**PROTOCOL FOR NEW ZEALAND PREP STUDY: NZ PrEP**

**Aims and/or hypothesis**

The overall aim of this research is to assess the implementation of a novel HIV prevention intervention (PrEP or pre-exposure prophylaxis) at Auckland Regional Sexual Health Service (ARSHS) clinics to individuals at high risk of HIV infection. The purpose is reduce new HIV infections in participants and eventually the rest of NZ.

**Specific objectives are to investigate:**

a) Acceptability of PrEP for those invited into the study; by measuring adherence; duration; retention;

b) Risk behaviours on PrEP including sexual partnering; condom use; STI and HIV incidence;

c) Factors (socio-demographic and attitudes) associated with PrEP acceptability, adherence, retention and behaviours;

d) The views and experiences of PrEP users including disclosure; stigma; sexual negotiation.

**METHOD**

**Design: Open-label single-arm treatment evaluation study.**

Participants will be recruited consecutively from HIV negative Takataapui, gay and bisexual men who have sex with men (GBM) attending Auckland Regional Sexual Health Service (ARSHS) who fit the study inclusion criteria.

**Inclusion Criteria**

To be eligible to participate men will have to:

* Be aged 18 or over and be eligible for funded care in New Zealand
* Be resident in Auckland
* Be willing and able to provide informed written consent for participation
* Be willing and able to take part in all required study procedures
* Be willing to provide telephone number(s) and/or email addresses to be contacted during the study period
* Have reasonable proficiency in written and spoken English (necessary to complete attitude, behavioural and lifestyle surveys)

They must also have the following behavioural eligibility criteria :

* Being likely to have multiple events of condomless anal intercourse (CAS) in the next 3 months (sustained risk) and also have any of the following:
* A regular sexual partner of an HIV-infected man who is not on anti-retroviral therapy or has detectable viral load with whom condomless anal sex has occurred in the previous 3 months OR
* At least one episode of receptive condomless anal intercourse with any casual male partner with HIV infection who is not on anti-retroviral therapy or with a male partner of unknown HIV test status in the previous 3 months OR
* A diagnosis of rectal gonorrhoea or rectal chlamydia during the previous 3 months OR
* Other high-risk behaviour such as a history of methamphetamine use in the previous 3 months

**Exclusion Criteria**

Potential participants will be excluded for any of the following reasons:

* Anyone who is HIV-1 infected at baseline or who has symptoms consistent with acute HIV infection
* Anyone unwilling to adhere to any of the required study procedures including attendance at scheduled assessments.
* Anyone unwilling to provide written consent to participate
* Anyone with an estimated creatinine clearance (glomerular filtration rate [GFR]) of less than 60ml per minute.
* Anyone with clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity (including nausea, vomiting, unusual or unexpected stomach discomfort, and weakness)
* Anyone concurrently taking a nephrotoxic agent (e.g., high-dose non-steroidal anti-inflammatory drugs / NSAIDs)
* Anyone who has an allergy to tenofovir disoproxil fumarate and/or emtricitabine (based on self-report or recorded).
* Anyone with mental health issues, memory loss or other cognitive impairment or intellectual disability that may compromise participant safety and/or regimen adherence
* Anyone with co-existing factors or conditions that may compromise a participant’s retention in the study (eg incarceration, planned relocation or potential absence from Auckland for a period of 3 months or longer during the course of the study

**Sample Size**

Recruitment will continue until 150 participants have been enrolled or 12 months from the initiation of the study-whichever occurs sooner- to allow for a minimum of 12 months of follow-up time. The proposed sample size is limited by available funding and the requirement that the ARSHS be able to absorb the anticipated demand within its current contracted volumes; however it is large enough to achieve the study aims for an open-label single-arm treatment evaluation study as no randomization and blinding procedures will be used and therefore do not need to be accounted for in analyses.

 It is important for reasons of equity and access that participants are representative of the Auckland region community of Takataapui, gay and bisexual men who have sex with men. Previous studies have found that non-European ethnicity is associated with lower rates of retention and adherence to medication and follow-up. Therefore recruitment of the 150 participants will be in quotas: 75 European, 75 non-European (30 Maori, 30 Pacific, 15 Asian).

Power calculation 1: We will have 85% power to detect if retention of non-Europeans at 48 weeks is 60% or lower vs 80% in Europeans if non-Europeans comprise half (n=75) the entry sample.

Power calculation 2: We will have 81% power to detect a change in high risk behaviour from 10% at baseline to 21% at 48 weeks if 120 participants (80%) are retained.

Power calculations were informed by the following data. In a US PrEP demonstration project, patient retention at 48 weeks was 79%, being lower (63%) among African American GBM.18 In a UK PrEP demonstration project, 10% of patients on PrEP at baseline reported 10+ condomless sex partners in the prior 3 months, increasing to 21% at 48 weeks.

 The participants’ demographic data will be reviewed when 50% of the sample has been enrolled into the study. Specific community engagement will be arranged to increase and encourage uptake by specific sectors of the community, for example of Tatataapui, Asian or Pacific participants if quotas are not fulfilled.

**Recruitment and Enrolment**

GBM at elevated HIV risk will be recruited via: (i) patients attending SHCs for routine HIV and STI screening or treatment; (ii) a study waiting list ([www.nzaf.org.nz/news-and-media/news/update-prep-demonstration-project/](http://www.nzaf.org.nz/news-and-media/news/update-prep-demonstration-project/)); (iii) a dedicated study website; (iv) targeted promotion on social media and dating apps; (v) community partner organisation networks and media releases; (vi) GP or self-referral.

**Determining Eligibility and Clinical Data collection**

All men attending ARSHS who are potentially eligible and interested in participating will be given verbal information and a copy of the participant information sheet about the study purpose and procedures in the initial screening consultation. They will undergo routine standard of care procedures including serology for HIV, syphilis, hepatitis A, B and C, and multi-site chlamydia and gonorrhea testing by Becton Dickenson ViperTM . Additional tests will include renal and liver biochemistry tests and urinalysis to check for pre-existing renal or liver disease and proteinuria.

The participant information sheet will outline potential risks and benefits of PrEP and the study procedures that will need to be adhered to, including the requirement for regular attendance for clinical follow-up and testing and completion of on-line behavioural surveys. They will be advised that written consent is required to participate in the study and they will be given copies of the consent form and participant information sheet to take away and review. (Visit 0 on attached schedule of visits).

Visit 1 will be scheduled a week later with the study research nurse. This will be to discuss and review results from the initial visit, treat any diagnosed sexually transmitted infections (STIs) and to ensure the person has read and understood the participant information sheet. The nurse will answer any questions they may have regarding participation in the study and will explain all test results, check for exclusion criteria and explain the consent form. All those testing positive for HIV will receive usual care with further investigations and clinical follow-up arranged with ARSHS at the time of diagnosis.

HIV seronegative participants will be enrolled into the study if there are no exclusion criteria and they are prepared to give written informed consent. Fully funded medication will be provided to participants during the study period of 24 months. It is anticipated that Truvada will be licensed as PrEP by Medsafe within the next 12 months as Gilead has lodged an application now that it has been approved in Australia. If participants wish to continue PrEP once the study is completed they will be advised they can continue to access this from the ARSHS however it will no longer be funded.

All participants will also receive risk reduction counseling with a peer educator at Visit 1 and be given free condoms. After which all participants will receive a prescription for a fixed-dose co- formulation of FTC and TDF (i.e., TRUVADA) prescribed for daily administration orally. (Each FTC/TDF tablet contains 200 mg of FTC and 300 mg of TDF (equivalent to 245 mg of tenofovir disoproxil). The study product will be supplied by Gilead Sciences (Foster City, USA). The nurse will discuss adherence, possible adverse effects of the medication and symptoms of HIV seroconversion. Participants will be supplied with the phone numbers of the research nurse and the ARSHS 0800 number to ring if they have any questions or concerns about the study or the medication, or if they experience any possible symptoms of HIV seroconversion. They will also be supplied with contact phone numbers for Maori health support if required (see participant information sheet).

All participants will be phoned by the research nurse 1 week after commencing PrEP to check for any adverse effects or adherence issues. (Telephone consult week 1 on attached schedule of visits)

Further follow-up visits will be scheduled 3 monthly during routine clinics at ARSHS (see attached schedule of visits). Adherence will be assessed by self-report and participants will be asked about possible side effects or possible HIV seroconversion symptoms. Any serious adverse events such as anaphylaxis or renal toxicity will be reported as soon as possible to Gilead Sciences.

Risk reduction and condom use will be routinely discussed at each follow-up visit to reinforce the initial risk-reduction counselling. Testing for HIV, STIs, and renal and liver biochemistry tests will be conducted at each of the scheduled follow-up visits by clinical staff. A sample of blood will also be taken to be stored for testing overseas for therapeutic drug monitoring.

Participants will be reminded to complete their on-line behavioural survey at each follow-up visit. If this is not completed within 3 days of each study visit they will receive reminder prompts from ARSHS staff.Clinical staff will be provided with a checklist for each visit to ensure all study procedures are adhered to. The research nurse will contact all participants within 7 days of each visit to inform them of their test results. Those with any incident HIV infections or STIs will be recalled for treatment and further investigations if indicated as per normal clinic protocols. If there are any abnormal results indicating that medication should be discontinued, they will be recalled to the clinic for further assessment with a doctor. Those that choose to withdraw from the study for any reason will be clinically followed up if they have been at risk of acquisition of HIV or other sexually transmitted infections or have had any adverse reactions to study medication.

**Adherence to PrEP**

Adherence is critical for PrEP to be effective in preventing HIV acquisition.

Adherence will be assessed by 4 measures:

* Self-report
* Pharmacy dispensing records
* Behavioural surveys
* Therapeutic drug monitoring

**Clinical Data Collection**

The research nurse will enter participant clinical data into a password-protected database set up specifically for this study. The database will be stored securely in the network drive of a password-protected Auckland District Health Board (ADHB) computer behind ADHB firewalls for later analysis. Participants’ records will be assigned a unique numeric identifier so the study data can be linked to their health records. No other unique patient identifying information will be entered into the study database.

**On-line Data Collection**

Participants will also be required to complete an on-line self-administered attitude, behavioural and lifestyle survey within 3 days of enrolment and will be asked to complete further surveys within 3 days of each study visit or if they withdraw for any reason. Those that decline PrEP will also be invited to complete the on-line behavioural survey which will include questions on their reasons for declining PrEP, so that characteristics of those that decline PrEP can be compared with those of participants. The behavioural survey will collect data on demographics of participants such as age, ethnicity, educational status. There will be further questions about attitudes to PrEP use, perceived benefits and disadvantages of PrEP, adherence to PrEP, numbers of regular and casual sexual partners following commencement of PrEP, use of recreational drugs and numbers of episodes of condomless anal sex encounters with both casual and regular partners.

The behavioural survey will be hosted on a secure remote website that is password protected and accessible only by members of the research team. The behavioural survey will not ask for nor record a person’s full name. Participants will complete their behavioural surveys by providing the unique participant numeric identifier allocated to them at clinic enrolment. They will be provided with a card containing details of their unique identifier, the website address of the survey and contact details of the research team if they have any questions. This information will also be emailed or tested to them following their enrolment visit. Unique participant identifiers are necessary to monitor whether participants’ experiences e.g. condom use have changed over time longitudinally, and in order to link respondents’ self-reported behaviours with their biological and study related data collected at each clinic assessment. The behavioural dataset will be periodically downloaded from the survey website and stored securely at the University of Auckland, School of Population Health behind University firewalls and access will be password protected. Responses to the survey will be pooled at the University of Auckland.

**Main outcome measures will be:**

* Time to accrual of 300 person years of follow-up on TRUVADA
* Seroconversion-free time on PrEP
* Time to discontinuation  of PrEP
* Adherence of prescribed doses taken orally in the prescribed period
* Incidence of HIV
* Incidence of STIs -rectal gonorrhea, chlamydia,  syphilis and viral hepatitis
* Incidence of adverse reactions –any serious adverse reactions that occur will be notified to Gilead Sciences as soon as possible
* Any adverse events leading to interruption or discontinuation of the study product  (TRUVADA)
* Psychological and behavioural impact of PrEP including quality of life, effect on relationships, numbers of sexual partners, condom use and recreational drug use etc(see draft survey questionnaire).

**Data Analysis**

Analysis will only be conducted on grouped data and the researchers will ensure that no one person’s responses can be identified when the results are reported or summarised. Linkage of clinical and behavioural databases will be done using the unique study identifying numbers generated at enrolment. Analyses will be conducted using appropriate longitudinal regression models with time-varying exposures.

| **Procedures** | **Screening** **(Visit 0)** | **Baseline** **(Visit 1)** | **Telephone consult** **Week 1** | **Visit 2****Week 4** | **Visit 3****Week 12** | **Visit 4****Week 24** | **Visit 5****Week 36** | **Study Completion****Week 48** | **Premature Discontinuation** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Consent Form |  | X |  |  |  |  |  |  |  |
| Assessment of Eligibility Criteria | X | X |  |  |  |  |  |  |  |
| Review of Medical History3 | X |  |  |  |  |  |  |  |  |
| Sexual History4 | X | X |  | X | X | X | x | X | X |
| Review of Concomitant Medications  | X | X |  | X | X | X | x | X | X |
| Review of Adherence/side effects |  |  | X | X | X | X | x | X | X |
| Risk reduction counselling with peer educator |  | X |  |  |  |  |  |  |  |
| On-line behavioural Survey(within 3 days of visit) |  | X |  |  | X | X | X | X | X |
| TRUVADA® Prescription |  | X |  | X | X | X | X |  |  |
| Physical Examination | Symptom-Directed | X |  |  |  |  |  |  | X | X |
| Observations (BP, BMI) |  | X |  |  |  |  |  | X | X |
| Assessment of Adverse Events |  |  | X | X | X | X | x | X | X |
| Clinical Laboratory | Creatinine, eGFR, LFTS | X |  |  | X | X | X | x | X | X |
| LFTs | X |  |  | X | X | X | x | X | X |
| P/C ratio |  |  |  |  | X | X |  | X | X |
| Urinalysis10 | X |  |  | X | X | X | X | X | X |
| Syphilis serology | X |  |  | X | X | X | x | X | X |
|  | HIV serology | X |  |  | X | X | X | X | X | X |
| Concomitant STIs | Multisite CT/NG11 | X |  |  | X | X | X | x | X | X |
| HAV & HBV serologies | X |  |  |  |  |  |  |  |  |
| Hepatitis screening | HCV Ab | X |  |  |  |  | X |  | X | X |
| Therapeutic Drug Monitoring |  |  |  |  |  | X | X | X | X | X |