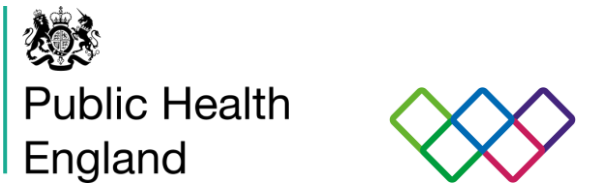

TRIAL PROTOCOL

Protocol Title:	PrEP Impact Trial: A pragmatic health technology assessment of PrEP and implementation
Short Title:	PrEP Impact Trial
Protocol Number	SSCR104
Version	3.0, 19 Jun 2018
Chief Investigator:	Dr Ann Sullivan
Sponsor:	Chelsea and Westminster Hospital NHS Foundation Trust

GCP Compliance Statement
This trial will be conducted in compliance with the protocol, the principles that have their origin in the Declaration of Helsinki 2013 and all applicable regulatory requirements

Synopsis

Title:	PrEP Impact Trial: A pragmatic health technology assessment of PREP and implementation
Short title:	PrEP Impact Trial
Protocol Number:	SSCR104
Trial drug:	Tenofovir Disoproxil (TD)/ Emtricitabine (FTC) The generic product, manufactured by Mylan, is bio-equivalent to the branded product (Truvada) and is provided off label for event-based dosing in accordance with established practice supported by clinical evidence.
Background and rationale:	New prevention efforts are required to reduce the estimated 4,700 incident HIV infections occurring annually in England, of which 2,800 occur among men who have sex with men (MSM). Tenofovir containing regimens used as HIV PrEP are highly effective at reducing HIV acquisition. The data from the PROUD trial in the UK reinforced the evidence for efficacy, though the relatively small sample prevented the results being generalised to all GU clinic attendees and left unanswered key questions about large-scale use of PrEP. The PrEP Impact Trial aims to address these outstanding questions about PrEP, eligibility, uptake and duration of use of PrEP through expanding the assessment to the scale required to obtain sufficient data. In addition the new trial will assess under real world conditions the impact of PrEP on new HIV diagnoses and on sexually transmitted infections, compared to historical controls. The results will inform service commissioners about how to support clinical and cost effective PrEP access in the future.
Aim:	To test the hypothesis that consensus estimates using best available data on PrEP need, uptake and duration of use are correct and, if not, provide accurate measures across the complexity of the population likely to benefit from this medicinal product. This is required to determine the commissioning of future access to PrEP.
Objectives:	**1.** To measure PrEP-eligibility, PrEP-uptake, duration of PrEP-eligibility and duration of PrEP-use (PrEP prevention care continuum) among Genitourinary Medicine (GUM) clinic attendees, **2.** To determine whether or not incident HIV infections in trial participants are due to non-adherence or biological failure, **3.** To measure change over time in HIV diagnoses and incidence rate in those at high HIV risk,

	4. To measure change over time in bacterial STI diagnoses and incidence rate in those at high HIV risk, **5.** To measure the PrEP 'prevention care continuum' by clinic throughput and in different regions.
Design:	Prospective open label health technology assessment.
Treatment of participants:	Two prophylaxis schedules for PrEP will be available for MSM and trans-women populations: daily or event-based dosing (EBD). EBD cannot be recommended for heterosexuals and transgender men as this technology has not been assessed for effectiveness, nor for participants with active hepatitis B infection due to the risk of hepatic flares on withdrawal. Therefore, daily PrEP will be offered to these participants.
Methodology:	Potentially eligible participants will be identified following a clinical risk assessment primarily during routine sexual health clinic visits, but may be contacted following review of the clinic database. Other methods such as outreach activities, and through community organisations and social media, may be used to identify potentially eligible patients for referral to a local genitourinary medicine (GUM) clinic. Participants who consent to enrol in the trial will be allocated a trial ID and be prescribed PrEP at a GUM clinic. Routine clinic records and the standard data routinely extracted into the national GUM Clinic Activity Dataset (GUMCAD) database will be used to capture clinical and prescribing data. The subject ID will be linked to relevant GUMCAD record using the subject ID number, SOUNDEX code and semi-anonymised GUM clinic number in the trial database. Adverse events will be reported using the 'Yellow card' system and logged in the trial database for central monitoring. Dispensing data will also be collected for central monitoring. In line with national guidance and the evidence from efficacy trials, at each visit participants will be offered PrEP as part of an active risk reduction intervention, including health education and safer sex promotion, to reduce and modify high risk behaviour. This may include the provision of free condoms, behaviour change interventions, other biomedical interventions such as post-exposure prophylaxis where relevant, the diagnosis and treatment of sexually transmitted infections (STIs), and regular HIV testing. Participants who are starting PrEP are recommended to have a one month safety check (which can be done in person, on the phone or via email) and then

	quarterly visits depending on ongoing risk, with clinical risk assessments and tests performed according to the visit schedule and recommended clinical practice.
Planned Sample Size:	13,000 participants
Participant population:	The participant populations for this trial will be men and women attending GUM clinics who belong to one of three populations recognised to be at high risk for HIV, namely: **A. Men (cisgender and transgender) and transgender women who:** 1. Have sex with men 2. Have had an HIV negative test during an earlier episode of care in the preceding year 3. Report condomless intercourse (excluding oral) in the previous 3 months 4. Affirm their likelihood of having condomless intercourse (excluding oral) in the next 3 months **B. HIV negative partners of an HIV positive person when:** 1. The HIV positive partner is not known to be virally suppressed (<200 copies/ml for 6 months or more) 2. Condomless intercourse (excluding oral) is anticipated before treatment of the HIV positive partner takes effect **C. HIV negative persons who:** 1. Are clinically assessed and considered to be at similar high risk of HIV acquisition as those with a serodiscordant partner who is not known to be virally suppressed
Inclusion Criteria:	**Participants** will be considered eligible for trial enrolment if they fulfil all the following individual eligibility criteria: 1) Belong to one of the three high HIV risk populations described above; 2) Aged 16 years or over (no upper limit); 3) Considered to be HIV negative on the day of enrolment; 4) Willing and able to provide informed consent; 5) Willing to adhere to the recommended PrEP regimen; 6) Willing to re-attend the trial clinic at appropriate intervals for risk assessment
Exclusion Criteria	Participants will not be considered eligible for trial enrolment if they fulfil any of the following exclusion criteria:

	1) An acute viral illness that could be due to HIV seroconversion 2) Any contraindication to Tenofovir Disoproxil (TD)/ Emtricitabine (FTC)- according to the current package insert or SmPC
Number of Prescribing Centres:	Prescribers that meet agreed site participation standards will be selected from the 232 Genitourinary Medicine (GUM) clinics in England. The decision to include a prescriber will be made by the sponsor. The aim is to establish a wide geographical spread of trial sites with prescribers in urban and rural settings; in high, medium and low throughput clinics; and in clinics with predominantly MSM and non-MSM eligible populations.
Duration of the trial:	4.5 years (33 month recruitment period)
Dose and Route of Administration:	Drug: Tenofovir Disoproxil (TD)/ Emtricitabine (FTC). Each film-coated tablet contains 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (as maleate). Regimen: Daily or event-based regimens (EBD). Daily involves taking 245 mg TD and 200mg FTC once a day. EBD will involve taking a double dose before sex and then single doses 24 and 48 hours after the initial dose. EBD is not recommended for heterosexual men, heterosexual women, and transgender men due to lack of trial efficacy data to support this regimen in these risk groups. Route of administration: Oral
Trial Outcomes:	1. Proportion of GUM clinic attendees that meet PrEP eligibility criteria, the proportion that is prescribed PrEP per year and the duration of PrEP-eligibility and PrEP-use among users. 2. HIV and STIs: a. HIV diagnoses reported by sites and identified through the national surveillance dataset b. STI diagnoses (gonorrhoea, chlamydia, syphilis and hepatitis C) reported in the national surveillance dataset 3. Adverse Events a. Serious suspected adverse drug reactions reported using the yellow card system b. Antiretroviral resistance associated mutations in participants with incident HIV infection

GENERAL TRIAL INFORMATION

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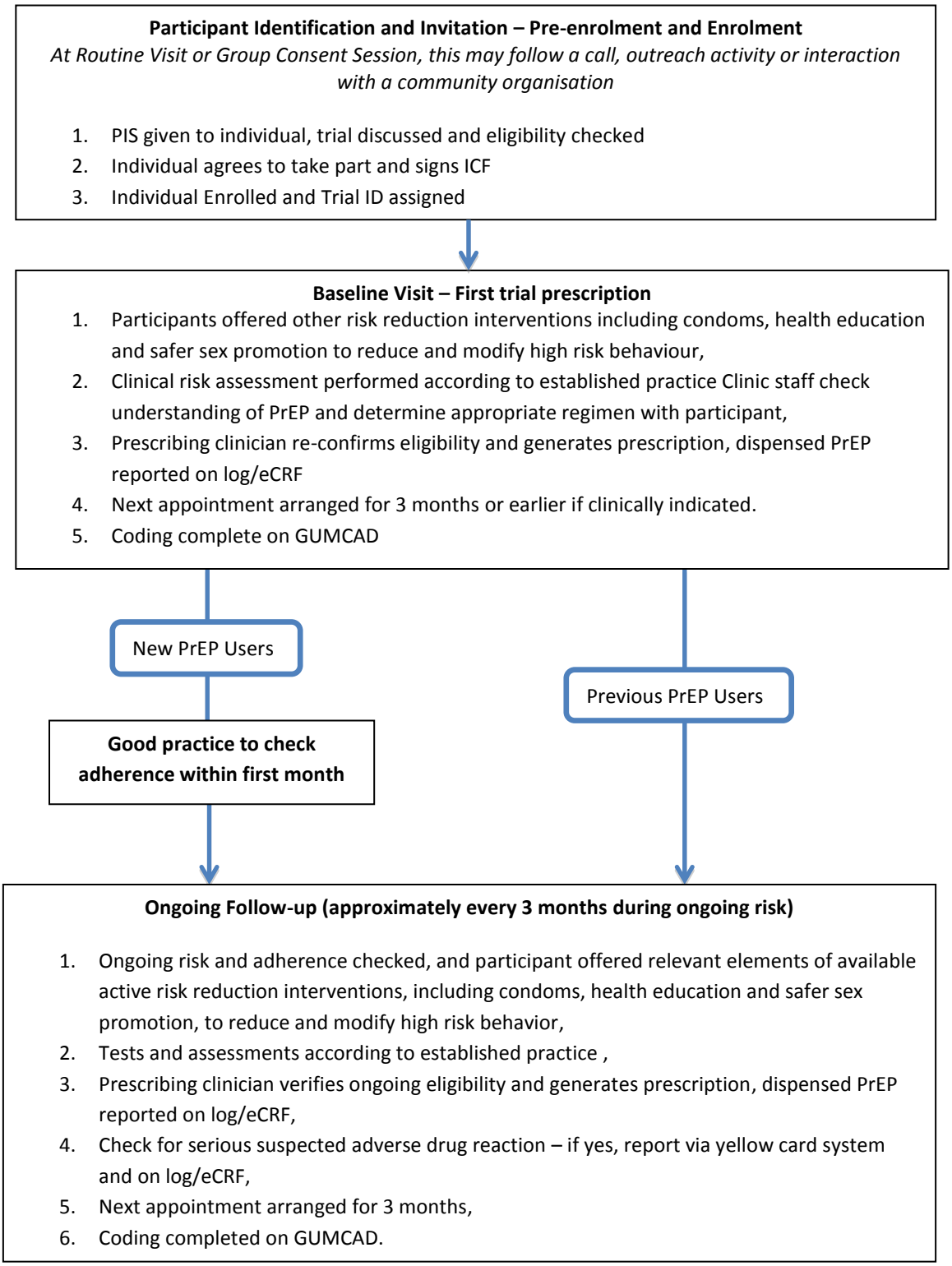
TRIAL SCHEMA



List Of Abbreviations And Definitions Of Terms

AIDS	Acquired Immune Deficiency Syndrome
CM	Concomitant Medication
EBD	Event Based Dosing
FPFV	First Patient First Visit
GCP	Good Clinical Practice
GP	General Practitioner
GUMCAD	Genitourinary Medicine Clinic Activity Database
HARS	HIV and AIDS Reporting System
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH-GCP	International conference of harmonization good clinical practice
MHRA	Medicines and Healthcare products Regulatory Agency
MSM	Men who have sex with men
SmPC	Summary of Product Characteristics
PIS	Participant Information Sheet
PrEP	Pre-exposure prophylaxis (PrEP)
UPCR	Urinary Protein Creatinine Ratio

TABLE OF CONTENTS

1. BACKGROUND AND RATIONALE

In the UK sustained prevention efforts have not reduced the rate of HIV acquisition by men who have sex with men (MSM) [1]. HIV incidence overall in MSM Genitourinary medicine (GUM) clinic attendees remains at about 1.34% annually, and estimates for Black African heterosexuals (0.17% per year) remain higher than for non-MSM populations overall (0.03% per year). The total cost of caring for those living with HIV will rise inexorably as numbers infected increase. New prevention initiatives are needed to reduce the estimated 4,700 incident infections occurring annually, of which 2,800 occur in MSM. Tenofovir containing regimens used as HIV Pre-Exposure Prophylaxis (PrEP) are highly effective at reducing the risk of HIV acquisition [2-4], and PrEP is recommended as an effective component of an active risk reduction intervention by the European AIDS Clinical Society (EACS) [5], the European Centre for Disease Prevention and Control (ECDC) [6], and the World Health Organisation (WHO) [7].

In the UK, the PROUD trial was designed to measure effectiveness when participants were aware they were taking PrEP. It was stopped early as the high HIV incidence in MSM not on PrEP (9% annually) allowed the strength of PrEP effectiveness to be measured sooner than expected [8]. Therefore, while the safety, efficacy and potential effectiveness of oral PrEP are well established, a number of key questions remain and heterosexual patients were not included in the trial. In this context, NHS England led a programme of work to consider how PrEP as an intervention could be planned and commissioned, based on the available data and plausible assumptions about PrEP eligibility, uptake, adherence and duration of use. Subsequently, PHE advised that before PrEP is used on a substantial scale in England, a better option would be to conduct a trial to address current uncertainties in the policy assumptions. A trial would prioritise these questions about the PrEP 'prevention care continuum' and ensure the required answers are obtained.

Proposed PrEP eligibility criteria developed by a multi-disciplinary and multi-stakeholder panel, as revised in October 2016, used the Genitourinary Medicine clinic activity dataset (GUMCAD) to identify the sub-group of MSM with a prior negative HIV test at that clinic in whom HIV incidence was high (3.3% annually) – patient population A , point 2 [9]. The proportion of attendees who had already contracted a bacterial STI (33%) was used to approximate the

proportion thought likely to report condomless sex in the previous 3 months and likely to have repeated condomless sex in the next 3 months (source: GUMCAD, HIV & STI Department, Public Health England, HIV incidence analyses 2012 to 2017). However, there is considerable uncertainty about this approximation for the proportion that would be clinically risk assessed as at high HIV risk and there is competing data from clinic surveys to suggest the proportion could be as high as 60% [10].

The likely uptake of PrEP among those who meet eligibility criteria is unknown, especially when it is recommended to them by a clinician; current estimates are based upon North American experience [10]. It is expected that PrEP users will move in and out of periods of risk and, therefore, may be on PrEP for varying amounts of time, the duration of which is another uncertainty. Using GUM clinic data from 2010 to 2015, the proportion at high-risk in year 1, defined by diagnosis of a bacterial STI in the past year, who remained at high-risk in years 2 through 6 is 27%, 13%, 8%, 5%, and 3%, respectively. Although, this suggests large turnover in those at high risk, this is based on recurrent rates of bacterial STIs and not on history of condomless sex. If the average duration of periods of condomless sex is substantially greater than a year then it would imply a considerable increase in the cumulative numbers of MSM requiring PrEP.

Identifying and engaging individuals in other populations at high risk of HIV, including black Africans and transgender men and women, will be crucial to maximising the potential benefits of PrEP. However, the number of clinic attendees in populations other than MSM who will be deemed as being at high risk of HIV acquisition and eligible for PrEP is unknown.

There is little doubt that, when taken correctly, PrEP can significantly reduce the risk of acquiring HIV for an individual. Nonetheless, when delivered at scale to a population, many factors may influence the impact of PrEP. Investigation of each reported HIV seroconversion in those who begin PrEP within the trial will help to assess the extent of PrEP adherence and provide an indication of effectiveness. Another concern about PrEP use is the potential increase in condomless sex with a consequent increase in bacterial STIs, and there is evidence from other countries that this is happening. Participants in PROUD were already at extremely high risk of HIV and other STIs, so extrapolating from these data may be falsely re-assuring. Those accessing PrEP in a large-scale trial may have a lower STI risk prior to taking PrEP and greater

scope for risk compensation when taking PrEP (compared to PROUD participants). However, given HIV and STI incidence has been monitored using GUMCAD in MSM clinic attendee sub-groups for over five years, the population impact of a large-scale PrEP trial on HIV and bacterial STI incidence will be measured both for those taking and not-taking PrEP and stratified by risk markers.

Therefore, this trial aims to address the outstanding questions agreed between Public Health England, NHS England and professional and community stakeholders. For sufficiently robust answers concerning the components of the PrEP continuum of prevention care (% eligible, uptake, duration, etc.) across the heterogeneity of clinics, clinic attendees and eligibility criteria, a trial size of at least 10,000 person years PrEP is required. To mitigate against future geographical inequity in PrEP provision as many clinics as possible should be recruited to the trial. Trial design, methods and data flows should support regular (i.e. quarterly) 'one-to-one' clinical risk assessments to ensure PrEP is delivered 'as part of an active risk reduction intervention including health education and safer sex promotion' [9].

Essential to any future PrEP programme will be the ability to monitor and audit compliance with eligibility criteria and repeated clinical risk assessments. The central role of the GUMCAD information system to the monitoring and evaluation of PrEP has been endorsed by all stakeholders.

2. TRIAL OBJECTIVES

1. To measure PrEP-eligibility, PrEP-uptake, duration of PrEP-eligibility and duration of PrEP-use (PrEP prevention care continuum) among Genitourinary Medicine (GUM) clinic attendees,
2. To determine whether or not incident HIV infections in trial participants are due to non-adherence or biological failure,
3. To measure change over time in HIV diagnoses and incidence rate in those at high HIV risk,
4. To measure change over time in bacterial STI diagnoses and incidence rate in those at high HIV risk,
5. To measure the PrEP 'prevention care continuum' by clinic throughput and in different regions.

3. TRIAL DESIGN

The design is prospective and open-label. The trial is classed as non-interventional as patients will be using licensed products prescribed according to established clinical practice.

3.1 Sites

In order to include all sites from across urban and rural settings and in high, medium and low throughput clinics, all GUM clinics in England (Level-3 Sexual Health Services) will be eligible to take part in the trial, providing they meet the following criteria:

1. Access to 4th generation HIV ELISA tests,
2. Access to a local laboratory that can analyse serum creatinine,
3. PrEP SHHAPT O codes implemented into existing patient record systems before participants are recruited,
4. Reporting PrEP codes with clinic activity and diagnoses using enhanced GUMCAD to PHE on a monthly basis,
5. Have suitable systems in place to prescribe and dispense PrEP to participants,
6. Ensure adequate capacity to deliver STI and HIV testing according to standard of care, in line with established clinical practice,
7. Comply with good clinical practice requirements.

Sites will be required to:

- Screen clinic attendees for PrEP-eligibility at each new episode of care
- Conduct patient recruitment and consent procedures,
- Assign O codes as specified in the GUMCAD technical specification,
- Complete the relevant data entry into the trial database (eCRF),
- Report recruitment figures monthly to the trial sponsor,
- Report any suspected or confirmed HIV seroconversion in a trial participant to the trial sponsor within a week of the suspected or confirmed positive HIV test result. Site should also ensure the patient is added to the HIV & AIDS Reporting System (HARS) as per routine clinical practice,
- Provide the sponsor with at least monthly PrEP-dispensing reports.

Participants will only be able to access PrEP through approved participating GUM clinics. The Sponsor and Public Health England will have overall responsibility for site and investigator selection, but the decision to include a site will be taken by the Sponsor.

3.2 Participant assignment to clinics

Participating GUM clinics will be assigned recruitment targets which will be allocated to ensure inclusion for MSM and non-MSM participants. Recruitment will be monitored centrally.

3.3 Inclusion and Exclusion Criteria

Inclusion Criteria

The participant populations for this trial will be men and women attending GUM clinics who belong to one of three populations recognised to be at high risk for HIV, namely:

A. Men (cisgender and transgender) and transgender women who:

1. Have sex with men
2. Have had an HIV negative test during an earlier episode of care in the preceding year
3. Report condomless intercourse (excluding oral) in the previous 3 months
4. Affirm their likelihood of having condomless (excluding oral) intercourse in the next 3 months

B. HIV negative partners of an HIV positive person when:

1. The HIV positive partner is not known to be virally suppressed (<200 copies/ml for 6 months or more)
2. Condomless intercourse (excluding oral) is anticipated before treatment of the HIV positive partner takes effect

C. HIV negative persons who:

1. Are clinically assessed and considered to be at similar high risk of HIV acquisition as those with a serodiscordant partner who is not known to be virally suppressed

Participants will therefore be considered eligible for trial enrolment if they fulfil all the following individual eligibility criteria:

1) Belong to one of the three at high HIV risk populations described above
2) Aged 16 years or over (no upper limit)
3) Considered to be HIV negative on the day of enrolment
4) Willing and able to provide informed consent
5) Willing to adhere to the recommended PrEP regimen
6) Willing to re-attend the trial clinic at appropriate intervals for risk assessment

Exclusion Criteria

Participants will not be considered eligible for trial enrolment if they fulfil any of the following criteria:

1) An acute viral illness that could be due to HIV seroconversion
2) Any contraindication to Tenofovir Disoproxil (TD)/ Emtricitabine (FTC) - according to the current package insert or SmPC

3.4 Number of participants

This trial aims to enrol 13,000 participants.

3.5 Time period of trial

The trial will last 4.5 years in total, including set-up and closedown. The recruitment period will last for 33 months with all participants completing the trial 36 months from first participant, first visit. The duration for each participant will vary depending when they are first enrolled during the 36 month period e.g. patients who enrol at 33 months would only be on the trial for 3 months. Once recruited, participants may stop and may restart PrEP, according to risk and eligibility, throughout the full duration of the trial.

4. TRIAL DESIGN

4.1 Trial drug regimen

The combination drug to be used in this trial is Tenofovir Disoproxil (TD)/ Emtricitabine (FTC), a generic form manufactured by Mylan. Both drugs are nucleot/side analogue HIV-1 reverse transcriptase inhibitors. The drug is UK licensed and used off label for event-based dosing in accordance with established practice supported by clinical evidence. It is bio-equivalent to the branded product (Truvada). The drug should be taken orally in accordance with the drug SmPC and current package insert. All participants will be supplied with the current version of the information leaflet commissioned by the BASHH MSM Special Interest Group (Appendix 1), in line with established practice.

Two treatment schedules will be available: daily and event-based dosing (EBD). The decision to take one regimen or the other will be decided following risk assessment and discussion between the prescribing clinician and The information leaflet (Appendix 1) contains text and pictures to describe how to take this regimen in the context of a single sex act and several sex acts over a number of days. EBD is not recommended for heterosexual men, heterosexual women, and transgender men as this regimen has not been evaluated in clinical trials in these risk groups.

4.2 Known safety profile of Tenofovir Disoproxil (TD) / Emtricitabine (FTC)

The most common adverse reactions in HIV-negative individuals are gastrointestinal [4, 11], headache [8], nausea [4, 12] and depression related events [2].

The use of PrEP, when given as the co-formulation of Tenofovir Disoproxil (TD)/ Emtricitabine (FTC) has been associated with a mild non-progressive decline in creatinine clearance [3, 4, 11, 13-15] that is reversible on discontinuation of drug [2, 16]. An association between decline in bone mineral density and PrEP use has also been documented [2, 4, 14, 17-19], but there is no association with increased fracture risk [4].

4.3 Dose Modifications and Interruptions

In the event of dose modifications, interruptions, overdoses and treatment discontinuations the Principal Investigator should be notified and the patient closely observed and managed according to the current SmPC and local guidelines.

4.4 PrEP discontinuation

Participants should stop PrEP in the event of any of the following reasons:

1. HIV infection;
2. Unacceptable toxicity or adverse event;

Participants may stop PrEP for any of the following reasons:

1. Any change in the participant's sexual behaviour or circumstances that justifies the discontinuation of PrEP;
2. On the recommendation of the Trial Steering Committee or termination of the trial by the sponsor or funder;
3. Participants may withdraw at any time and for any reason. They may withdraw without giving a reason but if one is given then this should be documented in the patient records;
4. Participants may be withdrawn at the discretion of the investigator, in the best interest of the participant.

Participants who are identified as HIV positive during baseline assessment or trial follow up will be managed according to local policies for linkage to HIV care.

4.5 Accountability & unused drugs

The investigator or delegate (e.g. pharmacist) has the responsibility to ensure that the study drugs are maintained throughout according to the storage conditions detailed in the current SmPCs. They are also responsible for ensuring that the dispensing and accountability complies with local approved procedures. Accountability records will be completed throughout the trial.

4.6 Compliance and adherence

Clinicians will assess adherence with participants at each PrEP appointment and offer support if necessary. Routinely collected data on number of pills dispensed and number of days between clinic visits will allow the adherence opportunity to be measured. Among trial participants who seroconvert whilst on PrEP, adherence will be assessed through participant-reported adherence (measured as 'the proportion of risk events covered by PrEP') and blood drug levels.

4.7 Other treatment

4.7.1 Post exposure prophylaxis

If a sex act is not protected by a condom or PrEP, participants may be advised to take post-exposure prophylaxis according to national guidelines.

4.7.2 Medications that are not recommended for concomitant use

Site investigators should familiarise themselves with the SmPC for the trial product being used. As per the SmPC for Tenofovir Disoproxil (TD)/ Emtricitabine (FTC), the following medications should not be taken concomitantly with the trial drug:

- Drugs containing Emtricitabine or Tenofovir Disoproxil Fumarate (TD) including Atripla, Emtriva and Viread,
- Adefovir dipoxil,
- Lamivudine and other cytidine analogues,
- Didanosine,
- Cidofovir and other medical products that compete for active tubular secretion,
- Drugs that reduce renal function.

4.7.3 Medications to be used with caution

Co-administration of PrEP with drugs that are eliminated by active tubular secretion may increase concentrations of Tenofovir Disoproxil (TD)/ Emtricitabine (FTC) or the co-administered drug. Such medications should be used with caution as per the SmPC for Tenofovir Disoproxil (TD)/ Emtricitabine (FTC) and may require more frequent monitoring of serum creatinine.

4.7.4 Treatment after HIV seroconversion

Participants who seroconvert should be investigated and managed according to local practice. See section 5.7

4.7.5 Treatment for active replication of hepatitis B virus

Participants with active hepatitis B virus who are on or require treatment for their hepatitis B can use daily Tenofovir Disoproxil (TD)/ Emtricitabine (FTC) if it is indicated as part of their hepatitis B treatment and should be under close supervision of a hepatologist. They should be counselled about the risk of onward transmission of hepatitis B and provided with condoms to use with partners who are not immune who should be vaccinated as soon as possible.

5 ASSESSMENTS AND FOLLOW-UP PROCEDURES

5.1 Patient Identification

Potentially eligible individuals will be identified by local investigators during routine enquiry about HIV risk at sexual health clinic visits. Potentially eligible individuals may also be identified through outreach activities, by community organisations and through social media. Individuals are also likely to self-identify their need for PrEP as mainstream media has, and will continue to report the plan to implement PrEP through a large scale trial. The participant information sheet will be publicly available through the trial website and individuals will be able to read this prior to visiting clinic, or whilst waiting to be seen. The website will also provide details of participating clinics.

5.2 Informed Consent

The consent process for the trial has been left deliberately flexible in order to accommodate the needs of individuals and variations in site requirements. Participants can provide informed consent at their local sexual health clinic as part of their routine visits or in the context of study-specific group consent sessions.

Written informed consent using the current approved version of the consent form for the trial must be obtained before PrEP is dispensed. Confirmation of consent must be documented in the

clinic notes. The right of the participant to refuse to participate in the trial without giving reasons must be respected. All participants are free to withdraw at any time.

5.2.1 Consent during routine visit

Participants that have been identified as potentially eligible for PrEP will be provided with the Participant Information Sheet (PIS) and invited to enter the trial by a healthcare professional during a routine visit. An explanation of the trial will be given and the individual will be given adequate time to consider their participation. This may be less than 24 hours if the individual requests to start immediately i.e. the Informed Consent Form (ICF) can be signed during the same visit they were initially approached. This is to ensure that PrEP can be provided as soon as possible to those deemed to be at imminent risk of HIV.

5.2.2 Consent during group consent sessions

Given the anticipated interest in trial participation, sites can also arrange group consent sessions in order to facilitate larger groups of potentially eligible individuals. The format of these consent sessions is flexible but would usually involve a group presentation to explain the trial followed by a question and answer session. Each individual would then be invited to sign the ICF on a one-to-one basis with an individual who has been adequately trained and is delegated to answer any additional questions and obtain consent.

5.2.3 Site Staff Responsibilities

Delegated staff are responsible for:

- Checking that the correct approved version of the PIS and ICF are used;
- Checking that information on the ICF is complete and legible;
- Checking that the participant has completed/initialled all relevant sections and signed and dated the ICF correctly;
- Making a record in the clinic notes relating to the informed consent process (i.e. information given, consent signed etc.);
- Following assignment of Trial ID:
    - Completing all required fields, including the trial identification number, on all copies of the consent form. Copies should then be filed in the patient's medical notes and/or investigator site files,

- Providing the participant with a copy of their signed ICF and PIS.

5.3 Study Subject ID Assignment

Once consent has been provided, participants will be assessed for eligibility and assigned a unique Study Subject ID number. The participants GUMCAD number and SOUNDEX should also be recorded on the trial register/database.

The first part of the Study Subject ID (5 characters/digits) represents the **Site ID**. The second part of the ID (5 digits) represents the sequential trial number for that participant. The Study Subject ID must be exactly 10 characters in length and the number of zero's decreases as you go into double and triple figures. There should be no space or 'hyphen' or 'underscore line' between any of the characters.

For example, for site ABCDE -

e.g. **ABCDE**00001, **ABCDE**00002, **ABCDE**00003… **ABCDE**00010… **ABCDE**00101

All participants enrolled on the trial must be recorded on the trial register which will be maintained at each site. The principal investigator, or delegate, is responsible for ensuring that this record includes the allocated trial ID number as well as the GUMCAD number and SOUNDEX code.

5.4 Assessments and Procedures

All assessments required to support PrEP are established practice in GUM clinics based on clinical evidence, including discussion of the trial regimen (daily or EBD). These are summarised in the Table of Standard Assessments and Trial Procedures.

Trial procedures are those that support collection of informed consent, review of inclusion/exclusion criteria which includes checking the record of previous HIV test results in the clinic, completion of the trial register/entry onto trial database and accounting for drug dispensed through the trial. It is envisaged that the large majority of individuals will enrol at a clinic they have previously visited but in circumstances where this is not the case a self-report of a preceding HIV test at another clinic will be accepted and should be checked. In exceptional circumstances heterosexual populations at imminent risk of acquiring HIV may present to clinic

with no previous HIV test and start PrEP on the basis of a negative point of care test, whilst awaiting the result of the 4th generation HIV ELISA following a clinical risk assessment.

5.4.1 Baseline/First Trial Prescription Visit

Following enrolment, and a discussion regarding the trial drug and regimen, assessments and procedures should be done in accordance with established practice based on clinical evidence and include:

- A blood specimen for a 4th generation HIV test must be taken on the day a participant starts PrEP, and in those continuing PrEP unless there is a documented negative 4th generation HIV test result that was collected within 4 weeks of enrolment
- A HIV point of care test is advisable if the participant is starting PrEP the same day and has not had a documented negative 4th generation HIV test within the last 4 weeks, Confirmation of Hepatitis B status with testing if there is no record in the clinic notes, and vaccination (course or booster) if indicated according to clinic guidelines,
- Hepatitis C testing according to established practice supported by clinical evidence,
- Renal assessment including a serum creatinine in all participants that are starting PrEP, and existing PrEP users who have not had a check in the preceding year or require more frequent monitoring (see section 4.7.3),
- STI screen for chlamydia, gonorrhoea and syphilis if indicated according to clinical guidelines and commissioned activity,
- Assessment of pregnancy risk and pregnancy testing, if required - confirmed pregnancy is not a contraindication to PrEP (see section 5.6),
- Prescribing and dispensing of drug according to local practice (see section 5.5) and sufficient to last until the next planned visit,
- Completion of GUMCAD codes within the patient record.

Once assessments have been undertaken, trial drug can be prescribed and dispensed. A record of dispensing should be made in the trial drug log/eCRF.

In line with national guidance, participants will be offered the relevant interventions from an active risk reduction intervention package to reduce and modify high risk behaviour. This may include the provision of free condoms, clean needles, behaviour change interventions, other biomedical interventions such as post-exposure prophylaxis where relevant, the diagnosis and treatment of STIs and a repeat HIV test within 4 weeks to close the window period on a particular risk.

5.4.2 Early Follow-up in New Starters

For participants who have not taken PrEP or PEP previously, it is good practice to check how the participant is getting on. This can be done by phone email or in person if a visit is indicated for other reasons.

5.4.3 3-monthly Follow-up

In line with established practice, 3-monthly follow up is advised. Standard assessments and procedures at this time should be done in accordance with established clinical practice based on clinical evidence and include:

- A 4th generation HIV test,
- STI screen for chlamydia, gonorrhoea and syphilis according to established practice supported by clinical evidence or if clinically indicated,
- Hepatitis C testing according to established practice supported by clinical evidence,
- Urinalysis and serum creatinine or urinary protein/creatinine ratio if indicated
- Pregnancy testing if indicated clinically (see section 5.6),
- Prescribing and dispensing of drug according to agreed local practice (see section 5.5),
- Completion of GUMCAD codes,
- MHRA Yellow card reporting if appropriate.

The clinician should check that the participant is still eligible for PrEP and wishes to continue, and should record this information using the GUMCAD codes. Once standard assessments have

been undertaken, study drug can be prescribed and dispensed. A record of dispensing should be made in the study drug log/eCRF.

Participants should be offered relevant interventions from active risk reduction services as per the First Prescription visit (Section 5.4.1).

5.4.4 Annual Follow-up

After each year on PrEP, the following procedures and assessments are advised:

- A 4th generation HIV test,
- STI screen for chlamydia, gonorrhoea and syphilis according to established practice supported by clinical evidence or if clinically indicated,
- Hepatitis C testing according to established practice supported by clinical evidence,
- Serum creatinine,
- Pregnancy testing if indicated clinically (see section 5.6),
- Prescribing and dispensing of drug according to agreed local practice (see section 5.5),
- Completion of GUMCAD codes,
- MHRA Yellow card reporting if appropriate.

The clinician should check that the participant is still eligible for PrEP, and should record this information using the GUMCAD codes. Once standard assessments have been undertaken, trial drug can be prescribed and dispensed. A record of dispensing should be made in the trial drug log/eCRF.

Participants should be offered relevant interventions from active risk reduction services as per the First Prescription visit (Section 5.4.1).

Table 1: Standard Assessments and Trial Procedures

	Recruitment/ Baseline	3-monthly	Annually
Trial procedures			
Inclusion/exclusion criteria	x[a]		
Informed consent	x		
Enrolment on trial database	x		
Record of drug dispensing	x	x	x
Standard assessments and procedures (as part of routine clinical care)			
HIV 4th Generation test	x[b]	x	x
HIV point of care test	x[b]		
Hepatitis B status confirmation (+/- testing and vaccination)	x[c]		
Hepatitis C testing	x[d]	x[d]	x[d]
Renal (Serum Creatinine to estimate creatinine clearance)	x[e]	x[e]	x
Urinalysis	x	x	
STI screen (Chlamydia, Gonorrhoea, Syphilis)	x	x	x
Assessment of pregnancy risk	x[f]	x[f]	x[f]
Prescribing and dispensing of drug	x	x	x
GUMCAD O codes assigned and entered	x	x	x
Yellow card check		x	x

(a) Eligibility will be determined on the basis of information routinely collected in clinic and during the informed consent process,
(b) If a 4th generation HIV test has been done within 4 weeks of baseline then a Point Of Care Test is not required,
(c) Hepatitis B status confirmation +/- vaccination according to national guidance,
(d) Hepatitis C testing according to established practice (which will differ between at risk populations) based on clinical evidence
(e) Serum creatinine if starting PrEP, or continuing PrEP and not done in the preceding year, or medically indicated,
(f) Cis- gender women and transgender men of childbearing potential in whom it is good practice to determine whether or not they are pregnant before prescribing.

5.5 Prescribing and dispensing drug

On completion of visit procedures and assessments, the clinician will be able to prescribe up to 3 months' supply of PrEP per visit. The drug should be prescribed and dispensed according to routine practice at the participating clinic.

A Trial Drug Log should be maintained at each site to document the amount of drug dispensed against the subject ID. GUMCAD codes should be completed relating to the number of pills prescribed.

5.6 Pregnancy and breast feeding

There is clinical trial evidence to suggest that PrEP is safe in pregnancy, and evidence that the risk of acquiring HIV is increased during pregnancy. Data also suggest that PrEP can be safely used when breast feeding, but with caution due to the quality of the evidence. Therefore, these are no contraindications to prescribing PrEP in this trial. It is good practice to determine the pregnancy status of a woman who is at risk of acquiring HIV and who could be pregnant in order to have an informed discussion about the risks and benefits of PrEP during pregnancy.

5.7 Procedures for assessing HIV seroconversion

Presumptive HIV infections should be confirmed according to criteria developed by UK Standards for Microbiology Investigations. A repeat sample should be obtained and reactivity confirmed by a sensitive HIV RNA assay.

In the event of a seroconversion that presents to the prescribing clinic, information on adherence to PrEP will be elicited along with a sexual history as part of established clinical practice. In line with established clinical practice, collection of a sample for analysis of drug levels (therapeutic drug monitoring) may be considered.

In accordance with national guidelines for newly diagnosed individuals, a genotypic drug resistance test should be performed to identify mutations which may have been transmitted from the infecting partner or acquired as a result of exposure to PrEP. This test should be performed on the earliest possible sample after seroconversion.

5.8 Procedures for assessing safety

Information on serious suspected adverse drug reactions, including effects that are well recognised, should be reported by healthcare professionals at trial sites through the 'Yellow card' system (https://yellowcard.mhra.gov.uk/) in line with MHRA guidance of 23 January 2015 and subsequent updates. A copy of the yellow card form (whether completed online or by paper) should be retained in the investigator site file in all instances. Sites are expected to be able to provide these forms upon request from the Sponsor.

Any safety events raised via the 'Yellow Card' system will also be documented in the eCRF. At each visit, the clinic staff will be asked to enter if a yellow card has been raised for the participant. If yes, the following data is required to be entered into the database (this information is requested on the yellow card form and can be transcribed by sites):

- Suspected reaction
- Date of suspected reaction
- Outcome
- Severity
- If the suspected reaction is considered to have resulted from a medication error

Trial Oversight Committees will be provided with the data captured on the eCRF for safety monitoring purposes. If a committee raises any concerns with the data or requires a more comprehensive review, yellow card forms that have been retained in the investigator site sile will be requested by the Sponsor.

Patient safety incidents that could have or did harm participants should also be reported through local incident reporting systems in line with routine clinical practice. Information on resistance mutations will be collected through the national HIV dataset.

5.9 Procedures for tracking patients across clinics

Patients often move between different sexual health services; we are anticipating that this could also occur within the context of this trial. Participants can be tracked across different clinics using their trial ID, which is assigned upon trial enrolment, but will not be able to be tracked via their GUMCAD number. GUMCAD numbers are allocated per patient and per clinic and therefore cannot be transferred across different services. In order to mitigate the risk of a participant enrolling twice, and hence taking two

places on the trial and affecting statistical analysis, patients will be asked to disclose that they are already on the trial if they move to a different clinic. This is stated in the participant information sheet and places importance of not double-enrolling on the trial from the perspective of denying another person access to PrEP. The participant's trial ID will be clearly documented on their copy of the completed informed consent form, which needs to be provided and verified when transferring to another clinic.

6 DEFINITION OF THE END OF THE TRIAL

The recruiting period is 33 months and the end of the trial is defined as 36 months from FPFV. Recruitment to the trial will be closely monitored by the Trial Steering Committee.

6.1 Treatment Compliance

The Chief Investigator will ensure that this trial is conducted according to the principles of the Declaration of Helsinki (1996) and meets all applicable regulatory expectations including, but not limited to, the Research Governance Framework, Research & Development policies and processes. In addition to this the sponsor will maintain oversight and quality management of this trial by undertaking regular monitoring activities and audits as appropriate.

6.2 Provision of treatment after the end of the trial

As the trial is non-interventional, post trial access to PrEP cannot be guaranteed to participants. PrEP is licensed for use in the UK and available to purchase privately, however it is currently unavailable on the NHS in England. All data generated from the trial will be presented to the TSC and provided to commissioners via the Oversight Board to inform future commissioning decisions on PrEP. The Board will seek to review the result of the research during the research period to minimise any gap in future commissioning and implementation decisions being taken. It is expected that the trial data will inform the commissioning of a PrEP programme to be implemented promptly on conclusion of the trial. Information will be shared with NHS England as commissioners of HIV drugs and local authorities as commissioners of sexual health services. It is anticipated that a national programme will be put in place with the expectation that PrEP will be available to all who are eligible, as informed by the data from this trial.

6.3 Early termination of the trial

The Funder, Sponsor or Chief Investigator may terminate either part of, or the entire trial for safety or administrative reasons. A written statement fully documenting the reasons for such a termination will be provided to the Ethics Committee and the Regulatory Authority as appropriate.

7 ADVERSE EVENTS

Information on serious suspected adverse drug reactions, including effects that are well recognised, will be reported through the 'Yellow card' system (https://yellowcard.mhra.gov.uk/). Patient safety incidents that could have or did harm participants should also be reported through local incident reporting systems in line with routine clinical practice. Any safety events raised via the 'Yellow Card' system will also be documented in the trial database.

Routine data will be collected on the presence of resistance mutations that are likely to have been selected by tenofovir disoproxil (K65R) or emtricitabine (M184V/I) or which preclude use of either drug in the treatment of HIV. See section 5.8 for procedures.

8 STATISTICAL CONSIDERATIONS AND DATA MANAGEMENT

8.1 Sample Size

The trial will recruit from the 'total' GUM clinic attending population in participating trial clinics. This is a subset of the 'total' GUM clinic attending population. A proportion of the attendees in participating GUM clinics will meet the trial eligibility criteria and of these the trial will recruit a total of 13,000 participants to receive PrEP. Estimates from GUMCAD 2016 suggested that the total eligible MSM population across all GUM clinics was approximately 10,000. The 10,000 target was considered sufficient to allow the size of the total eligible population (MSM and women and others) across all GUM clinics to be estimated with a precision within the range ± 480 to ±1150. These precision estimates were derived from a range of simulations using a number of assumptions derived from available GUMCAD data at the time. These include: the proportion of MSM meeting the eligibility criteria (estimated range 20% to 60%), the percentage of MSM at high risk (percentage with a bacterial STI in past year 25% to 55%), and percentage of non-MSM eligible (20% of the eligible MSM population).

Before the trial began and assuming that PrEP uptake in the eligible population lay within the range 20% to 60%, a trial size of 10,000 participants was deemed to be sufficient to estimate the precision for PrEP uptake within ± 3%.

Co-variates of major interest include clinic, clinical history of genital and rectal bacterial STI, geographical area of the country, age, and ethnicity. The possible combinations of these co-variates results in potential for large standard errors when considering sub group analysis.

Therefore, assuming that the smallest critical sub-group represents 5% of the trial population, the sample size of 10,000 provides a sufficiently narrow precision within each sub-group of 500 participants about the estimated numbers of eligible attendees (±44 to ±64) and the precision around the estimated proportion taking up the offer of PrEP of ±6%.

The distribution, and the average duration of PrEP use are dependent upon the risk spectrum of the eligible population, and their duration of eligibility.

Based on the cumulative accrual of over 7,000 in the first 8 months of opening, mainly MSM, the Trial Management Group and independent Steering Committee, supported by the NIHR, have advised NHS England and the Association of the Directors of Public Health (ADsPH) that increasing the original sample size of 10,000 to 13,000 would provide useful additional data and address concerns about the representativeness of those who were recruited to the trial over the initial few months. A trial with 13,000 participants should be sufficient to enable the detection of meaningful differences in duration between sub-groups of participants. However, both the mean and variance of the duration of PrEP use is currently unknown. If there is substantial variance in the duration distribution then excessive differences may fail to be detected in small sub-groups.

8.2 Trial Outcomes

1. Proportion of Genitourinary Medicine (GUM) clinic attendees that meet PrEP eligibility criteria, the proportion that is prescribed PrEP per year and the duration of PrEP-eligibility and PrEP-use among users.

2. HIV and STIs:
    a. HIV diagnoses in national dataset
    b. STI diagnoses (gonorrhoea, chlamydia, syphilis and Hepatitis C) in national dataset
3. Adverse Events
    a. Serious suspected adverse drug reactions reported using the yellow card system
    b. Antiretroviral resistance associated mutations in participants with incident HIV infection

8.3 Statistical Analysis

All analyses will be performed using STATA data analysis and statistical software version 13 or higher. Preliminary data review, analysis and presentation may be conducted throughout study duration at the request of the Trial Steering Committee. A detailed description of the analyses to be performed is outlined in the Statistical Analysis Plan (SAP). The analysis will address all outcomes of the trial and a descriptive baseline analysis will also be performed. Safety data will be extracted from 'yellow card' submissions.

To address the trial objectives, the following analyses will be undertaken:

1) PrEP eligibility: the total eligible population (numerator) will be estimated from the 'total' GUM attending clinic population (denominator). The clinic attending population will be categorised as 'eligible' or 'non-eligible' in participating clinics. Therefore, to estimate numbers eligible for PrEP among the 'total' GUM clinic attending population, a finite population correction will be used based on the total number of GUM clinics with post-hoc stratification weighting as necessary to account for observed differences between the sample and population with respect to important patient characteristics such as sexual orientation and age group.
2) Uptake of PrEP: The numerator is the population taking up an offer of PrEP, and denominator is the eligible population in participating GUM clinics. The uptake of PrEP will be estimated using a binomial generalised linear model with logarithmic link function, taking into account heterogeneity of clinics. An analysis of the predictors of PrEP uptake will be made, and will include time as a variable. There is a dynamic aspect to PrEP uptake (e.g. starting, stopping, restarting) which will be taken into consideration.
3) Duration of PrEP eligibility and use: Participants in the trial can be in one of three states: 'eligible for PrEP and on PrEP', 'eligible for PrEP but not on PrEP', and 'currently ineligible for PrEP'. Participants will move between these states. The analysis will use a multi-state model to estimate the

probability of being in one of the states, the proportions in each state, the average duration in a given state, and transition between the states. A panel-data hazards model will be used to take into account difficulties with analysis such as between clinic variation, and the potential for more than one PrEP prescription per participant. A Gaussian random effect model will be used to enable between clinic variation to be modelled. The analysis will allow for subjects to drop out and re-enter the analysis dependent on eligibility status and will allow for multiple periods of PrEP use over time.

All analyses will include subject level covariates to assess differences between sub-groups. A time to event analysis will be used to estimate HIV incidence and will incorporate a 'cure fraction' model to take into account that the large majority of participants will not reach a HIV infection end-point. A mixed effects interrupted time-series analysis will be used to estimate the difference in the numbers of new HIV diagnoses between the pre-trial and during-trial periods in participating clinics. A time series analysis using conditional risk set model will be used to estimate STI incidence in those receiving PrEP due to the recurrent nature of STIs.

In addition, particular care will be required in the interpretation of the analyses due to the potential for risk spectrum[1] and health-seeking behaviour[2] biases. An outline of how these biases may be investigated and accounted for in the analyses is provided in the statistical analysis plan.

1. Risk Spectrum bias refers to the phenomenon that different clinics may have a different mix of patients in terms of risk. There may also be a difference in risk within clinics over time. For example, those participants who are enrolled into the trial early may report different levels of risk compared to those who are enrolled later on.

2. Health Seeking Behaviour bias refers to the phenomenon that participants coming forward to clinical services may be at different levels of risk compared to those who do not.

8.4 Health Economic Analysis

The PrEP Impact trial findings will be used to update existing PHE and University College London (UCL) PrEP economic evaluation model(s) to inform NHS England of the likely cost-effectiveness and budgetary impact of PrEP delivery via GUM clinics in England.

The economic evaluation will bring together findings from this trial, with an aim to provide an updated preliminary report around 25-30 months into the trial, to inform NHS England of the likely cost-effectiveness and budgetary impact of PrEP delivery via GUM clinics in England. This will involve

updating the existing PHE PrEP economic model(s) using trial findings on HIV risk of individuals who took up PrEP, PrEP effectiveness, risk compensation (changes in bacterial STI diagnosis rates), and duration of PrEP use. The timing proposed for the preliminary report is to enable NHS England to consider best available evidence and make recommendations around a potential PrEP policy, potentially allowing for seamless transition from the trial to a programme. A full economic evaluation report will be finalised following conclusion of the trial.

8.5 Data Recording and Handling

Data relating to patient demographics, , service provision, PrEP eligibility, outcome of PrEP offer, STI/ HIV diagnoses and PrEP prescribing will be collected through the national surveillance and monitoring system, the Genitourinary Medicine Activity Dataset (GUMCAD). The GUMCAD is a mandatory national reporting system that collects data on all sexual health attendances, service provision, STI diagnoses and HIV infection from all GUM and other commissioned non-GUM sexual health services. It is an electronic pseudo-anonymised disaggregated patient level dataset that is reported by over 600 services**.** In order to maintain confidentiality, subjects are identified only by clinic number and clinic subject number.

Trial specific data will be collected through a web-based trial data collection tool (eCRF), maintained by the trial sponsor. This will include a record of the subject ID number, GUMCAD clinic and subject numbers and SOUNDEX code, allowing this minimal PrEP user data to be linked to the GUMCAD and HARS information systems. Linkage will occur monthly in line with GUMCAD reporting schedules.

8.6 Source Documentation and Trial Data

Details relating to participant visits will be recorded in the clinic patient record (source documentation). Data for the trial will be reported in the Genitourinary Medicine Activity Dataset (GUMCAD) returns to Public Health England. GUMCAD is a mandatory national electronic reporting system and is based upon a standardised extract from each patient record. Pseudo-anonymised disaggregated patient level data is collected on all sexual health attendances, service provision, STI diagnoses and HIV infection from all GUM and other commissioned non-GUM sexual health services. The GUMCAD record, with the addition of the new PrEP 'O' codes to enable PrEP eligibility, offer, uptake and duration of use to be monitored at participant level, will form the spine of the trial information system.

The record of consent will be held by the trial sites. Prescribing and other trial specific data will be recorded in the eCRF held by the trial sponsor. The unique participant GUMCAD number and SOUNDEX will also be collected and used to link the datasets.

8.7 Data Management

Data collected through GUMCAD will be submitted to the GUMCAD team at PHE through the secure HIV and STI Web Portal (HSWP). Use of the portal requires a username and password which can be obtained from the GUMCAD team at PHE Colindale. The portal supports the Transport Layer Security (TLS) method of communication. Further details are available in the GUMCAD technical guidance. Trial specific and prescribing data in the eCRF will be submitted on a regular basis to the sponsor. For any patients who seroconvert additional data will be collected in line with established practice (see section 5.7 above) and used to augment the Trial data collected via the eCRF and via HARS.

8.8 Information governance

Data will be reported to Public Health England through GUMCAD. GUMCAD is an electronic, pseudo-anonymised patient-level dataset reported by sexual health services. Regular data returns will be transmitted electronically to PHE through the secure HIV and STI Web Portal. Use of the portal requires a username and password, which can be obtained from the GUMCAD team at PHE Colindale, and agreement with PHE's HIV & STI Department Data Sharing Policy. The portal supports the Transport Layer Security (TLS) method of communication.

8.9 Archiving and storage of data

Following completion of the trial, subject records, and other trial documentation will be retained by the Investigator in accordance with sponsor SOP and Good Clinical Practice (GCP) and applicable regulatory requirements.

9 QUALITY CONTROL AND QUALITY ASSURANCE

9.1 Monitoring Arrangements

The purpose of monitoring is to verify that the rights and well-being of human subjects are protected; that trial data are accurate, complete and verifiable with source data; that the trial is conducted in compliance with the protocol, GCP and the applicable regulatory requirements.

The sponsor will monitor trial sites in accordance with the current monitoring plan. The monitoring plan will be based on the trial risk assessment and monitoring activities will be performed centrally with on-site visits, if triggered. If a site visit is triggered, the Investigator must agree to allow the trial monitor and authorised representatives of the Sponsor, to inspect all corresponding source documents, e.g. original medical records, subject records and laboratory raw data, access to the clinical supplies, dispensing and storage areas and agree to assist with their activities if requested. The Investigator should provide the required information for remote monitoring and adequate time and space for monitoring visits if triggered. The monitor will query any missing or spurious data with the Investigator, which should be resolved in a timely manner.

9.2 Quality Assurance

For the purpose of compliance with GCP and regulatory agency guidelines, it may be necessary for sponsor authorised Quality Assurance personnel and/or authorised personnel from an external regulatory agency to conduct an audit/inspection of an Investigational site. The purpose of an audit is to assess the quality of data with regard to accuracy, adequacy and consistency, and to assure that studies are in accordance with Good Clinical Practice.

The Investigator will be given sufficient notice to prepare for such visits, which are planned to take usually between one and two days and may be conducted at any stage during the trial. The audit will involve the review of all trial related documentation, which is required by GCP to be maintained by each site, review of drug storage, dispensing and return, review of all trial related supplies and review of source documents.

10 ADMINISTRATIVE PROCEDURES

10.1 Ethics Approval

10.1.1 Initial Approval

Prior to the enrolment of participants, there must be NHS Research Ethics Committee (REC) written approval of: the conduct of the study at named sites, the protocol, the PIS and ICF, any other written information that will be provided to individuals before or when they are participants, and of any advertisements that will be used.

10.1.2 Approval of Amendments

Proposed amendments to the protocol and aforementioned documents must be submitted to the NHS REC for approval. Amendments requiring REC approval may be implemented only after a copy of the REC's approval letter has been obtained. Amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented prior to receiving Sponsor or REC approval. However, in this case, approval must be obtained as soon as possible after implementation.

10.1.3 Annual Safety Reports and End of Trial Notification

The REC will be sent annual safety updates in order to facilitate their continuing review of the study (reference. ICH GCP E6 Section 3.1.4) and will also be informed about the end of the trial, within the required timelines.

10.2 Insurance Provisions

The sponsor will take out appropriate insurance cover for this trial.

10.3 Informed Consent

The Principal Investigator at each site will:

- Ensure that each patient is given full and adequate oral and written information about the study including the background, purpose and risks/benefits of participation.
- Ensure that each patient is notified that they are free to withdraw from the study at any time.

- Ensure that each patient is given the opportunity to ask questions and allowed sufficient time to read and understand the information sheet.
- Ensure each patient provides signed, dated informed consent before undergoing any study specific procedure.
- Ensure the original copy of the signed, dated Informed Consent Form is stored in the Investigator site file and a copy is also filed in the medical records.
- Ensure that each patient receives a copy of the signed, dated Informed Consent Form.

Informed Consent can be obtained by any adequately trained healthcare professional who has been delegated to perform this task.

10.4 Contact with General Practitioner

It is not necessary for the GP to be contacted concerning this study. If the patient requests that the investigator communicate with the GP regarding the study, it is the principal investigator's responsibility to consider this and the decision should be documented in the patient notes.

10.5 Publication Policy

All or part of the trial results will be communicated, orally presented, and/or published in appropriate scientific journals. Full anonymity of subject's details will be maintained throughout. Data will be shared in a manner to avoid deductive disclosure in line with good data handling. Subjects wanting to see the results of the trial can request a copy of the article(s) from the investigators once it has been published, and appropriate links will be posted on the trial website. The community engagement group will advise the TMG on the best method to disseminate the results to the trial community and beyond.

10.6 Drug Accountability

The investigator will ensure that the trial drug will only be used in accordance with the protocol. Drug supplies will be kept by the provider in a secure, limited access storage area under the recommended storage conditions according to usual practice.

The drug delivery provider will ensure that records are maintained showing the receipt and disposition of all trial supplies. Dispensing information will be recorded on the trial database for each patient including the date and quantity of trial drug dispensed.

11 OVERSIGHT AND TRIALS COMMITTEES

11.1 Trial Management Group (TMG)

A TMG will comprise of the Chief Investigator, national co-investigators, including PHE co-investigators, BASHH representatives, community representatives and sponsor members. Notwithstanding the legal obligations of the Sponsor and Chief Investigator, the TMG will have operational responsibility for the conduct of the trial. Further details regarding the responsibilities, membership and timing of meetings will be defined in the TMG charter.

11.2 Trial Steering Committee (TSC)

The TSC will have joint clinical and community chairs and comprise membership from the TMG plus independent members, including from national professional organisations (British HIV Association and the British Association for Sexual Health and HIV). The role of the TSC is to provide overall supervision for the trial and provide advice to the Trial Management Group on operational matters. The TSC will review data in order to see if sufficient data are accumulating to ensure that the trial questions will be answered satisfactorily. It will review the protocol prior to initiation and meet after 5,000 participants have enrolled or after the first six months, or whichever is sooner. Thereafter, the TSC will convene on a six monthly basis. The TSC will make recommendations regarding the feasibility of trial and feed this back to the Programme Oversight Board. Further details will be presented in the TSC Charter.

11.3 Role of the Study Sponsor

The sponsor is responsible for notifying the Ethics Committee within 90 days of the final participant visit that the trial has closed, or within 15 days of a decision to close the trial prematurely, and for provision of a summary report within one year of closure.

11.4 Participant and Public Involvement

Design and Set-up Activities:

A Community Advisory Group formed by representatives of community organisations, participants in PROUD (a PrEP effectiveness trial) and potential participants was established to advise on the development of the PrEP Impact protocol. This included agreement on the eligibility criteria and consultation of all participant-facing material such as the patient information sheet and recruitment materials.

Duration of the Trial:

The Community Advisory Group will transition into a Community Engagement Group for the duration of the trial. Members will be closely involved in reviewing trial progress and any subsequent findings. Participants will be invited to comment on the running of the trial via this community engagement group as well as through participant involvement meetings facilitated by members of the community engagement group. The trial website will be regularly updated with news from the trial to keep participants and the public informed of trial progress .

Dissemination of Results:

Trial results will be disseminated to the public and participants via the Community Engagement Group, public statements and the trial website. A Programme Oversight Board (with community representatives) has been formed to ensure trial results are acted upon promptly. Further details regarding ongoing updates to key stakeholders will be outlined in the trial communication strategy.

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19. Mulligan, K., et al., *Effects of Emtricitabine/Tenofovir on Bone Mineral Density in HIV-Negative Persons in a Randomized, Double-Blind, Placebo-Controlled Trial.* Clinical Infectious Diseases, 2015. **61**(4): p. 572-580.

13 PROTOCOL SIGNATURE PAGES

SPONSOR AND CHIEF INVESTIGATOR SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the trial Sponsor:

Name: (please print)	
Signature:	
Date:	

Chief Investigator:

Name: (please print)	
Signature:	
Date:	

STATISTICIAN OR STUDY ANALYST SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Statistician or Study Analyst agrees to conduct the trial in compliance with the approved protocol, Statistical Principles for Clinical Trials, ICH E10 and will adhere to GCP guidelines, the Sponsor's SOPs and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Statistician or Study Analyst:

Name: (please print)	
Signature:	
Date:	

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I agree to conduct the trial in accordance with GCP and the applicable regulatory requirements and with the approved protocol

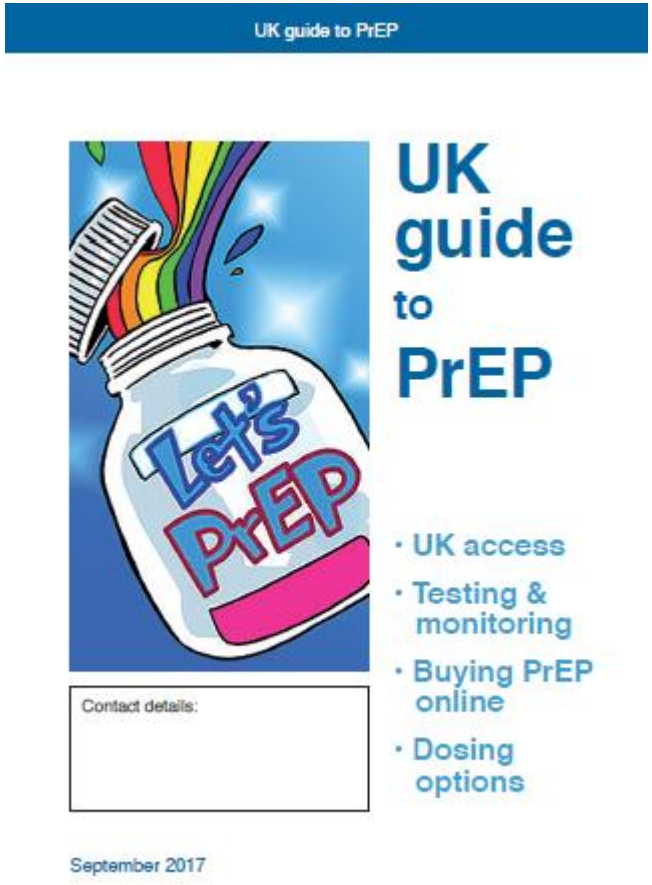
I agree to comply with the procedures for data recording / reporting

I agree to permit monitoring, auditing and inspection and to retain the trial related essential documentation for the period of time required according to ICH-GCP.

Site ID and Site Name:	
Name: (please print)	
Signature:	
Date:	

14 APPENDICES

Appendix 1 – Guide to PrEP Leaflet



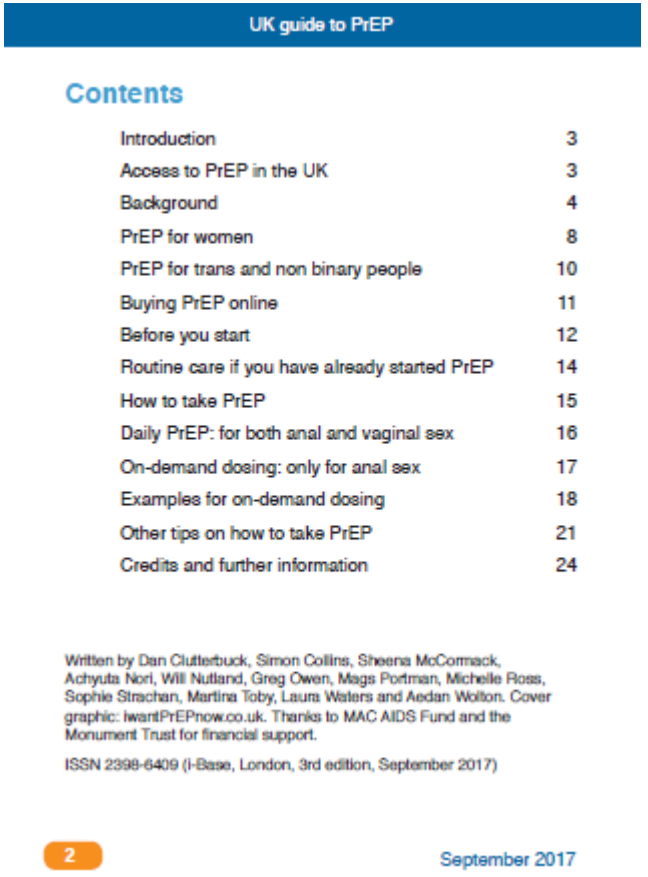
UK guide to PrEP

UK guide to PrEP

- UK access
- Testing & monitoring
- Buying PrEP online
- Dosing options

Contact details:

September 2017



UK guide to PrEP

Contents

Written by Dan Clutterbuck, Simon Collins, Sheena McCormack, Achyuta Nori, Will Nutland, Greg Owen, Mags Portman, Michelle Ross, Sophie Strachan, Martina Toby, Laura Waters and Aedan Wolton. Cover graphic: iwantPrEPnow.co.uk. Thanks to MAC AIDS Fund and the Monument Trust for financial support.

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Introduction

This booklet is a guide to PrEP in the UK.

It was first written to support people who were buying PrEP online. This edition is also for people who are prescribed PrEP or are part of a research study.

PrEP currently refers to a combination pill containing tenofovir DF (TDF) and emtricitabine (FTC). When taken correctly, PrEP greatly reduces the risk of HIV sexual transmission.

Access to PrEP in the UK

There have been several developments since the previous edition of this guide.

- NHS Scotland now provides PrEP.
  For more details see: www.prep.scot
- NHS England does not currently provide PrEP. Instead roughly 10,000 people can get PrEP in the PrEP IMPACT trial. IMPACT starts in September 2017 and will run for three years, but the study might enrol quickly.
- NHS Wales are now running a similar study called PrEPARED that currently has no cap on enrolment.
- PrEP is not currently available in Northern Ireland.
- The DISCOVER study (already enrolled) is comparing current PrEP to a newer version.
- Many people are likely to continue to buy generic PrEP using online pharmacies.

Background

What is PrEP?

PrEP stands for pre-exposure prophylaxis. PrEP is taken before sex, so it is pre-exposure. Prophylaxis means to prevent infection. So HIV negative people can use PrEP to prevent them from becoming HIV positive.

Currently, PrEP uses oral tablets that include two drugs: both tenofovir DF (TDF) and emtricitabine (FTC). The main brand name for this is Truvada, but generic (non-branded) versions are also available.

Both TDF and FTC have been widely used to treat HIV. PrEP was approved in the US in 2012 and in Europe in 2016.

Who would benefit from taking PrEP?

If you are HIV negative and don't always use condoms, then PrEP could reduce your risk of HIV.

Other factors related to a higher risk of HIV include:

- A recent STI (especially rectal infection or syphilis).
- Recent need for PEP (post-exposure prophylaxis).
- Using recreational drugs used for chemsex (crystal meth, mephedrone and GHB).
- If your HIV positive partner is finding it difficult to be adherent to their HIV meds.

Please speak to your doctor or nurse about how these risks affect you.

Is there anyone who should not take PrEP?

PrEP should NOT be used:

- By people who are HIV positive.

PrEP is usually not needed if:

- The negative person only has HIV positive partners who are on ART with undetectable viral load. An undetectable viral load means that an HIV positive person is not infectious.
- If you are happy and able to always use condoms.

How well does PrEP work?

PrEP is highly effective at reducing the risk of HIV infection. PrEP works extremely well if taken correctly.

Globally, out of tens of thousands of people taking PrEP, only three HIV infections have so far been reported from when people were actually taking PrEP. Of these, two cases were due to drug resistant HIV which is rare in the UK (see page 7).

PrEP and side effects

The majority of people taking PrEP do not get side effects.

However, like all other medicines, PrEP has the potential to cause side effects. In studies, mild nausea, diarrhoea, bloating and headache were reported in the first month by less than 1 in 10 people. These side effects then usually stop.

Occasionally, PrEP can cause more serious side effects that reduce kidney function and/or bone health. This is why monitoring blood tests are used before and during treatment.

PrEP and drug resistance

If you take PrEP correctly, the chance of drug resistance is very low.

Firstly, resistance relates to HIV and not the person. So an HIV negative person can't be resistant. Secondly, resistance is only a risk if you become HIV positive. Even then the risk is low.

The risks of drug resistance are from:

- Starting PrEP without knowing that you are already HIV positive. This is why the HIV test before PrEP is essential.
- Becoming HIV positive during a break from PrEP and then not having an HIV test before restarting.
- Missing too many PrEP doses, so that drug levels are too low to prevent HIV infection.
- Contact with drug-resistant HIV. This is very rare: globally, only two cases have been reported of PrEP not working because of drug-resistant HIV.

PrEP and other STIs

PrEP does not protect against other STIs. Condoms can help prevent against many other STIs.

Although STIs are mostly easy to treat, symptoms can sometimes be unpleasant and sometimes serious. This is why regular testing for STIs is a good idea.

The HPV vaccine can protect against genital warts and cervical/anal cancers. It is newly available for some gay men.

Does PrEP interact with other medicines?

PrEP does not interact with most other medicines. But if you are prescribed other meds, always tell your doctor (including your GP) that you are taking PrEP. You can also ask a pharmacist to check for drug interactions, including with over-the-counter meds.

One important exception is that TDF does interact with some non-steroidal anti-inflammatory drugs (NSAIDs), especially diclofenac.

Taking both drugs together can cause kidney problems. Other NSAIDs include ibuprofen and naproxen. Avoid using these meds if you are taking PrEP, or let your doctor know if you need to take them.

PrEP is very safe for trans and non binary people taking hormone therapy (see page 10).

Info on interactions between PrEP and other meds, including hormone treatment is on this site from Liverpool University:

www.hiv-druginteractions.org

UK guide to PrEP

PrEP for women

Why take PrEP?

Women who are at high risk of HIV can use daily PrEP as a way to stay HIV negative.

The highest risk for HIV is if you don't always use condoms with a partner or partners who might be HIV positive. But only if they are either not on treatment or not taking all their meds.

Condoms protect against HIV. HIV positive people cannot transmit HIV if they have undetectable viral load on treatment.

Other reasons to consider PrEP

- If condom use is difficult or impossible to negotiate.
- If you have sex for money, or receive gifts for sex.

AND

If your partner or partners might be at risk of HIV.

For example:

- If your partner is from a country where HIV is common.
- If your partner is bisexual or has other partners.
- If you have recently migrated to the UK.
- If you or your partners inject drugs and share injecting equipment.

Contraception

It is safe to use PrEP with most hormonal contraception (ring, patch, the pill, or an implant). PrEP will not affect your contraception. And the contraception will not affect PrEP.

Pregnancy

If you are planning a pregnancy or not using contraception, daily PrEP can make sure that you don't become HIV positive.

But if you know that your partner is HIV positive, it is better for him to be on treatment first. If his viral load is undetectable, there will be no additional benefit from you using PrEP.

However, if you become pregnant while taking PrEP, please talk to your doctor. This is because recommendations on using PrEP during pregnancy were being revised when this booklet went to print.

Breastfeeding

Outside the UK, many women living with HIV have been using daily PrEP drugs for HIV treatment during breastfeeding.

Only very amounts of FTC and TDF are present in breast milk. This is much less than babies use as treatment (2% for FTC and 0.03% for TDF).

This suggests that daily PrEP can be used safely if you breastfeed.

New UK website on women and PrEP

A new UK community site has lots of info on PrEP and women.

womenandprep.org.uk

PrEP for trans and non binary people

PrEP is safe and effective for people who are transgender or non binary.

Dosing choices depend on the type of sex, but generally daily dosing is recommended.

Anyone having vaginal/frontal sex needs to take daily PrEP at least six days a week. This is to make sure PrEP levels are high enough in these tissues to provide protection.

On-demand dosing can only be used if your only risk is from anal sex.

PrEP is very safe with hormone treatment. Even though you might worry about drug interactions, your homone levels will not be affected.

An excellent resource on drug interactions between hormone treatments and other HIV meds is this leaflet from Liverpool University:

tinyurl.com/y9k6ym6f

www.hiv-druginteractions.org/printable_charts

Ongoing studies are looking at hormones and PrEP in trans women. This will hopefully also be studied in trans men.

CliniQ is a London-based specialist clinic providing sexual health and well-being services for trans people. This group is also producing new resources about PrEP.

cliniq.org.uk

Buying PrEP online

It is legal to buy generic PrEP online, sourced from outside the EU, so long as this is for personal use.

Generic PrEP is a version containing the same medicine, but made by a company that does not own the patent in Europe. Personal use is defined as up to three months of daily PrEP.

Two widely used versions of generic PrEP are Tenvir-EM (from Cipla) and Ricovir-EM (from Mylan). Both versions are approved by the US FDA, which is essential. Other generic versions of PrEP with this approval are listed at this page:

www.fda.gov/InternationalPrograms/PEPFAR/ucm119231.htm

Sometimes buying PrEP online might take a while for the drugs to arrive. It is best to order at least a month in advance.

Make sure that you order a combined pill that contains both TDF and emtricitabine. For example, you need Tenvir-EM or Ricovir-EM rather than just Tenvir or Ricovir.

Several UK community websites have information about how and where to buy PrEP online.

iwantprepnow.co.uk

prepster.info

i-base.info/qa/category/prep

There is always a caution when buying anything online. However, 56 Dean Street (a sexual health clinic in London) reported good drug levels using versions of generic PrEP listed on iwantPrEPnow. No HIV transmissions were reported from 400 people using generic PrEP for a year. [1]

Some clinics will support you and provide advice and testing if you buy PrEP online. However, the NHS is only responsible for meds that it supplies, for example, for the generic PrEP used in the IMPACT study.

The community websites on page 11 will make sure you get the right pills.

Reference

1. Nwokolo N et al. IAS 2017, Abstract WEPEC0962. http://programme.ias2017.org/Abstract/Abstract/5033

Before you start

First, please talk to a health advisor, nurse or doctor at the clinic. These people can help you if you want to take PrEP, or are already taking it.

It is important to have an HIV test before or as you start PrEP.

PrEP can only be used if you are HIV negative. If you are already HIV positive and don't realise it, you could develop drug resistance.

Ask for a '4th generation' HIV blood test. This is also called a 'antigen/antibody' test. This tells you your HIV status roughly four weeks ago.

Most finger prick tests are currently '3rd generation'. They tell you your HIV status 2-3 months ago. So don't rely on a finger prick test before you start PrEP, if you have a more recent risk.

If you are just starting PrEP and had a risk in the last four weeks, have another 4th generation HIV test four weeks

after starting. This is just to be sure an early infection was not missed.

Be careful about starting PrEP if you have flu-like symptoms *and* had a recent HIV risk. This is in case these symptoms are related to a recent HIV infection.

If you are starting PrEP after PEP, it is best to start straight away if you need to. Ideally you should have a 4th generation HIV test after you finish PEP/start PrEP. Then have another test four weeks after starting PrEP.

Check your kidneys

Kidney tests just involve a blood test for creatinine. Sometimes it also includes a urine test for protein. These tests should ideally be done just before or on the day you start.

Check for other sexually transmitted infections (STIs)

HIV and STI tests are a great idea for anyone with an active sex life. This is whether you use PrEP or not.

Test for hepatitis B (HBV)

Testing for hep B is essential. This is because PrEP meds are active against both HIV and HBV.

This is a good time to have this vaccine, or to boost a previous vaccine. Although vaccine shortages in 2017 might mean you need to wait, please still ask your clinic about this.

You can still use PrEP if you have HBV, but it needs to be used more carefully. People with HBV need to take PrEP every day, with medical advice, especially if you want to stop.

Routine care if you have already started PrEP

Once you have started PrEP, monitoring is just as important. If you are currently using PrEP and have not been monitored, talk to the clinic about doing this now.

Every 3-4 months

- Have a '4th generation' HIV blood test. This is also called and 'antigen/antibody' HIV blood test.
- Have a full screen for other STIs.
- Have a urine dipstick test for protein when you have your STI check up; if there is more than a trace, an additional blood or urine test can be sent off for kidney function.
- An additional blood test for kidney function may be required if you are older than 40 or are at risk of kidney problems.

Every 12 months

- Have a blood test to check your kidney function.
- Test for hepatitis C if you are having sex with gay men.

For trans and non binary people

If you have concerns about hormone interactions please speak to your doctor. Apart from ethinylestradiol (which should not be used with PrEP), hormone levels are not be affected.

However, if this is something you are worried about, it is important to talk to your doctor about your concerns.

How to take PrEP

This section discusses different ways that you can take PrEP.

This involves allowing for the time HIV needs to take hold (around 1 to 3 days). Also, to allow for PrEP to be absorbed and reach active levels (from a few hours to a day).

PrEP is likely to be most effective when both PrEP drugs are at protective levels before you have sex. However, any PrEP, even if late, will be better than none.

Drugs absorption and dosing options

Your body takes time to absorb drugs. Therefore, PrEP should be taken both BEFORE sex (to let the levels build up) and AFTER sex (to keep levels high).

Also, each drug is different. Emtricitabine is absorbed rapidly, giving early protection within hours, but levels drop more quickly. However, TDF takes up to 24 hours to reach rectal and genital tissue, but it then stays at higher levels for longer.

You can take PrEP in different ways depending on your circumstances and how often you have sex.

For vaginal sex, you need to take daily PrEP at least six days each week. You also need to take PrEP for ideally a week to reach protective drug levels. This is because PrEP is absorbed differently in vaginal tissue compared to rectal tissue.

For anal sex, there is more evidence supporting daily PrEP. But on-demand dosing was very effective for anal sex in IPERGAY. This involved taking two pills before sex as a double dose, a single dose 24 hours after the first double dose and another single dose, 48 hours later.

On-demand dosing is NOT suitable for women or transgender women having vaginal sex. On-demand dosing is NOT suitable for transgender men for vaginal/frontal sex. In all these cases, daily PrEP dosing is recommended.

For men whose only risk is insertive sex (vaginal or anal), on-demand dosing is likely to be okay, just that there is more data for daily PrEP.

Please talk to your doctor about the best dose and timing that will be most suitable for you.

Daily PrEP: for anal and vaginal sex

Most PrEP studies have used daily PrEP.

Taking PrEP every day will make sure that there are protective drug levels 24 hours a day, 7 days a week. This means you do not have to plan PrEP for when you might have sex.

If you generally have sex every week, daily PrEP has the advantage of being an easier routine. Also, missing an occasional dose is unlikely to make a difference.

- If you are just about to start daily dosing but think you may have a risk within the next few days, start with a double dose.
- For anal sex, four or more daily doses each week will give good protection, especially after the first week.
- Remember that for vaginal sex you need to take PrEP every day.

On-demand dosing: only for anal sex

For people who do not want to take a daily pill there is an option to just use PrEP when you need it. This is called "on-demand dosing" (or event-based dosing).

Just taking PrEP before and after a risk is very effective. This option is important if you don't often have anal sex without condoms. Also, if you usually know when you will have sex.

If you are buying PrEP online, on-demand dosing will be less expensive because you need fewer pills and this might also reduce side effects. However, on-demand dosing can't be used if you have hepatitis B.

On-demand dosing involves:

1. Taking a **double dose** of PrEP (two pills) before you have sex. Ideally this should be between 2 and 24 hours before sex as this dosing was used in the IPERGAY study.
2. Taking a single pill 24 hours after the double dose.
3. Taking another single pill the following day, 24 hours later.

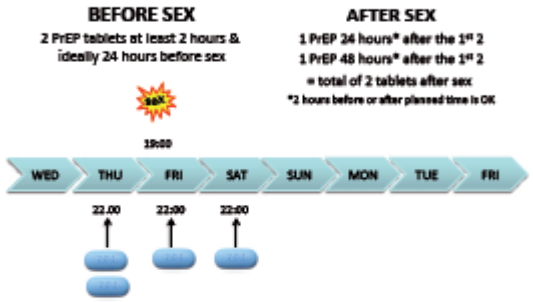
You should aim to take a single pill 24 hours and 48 hours after the first double-dose.

Although the pre dose is important for the highest protection, if you miss or are late with the pre dose, taking the double dose as soon as possible will still give some protection.

The next three pages shows several on-demand examples.

Examples for on-demand dosing

1. On-demand dosing: If you have sex once a week



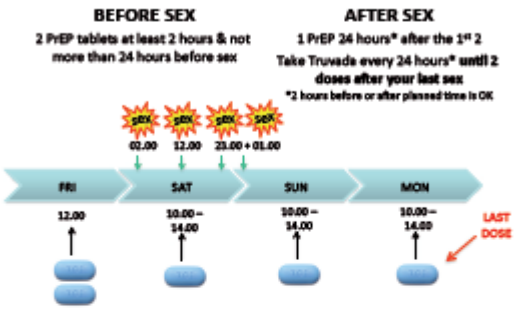
If you think you might have sex on Friday or over the weekend, you could take two pills on Thursday, i.e at 10 pm.

If you have sex on Friday at 7 pm, then you would take a single pill on both Friday and Saturday at around 10 pm.

These times can be approximate. You still get good protection if you took the Thursday dose at 6 pm and had sex on Friday at 11 pm. **Even if the pre dose is only two hours before sex, or just before sex, or even after sex, some PrEP is always better than none.**

From having sex once, on-demand dosing involves four pills.

2. On-demand dosing: Sex several times over a few days



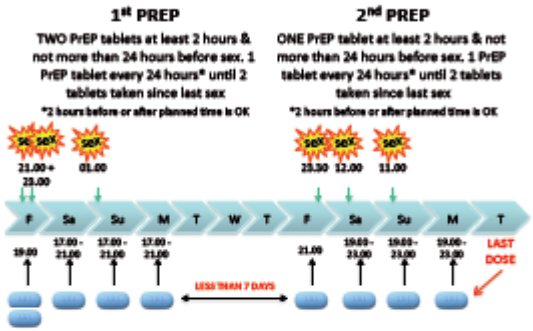
Take your double dose as usual 2 to 24 hours before sex.

If you have sex on Saturday, and a few times until Sunday at 1 am, continue to take a single pill every day at around the same time until you have had two doses after sex. Using the example above, your last dose would be on Monday.

If you don't have sex on Saturday or Sunday, but might still have sex on Monday, you only need to continue with a single pill on Sunday and Monday. This is because you will already have good levels of PrEP. Continue taking PrEP daily until you have had two sex-free days, i.e. until Wednesday.

If you start PrEP but then don't have sex on Saturday, and have no plans to have sex on Sunday or Monday, there is no need to take PrEP on any of these days.

3. On-demand dosing: Sex several times, then more sex less than seven days after the last PrEP dose



If there are less than seven days between the end of one on-demand dosing period and the beginning of another, you only need to take one single PrEP tablet when you restart.

If it is more than seven days since your last PrEP dose, start again with a double dose of two pills.

Other tips on how to take PrEP

What to do if you miss a pill

If you miss one, or even two pills occasionally, this will be fine. Don't stop PrEP, just carry on once you remember. Drug levels will still be high enough to protect against HIV. If you are missing several doses each week, please talk to the clinic about support.

If you use daily dosing and miss more than a week of pills, then restart with a double dose (two pills) and then continue with one pill a day.

Never take more than one double dose when you start PrEP. You only need one double dose at the start. More than one double dose in a week may be harmful.

Do not take more than a total of seven pills in one week.

- A pill box makes it easy to see whether you have taken or missed a dose. They only cost £1 or so from a pharmacy.
- Pick a regular time and try to stick to this each day. Link it to a routine task like brushing your teeth. It doesn't have to be the exact same time but it will help get you into a routine.
- If you have a break from PrEP and have risks during this time, it is important to have another HIV test.
- With on-demand dosing, if you miss the BEFORE dose completely, still take a double dose AFTER sex, and continue daily. Contact your clinic in case PEP is recommended (see below). Missed doses matter more if you are using on-demand rather than a daily dosing.

Is PEP recommended if I am on PrEP?

PEP stands for post-exposure prophylaxis and involves taking a combination of three HIV meds for one month.

PEP is rarely used, but if you do need it, the earlier you start PEP, the more likely it will work. PEP can be prescribed up to 72 hours after sex.

- If you have a risk when you haven't been taking PrEP, or enough PrEP, contact a clinic to discuss whether you might need PEP.
- Taking a double-dose of PrEP (if you still have some left) is a good idea as the earlier PEP is started the better it works.

Can I switch between daily and on-demand based dosing?

If you are able to use on-demand dosing, PrEP is very adaptable if your circumstances change.

If your HIV risk changes, you can stop and restart PrEP, or change the way in which you take it. PrEP can be individualised to your needs at different times.

Talk through ways of taking PrEP at your clinic and about how to stop or restart when you need to.

On-demand dosing is NOT an option:

- If you have hepatitis B.
- For women who want protection during receptive vaginal sex, as a seven day lead-in is needed.
- For trans women and trans men and non binary people who want protection from receptive vaginal/frontal sex.

Can I stop PrEP completely?

As with the flexibility for dosing, you might decide that you want to stop PrEP altogether.

Discuss your decision to stop with clinic staff.

You might want to discuss plans to stop PrEP with partner(s) and get tested for HIV and other infections together. Make sure you use a 4th generation HIV test four weeks after the last risk.

How you stop PrEP depends on which dosing you use.

Daily dosing: continue daily PrEP for seven days after the last time you had sex.

On-demand dosing: If you had a recent risk, continue taking PrEP at your regular time for another 48 hours. This means taking two doses, one for each of the two days after your last risk.

If in the future your circumstances change again, it is easy to restart PrEP.

If you stop PrEP and have a risk afterwards, contact your clinic in case post-exposure prophylaxis (PEP) might be needed. In the cases when PEP is used, it needs to be started as soon as possible (see page 22).

Credits and further information

This leaflet was produced by doctors and community advocates from the following organisations.

BASHH (SIG MSM)	www.bashh.org
HIV i-Base	i-base.info/prep
iwantprepnow.co.uk	iwantprepnow.co.uk
PrEPster.info	PrEPster.info
56 Dean Street	facebook.com/56DeanStreet
Mortimer Market Centre	cnwl.nhs.uk/service/mortimer-market-centre
cliniQ: sexual health for trans people	cliniq.org.uk
Sophia Forum	sophiaforum.net

Additional links:

PrEP in Scotland	prep.scot
PrEP in Wales	tinyurl.com/ycm2hfbw
IMPACT trial	prepimpacttrial.org.uk
Drug interactions	hiv-druginteractions.org
Trans people and PrEP	cliniq.org.uk
PrEP guidelines	bashh.org and bhiva.org
HPV vaccine for gay men	i-base.info/htb/31151

Appendix 2 - BHIVA Practical PrEP Guidance

BHIVA–BASHH Position Statement on PrEP in UK

Appendix 1: Practical guidance for healthcare workers

Sheena McCormack, Sarah Fidler, Laura Waters, Yusef Azad, Tristan Barber, Gus Cairns, Valentina Cambiano, Dan Clutterbuck, Monica Desai, David Dunn, Julie Fox, Yvonne Gilleece, Margaret Kingston, Charles Lacey, Heather Leake Date, Fabiola Martin, Alan McOwan, Anthony Nardone, Koh-Jun Ong, Roger Pebody, Andrew Phillips, Mags Portman, Killian Quinn, Iain Reeves, Ann Sullivan, George Valiotis

Purpose of the update and appendix

This update follows the NHS England update on the commissioning and provision of pre-exposure prophylaxis (PrEP) for HIV prevention (https://www.england.nhs.uk/2016/03/prep). The Appendix contains practical guidance for healthcare workers.

BHIVA–BASHH Position Statement on PrEP in the UK: Appendix 1

Who might need PrEP?

The risk of acquiring HIV is increased in:

1. MSM/trans women/trans men reporting condomless anal intercourse in the last 3/12 months and likely to do so again in following 3/12 months
2. The sexual partners of people who are HIV positive with a detectable viral load
3. HIV negative heterosexuals who have had condomless sex with a HIV positive individual, and likely to have condomless sex again with the same person, or another person with a similar status

Individuals fulfilling one of the criteria above who have requested PEP or had a bacterial STI in the last year or at the current visit should be considered at particularly high risk of HIV acquisition.
Partners of HIV-positive individuals should preferably be seen both with and without their partner if possible.
Individuals may present already on PrEP or with the intention to seek PrEP privately/online.

History and discussion to document

- Timing of last condomless sex acts
- HIV and STI screens in the last year, and date of the last HIV test
- History of bone or renal disease
- Importance of 3-monthly HIV/STI screen
- Importance of taking Truvada as directed
- Risks and benefits of online purchase of generic drug
- Risk reduction including information and support with chemsex as appropriate

Recommended tests

- Before or at time of starting PrEP:
  - 4th generation venous blood HIV test
  - Consider POCT and start PrEP same day if negative
  - HBV surface antigen (and start vaccination if immunity unknown; on-demand Truvada is not recommended in chronic hepatitis B infection and if continuous PrEP is started, hepatology review is required before cessation)
  - Serum creatinine and eGFR
  - Urinalysis
- On PrEP:
  - 3-monthly 4th generation venous blood HIV test +/- POCT
  - 3-monthly STI screen for MSM [*as per BASHH 2014 MSM guidance*]; STI screen as appropriate for heterosexuals
  - Urinalysis every visit (further investigation if protein 1+ or more)
  - Annual creatinine/eGFR (more frequent if abnormal at baseline or proteinuria or >50 or on concomitant medications that are relevant to renal function)

Note: POCT useful on the day of starting, and at any visit if risks were taken during a period when PrEP was not as per national guidelines on HIV testing.

2

Dosing

Event-based dosing for a single sex act comprises two tablets 2–24 hours before sex, one tablet 24 hours (22–26 hours) after the first dose, and another tablet 48 hours (46–50 hours) after the first dose.

- Heterosexuals/trans men/trans women: event-based dosing has not been investigated in heterosexuals; based on this and pharmacokinetic concerns, we recommend daily PrEP and do not recommend event-based PrEP. In the absence of other data, trans women and trans men should also be offered daily PrEP
- MSM: as daily and event-based PrEP showed similar efficacy, event-based PrEP should be discussed and offered.

Assessing adherence and adverse events

- Assessment 1-month after commencing PrEP (face-to-face, telephone, email or text) provides the opportunity to review adherence, adverse events and HIV/STI window periods
- Reasons for non-adherence including adverse events should be elicited and documented at each follow-up visit. Additional support, practical or psychological may be required. Adverse events should be reported through the yellow card scheme at https://yellowcard.mhra.gov.uk/

Coding and data collection

- Until processes for formal coding and outcomes monitoring are established, we strongly encourage clinics to collect data locally for visits when PrEP is started, continued or interrupted (including when interrupted because no longer at risk)

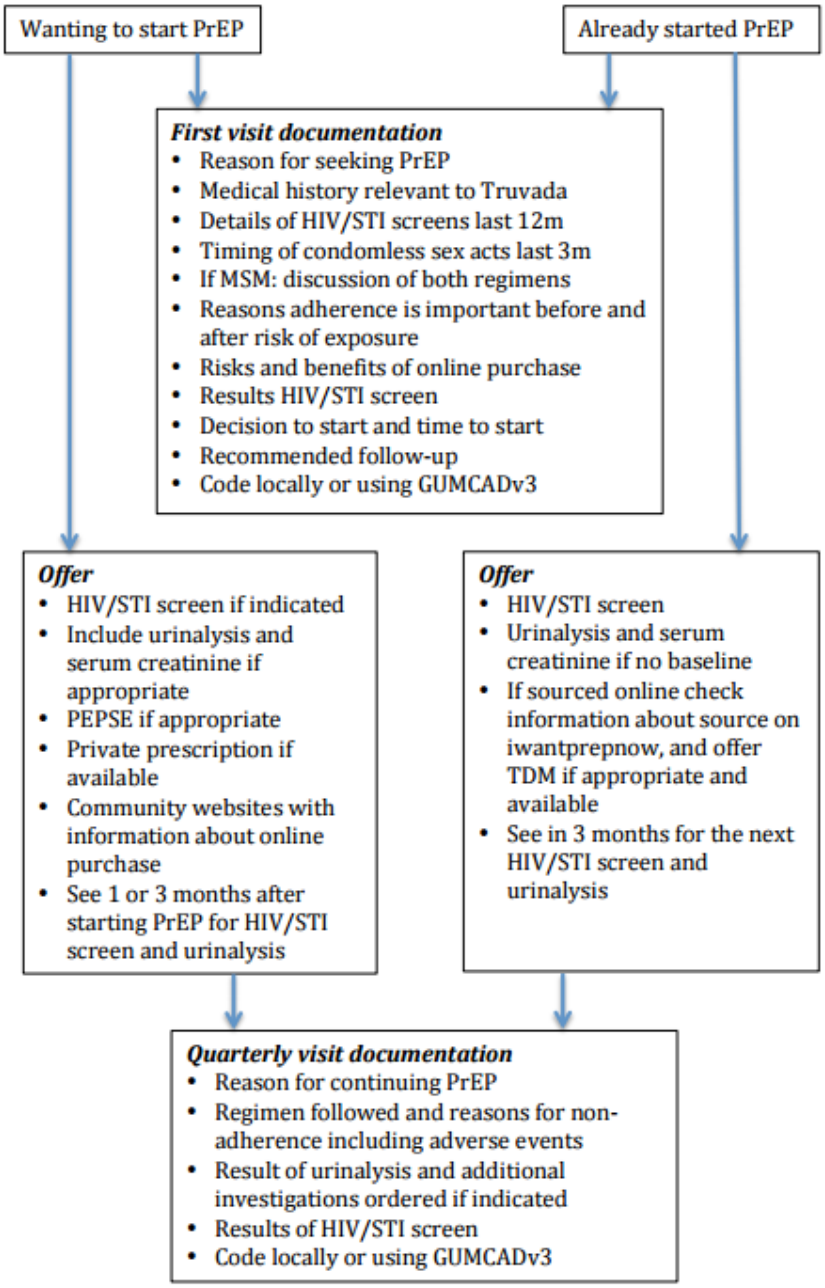
Online purchase of generic tenofovir/emtricitabine

- It is legal for a patient to obtain 3 months of generic drug via the internet for personal use
- A prescription is not required but some sellers may request this.
- The website www.iwantprepnow.co.uk has been set up by community advocates to provide information about PrEP and links to sellers. Sellers are added to the site only when generic drug has been purchased with no problems and therapeutic drug monitoring (TDM) has been carried out in at least one person showing presence of the drug.
- Supportive clinicians are working with 'I Want PrEP Now' to ensure generic drug efficacy, as far as possible, by sharing TDM results with an agreement to disseminate information if an unsatisfactory TDM result is obtained

Supplementary information that might be useful for clinics

- ***Flow chart***
- ***PrEP user information leaflet.*** This leaflet draws on the information provided by the Dean Street PrEP clinic, and the PROUD clinics, which are supporting PrEP users in their GU clinics, particularly Mortimer Market (Mags Portman) and King's (Killian Quinn). The draft was reviewed and amended by Simon Collins and Greg Owen as well as Dan Clutterbuck.
- ***Infographics.*** With thanks to Jean-Michel Molina and the IPERGAY team for providing the infographics for event-based dosing and to Laura Waters for providing a choice of symbols. These were sent to 128 PROUD participants for review. Of 17 who responded, 10 preferred the stick men.

Flow chart of procedures



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