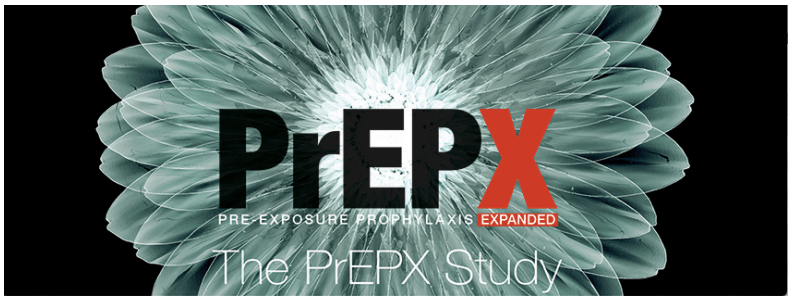
STUDY PROTOCOL

The PrEPX Study
Pre-exposure Prophylaxis Expanded



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GLOSSARY

This glossary includes terms and acronyms used in this document. Some terms apply generally to the field of HIV research; others have definitions that apply specifically to this study.

ACCESS	The Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of STIs and BBVs
AE	Adverse event
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral therapy
BMD	Bone mineral density
CVF	Cervicovaginal fluid
CLAI	Condomless anal intercourse
CLRAI	Condomless receptive anal sex
CRF	Case report form
DBS	Dried blood spot
DSMB	Data Safety and Monitoring Board
FTC	Emtricitabine
FTC-TP	Emtricitabine triphosphate
GBM	Gay, bisexual men
HIV	Human Immunodeficiency Virus
HIV serodiscordant relationship	A (sexual) relationship in which both partners are known (as a result of testing) to be different HIV serostatus, e.g. HIV positive and HIV negative
HIV serostatus	A person's antibody status in relation to HIV infection, i.e. HIV negative (confirmed by testing), HIV positive (confirmed by testing, or unknown (untested)
IUAI	Insertive unprotected anal intercourse
MSM	Men who have sex with men
NPEP	Non-occupational post-exposure prophylaxis
NSP	Needle-syringe program
PrEP	Pre-exposure prophylaxis
PWID	People who inject drugs
RCT	Randomised clinical trial
RNA	Ribonucleic acid

RAI	Receptive anal intercourse
SAE	Serious adverse event
SMS	Short message service
SOC	Standard of care
SPVL	Semen plasma viral load
STI	Sexually transmitted infection
TDF	Tenofovir disoproxil fumarate
TDF-DP	Tenofovir diphosphate
TDV	Tenofovir-emtricitabine (Truvada)
UAI	Unprotected anal intercourse
VPCNSS	Victorian primary care network for sentinel surveillance on blood borne viruses and sexually transmitted infections

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1. BACKGROUND AND RATIONALE

1.1 Introduction

HIV infection is a global epidemic that is concentrated in the poorest countries in the world and in populations that are marginalised through stigma, poverty and politics (1). Australia had approximately 27,000 people living with HIV infection at the end of 2014 of whom approximately 3,350 people remained undiagnosed with HIV infection (2).

For reasons that are not fully understood, over the past decade Australia has had a sustained increase in the annual numbers of new HIV diagnoses, which has stabilised over the past three years. In 2012, there were 1,064 new HIV diagnoses and 1,028 and 1,081 new diagnoses in 2013 and 2014, respectively (2). In Victoria, new HIV diagnoses have remained stable around 300 cases per year for several years, albeit we saw a slight decline in 2015 with 284 new HIV diagnoses (3). Hence new HIV prevention measures are critical to reduce new HIV infections and the current leading new prevention measure is HIV pre-exposure prophylaxis (PrEP). HIV PrEP, in its current form involves taking a daily dose of Tenofovir (TDF) co-formulated with Emtricitabine (FTC) (TDF/FTC), which in its patented form is Truvada® and is manufactured by Gilead Sciences.

In Australia, the incentive to end new HIV infections is particularly acute because at the World AIDS 2014 Conference, held in Melbourne, all State and Territory Health Ministers and the Commonwealth Health Minister pledged to end new HIV infections by 2020. Notably, however, Victoria had already taken a step towards ending new HIV infections by 2020 when it launched Australia's first HIV PrEP Demonstration Project, VicPrEP, in June 2014. The Victorian VicPrEP demonstration project is a study of 110 participants who are provided with daily TDF/FTC for HIV prevention, in combination with other HIV prevention measures such as condom use and regular testing for sexually transmitted infections (STIs).

HIV PrEP Demonstration Projects are designed to measure how *effective* PrEP is when it is taken from the rigors of a randomised controlled trial (RCT) setting and implemented in the community setting. PrEP demonstration projects thus far have typically measured not only the incidence of HIV infections (e.g. the direct efficacy of PrEP), but also medication adherence, behavioural change, stigma, acceptability and rates of incident STIs.

Prior to the VicPrEP study opening for enrolment in June 2014, there had been several RCTs that demonstrated that daily HIV antiretroviral therapy (ART) in the form of Tenofovir alone or Tenofovir plus Emtricitabine is highly efficacious as HIV PrEP. In these RCTs, PrEP has been shown to reduce the risk of

HIV acquisition in HIV negative men who have sex with men (MSM) by 44% (4), by> 70% in heterosexuals (5, 6) and by 50% in people who inject drugs (PWID) (7). Notably two placebo-controlled RCTs that enrolled women at risk of HIV infection in Sub-Saharan Africa (the Fem-PrEP (8) and VOICE (9) showed no benefit between active drug versus placebo. These findings were considered at the time to be largely the result of low medication adherence, although recent data suggest that women need to take a full seven doses per week of Truvada® to achieve the highest protection against HIV (10). In December 2015, the results of a new PrEP RCT became available. This study, the "IPERGAY" study that was undertaken in France, found that peri-coital TDF/FTC versus peri-coital placebo reduced HIV transmissions by 86% (11).

In addition, since VicPrEP commenced there have been publications with report on outcomes from several PrEP demonstration projects (12-15). In a 72 week, open-label extension study (The OLE study) of gay and transgender women who had previously been in PrEP trials, the incidence of new HIV infections was 0.0, 0.6 and 2.3 per 100 person years for those participants whose Tenofovir diphosphate blood levels were consistent with use of four or more, 2-3, and less than two TDF/FTC tablets per week (12), thus demonstrating the importance of adherence to PrEP in the prevention of HIV infection. In a UK demonstration project, known as the PROUD study, participants were randomised to receive immediate or deferred (by 12 months) Truvada® as PrEP. The PROUD study found that there was an 86% reduction in HIV transmissions in those randomised to the immediate versus the deferred arm (13). Three participants who were randomised to the immediate arm of the PROUD study acquired HIV. Of these, one appears to have had early and undiagnosed HIV infected at his baseline visit and the two other study participants did not appear to have been taking PrEP at the time they became HIV infected, based on evaluation of their clinic visits and pharmacy records (13). In San Francisco, a study of 657 people receiving PrEP through the Kaiser Permanente Healthcare system reported that there were no incident HIV infections over 12 months of follow-up (14). In a 48-week PrEP Demonstration Project undertaken in three cities within the USA that enrolled 587 people, there were two incident HIV infections, both occurring in individuals whose blood levels of Tenofovir were consistent with them taking two or less doses of TDF/FTC weekly (15). Since VicPrEP commenced 19 months ago, two study participants have been diagnosed with HIV infection. One participant was diagnosed with acute HIV infection 29 days after study enrolment, but he had not picked up his TDF/FTC script and reported that he never commenced TDF/FTC. The second patient was thought to have acute HIV infection at baseline, but this was not diagnosed because his HIV Ag/Ab ELISA test was negative at baseline and the study participant did not have a history of any recent possible HIV exposures. The study participant did not commence TDF/FTC until 14 days after his baseline visit and was diagnosed with HIV infection one month after commencing PrEP (Lal et al, manuscript in preparation).

Recently the first documented case of TDF/FTC PrEP failure was reported, from Canada (16). The individual had evidence drug levels in his blood that were consistent with TDF/FTC use at the time that he became infected with multi-drug resistant HIV (16). This case will be discussed in more detail below in the safety section in terms of the very low risk of infection with drug-resistant HIV in individuals taking TDF/FTC for HIV PrEP in Australia.

Broadly, therefore, these PrEP Demonstration projects show that in the community setting, PrEP is highly efficacious in the direct prevention TDF/FTC of HIV infection and that medication adherence is integral to the success of TDF/FTC as HIV PREP.

At an ecological level, the introduction of freely available PrEP in 2013 to people at risk of HIV infection in San Francisco has been associated with a 30% decline in new HIV infections (17). In 2012 when there was minimal PrEP use in San Francisco, 426 new HIV infections were reported. During 2013, TDF/FTC was made freely available for use as PrEP in San Francisco. Following this, the number of new HIV infections fell to 359 in 2013, and 279 in 2014. Grant et al estimated that during 2013-2014, 16,089 people were eligible for PrEP in San Francisco and that 5,059, or 31% of those eligible for PrEP were receiving it (17). Importantly, of those receiving PrEP approximately 65% were at very highest risk of HIV infection while PrEP use by those reporting none, or few HIV risk factors was 10% or less, suggesting that PrEP attracted those most at risk of HIV infection (17). Rates of HIV virological suppression in individuals with diagnosed HIV infection during 2013 in San Francisco were stable at 64% when compared to rates of 63% during both year, 2011 and 2012 (18). This is the first study to suggest that widely available PrEP may have a significant impact on the rate of HIV infections at a population level. In the United Kingdom, a recent modelling study supported these findings from San Francisco by demonstrating that the use of PrEP could be highly effective at the population level and could outperform other HIV prevention interventions including regular HIV testing, HIV test-and-treat measures and behavioural change (19).

The caveats to these findings from Grant et al of the potential impact of widely available PrEP having decreased new infections in San Francisco are (i) in 2013, for the first time, the San Francisco Department of Public Health was able to determine what the rates of HIV virological suppression in diagnosed HIV positive residents of San Francisco after they had excluded diagnosed HIV+ individuals who had moved away from San Francisco during 2013 and therein found that the rate of virological suppression was higher at 73% (18). Hence it remains possible that there have been rising rates of virological suppression in HIV positive people in San Francisco and that this may have contributed to the falling rates of new HIV infection between 2012-2014. Also, these data have been presented only at a conference (17) and have not yet been published.

As a result of the success of these PrEP RCTs and demonstration studies, the CDC and the World Health Organisations have issued clinical guidance documents to help health care workers to provide PrEP to people at risk of HIV infection (20, 21). Of note, in September 2015 WHO recommended that *all* people at substantial risk of HIV infection, irrespective of exposure group, should be offered PrEP (21). In addition, Australia has developed its own PrEP guidance document, based upon the CDC 2014 guidelines (22).

However, whilst TDF/FTC has been licensed for use as HIV PrEP in the United States, Canada, Kenya, South Africa and Israel it is not been registered by the Australian Therapeutic Goods Administration (TGA) and hence is not available for use as PrEP. Gilead Sciences currently has Truvada® before the Australian Therapeutic Goods Administration (TGA) for approval for the indication of HIV prevention and we believe at the time of writing that they have made a submission to the Pharmaceutical Benefits Advisory Committee (PBAC) to have Truvada® subsidised and listed on the PBS for the purpose of HIV prevention. The likelihood that PBAC will approve Truvada® for HIV prevention is high, however it is not possible to predict exactly when Truvada® might become PBS listed and may not be until early to mid-2017, or later.

Thus in the setting where the World Health Organisation has recommended PrEP, where there is a hiatus in access to subsidised Truvada® in Australia and where Australia had pledged to end new HIV infections by 2020, the Victorian Health Minister announced on January 30th 2016 that the State Government would provide funding for a study that will enrol 2,600 people to determine whether the widespread availability of PrEP would reduce new HIV infections in Victoria. The study also serves the dual purpose of making PrEP available to Victorians, pending TGA and PBAC approval. Apart from New South Wales, which announced a similar 3,700 person PrEP population-level study on December 1st 2015, no other national or international state, territory or country has committed to undertaking a PrEP population-level study of this size.

Hence in this protocol we outline the proposed HIV prevention, population-level study PrEPX that is designed to provide generic TDF/FTC to 2,600 people in order to achieve a significant decline in new HIV infections in Victoria over the next few years. PrEPX will provide important information on the impact of this intervention on new HIV diagnoses in Victoria and ancillary information including behavioural change, adherence, STI rates and broader health outcomes that may be associated with study participants attending for PrEP medical visits on a quarterly basis.

Relative effectiveness of HIV prevention strategies currently available in Australia

The results of these PrEP RCTs compare to the effect of other HIV risk reduction strategies: consistent condom use in men who have sex with men (MSM) (67%) (23), and heterosexuals (80%) (24), regular testing for HIV infection (every 10% increase in uptake of annual testing by MSM in Australia would see a decrease of 22-27 new HIV infections annually) (25), regular testing for other sexually transmitted

infections (STIs) and the introduction of needle-syringe programs (NSPs) (mean annual decrease in HIV diagnoses in numerous international settings (6-20%) (26).

Uptake of HIV prevention measures currently available in Australia

The currently available HIV risk reduction strategies have varying uptake in the Australian populations who are most at risk of HIV infection. In Australia 75% of all new HIV diagnoses occur in MSM (27) and while consistent condom use is the commonest HIV prevention strategy used by HIV negative Australian MSM (28), only one-third report consistent condom use (28). The Australian STIGMA guidelines recommend that all MSM should have annual HIV and STI testing (29) and that testing rates should increase to 3-6 monthly in MSM who have sex without condoms, multiple partners or have been diagnosed with an STI (29). Sixty per cent of gay men report having annual HIV testing in the gay community periodic survey, and this figure remains unchanged over the past decade (28). In a survey of four primary care clinics in Victoria, annual HIV and STI re-testing rates were lower (35%) and in those MSM at higher risk of HIV infection, six-monthly re-testing rates were as low as 15% (30). It is important to note that other HIV risk reduction strategies are used by gay men, which include sexual positioning and disclosure of HIV serostatus, the latter having increased to nearly 40% in HIV+ men in 2012 (28).

Approximately 25% of new HIV diagnoses occur in heterosexuals in Australia (31). In one study undertaken in family planning clinics, consistent male condom use was reported in only 16% of women using male condoms as their sole protection against pregnancy (32). A periodic survey of condom use and STI testing in young Australian people is currently underway by the Centre for Social Research in Health with results expected in 2014 (28). No data are available about condom use by HIV+ heterosexuals in Australia but in a European study of HIV+ heterosexuals, half of whom were in a serodiscordant relationship, consistent condom use with a regular partner was reported by 51% of women and 59% of men (33).

Approximately 6% of all new HIV diagnoses occur in people who inject drugs (PWID) but approximately half of these occur in men who have sex with men. The prevalence of HIV infection in people attending NSPs in Australia is approximately 1% (34) and is the result of the early introduction in 1986 of NSPs to prevent HIV infection among the injecting drug using populations in Australia. Despite the availability of NSPs, re-use of needles and syringes was reported in 21% of participants surveyed in the Kirby NSP study in 2011 (34).

Broadly therefore, the uptake of the currently available HIV prevention strategies is sub-optimal and whilst efforts are being made to increase consistent condom use and HIV and STI testing rates and to sustain and encourage use of NSPs, in the setting of rising HIV infection rates more HIV prevention strategies are needed. PrEP represents a new strategy to add to Australia's HIV prevention repertoire.

Factors that will influence whether the PrEPX study will reduce new HIV infections in Victoria over the next few years.

The likelihood that the uptake of PrEP by people at high risk of HIV infection in the PrEPX study will reduce new HIV infections in Victoria over the next few years is predicated upon several key factors including PrEP uptake, medication adherence, risk compensation, safety, acceptability, the transmission of drug-resistant virus, feasibility and the medication's antiviral and pharmacokinetic properties. Some of these factors have been evaluated in the abovementioned RCTs and demonstration projects and are reviewed below.

PrEP Uptake

Australia has excellent data on the likely uptake of PrEP by gay and bisexual men although data from HIV+ heterosexuals and people who inject drugs (PWID) are lacking. In 2011, approximately 28% of 1,161 HIV negative and untested gay and bisexual Australian men who were surveyed in the online PrEPARE project reported a willingness to use PrEP to prevent HIV infection (35). In a follow-up survey in 2013, of 1,223 participants, 23% of participants were willing to use PrEP (36). In 2015, this number rose to 32%. Furthermore, in 2015, 77% of survey respondents had heard of PrEP and 29% knew someone who had used PrEP (37). In the 2015 PrEPARE survey, of 307 Victorian respondents, 38% were both eligible and willing to use PrEP (personal communication, M.Holt). Hence a relatively high proportion of Victorian gay and bisexual men are aware of PrEP, eligible and willing to use PrEP. This is reflected also by the fact that currently approximately 700-800 Victorians are importing generic TDF/FTC for personal use as HIV PrEP. These estimates are derived from details provided by Melbourne's high caseload S100 general practices whose doctors are providing the medical supervision and prescriptions for people self-importing PrEP.

Medication adherence

Adherence to PrEP medication varied across the earliest PrEP studies undertaken. In studies of heterosexuals at risk of HIV, and heterosexual couples who were HIV serodifferent, using refill-based assessment, or self-report, adherence rates of PrEP ranged from 90-95%. In some, but not all of these studies these high rates of adherence by self-report were corroborated by finding detectable drug in a high proportion of study participants (See Table 1). In counterpoint, the two studies of heterosexuals with the lowest proportion of patients with detectable drug, the VOICE study (8) and Fem-PrEP (9) were undertaken in women at risk of HIV infection in Africa. In the Fem-PrEP study it was hypothesized that low pill use was a result of low perception of risk of HIV infection and also difficulty managing daily pill regimens (8). The VOICE study ascribed the poor efficacy of PrEP which was studied for use as a gel, or an oral formulation, to poor adherence to the gel and the oral study drug (9).

In studies of PrEP in gay, bisexual men (GBM) and transgender women, it appears that adherence to PrEP as measured by levels of detectable drug in plasma, PBMCs or red blood cells has increased considerably over time. In the initial study of PrEP in GBM and transgender women, the iPrEX study, which was published in 2010 self-reported adherence was 95%, but detectable drug was found only in 50% of a subgroup of study participants (4), (Table 1). However in a recent randomized, placebo- controlled trial published in late 2015, 86% of participants had evidence of study drug in their plasma, which was consistent with having taken the study drug in the previous seven days (11). Similarly in more recently published PrEP demonstration projects, high levels of PrEP adherence by self-report and other measures have been corroborated by protective drug levels in blood in a high proportion of participants. For example in the US PrEP Demo study, of 294 participants who attended study visits, the concentrations of Tenofovir-diphosphate in blood were protective in 86%, 85%, 82%, 85%, and 80% of participants at weeks 4, 12, 24, 36, and 48, respectively (15), (Table 1). In the VicPrEP study, where 115 individuals at risk of HIV infection were offered daily TDF/FTC, we found that 94% and 99% of participants reported taking more than 90% of doses at three and six months, respectively, (Lal et al, manuscript in preparation). Further we found evidence that the median percentage of days that participants had TDF/FTC available between clinic visits was 114% and 99% at months three and six, respectively. This evidence of high adherence was corroborated by further findings that 90% of VicPrEP participants had evidence of consistent dosing and protective levels of Tenofovir diphosphate in their blood (38), (Table 1).

Hence as confidence in the efficacy of TDF/FTC has increased, we are seeing evidence in the more recent randomized controlled trials and in the 'real world setting' of PrEP Demonstration Projects, including Victoria's PrEP Demonstration Project, that people using PrEP for HIV prevention are highly adherent to their PrEP medications.

Table 1. Self-reported adherence to study drug and drug levels in blood and Red Blood Cells from PrEP randomized controlled trials and Demonstration Projects and Year Study Published

Study	Study population	Self-reported adherence to study drug	Proportion with detectable study drug in blood	Year study published
Randomised Controlled Trials				
iPrEX	MSM	95%	50%	2010
Partners PrEP	Heterosexuals in HIV serodiscordant relationship	Self-report not reported but 97% of dispensed pills were taken	82%	2012
TDF2 study	Heterosexual men and women	94%	80%	2012
Bangkok Tenofovir Study	People who inject drugs	83.8%	67%	2013
VOICE study *Closed for futility	Women	90%	<30%	2015
Fem-PrEP *Closed for futility	Women	95%	35%	2012
IPERGAY	MSM and TG		86%	2015
PrEP Demonstration Projects				
OLE	MSM and TG		71%	2014
US Demo Study	MSM		86%, 85%, 82%, 85%, and 80% of participants at weeks 4, 12, 24, 36, and 48, respectively had protective levels of Truvada® in their blood	2016
PROUD Study	MSM		100%	2015
VicPREP	MSM		95% had detectable levels in plasma and 90% had protective levels of Truvada® in their blood	2015

The importance of adherence to the efficacy of PrEP in reducing the risk of HIV infection has been highlighted in the iPrEX trial (4) which was supported by findings from the STRAND study (39). In the iPrEX study drug levels were measured in 34 patients who became HIV infected and in 43 seronegative control patients in the active arm and drug was present in 9% and 51% of patients, respectively. In subsequent analyses, having detectable study drug in the blood lowered the odds of HIV infection by 12.9, corresponding to PrEP affording a relative risk reduction of 95% (95%CI, 70-99; p<0.001) (4).

Subsequently the STRAND study was undertaken to quantify the relationship between the level of adherence and drug concentration (39). Here, HIV negative volunteers were given daily, four-times weekly and twice-weekly TDV. Patients steady-state intracellular levels of TDF were determined and the median intracellular levels of Tenofovir diphosphate for daily, four doses per week and two doses per week were determined (39). Applying these findings to the levels of drug found in those patients enrolled in the active arm of the iPrEX study, Anderson et al were able to show that those patients whose blood levels of Tenofovir diphosphate were compatible with daily dosing had a 99% reduction in risk of HIV infection, those with levels compatible with four doses per week had a 96% reduction and those with levels compatible with two doses per week, a 76% risk reduction (39). These results compare to the overall intention-to-treat analysis result that showed a 44% reduction in the incidence of HIV (4).

More recently three PrEP open label extension studies reported their findings that the incidence of HIV infection was 4.7 infections per 100 person-years if drug was not detected in dried blood spots, 2.3 infections per 100 person-years if drug concentrations suggested use of fewer than two tablets per week, 0.6 per 100 person-years for use of two to three tablets per week, and 0.0 per 100 person-years for use of four or more tablets per week (p<0.0001) (12). Hence this study strongly reiterates the importance of adherence to PrEP.

Behavioural Risk compensation

Table 2 outlines behavioural change that has been reported across a number of PrEP randomized controlled trials and PrEP Demonstration Projects, including VicPrEP.

None of the six published PrEP RCT studies reported an increase in sexual or injecting risk behaviour, nor did a safety study undertaken by CDC in the United States (40) (see Table 2). However an increase in sexual risk taking was reported in a follow-up study by the Partner's PrEP study group (41). The original Partner's PrEP study enrolled 4,758 HIV heterosexual serodiscordant couples who were randomized to receive TFV, TDV or placebo. The study found that TFV and TDV afforded 67% and 75% reduction in HIV acquisition versus placebo, respectively and the results were reported in July 2011 (5). Following the study's unblinding, those couples who had been assigned to the active arm during the study were told that they had been on the active arm and they were then maintained on PrEP medication and followed for a further

12 months in order to study any behaviour change on open label PrEP. The Partner's PrEP follow-up study reported that there was no increase in the frequency of unprotected sex between partners within the relationship, however there was a small but significant increase in the frequency of sex without condoms with partners outside of the relationship during the 12 months after the study was unblinded, compared to the 12 month period prior to the study being unblinded (6.8 versus 6.2 sex without condom acts, respectively) (41). The authors noted that this was a small increase and that there was no accompanying increase in STIs or pregnancy.

In the PROUD study, which was a UK PrEP demonstration, the researchers found evidence of an increase in condomless anal intercourse (CLAI) in a subset of study participants who were randomized to receive immediate PrEP versus deferring PrEP for one year (13), (Table 2). Similarly in a review of gay men receiving PrEP in San Francisco through the private healthcare provider Kaiser Permanente, at six months condom use was unchanged in 56%, decreased in 41% and increased in 3% compared to baseline in a subset of study participants who were surveyed (14). In this study the number of sexual partners was unchanged in 74%, decreased in 15% and increased in 11% (14). In the VicPrEP study we saw a significant decrease in condom use with regular and casual partners at the six, but not three month study visit surveys (42). We evaluated condom use by asking participants to rate their condom use with regular and casual partners, using a Likert scale. In this scale condom use was denoted as follows: 1. Never, 2. Some of the time, 3. Half of the time, 4. Most of the time, 5. Always. For regular partners the mean Likert scores at baseline and six months were 2.04 (SD 1.53) and 1.66 (SD 1.35) and in regression analysis the b coefficient for comparison was -0.61 (95% CI, -1.02- -0.21) (Lal et al, manuscript in preparation). For casual partners the mean Likert scores at baseline and six months were 3.08 (SD 1.31) and 2.50 (SD 1.19), respectively and in regression analysis the b coefficient for comparison was -0.61 (95%CI, -0.90, -0.33) (Lal et al, manuscript in preparation). There was no change in the number of partners or number of sex acts in VicPrEP participants at three or six months. However VicPrEP participants were likelier to ask their HIV positive sexual partners about their most recent HIV viral load at six months, OR 0.44 (CI 0.01, 0.88).

Hence in three studies, the PROUD study, the Kaiser Permanente Study and the VicPrEP study there has been a decrease in condom use associate with PrEP use. However at baseline, the rate of condomless anal sex (50%) in VicPrEP participants was lower than the range (60-70%) observed in other overseas studies (4, 11, 43) suggesting that VicPREP participants had greater relative opportunity to reduce condom use compared to participants in studies where condom use was already very low at baseline. Furthermore the reduced condom use reported in these three studies, may be a result of people having greater confidence in TDF/FTC's ability to prevent HIV infection as more studies are published to support its efficacy.

Table 2. Change in sexual or injecting drug used behaviour reported in PrEP Randomized Controlled trials and one follow-up study to date

Study	Study population	• Change in Sexual or injecting drug using behaviour
Randomised controlled trials		
iPrEX	MSM	• Decrease in number of sexual partners with whom having RAI and increase in proportion of partners who used condoms • **60% CLRAI at baseline**
Partners PrEP	Heterosexuals in HIV serodiscordant relationship	• Decrease in sex without condoms
Partners PrEP follow-up study	Heterosexuals in HIV serodiscordant relationship	• No increase in frequency of sex without condoms between partners within the relationship **27% reported condomless sex at baseline** • An increase in the frequency of sex without condoms with partners outside of the relationship
TDF2 study	Heterosexual men and women	• 80% condom use reported at baseline remained stable through the study, a significant decrease in the number of sexual partners.
Bangkok Tenofovir Study *Note: 87% of patients had directly observed therapy	People who inject drugs	• Significant reduction in number of participants injecting drugs, decrease in sharing needles and decrease in number of sexual partners
IPERGAY	MSM	• No difference in the number of sex acts • No difference in proportion of episodes of anal sex without condoms (was high at 70% in both arms at baseline and end) • Significant difference with fewer partners in the placebo group
Demonstration Projects		
US PrEP Study Liu 2015	MSM	• Mean number of anal sex partners declined • Mean unprotected anal sex episodes remained stable but was high at 65.5% and 65.6%
US CDC Safety study	MSM	• Mean number of partners decreased significantly • Proportion reporting unprotected

		anal sex declined significantly • Mean number of unprotected anal sex acts remained stable
PROUD McCormack 2015	MSM	• 21% in PrEP arm versus 12% in deferred arm reported CLAI with 10 or more partners in a subset of study participants who completed baseline and follow-up surveys (p=0.03) • No difference in the number of sex partners between study arms at 12 months (p=0.57)
iPrEX OLE and ATN 082 and the US Safety Study	MSM and transgender	• Over 72 weeks of follow-up there was a decrease in CLAI in PrEP arm (34% to 25%) and non-PREP arms (27% to 20%) • There was a decrease in the total number of sex partners in PrEP and non-PrEP study arms
Kaiser Permanente Volk 2015		• Condom use was unchanged in 56%, decreased in 41% and increased in 3% in a subset of 188 substudy participants who were asked about behaviour • The number of sex partners was unchanged in 74%, decreased in 15% and increased in 11% in a subset of 188 substudy participants who were asked about behaviour

CLAI: condomless anal intercourse. CLRAI: condomless receptive anal intercourse

Safety

Overview

To date TFV and TDV have been well tolerated in a number of study populations including the RCTs mentioned above and in several studies dedicated to studying the safety of PrEP regimens (40, 44-46). There have been no reports of a difference in deaths or serious adverse events across different study arms in PrEP RCTs (4-6, 44-46). Nausea (4, 6-8), unintentional weight loss, vomiting (6-8), dizziness (6), back pain (44), bone mineral density (BMD) loss (47) and elevated ALT levels (8) have been have been reported to occur more commonly in the active study arm of PrEP trials. In the Fem-PrEP study there was a trend towards higher rates of drug discontinuation because of hepatic or renal abnormalities in the TDV arm (p=0.051).

Bone mineral density

In a substudy of the US CDC PrEP safety study, Liu et al undertook the only PrEP study to measure BMD thus far (47). This sub-study was important because TFV use has been associated with reduced BMD in HIV+ patients (48). The US CDC PrEP study had four study arms: patients were randomized to commence TFV, or placebo immediately for 24 months, or were randomized to wait for 9 months and then commence either TFV or placebo for a period of 13 months (44). In the BMD substudy a small but significant decrease in BMD relative to baseline occurred in participants receiving TFV versus pre-treatment/placebo group. The authors reported a 1.1% mean net decrease in BMD in the TFV vs. pre-treatment/placebo group at the femoral neck (95% CI 0.4–1.9%, p= 0.004) and an 0.8% net decline at the total hip (95% CI 0.3–1.3%, p = 0.003); at the L2–L4 spine, there was non significant decrease in BMD (0.7% decline, 95% CI 0.1–1.5%, p = 0.11) (47). There was no significant difference in fracture rates between those receiving TFV versus placebo, although the study was not powered to detect a different in fracture rate (47). Overall at 24 months, 13% of participants taking Tenofovir versus 6% of participants taking placebo experienced a >5% BMD loss at the femoral neck (47). Interestingly in this study, the authors noted that at baseline 9.5% of MSM had low BMD with at least one Z-score ≤-2.0, with 17 cases at the L2–L4 spine, 5 at the total hip, and 1 at the femoral neck (47). In univariate analysis, the use of amphetamines and inhalants were significantly associated with lower baseline BMD and use of supplemental calcium or vitamin D were associated with less likely likelihood of low baseline BMD (47). Liu et al note that larger future studies will need to be done to study BMD loss in participants in PrEP studies including clinical endpoint evaluation (47).

There is no evidence that Tenofovir diphosphate is associated with an increase in fracture risk. Recently the US PrEP Demo study reported that 12 bone fractures occurred during the study and that all but one (tooth fracture) was explained by trauma, and that none was related to PrEP (15).

More recently, data were presented from the iPrEX study that showed that bone mineral density loss occurred in study participants on the active drug arm, and more so in those participants who blood levels of study drug suggested good adherence (49). Importantly however, bone mineral density returned to baseline levels in all study participants on the active drug arm, within approximately 12- 18 months (49).

Renal function

In a meta-analysis, Tenofovir use in HIV+ patients was found to be associated with a statistically significant loss of renal function with the effect being judged as clinically modest (50). Tenofovir use was not associated with increased risk of fractures, hypophosphatemia or proteinuria (50).

Overall Tenofovir use in PrEP studies has not been associated with significant renal problems as outlined in Table 3 although some patient populations may be at a higher risk for renal decline whilst taking Truvada® for PrEP.

In the recently published report on the US PrEP Demo study, 23 occurrences of elevated creatinine levels occurred in 13 of 557 individuals (2.3%), including 22 grade 1 and 1 grade 2 events (Liu 2016). On repeat testing, only 3 elevations among 3 participants were confirmed, and all episodes of creatinine elevation resolved within 2 to 20 weeks without stopping PrEP (15).

In a recent conference report that updated the published US PrEP Demo Project findings, the median decline in creatinine clearance was 6 ml/min (5%) from baseline to week 12 and it then remained stable through to week 48 (p=0.96), with no differences by race/ethnicity, weight, or use of non-steroidal agents. New onset eGFR < 70 was commoner in those with baseline eGFR < 90 and was seen more obviously in people over the age of 45 (51). However, in a multivariable analysis, age <25 years, use of medications for hypertension or diabetes, and red blood cell TFV-DP levels consistent with taking two or more doses/week of TDF/FTC were independently associated with greater creatinine clearance loss. The authors reported that younger PrEP users may warrant increased monitoring of renal function and that perhaps older PrEP users may ultimately need to take fewer doses of TDF/FTC each week to preserve their renal function (51).

In counterpoint to the findings from the abovementioned study by Liu et al, another study that was reported at the 2016 CROI conference and that examined the relationship between levels of Tenofovir and Emtricitabine in hair and eGFR found that younger people were less likely to experience a decline in eGFR (52). In this same study, the authors reported that the odds of the eGFR falling below 70 ml/min increased with increasing quartiles of Tenofovir and Emtricitabine hair concentration (OR 4.4 (1.1-17.4) for 4th TFV hair quartile, p trend 0.045; OR 4.0 (0.9- 17.2). The authors suggested that more frequent renal monitoring may be warranted for older people and people whose baseline eGFR is less than 90 mls/minute which supports the findings of Liu et al (51). We have not yet evaluated VicPrEP participants' renal function over time

Table 3. Renal abnormalities in participants in PrEP randomized controlled trials

Study	Study population	Renal abnormalities
iPrEX	MSM	Trend towards more creatinine elevation in the TDV group (p=0.08) Participants with higher levels of TFV and FTC in hair were likelier to have decreased eGFR Older people and people with eGFR < 90mls/minute may need more frequent renal monitoring
Partners PrEP	Heterosexuals in HIV serodiscordant relationship	No significant difference between elevated creatinine levels in TDV or TDF or placebo groups
TDF2 study	Heterosexual men and women	No significant difference between elevated creatinine levels in TDV or placebo groups
Bangkok Tenofovir Study	People who inject drugs	No significant difference between renal disease, increased creatinine, decreased phosphorous in TDF or placebo groups
VOICE study *Closed for futility	Women in Africa	Not available
Fem-PrEP *Closed for futility	Women in Africa	A significant increase in increased creatinine observed in women on TDV arm (n=20/1033 participants) versus placebo (n=5/1025 participants) p= 0.02
US PrEP Study	MSM	No grade 3 or 4 elevations in creatinine occurred. Grade 1 and 2 elevations were uncommon and most resolved Age <25 years, use of medications for hypertension or diabetes, and red blood cell TFV-DP levels consistent with taking two or more doses/week of Truvada® were independently associated with greater creatinine clearance loss New onset eGFR < 70 was commoner in those with baseline eGFR < 90 and was seen more obviously in people over the age of 45
Mutua et al	MSM and female sex workers in Kenya	Mild creatinine elevations (1.1-1.3 times upper limit of normal) in 3 participants in the TDV arm versus placebo. These resolved spontaneously on study drug. Two cases of abnormal creatinine clearance (1 on active drug, 1 on placebo). Both resolved spontaneously
Kibengo et al	Heterosexuals in HIV serodiscordant relationship	Mild and moderate elevation in serum creatinine occurred two study participants receiving TDV and both resolved spontaneously on study medication. Seven cases of reduced creatinine clearance occurred: 5 in the TDV arm and 2 in the placebo arm. All resolved without interrupting study medication.

Acceptability

Factors that can be used to evaluate the acceptability of PrEP include the quality of the experience of using daily medications, attitudes of friends and sexual partners towards the person taking PrEP, affordability, quality of the interactions with health care providers around PrEP eligibility and use and the tolerability of side effects.

PrEP use is associated with feeling safer during sex and may offset the individual's fear of acquiring HIV, fear of having no control over their partner's condom use or their partner's choice to use HIV antiretrovirals and fear of experiencing intimate partner violence (53). A desire for greater intimacy has been seen also as a significant factor that motivates MSM to use Prep (54). In the VicPrEP study we found that concern about HIV infection was significantly reduced at month 6 by study participants (55).

Drug resistance

Drug resistance has been reported in individuals participating in PrEP trials but the number of reported cases are very low and mostly reflect individuals who enter the study with acute HIV infection that is not detected with HIV antibody/antigen testing, (Table 4). The majority of cases of drug resistance have been observed in those study participants who were discovered retrospectively to have been HIV infected at baseline with wild type virus and then received active study drug, which led to the development of drug resistance, or those who were discovered retrospectively to have been HIV infected at baseline with a drug-resistant virus. Only a handful of patients who were HIV negative at study baseline developed drug resistance whilst receiving PrEP, which has been largely ascribed to patients' poor adherence to study medication (4). In VicPrEP we had one patient with undiagnosed HIV infection at baseline wherein he had a negative HIV antibody/antigen ELISA test (Lal et al, manuscript in preparation). He commenced Truvada® 14 days after his baseline visit and his HIV infection was diagnosed one month after commencing PrEP and had developed the M184V mutation alone. On retrospective testing his HIV RNA level was undetectable at his baseline visit (Lal et al, manuscript in preparation), (Table 4).

Table 4. Reports of antiretroviral drug resistance in participants in PrEP randomized controlled trials

Study	Study population	Drug resistance
Randomised Controlled Trials		
iPrEX	MSM	Of the 10 subjects who were found retrospectively to be infected at baseline, one subjects was found to have transmitted FTC resistance (M184V); one subject acquired the M184V mutation during the first four weeks of the study whilst on the TDV study arm and one subject had an M184I mutation at week 4 on the TDV study arm, but their baseline resistance profile could not be ascertained No FTC or TDF resistance was observed in the 36 subjects in the TDV group and 64 subjects in the placebo group who became infected with HIV during the trial.
Partners PrEP	Heterosexuals in HIV serodiscordant relationship	Two of eight subjects who were found retrospectively to be HIV infected at baseline developed drug resistance: one patient randomised to TDV developed the M184V mutation and one patient randomised to TDF developed the K65R mutation. One patient who acquired HIV during the study developed the TDF mutation, K65N
TDF2 study	Heterosexual men and women	One subject who was found retrospectively to be HIV infected at baseline and who was randomised to TDV developed drug resistance: the M184V mutation at month 1 and the M184V, K65R, A62V mutations at month 7. One subject assigned to the placebo arm who was uninfected at baseline developed the K65R mutation which was reported as 'intermittent and at low levels, < 1%'
Bangkok Tenofovir Study	People who inject drugs	None detected
VOICE study *Closed for futility	Women in Africa	N/A
Fem-PrEP *Closed for futility	Women in Africa	Five cases of drug resistance to FTC were reported by this study group although the details are not entirely clear: one case occurred in a subject randomised to the placebo arm; one case occurred in a subject who had not received TDV for 48 weeks; three cases did occur in subjects on TDV and were reported within 12 weeks of study enrolment.

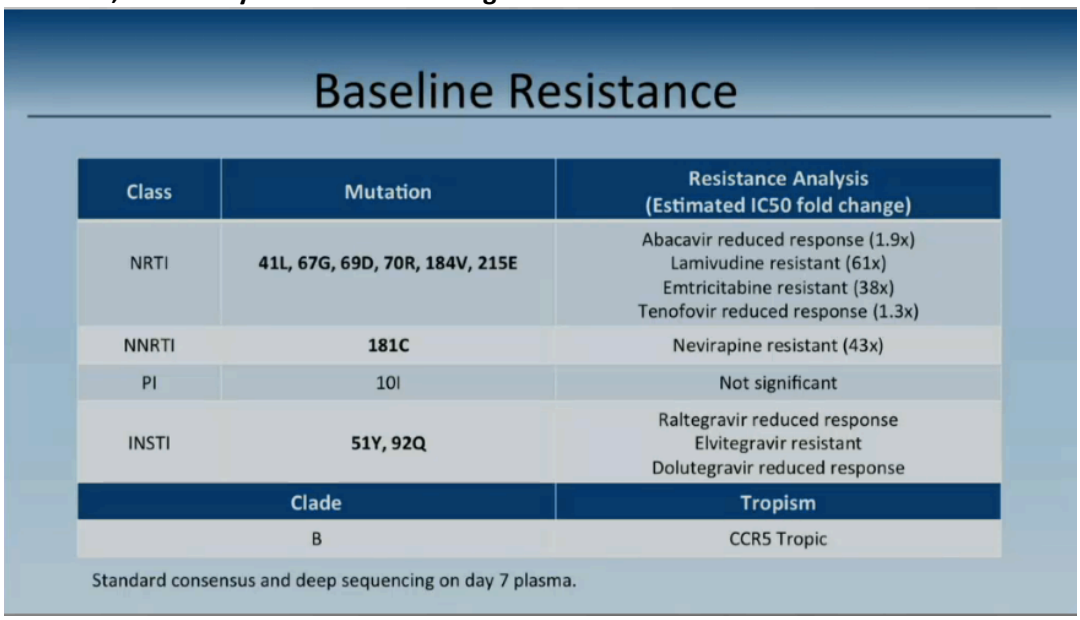
IPERGAY study	MSM in France	None of the 16 participants who acquired HIV-1 infection after enrollment had resistance mutations to study medications
US PrEP Study	MSM	Five seroconversions occurred in the study. One participant alone who had undiagnosed acute HIV infection at baseline developed drug resistance after commencing Truvada®and had the M184MI mutation.
VicPREP	MSM	An individual had undiagnosed HIV infection at baseline and commenced Truvada® 14 days after his baseline visit. HIV was diagnosed 30 days after he commenced Truvada® and HIV genotyping showed that the patient had the M184V mutation.

Several modeling studies have been undertaken to address the risk that the use of PrEP may lead to widespread drug resistance especially in countries with high HIV prevalence and limited antiretroviral options and where the same medications used for PrEP and HIV treatment will be the same (56). Although there is some debate in the literature (56), it appears from modeling studies that PrEP and ART, used to treat HIV infection, will *both* drive ART resistance, but the greater driver of resistance will be ART and not PrEP (56).

Recently the first documented case of Truvada® PrEP failure was reported, from Canada (16). The individual had blood drug levels performed 24 days after his HIV infection was diagnosed and between 38 and 52 days after he had had multiple likely exposures to HIV. The individual's drug levels were consistent with him having been above the steady state of Tenofovir-diphosphate during the time that he was exposed to HIV. The patient's virus was characterised with genotyping and was found to be multi-drug resistant as shown in Figure 1.

The likelihood of acquiring TDF/FTC resistance in Australia is very low. Recently the START study reported on the overall rate of HIV transmitted drug resistance in 1,946 newly diagnosed HIV+ individuals enrolling into the START study (57). Overall, Australians enrolling into the START study had the highest rate of transmitted antiretroviral drug resistance at 17.5%. But of the 1,946 people that were evaluated for transmitted drug resistance overall in this study, only 0.3% had the key mutations that confer Tenofovir resistance (57). A 2009 study from the Victorian Infectious Diseases Reference Laboratory (VIDRL), found that 16% of 466 HIV+ Victorians who had been diagnosed with HIV infection between 1996 and 2007 had evidence of being infected with a drug resistant strain. However the commonest drug mutations were not those that confer primary Tenofovir or Emtricitabine resistance with only five of 466 people studied having mutations against Emtricitabine and none with the K65R mutation (58).

Figure 1. HIV resistance profile from the first person known to have experienced failure of Truvada® as HIV PrEP, secondary to transmitted drug resistance.



Baseline Resistance

Class	Mutation	Resistance Analysis (Estimated IC50 fold change)
NRTI	**41L, 67G, 69D, 70R, 184V, 215E**	Abacavir reduced response (1.9x) Lamivudine resistant (61x) Emtricitabine resistant (38x) Tenofovir reduced response (1.3x)
NNRTI	**181C**	Nevirapine resistant (43x)
PI	10I	Not significant
INSTI	**51Y, 92Q**	Raltegravir reduced response Elvitegravir resistant Dolutegravir reduced response
Clade		**Tropism**
B		CCR5 Tropic

Standard consensus and deep sequencing on day 7 plasma.

Knox et al, CROI 2016, Abstract 196aLB

Feasibility: Factors that can be used to evaluate feasibility of a PrEP program include for the PrEP consumer, the cost of medication, the ease of attending medical appointments and picking up medications at pharmacies and factoring daily medication use into their lifestyles. For the healthcare providers such as clinic doctors and nurses and pharmacists, factors include ease with raising PrEP as a subject, time required to discuss patients' PrEP eligibility, time and ease doing required screening for PrEP eligibility, time required to assess patients' subsequent PrEP adherence and behaviour. Currently international demonstration projects that are measuring PrEP feasibility have not reported on their findings yet and the VicPREP study has yet to analyse its findings vis a vis feasibility

Cost effectiveness: In a systematic review of modeling studies of the cost and impact of PrEP for HIV prevention, the authors stated that the delivery of PrEP to key populations at high risk of exposure appears to be the most cost-effective strategy (59). Within concentrated epidemics such as MSM in the United States, which is broadly comparable to the concentrated epidemic of HIV in MSM within Australia, they reported that PrEP may have a substantial impact on the HIV epidemic, but may not be affordable at current drug prices (59). Ouellet et al found that the 'on demand' pericoital PrEP schedule that was tested in the IPERGAY study (11) was cost-saving to cost-effective (60). In the UK PrEP demonstration project, PROUD, the incidence of HIV in those participants who were randomized to defer PrEP for 12 months was 9.0 per 100 person years. The study found that immediate versus deferred PrEP was associated with an 86% reduction in the risk of HIV infection and that the number needed to treat to prevent one HIV infection was only 13. The cost-effectiveness analysis of the PROUD study is pending, and it is anticipated

that it will be cost-effective. Australia has undertaken one PrEP cost-effectiveness study to date, which showed that PrEP was cost-effectives for HIV serodiscordant couples (61). New cost-effectiveness studies for PrEP in the Australian scenario are anticipated.

PrEP: antiviral properties and pharmacology:

The aforementioned randomized, controlled trials that demonstrated PrEP's efficacy used TDF in either tablet form (alone, or as TDF/FTC), or as 1% vaginal gel. TDF and FTC are HIV-1 nucleot(s)ide reverse transcriptase inhibitors (39). Both drugs are also active against hepatitis B. Both drugs undergo activation via intracellular phosphorylation. TDF and FTC compete with endogenous deoxynucleot(s)ides for incorporation into the HIV reverse transcriptase enzyme wherein they lead to premature HIV DNA chain termination. TDF and FTC have suitable pharmacokinetic profiles that permit daily dosing (39) which affords variable levels in tissue compared to plasma. Table 5 provides a summary of the half-lives, steady states and concentration of TDF and FTC in a number of tissue compartments. Of note there are variable concentrations of Tenofovir and emtricitabine and their active metabolites in different secretions and tissues. Broadly, TDF concentration is much greater in rectal tissue than in vaginal or cervical tissue or cervicovaginal fluid (CVF) and seminal plasma. FTC concentration is greater in vaginal and cervical tissue and CVF and seminal plasma than in rectal tissue. In a study of healthy HIV negative volunteers, concentrations of Tenofovir and Emtricitabine metabolites in cervical and vaginal tissues, although higher than levels found in plasma, were ten to one hundred times lower than those found in rectal tissue. The authors of this study suggest that perhaps the failure of the VOICE and Fem-PREP studies may in part be due to poor concentration of these drugs into the female genital tract (62).

Further work by this group was recently published and reported that colorectal concentrations of the active metabolite, Tenofovir diphosphate were 10 times higher than female genital tract concentrations (10). Their model predicted that ≥98% of the population achieved protective mucosal tissue exposure by the third daily dose of TDF/FTC. However, the authors noted that a minimum medication adherence of 6/7(85%) doses/week was required to protect female genital tract tissue from HIV, while 2/7(28%) doses/week were required to protect colorectal tissue (10).

Further to this, recent data show that approximately seven days of daily TDF/FTC are required to achieve highly protective levels of Tenofovir diphosphate in PBMCs and rectal mononuclear cells (63). This study also found that the levels of Tenofovir diphosphate that provide > 90% protection were present in PBMCs for approximately one week after the last dose of TDF/FTC was taken. The authors recommended that individuals who wish to cease TDF/FTC for PrEP should take a 28-day course of TDF/FTC after their last episode of unprotected sex (63). This recommendation is supported by animal models that have been used to study HIV non-occupational post-exposure prophylaxis (NPEP), where those animals that received less than 28 days of Tenofovir after HIV exposure had a higher likelihood of acquiring SHIV (64).

Table 5. Half-lives, steady states and concentrations of TDF and FTC in blood plasma, peripheral blood mononuclear cells, genital secretions, vaginal, rectal and penile tissue

	Tenofovir	Emtricitabine
Blood plasma	T ½ 31 (65) -47 (62) hours	T ½ 37 (65)-49 (62) hours
PBMCs*	Half life 164 hours (65) Steady state: 25 days (39)	Half life 39 hours (65) Steady state: 6 days (39)
Cervicovaginal fluid	AUC** $_{1\text{-}14d}$ ratio of CVF to blood plasma is 2.6 (62)	AUC** $_{1\text{-}14d}$ ratio of CVF[†] to blood Plasma is 27 (62)
Seminal plasma	AUC** $_{1\text{-}14d}$ ratio of seminal plasma to blood plasma is 1.0 (62)	AUC** $_{1\text{-}14d}$ of seminal plasma to blood plasma is 4.5 (62)
Vaginal tissue	TDF can be measured in tissue for up to 10 days after a single dose (62) TDF-TP[††] can measured in tissue for up 14 days (62) Concentration is lower than in rectal tissue (62)	FTC can be measured in tissue for up to 10 days after a single dose (62) Exceeds concentration in blood by 7-fold (62) FTC-TP[▲] can measured in tissue for 24-48 hours only (62)
Cervical tissue	TDF can be measured in tissue for up to 10 days after a single dose TDF-DP detectabiliity not quantified (62) Concentration similar to vaginal Tissue (62)	FTC detected in tissue for up to 10 days after a single dose FTC-TP detected for only 24 hours after a single dose (62) 4-fold higher concentration than TDF (62)
Rectal tissue	TFV AUC $_{1\text{-}14d}$ ratio of rectal tissue to Blood plasma is 34 (62) Both TDF and TDF-DP detected in rectal tissue for 14 days after single Dose (62)	AUC $_{1\text{-}14d}$ ratio of rectal tissue to blood plasma not known but is substantially lower than TDF (62) FTC detected in rectal tissue for 14 days after a single dose (62) FTC-TP detected for only 48 hours after a single dose (62)
Penile tissue	Not known (66)	Not known (66)

*PBMCs: peripheral blood mononuclear cells. **AUC: Area under the curve. [†]CVF: cervicovaginal fluid
[††]TDF-DP: tenofovir- diphosphate, the active intracellular phosphorylated metabolite of TDF. [▲]FTC-TP: the active intracellular phosphorylated metabolite of FTC.

The generic co-formulated Tenofovir and Emtricitabine that will be used in the PrEPX study was considered to be bio-equivalent to Truvada® in a report prepared by an independent review commissioned by the New South Wales Department of Health that will be shared with the Alfred Health

Human Research and Ethics Committee members as part of the ethics review process for the PrEPX study. Hence the abovementioned pharmacological properties and tissue penetration characteristics of the generic Tenofovir and Emtricitabine are considered to be comparable to patented Truvada®.

Sexually Transmitted Infections in PrEP Randomised Controlled Trials and PrEP Demonstration Projects

In the majority of PrEP studies to date, the incidence of STIs has not increased. However, in two recent studies, the Kaiser Permanente study and the VicPrEP study, an increase in STIs has been observed (Table 6). In VicPrEP, we saw a 50% increase in the number of people with STIs after six months of PrEP (Lal et al, manuscript in preparation). To further examine this finding we are testing associations between change in condom use and rate of STIs in VicPrEP (Lal et al, manuscript in preparation) because it would be plausible that decreased condom use would be associated with an increase in STIs. However, another possible explanation for this finding is that we are testing participants more often for STIs hence we are finding more STIs. We have not observed an increase in the number of partners, or sex acts over time in VicPrEP participants to explain this finding. However, if study participants were having more group sex that might explain this rise in STIs. However we did not collect data about group sex practices in VicPrEP. It is worth noting that in those PrEP studies of MSM where no increase in STIs was noted, some of those studies did not provide much (4, 12) or any (14) (Kaiser Permanente) baseline STI data for comparison over time. Furthermore, STI rates were already high at baseline in the PROUD study, for example, where approximately 65% of participants had an STI at baseline, perhaps making a significant increase in STIs rates less likely (13).

Of note, in the abovementioned PrEP Demonstration Projects, PrEP's efficacy at preventing HIV infection was not undermined by the high proportion of participants with incident STIs during the time they were on PrEP which ranged from 25%-65%.

Table 6. Sexually Transmitted Infections reported in PrEP Randomised Controlled Trials and PrEP Demonstration Projects

Study	Study population	Change in STIs
Randomised controlled trials		
iPrEX	MSM	• Very little data on baseline STI prevalence: 13% + syphilis serology and 37% HSV2 Ab positive • Routine follow-up STI testing was done every 24 weeks and no rectal swabs were done routinely! 12 weekly testing for STI was done in those who were symptomatic. See Table 4 in Suppl. NO data on incident STIs
Partners PrEP	Heterosexuals in HIV serodiscordant relationship	• STI prevalence was 6-9% at baseline • Approximately 5% study participants had incident STIs in follow-up and no difference between study arms
Partners PrEP follow-up study	Heterosexuals in HIV serodiscordant relationship	• No difference between the study arms in the frequency of STIs over follow-up in OLE
TDF2 study	Heterosexual men and women	• Baseline: 35% seropositive for HSV2, gonorrhoea 2%, chlamydia 7-9%, syphilis approx. 1% • No information on follow-up rate of STIs
Bangkok Tenofovir Study	People who inject drugs	• No data collected on STIs at all
IPERGAY	MSM	• Baseline rates of STIs were 31% and 25% in the active drug arm and the placebo arm, respectively. • No difference in the proportion of people with new STIs during follow-up in active (41%) vs placebo arm (33%) • 5 people got hep C (1%)
Demonstration Projects		
US PrEP Study	MSM	• STI incidence was 90/100 person years but did not change over time
PROUD	MSM	• At baseline 63-65% had any STI • In follow-up 57% in immediate and 50% in the deferred arm had new STI p = ns • 6 cases of hepatitis C (3 in each arm)
iPrEX OLE and ATN 082 and the US Safety Study	MSM and transgender	• No baseline STI prevalence provided • Participants were tested every 24 weeks for syphilis, HSV or urethritis or if symptoms were present • The incidence of syphilis was the same in PrEP and non-PrEP study arms (7.2 versus 5.4 per 100 PY ns) • No other data provided
Kaiser		• No baseline STI data available

Permanente		• 30% had an STI at 6 months • 50% had an STI at 12 months
VicPrEP	MSM	• At baseline, 25% of participants had evidence of prior syphilis • At baseline, 12% of participants had an STI • At six months, 24% of participants had an STI

Potential broader health outcomes for PrEPX study participants

Recent reports have provided information on key health issues in Australian men (67, 68). These issues include weight, blood pressure, consumption of alcohol and cigarettes and mental health. These reports on the health of Australian men found that:

- More than one in four males aged 20-20 were current smokers compared to one in ten men aged 70 years or older
- On a single occasion of drinking, 1 in 10 males aged 50–59 (11%) and 60–69 (10%) were at risk of injury at least daily (every day or most days)
- About one-quarter (26%) of males aged 25 and over had high blood pressure, increasing from 13% of those aged 25–34 to 44% of those aged 75 and over
- In 2007, an estimated 1.1 million (17%) males aged 25–85 experienced a mental disorder in the previous 12 months
- In younger men only 50% or less undertake regular skin care check
- Men are less likely to participate in Bowel Cancer Screening Programs in Australia
- 30% or less of mean aged 15-34 years have discussed a healthy lifestyle with a health professional in the previous 12 months

Compounding these issues is the fact that the use of health services by Australian males is considerably lower than that of women. Reasons for this may include limited opening hours, less access to male health professionals, not feeling comfortable stating the reason for the health visit, and feeling discomfort in the waiting room and the societal norms that hold that men should be self-reliant, capable of controlling emotions and pain (67).

Similarly other individuals with different HIV exposure groups may not have adequate opportunities to address different health issues with healthcare practitioners. Participation in PrEPX will give individuals and their healthcare providers a regular opportunity to address different health issues including healthy lifestyles. Using the ACCESS system, its GRHANITE software will be able to determine what the proportion of study participants receive treatment for common health problems and what proportion engage in health prevention measures with their doctors during the course of the study.

1.2 Rationale for selected study design

PrEP randomised controlled trials and PrEP Demonstration Projects have demonstrated that the use of TDF/FTC is highly efficacious in the prevention of HIV infection, with only one documented failure of TDF/FTC having occurred in a person with transmitted drug resistance. The safety of using TDF/FTC for periods of 1-3 years has been evaluated and, overall, it appears to be safe. The safety profile of longer-term use of TDF/FTC, for example for period of 3-5 years or longer, has not been established.

Adherence rates to PrEP have increased over time and in Victoria, PrEP adherence rates that confer very high protection against HIV infection have been seen in approximately 90% of VicPrEP participants. In some studies, including VicPrEP, sexually transmitted infections have increased and condom use has declined. However interpretation of these findings is not straightforward and requires further follow-up combined with the planning and implementation of innovative STI prevention strategies. Furthermore, individuals who receive PrEP attend their healthcare practitioners on a quarterly basis, which may afford individuals the opportunity to enhance other aspects of their health including blood pressure management, assistance with managing drug and alcohol and cigarette use, skin checks and vaccinations.

In Australia, and within Victoria, the knowledge of, interest and willingness to use PrEP is high amongst gay and bisexual men. This new strategy, when combined with other HIV prevention measures, is likely to greatly reduce the incidence of new HIV infections in Australia when uptaken by substantial proportions of populations at risk of HIV infection.

Table 8. STUDY AIMS AND HYPOTHESES AND DATA REQUIRED

Primary Aim	Primary Hypothesis	Data required
1.0 INCIDENCE OF NEW HIV INFECTIONS IN VICTORIA		
1.1 To determine if the provision of generic Tenofovir + Emtricitabine to 2,600 HIV negative people whose sexual and/or injecting behaviour is associated with a high chance of HIV acquisition, will lead to an overall 25% decline in new HIV infections across Victoria and a 30% decline in new HIV infections in MSM over the following 12-36 months	That the provision of generic Tenofovir + Emtricitabine for HIV pre-exposure prophylaxis to 2,600 people whose sexual and/or injecting behaviour is associated with a high chance of HIV acquisition, will lead to greater than a 20% decline in new HIV infections across Victoria and a 30% decline in new HIV infections in MSM over the following 12-36 months.	Pre-implementation and follow-up HIV test results that will be acquired through the ACCESS GP Network and the ACCESS Sexual Health Centre Network
1.2 To determine any factors associated with incident HIV infection	That medication adherence will be associated with incident HIV infection	Demographic and basic risk behaviour data collected through ACCESS and adherence measures. Results of DBS tests that are performed on all study participants who become infected with HIV during the study
Secondary Aims	**Secondary Hypotheses**	**Data required**
2.0 BEHAVIOUR		
2.1 To determine baseline patterns of sexual and injecting behaviour in study participants and any change in these patterns over study follow-up	<u>For MSM study participants</u> • That condom use for anal sex with regular and casual partners will decline over time • That casual partner numbers will not change significantly over time • That assessment of HIV+ sexual partner's/s' HIV viral load will increase over time <u>For PWID study participants</u> • That injecting drug use will decline over time	Using data from ACCESS questionnaires Using data from follow-up ACCESS questionnaires

	For heterosexual study participants • That condom use for vaginal and/or anal sex will decline over time • That assessment of HIV+ partner's/s' HIV viral load will increase over time	
2.2 To explore baseline attitudes to PrEP **2.3** To explore reasons for using PrEP including peer pressure to stop using condoms **2.4** To explore attitudes around whether sexual behaviour has changed since PrEP became widely available in Victoria in 2014	• That PrEP is currently an acceptable new HIV prevention strategy • That there is peer pressure to stop using condoms now that PrEP is available	Using baseline data from the 260 study participants who do the online surveys and using information obtained from face-to-face interviews with 30 study participants
Secondary Aims	**Secondary Hypotheses**	**Data required**
3.0 SEXUALLY TRANSMITTED INFECTIONS, HEPATITIS C AND HIV		
3.1 To determine the baseline prevalence of incident STIs **3.2** To determine what proportion of study participants have evidence of previous syphilis at baseline **3.3** To determine the baseline prevalence of hepatitis C Ab positivity **3.4** To determine the baseline prevalence of early and chronic HIV infection	That the baseline prevalence of STIs will be approximately 12% That approximately 20% of study participants will have evidence of prior syphilis That approximately 5% of study participants will be HCV antibody seropositive at baseline That approximately 1-2% of study participants will be HIV seropositive at baseline	Pre-implementation and follow-up test results that will be acquired through ACCESS
3.5 To determine when the study participants' last HIV and STI tests were performed **3.6** To determine how many STIs the study participants reported in the previous 3 months (pre-stratify into baseline PrEP and non-PrEP users) **3.7** To determine what proportion of study participants met the STIGMA guidelines over the	That approximately 38% will have had STI testing within the previous 12 months That approximately 14% had STIs in the previous 12 months That six-monthly STI re-testing will be between 15%-20% of participants	Pre-implementation and follow-up test results that will be acquired through ACCESS

previous 12 months, e.g. ask how many times the study participant had tests for STIs and HIV in the past 12 months		
3.8 To determine whether there is an increase in STIs from baseline over study follow-up and any associated factors **3.9** To determine the rates of change of specific STIs from baseline through study follow-up **3.1.1** To determine the incidence of hepatitis C infection from baseline over study follow-up and any associated factors	That there will be a doubling of the number of people with STIs at six months compared to the number with STIs at baseline That a decline in condom use and group sex will be associated an increase in STIs That approximately 1% of study participants will acquire hepatitis C infection	Pre-implementation and follow-up test results that will be acquired through ACCESS
3.1.2 To explore baseline attitudes towards STIs and change in attitudes towards STIs **3.1.3** To explore at baseline whether study participants ask their partners about their STI status and whether there is any change in this behaviour	That individuals' reports of feelings about having STIs will range from perceiving that they are an inevitable outcome of sex, to feelings of shame That over time, study participants will report more discussion and disclosure of their STI status	Using data from the 260 study participants who do the online surveys and using information obtained from face-to-face interviews with 30 study participants
Secondary Aims	**Secondary Hypotheses**	**Data required**
4.0 ADHERENCE		
4.1 To determine adherence from baseline through follow-up (pre-stratify into baseline PrEP and non-PrEP users)	That adherence by all measures will show that 90% or more of study participants are using between four to seven doses of Tenofovir + Emtricitabine weekly	Using data from the 260 study participants who do the online surveys Alfred Clinical Research Pharmacy will be able to ascertain PrEP dispensing patterns for all study participants Refill based assessment can be ascertained by looking at patient quarterly HIV/STI testing dates through ACCESS and dates that PrEP prescriptions are dispensed

5.0 ACCEPTABILITY		
5.1 To determine how acceptable PrEP is to study participants at baseline through study follow-up (pre-stratify into baseline PrEP and non-PrEP users) **5.2** To determine how acceptability of PrEP changes from baseline over study follow-up (pre-stratify into baseline PrEP and non-PrEP users)	That study participants will report broadly that PrEP is an acceptable HIV measure	Using data from the 260 study participants who do the online surveys Using data from in-depth qualitative interviews at baseline and study end
6.0 HEALTH BENEFITS ASSOCIATED WITH PARTICIPATING IN THE PrEPX STUDY		
6.1 To determine the last time that the study participant has seen a general practitioner **6.2** To determine the proportion of study participants who have a regular GP at the time of enrolling into the PrEPX Study	That a high proportion of male study participants especially between the ages of 25-34 will not have seen a general practitioner in the previous 12 months That a relatively high proportion of male study participants especially between the ages of 25-34 will not have a regular general practitioner	Using data from baseline clinical surveys
7.To determine at baseline at months 12 and study end **7.1** What proportion of study participants use non-prescription (illicit) drugs **7.6** What proportion of study participants drink more than the recommended amount of alcohol **7.2** What proportion of study participants are on vareniciline or nicotine replacement therapy **7.3** What proportion of study participants are on anti-hypertensive agents **7.4** What proportion of study participants are on lipid-lowering agents **7.5** What proportion of study participants have	That enrolment in the PrEPX study will be associated with the uptake of preventive and therapeutic health measures in PrEP Study participants	Using data from baseline clinical surveys and the ACCESS system

had a pap smear **7.**6What proportion of study participants are on opioid substitution therapy **7.7** What proportion of study participants are on medication to help prevent alcohol use **7.8** What proportion of study participants are on anti-depressants **7.**9 What proportion of female study participants over the age of 55 have had a mammogram **7.1.1** What proportion of study participants over the age of 50 have had faecal occult blood testing **7.1.2** What proportion of study participants have had a skin cancer diagnosed		
8.0 CHANGES IN THE HEALTHCARE SETTINGS INVOLVED IN THE PrEPX STUDY		
8.1 To determine how many PrEP patients were seen at the clinics and pharmacies at baseline and compare that to the number seen at month 12 and study end **8.2** To determine how many EFTs were created in the study clinics and pharmacies from baseline to month 12 and study end in response to participating in the PrEPX study	• That clinics and pharmacies will see at least a doubling of patients presenting for PrEP in response to PrEPX • That clinics will need to increase the number of new clinics and EFTs in response to PrEPX • That some clinics and pharmacies may undergo an increase in new floor space in response to PrEPX	• Using data obtained from questionnaires completed by the participating study clinics
8.3 To determine how many HIV and STI tests were performed in the month prior to PrEPX commencing and compare that to the number performed in the month prior to PrEPX completing patient follow-up	• That clinics will see at least a tripling of HIV and STI testing in response to PrEPX	• Using data obtained from questionnaires completed by the participating study clinics
8.4 To determine if there had been a change in the relationship with the clinics' Pathology service	• That some clinics may negotiate new terms with their pathology providers	• Using data obtained from questionnaires completed by the participating study clinics

providers over the time of the PrEPX study as a result of the PrEPX study		
8.5 To determine if there is a decrease in NPEP consultations and prescriptions over the time of the study	• That there will be a decrease in the number of NPEP consultations and prescriptions over the time of the study	• Data will be determine the Victorian NPEP monthly data report which is generated by the Dept of Infectious Diseases, Alfred Health
9.0 CHANGES IN THE WORK OF THE PEAK ORGANISATIONS ASSOCIATED WITH THE PREPX STUDY		
9.1 To determine how many EFTs were created, or lost from baseline to month 12 and study end in response to participating in the PrEPX study	• That some of the national peak organisations may increase their EFTs in response to the PrEPX study	• Using data obtained from questionnaires completed by the participating Peak Organisations

2. STUDY DESIGN

2.1 DESIGN

This is a multi-site, prospective, open-label, population-level PrEP demonstration study, the primary aim of which is to determine whether the use of daily PrEP by 2,600 Victorians who are at high risk of HIV infection will reduce the number of new HIV infections in Victoria in the following one to three years. Participants will be provided with daily co-formulated generic Tenofovir + Emtricitabine for a period of 21 months, or less if Truvada® is subsidised on the PBS during that 21 month period at which time study participants may elect to use Truvada® whilst remaining in the study.

3.1.1 Study sites

Participants will be recruited from seven sites: Prahran Market Clinic, Centre Clinic, Northside Clinic, PRONTO!, an ERA clinic in the city of Melbourne, the Melbourne Sexual Health Centre HIV Integrated Prevention (HIP) clinic and the Alfred Hospital HIP clinic. Potentially eligible individuals can self-refer to these clinics, or will be identified by clinic staff as being eligible whereupon they will be invited to participate in the study. All participants will be offered PrEP in conjunction with all other available Standard of Care (SOC) HIV prevention measures.

3.1.2 Data collection

This study will utilise data collected via the ACCESS system at Prahran Market Clinic, Centre Clinic, Northside Clinic and PRONTO! which participate in the ACCESS GP Network surveillance system (Alfred Health Human Ethics Committee 6/14), at the Melbourne Sexual Health Centre which participates in the ACCESS Sexual Health Centre Network (Alfred Health Human Ethics Committee 224/08) and ACCESS participating laboratories (Alfred Health Human Ethics Committee 90/12). The ACCESS system also collects data from several Pathology Services in Melbourne that are affiliated with the abovementioned clinics. These Pathology Services include Healthscope, VIDRL and Dorevitch Pathology.

The Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of STIs and BBVs (ACCESS) is a collaboration between the Burnet Institute, the Kirby Institute and the National Serology Reference Laboratory (NRL) in partnership with numerous other stakeholders and participating sites. ACCESS is a surveillance system that is in place in the aforementioned clinics. ACCESS involves the routine and ongoing collection of de-identified, clinical data from patients attending these clinics. The participating clinics have provided clinic-wide consent for their patients' data to be collected; hence the clinic patients are not required to individually consent to their data being collected. HIV, STI and bloodborne virus (BBV) test results are routinely collected by the ACCESS system from patients who attend these

clinics. The patients' test results can also be collected from Healthscope, VIDRL and Dorevitch Pathology through the ACCESS system.

For the purpose of PrEPX, however, PrEPX study participants *will* be asked to consent to the PrEPX researchers having access to participants' HIV and STI and BBV test results that have been obtained through ACCESS. We will also ask PrEPX study participants to consent to having broader medical information about other test results and prescriptions that are discussed in detail in sections below collected by ACCESS. ACCESS uses the GRHANITE™ Data Extraction software, which was developed by the University of Melbourne. GRHANITE™ interfaces with the clinics' Patient Data Management systems to extract patients' specific test results and other medical information including prescriptions. Use of the ACCESS data system in the PrEPX study obviates the need to have manual extraction of the follow-up data from 2,600 participants, alleviating the burden on both patients and clinics and helping facilitate a 'real-world' PrEP implementation environment. PrEPX study participants' data will be sent from ACCESS to the PrEPX database, which will be housed at the Department of Infectious Diseases Alfred Hospital. Importantly, ACCESS uses software that removes any patient identifying details before the test results are extracted from the clinics' or the pathology labs' computers, thus protecting the patients' privacy. These de-identified test results are sent to the Burnet Institute. However, for the purpose of the PrEPX study, the ACCESS system will use specially designed linkage keys so that we can identify the participants in the PrEPX study. This will allow us to follow participants' test results over time. When we have participants identifying details through ACCESS, they will be assigned a code that can only be linked back to the participants by using a decoding key, which will be stored separately under lock and key and only known to a few members of the research study team.

Of note, patients attending the Era Health clinic in Bourke Street and the Alfred Hospital HIP clinic will not have any test results or general medical data extracted from their records. Patients attending the Era Health Clinic in Bourke Street will have their blood tests results available via ACCESS because ACCESS also interfaces with several pathology laboratories in Victoria including Healthscope Pathology, which is used by Era Health Clinic patients. Participants at the Alfred HIP clinic will have their blood test results manually extracted by a study nurse from PowerCHART.

At each study visit PrEPX study participants who attend Prahran Market Clinic, Centre Clinic, Northside Clinic and PRONTO! and the Melbourne Sexual Health Clinic which are all part of the ACCESS network, will complete questions that are included as part of ACCESS surveillance system. The questions will ask about gender, country of birth, reasons for HIV and STI tests, sexual behaviour, drug and alcohol use over the previous six months. These data will be entered by participants on electronic password

protected tablets. Data from these tablets will be stored on the local clinic server and extracted and managed using a secure electronic data capture system (REDCap). Study participants attending the Era clinic and The Alfred HIP clinic will not have these data collected.

As part of the study design, five community pharmacies that are affiliated with and in close proximity to the abovementioned community medical clinics have agreed to become PrEPX study sites so that PrEPX participants can obtain their study medications as if it were a 'real world' situation. These pharmacies will dispense PrEP to PrEPX participants in addition to the Alfred Hospital pharmacy and the Melbourne Sexual Health Centre pharmacy. This novel approach to providing HIV antiretroviral prevention therapy in the community setting complements the national legislation that was enacted in July 2015 that permits S100 HIV antiretrovirals to be dispensed from community based pharmacies and indeed, several of these proposed pharmacy study sites are already dispensing HIV antiretroviral medications to their HIV positive patients.

3.1.3 Baseline Data Collection

At baseline the following data will be collected from *all* study participants: age, gender, date of birth.

Patients attending the clinics participating in ACCESS will be asked questions about gender, country of birth, reasons for HIV and STI tests, sexual behaviour, and drug and alcohol use over the previous six months. For participants attending the ACCESS clinics, ACCESS will extract data at baseline on the study participants' current use of anti-hypertensive agents, use of anti-smoking medications, nicotine replacement therapy, lipid-lowering agents, opioid substitution therapy, medication for alcohol dependency, anti-depressants, history of any vaccinations, pap smears, mammograms (for women over 55 years of age), faecal occult blood test results (for participants over 55 years of age) and a diagnosis of skin cancer in the past 12 months. Of note, patients attending the Era Health clinic in Bourke Street and the Alfred Hospital HIP clinic will not have any general medical data extracted from their records.

The following tests will be performed at baseline on all study participants: a 4th generation HIV antibody/antigen combo test, STI tests for chlamydia, gonorrhoea, syphilis, hepatitis B surface antigen and antibody, hepatitis C antibody, serum creatinine, eGFR, electrolytes, liver function tests and a urine albumin: creatinine ratio (ACR). These results will be extracted from the ACCESS system for those patients attending ACCESS affiliated sites. In the case of the Era Health clinic site, its study participants' results will be extracted from the Healthscope Laboratory which is affiliated with Era Health. In the case of Alfred Hospital study participants' results will be obtained by manual data extraction from PowerCHART.

In some cases, participants may give a script for TDF/FTC on the same day as the baseline tests are performed, so that the study participant can commence PrEP immediately. These participants will be considered by their doctor to be very unlikely to have undiagnosed HIV infection, or undiagnosed hepatitis B infection, or undiagnosed kidney disease. Those participants whose baseline HIV ELISA is positive and who have already started TDF/FTC will be given the option of ceasing TDF/FTC , or commencing full treatment for HIV infection. Participants who have started PrEP and are found to have undiagnosed hepatitis B infection will be advised to remain on PrEP and will be referred to a hepatitis B expert for further evaluation and monitoring. Participants who are unexpectedly found to have poor kidney function with an eGFR below 60 mLs per minute will be advised to cease TDF/FTC and their doctor will discuss other options to minimise their chances of becoming infected with HIV.

Any participant who is diagnosed with HIV infection at study baseline will be offered the opportunity to commence HIV treatment as soon as possible and will be referred for specialist advice as required.

Any participant who is diagnosed with a sexually transmitted infection at baseline will be provided with appropriate treatment for the infection/s.

Any participant who is identified at baseline as having chronic hepatitis B will be referred to hepatitis B specialists who will evaluate and monitor the patient during the study according to best standards of clinical practice. These participants will have hepatitis B DNA levels performed prior to commencing generic Tenofovir + Emtricitabine. These participants will be counselled at baseline and during the study that daily use of Tenofovir + Emtricitabine is necessary because intermittent use of Tenofovir + Emtricitabine cause a flare of hepatitis B infection. Those PrEPX study participants who are found to be hepatitis B non-immune at baseline will receive hepatitis B vaccination as per current Australian standards of care.

Participants who are identified at baseline as having chronic hepatitis C will be referred for specialist medical advice to provide the current standard of care for hepatitis C management.

Ten percent of enrolled participants will be asked to complete an online behavioural survey at baseline about their sexual practice, attitudes and use of conventional methods for practicing safe sex, HIV/STI testing history, socio-demographics and quality of life.

Thirty participants will be invited also to complete in-depth, one-on-one qualitative interviews at baseline.

Clinical and pharmacy study sites will be evaluated with a questionnaire at baseline about the number of patients who attend for PrEP, how many EFTs are currently devoted to providing services for people seeking PrEP service, how/if patients are followed up to help them with script re-fills and any logistical

changes required to manage PrEP patients. For clinics further questions about STI and HIV testing rates and relationship with pathology service provider will be asked.

3.1.4 Follow-up data collection

During follow-up, those study participants who attend clinics participating in the ACCESS system will provide routine HIV and other STI and behavioural data each time they visit participating clinics for PrEP or intermittent HIV/STI testing. Study participants attending the Era clinic and The Alfred HIP clinic will not have these data collected. This data follow-up will allow us to determine whether any behavioural change occurs in PrEPX study participants.

During follow-up, those study participants who attend clinics participating in the ACCESS system will have any of their information regarding being prescribed anti-hypertensive agents, anti-smoking medications, nicotine replacement therapy, lipid-lowering agents, opioid substitution therapy, medication for alcohol dependency, anti-depressants or any vaccinations be captured at 12 months and at study end through ACCESS. Study participants attending the Era clinic and The Alfred HIP clinic will not have these data collected. This data follow-up will allow us to determine whether there are additional health benefits outside of HIV prevention by attending for quarterly PrEP visits, such as treatment of hypertension, active management of smoking, alcohol, or illicit drug use, management of depression, receipt of appropriate vaccinations, having gender and age-appropriate investigations such as pap smears, mammograms and faecal-occult blood tests and evaluation for skin cancers

During follow-up a 4^{th} generation HIV antibody/antigen combo test and STI tests for chlamydia, gonorrhoea and syphilis will be performed every three months, as per the Australian PrEP Guidelines (22).

During follow-up, urine albumin: creatinine ratio (ACR), serum creatinine and eGFR will be performed every six months, as per the Australian PrEP Guidelines (22). Clinicians may elect to perform these renal function tests more frequently based on the study participant's age, intercurrent medical conditions and intercurrent medication use. Hepatitis C antibody testing will be repeated at months 12 and 21. These results will be extracted from the ACCESS system for those patients attending ACCESS affiliated sites. In the case of the Era Health clinic site, its study participants' results will be extracted from the Healthscope Laboratory, which is affiliated with Era Health. In the case of Alfred Hospital study participants' results will be obtained by manual data extraction from PowerCHART

During follow-up any participant who is diagnosed with HIV infection will be offered a number of different therapeutic and support options. The participants doctor individual will offer the participant a number of different treatment options and will offer all participants the opportunity to see an HIV specialist physician. Different options will including choosing to cease all treatment, to stay on the

TDF/FTC plus add in one or two other antiretroviral agents, to cease the TDF/FTC and commence other antiretroviral agents to achieve rapid HIV virological suppression. Where possible the participant's HIV genotype will be performed.

Any participant who is diagnosed with a sexually transmitted infection during follow-up will be provided with appropriate treatment for the infection/s.

Any participant who is diagnosed with hepatitis B, or hepatitis C during follow-up will be referred for specialist advice.

Those participants who completed the online baseline behavioural survey will be asked to complete the survey every six months until study end.

Those 30 participants who completed in-depth, one-on-one qualitative interviews at baseline will have a second in-depth, one-on-one qualitative interview at month 21 (study end).

3.1.5 Evaluation of medication adherence

Medication adherence will be evaluated by four methods: (1) online self-report from the 260 participants who agree to participate in the online surveys; (2) through in-depth interviews with study participants; (3) Alfred Clinical Research Pharmacy will be able to ascertain PrEP dispensing patterns for all study participants and (4) by combining data obtained from ACCESS to indicate the dates when study participants attended their quarterly PrEP clinic visits, and combining this with data from Alfred Clinical Research Pharmacy on the study participants' PrEP dispensing dates, we will be able to derive refill-based assessment results for study participants every six months and (5) Dried blood spot testing to evaluate blood levels of Tenofovir and Emtricitabine will performed on any study participants who become infected with HIV during the study,

3.1.6 Co-payments for study medication

As part of the study design and similar to what the VicPrEP study participants did, all PrEPX study participants will be required to pay the usual co-payment that they would have to pay, if Truvada® were currently subsidised on the PBS for use as PrEP. The 2016 co-payment costs are $6.20 for concession card holders or $38.30 for non-concession card holders. Payment for study drug will be required every 3 months at the time participants collect their PrEP medication from any of the participating pharmacies. Although this is not standard practice for patients to pay for study medication, this is a critical aspect of this 'real life' population-level, demonstration project.

Clinical and pharmacy study sites will be at month 12 and study end to determine the impact of providing a PrEP service, through the PrEPX study upon the number of patients who attend for PrEP,

how many EFTs needed to be created to support the PrEP service and the amount of extra floor space needed to be created to accommodate the PrEP service.

3.2 STUDY PARTICIPANTS

The PrEPX demonstration project will individuals who are at risk of HIV infection and who consent to participate in the project.

3.3 SAMPLE SIZE

2,600 HIV-negative people at risk of HIV infection and who wish to receive PrEP will be recruited through the abovementioned participating clinics.

The sample size estimate for the PrEPX study was undertaken as follows. There are an estimated 300 *new* HIV infections per year in Victoria; this is based on back-calculation methods which have used available surveillance data and a modelling framework to estimate these levels for recent years and demonstrated that in the Australian context, with high and fairly stable testing rates, numbers and trends in HIV notifications are a strong surrogate marker for the actual number of and trend in new infections (69-72). Approximately 75% of all new HIV diagnoses in Victoria occur in MSM, that is 300 new HIV infections x 75% = 225 new infections occur in MSM annually in Victoria.

We determined that a thirty percent reduction in new HIV infections in MSM, which would represent an overall 23% (=75%x30%) decline across Victoria, would be a meaningful outcome at a population level, of scaling up PrEP through the PrEPX study.

Although the PrEPX study is open to all Australians at risk of HIV infection, irrespective of HIV exposure type, we powered the study using HIV incidence estimates from a gay male cohort, the HIM study (73). This is because a majority of new HIV infections occur among MSM and there are not adequate, local epidemiological data to determine the risk of HIV infection in Australian heterosexuals and people who inject drugs to inform the estimation of required patient sample size for PrEPX. We expect that a majority of participants will be MSM (at least proportional to the incident cases in Victoria) and therefore we have powered the study to reflect this, which we expect to be a conservative estimate.

The only cohort study in Australia to measure HIV incidence was the HIM study, among gay and bisexual men in Sydney in the early-to-mid 2000s. Wilson has shown that the per-capita transmission rate has remained relatively stable since that period (74). The per-capita transmission rates in NSW and Victoria are also similar and the rate of new diagnoses per 100,000 population is similar between the jurisdictions. Since the total number of people living with HIV in Victoria, and the rest of Australia, has been increasing due to ART, it is reasonable to

assume that the incidence has not decreased substantially and may have increased. In the HIM study, the incidence of HIV infection overall was 0.78 per 100 person years (PY). However, 24% of HIM cohort participants were at high risk of HIV infection with an HIV incidence of 2.78 per 100 PY. The cohort participants at higher HIV risk are analogous to people eligible for PrEP in this study based on very similar behavioural characteristics in the cohort and the PrEP eligibility criteria.

To reduce the number of new HIV infections in MSM in Victoria by one-third, we would need to prevent 68 cases of new HIV infection (225x30%= 68). These 68 averted infections would occur among MSM at higher risk who are eligible for PrEP, with baseline incidence assumed to be of the magnitude measured from the higher risk HIM cohort (2.7 per 100PY).

Therefore, to calculate the number of men required in this study to detect a 30% reduction in incidence we divide the 68 cases prevented by the incidence rate of 0.027 = 2,518. Hence, approximately 2,600 participants will be required. For a reference, the total number of MSM at risk of HIV in Victoria is estimated to be 225/0.78 per 100PY = 28,846 and the total number of MSM at high risk and targeted for the study will be the proportion of MSM at high risk, 24% (as per the HIM study) multiplied by the number of Victorian MSM at risk. That is, our target population size will be 28,846 x 0.24= 6,923 MSM. Hence, 2,600/6,923 = 37% of MSM who are at highest risk of HIV infection will be offered PrEP coverage.

This estimate of providing a 37% PrEP coverage of gay and bisexual men at highest risk of HIV infection compliments the estimates of the 2015 PrEPARE survey which found that 38% of the 307 Victorians gay and bisexual men surveyed, were both willing and eligible to use PrEP (37).

The feasibility of providing coverage to 2,600 MSM at high risk of HIV in Victoria appears to be high as discussed in section 1.2.1. To reiterate, in Victoria there are 110 people receiving PrEP through the VicPrEP Study and approximately 700 Victorians currently are importing generic Tenofovir-Emtricitabine for personal use as HIV PrEP. These latter estimates are derived from details provided by Melbourne's high caseload S100 general practices that are providing the medical supervision and prescriptions for people self-importing. Furthermore approximately 1,200 people have registered their interest in the PrEPX study of whom approximately 70% are not self-importing PrEP. Hence, we assume that we will have approximately 110 *plus* 700 *plus* 734 = 1,600 people who will seek to enter PrEPX within the first six to eight months of the study opening. Given the high rate of knowledge of PrEP and current use of PrEP in Victoria, we anticipate that we will reach an enrolment of 2,600 people.

It is quite plausible that PrEP will in fact reduce new HIV infections by more than 68 cases if the actual incidence of HIV infection is higher than 2.7 per 100 PY. In the UK PROUD PrEP study, for example, the incidence of HIV infection in those study participants who were randomised to the deferred arm, their HIV incidence was 9.0 per 100 PY (13).

3.4 STUDY SITES

The PrEPX study project will be implemented at the following seven clinical sites: Prahran Market Clinic, The Centre Clinic, Northside Clinic, PRONTO!, an ERA clinic in the city of Melbourne, the Melbourne Sexual Health Centre HIV Integrated Prevention (HIP) clinic and the Alfred Hospital HIP clinic

All sites will have the capacity to comply with the protocol, project-specific procedures, and all applicable regulations. Appropriate ethics and IRB approvals, for the purpose of this project, will be obtained at all seven participating sites.

All sites have a reception room, waiting area, physical examination rooms, counselling rooms, a medication storage area, a data management area and access to laboratory facilities.

Table 9. The pharmacies that will be participating in the PrEPX study.
* Denotes that the pharmacy is a community pharmacy

Suburb	Pharmacy	Study Pharmacy- Study clinic affiliation
Fitzroy	John Silverii's Pharamcy*	Northside Clinic
Collingwood	Newton & Leung Pharmacy*	Pronto!
Carlton	MSHC Pharmacy	Melbourne Sexual Health Centre
Prahran	Prahran Centre Pharmacy	Prahran Market Clinic
	Alfred Clinical Trial's Pharmacy, Alfred Centre	The Alfred Hospital
	Healthsmart Pharmacy at The Alfred*	The Alfred Hospital
St Kilda	Russell Frajman Pharmacy*	Centre Clinic

The PrEPX Community pharmacy drug accountability requirements will be as per Good Clinical Practice guidelines and are as follows:

- There will be an authorised study pharmacist/assistant who has received study training, signed the training log, and who is delegated by site investigator on the delegation/signature log
- The pharmacy will be able to store study drug in a restricted access facility which the study pharmacist/pharmacy assistant can access
- Continuous temperature monitoring with 24-hour temperature excursion alarm will be available in the pharmacy; there will be a temperature log recording the temperatures [minimum requirement daily min and max temperature readings]
- There will be timely documentation of:
    - The training log
    - The delegation/signature log
    - The drug accountability logs – quantity received / quantity dispensed / quantity returned / quantity disposed

These requirements will be audited during the study every 6 months

3.5 STUDY DURATION AND RECRUITMENT SCHEDULE

The study will run from 30/06/2016 to 30/03/2018. Recruitment of the participant sample will take place June 30th 2016. It is anticipated that full recruitment will be complete by March 2017. Study participants will be followed for a period of 21 months.

4. PARTICIPANTS

4.1 INCLUSION CRITERIA

Gay, bisexual, transgender, heterosexual people and people who inject drugs are eligible for this study and must meet the five criteria listed below. Further individualised behavioural inclusion criteria for gay, bisexual, transgender, heterosexual people and people who inject drugs are provided in sections below.

1. Age ≥18 years
2. Willing and able to provide written informed consent
3. Documentation of an HIV negative test performed at both screening visit and enrolment
4. Have a creatinine clearance of > 60mL per minute (via Cockroft-Gault formula)
5. Able to provide street address and/or telephone number and/or email address to be contacted during the period of the demonstration project

In addition to the five criteria listed above and the different behavioural criteria listed below, evaluation and consideration should be made of any social, emotional and psychological component that may be contributing to the individual's request for PrEP. PrEP use is associated with feeling safer during sex and may offset the individual's fear of acquiring HIV, fear of having no control over their partner's condom use or their partner's choice to use HIV antiretrovirals and fear of experiencing intimate partner violence (53). A desire for greater intimacy has been seen also as a significant factor that motivates MSM to use Prep (54). In the VicPrEP study we found that concern about HIV infection was significantly reduced at month 6 by study participants (55).

The behavioural eligibility criteria listed below for Gay, Bisexual, Transgender and Heterosexual people and people who inject drugs have been adapted from the Australian PrEP Guidelines (22).

Eligibility criteria for Gay, Bisexual and Transgender people

If the study participant is likely to have multiple events of condomless anal intercourse (CLAI), with or without sharing intravenous drug use (IDU), in the next 3 months (indicating sustained risk) AND has any of the following:

- Is a regular sexual partner of an HIV-infected male partner with whom condoms were not consistently used in the last 3 months (HIV positive partner is not on treatment and/or has detectable HIV viral load)
- At least one episode of receptive CLAI with any casual HIV-infected male partner or a male partner of unknown HIV status in the last 3 months
- A diagnosis of rectal gonorrhoea, chlamydia and/or syphilis during the last 3 months or at screening
- Has used methamphetamine in the last 3 months
- Has had more than one episode of anal intercourse in the last 3 months when proper condom use was not achieved (e.g., condoms slipped off or broke)
- The study participant is uncircumcised and reports more than one episode of insertive CLAI in the last 3 months where the serostatus of their partner was not known, or the partner was HIV positive and not on antiretroviral treatment.

Gay, bisexual and transgender people who do not report any of the above risk factors should still be considered at risk of HIV infection and evaluated on a case-by-case basis. The rationale for this case-by-case approach is based on the following: it is highly likely that some study participants will feel uncomfortable disclosing to their usual doctor, or usual healthcare provider that they have not been, *and may not in the future practice safer sex, or safe injecting practices*, therefore they may under-

report their HIV risk factors; this may also hold for individuals who have never attended the clinic before and do not yet feel comfortable disclosing their previous and planned sexual activity to the new healthcare provider; the likelihood of people seeking PrEP who do *not* have high HIV risk factors is low: the experience with VicPrEP is that only those MSM at highest risk presented for PrEP (Lal et al, manuscript in preparation); in San Francisco, in two surveys of MSM using PREP, between 79% and 88% of the survey respondents reported high HIV risk factors (17).

Eligibility criteria for Heterosexuals and Transgender people

If the study participant is likely to have multiple events of condomless anal or vaginal intercourse (CLAI or CLVI, respectively), with or without sharing IDU, in the next 3 months (indicating sustained risk)

AND

- Is a regular sexual partner of an HIV-infected man or woman with whom condoms were not consistently used in the last 3 months (HIV positive partner is not on treatment and/or has detectable viral load)

Heterosexuals and transgender people who do not report any of the above risk factors should still be considered at risk of HIV infection and evaluated on a case-by-case basis. The rationale for this case-by-case approach is based on the following: it is highly likely that some study participants will feel uncomfortable disclosing to their usual doctor, or usual healthcare provider that they have not been, *and may not in the future practice safer sex, or safe injecting practices*, therefore they may under-report their HIV risk factors; this may also hold for individuals who have never attended the clinic before and do not yet feel comfortable disclosing their previous and planned sexual activity to the new healthcare provider; the likelihood of people seeking PrEP who do *not* have high HIV risk factors is low.

Eligibility criteria for People who Inject Drugs

If the study participant is likely to have multiple events of sharing needles or injecting equipment with an HIV positive individual or a homosexually active man and has inadequate access to safe injecting equipment in the next 3 months (indicating sustained risk)

AND

- Has been sharing needles or injecting equipment with an HIV positive individual or with a homosexually active man in the last 3 months

People who inject drugs who do not report any of the above risk factors should still be considered at risk of HIV infection and evaluated on a case-by-case basis. The rationale for this case-by-case approach is based on the following: it is highly likely that some study participants will feel

uncomfortable disclosing to their usual doctor, or usual healthcare provider that they have not been, and *may not in the future* use safe injectable practices, therefore they may under-report their HIV risk factors; this may also hold for individuals who have never attended the clinic before and do not yet feel comfortable disclosing their injecting drug use with the new healthcare provider; the likelihood of people seeking PrEP who do *not* have high HIV risk factors is low.

4.2 EXCLUSION CRITERIA

Individuals with any of the following will be excluded:

1. HIV as confirmed by HIV antibody and western blot testing
2. Signs and/or symptoms of acute HIV infection
3. Unwilling to provide consent to follow-up
4. A creatinine clearance of < 60 mL per minute (via Cockroft-Gault formula)
5. Current use of any of the following: ART, including nucleoside analogues, non nucleoside reverse transcriptase inhibitors, protease inhibitors or investigational antiretroviral agents, interferon (alpha, beta or gamma) or interleukin (e.g. IL-2) therapy, any investigational agents which may interact or affect PrEP medication and any nephrotoxic agents
6. Concomitant participation in another clinical trial using investigational agents, including placebo-controlled agents
7. At enrolment, has any other condition that, based on the opinion of the treating physician, would make participation in the project unsafe

5 STUDY OUTLINE

5.1 INVESTIGATION PLAN

For all study participants

At baseline all participants will have a venepuncture for a 4th generation HIV antibody/antigen combo test, STI tests for chlamydia, gonorrhoea, syphilis, hepatitis B surface antigen and antibody, hepatitis C antibody, serum creatinine, eGFR, electrolytes, liver function tests and a sample of urine will be collected for urine albumin: creatinine ratio (ACR).

Study visits will be scheduled in accordance with current standard of care practice, as per Australia's STI (29) and PrEP guidelines (22) participants will be have HIV and STI testing every three months and results of these tests will be acquired through the ACCESS system. During follow-up, urine albumin: creatinine ratio (ACR), serum creatinine and eGFR will be performed every six months, as per the Australian PrEP Guidelines. Hepatitis C antibody testing will be repeated at months 12 and 21.

Individuals who acquire hepatitis C during the study will be referred to a hepatitis C specialist to receive evaluation and management of their hepatitis C.

Broader health information about study participants that is described in Section 3 Study design will be acquired at baseline, month 12 and study end through the ACCCESS system.

For the 260 participants who agree to undertake online surveys, they will perform online surveys at baseline, months 6, 12, 18 and 21.

Fifty participants will be invited also to complete in-depth, one-on-one qualitative interviews at baseline and at month 21 (study end).

Participants who are identified at baseline as having chronic hepatitis B will be referred to hepatitis B specialists who will assist in monitoring the patient during the study according to best clinical standard of practice.

5.2 STUDY PROCEDURES-SCHEDULE OF ASSESSMENTS

Table 10. PrEP for MSM, Bisexual, Transgender people, Heterosexuals and People who Inject Drugs

Assessment	Screening/ Study entry	3 months	6 months	9 months	12 months	15, 18, 21 months
Informed consent sought	Yes	No	No	No	No	No
Clinical Procedures- SOC • 4th gen HIV antibody/antigen combo test • STI testing ○ Genital swab(s) ○ Pharyngeal swab ○ First-catch urine • Syphilis serology • HBsAg and Hep B sAb • Pregnancy test for sexually active, pre-menopausal women	Yes	Yes	Yes	Yes	Yes	Yes
HBsAg and Hep B sAb Document Hep B vaccination status	Yes	No	No	No	No	No
Hepatitis C Ab	Yes	No	No	No	Yes	Month 21
Clinical procedure- non-SOC Electrolytes/Serum creatinine	Yes	No	Yes	No	Yes	Month 18 and 21
Sentinel Surveillance Survey	Yes	Yes	Yes	Yes	Yes	Month 18
Online behavioural survey for 260 participants	Yes	No	Yes	No	Yes	Months 18 and 21
In depth qualitative interview for 30 participants	Yes	Yes	Yes	Yes	Yes	Months 15,18 and 21

5.3 RECRUITMENT

We anticipate that a number of study participants will self-refer to the study sites in order to enrol into the PrEPX study. In addition participants may be recruited by direct approach by healthcare providers at each study site. Participants who are eligible will be informed about the study and at the screening appointment they will be provided with the Patient Information and Consent form (PICF). Following the study entry visit, there will be follow-up visits at three-monthly intervals, which is standard of care, as per the Australian PrEP and STI guidelines. Participants will not be compensated for their time.

5.4 INFORMED CONSENT PROCESS AND ENROLMENT PROCEDURE

Consent must be documented by the participant's dated signature on a Consent Form along with the dated signature of the person conducting the consent discussion. Informed consent is an on-going process throughout the study, and is not simply one signature obtained prior to participation. For those participants who are approached by their clinic to consider enrolment into the study, it will be emphasised that non-participation does not in any way affect the participant's relationship with their treating doctor, or the clinic. A copy of the signed and dated consent form should be given to the participant before participation in the trial. All subjects should be informed in a timely manner of any new information that becomes available during the course of the study that may affect the participant's willingness to continue in the study.

5.5 STUDY ENDPOINT EVENTS

All participants will be followed until one of the events listed below occurs. Subsequent procedures will depend on the type of event:

1. Seroconversion of the participant
    a. If a participant seroconverts while taking PrEP their healthcare provider will discuss with them the relative merits of ceasing PrEP, or switching to an antiretroviral regimen that may or may not contain generic Tenofovir + Emtricitabine with the aim of providing rapid and complete HIV virological suppression. In all cases, HIV specialist advice will be sought by the healthcare provider.
    b. If any participant chooses to cease taking PrEP and withdraw from the PrEPX study during the 21 month study period, HIV testing will be performed at weeks 4 and 12 after cessation their last possible HIV exposure and participants will be advised to continue the study drug for a for a period of 28 days from their last possible HIV exposure.

2. Loss to follow-up of the participant after exhaustive measures to contact the participant fail
    a. All efforts will be made to contact the participant and the participant will be invited to attend a clinic visit
    b. If contact fails, data collection will end
3. The study is completed
    a. All follow up procedures are terminated.
    b. All remaining participants will be informed of the study's completion and the options for accessing ongoing PrEP.

5.6 ACCESS TO IDENTIFIABLE DETAILS

Responsibility for communication and follow-up with study participants will be shared between study research staff and research nurses at the seven participating clinic sites. Frequent communication between the project leader and site staff will ensure time critical aspects of the study are achieved and that maximum follow-up is reached.

The PrEPX principal investigator Dr Edwina Wright, Dr Mark Stoove who helps oversee ACCESS, Dr Dean Murphy who will oversee the behavioural surveys and the face-to-face interviews, the PrEPX project study manager and the ACCESS database manager will have access to some or all of the identifying personal details (e.g. name and contact details) of all study participants. These details will be stored securely at the Burnet Institute, the Alfred Hospital and UNSW Centre for Social Research and Health, in hardcopy or electronically. No other personnel will have access to these personal details. Research nurses and doctors at the seven participating sites will have access to the identifying personal details of the study participants attending their clinic only.

5.7 BEHAVIOURAL SURVEYS

The behavioural survey component of the study will be conducted using NetQ and NVivo Software that has been used extensively by the Centre for Social Research in Health for cross-sectional and small cohort studies.

5.7.1 Online questionnaires

Each person will be assigned a unique participant code that is used to link their behavioural data and clinic visit data. Participants will complete the survey at home, or another personal location and an email will be sent to the email address that they provide. This email will contain a URL with a secure link to the survey software. In this case the participant is not required to enter a participant code, as the email address will be linked to the unique participant code. Confidentiality of participants who join the study will be protected by the automatic survey system. Participant email addresses and/or numbers will be stored in a secure registration

module separate from the questionnaires module. Participants will also be asked to choose a unique username and password to enable their secure access to the 6-monthly questionnaires. At the end of each completed survey, the system will generate a final database that will contain no identifiers, ensuring that breach of confidentiality is not possible during analysis or dissemination of data and findings. Only the researchers involved in the project will have access to the collected data.

5.7.2 In-depth face-to-face interviews

Approximately 30 participants will be interviewed about their experiences of taking PrEP, what taking PrEP means to them, and their reasons for taking part in the project.

Participants will be interviewed at two time points. The first interview will take place ~ 1 month after commencement of PrEP and a follow-up interview approximately at month 21.

The interviews will take place face-to-face and will be conducted by a trained researcher who is not connected to the clinical arm of the project. Interviews will be audio-recorded then transcribed by a professional transcriber. The written transcripts will be de-identified by the lead researcher of this study arm, by which all potentially identifying information about them will be removed. Each participant will be assigned a pseudonym, as will other people referred to in the interviews.

Any information provided as part of the interview will not be connected to individual participant responses from the online questionnaires, clinic visit data or laboratory data. Further, any information provided by participants in these interviews will not be discussed with the individual's service provider.

6 SAFETY

6.1 COMMENCEMENT OF PREP

When a participant commences PrEP, their treating doctor or healthcare provider will discuss with them the following-

- Use of condoms and adherence to safer sex practices should be maintained as best as possible throughout the study. Regular condom use will help to prevent sexually transmitted infections from occurring. Regular condom use and safer sex practices will also help protect again HIV infection for those individuals who are not able to maintain good adherence to PrEP.
- For men it takes seven days of daily Tenofovir + Emtricitabine before protective levels within the rectal tissues are achieved. For women it takes 21 days of daily Tenofovir + Emtricitabine before protective levels are achieved in the vaginal and cervical tissues.
- That the participant will be receiving generic Tenofovir + Emtricitabine which is made by the pharmaceutical company Mylan. Mylan's Indian facilities which produce its generic Tenofovir + Emtricitabine have been approved by the Therapeutic Goods Administration (Australia), the Federal Drug Administration (USA), the World Health Organisation, the Medicines and Healthcare Products Regulatory Agency (U.K.) and Medicines Control Council (South Africa)
- The generic Tenofovir + Emtricitabine co-formulated study drug is bioequivalent to the patented drug Truvada® and the Alfred Human Research and Ethics Committee has seen an independent report from the University of NSW that attests to this.
- That side effects of TDF and TDV when used as HIV PrEP have been reported and include nausea, back pain, dizziness and vomiting
- If a participant acquires HIV infection during the study their healthcare provider will discuss with them the relative merits of ceasing PrEP, or switching to an antiretroviral regimen which will be informed by a genotypic drug test, and that may or may not contain generic Tenofovir + Emtricitabine with the aim of providing rapid and complete HIV virological suppression. In all cases, HIV specialist advice will be sought by the healthcare provider
- That women need to strictly take seven daily doses of Tenofovir + Emtricitabine to achieve the same protective levels that men may achieve by taking fewer than seven doses of Tenofovir + Emtricitabine
- That there has been one case of reported PrEP failure in a person who was taking daily TDF/FTC. This person was infected with a multi-drug resistant virus that appears to have been able to overcome any protective benefit of TDF/FTC.
- That during the study it is possible that the drug Truvada® may become listed on the Pharmaceutical Benefits Scheme and be subsidised for use as HIV prevention. The study

participant may choose to stay on generic TDF/FTC or switch to Truvada®. If the study participant switches to Truvada® they will remain eligible to stay in the PrEPX study.

6.2 PrEP CESSATION

For participants who are due to complete the study, or who wish to stop taking PrEP earlier than the study period, or who withdraw from the study, he/she will be advised by their treating doctor that-

- The participant they should inform their treating doctor immediately and continue to take PrEP for 28 days after their last possible HIV exposure
- After PrEP cessation, duration of protective levels of the study drug (generic TDF/FTC) is approximately one week
- Following PrEP cessation, safer sex practices and NPEP will help to minimise the risk of HIV and STI acquisition

6.3 INCIDENTS REPORTING AND REFERRAL

Data Safety Monitoring Board (DSMB) Terms of Reference

The role of the DSMB is to assess at intervals the progress of the PrEPX demonstration study including safety data and efficacy endpoints. The board will then recommend whether to continue, modify or stop the study.

Membership

Membership of the Data Safety Monitoring Board (DSMB) will consist of two Infectious Diseases physicians who are experts in HIV clinical care, an Infectious Diseases physician who is an expert in epidemiology and clinical trials and an expert clinical research nurse manager, and a representative of the HIV community. All members will be independent of the funding body - the Victorian Department of Health. The members have been nominated by the Protocol Steering Committee (PSC) and are identified in Appendix A. The members will be provided with a copy of the study protocol.

Study summary

PrEPX is a population-level PrEP demonstration project which is designed to determine whether the provision of generic Tenofovir + Emtricitabine to 2,600 individuals for a period of 21 months will reduce new HIV infection in Victoria over the following 1-3 year. This is a non-randomised, prospective, open-label multi-site study of HIV-negative participants who are at high risk of HIV infection and who will receive daily generic Tenofovir + Emtricitabine in addition to SOC, over a period of 21 months

Meeting schedule and format

The DSMB will meet at the Infectious Diseases Unit at the Alfred Hospital, or via teleconference at 9 and 18 months. Secretarial assistance will be provided by the Infectious Diseases Unit at the Alfred Hospital. To provide information and assistance, DSMB meetings will be attended exofficio by the Principal Investigator, Associate Professor Edwina Wright or her delegate. These personnel will attend the DSMB to provide a verbal update on trial progress, and be available to answer questions arising during the meeting, but will not sit in the meetings.

The DSMB report will be provided to the Chair 10 days prior to the scheduled meeting for review. Once approved by the chair the report will be circulated to all DSMB members no less than 1 week prior to the meeting date. All data presented at the DSMB meeting will be confidential and no details can be discussed with anyone other than DSMB members and study investigators. The duration of the DSMB membership will cover the duration of the study including review of the post study final report. If a member leaves the PSC will be responsible for selecting a replacement.

Notification of major changes to the study design

The Chair of the DSMB will be notified of all protocol amendments at the time of HREC approval. Prior to any DSMB meeting, the members will be provided with the most recent version of the protocol and a summary of changes from the previously approved version.

Safety data to be presented to the DSMB will include:

- All Serious Adverse Events (SAEs) and suspected unexpected serious adverse reactions (SUSARs)
- All pregnancies
- The DSMB may ask for further details or summaries of data as they regard appropriate.
- On an Ad Hoc basis at any time, as requested by the investigators

DSMB recommendations:

At each DSMB review of full safety and efficacy data, the DSMB will recommend to the Protocol Steering Committee one of the following courses of action:

- Continue the study without modification
- Pause enrolment pending either resolution of specific issues or amendment of the protocol as specified
- Terminate the study

Verbal communication of the DSMB recommendation will be made to the principal investigator within 24 hours of the DSMB meeting, with formal written communication to follow within one week.

Stopping/change rule:

The DSMB will give serious consideration to recommending termination of the PrEP accept arm of the study in the event of:

- An increase in the number of Serious Adverse Events (including HIV seroconversions and positive STI test results) to a level considered unacceptable by the DSMB
- Any increase in the adverse events raising concerns of subject safety

SEE APPENDIX A: *DATA MONITORING BOARD* ***SEE APPENDIX B:*** *DATA MONITORING BOARD SKELETON KEY*

6.4 PROTOCOL STEERING COMMITTEE (PSC)

The PSC will review study recruitment, follow-up, incidents and ethics concerns every six (6) months. The PSC will comprise study investigators and representatives from relevant community organisations. See Appendix B for full details of the PSC.

6.5 STUDY MONITORING & ADVERSE EVENTS

Study monitoring will include, but not be limited to, verification of the accuracy and completeness of the baseline CRFs, and extraction of the data every three months, evaluation of recruitment, compliance with inclusion and exclusion criteria, review of adverse events, assessment of data security, documentation regarding changes to personnel, adherence to standard operating procedures, management of study medication, compliance with the protocol and documentation of protocol amendments. Any discrepancies, violations found or data clarification required will be documented in a written report. Monitoring visits will be scheduled 6-monthly during the recruitment period and then annually until the study has been completed.

Serious adverse events (SAEs) may occur in the course of this study and will be recorded on the serious adverse event case report forms. All serious adverse events and deaths should be reported to the Study Co-ordinator within seven days. The co-ordinating centre will report any serious adverse event that fulfils the criteria for expedited reporting (unexpected and drug related events) to appropriate regulatory authorities within the required reporting timeframe. Serious adverse events will be reported to the DSMB and to the ethics committee as required by the ethics committee reporting procedures.

An SAE is defined as - any adverse event that fulfils one of more of the following criteria:

- Is life-threatening (Note: the term life-threatening in this definition refers to an event in which the patient was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Results in death
- Requires in-patient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

For the purposes of this study, HIV seroconversion will be defined as an Adverse Event

6.6 RENAL DYSFUNCTION

Renal function will be monitored by creatinine clearance, as calculated by the Cockcroft Gault equation, at study entry visit (prior to commencing generic Tenofovir + Emtricitabine) and at the months 6, 12, 18 study visits. A potential participant with a screening (pre-generic Tenofovir + Emtricitabine) creatinine clearance of <60ml/min will be excluded from the study. Any participant with a month 6, 12, or 18 creatinine clearance of <50 ml/min should be retested within 7 days. If the level is confirmed as <50ml/min on retest, generic Tenofovir + Emtricitabine should be discontinued. The participant should be followed weekly until creatinine clearance stabilises or increases to ≥ 60ml/min and consideration of re-commencing PrEP should be considered. Any participant with a month 18 creatinine clearance of <50 ml/min should be retested within 7 days and if the level is confirmed as <50ml/min on retest, the participant should be followed regularly until creatinine clearance stabilises or increases to ≥ 60ml/min.

7 ANALYSIS PLAN

7.1 QUANTITATIVE DATA ANALYSES

Following the baseline patient visit, the investigator or designated site staff member may fax, post or email the consent form and the patient's date of birth and contact details to the PrEPX coordinating centre at the Alfred Hospital. The patient's name, date of birth and clinic site will be assigned a specific PrEPX Study ID and the linkage of the identifiable details and the PrEPX Study ID will be kept under lock and key, separate from any other study documents, or databases. The PrEPX Study ID will be entered into the patient's medical records at their clinic and thus the ACCESS Software system, GRHANITE, will be able to identify that patient as being a PrEPX study participant. This will allow baseline results and subsequent study results to be identified as being from a PrEPX study participant as described in detail in section 3.0.

The investigator and the clinic where the study will be conducted will permit trial-related monitoring, audits, ethics committee review and regulatory inspection providing direct access to the source documents. At the coordinating centre all data will be de-identified and only stored with the unique PrEPX Study ID.

STATISTICAL ANALYSES

Primary Endpoint

We will monitor the rate of new HIV infections in Victoria for a period of 36 months after the PrEPX study commences. Analyses of changes in the rates of HIV infection will be undertaken using Mann-Whitney U and chi-square tests to determine whether there has been a significant decline in new HIV infections during this 36-month period, compared to the 36 months prior to PrEPX commencing.

We will undertake analyses to determine whether or not other factors such as an increase in background HIV and STI testing rates during the PrEPX study period and an increase in the background rate of HIV virological suppression of HIV positive people living in Victoria during the PrEPX study period may have contributed to any decrease in new HIV infections using Cox proportional and logistic regression analyses to calculate hazard or rate ratios and odds ratios (ORs), respectively, with 95% confidence intervals (CIs).

Secondary Endpoints

Analyses of behavioural change over time in response to questions asked on the online survey and in the ACCESS questionnaires will be analysed using generalized estimating equations to model the categorical and linear slopes for each outcome measure. We have chosen generalized estimating equations since these models do not employ assumptions about the distribution of random (unobserved) variables, which are included in a mixed- or random-effects regression. The estimated slope is a population-averaged value that provides information about the expected change in a population subsequent to the use of pre-exposure prophylaxis

De-identified data will be grouped for analysis. Statistical analysis will be performed in accordance with the protocol using SPSS software, and statistical significance will be defined as a p-value <0.05. All statistical tests will be two-tailed. Continuous variables will be expressed as median and interquartile range and categorical variables as proportions.

7.2 QUALITATIVE DATA ANALYSES

The qualitative data generated from the interviews will be thematically analyzed. A coding frame will be developed based on the study research questions and the existing literature on the use of ARVs as PrEP. Interviews will be coded using NVivo software. Coding will be conducted on the first four interviews to check for consistency with the coding frame and the coding frame will be adapted if necessary to incorporate new themes that were not anticipated. This ongoing analysis will also allow for any variations to the interview schedule.

7.3 DATA ANALYSIS AND DATA LINKAGE-ACCESS

This has been addressed in detail in section 3.0

8 STORAGE AND ARCHIVING

The project leader and research nurses are responsible for ensuring that the data collected are complete, accurate and recorded in a timely manner. Any discrepancies will be notified to the project leader for clarification and regularly discussed with the study investigating team.

The project leader is responsible for the data collection process, quality of data and data storage. The project leader will also develop and maintain the participant and couple numbering system. The records of participant identifiers will be stored separately from their study records, and this database will be maintained by the project leader. All participant study records will be clearly labeled to ensure that they are not accidentally destroyed or incorrectly used in the matching of couples for analyses.

All hardcopy and electronic files will be stored indefinitely, as per Alfred Health policy.

9 ETHICAL APPROVAL

The principal investigator is responsible for obtaining ethics committee approval of the protocol in compliance with the local regulatory requirements prior to recruiting any participant into the study. The approval must clearly identify the protocol and all documents approved by the ethics committee, including version numbers of the protocol and informed consent.

The principal investigator will also obtain approval for any amendments to the protocol or informed consent during the course of the study. The principal investigator and co-investigators will comply with all ethics committee reporting requirements for serious adverse events, annual updates and end of study reports, and will agree to abide by the governing ethics committee conditions of approval.

A copy of the signed and dated consent form will be given to each participant before participation in the study. Ethics committees will review and approve the initial and any amended consent forms prior to use in the study. The participant will be informed in a timely manner of any new information that becomes available during the course of the study that may affect the participant's willingness to continue participation.

This study will be conducted in accordance with the ethical principles laid out in the Declaration of Helsinki and the National Statement on Ethical Conduct in Research Involving Humans.
Ethical approval for this study will be sought from the following ethics committees:

- The Alfred Hospital Human Research Ethics Committee

10 LEGAL ISSUES

The investigator team will consult with The Alfred Hospital legal team if/when necessary, throughout the course of the study. The study will have procedures for addressing any legal issues arising during the course of the study and both the PSC and The Alfred Hospital HREC will ensure all legal concerns are dealt with in an appropriate manner, in accordance with local and regulatory requirements.

The legal risks to participants in this study are minimized by the following:

Participants are legally informed of their at risk status by their treating medical practitioner. All participants will be required to sign a PICF, acknowledging their at-risk factors for acquiring HIV infection.

All standard of care measures will be used to ensure enrolled participants remain HIV negative.

This study will be conducted in accordance with local and federal regulatory requirements.

11 PUBLICATION AND AUTHORSHIP

Issues around publication from this study and authorship of publications are based on institutional guidelines from Monash University's Department of Medicine, incorporating The Alfred Hospital in conjunction with the International Committee of Medical Journal Editors.

1. Authorship of publications using data from the PrEPX Study must conform to the standards of the meeting or journal where the research findings will be reported.
2. All investigators named on the study protocol will be invited to be an author on each paper, as will any other investigators/individuals that make a substantial contribution. It is not necessarily expected that all investigators named on the study protocol who are invited to be authors will opt to be authors on each paper arising from the study.
3. Investigators who make a written statement that they meet *each* of the following conditions will be included as a co-author, as recommended in the authorship considerations proposed by the International Committee of Medical Journal Editors:
    i) Substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; ***and***
    ii) Drafting the article or revising it critically for important intellectual content; ***and***
    iii) Final approval of the version to be published.
4. All prospective authors of all publications should be notified of publication plans in sufficient time to participate fully in authorship or otherwise to have input into the content and review of the manuscript.

5. Authorship order will depend on the relative contribution of the individual authors. Procedures for deciding order of authorship should be developed by consensus of the authors at the earliest appropriate time in the development of the manuscript or presentation. In general, the first named author will be the individual who writes the manuscript/presentation. In general, the senior (last) author will be a senior investigator who has expertise in the subject matter of the manuscript/presentation, and who has closely supervised the writing of the manuscript/presentation.
6. Acquisition of funding, collection of data or general supervision of the research group alone does not constitute authorship.
7. If the number of people meeting the journal's or meeting's criteria for authorship is greater than the journal or meeting standards allow, a collective authorship designation may be used if allowed by the journal or meeting. The specific designation will be decided by consensus of the authors. If a collective authorship is used, the persons responsible for the publication or presentation (i.e. those who otherwise would have been individually named as authors) will be specified in a manner agreed to by the journal or meeting.
8. At an appropriate place in the publication or presentation, as consistent with the standards of the journal or meeting, one or more statements should specify:
    i) Acknowledgment of contributions that do not justify authorship, including technical help and financial or material support; and
    ii) Financial relationships that may constitute a perceived conflict of interest.
9. Each person acknowledged by name should give permission in writing or by email to be acknowledged. Exceptions may be made if the person is deceased or cannot be contacted.
10. This policy applies regardless of the organisation or institution of the investigator responsible for drafting the publication or presentation.
11. A copy of this policy will be included in all PrEPX sub-agreements, sub-contracts, sub-grants, or sub-study agreements.
12. This policy also encompasses the publication and presentation of data from any future sub-studies.

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APPENDIX A

Members of the DSMB

Chair: Associate Professor Allen Cheng is a clinician, researcher and biostatistician with expertise in chairing large, multi site clinical trials. In addition, Allen has a PhD in epidemiology, which will be helpful for conducting this trial.

Members:

- Professor Jenny Hoy is Director of the Victorian HIV Service and has extensive experience in clinical and observational drug trials.
- Dr Julian Elliot is Head of the Infectious Diseases Clinical Research Unit and will provide ongoing clinical advice as required for the DSMB.
- Ms Janine Roney is Unit Manager of the Infectious Diseases Clinical Research Unit and will provide feedback in regards to operational, logistical and site-specific requirements for the purpose of this study.
- John Manwaring is the community representative from the Victorian AIDS Council. John will be the designated community representative.

APPENDIX B

PROTOCOL STEERING COMMITTEE

The Protocol Steering Committee (PSC) will meet every six months to review recruitment, patient follow-up, incidents and ethics. The PSC is made up of the investigators and representatives from community-based HIV organisations. The members are:

- A/Prof Edwina Wright- Alfred Hospital, Monash University & Burnet Institute
- Mr Brian Price- Alfred Health
- Prof John de Wit- UNSW's Centre for Social Health in Research
- Prof Sharon Lewin- Alfred Hospital, Monash University & Burnet Institute
- Mr Michael West- Victorian Department of Health & Human Services
- Prof Christopher Fairley- Melbourne Sexual Health Centre & The University of Melbourne
- Dr Norman Roth- Prahran Market Clinic
- Dr Ban Kiem Tee- Centre Clinic
- Dr Richard Moore- Northside Clinic
- Mr Simon Ruth- Director, Victorian AIDS Council
- Mr Colin Batrouney- Manager of Health Promotion, Victorian AIDS Council/Gay Men's Health Centre
- Ms Levinia Crooks-Executive Director- Australasian Society for HIV Medicine
- Ms Anne Mak- The Alfred Hospital, Clinical Trials Pharmacy
- Ms Luxshimi Lal- VicPrEP

APPENDIX C- DSMB Skeleton Summary Tables

Table 1. Recruitment, follow-up and study entry characteristics

Patients screened but not recruited
Ineligible (including screening failures)
Refused
Patients recruited
Patients recruited but declined PrEP
Patients recruited but lost to study follow-up
Duration of follow-up (months; median (min, max))
N (%) of patients completed 12m PrEP
Duration of PrEP (months; median (min, max))
N (%) of patients completed study
Age (mean years (SD))

Deaths

Table 2. Reasons for loss to study follow-up

Study ID	Date enrolled	Date of last study visit	Reason lost to f/up

Table 3. Serious adverse events

Study ID	Age	Sex	Date onset	Date resolved	Event description	Category of experience	Relationship to study drug	Expectedness

Table 4. Adverse events (including HIV seroconversions and STI positive test results)

Study ID	Age	Sex	Date onset	Date resolved	Event description	Category of experience	Relationship to study drug	Expectedness

Table 5. List of laboratory adverse events

Study ID	Parameter	Grade	Study visit