



STUDY PROTOCOL

The Victorian Pre-Exposure Prophylaxis Demonstration Project

The VicPrEP Study



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- Associate Professor Michelle Giles
- Mr Dean Murphy
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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:

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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. Terms with specific meanings for this study are denoted with an asterisk (*).

AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ART	antiretroviral therapy
BMD	bone mineral density
CVF	cervicovaginal fluid
CRF	case report form
DBS	dried blood spots
DSMB	Data Safety and Monitoring Board
FTC	emtricitabine
FTC-TP	emtricitabine triphosphate
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)
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
RUAI*	receptive unprotected anal intercourse
SAE	serious adverse event
SMS	short message service
SOC	standard of care package
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

SUMMARY

Study Title (short)	The VicPrEP Study
Protocol Version	4.0 Dated May 15, 2014
Objectives	<p>Primary Objectives</p> <p>1. To determine in HIV negative individuals at risk of HIV infection</p> <ul style="list-style-type: none"> • The uptake of PrEP and the reasons for choosing or choosing not to commence PrEP • Whether the uptake versus non-uptake of PrEP is associated with decreased HIV risk behaviour and a decreased likelihood of future HIV and STI infections <p>2. To determine in HIV negative individuals at risk of HIV infection who choose to use PrEP medication during a 12 month period</p> <ul style="list-style-type: none"> • The duration and pattern of use of PrEP • The adherence to PrEP medication • Whether compared to the 3 month period prior to study enrolment, there is any change in sexual behaviour during and after PrEP use for a total period of 24 months following study enrolment • The acceptability of PrEP • The safety of PrEP medication • The feasibility of participating in a PrEP Service in Victoria • The incidence of HIV infection for a total period of 24 months following study enrolment • The incidence of STIs for a total period of 24 months following study enrolment • Whether compared to the 3 month period prior to study enrolment, there is any change in the HIV and STI testing patterns after PrEP use for total period of 24 months following study enrolment • The number of HIV serodiscordant couples who achieve conception whilst using PrEP • The average duration of PrEP use by HIV serodiscordant couples prior to successful conception occurring • The number of HIV serodiscordant couples who achieve conception whilst using PrEP and who achieve subsequently a successful delivery • The health status including the presence of birth defects, in neonates who were conceived during the time that their HIV negative mother was using PrEP <p>3. To determine in HIV negative individuals at risk of HIV infection who choose NOT to use PrEP but who agree to participate in the study</p>

	<ul style="list-style-type: none"> • The sexual behaviour and HIV and STI testing patterns for a total period of 24 months following study enrolment • The incidence of HIV infection and other STIs for a total period of 24 months following study enrolment <p>4. To determine from the healthcare providers involved in the Victorian PrEP Demonstration Project</p> <ul style="list-style-type: none"> • The feasibility of providing a PrEP service in Victoria <p><u>Secondary objectives</u></p> <ul style="list-style-type: none"> • To determine the factors associated with the decision to take PrEP • To determine the factors associated with adherence to PrEP medication including demographics, acceptability and medication side-effects • To determine the factors associated with safety and PrEP use • To determine the factors associated with behavioural change and PrEP use • To determine the factors associated with HIV and STI testing and PrEP use • To determine the factors associated with the acceptability of PrEP • To determine the factors associated with a feasible PrEP service in Victoria
Study Design	A multi-site, open-label PrEP demonstration project
Planned Sample Size	200 enrolled participants (From four high caseload HIV/STI clinics in Victoria and the Chronic Viral Illness Clinic, Royal Women’s Hospital, Melbourne)
Selection Criteria	HIV negative people at risk of HIV infection, including MSM and HIV serodiscordant couples.
Study Procedures	<p>Recruitment and enrolment will be through one of the five participating sites. Study entry assessment will include: (1) study entry interview (collection of information about socio-demographic factors, relationship history, knowledge, awareness and attitudes to HIV (2) HIV and STI testing and pregnancy testing.</p> <p><u>Active follow-up:</u> 100 of the enrolled participants will consent to take truvada PrEP for a period of 12 months and 100 will decline PrEP. All participants will be asked to complete study entry evaluations including clinical status, HIV and STI testing, and an online survey regarding behaviour and sexual practices. Participants who accept PrEP will repeat these at 3-monthly study visits for one year, and asked for consent to access routine blood samples to determine adherence to PrEP medication.</p>

	<p>A random subset of participants who accept PrEP [approximately 20%] will also be asked to participate in an in-depth one-on-one qualitative interview about their use of PrEP, to evaluate the study and provide feedback on the experience and use of PrEP. This interview will take place after taking PrEP for about one month, and again 12 months later.</p> <p><u>Post study follow-up:</u></p> <p>Participants who accept PrEP will be followed for a total of 24 months after entering the PrEP demonstration project. Whilst they are in the project and taking PrEP they will have 3 monthly STI and HIV testing. After they have completed PrEP they will be followed by accessing their STI and HIV testing results through the VPCNSS for 12 months.</p> <p>Participants who decline PrEP will be followed for a total of 24 months after study entry by accessing STI and HIV testing results through the VPCNSS.</p> <p>All participants enrolled into the VicPrEP study will be reviewed as necessary, according to Victorian standard of care guidelines.</p>
<p>Considerations</p>	<p>VicPrEP is a demonstration project investigating the adherence, behavioural change, acceptability, safety, and feasibility of the use of HIV PrEP in the Victorian community. The nature of a demonstration study is to study patients who can feasibly be recruited. Based on Australian research undertaken by members of our study team regarding the likelihood of PrEP use in HIV negative gay or bisexual men and the likely uptake of healthy, fertile HIV serodiscordant couples we have estimated that approximately 100 patients willing to accept PrEP could feasibly be recruited into the study over a two year period. This number of patients may reasonably allow us to undertake regression analyses to determine whether a number of baseline covariables are associated with PrEP adherence, behavioural change and acceptability. However the study sample size was necessarily chosen based on feasibility of recruitment and not based upon power calculations.</p>
<p>Study Duration</p>	<p>Approximately 4 years. The recruitment period will be 2 years in duration, and each participant will be followed for 24 months.</p>

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1. BACKGROUND AND RATIONALE

1.1 BACKGROUND

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 has approximately 25,000 people living with diagnosed HIV infection (2) but also has between 5,000- 10,000 people who are HIV infected but remain undiagnosed (3).

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. In 2012, there were 1253 new HIV diagnoses reported: this is the highest number reported in 20 years (4).

There have been a number of recent trials that have demonstrated that daily HIV antiretroviral therapy (ART) can be used for HIV pre-exposure prophylaxis (PrEP). PrEP has been shown to significantly reduce the risk of HIV acquisition in HIV negative men who have sex with men (MSM) (5), heterosexuals (6, 7) and people who inject drugs (PWID) (8) when combined with other HIV prevention measures. As a result of the success of these studies, clinical guidance documents to help health care workers to provide antiretroviral therapy as HIV pre-exposure prophylaxis (PrEP) to people at risk of HIV infection have been issued by the US Centres for Disease Control (CDC) (9-11) and the World Health Organisation (WHO) (12).

It is important to understand how PrEP will be used in the community setting, outside of the rigors of randomised controlled trials. Poor adherence to PrEP medication has been associated with poorer efficacy and if individuals receiving PrEP increase their sexual or injecting risk behaviour (risk compensation) this may undermine the efficacious benefits of the PrEP regimen. The evaluation of how effective a new prevention strategy like PrEP will be in a community can be undertaken in PrEP demonstration projects (12). PrEP demonstration projects measure the key factors that will make a strategy effective: adherence, acceptability, risk compensation, safety and feasibility. A number of PrEP demonstration projects are currently underway internationally (13).

Australia vitally needs new HIV prevention strategies. In this protocol we outline the Victorian PrEP Demonstration project, which will enrol MSM and heterosexuals including those wishing to conceive who are at risk of HIV infection in Victoria.

PrEP is a novel, efficacious HIV prevention strategy

HIV pre-exposure prophylaxis when given as daily oral antiretroviral therapy and coupled with traditional HIV prevention measures, is a new and efficacious HIV prevention strategy. Several recent placebo, randomised-controlled studies (RCTs) have shown that daily tenofovir, or daily tenofovir *plus* emtricitabine (Truvada™) reduce HIV transmission by $\geq 44\%$ in MSM (5), $> 70\%$ in heterosexuals (the Partners PrEP study (6) and the TDF2 study (7) and by 49% in people who inject drugs (the Bangkok Tenofovir Study (8)). Notably two placebo RCTs that enrolled African women at risk of HIV infection (the Fem-PrEP (14) and VOICE (15) showed no benefit between active drug versus placebo and these findings are thought to be largely the result of poor medication adherence. Currently there are no international RCTs that have evaluated PrEP use in HIV serodiscordant couples seeking to conceive.

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%) (16), and heterosexuals (80%) (17), 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) (3), 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%) (18). Furthermore Australia has assisted reproduction programs designed to assist HIV serodiscordant couples seeking to conceive, most notably the Chronic Viral Illness program at the Royal Women's hospital (19). The CVI program recently reported on 39 HIV serodiscordant couples who had assisted reproduction through their service without any HIV transmissions and with a pregnancy rate per cycle of $> 15\%$ (19). As reviewed by Giles et al, international studies show that thousands of cycles of treatment have been given in assisted reproduction programs in Europe and the USA without a single HIV seroconversion occurring in the HIV negative female partner of the HIV positive man (20). These data suggest that risk of HIV infection within an assisted reproduction program is $< 1/6,000$ which is much lower than the known risk of HIV infection per exposure for receptive penile-vaginal sex (20).

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 (4) and while consistent condom use is the commonest HIV prevention strategy used by HIV negative Australian MSM (21), only one-third report consistent condom use (21). The Australian STIGMA guidelines recommend that all MSM should have annual HIV and STI testing (22) 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 (22). 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 (21). 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% (23). 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 (21).

Approximately 25% of new HIV diagnoses occur in heterosexuals in Australia (2). 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 (24). 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 (21). 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 (25).

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% (26) 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 (26).

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 contribute to PrEP being an effective HIV prevention strategy

The likelihood that PrEP will be an effective new HIV prevention strategy in Australia is predicated upon several key factors including **PrEP uptake, medication adherence, risk compensation, safety, acceptability, the development of drug resistance, feasibility, cost-effectiveness and the medication's antiviral and pharmacokinetic properties**. Some of these factors have been evaluated in the abovementioned RCTs and other studies and are discussed below.

PrEP uptake

Australia has excellent data on the likely uptake of PrEP by MSM although data from HIV+ heterosexuals are lacking. In 2011 approximately 28% of 1161 HIV negative and untested gay and bisexual Australian men surveyed in the PrEPARE project reported a willingness to use PrEP to prevent HIV infection (27). In a follow-up survey of 1223 participants undertaken in 2013, 23% of participants were willing to use PrEP (28). In both studies a number of variables were used to assess willingness to use PrEP including willingness to pay, having to take pills every day, concerns about efficacy and perceived need (27, 28). Factors associated with willingness to use PrEP included younger age, anal sex with casual partners and perceiving oneself to be at risk of HIV (27). International studies report higher levels of willingness to use PrEP in up to 80% of participants surveyed. However some of these studies have been done in countries with very high HIV prevalence (29) and have not used several variables to assess willingness (27). Interestingly, in the United States where tenofovir-emtricitabine (TDF) is licensed for use as HIV PrEP, there has been minimal uptake of PrEP with reports of less than 2,000 prescriptions TDF for PrEP filled since the FDA licensed it in July 2012. This observation corroborates the more conservative estimates from Holt et al that perhaps only one quarter of eligible MSM will use PrEP (27, 28).

Medication adherence.

Following publication of the studies that demonstrated PrEP's efficacy in MSM, heterosexuals and PWIDs, it became clear that whilst individuals were reporting very high medication adherence rates, their actual adherence was much lower, as measured by the level of study drug in blood (Table 1). Whilst self-reported use of medication was mostly > 90% in these studies, in cross-sectional blood sampling of patients in the study, drug was detectable in <30-82% of patients.

Table 1. Self-reported adherence to study drug and drug levels in blood from six PrEP randomized controlled trials

Study	Study population	Self-reported adherence to study drug	Proportion with detectable study drug in blood
iPrEX	MSM	95%	50%
Partners PrEP	Heterosexuals in HIV serodiscordant relationship	Self-report not reported but 97% of dispensed pills were taken	82%
TDF2 study	Heterosexual men and women	94%	80%
Bangkok Tenofovir Study *Note: 87% of patients had directly observed therapy	People who inject drugs	83.8%	67%
VOICE study *Note: full results not yet published *Closed for futility	Women	90%	<30%
Fem-PrEP *Closed for futility	Women	95%	35%

A number of factors have been proposed to explain these findings. Notably, when patients entered these studies there were no data about whether the drug would actually work and because these studies were placebo-controlled, patients were unaware of whether they were receiving active medication or placebo. The two studies with the lowest proportion of patients with detectable drug in blood, the VOICE study (14) and Fem-PrEP (15) 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 (14). Full results from the VOICE study are yet to be published. There are no data on adherence in HIV serodiscordant couples using PrEP whilst trying to conceive.

Factors associated with adherence

From the studies shown in Table 1 the following factors have been associated with adherence.

Higher adherence

- Trust and relationship support (6)
- Older age, ≥ 40 years (8)
- Female gender (8)
- Polygamous marriage (6)

Poorer adherence

- Intermittent versus daily dosing (30)
- Post-coital dosing as part of the PrEP regimen (30, 31)
- Younger age (6)
- Having less sex (6)
- Heavy alcohol use (6)
- PrEP use for longer than 6 months (6)

The importance of adherence to the efficacy of PrEP in reducing the risk of HIV infection has been highlighted in the iPrEX trial (5) and the STRAND study (32). 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; $p < 0.001$) (5).

Subsequently the STRAND study was undertaken to quantify the relationship between the level of adherence and drug concentration (32). Here, HIV negative volunteers were given daily, four-times weekly and twice-weekly TDV. Patients steady-state intracellular levels of TDV were determined and the median intracellular levels of tenofovir (TFV) for daily, four doses per week and two doses per week were determined (32). 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 TFV 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 (32). These results compare to the overall intention-to-treat analysis result that showed a 44% reduction in the incidence of HIV (5).

Risk compensation

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 (33) (see Table 2). However an increase in sexual risk taking was reported recently in a follow-up study by the Partner's PrEP study group (34). 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 (6). 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) (34). The authors noted that this was a small increase and that there was no accompanying increase in STIs or pregnancy. This study finding highlights the importance of doing PrEP demonstration projects and led to a recommendation in the Lancet editorial accompanying this follow-up study that practitioners should counsel PrEP users about risks both within serodiscordant relationships and with casual Partners (35). There are no data currently available about risk compensation in HIV serodiscordant couples using PrEP in order to conceive

Factors that have been associated with an increase in sexual risk behaviour have been reported in MSM and include use of amphetamines, poppers and agents used to treat erectile dysfunction (33). The Partners PrEP follow up study which was undertaken in heterosexuals did not report on factors associated with increased sexual risk taking (34).

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
iPrEX	MSM	Decrease in number of sexual partners with whom having RAI and increase in proportion of partners who used condoms
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 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
VOICE study *Note: full results not yet published *Closed for futility	Women in Africa	N/A
Fem-PrEP *Closed for futility	Women in Africa	Significant reduction in the number of partners, vaginal sex and sex without a condom
US PrEP Study	MSM	Mean number of partners and reporting of unprotected anal sex declined significantly. Mean unprotected anal sex episodes remained stable.
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

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 (30, 31, 33, 36); . There are no data on safety in the HIV negative partner within an HIV serodiscordant couple using PrEP whilst trying to conceive. There have been no reports of a difference in deaths or serious adverse events across different study arms in PrEP RCTs (5-7, 30, 31, 36). Nausea (5, 7, 8, 14), unintentional weight loss, vomiting (7, 8, 14), dizziness (7), back pain (36), bone mineral density (BMD) loss (37) and elevated ALT levels (14) 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 (37). This sub-study was important because TFV use has been associated with reduced BMD in HIV+ patients (38). 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 (36). 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%, $p = 0.11$) (37). There was no significant difference in fracture rates between those receiving TFV versus placebo, although the study was not powered to detect a difference in fracture rate (37). Overall at 24 months, 13% of participants taking tenofovir versus 6% of participants taking placebo experienced a >5% BMD loss at the femoral neck (37). 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 (37). 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 (37). 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 (37).

Renal function

In a recent meta-analysis, TFV 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 (39). TFV use was not associated with increased risk of fractures, hypophosphatemia or proteinuria (39). Overall TFV use in PrEP studies has not been associated with significant renal problems as outlined in Table 3.

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)
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 *Note: 87% of patients had directly observed therapy	People who inject drugs	No significant difference between renal disease, increased creatinine, decreased phosphorous in TDF or placebo groups
VOICE study *Note: full results not yet published *Closed for fertility	Women in Africa	Not available
Fem-PrEP *Closed for fertility	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 there was no significant difference in their frequency between active drug and placebo groups
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.

Safety issues for women who become pregnant whilst using PrEP medication

The United States based antiretroviral pregnancy registry has been designed to provide an early signal of major teratogenic effects associated with prenatal exposure to a number of antiretroviral agents including emtricitabine (FTC) and TDF. This is a prospective, voluntary exposure-based registry which serves as an observational study is designed to collect and evaluate data on the outcomes of pregnancy where there have been exposures to HIV antiretroviral agents. The registry reports that in data obtained through to July 2012, in women who have been exposed during the first- trimester to agents listed in the registry, that the prevalence of birth defects was 3.00 per 100 live births (95%CI 2.6-3.4). This prevalence was not significantly different among women exposed during the second or third trimester, (2.8 per 100 live births) giving a prevalence ratio of 1.06 (95%CI 0.88-1.28). Comparing these data to the CDC's birth defects surveillance system which has a prevalence of 2.72 birth defects per 100 live births, these data are not substantially different .

The US antiretroviral pregnancy registry lists the prevalence of birth defects for FTC as 2.5% (95%CI 1.7-3.7) that is 27 birth defects/1068 live births. It lists the prevalence of birth defects for TDF as 2.4% (95%CI 1.7-3.3) that is 39 birth defects/1612 live births .

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. Currently international demonstration projects that are measuring PrEP acceptability have not reported on their findings yet.

Drug resistance

Drug resistance has been reported in individuals participating in PrEP trials but the number of reported cases are very low. (See 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 during the study, which has been largely ascribed to patients' poor adherence to study medication (5). See Table 4.

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

Study	Study population	Drug resistance
iPrEX	MSM	<p>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</p> <p>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.</p>
Partners PrEP	Heterosexuals in HIV serodiscordant relationship	<p>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.</p> <p>One patient who acquired HIV during the study developed the TDF mutation, K65N</p>
TDF2 study	Heterosexual men and women	<p>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.</p> <p>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%'</p>
Bangkok Tenofovir Study *Note: 87% of patients had directly observed therapy	People who inject drugs	None detected
VOICE study *Note: full results not yet published *Closed for futility	Women in Africa	N/A

Study	Study population	Drug resistance
Fem-PrEP *Closed for fertility	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.
US PrEP Study	MSM	Seven seroconversions occurred in the study. None occurred in participants randomised to the TDF arm. No K65R mutations were reported in these patients

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(41). Although there is some debate in the literature (41), it appears from modeling studies that both PrEP and ART use for HIV infection will drive ART resistance, but the greater driver of resistance will be ART and not PrEP (41).

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.

Cost effectiveness: In a recent 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 (42). 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 (42). Of note, TDV is not licensed in Australia for HIV PrEP although individuals can purchase it using a private script at a cost of approximately A\$800 per month.

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 (32). 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 (32) 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.

An individual needs to take a daily dose of TDF or TDV for 21 days to achieve a steady state intracellular concentration of 100 femtomoles per million PBMCs of tenofovir-diphosphate, the active metabolite (43). Hence for couples seeking to conceive, it will be advised that the HIV negative partner begins +TDV at least 3 weeks prior to having unprotected intercourse or undertaking self-insemination.

There is little guidance available on the advice to give to patients on how to safely stop taking TDV. In animal models that have been used to study HIV non-occupational post-exposure prophylaxis (NPEP), animals that received less than 28 days of tenofovir after HIV exposure had a higher likelihood of acquiring SHIV (44). Indeed 28 days of TDV is the recommended duration in the Australian national NPEP guidelines following HIV exposure. Given that the active phosphorylated metabolites of TDF has not been fully quantified in cervical tissue and that the active metabolite of FTC may only be detected for 24-48 hours in vaginal and cervical tissue, we are proposing to recommend that individuals should continue on TDV for a total of 28 days after their last episode of sex without condoms.

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 $\frac{1}{2}$ 31 (45) -47 (46) hours	T $\frac{1}{2}$ 37 (45)-49 (46) hours
PBMCs*	Half life 164 hours (45) Steady state: 25 days (32)	Half life 39 hours (45) Steady state: 6 days (32)
Cervicovaginal fluid	AUC** $_{1-14d}$ ratio of CVF to blood plasma is 2.6 (46)	AUC** $_{1-14d}$ ratio of CVF [†] to blood Plasma is 27 (46)
Seminal plasma	AUC** $_{1-14d}$ ratio of seminal plasma to blood plasma is 1.0 (46)	AUC** $_{1-14d}$ of seminal plasma to blood plasma is 4.5 (46)
Vaginal tissue	TDF can be measured in tissue for up to 10 days after a single dose (46) TDF-TP ^{††} can measured in tissue for up to 14 days (46) Concentration is lower than in rectal tissue (46)	FTC can be measured in tissue for up to 10 days after a single dose (46) Exceeds concentration in blood by 7-fold (46) FTC-TP [▲] can measured in tissue for 24-48 hours only (46)
Cervical tissue	TDF can be measured in tissue for up to 10 days after a single dose TDF-DP detectability not quantified (46) Concentration similar to vaginal Tissue (46)	FTC detected in tissue for up to 10 days after a single dose FTC-TP detected for only 24 hours after a single dose (46) 4-fold higher concentration than TDF (46)
Rectal tissue	TFV AUC $_{1-14d}$ ratio of rectal tissue to Blood plasma is 34 (46) Both TDF and TDF-DP detected in rectal tissue for 14 days after single Dose (46)	AUC $_{1-14d}$ ratio of rectal tissue to blood plasma not known but is substantially lower than TDF (46) FTC detected in rectal tissue for 14 days after a single dose (46) FTC-TP detected for only 48 hours after a single dose (46)
Penile tissue	Not known (47)	Not known (47)

*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.

PrEP and conception

A small amount of observational data have been published, but no RCTs have examined the use of PrEP for conception. A study by Vernazza et al (48) described their program which began in 2004. Couples were informed about all potential options to reduce HIV transmission risk. Couples also received written information informing them about the off label use of antiretroviral drugs for PrEP. During the first three years of the program couples received information about two alternative methods to conceive: insemination with processed semen at the clinic or timed intercourse with PrEP. In 2007, timed intercourse with PrEP became the principal method proposed. The PrEP regimen used consisted of two doses of TDF. The first, taken by the female in the morning of the LH-peak, and a second the next morning. Intercourse was timed at the evening after the second dose of TDF. 53 couples had a total of 244 documented unprotected events. None of the HIV negative individuals seroconverted. Pregnancy rates were as follows: 26% for the first attempt then up to 66% after five attempts. Pregnancies plateaued at 75% after 12 attempts. Six women in their program were over the age of 40, and one conceived but had a miscarriage (48).

A second small series has been presented in abstract form only (49). This group reported their experience at two institutions in the United Kingdom where 28/51 couples were deemed suitable for PrEP. Six couples completed >1 cycle with 5 pregnancies, 2 live births, one ongoing twin pregnancy and two miscarriages. Truvada was given as per protocol designated times (49).

A recent report (50) has provided interim guidance for clinicians considering the use of PrEP for the prevention of HIV infection in heterosexually active adults. Although this report is not specifically directed at the use of PrEP for conception it does state the following; "women who became pregnant during the PrEP trials were discontinued promptly from medication so the safety of chronic fetal exposure could not be assessed adequately. Therefore, decisions to continue PrEP during pregnancy require additional consideration.....Both TDF and FTC have been used among HIV infected pregnant women... data.... indicate no evidence of adverse effects among fetuses exposed to TDF or FTC" (10) .

In addition, this report states that the CDC now considers that PrEP use may be one of several options to help protect the HIV-negative partner in discordant couples during attempts to conceive. It recommends regular HIV tests for women receiving PrEP for the purpose of conception and the decision whether to continue PrEP if the woman becomes pregnant should be based on an assessment

of ongoing risk for HIV exposure and after a discussion between the health care provider and currently available information regarding the potential risk and benefit of continuing PrEP (10). Of note, HIV negative women who are pregnant have a two-fold higher risk of HIV infection than HIV negative women who are not pregnant, hence in some HIV negative women there may be benefit in maintaining PrEP throughout their pregnancy (10)

The use of PrEP in the Royal Women's Hospital chronic viral illness (CVI) assisted reproduction program for HIV serodiscordant couples is due to commence in 2014, but currently couples would have to pay for their PrEP medication with a private prescription.

As noted above, we will recommend that for couples seeking to conceive that the HIV negative partner begins TDV at least 3 weeks prior to having unprotected intercourse or undertaking self-insemination. The recommendation regarding the duration that an HIV negative women who has conceived whilst taking TDF will be made in consultation with the woman and taking into account

- (i) our overall recommendation that TDV should be continued for 28 days after the known last HIV exposure
- (ii) the theoretical but unproven risk to the foetus versus the benefit to the woman of extending TDV to 28 days,
- (iii) any side effects that the patient may be experiencing that may be attributable to Truvada and
- (iv) whether sex without condoms is likely to continue throughout the pregnancy .

Demonstration projects

PrEP implementation studies afford the opportunity, outside of the setting of a blinded, randomized placebo-controlled clinical trial, to determine (1) the impact of open label PrEP upon *sexual behaviour* (where increased risk behaviour may reduce PrEP's efficacy); (2) the *levels and patterns of adherence* to PrEP (where poor or intermittent adherence with ongoing risk behaviour would reduce PrEP's efficacy) and (3) the *acceptability* of PrEP (its impact upon peoples' relationships, lifestyles and quality of life), (4) feasibility and (5) safety. As noted above, a number of PrEP demonstration projects are underway or planned internationally (13).

The VicPrEP demonstration project will demonstrate how PrEP can be implemented feasibly, safely and effectively in Victoria, Australia, through an accessible program targeted at those at highest risk of HIV acquisition.

1.2 RATIONALE

Several randomized placebo-controlled trials **have shown that PrEP is efficacious**. The next step is to undertake open-label PrEP demonstration studies to determine ***how effective PrEP will be as a strategy in the community***, outside of the setting of randomized placebo-controlled clinical trials. The need to translate the results of the PrEP efficacy studies into the ‘real world’ has been exhorted recently in editorials in *The Lancet* and *The New England Journal of Medicine* (51-53)

PrEP Demonstration projects are designed to measure (1) the impact of open label PrEP upon *sexual behaviour* (where increased risk behaviour may reduce PrEP’s efficacy); (2) the *levels and patterns of adherence* to PrEP (where poor or intermittent adherence with ongoing risk behaviour would reduce PrEP’s efficacy, (3) the *acceptability* of PrEP (its impact upon peoples’ relationships, lifestyles and quality of life), (4) feasibility and (5) safety. International PrEP demonstration studies will examine PrEP’s effectiveness within populations in countries that vary according to wealth, culture, ethnicity, civil and political rights, and health infrastructure and provision.

The VicPrEP demonstration project will demonstrate how PrEP can be implemented feasibly, safely and effectively in Victoria, through an accessible program targeted at those at highest risk of HIV acquisition.

Based upon findings from the iPrEX study, the TDV2 study, the Partners PrEP study and the Bangkok Tenofovir study, the US Centers for Disease Control (CDC) has issued guidance on how to evaluate and provide PrEP to MSM, heterosexual and PWID populations at risk of HIV infection (9-11). WHO has also issued guidance on PrEP for MSM, serodiscordant couples and transgender women (12).

The importance on introducing new HIV prevention strategies in Australia cannot be overstated: in 2012 we had the highest number of new HIV diagnoses (n=1,253) that we have had in the past 20 years (4). In Australia currently a standard of care ‘package’ of HIV interventions (henceforth referred to as ‘SOC’) is available to MSM at high risk of HIV infection. This ‘package’ comprises (1) provision of condoms, (2) safer sex education including consistent condom use, (3) recommendations to undergo screening 3-6 or 12 monthly for HIV and STIs (22) and (4) education about the availability of a 28-day course of antiretrovirals for HIV post-exposure prophylaxis (PEP) following an HIV exposure. However, as noted HIV infection rates have continued to rise in Australia over the past decade (54) and MSM remain the likeliest group to become infected (2).

The overall incidence of HIV in MSM is relatively low (0.78 per 100 PY) (55). However, a subgroup of homosexual men who are at high risk of HIV infection has been identified from a previous cohort study of initially HIV-negative gay men, the HIM Study (56). This high risk group had an HIV incidence of 2.7 per 100-PY (56) and were characterized by a history of (1) had unprotected anal intercourse (UAI) with a known HIV seropositive partner, or (2) had receptive UAI (RUAI) with a casual partner of unknown HIV serostatus, or (3) used crystal methamphetamine and oral erectile dysfunction medication (56). It has been estimated that if HIV prevention strategies could prevent HIV infection in these high risk groups, at least 30% of HIV infections in Australia could be averted (57).

It is important to emphasize that despite available treatments, HIV remains an incurable disease requiring lifelong treatment and is associated with a decreased life expectancy, high morbidity rates and high health costs (58).

Victoria has led Australia with the introduction of an HIV-point-of-care testing clinic in Melbourne. Two other PrEP demonstration projects are planned for NSW and Queensland but Victoria was the first study to be funded and will be the first study to enrol patients into a PrEP demonstration project. A vital opportunity now exists for Victoria to introduce PrEP into the repertoire of its HIV prevention tools. By undertaking a PrEP demonstration project, Victoria would show ongoing leadership to both Australian and international communities, many of whom will be visiting Victoria for the World AIDS conference in Melbourne, 2014.

This study is important also in the light of Australia's commitment to the UNAIDS 2011 Declaration, the commitment made by Australia's State and Territory Health Ministers in July 2013 to reach the UNAIDS targets of a 90% uptake of ART and a 50% reduction in new HIV diagnoses by 2015 and the Melbourne Declaration which highlights the need for Australian PrEP Demonstration Projects.

2. STUDY AIMS AND HYPOTHESES

Study Aim	Study Hypotheses	Data required
<p>1. Use of PrEP To determine the uptake, duration and pattern of PrEP use during a 12 month period In study subjects</p>	<p>That approximately 25% of eligible participants will choose to use PrEP That participants will use PrEP for a median of 6 months</p>	<ul style="list-style-type: none"> • Baseline/ Study entry evaluation of eligible participants • Participant questionnaires and feedback surveys (online and/or paper based) • Community feedback online surveys
<p>2. Adherence to PrEP To determine the adherence to PrEP study medication, and identify factors that facilitate or impede adherence.</p>	<p>That adherence to PrEP as determined by refill-based assessments, self-reported pill use and DBS testing will vary according to risk groups. Study subjects with HIV serodiscordant partners including couples wishing to conceive will have the highest adherence as determined dried blood spot testing. Anticipated adherence > 75% Study subjects with casual partners only, will have the lowest adherence as determine by DBS testing. Anticipated adherence: 50%</p>	<ul style="list-style-type: none"> • Pill count • Refill based assessment • Self report questionnaires (online and/or paper based) • DBS drug levels
<p>3. Feasibility of PrEP To determine the feasibility of, and factors that are key to implementing a successful PrEP program within the community.</p>	<p>That PrEP will be feasible for prescribers and study participants</p>	<ul style="list-style-type: none"> • Clinic staff feedback and formal meetings to discuss implementation through community centres • Reports on uptake, use of and rollout of PrEP from participating centres • In depth interviews of 20% of participants randomly selected

Study Aim	Study Hypotheses	Data required
<p>4. Acceptability and behaviour To determine the acceptability, including side effects and behavioural change, associated with use of PrEP.</p>	<p>That PrEP will be an <u>acceptable</u> HIV prevention strategy for study participants.</p> <p><u>Behaviour</u> <u>PrEP using study participants</u> That HIV risk behaviour will be maintained or will decrease in HIV serodiscordant couples That HIV risk behaviour may increase in participants and their casual partners That HIV risk behaviour will not increase outside the time of ovulation in heterosexual couples trying to conceive</p> <p><u>Non-PrEP using study participants</u> That there will be no change in number of partners or condom use in these study participants</p>	<ul style="list-style-type: none"> • Self-report and clinic based reporting of all associated side effects amongst Vic PrEP participants • Quarterly self-report sexual behaviour surveys (online and/or paper based) • In depth interviews
<p>5. HIV Acquisition risk To determine the risk of HIV transmission in populations using PrEP.</p>	<p>That the rate of HIV transmission will be lower in participants using PrEP, who are at greatest risk of contracting HIV. The study is unlikely to be powered to detect this</p>	<ul style="list-style-type: none"> • Routine HIV antibody laboratory testing • VPCNSS data
<p>6. STI/HIV Testing patterns Non-PrEP group</p>	<p><u>Non-PrEP using study participants</u> That 40% of non-PrEP receiving MSM participants will have 3-6 monthly testing as per the S TIGMA guidelines.</p>	<ul style="list-style-type: none"> • VPCNSS data

3. STUDY DESIGN

3.1 DESIGN

This is a multi-site, prospective, open-label PrEP demonstration project that aims to evaluate the uptake, acceptability, safety, and feasibility of emtricitabine and tenofovir disoproxil fumarate (Truvada®) as PrEP, administered orally, once daily to enrolled participants who engage in high-risk sexual practices. The demonstration project aims to enrol 200 participants on PrEP and 100 subjects who decline PrEP and receive SOC alone and another 100 subjects who accept PrEP plus SOC for 12 months.

Participants will be recruited from participating clinics in the Victorian community, including the Royal Women's Hospital, Melbourne, where potentially eligible individuals are identified and invited to participate. Participants will be followed up typically in the consenting case by case basis couples who are seeking to conceive may be able to have some consultations at either the Royal Women's Hospital or The Alfred Hospital to see Dr Michelle Giles.

Clinical, laboratory, online and qualitative assessments will be used in this study. Participants who do not accept PrEP will be offered SOC plus PrEP, however, it is anticipated that some participants will accept PrEP, at which time they will be invited to partake in a study entry online survey and access STI testing results and behavioural surveys as part of the VPCNSS for 24 months.

At study entry all participants will undergo a clinical review of HIV/STI risks related to their sexual practices in the previous 6 months, currently and in the future. Medical history, drug and alcohol use, and history of STIs will be documented at the study entry assessment. Rapid HIV testing, hepatitis B surface antigen, electrolytes, full blood examination, urinalysis, and kidney function tests will also be performed at the study entry assessment.

Couples seeking to conceive will have a full evaluation of their fertility status and undergo STI checks at the Royal Women's Hospital Chronic Viral Illness Program. HIV negative couples who are seeking to conceive will have a pregnancy test at baseline/study entry.

All enrolled participants will be asked to complete an online behavioural survey at study entry to assess sexual practice, attitudes and use of conventional methods for practicing safe sex, HIV/STI risk factors, and barriers to PrEP use.

and socio-demographics. As part of the study design ALL PrEP Accept study participants will be required to pay what would be the regular cost of Truvada, if it was available as PrEP. The cost is \$5.90 for concession card holders or \$36.10 for non-concession card holders, according to hospital/clinic policy. Payment for study drug will be required every 3 months, at the time participants collect their PrEP medication from either Alfred pharmacy or Melbourne Sexual Health pharmacy. Although this is not standard practice for patients to pay for study medication, this is a critical aspect of this 'real life' demonstration project, for without this co-payment we will not be able to evaluate realistically the feasibility and acceptability of this study.

All participants taking PrEP will undergo quarterly evaluation for side effects, renal toxicity, medication adherence, STI testing, HIV seroconversion, risk behaviour, blood drug levels, pharmacy drug refills and completion of an online survey in relation to adherence, acceptability and behaviour. Heterosexual women seeking to conceive will have monthly HIV antibody tests if they are HIV negative at baseline and monthly pregnancy tests whilst they are on PrEP.

Of note, medication adherence will be evaluated during the clinic visits, through the online survey, using refill-based assessments where pills dispensed are divided by the days between patient visits to the prescribing doctor and by measuring intracellular levels of tenofovir and emtricitabine.

Health care practitioners will also be surveyed about the feasibility of providing a PrEP service in an annual online survey form.

A small proportion (approximately 20%) of participants will also be asked to complete in-depth one-on-one qualitative interviews. Participants who choose not to use PrEP will undergo a study entry online evaluation of HIV risk behaviour, HIV/STI screening rates and results, use of NPEP, reasons for not choosing PrEP and their risk association thoughts on, and encounters with PrEP. Participants who choose not use PrEP will be asked to consent to accessing their STI testing results for 24 months, through the VPCNSS. All participants will be asked to evaluate the study and provide feedback.

All study participants, with the exception of those seeking to conceive will also undergo a period of follow-up (up to 24 months) for future HIV test results through data linkage with the Sentinel Surveillance Network. Differences in seroconversion rates and STI acquisition rates will be determined between both study arms by using data linkage between the State HIV registry and the Sentinel Surveillance Network data.

3.2 STUDY PARTICIPANTS

The PrEP demonstration project will be conducted among HIV serodiscordant MSM and heterosexual couples (including those trying to conceive), and other MSM and heterosexuals who are at risk of HIV infection, who consent to participate in the project.

3.3 SAMPLE SIZE

100 HIV negative people at high risk of HIV infection who are interested in receiving PrEP will be recruited through participating clinics and through targeted community advertising over a two-year period.

Another 100 eligible participants who do not wish to use PrEP, but are at high risk of HIV acquisition will be invited to consent and participate in the project.

VicPrEP is a demonstration project investigating the feasibility, safety and efficacy of PrEP in the Victorian community. As such, VicPrEP is not statistically powered.

3.4 STUDY SITES

The demonstration project will be implemented at five sites: four high caseload STI clinics in Melbourne, Victoria (Melbourne Sexual Health Centre, Carlton; Northside Clinic, North Fitzroy; The Centre Clinic, St Kilda and Prahran Market Clinic, Prahran) and the Chronic Viral Illness Clinic, Royal Women's Hospital, Parkville.

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 five 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, which are necessary to conduct this demonstration project.

3.5 STUDY DURATION AND RECRUITMENT SCHEDULE

The study will run from 01/03/2014 to 01/03/2018. Recruitment of the participant sample will take place from March 2014. It is anticipated that full recruitment will be complete by March 2016. Study participants will be followed for a period of two years.

4. PARTICIPANTS

4.1 INCLUSION CRITERIA

MSM and heterosexual people at risk of HIV acquisition, due to any high-risk sexual practices with casual and/or seropositive partners that have occurred during the past 3 months, or are occurring currently, or in the case of couples wishing to conceive, will occur in the next 12 months.

1. Age \geq 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 Cockcroft-Gault formula)
5. Evidence of risk for acquiring HIV-1 infection including any one of the following:
 - a. Unprotected receptive or insertive intercourse (anal and/or vaginal) with an HIV seropositive partner and/or
 - b. RUAI with casual partners whose HIV status is unknown (MSM only)
 - c. Uncircumcised male **and** IUI with casual partners whose HIV status is unknown (MSM only)
 - d. HIV serodiscordant couples wishing to conceive without the use of assisted reproduction
6. Able to provide street address and/or telephone number and/or email address to be contacted during the period of the demonstration project
7. Fluent in English

ADDITIONAL INCLUSION CRITERIA FOR COUPLES WISHING TO CONCEIVE

Inclusion criteria from the Royal Women's Hospital Chronic Viral Illness PrEP Protocol

- Semen analysis of male and fertility assessment of female performed at the Royal Women's Hospital (RWH) Chronic Viral Illness (CVI) Program show that the couple are fertile
- Woman has undergone pre-pregnancy health check as per the RWH CVI program including rubella serology and pap smear
- HIV + partner has had an undetectable plasma viral load for 3 months
- HIV+ male partner must have an undetectable seminal fluid viral load that has been performed through the TWH CVI program
- The female partner in the couple should have an education session provided by the CVI nurse regarding the use of a LH-test in the urine to determine the optimal time for conception effort

- The female partner must have a negative pregnancy test prior to PrEP being initiated by either herself or her HIV negative male partner
- Comprehensive counselling session will be provided regarding the practice of safe sex outside of the ovulation period
- Either partner will be vaccinated against hepatitis B if they are not protected prior to commencing PrEP

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 of symptoms of acute HIV infection
3. Signs of intercurrent sexually transmitted infection
4. Unable to attend scheduled follow-up assessments
5. Unwilling to provide consent to follow-up
6. A creatinine clearance of < 60 mL per minute (via Cockcroft-Gault formula)
7. Active, clinically significant medical problems including active tuberculosis, poorly controlled cardiac disease, previous or currently diagnosed malignancy requiring further treatment
8. Hepatitis B surface antigen (HBsAg) positive
9. Current use of any of the following: ART, including nucleoside analogs, 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
10. Severe inter-current illness
11. Concomitant participation in another clinical trial using investigational agents, including placebo-controlled agents
12. At enrolment, has any other condition that, based on the opinion of the treating physician, would make participation in the project unsafe; complicate interpretation of outcome data; or otherwise interfere with achieving the project objectives.

ADDITIONAL EXCLUSION CRITERIA FOR COUPLES WISHING TO CONCEIVE

Couples who are determined to be infertile following their evaluation at the RWH CVI program will not be eligible for PrEP in this study.

5. STUDY OUTLINE

5.1 INVESTIGATION PLAN

For MSM and heterosexuals not seeking to conceive

Participants will have a venepuncture at baseline for HIV antibody testing, serum creatinine and electrolytes, pregnancy tests in women and hepatitis B screening performed. STI screening will also be performed. Clinic visits will be scheduled in accordance with standard of care practice, where participants at risk of HIV acquisition will be followed up every 3 months, or sooner if the patient has any concerns or becomes unwell. At one month there will be a phone call from the patient's clinic to the study participants to ask about medication side-effects, medication adherence and safe sexual behaviour. If there is any concern about any of these, the study participant will be reviewed in the clinic. Other study visits will coincide with normal clinical monitoring. Standard of care STI and HIV testing will be performed every 3 months. A repeat serum creatinine and electrolytes will be performed at months 3 and 12 of PrEP treatment. Participants who choose to accept PrEP will be required to attend 4 study visits, which coincide with their routine clinic appointment. Participants who choose to use PrEP will be asked to consent to having their STI and HIV test results accessed for the purpose of this study, 12 months after they stop PrEP. See Table 6 below.

Participants who decline use of PrEP will also be asked to consent to having their STI and HIV test results accessed for a period of 24 months. See Table 7 below

For heterosexuals seeking to conceive and who are attending the Royal Women's Chronic Viral illness program

Clinic visits will be scheduled in accordance with standard of care practice. Study participants will be seen monthly at the CVI and will have monthly HIV antibody tests and pregnancy tests performed. See Table 8 below. For couples who conceive, the health status of neonates will be assessed for a period of 2 years.

The study will be conducted in accordance with the ethical principles laid out in the Declaration of Helsinki (1996) and the NHMRC National Statement on Ethical Conduct in Human Research (2007).

5.2 STUDY PROCEDURES-SCHEDULE OF ASSESSMENTS

Table 6 PrEP **Accept Arm for MSM and heterosexuals NOT wishing to conceive**

Assessment	Screening/ Study entry	3 months	6 months	9 months	12 months	13-24 months
Informed consent sought Baseline interview/ study entry questionnaire completed	Yes					
Telephone follow up call by clinic	No	Yes	No	No	No	No
Clinical Procedures- SOC <ul style="list-style-type: none"> • HIV antibody/antigen • STI testing <ul style="list-style-type: none"> ○ Genital swab(s) ○ Pharyngeal swab ○ First-catch urine • Syphilis serology • HBsAg 	Yes	Yes	Yes	Yes	Yes	Results for this period accessed if available from VPCNSS
	Yes	No	No	No	No	
Clinical procedure- non-SOC Electrolytes /Serum creatinine	Yes	Yes	No	No	Yes	No
Sample access/ storage <ul style="list-style-type: none"> • Dried Blood Spot (DBS) test 	Yes	Yes	Yes	Yes	Yes	No
Online behavioural survey	Yes	Yes	Yes	Yes	Yes	No
In depth qualitative interview	Yes up to 20% of	No	No	No	Yes	No

Table 7. PrEP Decline Arm

Assessment	Screening/ Study entry	3 months	6 months	9 months	12 months	13-24 months
Informed consent sought Baseline interview/ Study entry questionnaire completed	Yes	-	-	-	-	-
Clinical Procedures- SOC <ul style="list-style-type: none"> • HIV antibody/antigen • STI testing <ul style="list-style-type: none"> ○ Genital swab(s) ○ Pharyngeal swab ○ First-catch urine • Syphilis serology • HBsAg 	Yes	Results for this period accessed if available*	Results for this period accessed if available*	Results for this period accessed if available*	Results for this period accessed if available*	Results for this period accessed if available*
Clinical procedure- non-SOC Electrolytes/Serum creatinine	Yes	-	-	-	-	-
Online behavioural survey	Yes	-	-	-	-	-
In depth qualitative survey	-	-	-	-	-	-
Post-study online questionnaire	-	-	-	-	-	-

* from VPCNSS

Table 8. PrEP Accept Arm for couples wishing to conceive

Assessment	Screening/ Study entry	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Informed consent sought Baseline interview/ Study entry questionnaire completed	Yes	-	-	-	-	-	-	-	-	-	-	-	-
HIV antibody test	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pregnancy test	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ovulation test	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Clinical Procedures- SOC <ul style="list-style-type: none"> • HIV antibody/antigen • STI testing <ul style="list-style-type: none"> ○ Genital swab(s) ○ Pharyngeal swab ○ First-catch urine ○ Syphilis serology 	-	-	-	Yes	-	-	Yes	-	-	Yes	-	-	Yes
DBS Test	Yes	-	-	Yes	-	-	Yes	-	-	Yes	-	-	Yes
Other SOC tests <ul style="list-style-type: none"> • Rubella serology • Folic acid levels etc. 	Yes	-	-	-	-	-	-	-	-	-	-	-	-
In depth qualitative survey	-	-	-	Yes	-	-	-	-	-	-	-	-	-
Post-study online questionnaire	-	-	-	-	-	-	-	-	-	-	-	-	Yes

5.3 RECRUITMENT

Participants will be recruited by direct approach by study personnel at each site. Participants who are eligible will be informed about the study. At the screening appointment potential participants will be provided with the Patient Information and Consent form (PICF). Patients who consent to the study additionally consent to either accept or decline PrEP. Following the study entry visit, there will be four follow-up study visits at three-monthly intervals for those consenting to take PrEP. This 12-month period on PrEP will be followed by access to STI and HIV test results for a further 12 months post-treatment. All visits will coincide with the patients' regular clinic visits. The total study period, including 12 months post-treatment, is 24 months. 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. Participants may feel obligated to consent to the study because their usual treating doctor is involved. To minimise this effect, the consent discussions and procedures will be conducted by study personnel. It will also 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 listed events occurs. Subsequent procedures will depend on the type of event:

1. Seroconversion of the participant

- a. If a participant in the PrEP accept arm seroconverts while taking PrEP they will be instructed to cease taking PrEP immediately. Following this, no further study visits will be necessary but their STI test results will be followed to the end of the 24-month study period.
- b. If any participant in the PrEP Accept arm of the study chooses to cease taking PrEP prematurely, or at the end of the 12-month study period, HIV testing will be performed

at weeks 4 and 12 after cessation of PrEP. Participants who stop taking PrEP for any reason will be given enough Truvada to take daily, for a period of 28 days from their last possible exposure.

- c. Any participant who seroconverts, regardless of study arm, will be managed by standard of care procedures.
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 ends due to lack of participation.
 3. The study is completed
 - a. All follow up procedures are terminated.
 - b. All remaining participants are informed of the study's completion.
 4. An HIV negative attempting to conceive becomes pregnant and completes her follow-up dosing regimen of Truvada

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 four 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 project leader and project study manager will have access to the identifying personal details (e.g. name and contact details) of all study participants. These details will be stored securely at the Burnet Institute or 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 four 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

The study visit surveys can be completed at the time of the study visit on an iPad in the clinic.

Each person will be assigned a unique participant code that is used to link their behavioural data and clinic visit data. For participants completing the study entry survey at the clinic, this code is used to enter into the survey software to initiate the survey. For those participants who choose to complete the survey at home, an email will be sent to the address 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 in the PrEP Accept Arm (which involves repeat surveys at three-monthly intervals) will also be asked to choose a unique username and password to enable their secure access to the 3-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

A small number of participants (~20%) 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 one year later.

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 FOR MSM AND HETEROSEXUALS NOT WISHING TO CONCEIVE

When a participant commences PrEP, their treating doctor will advise the following-

- PrEP is NOT an alternative to use of condoms and adherence to safer sex practices.
- Continued use of condoms and adherence to safer sex practices should be maintained throughout the study, including whilst taking PrEP.
- It can take up to 21 days of treatment with study drug (Truvada) before protective levels within the body are achieved.
- That the protective effects of PrEP within the body have not been fully studied.
- If for some reason the participant chooses to stop taking PrEP, they should inform their treating doctor immediately.
- 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 whilst taking PrEP, the study drug will be ceased immediately and they will be referred for HIV specialist management

6.2 COMMENCEMENT OF PrEP FOR HETEROSEXUALS WISHING TO CONCEIVE

When an HIV negative participant in a couple wishing to conceive commences PrEP, their treating doctor will advise the following-

- PrEP is NOT an alternative to use of condoms and adherence to safer sex practices during the period when they are NOT trying to conceive.
- Continued use of condoms and adherence to safer sex practices should be maintained throughout the study, including whilst taking PrEP, when they are NOT trying to conceive.
- It can take up to 21 days of treatment with study drug (Truvada) before protective levels within the body are achieved therefore sex without condoms or semen self-insemination should not begin until the HIV negative partner has had at least 21 days of Truvada.
- That the protective effects of PrEP within the body have not been fully studied.
- If for some reason the participant chooses to stop taking PrEP, they should inform their treating doctor immediately.
- That side effects of TDF and TDV when used for HIV PrEP have been reported, and include nausea, back pain, dizziness and vomiting.
- That there is a theoretical but unproven risk to a developing foetus that is exposed to Truvada.

- If a participant acquires HIV infection whilst taking PrEP, the study drug will be ceased immediately and they will be referred for HIV specialist management.
- If a participant acquires HIV infection and become pregnant whilst taking PrEP, there is an increased risk that the foetus will be exposed to HIV and may become HIV infected.

6.3 PrEP CESSATION FOR MSM AND HETEROSEXUALS NOT WISHING TO CONCEIVE

For participants who are due to complete 12 months of PrEP or who wish to stop taking PrEP earlier than the 12 month period, or withdraws from the study, he/she will be advised by their treating doctor that-

- Participants should continue Truvada for 28 days following their last sex without condom exposure.
- After PrEP cessation, duration of protective levels of the study drug (Truvada) is not known
- Continued use of SOC, including safer sex practice should be maintained in order to reduce risk of HIV and STIs

6.4 PrEP CESSATION FOR HETEROSEXUALS WISING TO CONCEIVE

- For HIV negative women who become pregnant whilst using PrEP they will be advised that they can continue Truvada for 28 days following their last unprotected HIV sexual exposure, however whether or not the woman continues the truvada will be evaluated on a case-by-case basis and will depend upon the following considerations:
 - Patient choice after a discussion regarding the theoretical but unproven risk to the foetus versus unknown benefit to the woman extending to 28 days
 - Any side effects that the patient may be experiencing that may be attributable to Truvada
 - Whethersex without condoms is likely to continue throughout the pregnancy
- After PrEP cessation, duration of protective levels of the study drug (Truvada) is not known
- Continued use of SOC, including safer sex practice should be maintained in order to reduce risk of HIV during the pregnancy

6.5 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 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

VicPrEP is a demonstration project to determine the feasibility of PrEP in the real world situation through assessment of uptake, adherence, duration and pattern of PrEP use during a 12 month period. This is a non-randomised, prospective, open-label multi-site study of HIV-negative participants with high risk sexual practices receiving Truvada once daily in addition to SOC, over a maximum of 12 months.

Meeting schedule and format

The DSMB will meet at the Infectious Diseases Unit at the Alfred Hospital or via teleconference. Secretarial assistance will be provided by the Infectious Diseases Unit at the Alfred Hospital. To provide information and assistance, DSMB meetings will be attended ex officio 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.

Interim review of data

On-going review during the trial will occur after completed follow up of the first forty patients and at completion of the study. Data presented to the DSMB will include summaries of baseline/study entry patient characteristics (see Table 1). HIV seroconversion rates, positive STI result rates and PrEP refusal rates will be examined.

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.
- At any time as requested by the investigators
- At any time for the duration of follow up of the study participants i.e. up to 2 years following enrolment.

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 need to consider any changes to the design of the trial that are required on the basis of the preliminary safety results. 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

6.6 PROTOCOL STEERING COMMITTEE (PSC)

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

6.7 STUDY MONITORING & ADVERSE EVENTS

Study monitoring will include, but not be limited to, verification of the accuracy and completeness of CRFs, 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 at each patient visit 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 and positive STI test results will be defined as AEs.

If during the course of the study, a participant seroconverts and becomes HIV+, genotype resistance testing will be performed in order to identify any HIV ARV drug resistance.

6.8 RENAL DYSFUNCTION

Renal function will be monitored by creatinine clearance, as calculated by the Cockcroft Gault equation, at the study entry visit (prior to commencing Truvada) and at the month 3 and 12 study visits. A potential participant with a screening (pre-Truvada) creatinine clearance of <60ml/min will be excluded from the study. Any participant with a month 3 creatinine clearance <50ml/min should be retested within 7 days. If the level is confirmed as <50ml/min on retest, Truvada should be discontinued. The participant should be followed weekly until creatinine clearance stabilises, or increases to ≥ 60 ml/min. Any participant with a month 12 creatinine clearance of <50ml/min should be retested within 7 days, and if the level is confirmed as <50ml/min on retest, the participant should be followed weekly until creatinine clearance stabilises or increases to ≥ 60 ml/min.

7. ANALYSIS PLAN

7.1 LABORATORY ANALYSES (Dried Blood Spot Analysis-DBS)

Laboratory analyses will comprise of dried blood spot testing for drug adherence. All participants who choose to take PrEP will be asked to consent to having five drops of their blood spotted onto DBS cards for analysis. Analysis of the DBS samples will take place in a certified drug detection laboratory, using strict quality control measures for reliability and reproducibility. A/Prof Peter Anderson, from The University of Colorado, Denver, will oversee the DBS test analysis, as his laboratory is the only certified facility, which has validated the TDF/FTC detection assay for PrEP studies (32, 47, 59). This high sensitivity assay uses low blood volumes for intensive pharmacokinetic studies where blood volume limitations are an important consideration. The DBS assay protocol used to measure drug adherence for PrEP participants has shown to be highly accurate with excellent correlation demonstrated between TFV and FTC in DBS vs. plasma, supporting the use of DBS as an alternative for plasma pharmacokinetic studies (59).

7.2 QUANTITATIVE DATA ANALYSES

The data will be collected on study specific case report forms (CRFs). After enrolment each participant will be assigned a unique code. This code will be used on CRFs and any other collected data. Following each patient visit, the investigator or designated site staff member may fax, post or email the CRF to the coordinating centre. The data will then be entered on a database and reviewed for completeness and accuracy. Any discrepancies will be notified to the investigator for clarification. 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 study codes. 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. Proportions of participants with reported HIV seroconversion and other positive STI tests in both arms will be compared using the Chi-square test for categorical variables.

Feasibility of the study will be assessed by examining the proportion of all individuals approached to participate in the study who accept the use of PrEP. Feasibility will be defined as a minimum 25% of all individuals approached who accept the use of PrEP. Safety will be defined as a decrease in the number of both HIV seroconversions and positive STI results in the PrEP accept arm compared to the PrEP decline arm. Efficacy will be defined as a minimum of 75% adherence in those who use PrEP, as determined by refill-based assessment and DBS analysis.

7.2.1 STATISTICAL ANALYSES

VicPrEP is a demonstration project investigating the adherence, behavioural change, acceptability, safety, and feasibility of the use of HIV PrEP in the Victorian community. We anticipate that uptake of PrEP will be 1:4, that is 25% of people who are offered PrEP will accept to do so. In order to recruit 100 people who accept PrEP it will be necessary to approach 400 people in total. Based on the number of patients with risk factors for acquiring HIV seen at the four high-case load GP clinics and the Chronic Viral Illness Clinic, Royal Women's Hospital, we estimate that four hundred people could be approached about the study over a period of two years. A sample size of 100 PrEP acceptors and 100 PrEP decliners will enable multivariate analysis of demographic and social factors associated with the PrEP acceptance, with the ability to include up to 10 variables in any model. The study sample size was necessarily chosen based on feasibility of recruitment and not based upon power calculations.

7.3 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.

7.4 DATA ANALYSIS AND DATA LINKAGE-VPCNSS

The VPCNSS links risk behaviour information collected from individuals seeking testing at primary health clinics, with laboratory results. These data are transferred to the Burnet Institute electronically, using password-protected files. The data are line-listed and contain a unique patient identifier, gender, date of birth, postcode, country of birth, Indigenous status, date of STI test, reason for test, recent sexual behaviour and injecting drug use behaviour.

In Victoria (Australia), HIV surveillance involves case reporting of new diagnoses of HIV and AIDS to the Burnet Institute on behalf of the Department of Health, which is similar to the system employed for all other communicable diseases across Australia. The main purpose of surveillance for any communicable disease is to provide relevant, accurate and timely information to facilitate public health action to prevent or control the transmission of infection and minimise morbidity.

Demographic, risk behaviour and STI testing information will be extracted retrospectively from participating clinics for consented individuals. An individual's records can be linked on the patient identifier and date of birth so their testing behaviour can be determined over the study period (12 months for PrEP acceptors and 24 months for PrEP decliners).

8. STORAGE AND ARCHIVING

The project leader and research nurses are responsible for ensuring that the data collected is 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
- Royal Women's Hospital, Melbourne

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 PICEF, 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 VicPrEP 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 VicPrEP 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.
- Mr Brent Allan is the community representative from Living Positive Victoria. Brent will be the designated community representative.

APPENDIX B- 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
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Table 3. Serious adverse events

Study ID	Age	Sex	Date onset	Date resolved	Event description	Category of experience	Relationship to study drug	Expectedness
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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
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Table 5. List of laboratory adverse events

Study ID	Parameter	Grade	Study visit
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