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ORIGINAL PAPER

Predictors of Daily Adherence to HIV Pre-exposure Prophylaxis in Gay/Bisexual Men in the *PRELUDE* Demonstration Project

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Abstract

Adequate adherence to pre-exposure prophylaxis (PrEP) is critical to prevent HIV infection, but accurately measuring adherence remains challenging. We compared two biological [blood drug concentrations in plasma and peripheral blood mononuclear cells (PBMC)] and two self-reported measures (facilitated recall to clinicians and self-report in online surveys) and identified predictors of daily PrEP adherence among gay and bisexual men (GBM) in their first 12 months on *PRELUDE*, an open-label, single-arm PrEP demonstration project in New South Wales, Australia. 327 participants were enrolled; 263 GBM attended their 12-month follow-up visit (81% retention). Overall, 91% of blood samples had plasma drug concentrations indicative of taking 7 pills/week, and 99% had protective drug concentrations (≥ 4 pills/week). Facilitated recall to clinicians identified 99% of participants with protective adherence as measured by PBMC drug concentrations. Daily adherence measured by facilitated recall was associated with behavioural practices including group sex (aOR 1.33, 95% CI 1.15–1.53, $p < 0.001$). Retained participants maintained high adherence to daily PrEP over 12 months, confirmed by four different measures. Facilitated recall to clinicians is a suitable measure for assessing PrEP adherence in populations engaged in care where there is established trust and rapport with patients. Trial registration: ClinicalTrials.gov NCT02206555.

Keywords Pre-exposure prophylaxis (PrEP) · Adherence · HIV · Facilitated recall · Blood tenofovir concentrations

Introduction

In 2016, new World Health Organisation guidelines recommended pre-exposure prophylaxis (PrEP) as an additional HIV prevention tool for key populations at substantial risk of infection [1]. Prior to this, PrEP use was steadily increasing, albeit in a limited number of settings [2, 3], following several randomised controlled trials (RCTs) [4–8]. While some early trials showed poor efficacy due to low adherence [9–11], subsequent open-label extension studies [12, 13] and real-world implementation projects [14–17] have since confirmed that PrEP is highly effective at preventing HIV, particularly among gay and bisexual men (GBM) [18]. There is a well-documented dose–response relationship between PrEP efficacy and adherence [19], and accordingly, ensuring high levels of adherence to PrEP remains a central focus for prescribers and PrEP users alike.

Defining and monitoring medication adherence is not straightforward [20–22]. Self-reported indicators commonly over-estimate adherence [11, 23], while objective

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measures such as blood drug concentrations are often costly and impractical in a clinical setting [22]. Identifying affordable and effective strategies to monitor adherence to PrEP is becoming increasingly salient [11, 24], particularly in light of the UNAIDS target for three million people worldwide to be taking PrEP by 2020 [25].

Given that the majority of new HIV infections in Australia are in GBM [26], the *PRELUDE* Demonstration Project provided targeted PrEP to GBM at high risk of HIV in the most populous state of Australia, New South Wales (NSW) [27]. Four measures of adherence were investigated to assess whether self-report is a good approximation of biological markers of adherence, and to identify predictors of adherence to daily PrEP in a clinical setting over a 12-month period.

Methods

Study Design and Participants

The study design and methods have been reported previously [27]. Briefly, *PRELUDE* was an open-label, single-arm demonstration project evaluating targeted PrEP delivery. Participants were enrolled across eight study sites between November 2014 and April 2016. These clinics were lesbian, gay, bisexual, and transgender (LGBT) friendly and many participants had been attending these clinics for several years prior to study enrolment. Sites received standardised training according to the study protocol and were provided with a manual of operations. Regular monitoring (both on-site and real-time monitoring of electronic databases) was also conducted to ensure all procedures were followed accordingly.

Clinic visits were conducted at baseline, month one, month three, then quarterly thereafter and included testing for HIV, sexually transmissible infections (STIs) and pregnancy (where applicable), collection of adverse events and interim medical history, and a review of study eligibility, until study discontinuation or completion of follow-up. If eligibility criteria were met, participants were initially issued a prescription for a 30-day supply of study medication, then later a 90-day prescription was issued to cover the period between study visits. Following each visit, a link to an online behavioural survey was emailed to participants. No incentives to complete the online survey were provided. Participants with outstanding surveys were sent two email reminders before being contacted once by their clinic if their survey remained incomplete. All participants provided written informed consent. The study was approved by St Vincent's Hospital Human Research Ethics Committee in Sydney, NSW and registered under ClinicalTrials.gov (NCT02206555).

PrEP adherence was measured in four different ways: (i) tenofovir (TFV) concentrations in plasma (3-day lookback period), (ii) tenofovir-diphosphate (TFV-DP) concentrations in isolated peripheral blood mononuclear cells (PBMCs; 7-day lookback period), (iii) 7-day facilitated recall to clinicians at each study visit, and (iv) 90-day self-report in an online survey following each visit.

In this analysis, data are reported for GBM participants who completed their month 12 study visit. Demographic, sexual, and other risk behaviours in this cohort were compared to GBM who did not complete 12 months of study follow-up using Chi squared tests for independence.

TFV and TFV-DP Drug Measurements

Blood samples for drug quantification were obtained from the first approximately 100 consecutively enrolled participants at the three largest study sites 1, 6, and 12 months after PrEP initiation. Specimens were collected and transferred to St Vincent's Centre for Applied Medical Research, where they were stored at − 80 °C prior to shipment to the Johns Hopkins Clinical Pharmacology Analytical Laboratory for quantitative determination of plasma TFV and PBMC TFV-DP concentrations.

TFV and TFV-DP concentrations were quantified via previously described liquid chromatographic-tandem mass spectrometric methods [28]. Adherence metrics were based on previous pharmacokinetic benchmarks, and receiver operator curve analysis was conducted to optimize sensitivity of adherence reporting (≥ 90%) [19].

The lower limit of quantification (LLOQ) for TFV in plasma was 0.31 ng/mL, with plasma TFV concentrations ≥ 4.2 and ≥ 35.5 ng/mL consistent with a participant having taken four or seven pills in the last week, respectively [19]. In PBMCs, the LLOQ for TFV-DP was 50 fmol/sample. These results were converted to fmol/10^6 cells based on the lysate-specific number of PBMCs present in the sample. The median LLOQ, when normalized to cell count, was 2.26 fmol/10^6 cells. PBMC drug concentrations of ≥ 9.9 and ≥ 16.8 fmol/10^6 cells are consistent with four and seven pills taken in the previous week, respectively [19].

Self-reported Adherence Measures

At each study visit, clinicians asked participants how many PrEP pills they had taken in the previous 7 days, and recorded responses in the online case report forms. In the online survey, participants estimated the proportion of pills (or average number of pills per week) they had taken since their last survey (~ 90 days) using the following categories: none; less than 15% (about one pill a week); 15–29% (about two pills a week); 30–44% (about three pills a week); 45–59% (about four pills a week); 60–74% (about five pills a

week); 75–89% (about six pills a week); and 90–100% (all or almost all pills). For ease of comparison between adherence measures, all data were reported on a pills per week basis.

Adherence Definitions

All *PRELUDE* participants were prescribed daily PrEP. Thus, we defined *daily adherence* as reporting 7 pills/week by whichever measure being analysed. As previous research has shown that four pills per week is associated with a 96% HIV risk reduction [29], *protective adherence* was defined as taking four or more pills/week. The proportion of patients classified as adherent by each of the four measures used in this study were calculated separately for daily adherence and protective adherence.

Additional Data Collection

At baseline, participants were asked in the online survey about their ideal way to take PrEP (everyday; for periods of time when I am at high risk of getting HIV; only on specific occasions when I am at high risk of getting HIV), and at month 1 they were asked how long they would be willing to take daily PrEP. Every survey included detailed questions about the number and type (main regular, other regular, or casual) of sexual partners by HIV status, and anal intercourse events in the previous 3 months (insertive or receptive, with or without condom use). Data on drug and alcohol use, demographics, and attitudes were also collected.

Statistical Analysis

All statistical analyses were performed using STATA software (version 14.2, StataCorp). We compared: (1) participants who remained under follow-up at 12 months to those lost to follow-up prior to 12 months, and (2) those who participated in the blood sub-study to those who did not, using Pearson's χ^2 test, or Fisher's exact test where appropriate.

Among participants who attended their 12-month visit, we categorised adherence (7 pills/week, 4–6 pills/week, < 4 pills/week, or missing data/visit) for each measure, showing the number and proportion of participants in each category at each of the five study visits (months 1, 3, 6, 9, and 12). Trends across visits were assessed separately for each category and measure, as well as continuously across the study using a non-parametric test for trend across ordered groups.

Agreement between reporting methods was calculated using percentage agreement. Sensitivity and specificity were calculated using TFV-DP concentrations in PBMC samples, the current 'gold-standard' for PrEP adherence, as the comparator. Percentage agreement between measures was only calculated for month 12 samples to prevent violating the assumption of independence. Regression methods of generalised estimating equations, which are population-level models, were used to analyse longitudinal predictors of daily adherence over 12 months of follow-up, measured by facilitated recall to clinicians. This time-varying outcome measure was assessed at each study visit. It was selected as it contained the most complete data of the four adherence measures and has been shown to be effective in similar contexts [30]. Selected predictors included time-varying factors such as sexual behaviours and drug use, as well as age, highest level of education, and country of birth as reported at baseline. Study visit was also included as a continuous variable in the model to account for temporal changes. Variables individually associated with the outcome ($p < 0.05$) were included in the final multivariable model using forward stepwise regression. The final model was tested for collinearity by manually constructing a forward stepwise regression and inspecting how the addition of each variable changed the overall odds ratios.

Results

Sample Characteristics

Overall, 327 participants were enrolled in *PRELUDE*, and 265 (81%) attended the clinic for a month 12 follow-up visit (Fig. 1). An additional 7 participants (2%) transitioned onto an expanded PrEP access study [31] hence did not discontinue PrEP, although their data were only included until their final study visit. Full study results, including HIV incidence in the cohort, are reported in the primary outcome paper [32].

There were 263 GBM included in this analysis who had data available from their month 12 follow-up visit. In comparison to the 56 GBM who did not complete 12 months of follow-up, participants who completed 12 months of follow-up were significantly older (mean age 38 vs 33 years, $t = 3.4$, $p = 0.001$), and willing to use PrEP for greater than 12 months (85% vs 63%, $\chi^2 = 17.7$, $p < 0.001$).

Baseline characteristics have been reported previously [33]. Among the 263 GBM included in this analysis, most (n = 168, 64%) were born in Australia, employed full- or part-time (n = 206, 78%), and had a university-level education (n = 171, 65%). In the 3 months preceding their baseline study visit, 89% (n = 233) reported having casual sex partners, 34% (n = 90) reported crystal methamphetamine use, and 30% (n = 80) had used HIV post-exposure prophylaxis (PEP).

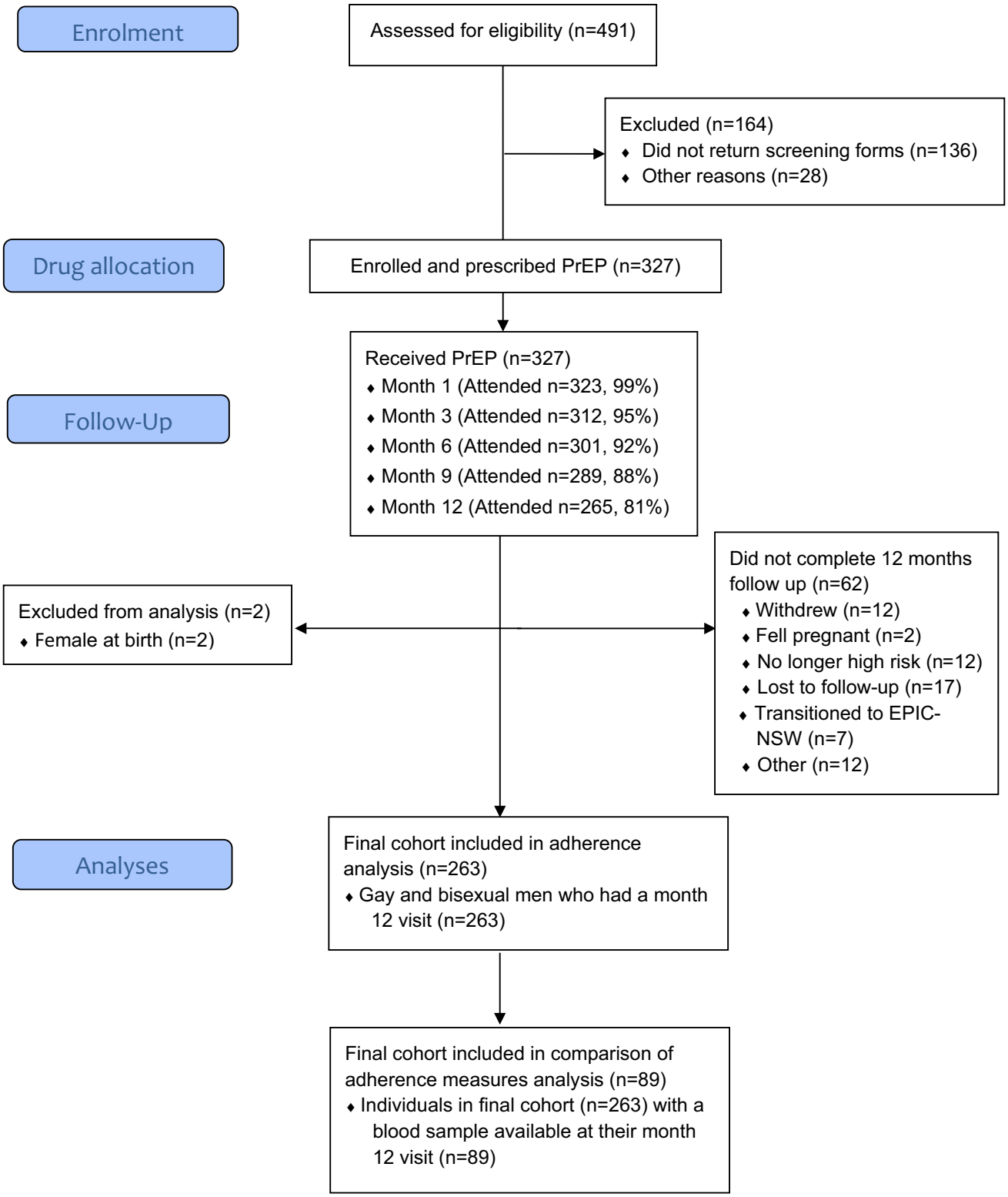

Fig. 1 Flow diagram of movement through the study

In comparison with participants who were not included in the blood sub-study (n = 167), participants who provided at least one blood sample (n = 96) were significantly more likely to report having used crystal methamphetamine (43% vs 29%, $\chi^2 = 4.8$, $p = 0.028$) or group sex (78% vs 64%, $\chi^2 = 5.6$, $p = 0.017$) in the 3 months prior to study enrolment.

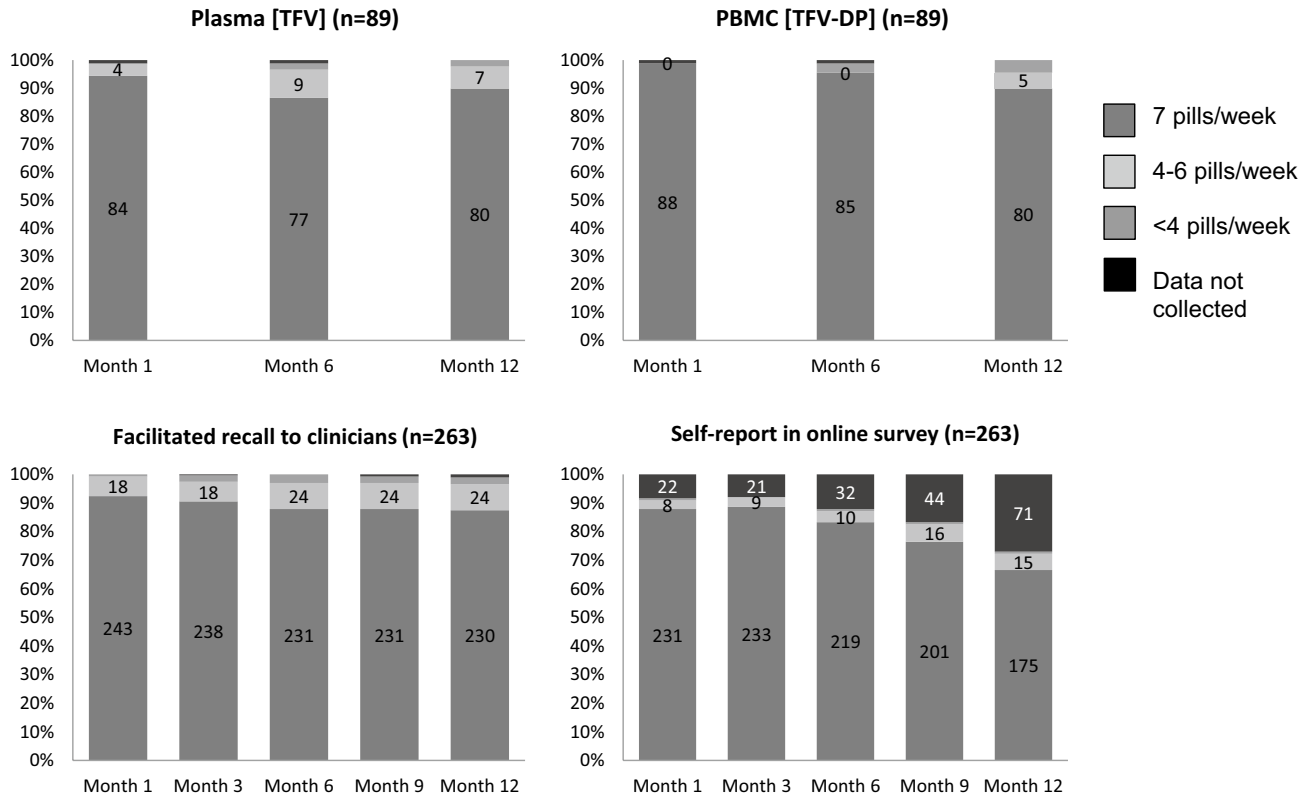

Fig. 2 Adherence across the study, by visit and adherence measure, among gay and bisexual male participants who completed the month 12 study visit. *PBMC* peripheral blood mononuclear cells, *TFV* tenofovir, *TFV-DP* tenofovir diphosphate

Adherence Levels and Trends Over Time

Figure 2 shows the proportion of GBM who were adherent to daily PrEP over 12 months of follow-up, according to each of the four measures.

Adherence Measured by Blood Drug Concentrations in Plasma

Amongst the 95 participants involved in the blood sub-study, 89 (94%) had plasma and PBMC samples collected at their month 12 visit. The remaining six participants attended their study visit outside the designated window so venepuncture was not conducted. In 91% (n = 254) of plasma samples, TFV concentrations were consistent with daily dosing, and 99% (n = 274) had protective drug concentrations.

There was no significant change over time in the mean TFV concentrations in plasma (z = − 1.02, p-trend = 0.306) or the proportion of participants who had plasma TFV concentrations indicative of daily PrEP dosing over time (z = − 1.45, p-trend = 0.148). Furthermore, there were no significant changes over time in the proportion of participants with plasma TFV concentrations consistent with having taken 4–6 pills (z = 0.98, p-trend = 0.328) or < 4 pills (z = 1.29, p-trend = 0.197) in the previous week.

Adherence Measured by Blood Drug Concentrations in PBMCs

TFV-DP concentrations consistent with daily and protective adherence were evident in 95% (n = 265) and 97% (n = 271) of PBMC samples, respectively. There was a significant decrease over time in the proportion of participants with TFV-DP concentrations consistent with taking 7 pills/week according to PBMC samples (100% at month 1 to 90% at month 12; z = − 3.24, p-trend < 0.001). There was also a significant decline in the mean TFV-DP concentration (122 fmol/10^6 cells at month 1 to 56 fmol/10^6 cells at month 12; z = − 7.23, p-trend < 0.001) over time, although average drug concentrations remained well above the protective threshold (9.9 fmol/10^6 cells) throughout the study.

There was a significant increase in the proportion of participants with PBMC TFV-DP concentrations indicative of taking 4–6 pills per week (0% at month 1 to 6% at month 12; z = 2.60, p-trend = 0.009), and a trend towards an increasing proportion of participants with PBMC TFV-DP

concentrations indicative of taking < 4 pills per week (0% at month 1 to 4% at month 12; z = 1.95, p-trend = 0.051).

Adherence Measured by Facilitated Recall to Clinicians

Participants reported taking seven pills in the previous week by facilitated recall at 90% of study visits (n = 1173), with a non-significant decline in reported daily adherence over time (z = − 1.72, p-trend = 0.086). Participants reported taking 4–6 pills per week and < 4 pills per week by facilitated recall at 8% (n = 108) and 2% (n = 28) of study visits, respectively, with no change over time (z = 1.28, p-trend = 0.201 and z = 1.08, p-trend = 0.280, respectively).

Adherence Measured by Self-report in Online Survey

Self-reported adherence over the previous 3 months was 94% overall. There was a significant decrease in self-reported daily adherence over time (96% at month 1 vs 91% at month 12; z = − 1.75, p-trend = 0.006). Furthermore, there was a significant increase in the proportion of participants who reported taking 4–6 pills per week (3% at month 1 to 6% at month 12; z = 1.99, p-trend = 0.046). No change was observed among the participants who reported taking < 4 pills per week (z = 0.50, p-trend = 0.616). No adherence data were recorded for 14% of visits (n = 190), and there was a significant increase in the amount of incomplete online behavioural surveys over time (2% at month 1 to 21% at month 12; z = 8.38, p-trend < 0.001).

Comparison of Adherence Measures

Sensitivity, specificity, and percentage agreement for participants with a blood sample at month 12 (n = 89) were calculated, comparing PBMC TFV-DP concentrations indicative of protective adherence to the four pills/week threshold for TFV concentrations in plasma, facilitated recall to clinicians, and self-report in online surveys (Table 1). Plasma TFV concentrations and facilitated recall to clinicians both had a sensitivity of 98.8% and a 95.5% agreement with protective adherence measured by PBMC TFV-DP drug concentrations.

Predictors of Adherence

Predictors of daily adherence to PrEP identified in the regression analysis are shown in Table 2. In univariate analyses, compared to GBM who reported taking less than seven pills in the previous week by facilitated recall to clinicians, GBM reporting daily PrEP use were significantly more likely to be aged over 40 years at baseline (OR 1.42, 95% CI 1.17–1.73, p < 0.001), attend a private study clinic (OR 1.60, 95% CI 1.26–2.04, p < 0.001), report group sex in the previous three months (OR 1.25, 95% CI 1.07–1.47, p = 0.004), and want to take daily PrEP (OR 1.14, 95% CI 1.01–1.29, p = 0.034). As the study progressed, participants were significantly less likely to report daily adherence (aOR 0.90, 95% CI 0.84–0.95, p < 0.001).

In multivariable analysis, only attending a private study clinic (aOR 1.50, 95% CI 1.07–2.11, p = 0.020) and reporting group sex in the previous 3 months (aOR 1.33, 95% CI 1.15–1.53, p < 0.001) remained significantly associated with daily adherence reported by facilitated recall (compared to reporting < 7 doses in the previous week). In contrast, length of time on the study was associated with decreased likelihood of reporting daily adherence (aOR 0.83, 95% CI 0.75–0.93, p = 0.001). The model was tested for collinearity, and no significant changes in odds ratios were observed, suggesting low levels of collinearity within the model. However, some small residual collinearity may not have been excluded.

Discussion

We found high levels of adherence to daily PrEP by four different measures among *PRELUDE* participants who attended their month 12 follow-up visit. The vast majority of participants had drug concentrations sufficient to protect against HIV throughout the study. However, 19% of participants were lost to follow-up by month 12. Adherence measured by facilitated recall to clinicians mirrored adherence

Table 1 Sensitivity, specificity, and percentage agreement of measures at identifying protective adherence (≥ 4 pills/week), compared to drug concentrations in peripheral blood mononuclear cells, in participants with a blood sample at month 12 (n = 89)

	Sensitivity (%)	Specificity (%)	Percentage agreement (%)
Plasma (TFV)	98.82	25.00	95.51
Facilitated recall to clinicians	98.82	25.00	95.51
Self-report in online survey	80.00	0.00	76.40

Table 2 Predictors of adherence to daily PrEP (compared to < 7 pills/week), based on facilitated recall to clinicians among gay and bisexual male participants attending their month 12 visit (n = 263)

	n of visits (%)	Univariate		Multivariate	
		OR (95% CI)	*p* value	aOR (95% CI)	p-value
Age group[a]					
< 30 years	320 (24%)	REF	–	REF	–
30 to < 40 years	460 (35%)	1.36 (0.86–2.16)	0.185	0.82 (0.38–1.75)	0.605
40 to < 50 years	415 (32%)	1.42 (1.17–1.73)	< 0.001	0.83 (0.51–1.35)	0.464
50 + years	120 (9%)	3.60 (1.68–7.68)	0.001	1.90 (0.59–6.11)	0.279
University educated[a]	855 (65%)	1.00 (0.80–1.25)	0.976		
Employed full or part time	976 (74%)	1.06 (0.98–1.15)	0.163		
Born in australia[a]	840 (64%)	0.80 (0.70–0.92)	0.001	0.80 (0.62–1.03)	0.087
Aboriginal or torres strait islander[a]	25 (2%)	1 (omitted)	–		
Met any high-risk criteria[a]	1085 (83%)	1.12 (0.85–1.47)	0.432		
Attended a private clinic	400 (30%)	1.60 (1.26–2.04)	< 0.001	1.50 (1.07–2.11)	0.020
Study visit[b]	1315 (100%)	0.90 (0.84–0.95)	< 0.001	0.83 (0.75–0.93)	0.001
Any STI[c]	257 (20%)	1.09 (0.86–1.38)	0.454		
Any crystal meth use[c]	371 (28%)	1.19 (0.93–1.53)	0.182		
Any injecting drug use[c]	200 (15%)	1.08 (0.79–1.47)	0.633		
Any binge drinking[c]	234 (18%)	1.02 (0.85–1.25)	0.752		
Any PEP use[a,c]	400 (30%)	0.94 (0.89–1.00)	0.040	1.01 (0.90–1.14)	0.839
Having an HIV+ main regular partner[c]	170 (13%)	0.83 (0.59–1.18)	0.304		
CLAI with a casual partner[c]	612 (47%)	1.22 (0.83–1.80)	0.310		
Any group sex[c]	684 (52%)	1.25 (1.07–1.47)	0.004	1.33 (1.15–1.53)	< 0.001
Willing to use PrEP for > 12 months[d]	1125 (86%)	1.21 (0.89–1.64)	0.223		
Want to take daily PrEP[a]	696 (53%)	1.14 (1.01–1.29)	0.034	0.92 (0.78–1.09)	0.328

aOR adjusted odds ratio, *CI* confidence interval, *CLAI* condomless anal intercourse, *OR* odds ratio, *PEP* post-exposure prophylaxis, *PrEP* pre-exposure prophylaxis, *STI* sexually transmissible infection

[a]From data at baseline

[b]Treated as a continuous variable

[c]In the 3 months preceding the survey

[d]From data at month 1

measured by plasma TFV concentrations, and both correlated well PBMC TFV-DP concentrations.

While the overall levels of adherence to daily PrEP among participants who remained under follow-up were high, there was a statistically significant decline in daily adherence measured by PBMC TFV-DP concentrations and self-report in the online survey. Encouragingly, these declines were offset by an increase in the proportion of participants taking 4–6 pills per week, and there was no statistically significant increase in the proportion of participants taking fewer than four pills per week by any of the four adherence measures. Thus, most individuals maintained protective drug concentrations throughout the study.

PRELUDE participants were early adopters of PrEP, and at high risk of HIV [34]. We found several predictors of daily PrEP adherence, including group sex and attending a private clinic, as opposed to a publicly-funded sexual health clinic. Group sex has been associated with other high-risk behaviours including injecting drug use and STI positivity [35, 36]. Similarly, previous studies have found higher PrEP adherence among individuals engaging in riskier sexual practices [37, 38]. Attending a private clinic was also associated with daily adherence to PrEP in the multivariable model. This may be due to private clients tending to be older and thus more financially stable. Older age was associated with daily adherence to PrEP in univariate analysis, whilst younger age has previously been associated with lower adherence to PrEP in GBM [39], heterosexuals [40] and injection drug users [41].

Adherence measured by plasma TFV concentrations and facilitated recall to clinicians had very high rates of agreement with the current 'gold-standard' measure, PBMC drug concentrations. Furthermore, both measures were highly sensitive in identifying participants with protective adherence. The low specificity of all measures in identifying non-adherers may be attributed to the small number of

participants that reported taking fewer than four PrEP pills/week, combined with the variable lookback periods between measures.

Over-estimating self-reported adherence is a common pitfall in drug trials, as has been noted by several PrEP studies [10, 11]. However, previous research has suggested that participants who self-report non-adherence are likely to be accurately reporting their pill-taking [23]. The statistically significant decline in daily adherence measured in PBMC TFV-DP concentrations was also evident in self-reported data from the online survey, and there was a small but non-significant decline in adherence measured by facilitated recall to clinicians. This suggests that participants accurately reported adherence, and data were captured in a way that reduced social desirability and recall bias [30]. Furthermore, there was no evidence of 'white-coat' dosing—when plasma drug concentrations are high but PBMC concentrations are low—which would indicate that participants only dosed shortly before study visits [42, 43].

In regards to the use of these adherence measures in regular clinical practice, each has distinct advantages and disadvantages. Whilst PBMC TFV-DP concentrations are often used as the 'gold-standard' for PrEP adherence, they can vary considerably within and between individuals [23]. Along with plasma concentrations, analysis is complex, and blood samples cannot provide immediate feedback for clinicians to be able to make decisions about whether a patient may need additional adherence support [22]. Self-reported adherence in online surveys, whilst a commonly used research tool, lacked the sensitivity of the other methods, although this may be improved with a shorter recall period. Thus, facilitated recall emerges as the prime candidate to measure adherence to daily PrEP. It is quick and easy to elicit from patients and provides an accurate representation of recent pill-taking, particularly in settings where there is established rapport between clinicians and clients, and honest discussions about adherence are possible.

For most of the study period, individuals could only obtain free PrEP in NSW if they were enrolled in *PRELUDE*; PrEP could be purchased online but at substantial cost to the user. As such, it is highly likely that participants who exited the study discontinued PrEP use. If participants did continue to access PrEP though other means, follow-up adherence data were not available, although this would have been a rare occurrence. There were myriad reasons for PrEP discontinuation, including changes in relationship status or level of risk, travel, or moving interstate or overseas. Whilst failure to present for study visits has been suggested as a marker of non-adherence [23], some individuals may simply start and stop using PrEP over time. Provided that individuals take PrEP when they are engaging in HIV risk events, periods of non-engagement with care are not a major cause for concern. Using PrEP continuously, but for shorter periods, can have a range of benefits including reduced costs and less potential for renal dysfunction or bone mineral density loss, both known to be associated with TFV use in a small proportion of individuals [44, 45]. While these benefits may be offset by additional difficulties with adherence, as was seen in the HPTN 067 study [46, 47], the ANRS-IPERGAY study of event-based PrEP dosing showed extremely high levels of adherence [8]. To date, there have been few demonstration studies which have monitored participants' pill-taking patterns in real-world settings [48, 49] and little literature exists on the concept of 'seasons of risk', so further work in this area is needed.

This study had several limitations. Firstly, the moderate sample size and homogeneity of participants may limit the generalisability, particularly with respect to predictors of adherence to daily PrEP. This cohort were at high risk of HIV and may be more health literate with better access to services than the broader GBM population, especially those outside of large urban centres. Based upon these data, PrEP implementation programs have been established more broadly across NSW and Australia [31, 50], with campaigns to promote PrEP awareness and uptake. Different periods of recall for each of the adherence measures complicated comparisons, but all measures were reported in equivalent doses per week for clarity. Furthermore, no measure of adherence was sensitive at identifying individuals who did not have protective adherence, but this was extremely rare in our cohort. Despite this, we continue to recommend using facilitated recall in environments where there is established trust and rapport between clinicians and patients. Asking about recent pill-taking behaviours in a non-judgemental manner and assuring patients there will be no repercussions for reporting sub-optimal or non-adherence enables clinicians to support patients in developing suitable pill-taking routines. Simple tools to collect information about sexual practices and pill-taking may help ease the difficulties that clinicians who do not have such experience or good rapport with their patients may face [51].

Nonetheless, the study also has several strengths. The majority of participants remained engaged with the study for 12 months and reported high levels of adherence to daily PrEP by each of the four measures. Detailed data were collected which gave important insights into the links between PrEP-taking and risk behaviours, and provided valuable, real-world information which can help guide future PrEP implementation. Finally, this study provides support for the use of facilitated recall to determine adherence to PrEP in routine clinical practice, simplifying reporting for clinicians and patients alike.

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Compliance with Ethical Standards

Conflicts of interest AEG has research funding from Seqirus, Gilead, Viiv, and in-kind research support from Hologic. He has received travel funding from Gilead. IBZ has received research funding and in-kind support (supply of the study medication) from Gilead Sciences Inc. Authors SJV, MAM, BGH, DJT, NR, AM, and RF declare that they have no conflicts of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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