Self-start HIV postexposure prophylaxis (PEPSE), to reduce time to first dose and increase efficacy

Julie M Fox [ID],[1,2] Ming Jie Lee [ID],[3] Cassandra Leach Fairhead,[4] Lesedi m Ledwaba-Chapman,[2] Achyuta V Nori [ID],[1] Orla McQuillan,[5] Yanzhong Wang,[2] Amanda Clarke,[6] Anatole Menon-Johansson[1]

ABSTRACT

Background Effectiveness of HIV postexposure prophylaxis (PEPSE) correlates with speed of uptake following HIV exposure. Time to first dose has not improved in the UK for over 10 years. On-demand pre-exposure prophylaxis (PrEP) has shown that people can self-start medication for HIV prevention.
We hypothesised that advanced provision of PEPSE (HOME PEPSE) for men who have sex with men (MSM) to self- initiate would reduce time to first dose following HIV exposure.

Methods Phase IV, randomised, prospective, 48-week, open-label study was carried out. MSM at medium risk of acquiring HIV were randomised (1:1) to immediate or deferred standard of care (SOC) HOME PEPSE. Every 12 weeks, participants self-completed mental health/risk behaviour surveys and had HIV/sexually transmitted infection (STI) testing.
HOME PEPSE comprised a 5-day pack of emtricitabine/tenofovir disoproxil fumarate/maraviroc 600 mg once daily initiated following potential exposure to HIV. If taken, participants completed a risk survey; PEPSE continuation was physician directed. Primary outcome was time from potential exposure to HIV to first PEPSE dose.

Findings 139 participants randomised 1:1; 69 to immediate HOME PEPSE and 70 to deferred HOME PEPSE. Median age 30 years (IQR 26–39), 75% white, 55% UK born and 72% university educated. 31 in HOME PEPSE and 15 in SOC arm initiated PEPSE. Uptake of HOME PEPSE was appropriate in 27/31 cases (87%, 95% CI: 71% to 95%). Median time from exposure to first dose was 7.3 hours (3.0, 20.9) for HOME PEPSE and 28.5 hours (17.3, 34.0) for SOC (p<0.01). HOME PEPSE was well tolerated with no discontinuations.
No significant differences in missed opportunities for PEPSE uptake, sexual behaviour or bacterial STI infections between treatment arms.

Interpretation HOME PEPSE reduced the time from exposure to first-dose PEPSE by 21+ hours, with no impact on safety. This significantly improves the efficacy of PEPSE and provides an option for people declining PrEP.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Postexposure prophylaxis (PEPSE) must be taken within 72 hours after possible exposure to HIV.
⇒ Macaque data suggest that within 24 hours is more effective than later.
⇒ In the UK, the average time to first dose is 24 hours.
⇒ Currently, PEPSE can only be obtained from sexual health clinics or accident and emergency units.

WHAT THIS STUDY ADDS

⇒ Self-start HOME PEPSE was safe to take and reduced the time from potential exposure to HIV to first PEPSE dose, from 29 hours to 7 hours that is, by 21 hours; this may have a significant benefit for effectiveness.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Self-start HOME PEPSE packs can be included as part of the toolbox of HIV prevention.

INTRODUCTION

The key to successful HIV prevention is availability and choice: as more options emerge, people need to be able to use them in the most effective way.

Postexposure prophylaxis for sexual exposure (PEPSE) was the original pericoital antiretroviral therapy (ART) intervention and has been available for over 20 years. Despite the widespread availability of highly effective pre-exposure prophylaxis (PrEP), demand for PEPSE remains high particularly among men who have sex with men (MSM).[1] To date, it is only available through clinic and emergency health services with delays in access well described.[2] In the UK, the median time to first PEPSE dose is 24 hours[3] and despite campaigns promoting PEPSE among MSM, no improvements in time to PEPSE initiation have been observed.[4] Barriers to access include limited out-of-hours availability, poor knowledge of PEPSE and negative experiences accessing PEPSE (including time delays and healthcare professional attitudes).[2 3]

The efficacy of PEPSE correlates with the time from exposure to PEPSE initiation,[5–10] with guidelines recommending PEPSE uptake within 72 hours of exposure.[11 12] This 72-hour window may be too long for receptive anal sex whereby following rectal simian immunodeficiency virus (SIV) challenge, PEPSE showed no protection if taken >24 hours postexposure and maximum protection within 2 hours of exposure.[13]

Approaches to improving the time to PEPSE uptake are therefore required. Self-initiated

on-demand PrEP and emergency contraception are already provided by health services but PEPSE has remained out of this scope. In Brazil, a 4-day PEPSE self-initiated starter pack was evaluated in a single-arm study and showed no negative behavioural effects but was not able to directly measure efficacy or time to first dose.[14]

We hypothesised that advanced provision of a 5-day PEPSE starter pack (HOME PEPSE) for MSM to self- initiate would reduce time to first dose following HIV exposure, be taken appropriately (according to UK PEPSE guidelines) and not impact HIV risk behaviour. The PEPSE regime, tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)/maraviroc once daily, was used to evaluate tolerability with potential for those who experienced side effects with first-line PEPSE regimes.[15]

METHODS

Study design and participants

A phase IV, randomised, prospective, open-label study was carried out whereby MSM at medium risk of acquiring HIV were randomised (1:1) to immediate HOME PEPSE or deferred standard of care (SOC) HOME PEPSE. Those allocated to receiving immediate HOME PEPSE, received a 5-day PEPSE pack and were followed up for 48 weeks. Those on deferred arm, accessed PEPSE through SOC (sexual health clinics or accident and emergency units) for 48 weeks then received HOME PEPSE for 24 weeks, ending the study at 72 weeks.

Participants were recruited from London (Guy's and St Thomas' NHS Foundation Trust), Brighton (Brighton and Sussex NHS Trust) and Manchester (Manchester University Hospitals NHS Trust) between January 2018 and October 2019. Inclusion criteria included male gender at birth, HIV negative within 4 weeks prior to or on day of randomisation and at medium risk of HIV acquisition. Medium risk was defined as: any one of: (a) condomless anal sex with a male on >1 occasion within the 90 days prior to randomisation, (b) bacterial sexually transmitted infection (STI) within the 90 days prior to randomisation, (c) use of PEPSE in the 12 months prior to randomisation following possible exposure to HIV through unprotected anal intercourse with a male. Participants assessed to be high-risk for HIV acquisition during the trial were referred for PrEP. Participant taking PrEP were not eligible to take part. Participants were followed up every 12 weeks for an STI screen and risk behaviour survey and all received counselling and written instructions when to initiate PEPSE according to UK guidelines.[11] Those initiating HOME PEPSE were instructed to contact the trial team and be seen to confirm that PEPSE uptake was appropriate and the remaining 21 days PEPSE dispensed.

For those taking PEPSE, the time from exposure to first dose was recorded and continuation of PEPSE was physician directed according to UK guidelines. Participants initiating HOME PEPSE completed diaries for the first 5 days to report adherence and solicited adverse reactions.

Loss to follow-up

Forty-eight people were lost to follow-up during the trial (26 HOME PEPSE and 22 SOC) (table 1). Participants who withdrew in the HOME PEPSE arm were slightly younger, more likely to be white, be in education, used PEPSE in the previous 12 months, less likely to work full time, have a university degree, be in a relationship and have STIs diagnosed in the previous 12 months (online supplemental tables 1 and 2). The demographics and sexual behaviour of those withdrawing was not different between study arms. Retention was influenced by an 18-month

Table 1 Summary of study withdrawals

Study period	Reason for withdrawal	
	HOME PEPSE N=69 randomised	SOC N=70 randomised
Baseline to week 48	12 Lost to follow-up 6 Withdrew consent 8 Started PrEP	11 Lost to follow-up 4 Withdrew consent 5 Started PrEP 2 HIV diagnosis
	26 Total withdrawals	22 Total withdrawals
Week 48 to week 72	N/A	4 Lost to follow-up 1 Withdrew consent 3 Started PrEP 1 Uncompliant with protocol
		9 Total withdrawals

N/A, not available; PEPSE, postexposure prophylaxis; PrEP, pre-exposure prophylaxis; SOC, standard of care.

stop in clinic visits due to SARS-CoV-2 and by participants being less invested to attend follow-up visits as they were not attending to collect study medication. Sixteen participants were withdrawn in order to start oral PrEP.

Outcomes

The primary outcome was time from exposure to first dose of PEPSE. Secondary outcomes were appropriateness of HOME PEPSE use, changes in risk behaviour, missed opportunities for PEPSE, HIV seroconversions (STI screening at every visit) and PEPSE side effects. A missed opportunity for PEPSE was defined as a sex act whereby PEPSE would have been recommended according to British Association for Sexual Health and HIV PEPSE guidelines.

Data for each participant from baseline to week 48 were included and expected person-years of observation was calculated assuming each participant attended all study visits. For participants that acquired HIV, we censored person-years of observation at the date of the first positive HIV test. For those remaining HIV negative, we censored at the date of the last study visit they attended.

Sample size

Using the UK-PEP uptake data (Benn communication), we determined that five PEPSE users in each group were needed to detect a 24-hour difference between the arms with 90% power at 5% significant level using a one-sided two-sample t-test. The total number of people to be recruited to achieve 5–10 people in each arm accessing PEPSE was estimated based on the 17% annual PEPSE uptake observed in the Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD) study.[16] Accounting for loss to follow-up, we calculated that 70 people in each arm needed to be recruited.

Statistical analysis

Randomisation allocation was determined using block randomisation via the MedSciNet system. All randomised participants were included in the final analysis on an intention-to-treat basis. We compared the time to first dose between treatment arms using a two-sided Mann-Whitney U test. Only appropriate uses of PEPSE were included in the analysis. To ensure observations were independent, the median time to first dose was used for participants that accessed PEPSE multiple times. We performed a sensitivity analysis using only the first and all observations to see if our treatment of participants with multiple PEPSE accesses was
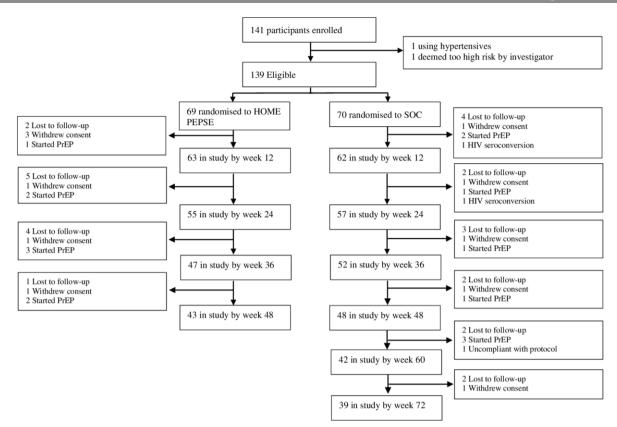
Figure 1 Consort diagram

robust. Appropriate use of PEPSE was summarised using counts and percentages, 95% CIs were calculated for the percentages using the Wilson interval without continuity correction.

Risk behaviour between treatment arms was compared using a two-sided Mann-Whitney U test. The STI and HIV incidence rates between treatment arms was compared using the incidence rate difference. We calculated exact 95% CIs for the incidence.[17] Questionnaire responses describing satisfaction with HOME PEPSE were summarised using counts and percentages. Associations between PEPSE uptake and lifestyle factors were assessed using Spearman's rank correlation. All analysis was performed with R (V.4.1.3).

Role of the funding source
The funders of the study had no role in the study design, data collection, data analysis, data interpretation or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS
Participant characteristics
One hundred thirty-nine individuals were randomised: 69 HOME PEPSE and 70 in the deferred SOC arm (figure 1figure 1). The median age was 30 years (IQR 26–39), 75% white ethnicity, 55% UK born and 72% university educated (table 2). Baseline characteristics were reasonably balanced between the two arms except for those in the HOME PEPSE arm were less likely to report a rectal STI, more likely to have entered the study based on recent PEPSE use and less likely to be born in the UK. The median number of condomless anal sex acts with a partner of unknown HIV status was two at baseline.

Safety and adherence
No serious adverse events were reported. Solicited adverse events from the first 5 days after starting HOME PEPSE showed that headache (11%) and dizziness (11%) were the most reported systemic reactions. Once-daily maraviroc was well tolerated—no participant chose to switch to a twice-daily dosing or stop HOME PEPSE because of side effects and no postural hypotension was observed.

Self-reported adherence to the self-start HOME PEPSE pack was 100% in all participants.

Uptake of PEPSE
In the first 48 weeks, 22/69 (32%) people started HOME PEPSE and 13/70 (19%) people started SOC PEPSE (p=0.071). Of these, six people in HOME PEPSE arm and two people in deferred arm accessed PEPSE more than once. Uptake of HOME PEPSE was appropriate in 27/31 cases (87%, 95% CI: 71% to 95%). The median time from exposure to first dose was 7.3 hours (3.0, 20.9) for HOME PEPSE and 28.5 hours (17.3, 34.0) for SOC (p<0.01). One participant in each arm took PEPSE >50 hours after potential HIV exposure (figure 2).

Of those initiating HOME PEPSE, 19/22 (85%) kept it at home, 1/22 kept it in a bag and 2/22 in other places.

Overall, 2/69 (3%) of people reported giving their HOME PEPSE to other people to use.

Speed of uptake was not associated with any sociodemographic factor but delays were associated with agreeing with the statement "I would worry about long-term effects of these medicines" (0.53 (95% CI: 0.18 to 0.76, p=0.006)) and also for the statement "I would like more intimacy in my life (0.38 (95% CI: 0.04 to 0.64, p=0.031)).

Table 2 Baseline demographic characteristics			
	Entire sample N=135	HOME PEPSE N=66	SOC N=69
Age at registration	30 (26, 39)	30 (27,40)	29 (26,37)
Age category (years)			
<25	19 (14%)	8 (12%)	11 (16%)
≥25	116 (86%)	58 (88%)	58 (84%)
Ethnicity			
White/Caucasian	101 (75%)	52 (79%)	49 (71%)
Black or African	9 (7%)	4 (6%)	5 (7%)
Oriental	6 (4%)	2 (3%)	4 (6%)
Other	19 (14%)	8 (12%)	11 (16%)
University degree	97 (72%)	45 (68%)	52 (75%)
Employment status			
Full time	98 (73%)	46 (70%)	52 (75%)
Part time	9 (7%)	4 (6%)	5 (7%)
Education	20 (15%)	11 (17%)	9 (13%)
Unemployed	8 (6%)	5 (8%)	3 (4%)
Born in the UK	74 (55%)	31 (47%)	43 (62%)
Not currently in a relationship	88 (65%)	43 (75%)	45 (75%)
Circumcised	37 (27%)	19 (29%)	18 (26%)
STI diagnosed in past 12 months			
Any	75 (56%)	34 (52%)	41 (59%)
Bacterial*	71 (53%)	32 (49%)	39 (57%)
Rectal†	42 (31%)	17 (26%)	25 (36%)
Number of HIV tests in past 12 months	3 (2, 4)	3 (2, 4)	3 (2, 4)
Used PEPSE in past 12 months	53 (39%)	30 (46%)	23 (33%)

Data presented as median (IQR) or n (%). Differences between the baseline characteristics of the arms ≥10% are highlighted in blue. Four participants (three in HOME PEPSE and one in SOC arm) did not complete the Baseline Questionnaire and were not included in the table. Eighteen participants did not complete the All Visits Questionnaire at baseline so were not included in the summary of relationship status.
*Gonorrhoea, chlamydia or syphilis.
†Rectal gonorrhoea or rectal chlamydia.
PEPSE, postexposure prophylaxis; SOC, standard of care; STI, sexually transmitted infection.

Risk behaviour

There was no difference between the arms for condomless sex acts with partners of unknown HIV status except for week 12, where SOC reported more acts than the HOME PEPSE arm (p=0.023). There was no significant difference in the incidence of bacterial STI between treatment arms over time (p=0.829).

In 98 person-years follow-up, 2 people (both in SOC) acquired HIV. One individual had repeatedly been advised to start PrEP due to ongoing high-risk sexual behaviour. The other participant was randomised to SOC and then immediately lost to follow-up until he tested positive elsewhere and subsequently attended for a withdrawal visit at around week 36.

Missed opportunities for PEPSE uptake

There was no difference between study arms in number of missed opportunities for PEPSE uptake. Twelve people reported >10 missed opportunities for PEPSE and seven of these people were in the SOC arm. Previous PEPSE use was not associated with less missed opportunities for PEPSE uptake (p=0.582).

DISCUSSION

This randomised controlled trial shows that providing medium-risk MSM with HOME PEPSE leads to a massive 20-hour reduction in time from sex to first dose of PEPSE. This significant improvement in speed of PEPSE uptake meant that most people took PEPSE within 24 hours of potential exposure which is associated with improvement in PEPSE efficacy compared with PEPSE initiated after 24 hours.[13 18] HOME PEPSE was taken safely without any negative consequences observed.

HOME PEPSE is therefore a feasible HIV prevention strategy for individuals at modest risk of HIV.

Although PrEP is highly effective and widely available in many settings, there remains a large number of people who are at risk of HIV in whom PrEP is either not wanted, not tolerated or not suitable as planned sex does not occur. In these individuals, HOME PEPSE could be an alternative option to support them in the event of a risk event to access an effective HIV prevention in a timely manner. Over 80% of participants kept their HOME PEPSE pack at home. To further increase speed of uptake, counselling to keep some tablets on person may form part of HOME PEPSE delivery recommendations.

This study focused on 5-day event based HOME PEPSE and showed excellent adherence and safety. With on-demand PrEP data highlighting that shorter course PEPSE may be sufficient, a short-course HOME PEPSE option for postcoital prevention will become increasingly possible. Short-course PEPSE efficacy trials are urgently needed.

Worryingly, compared with 2006,[19] we show that speed to first PEPSE dose through routine services has not improved at all. HOME PEPSE could solve this long-standing access delay. Missed opportunities for PEPSE uptake occurred in both groups and were limited to a small group of participants. Identifying these high-risk individuals for greater support and understanding their reasons for not accessing PEPSE or PrEP is essential. In contrast to the provision of PrEP to men[20] and similar to the advanced provision of emergency contraception to women,[21] HOME PEPSE was not associated with increased risk behaviour.

The strength of the study is the power obtained. The use of the deferred randomisation design and time to first dose as an efficacy proxy is an effective approach to studying PEPSE efficacy. Furthermore, the north-south geographical spread of large UK NHS centres for HIV prevention strengthens the results and generalisability. Compared with the PROUD study, our cohort reported less risk behaviour but remained at risk for HIV infection.[16] We were able to recruit a medium-risk cohort, shown by the risk behaviour being less than observed in the PROUD study but still at risk of HIV infection.

There are several limitations to this study. First, this was a realtevely small study and inferences made with caution. Second, the dropout rate observed was significant but did not affect the power of the primary outcome result. A third limitation is that this was a male-only study and as such results may not be extrapolated to other populations. However, as non-occupational PEPSE has been shown to be cost-effective only for receptive anal intercourse, this is the target group and thus our results have international significance.[18 22 23] Finally, we showed that TDF/FTC/maraviroc taken once a day had a favourable safety profile with no hypotension observed.

Conclusion

HOME PEPSE was taken appropriately by MSM, and dramatically reduced time from exposure to first dose, with no impact on safety. This approach may be incorporated into HIV prevention
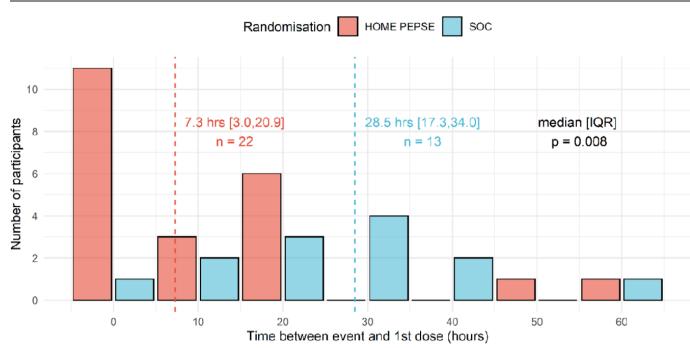
Figure 2

guidelines and increase the toolbox of prevention for at-risk people.

ORCID iDs
Julie M Fox http://orcid.org/0000-0002-0583-8019
Ming Jie Lee http://orcid.org/0000-0002-5244-0070
Achyuta V Nori http://orcid.org/0000-0002-3549-8289

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