



Daily and non-daily pre-exposure prophylaxis in African women (HPTN 067/ADAPT Cape Town Trial): a randomised, open-label, phase 2 trial

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Summary

Background The relative feasibility and acceptability of daily versus non-daily dosing of oral HIV pre-exposure prophylaxis (PrEP) among women are unknown. We aimed to investigate the feasibility of non-daily PrEP regimens in adult women.

Methods We did a randomised, open-label, phase 2 clinical trial (HPTN 067/ADAPT) of oral PrEP with emtricitabine plus tenofovir disoproxil fumarate at a research centre in Cape Town, South Africa. Participants were adult women (age ≥ 18 years) who received directly observed dosing once a week for 5 weeks followed by random assignment (1:1:1) at week 6 to one of three unblinded PrEP regimens for self-administered dosing over 24 weeks: daily; time-driven (twice a week plus a post-sex dose); or event-driven (one tablet both before and after sex). Primary outcomes were PrEP coverage (at least one dose within the 4 days before sex and one dose within 24 h after sex), pills needed or used to achieve regimen-specific adherence and coverage, and symptoms and side-effects. All analyses were by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01327651; the trial is completed and this report presents the final analysis.

Findings Between Sept 12, 2011, and Oct 3, 2012, 191 women were enrolled to the trial. 178 (93%) completed directly observed dosing and were randomly assigned one of the three PrEP regimens for the self-administered phase: 59 were allocated the daily regimen, 59 the time-driven regimen, and 60 the event-driven regimen. Median age of women was 26 years (IQR 21–37; range 18–52). In women allocated the daily regimen, 1459 (75%) of 1952 sex events were covered by PrEP, compared with 599 (56%) of 1074 sex events among those assigned the time-driven regimen (odds ratio [OR] 2.35, 95% CI 1.43–3.83; $p=0.0007$) and 798 (52%) of 1542 sex events among those allotted the event-driven regimen (2.76, 1.68–4.53; $p<0.0001$). Fewer pills were needed for complete adherence in women allocated non-daily regimens (vs daily regimen, relative mean 2.53 [95% CI 2.39–2.69] for the time-driven regimen and 4.16 [3.59–4.82] for the event-driven regimen; $p<0.0001$). Side-effects were uncommon. Eight HIV seroconversions occurred overall, with four documented during the self-administered phase (two with the time-driven regimen and two with the event-driven regimen). Adherence to the assigned regimen was 75% (7283 of 9652 doses taken) for women allocated the daily regimen compared with 65% for those assigned the time-driven regimen (2367 of 3616 doses taken; $p=0.0028$) and 53% for those allotted the event-driven regimen (1161 of 2203 doses taken; $p<0.0001$). When sex was reported in the previous week, PrEP drugs were detected (above the lower limits of quantification) more frequently in women assigned the daily regimen (73 [68%] of 107 samples) than in those allocated the time-driven regimen (42 [58%] of 72 samples) and the event-driven regimen (41 [41%] of 99 samples).

Interpretation Daily PrEP dosing resulted in higher coverage of sex events, increased adherence to the regimen, and augmented drug concentrations than did either time-driven or event-driven dosing. These findings support recommendations for daily use of PrEP with oral emtricitabine plus tenofovir disoproxil fumarate in women.

Funding HIV Prevention Trials Network.

Introduction

Pre-exposure prophylaxis (PrEP) with emtricitabine and tenofovir disoproxil fumarate is safe and effective for prevention of HIV acquisition among men and women.^{1–5} In 2012, the US Food and Drug Administration approved the co-formulation of emtricitabine with tenofovir disoproxil fumarate for use as PrEP in men who have sex with men (MSM) and women at high risk of HIV acquisition. In September, 2015, after reports were

published of ten randomised placebo-controlled trials that included thousands of trial participants, WHO issued a strong recommendation for use of oral PrEP containing tenofovir disoproxil fumarate in men and women at substantial risk of HIV.⁶

Observed effectiveness in trials corresponds with detectable concentrations of PrEP drugs in blood, indicating some use in the past week.⁷ PrEP efficacy in women was shown in two trials done in Africa and one in

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See [Comment](#) page e60

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Research in context

Evidence before this study

When the HPTN 067/ADAPT study was designed (protocol first approved in 2010), daily pre-exposure prophylaxis (PrEP) with oral antiretroviral drugs was being assessed in clinical trials in diverse populations and settings. No trial results other than the MSM Global iPrEx study were available in 2010. That landmark study was the first evidence that PrEP with antiviral agents could prevent HIV. Even in the absence of an established evidence base, the ADAPT protocol team was concerned that the prevention method of daily PrEP dosing would not match patterns of HIV risk-taking for most of the at-risk populations, because risk events were unlikely to occur on a daily basis. Furthermore, daily dosing of PrEP was selected for ongoing prevention trials based only on dosing intervals that were approved for treatment of HIV infection. The hypothesis was that less frequent dosing of PrEP might be sufficient for prevention and result in decreased drug costs and potentially lower risk of toxic effects that might increase acceptability and improve use. Since HPTN 067/ADAPT was designed, the findings of the Ipergay study in Canada and France have shown that coitally dependent PrEP can be highly effective, at least in men who have sex with men. At the time HPTN 067/ADAPT was designed, it was proposed that studying intermittent dosing could contribute important information about behavioural effects, adherence reporting, and counselling content. Establishing the potential benefits and feasibility of intermittent regimens in terms of coverage, acceptability, resistance, and uptake, as well as the potential effect on other risk-management strategies (eg, condom use), would also be crucial in the portfolio of research that will advise the real-world dissemination and implementation of combination

interventions. Two PrEP trials in African women (VOICE and FEMPrEP) were unable to show any prevention effectiveness, most likely because of low levels of daily use of PrEP by women taking part in the studies. The HPTN 067/ADAPT study would be useful even in the setting of negative daily dosing trials if it also identified ways to foster pill use reporting and active study participation.

Added value of this study

HPTN 067/ADAPT is the first study that specifically compares daily and non-daily open-label oral PrEP use within an African female population. This study adds to the growing evidence base that African women will take and can adhere to oral PrEP within an open-label framework. Adherence and coverage of sex events was higher with daily dosing than with an event-driven regimen. Previously, it was unknown which regimen would provide greater coverage.

Implications of all the available evidence

In view of the two negative efficacy trials in African women, the outcomes of HPTN 067/ADAPT are probably most important in that they counter the argument that African women are opposed to PrEP as a prevention modality. HPTN 067/ADAPT showed that when PrEP was offered in an open-label fashion, most women attempted to use PrEP in the assigned regimen. Moreover, a daily regimen would provide better HIV prevention outcomes than would an event-driven regimen because of improved coverage of sex acts with the daily regimen. In the context of preparation for PrEP rollout in South Africa, an evidence base for this type of information informs policy makers and practitioners on how to best implement and promote an oral PrEP regimen for African women.

Thailand.^{1,3,8} Two other trials in Africa among predominately young women showed no efficacy on an intention-to-treat basis, and medication was detected in less than a third of participants assigned the active regimen, raising concerns about the feasibility of effective oral PrEP use by young African women.^{9,10} Furthermore in these two studies, diminished PrEP use was noted among women who reported the most risky sexual practices.¹⁰ Thus, an urgent need exists for self-directed HIV-prevention strategies for African women.

In early reports of adherence in demonstration projects in the USA and among discordant couples in east Africa, data suggest high adherence with open-label PrEP,^{11,12} raising the possibility that when people know a product works, they can identify their periods of risk and take PrEP effectively. Unlike treatment adherence, which focuses on daily use of antiretroviral drugs to suppress viral replication, PrEP use is effective when used before and after sex that could confer exposure to HIV.¹³ Non-daily regimens linked to patterns of sexual behaviour can provide coverage of sex events while reducing tablet burden.⁴ On-demand PrEP before and after sex is effective among MSM;⁴ however,

findings of small blinded trials suggest low adherence to sex-event-driven dosing in African MSM, female sex workers, and serodiscordant couples.^{14,15} Measuring adherence to non-daily regimens was challenging in these two small studies, with different measures leading to diverse conclusions. Adherence to open-label PrEP and to regimens that are linked to patterns of sexual behaviour has not yet been investigated among African women.

The HPTN 067/ADAPT (Alternative Dosing to Augment PrEP pill Taking) study protocol included two non-African study sites that enrolled MSM and transgender women and one African site that enrolled heterosexual women; each study site was designed and powered for separate analyses to reflect the highly divergent social contexts. In this report, we present findings of the African study in heterosexual women (HPTN 067/ADAPT Cape Town Trial). We aimed to assess whether a non-daily regimen of oral PrEP would be more feasible for heterosexual African women at substantial risk of HIV acquisition, result in equivalent coverage of sex events, require fewer tablets, and result in fewer side-effects than a daily regimen.

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Methods

Study design and participants

The HPTN 067/ADAPT Cape Town Trial was a phase 2, randomised, open-label clinical trial of oral PrEP with emtricitabine plus tenofovir disoproxil fumarate in HIV-negative heterosexual women. The study was undertaken at the Emavundleni Prevention Centre (Cape Town, South Africa). This centre provides a comprehensive standard of prevention including on-demand HIV testing, male and female condoms, culturally appropriate risk-reduction counselling, various contraception options, sexually transmitted infection syndromic treatment, and post-exposure prophylaxis free of charge. It has a referral service for free antiretroviral therapy (ART) clinical services for individuals infected with HIV. The Emavundleni Prevention Centre serves the large township community of Crossroads, just outside of Cape Town, where HIV prevalence in antenatal care settings has been reported as high as 29%, with HIV incidence among women as high as 7% a year.¹⁶ The main risk of HIV transmission is from unprotected vaginal sex.

We included participants if they were born female or were transgender men, were aged 18 years or older, were literate (English or Xhosa), were willing and able to provide informed consent, were HIV-seronegative, and were immune to the hepatitis B virus (HBV). Further inclusion criteria were one or more of the following, taking place in the 6 months before enrolment: history of an acute sexually transmitted infection; history of transactional sex; intercourse without a condom with someone of unknown or positive HIV infection status; or self-report of more than one sex partner. We excluded women if they were pregnant, breastfeeding, or HIV-positive. We offered vaccination to women who were HBV-susceptible at screening and we allowed them to enrol in the study if immunity was detected. Participants agreed to use contraceptive methods during the study and injectable, implantable, and site-provided oral hormonal contraception. All women were assessed by medical practitioners for symptoms of acute HIV infection before enrolment.

Ethics committees of the Health Science Faculty of the University of Cape Town, the Emavundleni Community Advisory Board, and the Medicines Control Council of South Africa approved the protocol. The role of Gilead Sciences in the development of the protocol was restricted to handling of study drugs.

Randomisation and masking

We randomly allocated participants at week 6 to one of three PrEP dosing regimens: daily (one tablet every day); time-driven (one tablet twice a week, plus a post-sex dose); and event-driven (one tablet both before and after sex). The secure, web-based, computerised randomisation method was developed, implemented, and monitored by the Statistical Center for HIV/AIDS Research and Prevention (Fred Hutchinson Cancer Research Center, Seattle, WA, USA). Separate randomisation methods

were developed for every site and regimens were assigned in a 1:1:1 ratio with randomly varying block sizes of six, nine, or 12. Site staff and the site pharmacist received the random allocation. PrEP was dispensed at study visits in the Wisepill device (Wisepill Technologies, Somerset West, South Africa), with pouched refills for participants to use as needed. Since the study was open label, participants, study investigators, and data analysts were aware of treatment assignments.

Procedures

To provide steady-state drug concentrations independent of adherence variability, all participants had a 6-week lead-in before randomisation of directly observed dosing, which comprised one tablet of oral PrEP (emtricitabine plus tenofovir disoproxil fumarate) once a week for five observed doses followed by 1 week off drug. We took blood samples at weeks 4, 5, and 6 for pharmacological and other assessments; we also obtained hair samples. During this phase, we asked participants to familiarise themselves with the electronic drug monitoring (EDM) device Wisepill. To facilitate this process and allow for early troubleshooting, we dispensed a month's supply of a daily vitamin regimen for self-administration before randomisation.

At the time of the study, the daily PrEP regimen had growing support for efficacy; we made all participants aware of findings from PrEP studies as they became available over the course of the trial.¹⁻³ All PrEP was provided as open-label tablets of emtricitabine plus tenofovir disoproxil fumarate (Gilead Sciences, Foster City, CA, USA). We instructed all participants to take no more than two doses of PrEP in a 24 h period, no more than one dose in 2 h, and not to take more than seven doses a week. Furthermore, we told participants to take a dose when they remembered, if they forgot. We designed non-daily PrEP regimens based on evidence from an animal study to provide adequate coverage.¹⁷

The daily regimen was one tablet every 24 h. We did not stipulate a specific time of day for dosing. Time-driven dosing was two tablets per week (separated by about 3 days) plus a tablet after sex (preferably within 2 h). We did not specify days or times for dosing but we encouraged participants to identify the two days and times for consistency. We provided instructions for what to do when a dose after sex overlapped with a planned weekly dose day, and this scenario was rehearsed during regimen education sessions with on-site counsellors. The event-driven regimen was one tablet within 48 h before anticipated sex and another dose after sex (preferably within 2 h). We instructed participants to consider a sexual forecast question every day and take a dose even if there was a remote chance of having sex in the next 1–2 days, if they had not taken a tablet within the past 24 h. We provided instructions on how to adjust the dosing regimen if multiple sex events happened in a given week, and this scenario was rehearsed during regimen education sessions.

Participants self-administered PrEP for 24 weeks, with study visits to the research centre every 4 weeks and brief assessment interviews every week either in person at the research centre or by telephone (according to preference) to confirm dates and times for dosing (based on EDM data) and to obtain dates, times, and types of sex events for the previous week. Site staff who completed weekly interviews were not engaged in other aspects of the study and were tasked only with data collection at these interviews. Because the dispensing device recorded all opening events, irrespective of whether doses were added or removed, every recorded opening over the course of a given week (ie, EDM data) was reviewed with the participant. The participant could confirm the date and time of a dose, or adjust the EDM data according to whether a pill was removed and when it was taken. After obtaining all dosing information, participants were asked about sexual activity over the past week. We recorded days and times of sex events as well as unique partners, type of sex, partner HIV status, and condom use.

We obtained blood samples at every study visit for laboratory analysis. We did pharmacological assessments with blood samples obtained at weeks 10, 18, and 30. Every study visit included HIV testing and other laboratory assessments, adherence education and support discussions, risk-reduction counselling, collection of data for side-effects or adverse events, and PrEP dispensation. We based the adherence education and counselling used in our study on Next Step Counseling,¹⁸ a brief, participant-centred, strengths-based discussion. Drug concentration and EDM data were for data collection only and were not used to advise counselling discussions. A final study visit took place 1 month after completion of the 24-week self-administration period. Some participants engaged in qualitative interviews or focus groups during this PrEP-free period and within 3 months of their final study visit.

At screening, we analysed HIV and HBV serostatus, did safety testing (ie, complete blood count, creatinine, phosphate, aspartate aminotransferase, alanine aminotransferase, and urine dipstick), and gave participants a pregnancy test at the clinical site. We repeated safety testing at weeks 4, 10, 18, and 30. We also did HIV and pregnancy testing at enrolment, weeks 4 and 6, and every month thereafter or as needed. We did HIV rapid testing at every study visit. If the rapid HIV test was reactive, we did a western blot or ran the Aptima HIV-1 RNA qualitative assay (Hologic, Marlborough, MA, USA); we repeated this testing with a second sample obtained on a different date to confirm infection. Site laboratories prepared and stored plasma and peripheral blood mononuclear cell (PBMC) lysate samples.

Additional testing was done at the HPTN Laboratory Center (Johns Hopkins University, Baltimore, MD, USA). This work included confirmation of all seroconversion events; HIV RNA testing was done with samples from the visit before seroconversion to detect acute HIV infection. Samples from the final study visit

were tested with the Abbott Architect HIV-1/2 Combo (Abbott, Chicago, IL, USA) to confirm that participants who were not identified as seroconverters were not infected. We tested plasma and PBMC lysate for study drugs. We measured all drug analytes with liquid chromatographic tandem mass spectrometric analysis and using methods that were validated and peer-reviewed by the Division of AIDS Clinical Pharmacology Quality Assurance Program.¹⁹

Outcomes

The primary outcomes were coverage of sex events with PrEP dosing, number of PrEP doses needed to achieve 100% adherence and number of actual doses used, and self-reported symptoms and side-effects, compared between daily and non-daily (time-driven and event-driven) regimens. Secondary outcomes included adherence and drug detection. We gathered other psychosocial variables via computer assisted self-interview (CASI).

We calculated coverage based on weekly interview-adjusted EDM data and defined it as having at least one PrEP dose within 4 days (96 h) before and within 1 day (24 h) after sex events (appendix). Participants reported sex events every week. This definition can also be thought of as sexual-exposure-related dosing. We defined sex events as penetrative penile–vaginal or penile–anal sex irrespective of reported condom use, non-use of condoms, or their partner's HIV status. Coverage, thus, refers to the proportion of sex acts that had PrEP dosing covering the sex act, relative to total number of sex acts. Criteria for coverage were based on data for intracellular half-lives of tenofovir diphosphate and emtricitabine triphosphate and animal studies available at the time the protocol was written.¹⁷

We used data obtained for calculation of coverage to ascertain the total number of doses needed for full coverage of sex events during the self-administration period, for every participant. We used reported sex events and previous dosing to calculate the amount of the drug needed, assuming that a dose could meet criteria for post-sex and pre-sex doses when new sex events were close in time. Per regimen instructions, for full coverage, we capped the total number of doses needed at seven per week. The number of doses taken was derived from EDM data adjusted by the feedback obtained from the weekly interviews.

We assessed safety and tolerability throughout the study. We monitored proteinuria, glycosuria, creatinine clearance, and liver enzymes regularly, and we graded all adverse events and assessed them for relatedness to study treatment. We collated self-reported scores for common symptoms and side-effects (including headache and dizziness [neurological] and cramping, abdominal pain, and flatulence [gastrointestinal]) and compared them by study group. We discontinued PrEP at the time of any reactive HIV or pregnancy test and resumed study treatment only if confirmatory tests were negative.

See Online for appendix

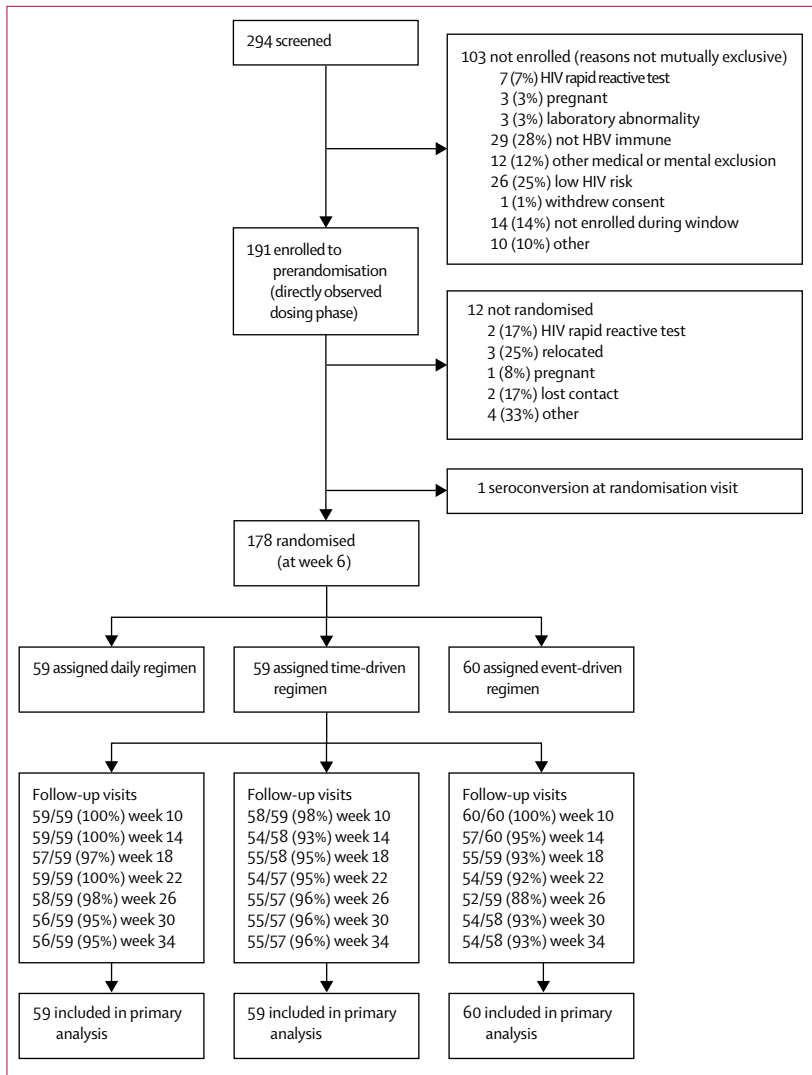


Figure 1: Trial profile
HBV=hepatitis B virus.

We continued to follow up pregnant and HIV-positive women, with pregnant women followed up for birth outcomes and participants with confirmed HIV infection followed up every 12 weeks until the last participant exited the study. We referred participants who acquired HIV infection for ongoing HIV care and management, including HIV viral load and HIV resistance testing.

We based adherence on EDM data that was adjusted by self-report data gathered at the weekly interviews. We defined adherence as the percentage of doses taken relative to the number of doses that should have been taken in view of the assigned regimen and reported sexual activity (appendix). Although drug concentrations are also a measure of adherence, the primary measure of adherence in this protocol was EDM-adjusted data reported every week to site staff. Several provisos were in place for calculation of non-daily adherence, allowing for the post-sex doses to also be one of the twice-weekly doses (time-driven) or as a pre-sex dose (event-driven) if the dosing pattern met prespecified criteria. Note that, unlike coverage, adherence to sex-dependent doses included oral sex because the instructions provided to participants included dosing for oral sex.

During the self-administered PrEP phase, we gathered blood and hair samples at weeks 10, 18, and 30 for retrospective analysis of drug concentrations (findings from hair samples are not reported here). We measured the amount of tenofovir in plasma and hair and the amount of tenofovir diphosphate—the intracellular activated form of the drug—in PBMCs. We also measured amounts of emtricitabine and its phosphorylated derivative. Amounts in plasma of tenofovir and emtricitabine reflect recent pill taking. Emtricitabine triphosphate and tenofovir diphosphate have long intracellular half-lives (>48 h and around 150 h, respectively); thus, their concentrations show longer term drug exposure.²⁰ The white-coat effect—whereby doses are taken on or just before a clinic visit—is less likely to affect the concentrations of these derivatives.²¹ Drug concentrations were a secondary and more objective measure of adherence.

Participants also completed CASI surveys at screening and at weeks 6, 18, and 30. The surveys included items quantifying risk perception, prevention practices, sexual behaviour, knowledge, attitudes, or beliefs about the regimen, and facilitators and barriers to adherence (not reported here).

Statistical analysis

We designed the study to have 90% power to test the non-inferiority hypothesis that the difference in the proportion of sexual events not covered by PrEP between either of the non-daily PrEP regimens (time-driven and event-driven) and the daily regimen was greater than 0.031, versus the alternative that the difference was less than 0.031. We assumed there would be 60 participants per regimen, the proportion of sexual events not covered by PrEP with the daily

	Daily regimen (n=59)	Time-driven regimen (n=59)	Event-driven regimen (n=60)
Age (years)	25 (21–37)	26 (21–33)	25 (21–37)
≤25	30 (51%)	27 (46%)	31 (52%)
Never married	47 (80%)	43 (73%)	52 (87%)
Secondary education completed	21 (36%)	20 (34%)	21 (35%)
Black ethnic origin	58 (98%)	59 (100%)	60 (100%)
Hormonal contraception	55 (93%)	56 (95%)	49 (82%)
Number of sex partners (past 3 months)*	1 (1–1)	1 (1–1)	1 (1–1)
Median sex events in past 3 months†	4 (2–10)	4 (1–12)	4 (2–10)
No condom‡	2 (0–7)	2 (0–5)	1 (0–4)
HIV seroconversions (after randomisation)	0 (0%)	2 (3%)	2 (3%)

Data are median (IQR) or number of women (%). *Data missing for one, nine, and three patients, respectively. †Data missing for one, five, and one patient, respectively. ‡Data missing for four, ten, and two patients, respectively.

Table 1: Participants' characteristics at randomisation

	Daily regimen (n=59)	Time-driven regimen (n=59)	Event-driven regimen (n=60)	Daily vs time-driven*	Daily vs event-driven*	p value†
Sex events reported over full study (n)	1952	1074	1542	1.74 (1.29–2.33)	1.20 (0.91–1.59)	0.0018
Sex events fully covered by PrEP‡	1459 (75%)	599 (56%)	798 (52%)	2.35 (1.43–3.85)	2.76 (1.68–4.53)	0.0006
Sex events partly covered by PrEP‡	431 (22%)	416 (39%)	638 (41%)	0.44 (0.29–0.69)	0.40 (0.25–0.63)	0.0005
Pre-sex dose taken	412 (21%)	317 (30%)	507 (33%)	0.64 (0.41–0.98)	0.55 (0.35–0.85)	0.0350
Post-sex dose taken	19 (1%)	99 (9%)	131 (8%)	0.10 (0.05–0.18)	0.11 (0.06–0.19)	<0.0001
Sex events not covered by PrEP‡	62 (3%)	59 (5%)	106 (7%)	0.56 (0.21–1.54)	0.44 (0.17–1.13)	0.17
Pills needed for 100% adherence (n)§	9652	3616	2203	2.53 (2.39–2.69)	4.16 (3.59–4.82)	<0.0001
Pills used (n)§	7349	2852	2000	2.46 (2.22–2.73)	3.49 (2.93–4.16)	<0.0001
Pills used as recommended (n)§¶	7283	2367	1161	2.92 (2.67–3.19)	5.96 (4.92–7.22)	<0.0001
Adherence as measured by adjusted EDM data (%)§	75%	65%	53%	10.0% (3.8–16.0%)	22.0% (15.3–30.0%)	<0.0001

Data are number (%), unless otherwise indicated. EDM=electronic drug monitoring. PrEP=pre-exposure prophylaxis. *For coverage results, data are odds ratio (95% CI); for sex event counts and pill counts, data are fold change in mean (95% CI). †p value is for the comparison between the three regimens. ‡100% coverage means all sex events (excluding oral sex) are covered by PrEP. Sex is covered fully by PrEP if at least one pill is taken 96 h before the sex event and at least one additional pill is taken within 24 h of the sex event (same coverage definition for all three regimens); partly covered means that participants either missed the pill before or the pill after the sex event; not covered means participants missed both pills. §Adherence is defined as the proportion of doses taken as recommended by the specific assigned regimen, determined by EDM (with the Wisepill device) and the weekly interview. ¶As recommended pills are those taken that met criteria for daily dosing (daily regimen), weekly or post-sex dosing (time-driven regimen), or pre-sex and post-sex dosing (event-driven regimen).

Table 2: Coverage of sex events by PrEP and adherence to the assigned regimen

regimen would be 0.10, and that participants would report an average of 50 sexual events over follow-up (about two a week). The interperson coefficient of variation in coverage was assumed to be 0.40 with a one-tailed α of 0.05.

All analyses were done in SAS version 9.4. The primary analyses compared PrEP coverage of sex events, the number of tablets taken over the 24-week self-administration period, and reported side-effects and symptoms between the three regimens. Other analyses included comparison of adherence, sex events, and drug concentrations between the three regimens. All analyses were by intention to treat. We calculated global p values comparing all three PrEP regimens and did pairwise comparisons between daily and non-daily regimens when the global p value was 0.05 or less. We used logistic regression for clustered data (generalised estimating equations [GEEs] with logit link and independent working correlation matrix) with robust SEs to compare the proportion of sexual events covered by PrEP dosing between the three regimens. We used similar methods to assess whether prevalence of neurological and gastrointestinal side-effects differed between the three regimens.

To ascertain whether the total number of pills used in the self-administered phase differed between PrEP regimens, since this number depends on sexual frequency and the ability to predict sexual frequency, we contrasted the three study regimens with a Poisson regression (with robust variance) for total pills, offset by total days of self-administration. We used a similar approach to compare the number of sex events between regimens. We calculated adherence for every individual as the number of pills taken divided by the number of pills needed for perfect adherence. We excluded periods

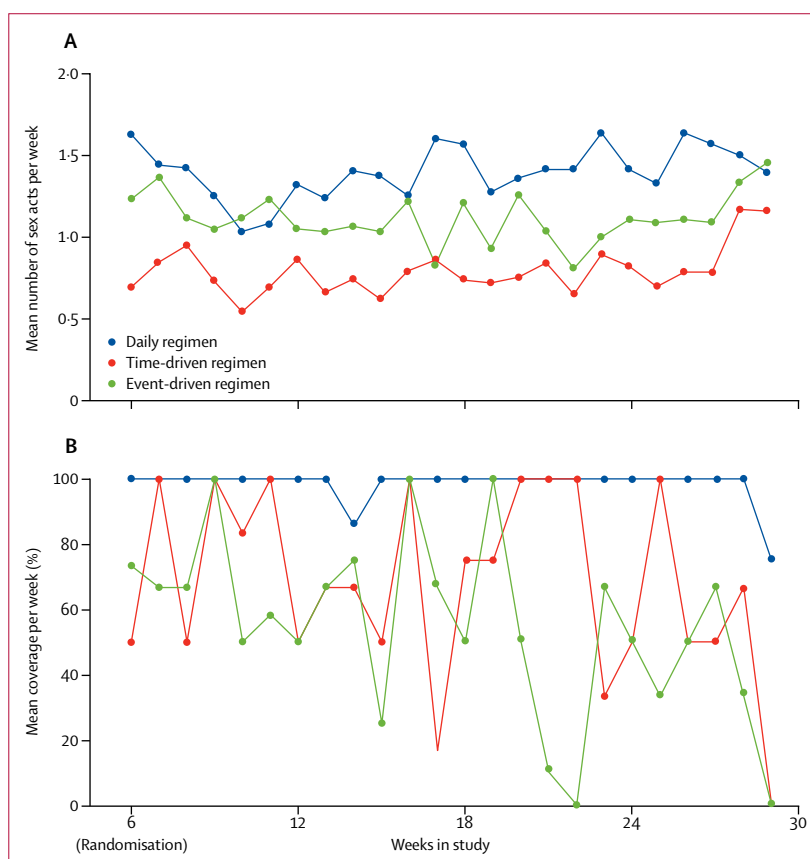


Figure 2: Mean number of sex acts per week (A) and coverage (B) during the self-administration phase

when participants were required to be off drug—eg, during pregnancy. We used one-way ANOVA and pairwise *t* tests to compare adherence between

	Daily regimen	Time-driven regimen	Event-driven regimen	p value†
Plasma tenofovir ≥ 0.31 ng/mL‡				
Week 10	55/59 (93%)	48/57 (84%)	29/37 (78%)	0.0819
Week 18	44/54 (81%)	43/54 (80%)	21/30 (70%)	..
Week 30	38/56 (68%)	31/55 (56%)	17/32 (53%)	..
Plasma tenofovir ≥ 2.5 ng/mL§				
Week 10	46/59 (78%)	38/57 (67%)	20/37 (54%)	0.0198
Week 18	31/54 (57%)	31/54 (57%)	11/30 (37%)	..
Week 30	30/56 (54%)	20/55 (36%)	10/32 (31%)	..
PBMC tenofovir diphosphate ≥ 5.2 fmol per 10^6 cells§				
Week 10	49/58 (84%)	45/58 (78%)	25/37 (68%)	0.0233
Week 18	41/57 (72%)	35/55 (64%)	10/30 (33%)	..
Week 30	30/56 (54%)	25/55 (45%)	12/31 (39%)	..
Plasma tenofovir ≥ 35.5 ng/mL¶				
Week 10	34/59 (58%)	11/57 (19%)	2/37 (5%)	<0.0001
Week 18	24/54 (44%)	9/54 (17%)	7/30 (23%)	..
Week 30	21/56 (38%)	8/55 (15%)	4/32 (13%)	..
PBMC tenofovir diphosphate ≥ 16.8 fmol per 10^6 cells¶				
Week 10	43/58 (74%)	25/58 (43%)	12/37 (32%)	<0.0001
Week 18	30/57 (53%)	20/55 (36%)	7/30 (23%)	..
Week 30	29/56 (52%)	12/55 (22%)	7/31 (23%)	..

Data are number with detectable drug/total number at each study visit (daily and time-driven regimens) or reporting sex in previous week (event-driven regimen). PBMC=peripheral blood mononuclear cell. †As expected refers to dosing as prescribed in the assigned regimen. ‡p value for comparison between regimens across study visits. ‡Above level of detection. §Consistent with two or more pills per week. ¶Consistent with seven pills per week.

Table 3: Proportion of participants with detectable drug concentrations as expected*

regimens. We dichotomised concentrations of tenofovir in plasma as detectable (defined by a value greater than the lower limit of assay quantitation) at 0.31 ng/mL (lower limit of quantification). Drug concentrations indicating different levels of adherence are based on 90% sensitivity threshold values from a directly observed dosing study:²¹ at least two pills in the previous week, amount of tenofovir in plasma of 2.5 ng/mL or greater, and amount of tenofovir diphosphate in PBMCs of 5.2 fmol per 10^6 cells or greater; or seven pills in the previous week, amount of tenofovir in plasma of at least 35.5 ng/mL, and amount of tenofovir diphosphate in PBMCs of at least 16.8 fmol per 10^6 cells. We used logistic regression GEEs to compare the prevalence of detectable drug levels in cis-gender women between regimens.

This trial is registered with ClinicalTrials.gov, number NCT01327651.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

	Daily regimen	Time-driven regimen	Event-driven regimen	p value*
Plasma tenofovir ≥ 2.5 ng/mL‡				
Week 10	32/40 (80%)	14/23 (61%)	20/37 (54%)	0.0080
Week 18	22/38 (58%)	17/25 (68%)	11/30 (37%)	..
Week 30	19/29 (66%)	11/24 (46%)	10/32 (31%)	..
PBMC tenofovir diphosphate ≥ 5.2 fmol per 10^6 cells‡				
Week 10	33/40 (83%)	16/23 (70%)	25/37 (68%)	0.0080
Week 18	29/39 (74%)	16/25 (64%)	10/30 (33%)	..
Week 30	19/29 (66%)	13/24 (54%)	12/31 (39%)	..
Plasma tenofovir ≥ 35.5 ng/mL‡				
Week 10	23/40 (58%)	5/23 (22%)	2/37 (5%)	<0.0001
Week 18	18/38 (47%)	6/25 (24%)	7/30 (23%)	..
Week 30	12/29 (41%)	4/24 (17%)	4/32 (13%)	..
PBMC tenofovir diphosphate ≥ 16.8 fmol per 10^6 cells‡				
Week 10	28/40 (70%)	8/23 (35%)	12/37 (32%)	<0.0001
Week 18	22/39 (56%)	8/25 (32%)	7/30 (23%)	..
Week 30	19/29 (66%)	8/24 (33%)	7/31 (23%)	..

Data are number with detectable drug/number who reported a sex event in previous week. PBMC=peripheral blood mononuclear cell. *p value for comparison between regimens across study visits. †Consistent with two or more pills per week. ‡Consistent with seven pills per week.

Table 4: Proportion of participants with detectable drug concentrations who reported sex in the previous week, by study visit

Results

Enrolment began on Sept 12, 2011, and ended on Oct 3, 2012. Transgender men were eligible for the study but all participants were cis-gendered. Of 294 women screened in Cape Town, 191 were enrolled into the 6-week prerandomisation phase (directly observed dosing). 178 women completed this phase and were randomly allocated to either the daily regimen (n=59), time-driven dosing (n=59) or event-driven dosing (n=60) for 24 weeks (figure 1). The last study visit was May 29, 2013. Median duration of follow-up for participants who attended the week 34 visit was 254 days (IQR 249–266). 177 (99%) of 178 participants were black South African, median age was 26 years (IQR 21–37; range 18–52), 142 (80%) had never been married, 147 (83%) were unemployed, and 62 (35%) had completed secondary education (table 1). 165 (93%) participants completed their week 34 visit, and this number did not vary by assigned regimen (figure 1).

The total number of sex events post randomisation for women allocated a non-daily regimen (time-driven or event-driven) was lower than that for participants assigned the daily regimen, with the reported number of sex events with the daily regimen almost twice that with the time-driven regimen (table 2; figure 2A). PrEP coverage of sex events was significantly higher with the daily regimen than with the time-driven (p=0.0007) and event-driven (p<0.0001) regimens (table 2; figure 2B). Incomplete coverage of sex events was mostly as a result of missed post-sex doses. The number of events not covered was low for all three regimens. Adherence to the assigned regimen as determined by adjusted EDM data

was higher with the daily regimen (75%) than with the time-driven (65%) and event-driven (53%) regimens (table 2). Reported coverage decreased over time for all regimens (figure 2B). Fewer pills were needed for complete adherence with the non-daily regimens, with women allocated the event-driven regimen needing far fewer pills than those assigned either the daily or time-driven regimen (table 2).

Two women seroconverted before randomisation and another (who was also found to be HIV-positive) did not undergo randomisation because of pregnancy (figure 1). Retrospective testing showed that an additional woman had acute HIV infection at randomisation; her data were excluded from the analysis. Four further participants seroconverted during the self-administered phase of the study, of whom two were assigned the event-driven regimen and two were allocated the time-driven regimen. Drug resistance mutations were detected in HIV from two of the eight participants who seroconverted. The woman who had acute infection at enrolment had the Lys65Arg mutation detected at the week 4 study visit before randomisation, during the observed dosing phase, and one woman allocated the time-driven regimen had Met184Ile and Lys65Arg detected. In both cases, Lys65Arg was detected only by next-generation sequencing.²²

A dose response was noted when comparing the number of reported pills taken in the previous week with plasma tenofovir concentrations (data not shown). The expected minimum dosing per protocol for women allocated the daily regimen was seven pills per week; with the time-driven regimen, minimum dosing was two or more pills per week, with the same number for the event-driven regimen if at least one sex event occurred in the previous week (table 3). Using a cutoff for amounts in plasma and PBMCs consistent with two or more pills, both plasma tenofovir and PBMC lysate tenofovir diphosphate concentrations were detected in more women allocated the daily regimen at the week 10, week 18, and week 30 study visits than in those assigned a non-daily regimen, and the same was true for women who reported sex in the previous week (table 4). In a subanalysis (for which the study was not powered sufficiently) comparing older women (age >25 years) with younger women (age <25 years) reporting sex in the previous week, detection of drugs in plasma and PBMCs—using drug concentrations equivalent to two or more pills and seven pills per week—was similar at all timepoints (table 5). Across all regimens and all ages, a substantial reduction was noted in the numbers of women with drug concentrations compatible with prescribed pill intake over the 30-week period.

Overall, side-effects of PrEP were uncommon and most were mild or moderate. Gastrointestinal and neurological symptoms predominated, with few women (<13%) at all study visits reporting headache, dizziness, and gastrointestinal events, with no differences by regimen (table 6). Side-effects predominated early in

	Age ≤25 years			Age >25 years		
	Daily regimen	Time-driven regimen	Event-driven regimen	Daily regimen	Time-driven regimen	Event-driven regimen
Plasma tenofovir ≥2.5 ng/mL*						
Week 10	19/23 (83%)	6/9 (67%)	8/18 (44%)	13/17 (76%)	8/14 (57%)	12/19 (63%)
Week 30	11/16 (69%)	3/7 (43%)	3/12 (25%)	8/13 (62%)	8/17 (47%)	7/20 (35%)
PBMC tenofovir diphosphate ≥5.2 fmol per 10⁶ cells*						
Week 10	20/23 (87%)	6/9 (67%)	12/18 (67%)	13/17 (76%)	10/14 (71%)	13/19 (68%)
Week 30	11/16 (69%)	4/7 (57%)	3/12 (25%)	8/13 (62%)	9/17 (53%)	9/19 (47%)
Plasma tenofovir ≥35.5 ng/mL†						
Week 10	14/23 (61%)	3/9 (33%)	1/18 (5.6%)	9/17 (53%)	2/14 (14.3%)	1/19 (5%)
Week 30	9/16 (56%)	1/7 (14%)	0/12 (0%)	3/13 (23%)	3/17 (17.7%)	4/20 (20%)
PBMC tenofovir diphosphate ≥16.8 fmol per 10⁶ cells†						
Week 10	15/23 (65%)	4/9 (44%)	6/18 (33%)	13/17 (76%)	4/14 (29%)	6/19 (32%)
Week 30	11/16 (69%)	2/7 (29%)	2/12 (17%)	8/13 (62%)	6/17 (35%)	5/19 (26%)

Data are number with detectable drug/number who reported a sex event in previous week. PBMC=peripheral blood mononuclear cell. *Consistent with two or more pills per week. †Consistent with seven pills per week.

Table 5: Participants with detectable drug concentrations reporting sex in the previous week, by age

	Daily regimen	Time-driven regimen	Event-driven regimen	Daily vs time-driven*	Daily vs event driven*	p value†
Any headache, dizziness, lightheadedness (n/N)	43/348 (12%)	20/331 (6%)	26/332 (8%)	2.19 (1.13–4.27)	1.66 (0.88–3.13)	0.057
Any gastrointestinal symptoms (n/N)	37/348 (11%)	29/331 (9%)	18/332 (5%)	1.24 (0.61–2.51)	2.08 (0.98–4.40)	0.14

n=number of visits at which side-effects reported. N=total number of visits. *Data are odds ratios (95% CIs). †p value is for the comparison between the three regimens across all follow-up visits.

Table 6: Visits at which neurological and gastrointestinal side-effects were reported

follow-up and largely returned to baseline by week 14 (figure 3). The number of grade 3 and 4 events per regimen were six or fewer and no difference was noted in grade 3 and 4 events per regimen. No non-trauma related fractures were recorded, and no regimen resulted in creatinine abnormalities.

Discussion

Most of the largely young, predominantly single, South African women in the HPTN 067/ADAPT study used oral PrEP as recommended, although adherence decreased over time. Daily dosing resulted in higher coverage of sex events, adherence, and drug concentrations compared with non-daily regimens. When stratifying by age, although numbers are small, the proportion of women with drug concentrations above the coverage threshold was similar in younger versus older age groups. These data are important since they represent, to our knowledge, the first evidence that young African women will take oral PrEP when offered as an option for HIV prevention.

We postulate that the daily regimen might have helped to foster daily habit formation. Daily dosing also precluded

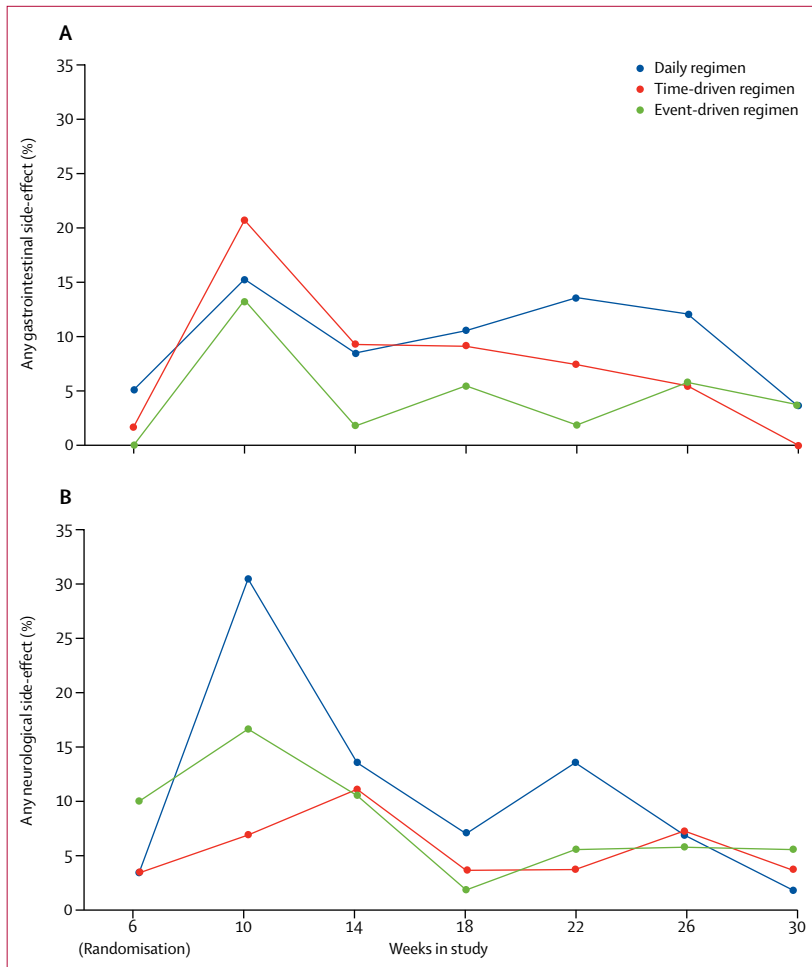


Figure 3: Gastrointestinal (A) and neurological (B) side-effects over time

the need to forecast sex and did not require special dosing activity after sex. In qualitative research done before HPTN 067/ADAPT, we found that women had more difficulty planning for sex than did men.²³ Although few sex events were not covered by PrEP (as defined in our study) across all three study regimens, partial coverage—in particular a missed dose after sex—was more common with the non-daily dosing regimens. The difficulty for women in adhering to the post-sex dose in our study was confirmed by qualitative data.²⁴ Pre-sex and post-sex dosing of a vaginal gel was effective in CAPRISA 004,²⁵ although this finding was not replicated in the FACTS 001 trial.²⁶ At the time that the HPTN 067/ADAPT study was being implemented, only daily dosing of PrEP had evidence for efficacy, as described in information provided to participants. Such information might have reduced motivation for PrEP use in women allocated a non-daily dosing regimen. PrEP use decreased over time for all regimens, suggesting an element of fatigue during the self-administered phase, including with the daily regimen. This tailing off could be ascribed to declines in sex

frequency; however, patterns of sex in the three regimens were constant over the 30 weeks (data not shown). PrEP is not expected to be dosed lifelong; however, fatigue in all types of dosing suggests that efforts are needed to ensure consistent adherence during times of use.

Although we did not assess efficacy in the HPTN 067/ADAPT study, our findings support recommendations for daily use of oral PrEP with emtricitabine and tenofovir disoproxil fumarate to prevent HIV infection in women. Findings of studies in MSM have shown efficacy for sex-driven PrEP dosing,⁴ and evidence suggests that fewer than seven doses of PrEP a week can prevent rectal HIV transmission.²⁷ Concentrations of tenofovir diphosphate in rectal mucosa after oral PrEP dosing with tenofovir disoproxil fumarate on its own or in combination with emtricitabine are 20–100-fold higher than are vaginal concentrations.²⁸ It is important to note that coverage (as defined in our study and based on available animal data at the time HPTN 067/ADAPT was designed) was thought to be protective dosing for sexual exposure in women. Available models now suggest that more consistent dosing is needed to achieve sufficient drug concentrations in vaginal tissue.²⁹

We reported the proportions of women who had drug concentrations consistent with taking more than two pills per week (ie, non-daily regimens), because this dose was the minimum needed on weeks when sex occurred, as recommended with non-daily regimens. However, we also looked at the proportions of women with detected amounts of drug in PBMCs consistent with taking at least seven pills per week at each of the timepoints (ie, with the daily regimen). Both these proportions were comparable, suggesting that many women allocated the daily regimen were attempting to follow this dosing schedule. A large proportion of women allocated the daily regimen achieved drug concentrations consistent with expected pill dosing, and more than a third of women assigned a non-daily regimen met expected amounts of drug, over the 24-week period. Differences between proportions of women with specific plasma or PBMC drug concentrations were similar, suggesting that so-called white-coat dosing (taking study drugs just before clinic visits) was not common practice in this cohort.

Intermittent (non-daily) PrEP dosing might save costs, particularly when sex is infrequent. The need to reduce costs of PrEP is pressing, particularly in settings where resources are limited. Other approaches to reduce drug costs include: use of tenofovir disoproxil fumarate alone, which was effective in heterosexual men and women;¹ decreasing drug pricing; cutting laboratory monitoring; and using PrEP in women who are most likely to benefit and only during periods of HIV risk (effective use).³⁰ When used by people at highest risk of HIV, Walensky and colleagues³¹ showed that PrEP could be cost-saving in the South African context, even with daily dosing. Helping women to self-identify and then gauge periods and circumstances of potential HIV exposure to ensure

effective adherence during these times are also areas for implementation research.

Similar to earlier trials, we found that side-effects of combination PrEP were uncommon and restricted to the first few weeks of use. Our study adds further reassuring data to the safety profile of PrEP, which is important because PrEP is increasingly regarded as part of standard prevention among many young, healthy, and at-risk individuals globally. Our data will also help to frame the need and frequency of laboratory safety monitoring. PrEP adherence was more consistent in our open-label study than in earlier randomised trials in similar populations—a pattern also seen in MSM.³² This finding probably reflects how open-label PrEP implementation allows for clear messaging about PrEP safety, efficacy, and the importance of adherence for achieving the desired high levels of protection.

In two placebo-controlled studies of a vaginal dapivirine ring in young women from southern and eastern Africa,³³ very high HIV incidence was recorded in this vulnerable population. Those study findings also highlighted the unique challenges of younger women in achieving sufficient adherence to benefit from potentially effective biomedical prevention methods.³³ In our study, although restricted in sample size and geographical reach, younger women had the same rates of adherence (as measured by amounts of drug in plasma) as did older women. Clear information that a product is safe and effective could be essential for prompting effective PrEP use in adolescents and younger users. In our qualitative work examining the barriers and facilitators to PrEP use and adherence in this cohort,²³ the importance of trust and belief that PrEP was both safe and effective were highlighted by women, as were unique challenges to dosing after sex—eg, interference with the post-sex experience (rest, sleep) and added demands of carrying doses because sex often occurred outside of one's home. Recommendations for relaxed dosing after sex, in our case within 2 h of sex to within 24 h of sex, might have addressed some of these challenges.

Several limitations caution against overgeneralisation of our results. Women allocated a non-daily regimen received warnings and messages about the paucity of data supporting the efficacy of non-daily regimens for HIV prevention in women. As such, results are not fully reflective of patterns of use for open-label effective PrEP regimens. Further, we did not anchor our study to HIV incidence between regimens, because our interest was on coverage and adherence rather than efficacy. Work is needed to ascertain whether non-daily dosing is an appropriate option for women.

Results from our study highlight the acceptability and feasibility of PrEP in young sexually active women in southern Africa. In sub-Saharan Africa, most of the estimated 1.4 million new HIV infections in 2015 alone occurred in this group of people.³⁴ Ensuring delivery of PrEP to women at risk—accompanied by education and support for optimum use—is an urgent priority and will

play a vital part in eliminating the long-standing disparities in HIV infections in sub-Saharan Africa.

Contributors

L-GB, SR, ES, and NY were involved in management of participants, data collection, and implementation of the study. L-GB, KRA, JPH, and RMG were involved in study design, writing of the protocol, and implementation of the study. MAM, CWH, PLA, VE, MS, EP-M, SHE, and LM were involved in data collection, laboratory investigations, safety management, and data analysis. L-GB, ML, JPH, BJD, MAM, CWH, PLA, VE, MS, EP-M, SHE, LM, and RMG were involved in data management, data analysis, and data interpretation. L-GB wrote the first draft of the report. All authors were involved in editing and finalising the report and approved the final version.

Declaration of interests

KRA has an unrestricted educational grant to the University of Michigan from Gilead Sciences. PLA receives study drug and contract work from Gilead Sciences. JFR is employed by Gilead Sciences. SHE has done collaborative research studies with Abbott Diagnostics. CWH has received research grants from ViiV, GlaxoSmithKline, the Gates Foundation, and the US National Institutes of Health, managed through Johns Hopkins; and is a consultant to RTI and UCLA. RMG is a site investigator for a clinical trial funded by Gilead Sciences to the San Francisco AIDS Foundation. L-GB has received donations of Truvada from Gilead Sciences for other PrEP demonstration projects. SR, ES, NY, JPH, MAM, VE, MS, EP-M, LM, ML, and BJD declare no competing interests.

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