deliver the intervention; all clinics were HIV care centers and also had experience with HIV prevention research. Whenever possible, operations for the intervention were designed to mirror implementation strategies used in public clinics, such as the use of text messages to remind participants about clinic appointments, so as to develop a scalable delivery approach.

Each clinic recruited HIV serodiscordant couples through referrals from voluntary counseling and testing centers, antenatal clinics, and ART clinics, and by conducting community outreach events that promoted couples-based HIV testing. Eligible couples were ≥ 18 years of age, sexually active, and intending to remain as a couple for at least one year. At the time of enrollment, HIV-negative partners had never used PrEP, had normal renal function (defined as an estimated creatinine clearance ≥ 60 mL/min using the Cockcroft-Gault equation with ideal body weight), were not infected with hepatitis B virus, and were not pregnant or breastfeeding. At enrollment, HIV-positive partners were not using ART and couples were excluded if the HIV-positive partner had WHO stage III or IV HIV disease conditions that indicated immediate need for ART. In addition, an explicit goal of the project was to recruit couples at high risk of HIV acquisition, in order to demonstrate PrEP delivery in couples most likely to benefit from the intervention. For that reason, couples were eligible only if they scored at least 5 points on a validated, empiric risk scoring tool which included variables for: age of the HIV-negative partner, marital status of the couple, any condomless sex within the couple during the past 30 days, male circumcision status of the HIV-negative partner, and HIV viral load of the partner living with HIV^{8,9}. Couples were encouraged to attend study visits together, scheduled 1 month after enrollment, 2 months later, and every 3 months thereafter for up to 24 months. At all visits, couples were offered comprehensive couples-based HIV prevention counseling, including condoms and syndromic management of sexually transmitted infections.

PrEP delivery. At enrollment, co-formulated emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) was offered to all HIV-negative participants as PrEP with a daily dosing schedule; participants electing not to initiate PrEP at enrollment were offered PrEP initiation at subsequent visits. PrEP was prescribed and dispensed at each study visit with participants being given 1, 2, or 3 bottles corresponding to the time until their next appointment date. Adherence counseling for PrEP was conducted using streamlined messages with a focus on individual barriers to daily use and methods to overcome barriers¹⁰. For participants using PrEP, serum creatinine was measured 1 month after initiation and every 6 months thereafter. Creatinine confirmatory testing was conducted in cases of a Grade 1 or higher elevation. PrEP was temporarily withheld pending confirmatory testing if the creatinine elevation was Grade 2 or higher. PrEP was permanently discontinued for confirmed Grade 2 or higher events or if creatinine clearance was < 50 mL/min.

Partners living with HIV were encouraged to initiate ART as soon as possible according to national guidelines. At the start of the study, ART was available in public clinics to people living with HIV whose CD4 count was <350 cells/uL or with clinical indication. Partway through the study, national guidelines in each country were revised to encourage ART initiation for any individual living with HIV in an HIV serodiscordant relationship. Thus, at that point, all partners living with HIV in this study became ART eligible. ART was available to participants through public clinics and at the demonstration project clinics. Participants living with HIV were evaluated for CD4 count and HIV RNA at study enrollment and at 6-monthly intervals during follow up.

HIV-negative participants using PrEP were encouraged to discontinue PrEP once their study partner living with HIV used ART for at least 6 months (Figure 1). Results from HIV RNA testing were not required to guide counseling about PrEP use and potential viral suppression to reflect the public delivery model in which HIV RNA testing was often unavailable. If available when PrEP discontinuation was considered, HIV RNA results could be used to identify the potential for non-adherence to ART; however, testing was conducted on a 6-monthly schedule timed to study start, not the ART initiation schedule, and testing may not have aligned with ART initiation. In lieu of requiring HIV RNA results, we adopted a conservative time of 6 months of ART use to obtain viral suppression based on data from HIV serodiscordant couples in clinical trials with carefully measured HIV RNA trajectories following ART initiation¹¹. The approach of using a calendar period since ART initiation is scalable in public clinics regardless of whether HIV RNA testing becomes more available.

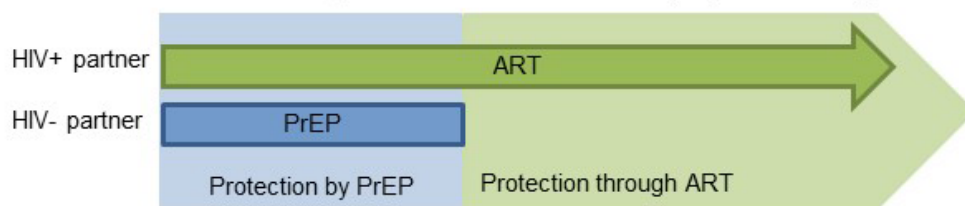
This strategy of time-limited PrEP use by the HIV-negative partner until the partner living with HIV sustained 6 months of ART use was included in counseling discussions with couples beginning with study screening. In cases of ART non-adherence, new sexual

partners with unknown HIV status or ART use disclosed by the HIV-negative partner, or pregnancy intentions within the couple, counselors encouraged the HIV-negative partner to continue PrEP.

PrEP adherence. We used medication event monitoring system (MEMS) caps to record all openings of PrEP pill bottles as our primary measure of adherence and self-reported use and pharmacy pill counts as additional measures of adherence; these were collected from all participants at all visits. Additionally, archived plasma from quarterly visits following PrEP dispensation was tested for quantification of tenofovir (TFV), the metabolized form of TDF, in a 15% random sample of participants. TFV levels were quantified using ultra-performance liquid chromatographic-tandem mass spectrometric (LC-MS/MS), with a limit of quantification of 0.31 ng/mL¹².

Incident HIV infection. HIV-negative partners underwent HIV testing prior to PrEP dispensing at each follow-up visit, following the national HIV rapid testing algorithms for Kenya and Uganda. Reactive results from rapid tests were confirmed with enzyme immunoassay (EIA) and HIV RNA quantification. For confirmed seroconverters, enrollment samples were quantified for HIV RNA; those positive for HIV RNA at enrollment were determined to have been infected prior to entry into the project. Seroconverters with negative HIV RNA results from enrollment samples were determined to have incident infections. For all seroconverters, archived plasma samples from the time point when seroconversion was detected underwent standard consensus sequencing of the *pol* region to detect HIV resistance. Additionally, for incident seroconversions, a sample from the study partner living with HIV was sequenced and sequences from both partners underwent phylogenetic analysis and posterior probability of linkage with the use of pairwise nucleotide distances between sequences to determine whether the incident infection likely originated with the study partner.

Scenario 1: PrEP used during first 6 months of ART use by a partner living with HIV



Scenario 2: PrEP used prior to ART initiation and during the first 6 months of ART use by a partner living with HIV

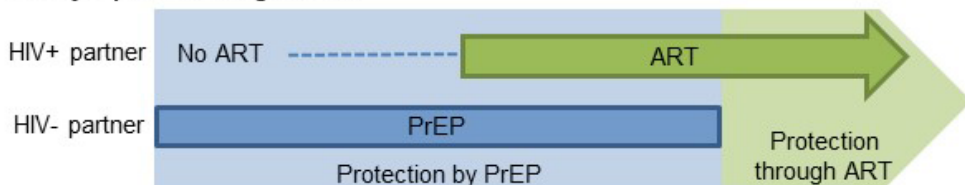


Figure 1. Strategy for PrEP delivery to HIV-negative persons with a partner known to be living with HIV.

Ethical statement

The study protocol was approved by the Human Subjects Division at the University of Washington (#STUDY00001674) and Ethics Review Committees overseeing each study site: Scientific Ethics Review Unit at the Kenya Medical Research Institute (SSC No. 2441), the Ethics Review Committee of Kenyatta National Hospital (P286/05/2012), and the AIDS Research Committee of the Uganda National Council of Science and Technology (ARC 135 and ARC126). All participants provided written informed consent.

Statistical methods. Characteristics of couples and patterns of PrEP use were summarized using descriptive statistics. Methods for developing a counterfactual comparison cohort have been described previously⁷. Briefly, we used data from the placebo arm of the prior Partners PrEP Study¹, a PrEP clinical trial conducted from 2008–2011 among HIV serodiscordant couples in the same research clinics, to simulate a comparable “non-intervention” cohort, frequency matched to the Partners Demonstration Project by HIV risk score and duration of study follow up. The mean number of HIV infections expected in the counterfactual population was averaged over 10,000 bootstrap samples and a 95% confidence interval was defined by the 2.5th and 97.5th quantiles. The incidence rate ratio was computed comparing actual HIV incidence observed in the current study to the mean estimate from the counterfactual population; a 95% confidence interval was calculated using a Poisson distribution, and the p-value was estimated from the bootstrap distribution. Additional bootstrap distributions were constructed with restriction to the age and gender of the HIV-negative partner (one per gender) and enrollment plasma HIV RNA concentrations of the partner living with HIV, to create stratified estimates for these subgroups. All simulations excluded data from couples (n=3) whose HIV-infected partner was determined retrospectively to have been using ART at study enrollment. The bootstrap analyses and descriptive statistics were conducted using SAS version 9.4 (SAS Institute) and figures were generated using Powerpoint 2016 (Microsoft, USA) and Tableau 10.3 (Tableau Software, Seattle, USA).

Results

Participant characteristics. In total, 1694 couples were screened and 1013 enrolled between November 2012 and August 2014. Participant visits were conducted through June 2016 when all had been followed for 24 months. Primary reasons for not being eligible to enroll included having a risk score <5, WHO stage >2 for the partner living with HIV, and abnormal renal values for the HIV-negative partner⁷. Three couples were excluded from the analysis due to retrospectively ascertained use of ART at enrollment. At baseline, a substantial proportion of couples had characteristics that were consistent with having high risk for HIV transmission: 41% of the partners living with HIV had plasma HIV RNA concentrations >50,000 copies/ml and 65% of couples reported condomless sex in the prior month (Table 1). Two-thirds of couples had HIV-negative male partners and 67% of these were not circumcised. Most couples were married (94%) and although the median time living together was 2.3 years (interquartile range [IQR] 0.8–6.3), very few couples had known their HIV discordant status more than a few months (median time known discordant 0.1 years, interquartile range [IQR] 0.1–0.3). Couples contributed a total of 1690.5 person-years of follow up time. Retention was above 83% at all visits.

Table 1. Characteristics of couples enrolled in the Partners Demonstration Project.

Characteristics of couples	N (%) or Median (IQR)
Total couples	1010
Married to each other	954 (94%)
Years living together	2.3 (0.8, 6.3)
Years aware of discordant status	0.1 (0.1, 0.3)
Proportion without children	570 (56%)
HIV risk score*	6 (6, 8)
Number of sex acts between partners, prior month**	5 (3, 10)
Any condomless sex acts between partners, prior month**	653 (65%)
Either partner had outside partners, prior month	118 (12%)
Characteristics of HIV-negative partners	
Male gender	677 (67%)
Age, years	30 (26, 36)
Education, years	8 (7, 12)
Any monthly income	868 (86%)
Circumcised, for male HIV-negative partners	452 (67%)
Characteristics of partners living with HIV	
Male gender	333 (33%)
Age, years	28 (23, 35)
Education, years	8 (6, 11)
Any monthly income	736 (73%)
CD4 cell count (cells/uL)	436.0 (272.5, 638.0)
Viral load (log ₁₀ copies/ml)	4.6 (3.9, 5.0)
Viral load >50,000 copies/ml	417 (41%)

*Score is out of a total possible 10 points; based on characteristics of age, marital status, children, circumcision status of negative male partner, and HIV viral load of partner living with HIV

**as reported by the HIV-negative partner

Nine hundred eighty-two (97%) of HIV-negative participants initiated PrEP, including 960 (95%) that initiated at enrollment into the project. Among women, 96.6% initiated PrEP and among men, 98.5% initiated PrEP. The median duration of PrEP use was 12 months (IQR 6–18) and condomless sex was reported at 41.2% of visits when sex with the study partner was reported.

Patterns of PrEP use and discontinuation. Overall, 88.1% of HIV-negative partners used PrEP until their partner living with HIV was using ART, including 51.3% who used PrEP for exactly 6 months following ART initiation by their partner (Figure 2). PrEP use for >6 months following ART initiation

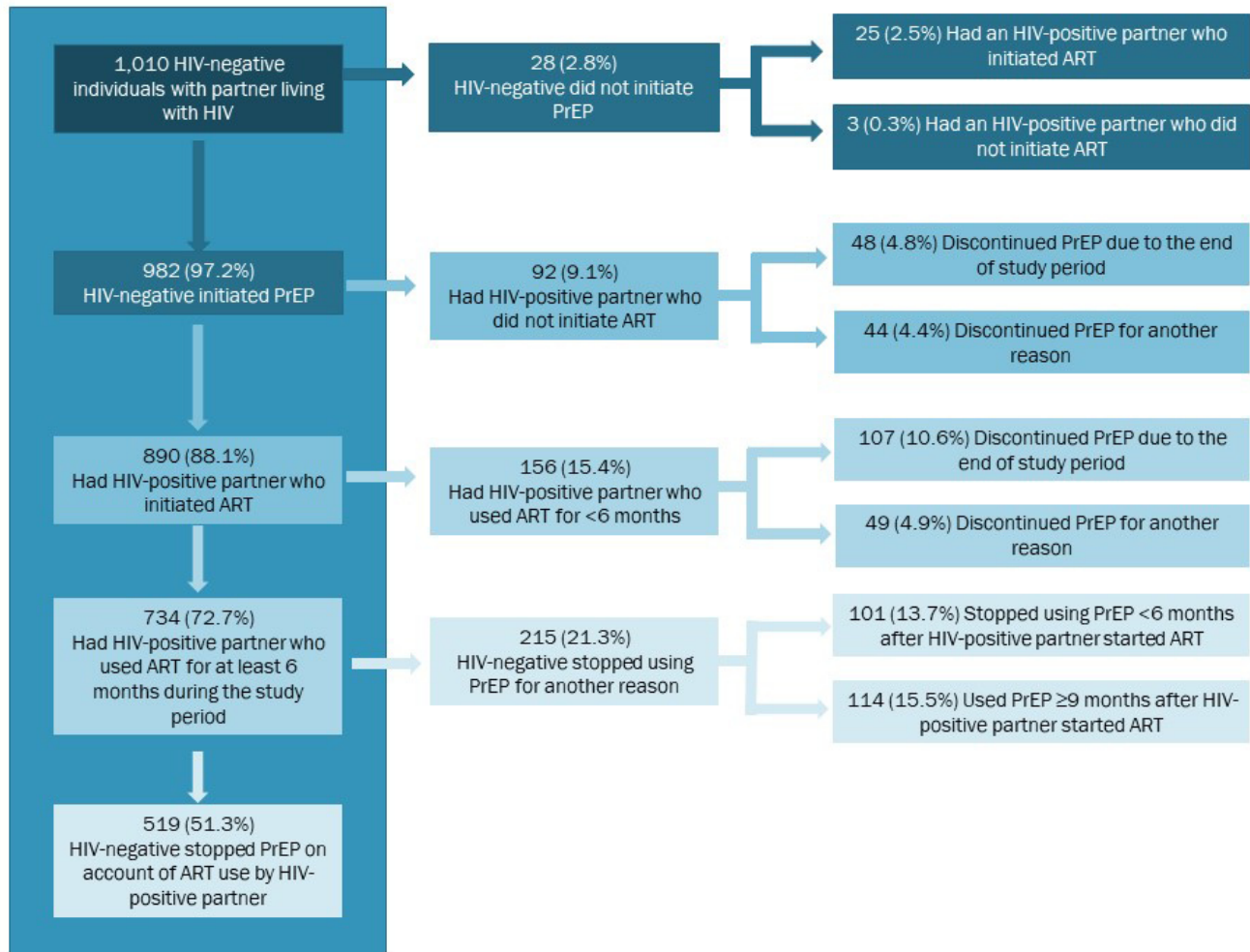


Figure 2. PrEP Use and Discontinuation by HIV-negative individuals with partners known to be living with HIV.

(by 114, 15.5% of PrEP users with at least 6 months of ART by the partner) was due to primarily to immediate fertility desires or current pregnancy (36.0% [41/114]), a desire for longer ART use by the partner living with HIV (15% [17/114]), or unsuppressed virus (12% [14/114]). For HIV-negative partners who did not use PrEP (n=28), 89.3% had partners living with HIV who initiated ART. Only 3 HIV-negative partners (0.3%) did not have protection from either PrEP or their partner’s ART use during follow up. Among the 734 HIV-negative participants who discontinued PrEP, 35 (4.8%) re-started PrEP before the end of the 2-year follow up period due to reasons that included fertility desires (n=14), concerns about ART use and/or viral load in the partner living with HIV (n=5), resolution of an adverse event (n=4), and new sexual partnerships (n=3).

During the follow up period prior to the partner living with HIV having used ART for 6 months (comprising 928.2 person-years), HIV-negative partners were dispensed PrEP for 602.4 person-years

(64.9%, Figure 3, orange sections). When PrEP was not dispensed (Figure 3, green sections), 46.6% included time when no sex with the study partner living with HIV was reported. Of the remaining time without PrEP, 26.1% of time without PrEP was due to a protocol-defined event (pregnancy, abnormal serum creatinine measurement, etc.) and 24.8% was due to participant decision. For 129.6 person-years (14.0% of all study time), participants missed study visits and were unable to be offered PrEP.

PrEP adherence. Among 140 participants randomly selected for TFV quantification at 607 visits following PrEP dispensation, 81% of samples had TFV detected (81% from women and 81% from men). MEMS data also were consistent with high adherence: 71% (72% from women and 68% from men) of visits had ≥80% of expected doses taken since the prior visit and 85% (84% from women and 85% from men) had ≥50% taken. Based on pharmacy pill counts, 87% (86% of women and 87% of men) and 96% (95% of women and 97% of men) of bottles had ≥80% and ≥50% of expected doses taken, respectively.

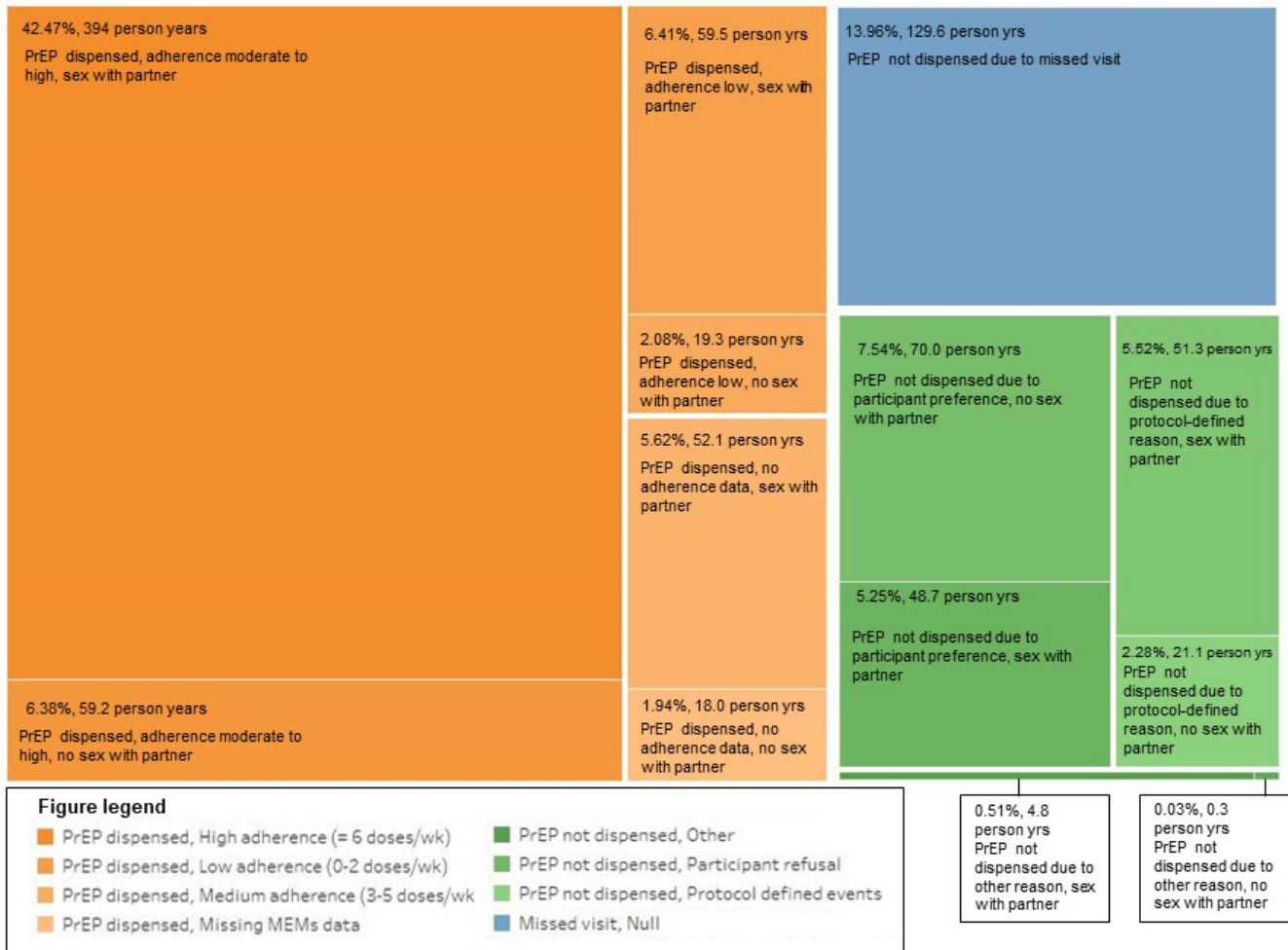


Figure 3. PrEP use by HIV-negative partners from the time of study enrollment through 6 months of ART use by HIV infected partners.

HIV incidence and intervention effectiveness. There were 18 seroconversions, including 4 incident seroconversions and 14 determined to have been infected at enrollment. Based on the 4 incident seroconversions, the observed incidence rate was 0.24 per 100 person-years (Table 2). Using bootstrapping methods with the placebo arm of the Partners PrEP Study, we estimated that 80.7 incident infections were expected in the absence of our intervention, resulting in an estimated incidence of 4.75 per 100 person-years. The incidence rate ratio was 0.05 (95% confidence interval [CI] 0=0.02-0.14) for an intervention effectiveness of 95% (95% CI: 86-98%). The intervention was highly effective in all subgroups examined including women (effectiveness=93%, p<0.0001), HIV-negative partners aged <25 (effectiveness=94%, p<0.0001), and among couples with HIV positive partners having HIV RNA ≥50,000 copies/ml at baseline (effectiveness=95%, p<0.0001).

Of the 4 individuals with incident HIV infection, none had TFV detected in plasma samples. The partners of three of these individuals were virally suppressed at the time when HIV was detected in

the initially HIV-negative partner, and all initially HIV-negative partners reported other sexual partners in addition to their study partner. Thus, partners who were not enrolled in the study (i.e., new or additional partners, whose HIV serostatus was unknown to the study) likely transmitted these infections. For the individual with incident HIV infection whose study partner had quantifiable HIV RNA when HIV was detected, analysis of the *pol* gene sequences from both partners revealed a likely linkage between two sequences. For this woman, her male partner had not yet initiated ART, as his CD4 count of 515 cells/mm³ did not qualify for initiation during the time when Ugandan ART guidelines required CD4 <350 cells/mL. None of the 4 people with incident infection had mutations conferring resistance to TDF or FTC. Five⁵ of the 14 participants determined to have been infected with HIV at enrollment had an M184V mutation consistent with resistance to FTC.

HIV protection at study end. After two years of follow up, 75.4% of couples had a partner living with HIV whose viral load was documented as suppressed and 8.5% had ART use by the partner

Table 2. Expected versus observed HIV incidence.

	Expectation from Partners PrEP Study*		Observed from Partners Demonstration Project		Incidence rate ratio (95% CI) p-value	Effectiveness (95% CI)
	N incident infections/ N years follow up	Incidence**	N incident infections/ N years follow up	Incidence**		
Overall incidence	80.7/1700.2	4.75	4/1682.3	0.24	0.05 (0.02, 0.14) p<0.0001	95% (86–98%)
By gender						
Women	42.0/553.0	7.60	3/560.4	0.54	0.07 (0.02, 0.23) p<0.0001	93% (77–98%)
Men	41.1/1144.6	3.59	1/1121.9	0.09	0.03 (0.00, 0.18) p<0.0001	97% (82–100%)
By age category						
HIV-negative partner <25 years old	17.1/344.7	4.97	1/332.0	0.30	0.06 (0.01, 0.46) p<0.0001	94% (54–99%)
HIV-negative partner ≥25 years old	62.7/1357.4	4.62	3/1350.3	0.22	0.05 (0.02, 0.15) p<0.0001	95% (85–98%)
By HIV RNA category						
HIV-positive partner HIV RNA ≥50,000 copies/ml	39.3/674.0	5.84	2/707.3	0.28	0.05 (0.01, 0.20) p<0.0001	95% (80–99%)
HIV-positive partner HIV RNA <50,000 copies/ml	41.4/1024.9	4.04	2/975.0	0.21	0.05 (0.01, 0.21) p<0.0001	95% (79–99%)

*The number of expected seroconversions and person-years do not sum precisely to the overall totals because each subgroup estimate is drawn from a separate bootstrapped counterfactual cohort model.

**per 100 person-years

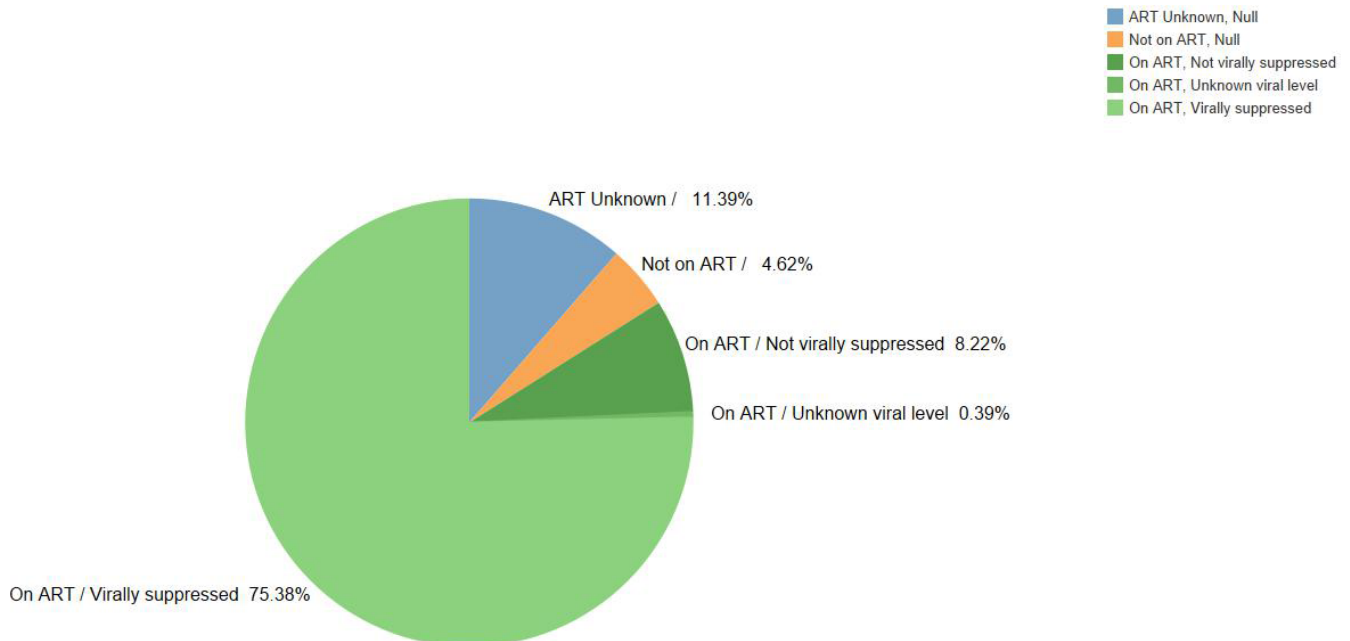


Figure 4. ART status within each couple at the end of the study follow-up.

living with HIV but did not have viral suppression or had unknown viral load levels (Figure 4). For 4.6% of couples (n=46 couples), ART was not being used by the partner living with HIV, including 20 couples who reported sex together in the past 3 months (15 with 100% condom use and 5 with some condomless sex).

Discussion

In this open-label evaluation of PrEP for HIV-negative partners within HIV serodiscordant couples, PrEP uptake and adherence were high and incident HIV was virtually eliminated. For 1010 HIV-negative persons followed for 2 years, PrEP was dispensed for 12 months on average. Since the beginning of our evaluation, ART guidelines have become more inclusive and ART use is more standard for all people living with HIV. These changes are likely to result in a shorter average duration of PrEP use since the time between HIV diagnosis and ART initiation and viral suppression is likely shorter for partners living with HIV. When PrEP was not used, a majority of people had HIV protection by their partner's ART use and viral suppression or had dissolved their partnership with their partner known to be living with HIV.

Our model of PrEP delivery was to introduce PrEP into couples-based HIV prevention and to recommend PrEP discontinuation once the partner living with HIV initiated and sustained ART. Almost all of the HIV-negative partners initiated PrEP and after two years of follow up, 75% of couples could rely on ART use and viral suppression in the partner living with HIV for protection against HIV transmission. Throughout the two-year follow up period, about half of the HIV-negative participants followed the PrEP strategy as our protocol intended, with PrEP used until their partner living with HIV had used ART for 6 months. Others used PrEP for longer or shorter periods overlapping with ART. These metrics demonstrate the feasibility for potentially implementing this strategy in East Africa as well as the ability to integrate PrEP into an existing clinical structure.

When PrEP was dispensed, adherence was moderate to high affording early protection from HIV acquisition and establishing a sustainable adherence behavior. Demonstration projects have shown greater adherence to PrEP than was observed in the clinical trials, potentially due to messages clearly describing the efficacy of PrEP and because they are often implemented in public clinics, which are more familiar than clinical trial settings. Importantly, adherence appears to align with HIV risk. Incident HIV infections occurred in our study in the absence of PrEP use and primarily outside of the study partnerships. These instances highlight opportunities to expand PrEP messaging to incorporate risk within newly forming relationships and with casual partners or transactional partners. For young people, especially those who are not yet married, messages need to be realistic and recognize the dynamic nature of relationships in order to encourage open communication with counselors and counseling grounded in realistic prevention strategies.

This intervention gave HIV-negative persons with partners living with HIV a means for engaging with healthcare and a primary prevention strategy. By engaging as couples, the partner living

with HIV gained familiarity with clinical care and antiretroviral use, enhancing their knowledge of ART programs with client trust and abilities to initiate ART faster¹³. This integrated approach provides support to each partner within the couple as well as the couple as a unit. Without PrEP, the HIV-negative partner has to rely only on condom use for primary prevention until the eventual identification of HIV, ART initiation, and sustained ART use with viral suppression. Condom use within marriage has been reported to be difficult due to cultural norms that discourage condom use within marriage, desires for pregnancy, and difficulties internalizing and coping with discordancy¹⁴.

Additional benefits of this intervention include improved relationship stability and strengthening communication and negotiation skills between couples that have been reported elsewhere^{15,16}. These benefits foster opportunities for couples to discuss their sexual behavior, plans for pregnancy, concerns about HIV risk, and other topics that are sensitive but important for reducing HIV risk¹⁷. By designing this study under an implementation science framework, we had an opportunity to refine standardized messages for couples about biomedical HIV prevention and pilot add-on components that would increase efficiencies in intervention delivery, such as HIV self-testing, less frequent monitoring of kidney function, and adherence support through text messages^{10,18–20}.

Within this study, microcosting analysis suggests cost-effectiveness, with the largest portion of costs owing to purchasing medication and laboratory monitoring²¹. Most PrEP users in this project needed PrEP for a limited time until ART use and viral suppression could be the primary mode of HIV protection. This attribute contributes to the cost-effectiveness of this delivery strategy but does not fully account for the frequency of re-starting PrEP during follow up beyond 2 years. Future evaluations within sustainable delivery programs will provide estimates of how frequently PrEP is re-started and the cost implications. As PrEP delivery programs are scaled up, identifying opportunities to improve efficiency from the patient and provider perspectives will reduce costs and potentially enhance effectiveness.

We measured adherence with MEMS caps and laboratory markers that are research tools and unlikely suitable for public clinics given their cost and logistical requirements (shipping samples to the US/central laboratory, provision of MEMS to each participant, etc.). However, programmatic scale up of HIV viral load testing is being implemented and can be used to guide counseling about ART adherence and prevention of transmission and to reinforce messages about PrEP adherence when viral load is not suppressed. In addition, we provided participants with a small reimbursement as a token of appreciation for their participation in research procedures and we cannot tease apart the degree to which this influenced participant retention in the project. A final limitation is that our model does not consider additional HIV risk factors, such as the frequency of condomless sex. During follow up, couples in the Partners Demonstration Project reported condomless sex more frequently than those in the comparison study and thus this group is likely to have higher risk.

PrEP delivery to HIV-negative individuals with partners known to be living with HIV was highly effective. HIV-negative participants used PrEP and most discontinued in parallel with sustained ART use by their partner living with HIV, transferring their HIV protection to their partner's ART use. Offering PrEP as a feature of existing ART programs must be done via messages and materials that are tailored for couples in order to reach members of HIV serodiscordant couples. While multiple venues for PrEP provision are likely needed in order to tailor services to different subpopulations, providing PrEP through ART clinics takes advantage of existing infrastructure, has benefits for both partners within HIV serodiscordant couples, and is feasible to roll out on a national level.

Data availability

Data are available upon request to the authors' research center, by emailing icrc@uw.edu with a concept sheet stating the objectives of the analysis and variables desired.

Competing interests

Gilead Sciences donated the PrEP medication but had no role in data collection or analysis. The authors disclosed no competing interests.

Grant information

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Partners Demonstration Project Team

Coordinating Center (University of Washington) and collaborating investigators (Harvard Medical School, Johns Hopkins University, Massachusetts General Hospital): Jared Baeten (protocol chair), Connie Celum (protocol co-chair), Renee Heffron (project director), Deborah Donnell (statistician), Ruanne Barnabas, Jessica Haberer, Harald Haugen, Craig Hendrix, Lara Kidoguchi, Mark Marzinke, Susan Morrison, Jennifer Morton, Norma Ware, Monique Wyatt

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Data management: DF/Net Research

Supplementary material

Supplementary File 1: Completed CONSORT checklist.

[Click here to access the data.](#)

Supplementary File 2: Completed CONSORT flow diagram.

[Click here to access the data.](#)

References

- Baeten JM, Donnell D, Ndase P, *et al.*: **Antiretroviral prophylaxis for HIV prevention in heterosexual men and women.** *N Engl J Med.* 2012; **367**(5): 399–410. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Grant RM, Lama JR, Anderson PL, *et al.*: **Preexposure chemoprophylaxis for HIV prevention in men who have sex with men.** *N Engl J Med.* 2010; **363**(27): 2587–99. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Thigpen MC, Kebaabetswe PM, Paxton LA, *et al.*: **Antiretroviral preexposure**

- prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med*. 2012; **367**(5): 423–34.
[PubMed Abstract](#) | [Publisher Full Text](#)
4. Baeten JM, Haberer JE, Liu AY, *et al.*: **Preexposure prophylaxis for HIV prevention: where have we been and where are we going?** *J Acquir Immune Defic Syndr*. 2013; **63**(Suppl 2): S122–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 5. AVAC Global Advocacy for HIV Prevention: **From Research to Rollout: Evaluations that move a product to the “real world”**. AVAC; 2013.
[Reference Source](#)
 6. AVAC Global Advocacy for HIV Prevention: **Ongoing and Planned PrEP Demonstration and Implementation Studies**. 2017.
[Reference Source](#)
 7. Baeten JM, Heffron R, Kidoguchi L, *et al.*: **Integrated Delivery of Antiretroviral Treatment and Pre-exposure Prophylaxis to HIV-1-Serodiscordant Couples: A Prospective Implementation Study in Kenya and Uganda**. *PLoS Med*. 2016; **13**(8): e1002099.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 8. Irungu EM, Heffron R, Mugo N, *et al.*: **Use of a risk scoring tool to identify higher-risk HIV-1 serodiscordant couples for an antiretroviral-based HIV-1 prevention intervention**. *BMC Infect Dis*. 2016; **16**(1): 571.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 9. Kahle EM, Hughes JP, Lingappa JR, *et al.*: **An empiric risk scoring tool for identifying high-risk heterosexual HIV-1-serodiscordant couples for targeted HIV-1 prevention**. *J Acquir Immune Defic Syndr*. 2013; **62**(3): 339–47.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 10. Morton JF, Celum C, Njoroge J, *et al.*: **Counseling Framework for HIV-Serodiscordant Couples on the Integrated Use of Antiretroviral Therapy and Pre-exposure Prophylaxis for HIV Prevention**. *J Acquir Immune Defic Syndr*. 2017; **74**(Suppl 1): S15–S22.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 11. Cohen MS, Chen YQ, McCauley M, *et al.*: **Prevention of HIV-1 infection with early antiretroviral therapy**. *N Engl J Med*. 2011; **365**(6): 493–505.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 12. Hendrix CW, Chen BA, Guddera V, *et al.*: **MTN-001: randomized pharmacokinetic cross-over study comparing tenofovir vaginal gel and oral tablets in vaginal tissue and other compartments**. *PLoS One*. 2013; **8**(1): e55013.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 13. Mujugira A, Baeten J, Kidoguchi L, *et al.*: **High levels of viral suppression among East African HIV-infected women and men in serodiscordant partnerships initiating antiretroviral therapy with high CD4 counts and during pregnancy**. *AIDS Res Hum Retroviruses*. 2017.
[PubMed Abstract](#) | [Publisher Full Text](#)
 14. Ngunjiri K, Mugo N, Celum C, *et al.*: **A qualitative study of barriers to consistent condom use among HIV-1 serodiscordant couples in Kenya**. *AIDS Care*. 2012; **24**(4): 509–16.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 15. Ware N, Wyatt M, Pisarski E, *et al.*: **Integrated delivery of antiretroviral treatment and pre-exposure prophylaxis to HIV-1 serodiscordant couples in East Africa: A qualitative evaluation study in Uganda**. Submitted.
 16. Ngunjiri K, Heffron R, Curran K, *et al.*: **I Knew I Would Be Safer. Experiences of Kenyan HIV Serodiscordant Couples Soon After Pre-Exposure Prophylaxis (PrEP) Initiation**. *AIDS patient care and STDs*. 2016; **30**(2): 78–83.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 17. Heffron R, Thomson K, Celum C, *et al.*: **Fertility Intentions, Pregnancy, and Use of PrEP and ART for Safer Conception Among East African HIV Serodiscordant Couples**. *AIDS Behav*. 2017.
[PubMed Abstract](#) | [Publisher Full Text](#)
 18. Ngunjiri K, Heffron R, Mugo N, *et al.*: **Feasibility and acceptability of HIV self-testing among pre-exposure prophylaxis users in Kenya**. *J Int AIDS Soc*. 2017; **20**(1): 21234.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 19. Haberer JE, Ngunjiri K, Muwonge T, *et al.*: **Brief Report: Context Matters: PrEP Adherence is Associated With Sexual Behavior Among HIV Serodiscordant Couples in East Africa**. *J Acquir Immune Defic Syndr*. 2017; **76**(5): 488–492.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 20. Mugwanya KK, Baeten JM, Wyatt C, *et al.*: **Brief Report: Frequency of Monitoring Kidney Function in HIV-Uninfected Persons Using Daily Oral Tenofovir Disoproxil Fumarate Pre-exposure Prophylaxis**. *J Acquir Immune Defic Syndr*. 2018; **77**(2): 206–211. Submitted.
[PubMed Abstract](#) | [Free Full Text](#)
 21. Ying R, Sharma M, Heffron R, *et al.*: **Cost-effectiveness of pre-exposure prophylaxis targeted to high-risk serodiscordant couples as a bridge to sustained ART use in Kampala, Uganda**. *J Int AIDS Soc*. 2015; **18**(4 Suppl 3): 20013.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

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George W. Rutherford 

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No new comments. All my suggestions have been incorporated. Thanks.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious disease epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 04 December 2017

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The article reports on the outcome of one of two global PrEP demonstration projects with HIV-1 sero-discordant couples as intervention recipients. The study is therefore a significant contribution to understanding uptake and use of PrEP in this target population in addition to the additional finding on PrEP effectiveness for the population. It is indeed a very useful addition to the literature already generated by the Partners Demonstration Project Team. A few issues however:

1. Title: Appropriate as the study had focused on the themes – uptake, use and effectiveness of PrEP in their study. The study is very relevant, given the impact PrEP can make on combination prevention.

2. Abstract: It will be helpful to have the study objective defined in the introduction of the abstract. The methodology does not state how the uptake of PrEP was assessed and this seems to be one of the objectives of the study.

3. Introduction: Detailed. The introduction considers the full context of the research topic and has gone to describe the impact of PrEP in serodiscordant partners when the HIV positive partner is not taking ART or in the short term (6 months) before the expected viral suppression.

4. Methods: The study noted: ‘whenever possible, operations for the intervention were designed to mirror implementation strategies used in public clinics so as to develop a scalable delivery approach’. This statement is critical. I suggest the authors identify implementation practices that are not routine public clinic practices that may have had impact on the observed results. For example, in real life, will clients be screened for hepatitis B virus before being placed on PrEP? Where clients provided transport reimbursements for this study and if yes, how did that affect adherence to study routine that may otherwise have impacted on missed appointments, loss to follow up (currently the study shows 14% of study time)? How were clients monitored and followed up for appointments for this project which may otherwise not happen in the routine public clinic practice? Can the quality of adherence messaging for this project be replicable in the public clinics? What will be the impact of these extra efforts (if applicable) in a scalable approach? We suggest the team reports on those project implementation strategies that are likely not going to be replicated in the public clinic practices that may impact significantly on the uptake, use and effectiveness of PrEP for sero-discordant couples.

The authors noted that HIV RNA tests were conducted at study enrolment and at 6 months intervals. “HIV negative partners were encouraged to discontinue PrEP once their study partners used ART for six months”. The viral load suppression is key to the effectiveness of PrEP and hence should be used to guide discontinuation at 6 months. Yet, these results were not used to guide decisions about discontinuation of PrEP at six months for clients. “HIV RNA results could be used to identify the potential for non-adherence to ART”. Why will the authors invest so much in the use of HIV RNA to identify non-adherence when they are already using other measures including self reporting, MEMS caps and blood levels of TDF? Particularly when they state at the discussion following microcosting, the largest costs were from drugs and laboratory monitoring which will have HIV RNA testing as a major component cost. What then was the justification for doing those tests for this study? What is the ethical implication of doing those tests and yet not using them as guide to make decisions about going off PrEP for this study? What is the ethical justification of taking these decisions when the study had made some other implementation decisions that were not routine practices in a public health clinic in Kenya and Uganda? The justification for this decision remains unclear to us and would give an impression that HIV RNA is not an important indicator in deciding when to stop PrEP. The new ART guidelines recommend viral load testing and it is key to achieving the 3

rd 90. Please do justify the reason for conduct of routine HIV RNA tests and yet not using the results for PrEP discontinuation decision making for this study.

The authors note that *If available when PrEP discontinuation was considered, HIV RNA results could be used to identify the potential for non-adherence to ART*. Can the authors provide clarity about the term 'could' in this statement? How can an algorithm of practice be developed when there are critical elements of a PrEP management process that is subjective in its implementation. It will be good to have some clarification on this practice by the PrEP team. We noticed the results showed that 12% of 114 clients who continued PrEP use beyond 6 months did so because of un-suppressed viral load. How was this determined if the HIV RNA results was not routinely used to guide the counselling session? Just curious and need clarity about this.

How frequently was PrEP dispensed for this study? How was PrEP used –daily or coitally dependent? How frequently were HIV tests conducted? It is important that these details are reflected in the manuscript. Where condoms provided to study participants and if so, how frequently?

The authors have a section dedicated to describe how PrEP adherence was measured. Adherence seems to be the buss word in the field. However, We think the authors captured what they assessed better when they used the word 'use'. We think what the authors tried to assess was truly use. Adherence implies sticking to a routine schedule. The clients were expected to use PrEP everyday not at a specific time schedule right?

Results

Extremely curious why WHO Stage >2 was a reason for non-eligibility of the HIV negative partner for enrolment on PrEP. How will such an enrolment strategy play out in the routine practice in a public clinic? Why should the HIV positive partners with WHO Stage >2 be screened out of the study? Is this not some form of bias?

We suggest this section be divided into section to help readers identify how the results are reflective of the objectives. Sections to show results on PrEP uptake, use and effectiveness will be great.

It would be good to highlight the profile (characteristics) of the 3% (n=28) of eligible participants who did not take up PrEP.

The study reports on those who used PrEP for more than 6 months and why. It will be good to know precisely how many people continued the use of PrEP 6-12 months and for 12-18 months. 12 months is a critical period for this study as this was stipulated in the study protocol as the time for study product access. The study highlighted the number that continued beyond 9 months.

Any gender differences in the profile of PrEP uptake and use? This is a very important study analysis that is missing from this manuscript. Very, very, very important especially in the context of PrEP use in a community where women are vulnerable in many ways.

Discussion

The last sentence in the first paragraph states that: *When PrEP was not used, a majority of people had HIV protection by their partner's ART use and viral suppression or had dissolved their partnership with their partner known to be living with HIV*. There were only 3 clients that changed sex partners. This does not fall into a category of majority.

The last sentence of the second paragraph states that: *These metrics demonstrate the feasibility of implementing this strategy in East Africa as well as the ability to integrate PrEP into an existing clinical structure.* This study DOES NOT demonstrate the ability to integrate PrEP into an existing clinical structure. The study did not measure any hospital related parameters that may impact positively or negatively on PrEP uptake, use and intake and so that conclusion is spurious. We suggest this be deleted or modified.

Column 2, paragraphs 3 that alludes to cost effectiveness. Most of the costs went to drugs and tests and we presume measuring viral loads must have been a capital cost. What is the cost-effectiveness of such intervention if it is implemented in public clinics where viral loads are done not for deciding the point of stopping PrEP but monitoring adherence, particularly when there are other measures for adherence.

A sentence in the last paragraph reads - *Offering PrEP as a feature of existing ART programs must be done via messages and materials that are tailored for couples.* We suggest that the paragraph be re-written to acknowledge that the suggestion is for sero-discordant couples.

For the PrEP demonstration project in Nigeria, we had identified a number of couples that do not want to access PrEP and TasP by coming to the clinic together as couples but as individuals. Did the study encounter such experience? Are there study limitations?

Strong points in the study

- Short term PrEP for 6 months
- High level of adherence
- Very few incident infections
- Improved couple relationships in sexual behaviour
- Implementation science strategy

Weak points in the study

- Needs more detailed description of PrEP
- More details of the implementation science strategy in the methodology
- Poor use of HIV RNA to identify point of viral suppression in the HIV positive partner.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 29 Jan 2018

Renee Heffron, University of Washington, Seattle, USA

We are grateful for the reviewers' efficient and generally favorable review. We have responded to each point below.

1. Title: Appropriate as the study had focused on the themes – uptake, use and effectiveness of PrEP in their study. The study is very relevant, given the impact PrEP can make on combination prevention.

Thank you for your favorable comment.

2. Abstract: It will be helpful to have the study objective defined in the introduction of the abstract. The methodology does not state how the uptake of PrEP was assessed and this seems to be one of the objectives of the study.

We have added a sentence to the Introduction to describe the manuscript objective and a phrase to the Methods describe how the uptake of PrEP was assessed. Due to the limit on abstract size, we have had to remove ~25 words in order to maintain these additions.

3. Introduction: Detailed. The introduction considers the full context of the research topic and has gone to describe the impact of PrEP in serodiscordant partners when the HIV positive partner is not taking ART or in the short term (6 months) before the expected viral suppression.

Thank you for your favorable comment.

4. Methods: The study noted: 'whenever possible, operations for the intervention were designed to mirror implementation strategies used in public clinics so as to develop a scalable delivery approach'. This statement is critical. I suggest the authors identify implementation practices that are not routine public clinic practices that may have had impact on the observed results. For example, in real life, will clients be screened for hepatitis B virus before being placed on PrEP? Where clients provided transport reimbursements for this study and if yes, how did that affect adherence to study routine that may otherwise had impacted on missed appointments, loss to follow up (currently the study shows 14% of study time)? How were clients monitored and followed up for appointments for this project which may otherwise not happen in the routine public clinic practice? Can the quality of adherence messaging for this project be replicable in the public clinics? What will be the impact of these extra efforts (if applicable) in a scalable approach? We suggest the team reports on those project implementation strategies that are likely not going to be replicated in the public clinic practices that may impact significantly on the uptake, use and effectiveness of PrEP for sero-discordant couples.

This is an important point and we have added some examples to the methods of how we mirrored public clinics processes. We have also added one point to the discussion about

participant reimbursement that was given as a token of appreciation for participation in the research procedures that were part of the intervention. Below, we have provided a few more details about the specific elements that the reviewer mentioned.

Hepatitis B – Globally, national guidelines are using various approaches to their recommendation about Hepatitis B testing prior to PrEP initiation. Guidelines in South Africa, for example, require Hepatitis B testing and resulting prior to PrEP initiation. In Kenya, however, guidelines suggest Hepatitis B antigen testing but PrEP can be initiated without this testing if laboratory facilities are not available and/or the testing is not feasible. Thus, our method aligns with public health approaches to date.

Reimbursement – We provided reimbursement to participants because some of the procedures (e.g. consenting and occasional blood draws) were research procedures and would go beyond the public clinic approach. We worked with ethics committees to minimize the amounts of reimbursement as much as was reasonable so as not to be an undue incentive for retention or PrEP use.

Participant monitoring and follow up – We followed systems at local ART clinics very closely when we designed our follow up procedures. Our primary method for tracking participants between study visits was by making phone calls or sending confidential text messages. To maximize participation at annual visits, people who had difficulty attending appointments were asked to gather at a central location near to their home and provided with transportation to the clinic.

Adherence counseling – We have published a separate manuscript (reference #10) that details our approach to counseling about this integrated PrEP and ART strategy, including the key messages for adherence counseling. By publishing this information, we intended to make the key counseling messages available and replicable in public clinics.

Public clinic practices – In an ongoing PrEP rollout project in Kenya in 24 public ART clinics, this strategy of integrating PrEP into HIV treatment services is being replicated (clinicaltrials.gov #NCT03052010).

5. The authors noted that HIV RNA tests were conducted at study enrolment and at 6 months intervals. “HIV negative partners were encouraged to discontinue PrEP once their study partners used ART for six months”. The viral load suppression is key to the effectiveness of PrEP and hence should be used to gage discontinuation at 6 months. Yet, these results were not used to guide decisions about discontinuation of PrEP at six months for clients. “HIV RNA results could be used to identify the potential for non-adherence to ART”. Why will the authors invest so much in the use of HIV RNA to identify non-adherence when they are already using other measures including self reporting, MEMS caps and blood levels of TDF? Particularly when they state at the discussion following microcosting, the largest costs were from drugs and laboratory monitoring which will have HIV RNA testing as a major component cost. What then was the justification for doing those tests for this study? What is the ethical implication of doing those test and yet not using then as guide to make decisions about going off PrEP for this study? What is the ethical justification of taking this decisions when the study had made some other implementation decisions that were not routine practices in a public health clinic in Kenya and Uganda? The justification for this decision remains unclear to us and would give an impression that HIV RNA is not an important indicator in deciding when to stop PrEP. The new ART guidelines recommend viral load testing and it is key to

achieving the 3rd 90. Please do justify the reason for conduct of routine HIV RNA tests and yet not using the results for PrEP discontinuation decision making for this study.

HIV RNA testing was conducted so we would have the strongest measure of ART adherence as possible for our research outcomes. We considered this testing to be a research procedure, however, since it was not available routinely in public clinics at the time of our study (2012-2016) and couldn't necessarily be a procedure replicated in public clinics. At this time, clinics were generally only referring for HIV RNA when virologic failure was suspected. Even today, HIV RNA testing is not routine and universal in public ART delivery in Kenya and Uganda. Thus, as a research procedure, we scheduled HIV RNA testing on a 6-monthly basis which was operationally more simple than aligning with individual ART initiation schedules. Since many people did not have a relevant HIV RNA result that was available during counseling about ART adherence and/or PrEP discontinuation, we did not *require* HIV RNA results to guide discussion about PrEP discontinuation. But of course, any relevant HIV RNA result could be used for counseling if it was available. We have explained that in the following sentence: "*If available when PrEP discontinuation was considered, HIV RNA results could be used to identify the potential for non-adherence to ART; however, testing was conducted on a 6-monthly schedule timed to study start, not the ART initiation schedule, and testing may not have aligned with ART initiation.*"

The laboratory testing that is discussed in relation to the microcosting is Hepatitis B and creatinine, which would be additional laboratory tests pertaining to PrEP that would need to be added into an existing HIV treatment program. The full paper on microcosting is cited in the references (#21).

6. The authors note that *If available when PrEP discontinuation was considered, HIV RNA results could be used to identify the potential for non-adherence to ART*. Can the authors provide clarity about the term 'could' in this statement? How can an algorithm of practice be developed when there are critical elements of a PrEP management process that is subjective in its implementation. It will be good to have some clarification on this practice by the PrEP team. We noticed the results showed that 12% of 114 clients who continued PrEP use beyond 6 months did so because of un-suppressed viral load. How was this determined if the HIV RNA results was not routinely used to guide the counselling session? Just curious and need clarity about this.

These data on PrEP continuation due to unsuppressed viral load were collected from the participant following their counseling session with study clinicians and counselors. For times when HIV RNA was conducted following ART initiation and results were available for discussion with the HIV-negative member and showed unsuppressed virus, some participants chose to continue PrEP because of these laboratory results. When HIV RNA was not available and a participant suspected suboptimal ART adherence by their partner, the participant could also choose to continue PrEP.

7. How frequently was PrEP dispensed for this study? How was PrEP used –daily or coitally dependent? How frequently were HIV tests conducted? It is important that these details are reflected in the manuscript. Where condoms provided to study participants and if so, how frequently?

We have ensured that all of these details are now clearly presented in the manuscript.

PrEP was dispensed at each study visit – enrollment, 1 month later, 2 months later, and every 3 months after that – with a daily dosing strategy. HIV testing was conducted at each study visit and always before PrEP was prescribed.

8. The authors have a section dedicated to describe how PrEP adherence was measured. Adherence seems to be the buss word in the field. However, We think the authors captured what they assessed better when they used the word 'use'. We think what the authors tried to assess was truly use. Adherence implies sticking to a routine schedule. The clients were expected to use PrEP everyday not at a specific time schedule right?

We thank the reviewer for this discussion. We generally use “adherence” as a more technical term referring to compliance with the daily dosing routine. We used the word “use” as a more colloquial and approachable term to encompass the ideas of PrEP initiation and adherence. Our intention was to look at PrEP adherence and patterns describing PrEP uptake, discontinuation, and re-initiation – “use” is a way to encompass all of this description of PrEP into a single word.

Results

9. Extremely curious why WHO Stage >2 was a reason for non-eligibility of the HIV negative partner for enrolment on PrEP. How will such an enrolment strategy play out in the routine practice in a public clinic? Why should the HIV positive partners with WHO Stage >2 be screened out of the study? Is this not some form of bias?

Since WHO stage >2 was a criteria for ART initiation, we wanted to be sure that people with WHO stage >2 sought immediate engagement with a regular ART clinic and were not caught up in any research procedures that might delay their ART initiation (e.g. additional screening visits). We have explained this in the methods saying that *“couples were excluded if the HIV-positive partner had WHO stage III or IV HIV disease conditions that indicated immediate need for ART.”*

10. We suggest this section be divided into section to help readers identify how the results are reflective of the objectives. Sections to show results on PrEP uptake, use and effectiveness will be great.

We have added section headers as suggested.

11. It would be good to highlight the profile (characteristics) of the 3% (n=28) of eligible participants who did not take up PrEP.

The number of people in this group are so few that we are unable to identify distinct characteristics of the people not initiating PrEP.

12. The study reports on those who used PrEP for more than 6 months and why. It will be good to know precisely how many people continued the use of PrEP 6-12 months and for 12-18 months. 12 months is a critical period for this study as this was stipulated in the study protocol as the time for study product access. The study highlighted the number that continued beyond 9 months.

The study availed PrEP access to participants for a 2-year period. We reported on 6 months specifically because of our guidance to discontinue PrEP once ART use had been

sustained by partners living with HIV for at least 6 months. We have reported the median duration of PrEP use as 12 months with an interquartile range of 6-18 months.

13. Any gender differences in the profile of PrEP uptake and use? This is a very important study analysis that is missing from this manuscript. Very, very, very important especially in the context of PrEP use in a community where women are vulnerable in many ways.

We have added gender-specific details to the manuscript with regards to PrEP initiation and adherence.

Discussion

14. The last sentence in the first paragraph states that: *When PrEP was not used, a majority of people had HIV protection by their partner's ART use and viral suppression or had dissolved their partnership with their partner known to be living with HIV.* There were only 3 clients that changed sex partners. This does not fall into a category of majority.

With this sentence, we were referring to the ~10% of person time when PrEP was not dispensed and there was no sex reported with the study partner. These person years represent approximately half of the time when PrEP was not dispensed and study visits were attended (see Figure 3).

15. The last sentence of the second paragraph states that: *These metrics demonstrate the feasibility of implementing this strategy in East Africa as well as the ability to integrate PrEP into an existing clinical structure.* This study DOES NOT demonstrate the ability to integrate PrEP into an existing clinical structure. The study did not measure any hospital related parameters that may impact positively or negatively on PrEP uptake, use and intake and so that conclusion is spurious. We suggest this be deleted or modified.

We have modified the sentence. We now say that, "These metrics demonstrate the feasibility for potentially implementing this strategy in East Africa as well as the ability to integrate PrEP into an existing clinical structure."

16. Column 2, paragraphs 3 that alludes to cost effectiveness. Most of the costs went to drugs and tests and we presume measuring viral loads must have been a capital cost. What is the cost-effectiveness of such intervention if it is implemented in public clinics where viral loads are done not for deciding the point of stopping PrEP but monitoring adherence, particularly when there are other measures for adherence.

The full data on microcosting that was conducted within this study can be found by reading reference #21 (Ying et al.). An additional manuscript with details of the costs for implementing this intervention in Kenya using Ministry of Health standards is under review.

17. A sentence in the last paragraph reads - *Offering PrEP as a feature of existing ART programs must be done via messages and materials that are tailored for couples.* We suggest that the paragraph be re-written to acknowledge that the suggestion is for sero-discordant couples.

We have added to the sentence to reflect this suggestion.

18. For the PrEP demonstration project in Nigeria, we had identified a number of couples that do not want to access PrEP and TasP by coming to the clinic together as couples but as individuals. Did the study encounter such experience? Are there study limitations?

In this demonstration project, we only screened people on the basis of being part of a couple.

Competing Interests: None

Reviewer Report 29 November 2017

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George W. Rutherford 

Department of Epidemiology & Biostatistics, University of California, San Francisco, San Francisco, CA, USA

This is a well written manuscript that describes results from a well-designed and executed demonstration project of tenofovir-emtricitabine (TDF-FTC) pre-exposure prophylaxis of HIV-seronegative sexual partners of patients recently diagnosed with HIV infection. The intervention was delivered during the pre-antiretroviral therapy (ART) phase of care and/or for the first six months of ART. The investigators compared the observed HIV incidence in uninfected partners (0.24 per 100 person years) with that observed during the Partners' PrEP Study (4.75 per 100 person years). The results are compelling and suggest an important role for short-term PrEP in serodiscordant couples in which the infected partner is beginning ART. This is an important paper that will likely change policy.

Some specific comments:

Page	Para	Comment
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5	2	I suggest adding the word "any" before "condomless sex" in the text. Is there any data on what proportion of acts of intercourse among these discordant couples that were unprotected by condoms?
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5	2	At the bottom of the first Results paragraph, the second to last sentence reads, "Ninety-seven (97%) of HIV-negative participants initiated PrEP..." This should be, I believe, "Nine hundred eighty-two".
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6		I found Figure 2 a little difficult to get through. It might be helpful to use terms like "HIV-positive partner" and be clear that you're talking about the uninfected partners in the third column of boxes. These are minor changes, but I think they'd enhance readers' quicker understanding.
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6	3	This comment may be more appropriate for the Methods, but how did the authors deal with protection afforded by condoms and abstinence? It would appear to me that these factors were not taken
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into account in the incidence calculations either from this study or the Partners' PrEP Study. I think this deserves some mention in the Discussion although I don't think it changes the overall intervention effectiveness calculated.

7 I realize the color coding for Figure 3 appears in the text. I suggest that the authors also include a legend with the figure. I would also suggest indicating in which box the single genetically linked transmission took place (I'm assuming it's the 6.41% (PrEP dispensed, adherence low, sex with partner).

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: infectious disease epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 29 Jan 2018

Renee Heffron, University of Washington, Seattle, USA

We are grateful for the review's efficient and favorable review. We have responded to each point below.

1. I suggest adding the word "any" before "condomless sex" in the text. Is there any data on what proportion of acts of intercourse among these discordant couples that were unprotected by condoms?

We have added "any" to the text, as suggested. Data on the frequency of condomless sex are presented in Table 1 where we describe that 65% of couples reported condomless sex during the 30 days prior to study enrollment. We have also added a detail to the Results that couples reported condomless sex at 41.2% of study visit.

2. At the bottom of the first Results paragraph, the second to last sentence reads, "Ninety-seven

(97%) of HIV-negative participants initiated PrEP...” This should be, I believe, “Nine hundred eighty-two”.

We have updated the sentence to read “Nine hundred eighty-two.” The “ninety-seven” was meant to spell out the percentage in the parentheses since it is at the start of the sentence but we agree that this is confusing.

3. I found Figure 2 a little difficult to get through. It might be helpful to use terms like “HIV-positive partner” and be clear that you’re talking about the uninfected partners in the third column of boxes. These are minor changes, but I think they’d enhance readers’ quicker understanding.

We have updated the figure and the figure title to use more comprehensive descriptions in the boxes and made sure that all the descriptions are in the perspective of the HIV-negative partner.

4. This comment may be more appropriate for the Methods, but how did the authors deal with protection afforded by condoms and abstinence? It would appear to me that these factors were not taken into account in the incidence calculations either from this study or the Partners’ PrEP Study. I think this deserves some mention in the Discussion although I don’t think it changes the overall intervention effectiveness calculated.

We did not adjust our effectiveness estimates for condom use because we wanted to estimate the level of risk including with the background level of condom use. Condom use at enrollment is a factor within the risk scoring tool that was used to screen couples for the Partners Demonstration Project and to select couples from the Partners PrEP Study for inclusion in the comparison cohort. Thus, condom use at enrolment was somewhat balanced in our effectiveness model. We have also added a sentence to the Discussion to draw this point to the reader’s attention.

5. I realize the color coding for Figure 3 appears in the text. I suggest that the authors also include a legend with the figure. I would also suggest indicating in which box the single genetically linked transmission took place (I’m assuming it’s the 6.41% (PrEP dispensed, adherence low, sex with partner).

We have added a legend to the Figure.

Competing Interests: None