Research Paper

Chemsex is not a barrier to self-reported daily PrEP adherence among PROUD study participants

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ABSTRACT

Background: Pre-exposure prophylaxis (PrEP) is a novel HIV prevention method whereby HIV-negative individuals take the drugs tenofovir and emtricitabine to prevent HIV acquisition. Optimal adherence is critical for PrEP efficacy. Chemsex describes sexual activity under the influence of psychoactive drugs, in the UK typically; crystal methamphetamine, gamma-hydroxybutyrate(GHB) and/or mephedrone. Chemsex drug use has been associated with increased HIV transmission risk among gay, bisexual and other men who have sex with men (GBM) and poor ART adherence among people living with HIV. This study assessed whether self-reported chemsex events affected self-reported daily PrEP adherence among PROUD study participants.
Methods: The PROUD study was an open-label, randomised controlled trial, conducted in thirteen English sexual health clinics, assessing effectiveness of Truvada®-PrEP among 544 HIV-negative GBM. The study reported an 86% risk-reduction of HIV from daily PrEP. Participants were asked about chemsex engagement at follow-up visits. Monthly self-reports of missed PrEP tablets were aggregated to assess adherence between visits. Univariable and multivariable regression analyses were performed to test for associations between chemsex and reporting less than seven out of seven intended doses(< 7/7ID) in the 7 days before and/or after last condomless anal intercourse(CAI).
Results: 1479 follow-up visit forms and 2260 monthly adherence forms from 388 participants were included in the analyses, with 38.5% visit forms reporting chemsex since last visit and 29.9% follow-up periods reporting < 7/7ID. No statistically significant associations were observed between reporting < 7/7ID and chemsex (aOR = 1.29 [95% CI 0.90–1.87], p = 0.168). Statistically significant associations were seen between reporting < 7/7ID and participants perceiving that they would miss PrEP doses during the trial, Asian ethnicity, and reporting unemployment at baseline.
Conclusions: These analyses suggest PrEP remains a feasible and effective HIV prevention method for GBM engaging in chemsex, a practise which is prevalent in this group and has been associated with increased HIV transmission risk.

Introduction

In November 2018, Public Health England (PHE) reported significant progress towards ending the HIV epidemic; the UNAIDS 90:90:90 targets had been met for England in 2017, and a 17% decline in new UK HIV diagnoses compared to 2016 (from 5,280 to 4,363) had been observed in both gay, bisexual and other men who have sex with men (GBM) and heterosexual groups (Nash S et al., 2018). The stepwise implementation of combination HIV prevention; condom provision, scale up of frequent HIV testing and prompt antiretroviral therapy

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(ART) after diagnoses, and pre-exposure prophylaxis (PrEP), has been identified as the primary drivers for the drop in HIV incidence in GBM. Despite these gains, just over half (53%) of all new HIV diagnoses in England in 2017 were among GBM, demonstrating that this group are disproportionately at risk of acquiring HIV (Nash S et al., 2018).

Pre-exposure prophylaxis (PrEP) is an innovative HIV prevention strategy for individuals at risk for HIV acquisition, such as GBM engaging in condomless anal intercourse (CAI) (McCormack, Fidler et al., 2016). Although PrEP is not yet routinely commissioned in England, it is available through the PrEP Impact Trial (Nash S et al., 2018; NHS England, 2017) and can be purchased online and by private prescription. PrEP's efficacy in reducing HIV incidence in GBM and heterosexuals has been documented widely (Baeten et al., 2012; Huang et al., 2018; (McCormack et al., 2016; Molina et al., 2015; Okwundu, Uthman & Okoromah, 2012) and in trials such as the PROUD study, an open-label, randomized controlled trial of 544 HIV-negative GBM, the reduction in HIV risk from daily PrEP was 86% (McCormack et al., 2016). Optimal adherence is critical to PrEP's efficacy in HIV prevention, in order to achieve protective drug levels in the blood (Desai, Field, Grant & McCormack, 2017; Fonner et al., 2016; Huang et al., 2018; Spinner et al., 2016) and consequently, studies reporting limited PrEP efficacy have detected low or no therapeutic drug levels, indicating poor adherence (Corneli et al., 2014; Grant et al., 2014; Haberer et al., 2013; Marrazzo et al., 2015; Van Damme et al., 2012).

Chemsex refers to the use of psychoactive drugs within a sexual context to enhance and facilitate sexual experiences (Public Health England, 2015). The international chemsex definition varies, but within the UK typically involves the use of one or more of the three drugs; crystal methamphetamine, gamma-hydroxybutyrate [GHB] and mephedrone. (Bourne, Reid, Hickson, Torres-Rueda & Weatherburn, 2015; Edmundson et al., 2018; Public Health England, 2015). Chemsex has been increasingly reported among UK GBM in recent years (Macfarlane, 2016; Ottaway, Finnerty, Buckingham & Richardson, 2017; Sewell et al., 2018; Tomkins, George & Kliner, 2019) but prevalence estimates vary considerably due to lack of a standardised definition of chemsex and lack of prevalence measurements among representative, national samples of GBM. Furthermore, much of the available literature on chemsex only uses reporting of drugs associated with chemsex as a proxy for chemsex *behaviour* (i.e. intentional sex under the influence of the psychoactive drugs crystal methamphetamine, gamma-hydroxybutyrate [GHB], mephedrone) and does not assess event-level data. (Edmundson et al., 2018; Sewell et al., 2018).

Chemsex drug use has been associated with a number of harms including; sexual and other behaviours carrying HIV and hepatitis C risk (such as CAI, group sex and multiple partners, fisting and injecting) (Bourne et al., 2015; Daskalopoulou et al., 2017; Glynn et al., 2018; Hegazi et al., 2017; Maxwell, Shahmanesh & Gafos, 2019; Ristuccia, LoSchiavo, Halkitis & Kapadia, 2018; Tomkins et al., 2019), HIV diagnosis (Halkitis, Levy, Moreira & Ferrusi, 2014; Kenyon, Wouters, Platteau, Buyze & Florence, 2018; Pakianathan et al., 2018; White et al., 2019) and suboptimal adherence to ART among people living with HIV (Daskalopoulou et al., 2014; Perera, Bourne & Thomas, 2017; Stuart, 2013). The evidence on chemsex impacting ART adherence includes a systematic review published in 2017, reporting chemsex drug users as having 23% higher odds of ART non-adherence than non-chemsex drug users (OR 1.23, 95%CI 1.10–1.38, I2 0%, $p = 0.372$) (Perera et al., 2017). However as described earlier, the majority of studies on chemsex associated harms use chemsex drug use as a proxy, therefore attributing these harms to chemsex behaviours directly is problematic.

Evidence assessing the effect of chemsex behaviour and chemsex drug use on individuals' PrEP adherence is limited and conflicting. One qualitative study among American PrEP-taking GBM reported associations between methamphetamine use and poor PrEP adherence, often in the context of group sex (Storholm, Volk, Marcus, Silverberg & Satre,

2017). Another American GBM study found similar associations with instances of "club drug" use (including GHB and methamphetamine) being correlated with missed PrEP doses on the same day (Grov, Rendina, John, & Parsons, 2018). Conversely, the same research also suggested that on average "club drug" users were no more likely to miss PrEP doses than non "club drugs" users (Grov, Rendina, John, & Parsons, 2018), and in another study among American GBM, methamphetamine use was shown not to be associated with decreased PrEP adherence (Hoenigl, Morgan, et al., 2019; Hoenigl, Morgan, et al., 2019). Interestingly, in an IPERGAY trial substudy, GBM reporting chemsex were *more* likely to report correct PrEP use during their most recent sexual encounter, which authors have explained by their additional finding that participants reporting chemsex also reported having a higher risk perception (Roux et al., 2018).

To our knowledge, there is currently no evidence assessing the impact of chemsex behaviours on PrEP adherence among GBM in England. This study explores the effect of reported chemsex episodes on daily PrEP adherence among PROUD study participants, to assess whether PrEP is likely to be an effective HIV prevention tool in periods around these high-risk events.

Methods

The PROUD study was an open-label, wait-listed, randomized controlled trial that was conducted in thirteen sexual health clinics in England, examining the real-world effectiveness of daily oral Truvada® as HIV PrEP. The study recruited 544 HIV-negative GBM between November 2012 and April 2014 who reported CAI in the previous 90 days and who considered they were likely to have CAI in the next 90 days. Participants were randomly assigned daily Truvada® either at study enrolment or after 12 months. Participants were followed up approximately quarterly with HIV/STI screening. In October 2014, interim analyses showed a large number of HIV infections in the deferred arm and evidence of PrEP being highly protective in the immediate arm, prompting a study design amendment whereby the X deferral arm participants still in the first 12 months of follow-up were given access to PrEP (McCormack, Dunn et al., 2016; . PROUD study design, baseline participant characteristics and results are described elsewhere (Dolling et al., 2016; Gafos, Brodnicki, et al., 2017; McCormack, Dunn et al., 2016;

From March 2015, participants were asked at each follow-up visit whether they had engaged in chemsex since last visit, on clinician-completed questionnaires. Specifically, these questionnaires asked, "Has the participant engaged in any of the following since their last visit: crystal meth, GHB/GBL or mephedrone immediately prior to, or during, sex ("chemsex")". Visit questionnaires answering yes to this question were used to define periods of chemsex engagement within the 90 days prior to follow-up visit dates (as follow-up visits were supposed to occur quarterly). Visit questionnaires were excluded from the analyses if they were from participants who were not currently taking PrEP or if the question on chemsex was not answered.

Participants were asked to complete monthly self-reported PrEP adherence questionnaires for the last month only; online, or on paper at follow-up visits. These adherence questionnaires asked participants how many days they missed PrEP tablets in the seven days before and seven days after last CAI (provided this had occurred in the preceding 30 days) and were used to assess adherence execution (Vrijens et al., 2012). Adherence questionnaires were eligible for our analyses if the completion date was within 90 days prior to the date on the visit questionnaire completion dates (and hence could be linked) and if the questions on missed PrEP were answered. We created a binary adherence outcome measure for participants reporting; taking all seven out of seven intended doses (7/7ID) in the seven days before and after last CAI, and participants reporting less than seven out of seven intended doses (< 7/7ID) in the 7 days before and/or after last CAI. It was not possible to conduct a robust analysis with an adherence

Table 1
Monthly and follow-up period PrEP adherence classifications.

Monthly PrEP adherence	
Seven out of seven intended doses (7/7ID)	**Less than seven out of seven intended doses (< 7/7ID)**
Participant reports missing 0 PrEP tablets in both 7 days before and 7 days after last CAI on monthly adherence form	Participant reports missing ≥1 PrEP tablet(s) in 7 days before and/or 7 days after last CAI on monthly adherence form
Follow-up period PrEP adherence	
Seven out of seven intended doses (7/7ID) within a follow-up period	**Less than seven out of seven intended doses (< 7/7ID) within a follow-up period**
All monthly adherence forms within follow-up period between visits report taking seven out of seven intended doses in the 7 days before and 7 days after last CAI	≥1 monthly adherence form(s) within follow-up period between visits reports less than seven out of seven intended doses in the 7 days before and/or 7 days after last CAI

outcome for participants reporting missing ≥4 PrEP tablets in the 7 days before and/or after last CAI, as the sample was too small.

The adherence questionnaires were aggregated to calculate an overall PrEP adherence measure for each follow-up period. If participants reported 7/7ID in all monthly adherence questionnaires within the visit follow-up period, then the entire follow-up period would be defined as reporting 7/7ID. If participants reported < 7/7ID any monthly adherence questionnaire within the follow-up period this would denote the follow-up period as reporting < 7/7ID. Monthly and follow-up period adherence classifications are described in Table 1.

Statistical analysis

Comparative analyses using univariable logistic regression were performed to assess associations between the outcome and exposure of interest (< 7/7ID within a follow-up period and chemsex reporting) and other covariates collected on baseline questionnaires at enrolment and visit questionnaires at each follow-up visit (demographics, lifestyle, sexual behaviour etc.). A forward stepwise approach was used for the multivariable model with chemsex, with variables entered where significant at $p < 0.1$. Since participants could contribute to the analysis multiple times, robust variance was used for logistic regression analyses to account for clustering. Data were analysed using STATA 15.1.

Results

Our sample consisted of 1,479 visit questionnaires, 2,260 monthly adherence questionnaires and 388 baseline enrolment questionnaires derived from 388 participants, between 3rd December 2014 and 28th October 2016. The median number of follow-up visit questionnaires per participant over the study period was four (interquartile range [IQR]: 2–5), and the median number of adherence forms per participant was five (IQR: 3–7). The median number of adherence forms within a visit form period was 1 (IQR: 1–2).

Baseline characteristics

Descriptive analyses of participants from baseline questionnaires are detailed in Table 2 and were highly similar to baseline characteristics reported for the total PROUD study population (Dolling et al., 2016). Among the 388 participants within this study, median age was 36 years (IQR 30–43), 82% reported being of white ethnicity, and 60.6% were UK born. Almost all participants described their gender as male (99%; 384), and their sexuality as gay/homosexual (95.1%; 369). Among the participants, 43.3% reported currently being in a relationship, 63.4% reported completing a university degree or higher, and 73.2% were in full-time employment.

Almost three quarters of participants (73.7%; 286) reported having used any recreational drugs in the three months prior to enrolment. Four in ten participants (43%; 167) reporting using one or more of the three chemsex-associated drugs, with a smaller proportion (12.9%; 50) reporting having used all three chemsex-associated drugs. 13.7%

reporting drinking alcohol daily or nearly every day.

Participant prep adherence and chemsex reporting during follow-up

Nearly a quarter (23.3%; 527/2,260) of all adherence forms within our sample reported < 7/7ID, with the majority (72.9%, 384/527) of these only reporting missing less than three intended doses in the week before *and* after last CAI. Chemsex and PrEP adherence reporting by participants at any time during their study period are described in Fig. 1. Just over half (52.8%, 205) of the participants ever reported engaging in chemsex on a follow-up visit questionnaire and just over half (53.1%, 206) ever had a follow-up period reporting < 7/7ID. Most participants (85.8%, 333) had one or more follow-up period reporting 7/7ID.

Follow-up period characteristics

Descriptive clinical, lifestyle and sexual behaviour characteristics from the 1,479 visit questionnaires are described in Table 3. Chemsex was reported on 38.5% visit questionnaires, 47.1% visit questionnaires reported group sex, 24% reported using sex toys and 13.9% reported fisting, since last visit. The median number of CAI partners in the 30 days prior to visit was 3 (IQR: 1–7). Only 8.8% of visit questionnaires reported an episode of injecting drug use and 20.1% reported powder cocaine use.

Factors associated with reporting less than 7 of 7 intended doses (≤7/7ID) within a follow-up period (Table 4)

The univariable analyses demonstrated no statistically significant ($p < 0.05$) association between chemsex engagement reported on follow-up visit questionnaires and reporting < 7/7ID within linked follow-up periods (OR = 1.29 [95% CI: 0.92–1.79], $p = 0.137$). Just over a third (33.2%) of follow-up periods linked to a visit questionnaire reporting chemsex since last visit reported < 7/7ID and 27.8% follow-up periods linked to visit questionnaires not reporting chemsex reported < 7/7ID.

Ethnicity, employment status and participants' baseline perception of their adherence ability were entered into the multivariable model assessing chemsex and reporting < 7/7ID within a follow-up period, as these were significant at $p < 0.1$ during the selection process. The association between chemsex and reporting < 7/7ID remained statistically non-significant at $p < 0.05$ (aOR = 1.29 [95% CI: 0.90–1.87], $p = 0.168$). Within the multivariable analyses, visit questionnaires from participants perceiving at baseline they may encounter adherence difficulties were significantly associated with reporting < 7/7ID at $p < 0.05$ (aOR = 1.88 [95% CI: 1.28–2.75], $p = 0.001$), as was reporting unemployment (aOR = 2.31 [95% CI: 1.06–5.04], $p = 0.036$) and Asian ethnicity (aOR = 3.12 [95% CI: 1.20–8.21], $p = 0.020$).

Although in the univariable analyses, visit questionnaires from participants in full-time education and aged 18–35 at baseline were significantly associated with reporting < 7/7ID within a follow-up

Table 2

Participant sample characteristics at baseline from linked enrolment questionnaires (*N* = 388 participants).

Demographics	n	(%)
Gender		
Male	384	(99)
Transgender	0	(0)
Sexuality		
Gay/homosexual	369	(95.1)
Straight/bisexual/other	15	(3.9)
Ethnicity		
White	318	(82)
Black	13	(3.4)
Asian	18	(4.6)
Other	36	(9.3)
Born in the UK		
No	151	(38.9)
Yes	235	(60.6)
Age (years)		
18–25	40	(10.3)
26–35	145	(37.4)
36–45	119	(30.7)
> 45	84	(21.7)
Maximum education level		
University degree or higher	246	(63.4)
A levels / equivalent	61	(15.7)
GCSEs / equivalent	38	(9.8)
Vocational training/other qualifications	23	(5.9)
Still in full-time education	10	(2.6)
Finished education with no qualifications	9	(2.3)
Employment status		
Employed/self-employed full-time	284	(73.2)
Employed/self-employed part-time	38	(9.8)
Unemployed	24	(6.2)
Student	16	(4.1)
Retired	16	(4.1)
Other	7	(1.8)
Relationship status		
In relationship, living with partner	113	(29.1)
In relationship, not living with partner	55	(14.2)
Not currently in an ongoing relationship	218	(56.2)
Lifestyle		
Recreational drug use in past 3 months		
No	92	(23.7)
Yes	286	(73.7)
Alcohol drinking frequency		
Never/Once	40	(10.3)
2 or 3 times a month	80	(20.6)
Once or twice a week	128	(33)
3 or 4 times a week	75	(19.3)
Nearly every day/Daily	53	(13.7)
Units of alcohol drank on a typical drinking day		
0–4	163	(42)
5–9	117	(30.2)
10 +	60	(15.5)
Perception of adherence ability throughout the trial		
Find easy to remember to take drug daily	250	(64.4)
Might forget to take doses, will find daily dosing difficult	122	(31.4)

Number of baseline enrolment questionnaires with missing data for gender (4); sexuality (4); ethnicity (3); born in the UK (2); education (1) employment (3) relationship status (2); recreational drug use (5); alcohol drinking frequency (12) alcohol units (48) perception of adherence (16)

period, these variables were not retained in the final multivariable model as they were no longer significant at *p* < 0.1.

Discussion

This analysis has shown no statistically significant association between reporting less than seven out of seven intended PrEP doses (< 7/7ID) and reporting chemsex event periods among GBM. Although the direction of association is similar to that observed in the meta-analysis by Perera et al. (2017) between chemsex and ART non-adherence, their

work focussed on reported use of drugs associated with chemsex only (i.e. not chemsex behaviour) and was assessed at the individual level. Our study assessed event-level data and measured specific reporting of chemsex behaviour by PROUD participants. Although ART and PrEP are both regular HIV-related medications used by GBM, they are taken for different purposes, the former to treat existing HIV infection, and the latter to prevent HIV acquisition. Therefore, motivations to adhere optimally will likely vary.

There is a growing amount of evidence suggesting that not all chemsex episodes or behaviours are inherently harmful, and that many GBM can successfully integrate sexualised drug use into their lives, whilst still being in control of their actions (Bourne, Reid, Hickson, Rueda & Weatherburn, 2014). Some sources report chemsex users as having relatively controlled drug use and maintaining safe sex strategies whilst under the influence of chemsex drugs (Graf, Dichtl, Deimel, Sander & Stover, 2018), or completely compartmentalising chemsex from the rest of their lives (Ahmed et al., 2016), suggesting that daily PrEP adherence around chemsex events can be achievable. A follow-up study of the TAPIR PrEP trial also found "less problematic" substance use to be a significant predictor of adequate adherence (Hoenigl, Hassan et al., 2019) and a recent study among Australian GBM has reported increased concurrent use of methamphetamines, Viagra and Truvada®-PrEP, demonstrating how PrEP can be added alongside chemsex drug use to mitigate against HIV risk (Hammoud et al., 2018).

It is also possible that GBM engaging in chemsex use tailored PrEP adherence strategies around periods of chemsex to ensure doses are not missed. Adapted PrEP adherence strategies documented among GBM engaging in sexualised drug use include habitually taking PrEP tablets at the start of the day and taking with other medications or when preparing for sex (Closson, Mitty, Malone, Mayer & Mimiaga, 2018). A study among thirty American GBM using PrEP and reporting illicit drug use found that although all individuals found that methamphetamine use negatively impacted PrEP adherence ability, many used innovative ways of remembering daily doses; 60% reported using reminder devices or memory techniques and 6.7% reported borrowing from peers and partners (Storholm et al., 2017).

Significantly higher odds of reporting < 7/7ID within a follow-up period were observed from participants reporting at baseline that they may forget PrEP doses, compared to those perceiving they would find daily dosing easy. If PrEP becomes routinely available in England, it would be beneficial for clinicians to ascertain patients' perception of their ability to adhere to PrEP during initial consultations, and provide adherence support where this is required. Compared to those of white ethnicity and those in full-time employment, follow-up periods from individuals of Asian ethnicity and those unemployed at baseline, also had significantly higher odds of reporting < 7/7ID respectively, highlighting additional population groups that may benefit from adherence monitoring and support.

Strengths and limitations

This study benefitted from PROUD's large sample size and extensive collection of demographic, sexual behaviour and lifestyle data, allowing us to examine and adjust for multiple potential correlates and confounders for PrEP adherence. Our baseline data was also highly representative of the entire PROUD study population (Dolling et al., 2016), indicating that questionnaire exclusion criteria did not skew sample characteristics. As PROUD was delivered through thirteen sexual health clinics in six major English cities, this allows the results to be generalizable to urban populations of GBM at risk of HIV in England. These results may not, however, be generalizable to "low-risk" and non-urban GBM.

A major strength for this study was being able to use data that explicitly asked participants whether they engaged in chemsex using a specific chemsex definition, instead of using chemsex drug use as a proxy for the chemsex behaviour. Of the of 415 PROUD participants
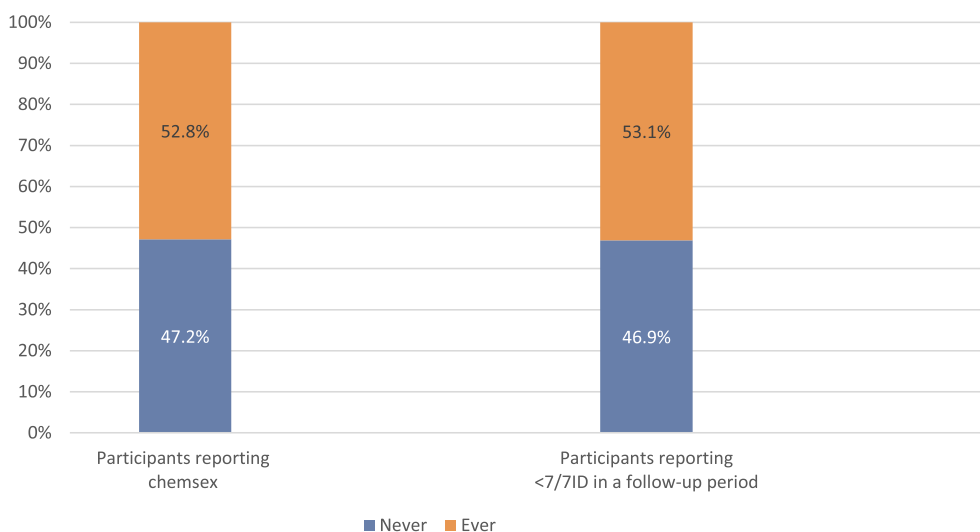
Fig. 1. Participant follow-up period PrEP adherence and chemsex reporting throughout trial follow-up (*N* = 388).

Table 3
Visit questionnaire sample characteristics (*N* = 1479 visit questionnaires).

Clinical	n	(%)
Illness preventing daily activities since last follow-up visit		
No	1359	(91.9)
Yes	120	(8.1)
Side effects to Truvada in last 30 days		
No	1433	(96.9)
Yes	38	(2.6)
Lifestyle		
Injected drugs since last follow-up visit		
No	1348	(91.1)
Yes	130	(8.8)
Snorted cocaine since last follow-up visit		
No	1182	(79.9)
Yes	297	(20.1)
Sexual behaviour		
Number of condomless anal sex partners since last follow-up visit		
0	77	(5.2)
1	362	(24.5)
2–5	606	(41)
> 6	433	(29.3)
Engaged in chemsex since last follow-up visit		
No	909	(61.5)
Yes	570	(38.5)
Engaged in group sex since last follow-up visit		
No	783	(52.9)
Yes	696	(47.1)
Used sex toys since last follow-up visit		
No	1124	(76)
Yes	355	(24)
Engaged in fisting since last follow-up visit		
No	1273	(86.1)
Yes	205	(13.9)
Follow-up period prep adherence		
< 7/7ID reported within last 90-day period		
No	1037	(70.1)
Yes	442	(29.9)

Number of follow-up visit questionnaires with missing data for side effects (8); injected drugs(1); number of condomless anal sex partners (1); fisting (1)

who completed acceptability questionnaires on the PROUD study design, 88% also reported feeling they could disclose sexual activity honestly, strengthening the validity of our exposure measurement (Gafos, Brodnicki, et al., 2017; . The longitudinal nature of PROUD meant multiple adherence data could be linked to multiple reported chemsex episodes over the study period; this would not have been possible if the analyses had been performed per participant, using an overall adherence measure for total individual follow-up time, and categorizing participants as chemsex and non-chemsex users. As both adherence and sexual behaviour may not be consistent for a participant throughout their trial follow-up, this was important to investigate, as much of the chemsex literature lacks event-level data (Edmundson et al., 2018). Visit questionnaires only asked participants one question about whether they engaged in chemsex, defined as using crystal methamphetamine, GHB/GBL or mephedrone immediately prior to, or during, sex. As the questionnaires did not ask participants to specify which of these three chemsex drugs were used, we were unable to assess associations between adherence and specific chemsex drug combinations.

Although some trials have observed self-reporting to provoke overestimations of adherence, it has also been demonstrated to be as accurate as refill and biological PrEP adherence measures in other trials (Amico et al., 2016; Lal et al., 2017; Montgomery et al., 2016; Vaccher et al., 2018) and self-reporting would have reduced social desirability bias compared to interviewing. Measuring adherence through missed doses before and after last condomless sex also meant adherence estimates were captured around critical risk periods for PrEP to be needed, however chemsex engagement itself could affect social desirability and recall bias when self-reporting adherence and recalling adherence, respectively.

An important drawback of this study is that reported chemsex events cannot be linked to the exact timeframe within the follow-up period where participants recorded missed pills. Further work is needed which asks GBM about PrEP adherence specifically during chemsex events. Our adherence classifications in Table 1 also meant that any single monthly adherence questionnaires reporting < 7/7ID would denote an entire follow-up period as reporting < 7/7ID. This would, however, most likely overestimate any negative impact of chemsex on adherence, which is contradictory to our findings. During data collection, we found that the majority of follow-up periods only had one linked monthly adherence questionnaire. As follow-up visits were supposed to be quarterly, this could mean there were months within a follow-up period where PrEP adherence was not captured on an adherence form. We are also aware that although follow-up visits were meant to be quarterly, in practise they did not always occur every 90 days, which was our cut-off for linking prior adherence forms to a follow-up visit date. Participants returning for follow-up visits were also almost exclusively doing so to obtain PrEP, hence participants who were adhering well to their PrEP may have been more likely to attend

Table 4

Factors associated with reporting less than 7 of 7 intended doses (< 7/7ID) in a follow-up period, from univariable and multivariable logistic regressions (N = 1479 follow-up visit questionnaires, N = 388 participants)[a].

		Reporting < 7/7ID in a follow-up period						
		Univariable					Multivariable	
		Total[c]	n[d]	(%)[e]	Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Baseline enrolment questionnaire variables - DEMOGRAPHICS								
Gender	Male	1465	442	(30.17%)				
	Transgender	-		(0.00%)				
Sexuality	Gay/homosexual	1397	416	(29.78%)	1	0.851		
	Straight/Bisexual/Other	66	21	(31.82%)	1.10 (0.41–2.99)			
Ethnicity	White	1196	336	(28.09%)	1		1	
	Black	51	22	(43.14%)	1.94 (0.78 –4.80)	0.151	1.78 (0.71 – 4.49)	0.222
	Asian	69	30	(43.48%)	1.97 (0.84 –4.63)	0.120	3.12 (1.20 – 8.21)	*0.020*[b]
	Other	151	50	(33.11%)	1.27 (0.76 –2.12)	0.368	1.13 (0.64 – 1.97)	0.678
Born in the UK	No	569	171	(30.05%)	1	0.977		
	Yes	905	271	(29.94%)	0.99 (0.70 –1.42)			
Age (years)[f]	18–25	148	62	(41.89%)	2.73 (1.48–5.04)	*0.001*[b]		
	26–35	532	181	(34.02%)	1.95 (1.21 –3.16)	*0.006*[b]		
	36–45	435	123	(28.28%)	1.49 (0.90 –2,47)	0.118		
	> 45	364	76	(20.88%)	1			
Maximum education level[f]	University degree or higher	965	282	(29.22%)	1			
	A levels / equivalent	201	65	(32.34%)	1.16 (0.70 –1.91)	0.565		
	GCSEs / equivalent	149	36	(24.16%)	0.77 (0.40–1.49)	0.441		
	Vocational training/other qualifications	92	32	(34.78%)	1.29 (0.67–2.49)	0.444		
	Still in full-time education	39	20	(51.28%)	2.55 (1.05–6.21)	*0.039*[b]		
	Finished education with no qualifications	29	7	(24.14%)	0.77 (0.24–2.44)	0.658		
Employment status	Employed/self-employed full time	1050	298	(28.38%)	1		1	
	Employed/self-employed part time	134	46	(34.33%)	1.32 (0.77–2.27)	0.318	1.48 (0.81–2.70)	0.203
	Student	107	43	(40.19%)	1.70 (0.88 –3.29)	0.118	1.57 (0.75 –3.30)	0.233
	Unemployed	77	30	(38.96%)	1.61 (0.72–3.62)	0.248	2.31 (1.06–5.04)	*0.036*[b]
	Retired	70	15	(21.43%)	0.69 (0.24–1.99)	0.491	0.53 (0.12 –2.35)	0.403
	Other	30	10	(33.33%)	1.26 (0.45–3.50)	0.655	0.53 (0.23–1.22)	0.138
Relationship status	In relationship, living with partner	429	110	(25.64%)	1			
	In relationship, not living with partner	192	55	(28.65%)	1.16 (0.64 –2.13)	0.621		
	Not currently in an ongoing relationship	851	277	(32.55%)	1.40 (0.92–2.12)	0.114		
Baseline enrolment questionnaire variables - Lifestyle								
Recreational drug use in past 3 months	No	371	114	(30.73%)	1	0.718		
	Yes	1071	312	(29.13%)	0.93 (0.61–1.40)			
Alcohol drinking frequency	Never/Once	169	46	(27.22%)				
	2 or 3 times a month	312	103	(33.01%)	1.32 (0.68 –2.55)	0.412		
	Once or twice a week	483	133	(27.54%)	1.02 (0.53 –1.95)	0.962		
	3 or 4 times a week	286	96	(33.57%)	1.35 (0.67 –2.71)	0.396		
	Nearly every day/Daily	190	48	(25.26%)	0.90 (0.43 –1.90)	0.790		
Units of alcohol drank on a typical drinking day	0–4	642	202	(31.46%)	1			
	5–9	442	129	(29.19%)	0.90 (0.60 –1.34)	0.597		
	≥10	212	58	(27.36%)	0.82 (0.50–1.34)	0.431		
Perception of adherence ability throughout the trial	Will find easy to remember to take drug daily	966	249	(25.78%)	1	*0.002*[b]	1	*0.001*[b]
	Might forget to take doses/ will find daily dosing difficult	462	175	(37.88%)	1.76 (1.23–2.51)		1.88 (1.28 –2.75)	
Follow-up questionnaire variables - Clinical								
Illness preventing daily activities since last visit	No	1359	398	(29.29%)	1	0.116		
	Yes	120	44	(36.67%)	1.40 (0.92–2.12)			
Side effects to Truvada in last 30 days	No	1433	426	(29.73%)	1	0.599		
	Yes	38	10	(26.32%)	0.84 (0.45 –1.59)			
Follow-up questionnaire variables - Lifestyle								
Injected drugs since last visit	No	1348	399	(29.60%)	1	0.684		
	Yes	130	42	(32.31%)	1.14 (0.62 –2.09)			
Snorted cocaine since last visit	No	1182	343	(29.02%)	1	0.25		
	Yes	297	99	(33.33%)	1.22 (0.87–1.72)			
Follow-up questionnaire variables – Sexual behaviour								
Number of condomless anal sex partners since last visit	0	77	20	(25.97%)	1			
	1	362	116	(32.04%)	1.34 (0.74 –2.43)	0.327		
	2–5	606	176	(29.04%)	1.17 (0.64–2.14)	0.619		
	≥6	433	130	(30.02%)	1.22 (0.64 –2.32)	0.539		
Chemsex engagement since last visit	No	909	253	(27.83%)	1	0.137	1	0.168
	Yes	570	189	(33.16%)	1.29 (0.92–1.79)		1.29 (0.90 –1.87)	
Group sex since last visit	No	783	249	(31.80%)	1	0.194		
	Yes	696	193	(27.73%)	0.82 (0.61–1.10)			

Table 4 (*continued*)

		Reporting < 7/7ID in a follow-up period						
		Univariable					Multivariable	
		Total[c]	n[d]	(%)[e]	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Used sex toys since last visit	No	1124	334	(29.72%)	1	0.843		
	Yes	355	108	(30.42%)	1.03 (0.74–1.44)			
Fisting since last visit	No	1273	386	(30.32%)	1	0.434		
	Yes	205	55	(26.83%)	0.84 (0.55–1.29)			

[a] Missing data from enrolment and visit questionnaires not included in logistic regression analyses.
[b] Association considered significant (*P* < 0.05).
[c] total number of follow-up visit questionnaires reporting row variable.
[d] total number of follow-up visit questionnaires reporting row variable and < 7/7ID within linked 90-day follow-up period.
[e] Row percentages based on non-missing data.
[f] Not included retained in final multivariable logistic regression analyses as p-value > 0.1 in multivariable model.

and contribute to our substudy cohort, potentially leading to an underestimation of any associations with reporting < 7/7ID.

Our adherence measure may seem stringent due to evidence that taking PrEP ≥4/7 days a week is sufficient protection against HIV acquisition during anal sex (Anderson et al., 2012; (Grant et al., 2014)). The same analysis was repeated with missing ≥4/7 days of intended PrEP doses around last CAI as the adherence outcome measure, and no significant association with chemsex was found, however the sample size was too small to provide robust estimates due to the low proportion of follow-up periods (95/1479) that qualified for inclusion.

Chemsex reporting was clinician-completed at follow-up visits, meaning chemsex may have been underreported due to social desirability or acquiescence bias. Participants were asked about their last CAI in the 30 days prior in order to maximise recall for the adherence data, but participants were asked about chemsex activity since last follow-up visit (approx. quarterly), potentially introducing recall bias. Some participants reported difficulty in remembering sexual activity during recall periods, and finding questionnaires laborious and the monthly adherence questionnaires specifically hard to remember to complete (Gafos, Brodnicki, et al., 2017; Nonetheless, 82% of participants completing acceptability questionnaires reported not minding completing the monthly adherence forms (Gafos, Brodnicki, et al., 2017;

As PROUD participants had regular contact with clinics and frequent questionnaires reviewing adherence, the Hawthorne effect (Wickstrom & Bendix, 2000) could have influenced the optimal adherence profiles observed, through modified behaviour provoking improved adherence, and not reflecting true adherence whilst not under observation. Further insight into how chemsex users adhere to PrEP outside a trial setting is needed. As this substudy only measured the implementation component of adherence, it would be beneficial to measure initiation and persistence of PrEP adherence in the context of chemsex, as these adherence components are important in terms of risk of HIV acquisition Gafos, White, et al., 2017; Vrijens et al., 2012). As participants were not paying for their PrEP, their adherence may also change if there is an individual financial cost.

Conclusion

These analyses suggest that chemsex is not a barrier to optimal PrEP adherence among the PROUD study cohort, and that PrEP remains a feasible and effective prevention tool among GBM in England engaging in a sexual behaviour that is associated with HIV risk. These data strengthen evidence of PrEP's effectiveness as a key combination prevention method in the UK's progress towards ending the HIV epidemic. Whilst regular monitoring is recommended to help chemsex users manage their risk of chemsex associated harms, including HIV

acquisition, it would be pertinent for clinicians to risk assess ethnic minority and unemployed individuals, or those with perceived adherence difficulties during initial PrEP prescribing, to ascertain if adherence support is needed.

Data Sharing

The PROUD data is held at MRC CTU at UCL, which encourages optimal use of data by employing a controlled access approach to data sharing, incorporating a transparent and robust system to review requests and provide secure data access consistent with the relevant ethics committee approvals. All requests for data are considered and can be initiated by contacting proud.mrcctu@ucl.ac.uk.

The basis for this project originated from a MSc research project undertaken by COH at the London School of Hygiene & Tropical

Medicine (LSHTM), and ethical approval for this MSc project was granted by LSHTM. Data was accessed from University College London (UCL) and the Medical Research Council (MRC) Clinical Trials Unit (CTU) through a clinical data disclosure agreement and PROUD sub-study proposal agreement.

Appendix A

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