

Interest in Switching to On-Demand HIV Pre-Exposure Prophylaxis (PrEP) Among Australian Users of Daily PrEP: An Online Survey

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We surveyed 970 PrEPX study participants to evaluate interest in switching from daily to on-demand PrEP in a study setting. Interested respondents ($n = 469$, 48%) more commonly reported PrEP cessation (adjusted odds ratio [aOR], 3.0; $P < .001$), difficulty with adherence (aOR, 1.6; $P = .029$), infrequent sex (aOR, 3.7; $P < .001$), and toxicity concerns (aOR, 2.7; $P < .001$).

Key words. event-based PrEP; HIV pre-exposure prophylaxis (PrEP); intermittent PrEP; on-demand PrEP.

INTRODUCTION

Currently, the only HIV pre-exposure prophylaxis (PrEP) regimen approved by the Australian Therapeutic Goods Administration (TGA) is once-daily use of co-formulated tenofovir and emtricitabine (TD*/FTC), and this is the only regimen studied in several large Australian PrEP trials. However, Australian and some international PrEP guidelines recommend that gay and other men who have sex with men (MSM) may consider an alternative option of on-demand PrEP dosing [1–4]. For individuals with infrequent HIV exposure events, on-demand PrEP offers the advantage of a lower pill burden than daily PrEP, with potential benefits that include lower financial cost and fewer adverse effects [5, 6].

The French IPERGAY trial assessed the efficacy of on-demand PrEP, wherein participants were randomized to take 2 pills of TD*/FTC or placebo at least 2 hours prior to sexual intercourse,

followed by one pill 24 hours and one pill 48 hours after the first dose [7]. IPERGAY observed a HIV risk reduction of 86% (95% confidence interval [CI], 40–98) in the active arm compared to placebo [7], and a 97% risk reduction (95% CI, 81–100) during their open label extension [8]. On-demand PrEP is the most commonly used PrEP method in France, with >70% of participants in a large clinic in Paris opting for on-demand PrEP versus daily [9]. Similar levels of enthusiasm for on-demand PrEP have not been observed in other parts of the world. In Amsterdam, 27% of PrEP study participants chose on-demand PrEP [10]. In London, on-demand PrEP use was reported by 16% of 293 participants enrolling into InterPrEP, a pharmacokinetic study of plasma TD*/FTC levels in MSM who ordered PrEP online [11]. In Sydney, prior to the publication of the IPERGAY results, 14% of 315 participants enrolling in a daily PrEP study (PRELUDE) between 2014 and 2016 reported at baseline that they were willing to use on-demand PrEP, and 20% reported willingness to use periodic PrEP, defined as short periods of daily dosing at times of increased HIV risk [12]. In Antwerp, Belgium, 23.5% of 200 participants enrolling in the Be-PrEP-ared demonstration project reported a preference for using on-demand PrEP at baseline [13].

We plan to conduct a study to determine the benefits of switching from daily to on-demand PrEP among users of daily PrEP. As there are no post-IPERGAY data to indicate the level of interest in on-demand PrEP among Australian PrEP users, in order to assess the feasibility of this future study, we conducted a survey of former participants of the PrEPX study to measure their interest in participating in a study of on-demand PrEP.

METHODS

The PrEPX study was an Australian demonstration study of daily PrEP conducted in Victoria, South Australia, and Tasmania, which enrolled over 5000 participants between July 2016 and March 2018, consisting mainly of MSM. The trial ceased both enrollment and provision of study medication on March 31, 2018, because the Australian Government's Pharmaceutical Benefits Scheme (PBS) listed PrEP on April 1, 2018, making it affordable and available to all Australian residents who had access to Australia's universal health insurance system, Medicare.

On November 23, 2018, a single email invitation was sent to all former PrEPX participants. This email explained that the PrEPX team was assessing the feasibility of a new study that would offer on-demand PrEP and that we wished to measure the interest of previous PrEPX study participants in participating in an on-demand PrEP study. The email explained the concept of on-demand PrEP, in accordance with the

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IPERGAY protocol, and contained a link to an online survey. The 15-question survey covered demographics, previous and current PrEP use, satisfaction with daily PrEP use, knowledge of on-demand PrEP, interest in starting on-demand PrEP, and reasons for having or not having interest in on-demand PrEP (Supplementary Appendix). Most questions had multiple answer options, and participants could select more than one answer. Several questions included free-text answer options. The online survey remained open for 2 months.

Collected data were analyzed descriptively, and, for proportions, we calculated 95% confidence intervals using the exact binomial method. Free-text answer options were analyzed thematically, where all free text answers were reviewed manually (by V.J.C.) and categorized as shown in Table 1. Univariate logistic regression analyses were used to assess associations between interest in on-demand PrEP and other survey questions. Survey questions with significant ($P < .1$) associations in univariate analysis were entered in a multivariate logistic regression model.

This survey was approved by the Alfred Health Ethics Committee, Melbourne, Australia (project 516/18).

RESULTS

The survey received 1008 unique responses, of which 22 were incomplete and 16 were not from PrEPX participants; therefore, 970 responses were analyzed, producing a response rate of approximately 20%.

The median age of respondents was 39 years (interquartile range [IQR], 31–49) (Table 1). 966 respondents (100%) were assigned the male sex at birth, and 961 (99%) reported having a male gender. Almost all respondents (99%, $n = 965$) reported having male sexual partners. To compare, in the overall PrEPX cohort, 99.2% of participants were male, 98.7% had sex with men, and they had a median age of 34 (IQR, 28–42) [14].

Current PrEP use was high (86%, $n = 830$) and 140 (14%) had stopped using PrEP. Reasons for having ceased PrEP included having perceived low HIV risk ($n = 76$, 54%), concern about long-term toxicity ($n = 21$, 15%), ongoing adverse effects ($n = 19$, 14%), logistical difficulties in obtaining PrEP, such as difficulties getting a clinic appointment ($n = 15$, 11%), financial cost ($n = 3$, 2%), difficulties maintaining adherence ($n = 3$, 2%), and unrelated health problems ($n = 3$, 2%). Of the 970 participants, 116 (12%) reported not being satisfied with daily PrEP, and reasons for dissatisfaction included concerns about toxicity (27%), infrequent need for PrEP due to infrequent sexual activity (27%), dislike of taking pills (20%), difficulty remembering to take pills (16%), renal problems (5%), and ongoing adverse effects (4%). These concerns were expressed more frequently by those who were interested in participating in an on-demand PrEP trial (Table 1).

Approximately one-third of respondents (37%, $n = 357$) reported prior knowledge of on-demand PrEP, sourced from

health professionals ($n = 79$, 22%), social media and internet sites ($n = 90$, 25%), friends and sexual partners ($n = 43$, 12%), and the gay press ($n = 11$, 3%).

Of the 970 respondents, 469 (48%) reported interest in participating in an on-demand PrEP study for the following reasons: prospect of less long-term toxicity ($n = 297$, 63%), having sex infrequently ($n = 282$, 60%), more convenience compared to daily PrEP ($n = 245$, 52%), lower financial cost ($n = 225$, 48%), and less ongoing adverse effects ($n = 106$, 23%) (Table 1).

Respondents who were not interested in participating in an on-demand PrEP study ($n = 501$) reported the following reasons as to why on-demand PrEP was not suitable for them: concerns about its effectiveness ($n = 338$, 67%) or feeling anxious (ie, less protected) ($n = 189$, 38%), concerns about not remembering to take a dose at least 2 hours before sex ($n = 292$, 58%), having spontaneous or unplanned sex (free text responses, $n = 76$, 15%), being at low risk of HIV and hence not needing PrEP (free text responses, $n = 18$, 4%), and having frequent sex and hence needing to take pills every day (free text responses, $n = 11$, 2%).

In multivariate analysis, interest in on-demand PrEP was associated with having stopped PrEP (adjusted odds ratio [aOR], 3.0; $P < .001$), dissatisfaction with daily PrEP (aOR, 2.0; $P = .027$), difficulty remembering to take pills every day (aOR, 1.6; $P = .029$), infrequently having sex with an HIV acquisition risk (aOR, 3.7; $P < .001$), concerns about long-term toxicity from PrEP (aOR, 2.7; $P < .001$), and having no prior knowledge of on-demand PrEP (aOR, 1.6; $P < .004$) (Supplementary Table 1).

DISCUSSION

Among 970 Australian users of daily PrEP, approximately half were interested in participating in an on-demand PrEP study, and this interest was most strongly associated with having sex infrequently and concerns about long-term toxicity. This is a higher level of interest in on-demand PrEP than was found in studies in Sydney, Amsterdam, Antwerp, and London [10–13]. Of the 52% of survey respondents who were not interested in on-demand PrEP, almost 60% were concerned that on-demand PrEP may not be as effective as daily PrEP and approximately 50% expressed concern that they may not be able to adhere to the more complicated on-demand PrEP pill regimen.

Two-thirds of interested respondents reported concerns about potential toxicity associated with long-term antiretroviral use. In the short to medium term, PrEP use can be associated with a decline in renal function and bone mineral density, although clinically significant toxicity is uncommon [15, 16]. Data on toxicity with longer-term PrEP use (eg, decades) are not available, and few data are available to assess whether on-demand PrEP is associated with less toxicity than daily PrEP. In the IPERGAY study, there was no significant decline in the mean slope of glomerular filtration rate (eGFR) in the TD*/FTC versus placebo arms over a median of 9.3 months follow-up [6].

Table 1. Respondent Characteristics and Perceptions of PrEP Use Stratified by Respondents Who Were Interested and Respondents Who Were Not Interested in On-Demand PrEP

	Total			Interested in On-Demand PrEP			Not Interested in On-Demand PrEP		
All (n, %; 95% CI)	970			469	48	(45, 52)	501	52	(48, 55)
Age (median, IQR)	39		(31, 49)	38		(31, 49)	40		(32, 49)
Current PrEP (n, %; 95% CI)	830	86	(83, 88)	367	44	(41, 48)	463	56	(52, 59)
Age (median, IQR)	40		(32, 49)	39		(31, 50)	40		(33, 49)
Ceased PrEP (n, %; 95% CI)	140	14	(12, 17)	102	73	(65, 80)	38	27	(20, 35)
Age (median, IQR)	36		(30, 46.5)	36		(31, 48)	35.5		(30, 41)
	<i>n</i>	<i>%</i>	<i>(95% CI)</i>	<i>n</i>	<i>%</i>	<i>(95% CI)</i>	<i>n</i>	<i>%</i>	<i>(95% CI)</i>
Satisfaction with daily PrEP^a									
Satisfied	854	88	(86, 90)	369	79	(75, 82)	485	97	(95, 98)
Dissatisfied	116	12	(10, 14)	100	21	(18, 25)	16	3	(2, 5)
Reason for dissatisfaction with daily PrEP									
Difficulty remembering	155	16	(14, 18)	115	25	(21, 29)	40	8	(6, 11)
Don't like taking pills	197	20	(18, 23)	146	31	(27, 36)	51	10	(8, 13)
Infrequent sexual activity	264	27	(24, 30)	217	46	(42, 51)	47	9	(7, 12)
Ongoing adverse effects	34	4	(2, 5)	25	5	(3, 8)	9	2	(1, 3)
Concerns of toxicity	266	27	(25, 30)	211	45	(40, 50)	55	11	(8, 14)
Renal problems	46	5	(3, 6)	37	8	(6, 11)	9	2	(1, 3)
Previous knowledge of on-demand PrEP									
Yes	357	37	(34, 40)	153	33	(28, 37)	204	41	(36, 45)
No	613	63	(60, 66)	316	67	(63, 72)	297	59	(55, 64)
Reason for interest in on-demand PrEP									
More convenient				245	52	(48, 57)			
Ongoing adverse effects				106	23	(19, 27)			
Concerns of toxicity				297	63	(59, 68)			
Less cost				225	48	(43, 53)			
Infrequent sex				282	60	(56, 65)			
Reason for no interest in on-demand PrEP									
Multi-choice responses:									
Less effective than daily							295	59	(54, 63)
Difficult regimen							262	52	(48, 57)
Would feel anxious							189	38	(33, 42)
Other (see free text)							187	37	(33, 42)
Free text responses:									
Less effective than daily							43	9	(6, 11)
Difficult regimen							30	6	(4, 8)
Unplanned sex							76	15	(12, 19)
Frequent sex							11	2	(1, 4)
Low HIV risk							18	4	(2, 6)

Bold text indicates percentage values that are higher than in the comparison group ("interested" vs "not interested") and if the confidence interval does not overlap the comparison percentage value.

Abbreviations: CI, confidence interval; IQR, interquartile range; PrEP, pre-exposure prophylaxis.

^a"Satisfaction with daily PrEP" was rated by participants on a Likert scale, from which we created a binary variable "satisfied vs dissatisfied" for analysis. However, all participants who responded to this question with any answer other than "very satisfied" were asked to list their reasons for dissatisfaction.

In the ADAPT study, creatinine elevation occurred in 9% of 178 participants at one study site, but it was not significantly different between participants in the daily, time-driven, and on-demand PrEP study arms ($P = .05$) [17].

Almost a third of respondents cited infrequent sex as reason for dissatisfaction with daily PrEP, and almost half of interested respondents cited infrequent sex as a reason for interest in on-demand PrEP. Similarly, the Be-PrEP-ared study found that participants who opted for on-demand PrEP reported lower numbers of recent sexual partners than participants who

opted for daily PrEP [13]. Also, the Amsterdam PrEP project found that 30% of participants switched between daily PrEP and on-demand PrEP (or vice versa) over a 2-year period, and having a higher number of casual sexual partners was associated with an increased chance of switching from on-demand PrEP to daily PrEP [18]. These findings highlight the need to examine the efficacy of on-demand PrEP for people who have sex infrequently. A post-hoc analysis of the IPERGAY data found a HIV risk reduction of 100% (95% CI, 20–100) for those participants who had sex infrequently [19]. However, given the

wide confidence interval range around this outcome, more data are needed to assess the efficacy of on-demand PrEP studies among people who have sex infrequently.

Most uninterested respondents reported concern that on-demand PrEP would be less effective than daily PrEP. Similarly, in the Be-PrEP-ared study, the most commonly cited reason for preferring daily PrEP was that it “seemed safer” [13]. For context, current Australian PrEP guidelines recommend daily use of PrEP, listing on-demand PrEP as an alternative method [1]. Additionally, all Australian PrEP trials have stipulated that participants must take PrEP every day, and this message has been reinforced by clinicians and community organizations. Given the current lack of convincing evidence for the efficacy of on-demand PrEP among MSM who use it infrequently, as described above, this concern about efficacy is reasonable. Also, PrEP efficacy is dependent on adherence, and many respondents foresaw difficulty in remembering to take on-demand PrEP, particularly in light of the spontaneous nature of some sexual encounters. The randomized placebo-controlled IPERGAY study found that 43% of participants took their on-demand PrEP as instructed [7], and this increased to 50% during the study’s open label extension [8]. PrEP coverage of sex acts also was assessed in the ADAPT study, in which participants were asked to either take daily PrEP, time-driven PrEP, or on-demand PrEP. At the Bangkok site of the ADAPT study, the PrEP coverage of sex acts was higher in the daily (85%) than in the on-demand PrEP arm (74%) ($P = .02$) [17]. This highlights the need for specific adherence support for on-demand PrEP, which could include smartphone reminder applications designed for the on-demand regimen and always carrying a double dosage of PrEP for initialization at unexpected times.

One limitation of our study is that only 20% of former PrEPX participants provided complete responses to our survey. However, participants who provided complete responses had similar characteristics to the overall PrEPX cohort and hence were likely to have formed a representative sample. A further limitation of our study is that we did not ask the participants whether they were currently taking on-demand PrEP. At the time of the survey, the only approved PrEP regimen in Australia was daily PrEP, and the PrEPX study intended to provide daily PrEP, but it is possible that some participants were using their PrEP in an on-demand fashion. We did, however, ask participants whether they had prior knowledge of on-demand PrEP.

Among Australian users of daily PrEP, interest in switching to on-demand PrEP was high but tempered by concerns around its efficacy and the relative complexity of this strategy when compared to daily PrEP. Future Australian studies of on-demand PrEP will need to be accompanied by education on its relative efficacy and by adherence supports that are specifically tailored to this method.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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