Retention, engagement, and adherence to pre-exposure prophylaxis for men who have sex with men and transgender women in PrEP Brasil: 48 week results of a demonstration study

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Summary

Background PrEP Brasil was a demonstration study to assess feasibility of daily oral tenofovir diphosphate disoproxil fumarate plus emtricitabine provided at no cost to men who have sex with men (MSM) and transgender women at high risk for HIV within the Brazilian public health system. We report week 48 pre-exposure prophylaxis (PrEP) retention, engagement, and adherence, trends in sexual behaviour, and incidence of HIV and sexually transmitted infections in this study cohort.

Methods PrEP Brasil was a 48 week, open-label, demonstration study that assessed PrEP delivery at three referral centres for HIV prevention and care in Rio de Janeiro, Brazil (Fundação Oswaldo Cruz), and São Paulo, Brazil (Universidade de São Paulo and Centro de Referência e Treinamento em DST e AIDS). Eligible participants were MSM and transgender women who were HIV negative, aged at least 18 years, resident in Rio de Janeiro or São Paulo, and reported one or more sexual risk criteria in the previous 12 months (eg, condomless anal sex with two or more partners, two or more episodes of anal sex with an HIV-infected partner, or history of sexually transmitted infection [STI] diagnosis). Participants were seen at weeks 4, 12, 24, 36, and 48 for PrEP provision, clinical and laboratory evaluation, and HIV testing. Computer-assisted self-interviews were also done at study visits 12, 24, 36, and 48, and assessed sexual behaviour and drug use. PrEP retention was defined by attendance at the week 48 visit, PrEP engagement was an ordinal five-level variable combining presence at the study visit and drug concentrations, and PrEP adherence was evaluated by measuring tenofovir diphosphate concentrations in dried blood spots. Logistic regression models were used to quantify the association of variables with high adherence (≥4 doses per week). The study is registered with ClinicalTrials.gov, number NCT01989611.

Findings Between April 1, 2014, and July 8, 2016, 450 participants initiated PrEP, 375 (83%) of whom were retained until week 48. At week 48, 277 (74%) of 375 participants had protective drug concentrations consistent with at least four doses per week: 183 (82%) of 222 participants from São Paulo compared with 94 (63%) of 150 participants from Rio de Janeiro (adjusted odds ratio 1·88, 95% CI 1·06–3·34); 119 (80%) of 148 participants who reported sex with HIV-infected partners compared with 158 (70%) of 227 participants who did not (1·78, 1·03–3·08); 67 (87%) of 77 participants who used stimulants compared with 210 (71%) of 298 participants who did not (2·23, 1·02–4·92); and 232 (80%) of 289 participants who had protective concentrations of tenofovir disphosphate at week 4 compared with 42 (54%) of 78 participants who did not (3·28, 1·85–5·80). Overall, receptive anal sex with the last three partners increased from 45% at enrolment to 49% at week 48 (p=0·17), and the mean number of sexual partners in the previous 3 months decreased from 11·4 (SD 28·94) at enrolment to 8·3 (19·55) at week 48 (p<0·0013). Two individuals seroconverted during follow-up (HIV incidence 0·51 per 100 person-years, 95% CI 0·13–2·06); both of these patients had undetectable tenofovir concentrations at seroconversion.

Interpretation Our results support the effectiveness and feasibility of PrEP in a real-world setting. Offering PrEP at public health-care clinics in a middle-income setting can retain high numbers of participants and achieve high levels of adherence without risk compensation in the investigated populations.

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Introduction

An estimated 800 000 individuals are living with HIV or AIDS in Brazil,[1] with men who have sex with men (MSM) bearing a disproportionate burden of the HIV epidemic.[2] In 2016, around 60% of reported HIV infections were attributed to male-to-male sexual contact, although MSM represent only 3·5% of the Brazilian population.[1,3] Disaggregated data for transgender women are unavailable,

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Research in context

Evidence before this study

We searched PubMed, Web of Science, Scopus, SciELO, and the Cochrane Controlled Trials Register from inception to July 4, 2017, with the keywords ((pre-exposure prophylaxis) OR (PrEP)) AND ((men who have sex with men) OR (MSM) OR (transgender) OR (TGW)) AND ((clinical trial) OR (demonstration study) OR (demonstration project)). Studies were not restricted in language but were restricted to human populations to exclude modelling (mathematical modelling or cost-effectiveness) studies. We screened abstracts to retrieve full text articles. We also checked reference lists of relevant studies and reviews in search of potentially relevant studies. This search identified five oral pre-exposure prophylaxis (PrEP) demonstration studies or implementation experiences.

Added value of this study

PrEP Brasil was a demonstration study to assess feasibility of daily oral PrEP with tenofovir disoproxil fumarate plus emtricitabine provided at no cost to men who have sex with men (MSM) and transgender women within the Brazilian public health system. To our knowledge, it is the first demonstration project for PrEP naive MSM and transgender women in Latin America and provides an approximation of what real-world clinical PrEP delivery might look like in Brazil and other settings in the region.

Implications of all the available evidence

The HIV epidemic in Brazil persists unabated among MSM and transgender women. According to official numbers, around 60% of HIV cases reported in 2016 were attributed to male-to-male sexual contact. For these populations, innovative HIV prevention interventions are important to help curb the epidemic. Our study offers evidence that PrEP offered at public health-care clinics in a middle-income setting can retain over 80% of participants over 48 weeks and achieve high levels of adherence consistent with at least four doses per week in more than 70% of the retained population, and was associated with low seroconversion rates.

but studies show a high prevalence of HIV infection in this population.[4] In Rio de Janeiro, the city with the second largest number of HIV/AIDS cases in Brazil, 31·2% of transgender women enrolled in a respondent-driven sampling study were living with HIV and almost a quarter had previously undiagnosed infections.[4] Moreover, 43·7% of the transgender women with newly diagnosed infections had a negative HIV test result in the previous 12 months.[4] Given their disproportionate burden of HIV, innovative prevention interventions are important to lower the risk of HIV for MSM and transgender women in Brazil.

Once-daily and on demand pre-exposure prophylaxis (PrEP) for HIV using tenofovir or emtricitabine is efficacious among MSM and transgender women[5–8] and uptake and adherence are high.[5,9,10] Adherence is one of the great challenges of effective PrEP implementation, particularly among young MSM and transgender women.[9,11] As PrEP moves from clinical trials into routine practice, adherence will determine how effective this therapy is at preventing HIV. PrEP is not meant to be a lifelong requirement, but high adherence is needed during periods of use when an individual is at risk of HIV. In Brazil, PrEP adherence among MSM and transgender women has been assessed in the context of clinical trials[5,6] and little is known about factors associated with adherence in real-world settings. Additionally, concerns exist about risk compensation, sexually transmitted infection (STI) risk, and long-term drug toxicity.

To our knowledge, PrEP Brasil is the first demonstration study for MSM and transgender women in Latin America. We previously reported high PrEP uptake and early adherence in PrEP Brasil.[12] In this paper, we report the final results of this prospective, open-label demonstration study assessing PrEP retention, engagement, adherence, safety, social benefits and harms, HIV and STI acquisition, and sexual behaviour, as well as preliminary results of a text messaging adherence intervention.

Methods

Study design and participants

PrEP Brasil was a 48 week, open-label, demonstration study that assessed PrEP delivery at three referral centres for HIV prevention and care in Rio de Janeiro, Brazil (Fundação Oswaldo Cruz), and São Paulo, Brazil (Universidade de São Paulo and Centro de Referência e Treinamento em DST e AIDS).[12]

In PrEP Brasil, eligible participants were MSM and transgender women who were HIV-negative, aged at least 18 years, resident in Rio de Janeiro or São Paulo, and reported one or more sexual risk criteria in the previous 12 months (eg, condomless anal sex with two or more partners, two or more episodes of anal sex with an HIV-infected partner, or history of STI diagnosis). Individuals presenting with creatinine clearance less than 60 mL per min, proteinuria (urine dipstick 1+ or more), positive hepatitis B surface antigen serology test, severe medical comorbidity, and use of antiretrovirals, interferons, or interleukins were excluded.

Institutional review boards at Instituto Nacional de Infectologia Evandro Chagas, Universidade de São Paulo (USP; São Paulo, Brazil), and Centro de Referencia e Treinamento DST/AIDS de SP approved the study and all study participants signed an informed consent form at prescreening and screening visits. The study was done according to the principles expressed in the Declaration of Helsinki.

	Retained until study completion	Not retained	Odds ratio (95% CI)	p value
Patients	375 (83%)	75 (17%)	..	..
Site location				
Rio de Janeiro	150 (83%)	30 (17%)	1 (ref)	..
São Paulo	225 (83%)	45 (17%)	1 (0·60–1·66)	1·00
Age, years				
18–24	92 (81%)	21 (19%)	0·80 (0·40–1·58)	0·52
25–34	179 (84%)	35 (16%)	0·93 (0·51–1·72)	0·83
≥35	104 (85%)	19 (15%)	1 (ref)	..
Length of schooling, years				
<12	93 (81%)	22 (19%)	1·26 (0·73–2·18)	0·41
≥12	282 (84%)	53 (16%)	1 (ref)	..
Race (n=370)				
White	205 (84%)	38 (16%)	1 (ref)	..
Black	47 (82%)	10 (18%)	0·87 (0·40–1·87)	0·72
Mixed	118 (81%)	27 (19%)	0·81 (0·47–1·39)	0·45
Gender				
Male	354 (83%)	71 (17%)	1 (ref)	..
Transgender female	21 (84%)	4 (16%)	1·05 (0·35–3·16)	0·93
Steady partner (n=365)				
Yes	194 (83%)	39 (17%)	0·96 (0·58–1·59)	0·87
No	171 (84%)	33 (16%)	1 (ref)	..
Perceived likelihood of getting HIV in the next year, % (n=365)				
0–25	169 (82%)	36 (18%)	1 (ref)	..
50–100	196 (84%)	36 (16%)	1·16 (0·70–1·92)	0·56
Previous HIV test in the past 12 months (n=365)				
Yes	301 (84%)	58 (16%)	1·14 (0·60–2·16)	0·70
No	64 (82%)	14 (18%)	1 (ref)	..
(Table 1 continues in next column)				
(Continued from previous column)				
Previous PrEP awareness (n=367)				
Yes	275 (84%)	53 (16%)	1·13 (0·64–1·99)	0·68
No	92 (82%)	20 (18%)	1 (ref)	..
Number of male condomless anal sex partners in the previous 12 months (n=365)				
<2	121 (85%)	22 (15%)	1 (ref)	..
≥2	244 (83%)	50 (17%)	0·89 (0·51–1·53)	0·67
Anal sex with HIV-infected partners (n=365)				
Yes	184 (83%)	39 (17%)	1·12 (0·50–2·50)	0·79
No	38 (81%)	9 (19%)	1 (ref)	..
Unsure	143 (86%)	24 (14%)	1·41 (0·61–3·29)	0·42
Sexually transmitted infection history in the previous 12 months (n=365)				
Yes	77 (89%)	10 (11%)	1·66 (0·81–3·38)	0·16
No	288 (82%)	62 (18%)	1 (ref)	..
Received text message*				
Yes	177 (86%)	30 (14%)	1·34 (0·81–2·22)	0·25
No	198 (81%)	45 (19%)	1 (ref)	..
Concentration of TFV-DP at week 4, doses per week (n=367)				
<4	78 (86%)	13 (14%)	1 (ref)	..
≥4	289 (87%)	44 (13%)	1·10 (0·56–2·13)	0·79

Data are n (%) unless otherwise indicated. TFV-DP=tenofovir diphosphate. *Participants who agreed to participate (94%) were randomly allocated to receive or not receive text messages; those who chose not to participate (n=29) were categorised as "No". PrEP=pre-exposure prophylaxis.

Table 1: **Study retention based on baseline sociodemographic and behavioural characteristics**

Procedures

After the enrolment visit, participants had visits at weeks 4, 12, 24, 36, and 48 for PrEP provision (tenofovir/emtricitabine) and clinical and laboratory evaluation, including HIV testing (appendix p 2). At all study visits, participants received brief risk reduction counselling and a short adherence support session. At the time of the study, PrEP was not available through the National Health System in Brazil; it was announced as a new prevention strategy on May 27, 2017, and provision started in January, 2018.

Demographics and sexual risk criteria in the past 12 months were assessed at prescreening and screening visits. Participants answered computer-assisted self-interviews at enrolment and study visits at weeks 12, 24, 36, and 48. The number of male, transgender women, and female partners was assessed. Questions referred to participants' last three partners during the 3 months before the interview. Those who responded that any of their three previous partners was a client (which was asked directly) were considered to have engaged in commercial sex. Similarly, dichotomous variables were created for condomless receptive anal intercourse and sex with an HIV-infected partner, both of which referred to the participant's last three partners during the 3 months preceeding the interview, and were defined as "Yes" if any of the three partners fulfilled these criteria.

See **Online** for appendix

Binge drinking and substance use were self-reported in computer-assisted interviews. Substance use was considered use of any of the following: marijuana, powder cocaine, crack cocaine, cocaine paste, amphetamines, solvents, hallucinogens or LSD, ketamine, GHB, ecstasy, heroin or methadone, morphine, codeine, or pethidine, benzodiazepines, poppers, or erectile dysfunction drugs,

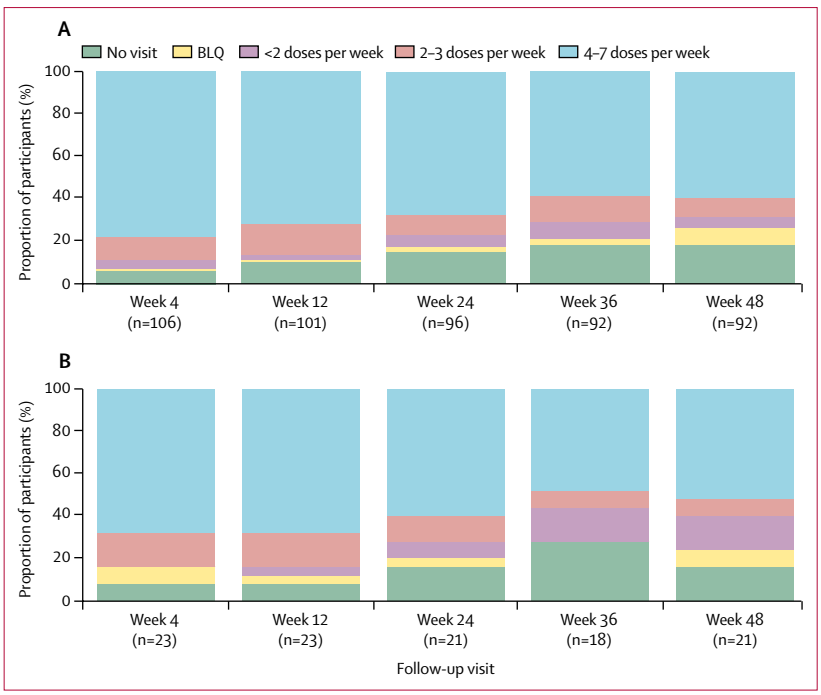

Figure 1: **PrEP engagement**
PrEP engagement by visit among (A) young men (18–24 years) and (B) transgender women. PrEP=pre-exposure prophylaxis. BLQ=below the limit of quantification.

which were in a predefined list of all substances participants could have used in the previous 3 months. For the purpose of the analyses, we defined stimulant use as use of cocaine (powder, crack, or paste), amphetamines, or club drugs (ecstasy, LSD, GHB, and ketamine) in the past 3 months. Depression was screened by use of the Patient Health Questionnaire-2 (PHQ-2) with a score of at least 3 as the cutoff for a positive result.[13,14] Risk perception, previous PrEP awareness, and HIV testing in the past year were assessed at the prescreening visit.

Dried blood spots were collected for tenofovir diphosphate and emtricitabine triphosphate assessments from all participants at week 4 and week 48; uptake and week 4 adherence results are published.[12] Transgender women and participants aged 18–24 years also had dried blood collected at all other visits (weeks 12, 24, and 36). Tenofovir diphosphate and emtricitabine triphosphate were measured using liquid chromatography-mass spectrometry or mass spectrometry at the University of Colorado Antiviral Pharmacology Laboratory (Denver, CO, USA) with standard procedures.[5,15,16] Dried blood spot cutoffs for adherence were determined by pharmacokinetic modelling studies from seroconversion outcomes in the iPrEX OLE study[5,17] recently confirmed using directly observed therapy.[18] These studies showed that a cutoff of less than 350 fmol per punch was consistent with taking less than two doses per week, 350–699 fmol per punch with two to three doses, and 700 fmol per punch or greater with four or more doses. Given the absence of HIV seroconversions in participants with dried blood spot tenofovir diphosphate concentrations consistent with taking four or more doses per week,[5] we defined this dosage as protective.

HIV testing according to the Brazilian Ministry of Health algorithm and pooled or individual HIV RNA were done at all visits. Incident syphilis infections were recorded if no previous infection was reported or if the participant had adequate treatment for a previous syphilis diagnosis and had a four-times increase in titre from the previous event, and this titre was at least 1:8. A rapid plasma reagin test was done and positive results were confirmed with a microhaemagglutination assay for *Treponema pallidum* (WAMA Diagnóstica, São Paulo, Brazil). Rectal *Chlamydia trachomatis* and *Neisseria gonorrhoeae* detection was done with the Abbott Real Time platform and the CT/MG Amplification Reagent Kit (Abbott Molecular, Des Plains, IL, USA) at enrolment and week 48. Hepatitis B was investigated at enrolment (hepatitis B antigen) and week 48 (hepatitis B surface antibody, total IgM antibodies to hepatitis B core antigen, and hepatitis B antigen). Individuals with negative hepatitis B antigen reporting no previous vaccine were referred for immunisation.

All adverse events were assessed at each visit and graded with the Division of AIDS adverse event grading table.[19] Grade 3 and 4 adverse events, serious adverse events, and creatinine concentrations and fractures were recorded. Additionally, at every visit, study staff inquired, followed up, and documented the occurrence of social harms, including the category and severity of social effect, disclosure of study participation, and action taken by staff and participants until resolution or study exit. Social harms were related to confidentiality, perceived HIV status, sexual identity, or other. Furthermore, a social benefit questionnaire was used to document positive social effects that the participant might have experienced because of participation in the project, with the following options: self-esteem, health-care, relationships (partner, family, friends, acquaintances, or other), desire to stay HIV-free, community, employment or income, or others. For these questionaires, other was an open ended response that the participant could write freely.

At the screening visit, we offered all participants the chance to join a pilot substudy of interactive text messages adapted from the WelTel study,[20] which showed efficacy in improving antiretroviral treatment adherence in Africa. All participants who agreed to participate were asked to complete a brief paper questionnaire on mobile phone use and texting practices. Individuals who agreed to participate in the substudy were randomly assigned (1:1) to receive messages or not. Once per week during the 48 weeks of the study, the text message "Are you okay?" was sent to all participants in the morning from an automated platform using a phone number not traceable to the clinic. Participants were instructed to

respond "Okay" or "Not okay". Participants who indicated that they were doing well received an acknowledgment "Thank you" text message. Those who indicated they were not doing well were contacted by the study coordinator or nurse within 48 h to help address any issues requiring support. If no response was received from the initial text message, a second message (with the same text) was sent on the same day in the evening. If no response was received within 24 h, the message schedule resumed on the weekly schedule. If no response was received for 3 consecutive weeks, this was followed by a call from study nurses. Participants were instructed that the intervention was not an emergency service and were provided with instructions of the practices for after hours concerns and emergencies.

Outcomes

PrEP retention was defined as attendance at the week 48 visit, irrespective of attendance at other study visits, as previously defined.[10] PrEP engagement was an ordinal five-level variable combining presence at the study visit and drug concentrations. Thus, the worst engagement level was a missing visit, the second level was visit attendance but no detectable medication (tenofovir diphosphate concentration undetectable), the third level was tenofovir disphosphate less than 350 fmol per punch, the fourth level was tenofovir disphosphate 350–699 fmol per punch, and the fifth level was tenofovir disphosphate 700 fmol per punch or greater.[10] PrEP adherence was the objective assessment of tenofovir on dried blood spot cards dichotomised into tenofovir diphosphate less than 700 fmol per punch and tenofovir diphosphate 700 fmol per punch or greater.

Statistical analysis

We presented variables describing the characteristics of individuals retained and not retained at week 48, and rates of PrEP engagement in terms of absolute numbers and proportions. We compared distributions using χ^2 or Fisher's exact tests, as appropriate. In the model for the entire study population, factors associated with PrEP adherence were evaluated with logistic regression models. Sexual behaviour and drug use reported at week 48 were used as predictors in the model, as these factors might change over time. Only variables statistically significant at $p<0·1$ after adjusting for site location were kept in the adjusted model. As tenofovir diphosphate concentrations for individuals aged 18–24 years were assessed at all visits, to control for correlation among observations, generalised estimating equation logistic models with autoregressive correlation matrix and robust variance were used to identify factors associated with PrEP adherence in this subpopulation.[21,22] In this model, time-dependent sexual behaviour and drug use for weeks 12, 24, 36, and 48 were used. Only variables that were statistically significant ($p<0·1$) after adjusting for site location and visit were retained in the

	Number of participants	Level indicative of ≥4 doses per week	OR (95% CI)*	p value	Adjusted OR (95% CI)	p value
Total	375	277 (74%)	..	..	..	..
Site location						
Rio de Janeiro	150	94 (63%)	1 (ref)		1 (ref)	
São Paulo	225	183 (81%)	2·68 (1·66–4·32)	<0·0001	1·88 (1·06–3·34)	0·03
Age, years						
18–24	92	67 (73%)	0·76 (0·38–1·50)	0·42	0·61 (0·29–1·30)	0·20
25–34	179	127 (71%)	0·58 (0·32–1·06)	0·07	0·49 (0·26–0·94)	0·03
≥35	104	83 (80%)	1 (ref)		1 (ref)	
Length of schooling, years						
<12	93	62 (67%)	1 (ref)		..	..
≥12	282	215 (76%)	1·13 (0·64–1·97)	0·67	..	..
Race						
White	205	161 (79%)	1 (ref)		1 (ref)	
Black	47	26 (55%)	0·49 (0·24–0·99)	0·05	0·66 (0·30–1·43)	0·29
Mixed	118	87 (74%)	1·04 (0·59–1·82)	0·90	1·10 (0·60–2·03)	0·75
Gender						
Male	354	264 (74%)	1 (ref)	..	..	..
Transgender female	21	13 (62%)	0·83 (0·32–2·16)	0·70	..	..
Housing situation						
Rent or own	242	186 (77%)	1·35 (0·80–2·26)	0·26	..	..
Other†	128	87 (68%)	1 (ref)	..	..	..
Steady partner						
Yes	202	147 (73%)	0·83 (0·52–1·34)	0·45	..	..
No	173	130 (75%)	1 (ref)	..	..	..
Had sex with client						
Yes	9	7 (78%)	1·51 (0·29–7·74)	0·62	..	..
No	366	270 (74%)	1 (ref)	..	..	..
Condomless receptive anal intercourse						
Yes	184	147 (80%)	1·72 (1·05–2·81)	0·03	1·34 (0·78–2·28)	0·29
No	191	130 (68%)	1 (ref)	..	..	..
Sex with HIV-infected partners						
Yes	148	119 (80%)	1·77 (1·06–2·94)	0·03	1·78 (1·03–3·08)	0·04
No	227	158 (70%)	1 (ref)	..	1 (ref)	..
Binge drinking						
Yes	241	179 (74%)	1·18 (0·72–1·96)	0·51	..	..
No	134	98 (73%)	1 (ref)	..	..	..
Stimulant use						
Yes	77	67 (87%)	2·30 (1·11–4·75)	0·02	2·23 (1·02–4·92)	0·04
No	298	210 (71%)	1 (ref)	..	1 (ref)	..

(Table 2 continues on next page)

	Number of participants	Level indicative of ≥4 doses per week	OR (95% CI)*	p value	Adjusted OR (95% CI)	p value
(Continued from previous page)						
Depression Patient Health Questionaire-2 score						
<3	352	261 (74%)	1 (ref)	..	..	..
≥3	23	16 (70%)	0·88 (0·34–2·29)	0·79	..	..
Sexually transmitted infection diagnosis‡						
Yes	66	47 (71%)	0·88 (0·48–1·61)	0·68	..	..
No	309	230 (74%)	1 (ref)	..	..	..
Gastrointestinal symptoms§						
Yes	152	117 (77%)	0·96 (0·57–1·61)	0·87	..	..
No	216	157 (73%)	1 (ref)	..	..	..
Received text message¶						
Yes	177	133 (75%)	1·04 (0·64–1·71)	0·87	..	..
No	198	144 (73%)	1 (ref)	..	..	..
Concentration of TFV-DP at week 4, doses per week						
<4	78	42 (54%)	1 (ref)	..	1 (ref)	..
≥4	289	232 (80%)	3·26 (1·88–5·65)	<0·0001	3·28 (1·85–5·80)	<0·0001

Data are n (%) unless otherwise indicated. Sociodemographic information (site, age, schooling, race, gender, and housing situation) refers to that recorded at the enrolment visit. Sexual behaviour and drug use information (steady partner, had sex with client, condomless receptive anal intercourse, sex with HIV-infected partners, binge drinking, and stimulant use) were obtained via computer-assisted self-interview at week 48 and refer to the previous 3 months. Depression Patient Health Questionaire-2 score refers to the baseline assessment. OR=odds ratio. TFV-DP=tenofovir diphosphate. *OR adjusted for site and age. †Includes living with friends or family, or in public housing. ‡Defined as week 48 diagnosis of rectal chlamydia, rectal gonorrhoea, or incident syphilis during the study follow-up. §Any of the following: abdominal pain, diarrhoea, flatulence, or nausea and vomiting reported at the week 4 visit. ¶Participants who agreed to participate (94%) were randomly allocated at baseline to receive or not receive text messages; those who chose not to participate (n=29) were categorised as "No".

Table 2: **Factors associated with protective tenofovir concentrations (four or more doses per week) at week 48**

adjusted model. Generalised estimating equation logistic models with robust variance were used to evaluate how the proportion of condomless anal intercourse and the proportion reporting drug use changed over time. Likewise, to evaluate how the mean number of partners changed over time, we used generalised estimating equation linear models. Incidence rates for HIV and syphilis were calculated by dividing the number of incident cases by the person-time of follow-up. Differences in proportions of participants with rectal chlamydia and gonorrhoea at enrolment and week 48 were evaluated using generalised estimating equation logistic regression. Analyses were done with Proc GENMOD available in SAS version 9.4.[23] The study is registered with ClinicalTrials.gov, number NCT01989611.

Role of the funding source

The funder of the study 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.

Results

PrEP Brasil was done between April 1, 2014, and July 8, 2016. Uptake and early adherence among MSM and transgender women included in the PrEP Brasil study have been described elsewhere.[12] 375 (83%) of 450 participants initiated on PrEP were retained at 48 weeks.

Retention in the study was not associated with sociodemographic (age, schooling, race, gender, or site location) or baseline behavioural (partner profile or sexual practices, perceived risk, or previous HIV testing) characteristics (table 1). Moreover, retention did not vary with PrEP awareness, STI history, or with achievement of protective concentrations of tenofovir diphosphate at week 4. Of the 75 (17%) participants not retained, two seroconverted before week 48, 25 withdrew consent, and 48 were lost to follow-up (appendix p 5). Younger participants were more likely to be lost to follow-up than to withdraw consent (appendix p 3).

PrEP engagement for the entire study population at week 48 showed that 75 (17%) of 450 participants had no visit, 24 (5%) had undetectable tenofovir diphosphate concentrations, 19 (4%) had concentrations less than 350 fmol per punch, 55 (12%) had concentrations of 350–699 fmol per punch, and 277 (62%) had concentrations of 700 fmol per punch or greater (appendix p 6).

Of the 113 participants aged 18–24 years, seven (6%) missed the week 4 visit, 12 (11%) missed the week 12 visit, 17 (15%) missed the week 24 visit, 21 (19%) missed the week 36 visit, and 21 (19%) missed the week 48 visit (p_{trend}=0·0002; figure 1). The percentage of participants achieving at least four doses per week decreased over time, from 88 (78%) at week 4 to 67 (59%) at week 48 (p_{trend}<0·0001). The percentage of participants achieving protective concentrations also decreased over time when considering only those who attended visits, with 88 (83%) of 106 participants in week 4, 81 (80%) of 101 participants in week 12, 76 (79%) of 96 in week 24, 66 (72%) of 92 in week 36, and 67 (73%) of 92 in week 48 (p_{trend}=0·013).

Among 25 transgender women, two (8%) missed visits at week 4, two (8%) at week 12, four (16%) at week 24, seven (28%) at week 36, and four (16%) at week 48 (p_{trend}=0·06). 17 (68%) had protective concentrations at week 4, 17 (68%) at week 12, 15 (60%) at week 24, 12 (48%) at week 36, and 13 (52%) at week 48 (figure 1). Among those who attended visits, the percentage with protective concentration was 17 (74%) of 23 participants at weeks 4 and 12, 15 (71%) of 21 participants at week 24, 12 (67%) of 18 particpants at week 26, and 13 (62%) of 21 participants at week 48 (p_{trend}=0·16).

Overall, 277 (74%) of 375 participants retained at week 48 had protective concentrations consistent with at least four

doses per week at week 48 (table 2). Daily dosing, defined as at least 1250 fmol per punch tenofovir diphosphate,[5,17,18] was achieved by 102 (27%) of 375 participants at week 48. Results from the adjusted logistic regression model show that the odds of achieving protective concentrations was higher among participants from São Paulo than Rio de Janeiro, and lower among participants aged 25–34 years than those aged 35 years or older (table 2). Additionally, those reporting sex with HIV-infected partners had increased odds of achieving protective concentrations at week 48, as did those reporting use of stimulants (table 2). The strongest predictor of protective concentrations at week 48 was having protective concentrations of tenofovir diphosphate at week 4 (table 2).

Among participants aged 18–24 years (table 3), factors associated with protective concentrations of tenofovir diphosphate were somewhat similar to those in the general study population, with protective concentrations at week 4 strongly predictive of protective concentrations at week 48. In this subpopulation, education and race were associated with protective concentrations of tenofovir at week 48, with higher education increasing and black race decreasing this likelihood (table 3). As shown in the overall model, sex with HIV-infected partners increased the odds of having protective concentrations, but having a steady partner decreased this likelihood (table 3). In this population, text messaging was associated with increased odds of achieving protective drug concentrations at week 48 (table 3).

The proportion of participants reporting condomless receptive anal sex with their last three partners did not vary substantially over time (figure 2). The mean number of sexual partners in the previous 3 months decreased from 11·4 (SD 29·94) at enrolment to 8·3 (19·55) at week 48 (p=0·0013); the median was 3 (IQR 1–10) at enrolment and 3 (1–8) at week 48. We found similar results among participants aged 18–24 years, although the percentage of participants reporting condomless receptive anal sex with their last three partners was higher (52% at enrolment and 61% at week 48; p_{trend}=0·20). In this subpopulation, the mean number of partners also decreased, from 11·9 (SD 31·45) at enrolment to 6·5 (13·32) at week 48 (p=0·0155). Among transgender women, the percentage of participants reporting condomless receptive anal sex was stable over time (p_{trend}=0·73), although the mean number of partners decreased (p_{trend}=0·0052). No association was observed for reported use of any illicit drug, stimulants, or poppers (all p_{trend} values >0·05).

Two individuals seroconverted during follow-up (one identified in week 24 and another in week 36), for an HIV incidence of 0·51 per 100 person-years (95% CI 0·13–2·06); both participants had undetectable tenofovir concentrations at their seroconversion visit. The first participant, who seroconverted at visit 24, had previous tenofovir concentrations consistent with less than two doses per week at weeks 4 (163 fmol per punch) and 12 (66 fmol per punch). The second participant had undetectable tenofovir concentrations at weeks 4, 12, 24, and 36 (at which point they seroconverted).

	Number of participants*	Concentration indicative of ≥4 doses per week†	OR (95% CI)‡	p value	Adjusted OR (95% CI)	p value
Total	106	0·76%	..	..	..	..
Site location						
Rio de Janeiro	54	69·5%	1 (ref)	..	1 (ref)	..
São Paulo	52	82·7%	2·16 (1·03–4·49)	0·04	1·02 (0·46–2·27)	0·95
Length of schooling, years						
<12	36	60·9%	1 (ref)	..	1 (ref)	..
≥12	70	83·8%	2·58 (1·17–5·68)	0·02	2·48 (1·03–5·97)	0·04
Race						
White	55	82·5%	1 (ref)	..	1 (ref)	..
Black	17	59·3%	0·34 (0·14–0·84)	0·02	0·35 (0·14–0·90)	0·03
Mixed	33	75·4%	0·81 (0·34–1·91)	0·63	0·83 (0·34–2·02)	0·68
Housing situation						
Rent or own	44	80·8%	1·69 (0·80–3·57)	0·17	..	..
Other§	62	72·4%	1 (ref)	..	..	..
Steady partner						
Yes	51	71·7%	0·48 (0·29–0·80)	0·0051	0·36 (0·19–0·66)	0·0010
No	41	81·0%	1 (ref)	..	1 (ref)	..
Had sex with client						
Yes	1	85·7%	1·51 (0·19–12·14)	0·70	..	..
No	91	75·8%	1 (ref)	..	..	..
Condomless receptive anal intercourse						
Yes	44	79·7%	1·01 (0·64–1·61)	0·96	..	..
No	48	71·8%	1 (ref)	..	..	..
Sex with HIV-infected partners						
Yes	33	84·6%	1·84 (1·03–3·28)	0·04	3·08 (1·56–6·07)	0·0012
No	59	70·9%	1 (ref)	..	1 (ref)	..
Binge drinking						
Yes	63	75·5%	0·98 (0·54–1·78)	0·94	..	..
No	29	77·2%	1 (ref)	..	..	..
Stimulant use						
Yes	14	84·3%	1·44 (0·70–2·95)	0·32	..	..
No	78	74·0%	1 (ref)	..	..	..
Depression Patient Health Questionaire-2 score						
<3	96	75·5%	1 (ref)	..	..	..
≥3	10	81·6%	1·46 (0·29–7·27)	0·64	..	..
Sexually transmitted infection diagnosis¶						
Yes	28	74·5%	0·94 (0·41–2·18)	0·89	..	..
No	78	76·7%	1 (ref)	..	..	..
Gastrointestinal symptoms‖						
Yes	41	75·5%	0·88 (0·40–1·95)	0·76	..	..
No	63	77·1%	1 (ref)	..	..	..

(Table 3 continues on next page)

	Number of participants*	Concentration indicative of ≥4 doses per week†	OR (95% CI)‡	p value	Adjusted OR (95% CI)	p value
(Continued from previous page)						
Received text message**						
Yes	56	80·4%	2·13 (1·02–4·47)	0·04	2·15 (0·99–4·66)	0·0518
No	50	72·0%	1 (ref)	..	1 (ref)	..
Concentration of TFV-DP at week 4, doses per week						
<4	17	50·8%	1 (ref)	..	1 (ref)	..
≥4	88	81·7%	4·43 (1·66–11·80)	0·0030	3·39 (1·12–10·27)	0·03

Sociodemographic information (site, age, schooling, race, gender, and housing situation) refers to that recorded at the enrolment visit. Time-updated information includes sexual behaviour and drug use (steady partner, had sex with client, condomless receptive anal intercourse, sex with HIV-infected partners, binge drinking, and stimulant use), which were obtained via computer-assisted self-interview at weeks 12, 24, 36, and 48 and refer to the previous 3 months. Depression Patient Health Questionaire score refers to the baseline assessment. OR=odds ratio. TFV-DP=tenofovir diphosphate.*Includes 106 participants who had at least one visit during follow-up. †Indicates average prevalence of having tenofovir concentrations consistent with at least four doses across 48 weeks (the average of values measured in weeks 12, 24, 36, and 48). ‡OR adjusted for site and visit. §Includes living with friends or family or in public housing. ¶Defined as week 48 diagnosis of rectal chlamydia or rectal gonorrhoea, or incident syphilis during study follow-up. ||Any of the following: abdominal pain, diarrhoea, flatulence, nausea, and vomiting. **Participants who agreed to participate (94%) were randomly allocated to receive or not receive text messages; those who chose not to participate (n=29) were categorised as "No".

Table 3: **Factors associated with protective tenofovir concentrations (four or more doses per week) at week 48 for participants aged 18–24 years**

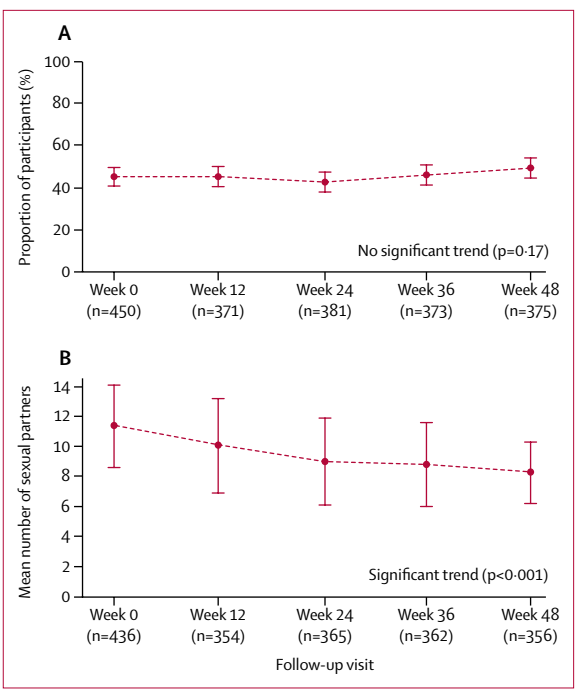

Figure 2: **Sexual behaviours among study participants**
(A) Percentage of participants reporting condomless receptive anal sex and (B) mean number of partners in the previous 3 months.

Prevalence of rectal chlamydia ranged from 36 (8%) of 450 participants at enrolment to 29 (8%) of 375 participants at week 48 (p=0·90). Prevalence of rectal gonorrhoea ranged from 22 (5%) of 450 at enrolment to 14 (4%) of 375 at week 48 (p=0·41). Among participants aged 18–24 years, prevalence of both rectal chlamydia and rectal gonorrhoea was higher than the overall population, although it did not increase over time, varying from 14 (12%) of 113 participants at enrolment to seven (8%) of 92 participants at week 48 for rectal chlamydia, and from 12 (11%) of 113 participants at enrolment to four (4%) of 92 participants at week 48 for rectal gonorrhoea (p>0·05 in both cases). Syphilis incidence was 9·0 per 100 person-years (95% CI 6·5–12·5), and was 6·2 per 100 person-years (95% CI 2·8–13·7) for those aged 18–24 years and 9·9 per 100 person-years (95% CI 6·9–14·3) for those aged 25 years and older. For transgender women, prevalence of rectal chlamydia ranged from one (4%) of 25 participants at enrolment to three (14%) of 21 participants at week 48 (p=0·26). Prevalence of rectal gonorrhoea was none (0%) of 25 participants at enrolment and one (5%) of 21 participants at week 48 (p=0·96). Syphilis incidence was 22·9 per 100 person-years (95% CI 9·5–55·0).

16 serious adverse events were reported during the study (appendix p 8), two of which were psychiatric (suicide attempts). No serious adverse events were assessed as related to study drug. Two grade 3 adverse events (diarrhoea and flatulence) and two grade 2 adverse events (malaise and nightmares) were considered related to study medication, which was permanently discontinued. Two bone fractures were reported during the study, both explained by trauma and unrelated to study drug. 18 creatinine elevations occurred in 12 participants, all classified as grade 1 (appendix). On repeat testing, only three of such creatinine elevations (from two participants) were confirmed. These creatinine abnormalities resolved in 4–8 weeks, without drug discontinuation. In three participants, creatinine elevation was attributed to an underlying disease (hypertension, gastroenteritis, and dehydration). Seven participants reported protein supplementation. At the end of the study, only one participant still had grade 1 creatinine elevation. All creatinine elevations were assessed as unrelated to study medication and no participants needed to interrupt study medication because of elevated creatinine concentrations. 21 (5%) of 450 participants reported 24 social harms. All social harm reports were related to stigma; 12 related to misperception of HIV status and 12 related to perception of being at high risk for HIV. Social benefits related to PrEP use were reported by 208 (46%) participants at least once during study follow-up. The most frequently reported benefits were "keeping me HIV-negative" (148 [71%] participants), "taking care of my health" (70 [34%] participants), "improving my HIV/STD knowledge" (43 [21%] participants), and "improving the relationship with my partner" (31 [15%] particpants).

Discussion

Our results showed high amounts of retention, engagement, and adherence to PrEP, supporting feasibility in a real-world setting in a middle-income country. Our findings are similar to those reported in other demonstration studies and by real-world PrEP implementation services in resource-rich settings.[10] We highlight two notable predictors of long-term adherence for both the overall cohort and among young participants (aged 18–24 years). First, the fact that early (ie, week 4) adherence was predictive of sustained adherence in the long term implies that interventions to improve adherence could be targeted to particular subgroups of PrEP users. Prompt identification of those who most need adherence support could enhance PrEP's effectiveness. The second predictor, that reported sex with HIV-infected partners predicted long-term adherence, might be related to higher risk perception in serodiscordant partnerships. Indeed, awareness and knowledge that an undetectable viral load equals untransmittable HIV is not disseminated in certain MSM communities.

Although PrEP adherence decreased over time in MSM aged 18–24 years (as observed elswhere[9]), those who received weekly text messages seemed more likely to achieve protective concentrations, suggesting that adherence support strategies to assist young MSM on PrEP, including technology-based strategies, are essential to achieve the desired impact on HIV incidence in this group. Similar findings were shown in the Partners PrEP study,[24] in which text messaging was used to measure both adherence and concurrent sexual behaviour. Additionally, a youth-tailored, text-message-based PrEP support intervention (Prepmate) was evaluated in a PrEP implementation study in the USA, and daily text message reminders and weekly text message check-ins were highly acceptable and used.[25] Nonetheless, our study highlights the importance of acknowledging social determinants, as young MSM of black race and less schooling showed decreased odds of achieving protective concentrations at week 48.

In a subgroup analysis of transgender women, we found that drug exposure decreased during follow-up, although it did not differ from adherence of MSM at week 4.[12] Nevertheless, most transgender women had protective drug concentrations for the first half of the study, and around half maintained these concentrations thereafter. These estimates are much higher than those reported in the iPrEx subanalysis results,[11] in which no seroconversions occurred among transgender women with detectable drug concentrations, but more than 70% were found to have taken few or none of their PrEP pills.

In our study, sexual risk behaviour remained high throughout, highlighting the importance of PrEP for this population. Despite this, HIV incidence was very low; the two seroconversions occurred in participants without detectable drug concentrations. No antiretroviral drug resistance was detected and both participants were immediately linked to medical care and offered antiretroviral therapy. We observed high syphilis incidence, similar to IPrEX OLE and to the US PrEP demonstration study.[5,10] High syphilis incidence was also seen among Brazilian HIV-uninfected partners enrolled in the Opposites Attract study (11·7 per 100 person-years; Baviton B, Kirby Institute, New South Wales University, Sydney, NSW, Australia, personal communication). This high syphilis incidence is alarming given that HIV acquisition is increased by two to nine times when syphilis is already present.[26]

We found no evidence of increased sexual behaviour over time, suggesting that risk compensation would not reduce the protective benefits of PrEP. Estimates of whether risk compensation occurs among MSM taking PrEP, and by how much, have been diverse.[6,7,10] Additionally, PrEP-related stigma has emerged as a substantial social harm that can arise from PrEP research participation, and this has been reported by different study populations from various regions.[27,28] In our study, reported social harms were related to stigma but their frequency was very low; by contrast, social benefits were reported by almost half of the cohort. The absence of any substantial renal toxicity or other clinical adverse events among participants was reassuring. Although renal injury from tenofovir disoproxil fumarate might require longer exposure than participants had in this study, these results support PrEP provision in primary care settings not requiring complex clinical and laboratory monitoring.

A major strength of this study was assessment of drug concentrations in all participants who attended week 4 and week 48 study visits, and in all visits for young participants (aged 18–24 years) and transgender women, thus providing robust evidence of PrEP engagement and adherence. Furthermore, the study was implemented at sites that are part of the public health system, through which most of the Brazilian population will access PrEP. However, several limitations should be acknowledged. The follow-up time might be too short to observe long-term outcomes. As the sites in this demonstration study are highly motivated sites that are well versed in PrEP science, their success in PrEP delivery might not be generalisable to other clinical settings in Brazil. Indeed, we have observed differences in participants from Rio de Janeiro (compared to São Paulo) showing decreased protective concentrations at week 48, a disparity that was not explained by demographic or behaviour characteristics and probably related to unmeasured confounding factors. Two of our sites participated in the iPrEx study,[6] for which adherence estimates were lower than those reported in this study, suggesting that increased awareness and knowledge of the efficacy of PrEP might lead to increased adherence over time. Although our study enrolled more transgender women than most other demonstration projects, they were still under-represented. Finally, the ORs reported in this study should not be misinterpreted as relative risks given the frequent occurrence of the outcome of interest.

In conclusion, PrEP offered at public health-care clinics in a middle-income setting can retain more than 80% of participants over 48 weeks and achieve high amounts of adherence consistent with at least four doses per week in more than 70% of the retained population. Evidence generated by PrEP Brasil, including cost-effectiveness results,[29] substantially contributed to inclusion of PrEP for MSM and transgender women as a public health programme in Brazil. More work is needed to increase and expand PrEP community awareness and uptake and to develop effective adherence support for younger MSM. Transgender women could benefit highly from PrEP demonstration studies tailored to them, including effective adherence support.

Contributors

BG and VGV conceived the study. BH, RBDB, and RIM managed the data and RIM, ICL, and PML did data analysis and visualisation. BH, SG, EGK, JVM, LF, LMSM, TST, and RV helped with the study and data acquisition. BG, BH, RBDB, PML, and VGV drafted the manuscript. EGK, JVM, RV, PLA, and AL revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Declaration of interests

AL has led studies in which study drug was donated by Gilead Sciences. PLA has received study drug donation, contract work, and a research grant from Gilead Sciences, paid to his institution. All other authors declare no competing interests.

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References

1 Ministerio da Saude. Secretaria de Vigilancia em Saude. Boletim epidemiologico HIV AIDS. Nov 20, 2016. http://www.aids.gov.br/pt-br/pub/2016/boletim-epidemiologico-de-aids-2016 (accessed Dec 30, 2017).

2 De Boni R, Veloso VG, Grinsztejn B. Epidemiology of HIV in Latin America and the Caribbean. *Curr Opin HIV AIDS* 2014; **9:** 192–98.

3 Barbosa Júnior A, Szwarcwald CL, Pascom AR, Souza Júnior PB. Trends in the AIDS epidemic in groups at highest risk in Brazil, 1980–2004. *Cad Saude Publica* 2009; **25:** 727–37 (in Portuguese).

4 Grinsztejn B, Jalil EM, Monteiro L, et al. Unveiling of HIV dynamics among transgender women: a respondent-driven sampling study in Rio de Janeiro, Brazil. *Lancet HIV* 2017; **4:** e169–76.

5 Grant RM, Anderson PL, McMahan V, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. *Lancet Infect Dis* 2014; **14:** 820–29.

6 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:** 2587–99.

7 McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *Lancet* 2016; **387:** 53–60.

8 Molina JM, Capitant C, Spire B, et al. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. *N Engl J Med* 2015; **373:** 2237–46.

9 Hosek SG, Rudy B, Landovitz R, et al. An HIV preexposure prophylaxis demonstration project and safety study for young MSM. *J Acquir Immune Defic Syndr* 2017; **74:** 21–29.

10 Liu AY, Cohen SE, Vittinghoff E, et al. Preexposure prophylaxis for HIV infection integrated with municipal- and community-based sexual health services. *JAMA Intern Med* 2016; **176:** 75–84.

11 Deutsch MB, Glidden DV, Sevelius J, et al. HIV pre-exposure prophylaxis in transgender women: a subgroup analysis of the iPrEx trial. *Lancet HIV* 2015; **2:** e512–19.

12 Hoagland B, Moreira RI, De Boni RB, et al. High pre-exposure prophylaxis uptake and early adherence among men who have sex with men and transgender women at risk for HIV infection: the PrEP Brasil demonstration project. *J Int AIDS Soc* 2017; **20:** 1–14.

13 de Lima Osório F, Vilela Mendes A, Crippa JA, Loureiro SR. Study of the discriminative validity of the PHQ-9 and PHQ-2 in a sample of Brazilian women in the context of primary health care. *Perspect Psychiatr Care* 2009; **45:** 216–27.

14 Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. *Med Care* 2003; **41:** 1284–92.

15 Castillo-Mancilla JR, Zheng JH, Rower JE, et al. Tenofovir, emtricitabine, and tenofovir diphosphate in dried blood spots for determining recent and cumulative drug exposure. *AIDS Res Hum Retroviruses* 2013; **29:** 384–90.

16 Zheng JH, Rower C, McAllister K, et al. Application of an intracellular assay for determination of tenofovir-diphosphate and emtricitabine-triphosphate from erythrocytes using dried blood spots. *J Pharm Biomed Anal* 2016; **122:** 16–20.

17 Anderson PL, Glidden DV, Liu A, et al. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. *Sci Transl Med* 2012; **4:** 151ra25.

18 Anderson P, Liu AY, Castillo-Mancilla J, et al. TFV-DP in dried blood spots (DBS) following directly observed therapy: DOT-DBS study. Conference on Retroviruses and Opportunistic Infections 2017; Seattle, WA, USA; Feb 13–16, 2017: abstr 419.

19 Division of AIDS table for grading the severity of adult and pediatric adverse events. Version 1.0, December 2004; Clarification August 2009. https://rsc.tech-res.com/docs/default-source/safety/table_for_grading_severity_of_adult_pediatric_adverse_events.pdf?sfvrsn=6 (accessed Dec 30, 2017).

20 Lester RT, Ritvo P, Mills EJ, et al. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. *Lancet* 2010; **376:** 1838–45.

21 Hanley JA, Negassa A, Edwardes MD, Forrester JE. Statistical analysis of correlated data using generalized estimating equations: an orientation. *Am J Epidemiol* 2003; **157:** 364–75.

22 Zeger SL, Liang KY, Albert PS. Models for longitudinal data: a generalized estimating equation approach. *Biometrics* 1988; **44:** 1049–60.

23 Allison PD. Logistic regression using SAS. Theory and application, 2nd edn. Cary, NC: SAS Institute, 2012.

24 Curran K, Mugo NR, Kurth A, et al. Daily short message service surveys to measure sexual behavior and pre-exposure prophylaxis use among Kenyan men and women. *AIDS Behav* 2013; **17:** 2977–85.

25 Liu A, Vittinghoff E, Von Felton P, et al. SMS support increases PrEP retention and adherence among young MSM and transgender women in Chicago. Adherence 2017; Miami, FL; June 4, 2017.

26 Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sex Transm Infect* 1999; **75:** 3–17.

27 Liu A, Cohen S, Follansbee S, et al. Early experiences implementing pre-exposure prophylaxis (PrEP) for HIV prevention in San Francisco. *PLoS Med* 2014; **11:** e1001613.

28 Tangmunkongvorakul A, Chariyalertsak S, Amico KR, et al. Facilitators and barriers to medication adherence in an HIV prevention study among men who have sex with men in the iPrEx study in Chiang Mai, Thailand. *AIDS Care* 2013; **25:** 961–67.

29 Luz PM, Osher B, Grinsztejn B, et al. The cost-effectiveness of HIV pre-exposure prophylaxis (PrEP) in high-risk men who have sex with men (MSM) and transgendered women (TGW) in Brazil. 21st International AIDS Conference; Durban, South Africa; 18–22 July, 2016.