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: 2.0, 24 Jul 2017

Chief Investigator: Professor Brian Gazzard

Sponsor: St Stephen's Clinical Research

Protocol Approval: St Stephen's Clinical Research

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

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<th>Title:</th>
<th>PrEP Impact Trial: A pragmatic health technology assessment of PREP and implementation</th>
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<tr>
<td>Short title:</td>
<td>PrEP Impact Trial</td>
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<tr>
<td>Protocol Number:</td>
<td>SSCR104</td>
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<tr>
<td>Trial drug:</td>
<td>Tenofovir Disoproxil (TD)/ Emtricitabine (FTC) either in its branded form (Truvada) or as a generic.</td>
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<td></td>
<td>The trial drug will be a UK or EU licensed drug for an off label use in accordance with established practice supported by clinical evidence. Depending on the current marketing authorisation for the specific drug(s) that are procured for the trial, the off-label use could be for PrEP or/and for event-based-dosing. Where branded product is supplied, it will be provided within the terms of this authorisation or off label for event-based use in accordance with established practice supported by clinical evidence. Where generic product is supplied, it will be bio-equivalent to the branded product and will be provided off label in accordance with established practice supported by clinical evidence.</td>
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<tr>
<td>Background and rationale:</td>
<td>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.</td>
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<td>Aim:</td>
<td>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</td>
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**Objectives:**


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.

<table>
<thead>
<tr>
<th>Planned Sample Size:</th>
<th>10,000 participants</th>
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<tr>
<td>Participant population:</td>
<td>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:</td>
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<tr>
<td></td>
<td><strong>A. Men (cisgender and transgender) and transgender women who:</strong></td>
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<tr>
<td></td>
<td>1. Have sex with men</td>
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<tr>
<td></td>
<td>2. Have had an HIV negative test during an earlier episode of care in the preceding year</td>
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<td></td>
<td>3. Report condomless intercourse (excluding oral) in the previous 3 months</td>
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<td></td>
<td>4. Affirm their likelihood of having condomless intercourse (excluding oral) in the next 3 months</td>
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<td></td>
<td><strong>B. HIV negative partners of an HIV positive person when:</strong></td>
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<tr>
<td></td>
<td>1. The HIV positive partner is not known to be virally suppressed (&lt;200 copies/ml for 6 months or more)</td>
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<tr>
<td></td>
<td>2. Condomless intercourse (excluding oral) is anticipated before treatment of the HIV positive partner takes effect</td>
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<tr>
<td></td>
<td><strong>C. HIV negative persons who:</strong></td>
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<tr>
<td></td>
<td>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</td>
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<table>
<thead>
<tr>
<th>Inclusion Criteria:</th>
<th>Participants will be considered eligible for trial enrolment if they fulfil all the following individual eligibility criteria:</th>
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<tbody>
<tr>
<td></td>
<td>1) Belong to one of the three high HIV risk populations described above;</td>
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<td></td>
<td>2) Aged 16 years or over (no upper limit);</td>
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<tr>
<td>Protocol Number</td>
<td>SCR104</td>
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</table>

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: To include Tenofovir Disoproxil (TD) alone or in combination with Emtricitabine (FTC). Tenofovir Disoproxil alone can only be recommended for participants at risk of HIV through heterosexual sexual risk due to lack of evidence for other populations. Tenofovir Disoproxil (TD): 300mg and Emtricitabine (FTC): 200mg

Regimen: Daily or event-based regimens (EBD). Daily involves taking 300mg 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
<table>
<thead>
<tr>
<th>Trial Outcomes</th>
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<tbody>
<tr>
<td>1.</td>
<td>Proportion of GUM clinic attendees that meet PrEP eligibility criteria, the proportion that is</td>
</tr>
<tr>
<td>2.</td>
<td>HIV and STIs:</td>
</tr>
<tr>
<td></td>
<td>a. HIV diagnoses reported by sites and identified through the national surveillance dataset</td>
</tr>
<tr>
<td></td>
<td>b. STI diagnoses (gonorrhoea, chlamydia, syphilis and hepatitis C) reported in the national</td>
</tr>
<tr>
<td></td>
<td>surveillance dataset</td>
</tr>
<tr>
<td>3.</td>
<td>Adverse Events</td>
</tr>
<tr>
<td></td>
<td>a. Serious suspected adverse drug reactions reported using the yellow card system</td>
</tr>
<tr>
<td></td>
<td>b. Antiretroviral resistance associated mutations in participants with incident HIV infection</td>
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</table>
**GENERAL TRIAL INFORMATION**

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**Funder:** NHS England

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**TRIAL SCHEMA**

**Participant Identification and Invitation – Pre-enrolment and Enrolment**
At Routine Visit or Group Consent Session, this may follow a call, outreach activity or interaction with a community organisation

1. PIS given to individual, trial discussed and eligibility checked
2. Individual agrees to take part and signs ICF
3. Individual Enrolled and Trial ID assigned

**Baseline Visit – First trial prescription**
1. Participants offered other risk reduction interventions including condoms, health education and safer sex promotion to reduce and modify high risk behaviour,
2. Clinical risk assessment performed according to established practice Clinic staff check understanding of PrEP and determine appropriate regimen with participant,
3. Prescribing clinician re-confirms eligibility and generates prescription, dispensed PrEP reported on log/eCRF
4. Next appointment arranged for 3 months or earlier if clinically indicated.
5. Coding complete on GUMCAD

**New PrEP Users**

**Previous PrEP Users**

**Good practice to check adherence within first month**

**Ongoing Follow-up (approximately every 3 months during ongoing risk)**
1. Ongoing risk and adherence checked, and participant offered relevant elements of available active risk reduction interventions, including condoms, health education and safer sex promotion, to reduce and modify high risk behavior,
2. Tests and assessments according to established practice,
3. Prescribing clinician verifies ongoing eligibility and generates prescription, dispensed PrEP reported on log/eCRF,
4. Check for serious suspected adverse drug reaction – if yes, report via yellow card system and on log/eCRF,
5. Next appointment arranged for 3 months,
6. Coding completed on GUMCAD.
<table>
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<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>AIDS</td>
<td>Acquired Immune Deficiency Syndrome</td>
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<td>CM</td>
<td>Concomitant Medication</td>
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<tr>
<td>EBD</td>
<td>Event Based Dosing</td>
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<td>FPFV</td>
<td>First Patient First Visit</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GP</td>
<td>General Practitioner</td>
</tr>
<tr>
<td>GUMCAD</td>
<td>Genitourinary Medicine Clinic Activity Database</td>
</tr>
<tr>
<td>HARS</td>
<td>HIV and AIDS Reporting System</td>
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<tr>
<td>HBV</td>
<td>Hepatitis B virus</td>
</tr>
<tr>
<td>HCV</td>
<td>Hepatitis C virus</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
</tr>
<tr>
<td>ICH-GCP</td>
<td>International conference of harmonization good clinical practice</td>
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<tr>
<td>MHRA</td>
<td>Medicines and Healthcare products Regulatory Agency</td>
</tr>
<tr>
<td>MSM</td>
<td>Men who have sex with men</td>
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<tr>
<td>SSAT</td>
<td>St Stephen’s AIDS Trust</td>
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<tr>
<td>SSCR</td>
<td>St Stephen’s Clinical Research</td>
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<tr>
<td>SmPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>PIS</td>
<td>Participant Information Sheet</td>
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<tr>
<td>PrEP</td>
<td>Pre-exposure prophylaxis (PrEP)</td>
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<td>UPCR</td>
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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 subgroups 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**

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 quarterly 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 10,000 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 drugs to be used in this trial are Tenofovir Disoproxil (TD)/ Emtricitabine (FTC) both of which are nucleotide/side analogue HIV-1 reverse transcriptase inhibitors. The HIV Pre-exposure prophylaxis (PrEP) Tenofovir Disoproxil (TD)/ Emtricitabine (FTC) will be UK or EU licensed and used off label in accordance with established practice supported by clinical evidence. Depending on the current marketing authorisation for the specific drug that is procured for the trial, the off-label use could be for PrEP or/and for event-based dosing. If branded product is supplied, it will be provided within the terms of this authorisation or off label for event-based use in accordance with established practice supported by clinical evidence. Where generic product is supplied, it will be bio-equivalent to the branded product and will be provided off label in accordance with established practice supported by clinical evidence.

The drug should be taken orally in accordance with the drug SmPC and current package insert.

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 participant.

Participants opting for the EBD regimen will be supplied with the information leaflet commissioned by the BASHH MSM Special Interest Group (Appendix 1) which 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 (TDF)/ 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:
  o 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,
  o Providing the participant with a copy of their signed ICF and PIS.

5.3 **Trial ID Assignment**

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

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.

- 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 4\textsuperscript{th} 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

<table>
<thead>
<tr>
<th>Trial procedures</th>
<th>Recruitment/ Baseline</th>
<th>3-monthly</th>
<th>Annually</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Inclusion/exclusion criteria</em></td>
<td>×&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Informed consent</em></td>
<td>×</td>
<td></td>
<td></td>
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<tr>
<td><em>Enrolment on trial database</em></td>
<td>×</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Record of drug dispensing</em></td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
</tbody>
</table>

**Standard assessments and procedures (as part of routine clinical care)**

- **HIV 4<sup>th</sup> Generation test**: ×<sup>b</sup> × × ×
- **HIV point of care test**: ×<sup>b</sup> × × ×
- **Hepatitis B status confirmation (+/- testing and vaccination)**: ×<sup>c</sup> × × ×
- **Hepatitis C testing**: ×<sup>d</sup> ×<sup>d</sup> ×<sup>d</sup> ×<sup>d</sup>
- **Renal (Serum Creatinine to estimate creatinine clearance)**: ×<sup>e</sup> ×<sup>e</sup> × ×
- **Urinalysis**: × × ×
- **STI screen (Chlamydia, Gonorrhoea, Syphilis)**: × × × ×
- **Assessment of pregnancy risk**: ×<sup>f</sup> ×<sup>f</sup> ×<sup>f</sup> ×<sup>f</sup>
- **Prescribing and dispensing of drug**: × × ×
- **GUMCAD O codes assigned and entered**: × × ×
- **Yellow card check**: × × ×

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(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 file 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 participants trial ID will be clearly documented on their copy of the completed informed consent form.

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. If recruitment is slower than anticipated and 10,000 participants are not likely to be recruited by the end of 36 months of the trial, the TSC will make a recommendation about the duration of the trial.

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 10,000 participants to receive PrEP.

Estimates from GUMCAD suggest that the total eligible MSM population across all GUM clinics is approximately 10,000. Therefore, the size of the total eligible population (MSM and non-MSM) across all GUM clinics can be estimated with a precision within the range ± 480 to ±1150. These
precision estimates have been derived from a range of simulations using a number of assumptions derived from available GUMCAD data. 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).

Assuming that PrEP uptake in the eligible population lies within the range 20% to 60%, a trial size of 10,000 participants will 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. A trial with 10,000 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. 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 and health-seeking behaviour 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 quarterly 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.
12 REFERENCES


13 Protocol Signature Page

Principal Investigator

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.

Name of Principal Investigator:  
Signature:  
Date:
14 APPENDICES

Appendix 1 – Guide to PrEP Leaflet

Buying PrEP online:
Safe use and
NHS monitoring

This booklet is for people who want to use PrEP that they buy online, or who are thinking about buying PrEP online.

PrEP refers to a combination pill containing tenofovir DF and emtricitabine. When taken correctly, PrEP dramatically reduces the risk of HIV sexual transmission.

PrEP is not currently provided free by the NHS, but some NHS clinics provide free monitoring and advice.

Although NHS England announced in June 2016 that PrEP would not be funded, NHS Scotland are still considering this.

Contact details:

This booklet was produced in June 2016. As information about PrEP is likely to change based on new research please see the online version on the i-Base website for updates.

Information in this booklet is meant to be used in discussion with your doctor.

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This booklet was written by doctors and community advocates from the following organisations.

HIV i-Base (www.i-Base.info), 56 Dean Street, Mortimer Market Centre, BASHH special interest group for men who have sex with men (MSM SIG), www.iwantprepnow.co.uk, www.PrEPeter.info and cliniQ.

Written by Dan Clutterbuck, Simon Collins, Sheena McCormack, Achyuta Nori, Will Nutland, Greg Owen, Mags Portman, Michelle Ross, Martina Toby, Laura Waters and Aedan Wolton.

June 2016
**PrEP: A bit of 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 – in this case HIV. So, PrEP is used by HIV negative people to prevent them from becoming HIV positive.

Currently PrEP uses oral tablets. For gay men and trans women PrEP needs to be a combination pill containing two drugs: tenofovir DF and emtricitabine. The brand name for this is “Truvada”, but generic versions include Tenvir-EM. More on this later.

Both tenofovir DF and emtricitabine are widely used medicines to treat HIV. The combined pill was approved for HIV treatment in 2004, and for use as PrEP in the United States in 2012.

Tenofovir DF as a single drug is supported by several studies for reducing risk from heterosexual (vaginal) sex.

**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 are related to a higher risk of HIV. These include:

- A recent STI (especially rectal infection or syphilis).
- Use of PEP (post-exposure prophylaxis).
- Using some recreational drugs (crystal meth, mephedrone or G) - also known as ChemSex.

Any of these mean you are likely to benefit even more from taking PrEP.

Discuss this with your doctor or nurse if you are not sure.

**Is there anyone who should not take PrEP?**

PrEP should not be used:

- By people who are HIV positive.
- PrEP is usually not necessary if:
  - The negative person is only having sex with HIV positive partners who are on treatment with an undetectable viral load. Being undetectable dramatically reduces the risk of transmission.

**How well does PrEP work?**

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

The PROUD study was carried out in several sexual health clinics in England. PROUD enrolled more than 500 gay and other men who have sex with men (MSM) and included some trans women. One group took daily PrEP as soon as they enrolled in the study. The other group started PrEP after a year.

In October 2014, PROUD reported that PrEP dramatically reduced the risk of HIV infection (by 86%). Nearly all new HIV infections occurred in people in the delayed PrEP group. The few infections that occurred in the immediate PrEP group were in people who were not actually taking PrEP.
**Guide to PrEP**

This means that the benefit of taking PrEP is likely to be higher than 86%.

The IPERGAY study, from France and Canada, also reported an 86% reduction in a similar high risk group of gay men and trans women. IPERGAY used event based dosing (EBD) rather than daily PrEP. There is more information on event based dosing later in the leaflet.

There are also good results from heterosexual studies. The Partners PrEP study in Africa report a 96% reduction in new HIV infections in people taking PrEP correctly.

**PrEP and side effects**

The majority of people taking PrEP do not report side effects. However, like all other medicines, PrEP has the potential to cause side effects. 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.

PrEP can also affect your kidneys which is why monitoring is important.

In the small proportion of people taking PrEP who developed reduced kidney function, these changes reversed on stopping PrEP. This risk is higher if you are older than 40 or if you already have reduced kidney function when you start PrEP.

PrEP can also reduce bone density by 1-5% - causing slight thinning of the bones. This loss reverses after PrEP is stopped.

This side effect might be more important if you already have low bone density related to other factors.

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**Guide to PrEP**

It might also be important if you are younger than 30 as your bones are still developing.

So far there have not been any reports of bone fractures related to PrEP use.

Event based PrEP might reduce the risk of these side effects, though this has not been formally studied yet.

**PrEP and drug resistance**

If you take PrEP correctly, there is very little chance of developing resistance.

If you become HIV positive while taking PrEP, there is a small risk of developing drug resistance to one or both drugs. This means that these drugs may not work as well in future treatment for HIV.

In PrEP studies, very few people became HIV positive whilst taking PrEP. In those who did, less than 1 in 20 developed drug resistance.

The highest risk of drug resistance is if you start PrEP when you are already HIV positive. It can also happen if you have a break from PrEP and don’t check your HIV status before restarting. Drug resistance is also possible if you don’t take enough doses for protection and become HIV positive.

In February 2016, a case was reported of someone who became HIV positive even though he was taking his PrEP correctly. This was because they caught HIV from a partner who was already resistant to the drugs in PrEP. This is a very rare event. Currently, drug resistance to tenofovir DF and emtricitabine is very uncommon in the UK.
**PrEP and other STIs**

PrEP will not protect against other STIs. This is an advantage of also using condoms.

Other STIs generally are manageable, but sometimes can cause unpleasant symptoms, some of which can be serious. This is why we suggest getting regular checks for STIs when you take PrEP and use condoms when you can.

**Does PrEP interact with any other medications?**

Tenofovir DF and emtricitabine don’t interact with many other medicines. (Interaction means that two or more drugs combined together can cause problems or side effects).

You should always tell your doctor (including your GP) if you are prescribed other medicines. You can also ask a pharmacist. Say you are taking PrEP so that they can check for any interactions, including with over-the-counter meds.

One important interaction is between tenofovir DF and non-steroidal anti-inflammatory drugs (NSAIDs), especially diclofenac. Together these can cause kidney problems. Other medicines from within this class include ibuprofen and naproxen. Avoid using these medicines if you are taking PrEP, or let your doctor know if you need to take them.

For trans people taking PrEP, there is no reason to expect PrEP will change the effectiveness of hormone therapy. This will hopefully be the focus of future direct studies.

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**Buying PrEP online**

It is legal to buy generic PrEP for personal use, sourced from outside the EU.

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 buying three months of daily PrEP.

One of the most widely-used versions of generic PrEP is called Tenvir-EM. This is manufactured by Cipla, a company approved by the US drug regulatory agency. It is important to only use generic versions of PrEP made by manufacturers with this approval. You can find a list here:

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

Some clinics can offer a blood test to see whether you have active drug levels.

This is called Therapeutic Drug Monitoring (TDM).

Your clinic might be able to advise you if someone else using the same PrEP medicine or supplier has already been tested. So far, TDM has not shown any problems with PrEP bought online and over 50 samples have been tested.

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 combination pill that contains BOTH tenofovir DF and emtricitabine.** This is especially important for gay men and trans women. For example, you need Tenvir-EM rather than Tenvir.
UK community websites have lots of information about PrEP and how to buy it online:

- iwantprepnow.co.uk
- prepster.info
- i-base.info/qa/category/prep

We cannot state that there is absolutely no risk if you choose to buy PrEP online because the PrEP is not sourced directly from the manufacturers.

Some clinics will support you and provide advice and monitoring if you buy PrEP online. But currently the NHS will not take responsibility for the pills, because the clinic has not supplied them.

So use the information on the websites above to make sure you are getting the right pills.

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**Before you start**

Please talk to a health advisor, nurse or doctor at the clinic. They can help you if you are planning to take, or are already taking PrEP.

It is important to have an HIV test before or as you start. PrEP can only be used if you are HIV negative. If you are already HIV positive and don’t realise it, you could develop resistance to drugs that you will need for treatment.

Ask for a ‘4th generation’ HIV blood test. This is also called a ‘combined antigen/antibody’ test. This tells you your HIV status approximately 4 weeks ago.

Most finger prick tests are currently ‘3rd generation’. They tell you your HIV status approximately 3 months ago. So don’t rely on a fingerprick test alone before you start PrEP.

If you are just starting PrEP and have a risk in the last 4 weeks, have another 4th generation HIV blood test 4 weeks after starting, just to be sure an early infection was not missed.

Don’t start PrEP if you have flu-like symptoms and a recent HIV risk. This is because you need to rule out very recent HIV infection called seroconversion.

If you are starting PrEP after PEP, it is best to start immediately if you have ongoing risks. Ideally you should have an HIV blood test around the time you finish PEP/start PrEP plus another HIV blood test 4 weeks into PrEP.
**Guide to PrEP**

**Check your kidneys**
Kidney monitoring just involves a blood test for creatinine, and a urine test for protein. These should ideally be done just before or on the day you start.

**Check for other sexually transmitted infections (STIs)**
This is always a good idea!

**Test for hepatitis B (HBV)**
This is essential because PrEP medicines are active against both HIV and HBV.
This is a good time to be vaccinated, or to boost a previous vaccine.

You can still use PrEP if you have Hepatitis B, 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.

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**Routine care if you have already started PrEP**

Once you have started PrEP, monitoring is 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 ‘antigen/antibody’ HIV blood test.
- Have a full screen for other sexually transmitted infections (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.

**Every 12 months**
- Have a blood test to check your kidney function.
Other considerations

Although PrEP is very effective at stopping HIV, it can also change how you feel about your sex life, including risks for HIV. Your clinic can provide a chance to talk about this in confidence.

Talk to your nurse, doctor or health advisor about how you feel about PrEP, and how PrEP affects the risks you sometimes take.

Other things affect taking risks, including how you feel about yourself, pressure from other people, and using alcohol and recreational drugs. Extra support is also available that can help with many of these issues.

Health issues: Tell the nurse or doctor if your health has changed, or if you start new medications.

Other sexually transmitted infections are important. This is a reason to still use condoms at least some of the time.

How to take PrEP

This section discusses different ways that you can take PrEP.

It takes a little time for HIV infection to occur. Even if the sex only lasted a few minutes, it takes about 30 minutes after sexual exposure for the virus to get through genital skin and enter the body. It then takes time for the infection to take hold, although when this happens varies for different people.

For PrEP to be most effective, the medicine needs to be at protective levels throughout this time. As the body takes a while to absorb drugs, this means PrEP needs to be taken both BEFORE sex and for several days AFTERWARDS.

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

For vaginal sex you need to take PrEP every day. You also need to take PrEP daily for two weeks (ideally three) to reach drug levels that give the highest protection. This is because PrEP does not get into the vaginal tissues as well as it gets into rectal tissues.

For anal sex daily PrEP has the most evidence. But other studies have used alternative dosing including event-based dosing (EBD) in IPERGAY. This involved taking two pills before sex as a double dose and a single pill 24 and 48 hours after.

Although there is less data on using EBD, it is likely to still be very effective.

EBD is NOT suitable if you are a cis woman having vaginal sex. There is limited evidence on PrEP requirements for trans women who only have vaginal sex; daily dosing is considered safer.
There is currently a lack of data about PrEP for trans men taking testosterone and having vaginal sex. Long term testosterone use causes changes in the vaginal tissue; we do not know whether this affects HIV risk or efficacy of PrEP.

Talk to your doctor about what dose and timing is suitable for you and the level of protection that you need.

**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.

For people who routinely have sex every week, daily PrEP is likely to be a better dosing option.

Daily PrEP allows some flexibility in that missing an occasional dose is not likely to make much 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, after two weeks of daily PrEP, 4 or more doses during the week will give good protection.
- Remember that for vaginal sex you need to take PrEP every day, and continue daily.

**Event Based Dosing (EBD): 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 option is important if you don’t have sex without condoms very often, and also if you usually know when you will have sex.

EBD is not recommended if you have hepatitis B.

If you are buying PrEP, event based dosing is also less expensive because you need fewer pills. Taking PrEP in this way may reduce the likelihood of developing kidney or bone problems because you would take fewer pills.

Taking PrEP before and after a risk is still very effective. But the “before-sex” dose is important. You need to make sure that there is enough medicine in the body when you have sex.

Event-based dosing involves:

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

You should aim to take two single pills after you have sex, roughly 24 hours and 48 hours after the first double-dose.

EBD is also sometimes called “on demand” dosing.

Real-life dosing examples are included on the next three pages.
Real-life examples for Event Based Dosing (EBD)

1. **EBD: If you have sex once a week**

   **BEFORE SEX**
   - 2 PrEP tablets at least 2 hours & ideally 24 hours before sex

   **AFTER SEX**
   - 1 PrEP tablet 2 hours after the 1st
   - 1 PrEP tablet 48 hours after the 1st
   - Total of 2 tablets after sex
   - *2 hours before or after planned time is OK*

   ![Weekly Dosing Chart]

   If you think you might have sex on Friday or over the weekend, you would ideally take two pills on Thursday; let's say you took them at 10 pm.

   If you have sex on Friday at 7 pm, then you would take a single pill on Friday and Saturday aiming to take the pill at around 10 pm. You have then had two doses after sex.

   These times are all approximate - you would 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 even just before sex, some PrEP is always better than none.
Other tips on how to take PrEP

What to do if you miss a pill

If you miss one, or even two pills occasionally, don’t stop PrEP. Just carry on once you remember. There is still likely to be enough drug in your body to protect against HIV. If you are missing several doses each week then talk to the clinic about support.

If you use daily dosing and miss more than a week of pills take a double dose (2 pills) if you know you are going to have a risk. Then carry on as normal with a daily pill.

Never take more than one double dose when you start PrEP. You only need one double dose at the start. Carrying on double dosing after the first dose is not needed and may do you harm.

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 - or contact i-Base who can post you one for free. (www.i-Base.org.uk)

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.
Guide to PrEP

If you have a risk in the future when you haven't been taking PrEP, contact a clinic as soon as possible to access PEP. The earlier you do this, the more likely that PEP will work. PEP is still prescribed up to 72 hours after sex.

If you still have some PrEP left, take daily PrEP to provide some protection before you get to the clinic. PEP stands for post-exposure prophylaxis and involves taking a combination of three HIV meds for one month.

**Tips on Event Based Dosing (EBD)**

If you are having sex over several days, try to aim for the same time and not to miss any doses. Think of an easy time for you to remember the doses after sex.

If you have sex again and it is 6 days or less since your last PrEP dose, you do not need to repeat the double dose. This is because there will still be some PrEP left in your body from your previous doses.

If you missed the BEFORE dose completely, still take a double dose AFTER sex, and continue daily, but contact your clinic. This is because using an additional HIV drug might be recommended, depending on the risk involved, to make PrEP into PEP.

Missing doses matters more if you are using EBD rather than a daily regimen.

Have an HIV test as soon as possible if you had a break from PrEP and remained at risk.

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**Can I switch between daily and event-based dosing?**

PrEP is a great way of reducing your risk of HIV, but your circumstances can change over time.

If you find 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.

Some people might start by taking daily PrEP and then switch to event-based PrEP if their risks are less frequent.

Others might start with event-based PrEP and then switch to protecting every week - and then switch to daily PrEP.

Others might switch between different dosing strategies every few months depending on how much risk they think they have, whether this is acceptable to them, the cost and other factors.

Use your visits to the clinic to talk through the ways of taking PrEP and how to stop or restart when you need to.

EBD is not recommended if you have hepatitis B.
Guide to PrEP

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.

If possible, discuss any plans to stop PrEP with partner(s) and get tested for HIV and other infections together. Make sure you both have a 4th generation HIV test four weeks after the last risk.

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

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

If you have stopped PrEP and have a risk in future, you should contact a clinic about PEP. Ideally this should be as soon as possible and no later than 72 hours after the risk.

You can use your PrEP meds immediately to cover the period until you get to the hospital for PEP.

Guide to PrEP

Credits and further information

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

BASHH special interest group MSM
www.bashh.org
HIV i-Base
www.i-base.info
iwantprenow.co.uk
www.iwantprenow.co.uk
PrEPster.info
www.PrEPster.info
56 Dean Street
www.facebook.com/56DeanStreet
Mortimer Market Centre
www.cnwl.nhs.uk/service/mortimer-market-centre
cliniQ: sexual health and well-being for trans people
www.cliniq.org.uk

Cover graphic: thanks to IwantPEPnow.co.uk
Appendix 2 - BHIVA Practical PrEP Guidance

BHIVA–BASHH Position Statement on PrEP in UK
Appendix 1: Practical guidance for healthcare workers

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Purpose of the update and appendix

8HIVA–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 PrEP 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:
  o 4th generation venous blood HIV test
  o Consider POCT and start PrEP same day if negative
  o 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)
  o Serum creatinine and eGFR
  o Urinalysis

• On PrEP:
  o 3-monthly 4th generation venous blood HIV test +/- POCT
  o 3-monthly STI screen for MSM [as per BASHH 2014 MSM guidance]; STI screen as appropriate for heterosexuals
  o Urinalysis every visit (further investigation if protein >1 or more)
  o 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.
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/](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.iwantpreppnow.co.uk](http://www.iwantpreppnow.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.
BHIVA–BASHH Position Statement on PrEP in the UK: Appendix 1

Flow chart of procedures

- Wanting to start PrEP
- Already started PrEP

First visit documentation
- Reason for seeking PrEP
- Medical history relevant to Truvada
- Details of HIV/STI screens last 12m
- Timing of condomless sex acts last 3m
- If MSM: discussion of both regimens
- Reasons adherence is important before and after risk of exposure
- Risks and benefits of online purchase
- Results HIV/STI screen
- Decision to start and time to start
- Recommended follow-up
- Code locally or using GUMCADv3

Offer
- HIV/STI screen if indicated
- Include urinalysis and serum creatinine if appropriate
- PEPSE if appropriate
- Private prescription if available
- Community websites with information about online purchase
- See 1 or 3 months after starting PrEP for HIV/STI screen and urinalysis

Quarterly visit documentation
- Reason for continuing PrEP
- Regimen followed and reasons for non-adherence including adverse events
- Result of urinalysis and additional investigations ordered if indicated
- Results of HIV/STI screen
- Code locally or using GUMCADv3

Offer
- HIV/STI screen
- Urinalysis and serum creatinine if no baseline
- If sourced online check information about source on iwantprepnow, and offer TDM if appropriate and available
- See in 3 months for the next HIV/STI screen and urinalysis