



AMPrEP

Amsterdam PrEP project

Biomedical Interventions for HIV Prevention in MSM in Amsterdam: a demonstration project

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LIST OF ABBREVIATIONS

ACS	Amsterdam Cohort Studies
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
AMC	Academic Medical Center
AR	Adverse Reaction
cART	combination Antiretroviral Therapy
CCMO	Central Committee on Research Involving Human Subjects
CDC	Centers for Disease Control and Prevention
CRF	Case Registration Form
EMA	European Medicines Agency
FDA	US Food and Drug Administration
FTC	Emtricitabine
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
IMPD	Investigational Medical Product Dossier
METC	Medical Research Ethics Committee
MSM	Men who have Sex with Men
NNT	Number Needed to Treat
NRTI	Nucleoside Reverse Transcriptase Inhibitor
PEP	Post-exposure Prophylaxis
PHSA	Public Health Service of Amsterdam
PrEP	Pre-exposure Prophylaxis
SAE	Severe Adverse Event
SHM	Stichting HIV Monitoring
STI	Sexually Transmitted Diseases
SUSAR	Suspected Unexpected Serious Adverse Reaction
TDF	Tenofovir
UAI	Unprotected anal intercourse
WHO	World Health Organization
WMO	Wet Medisch-wetenschappelijk Onderzoek met mensen
WBP	Wet Bescherming Persoonsgegevens (Personal Data protection Act)

PROJECT SUMMARY

Hypothesis: Public Health Service of Amsterdam (PHSA) can inform HIV-negative men who have sex with men (MSM) at high risk for HIV infection about and provide them with daily or intermittent pre-exposure prophylaxis (PrEP), to be taken as part of a comprehensive HIV risk reduction package. MSM can adequately make a choice between the two different intervention strategies and adhere to the chosen strategy. This comprehensive HIV prevention program has a good acceptability, feasibility and usability.

Objective: To investigate the uptake, acceptability and usability of a comprehensive HIV infection prevention program for high-risk MSM through 2 different intervention strategies (i.e. daily or intermittent PrEP) at the PHSA.

Study design: Evaluation study of a demonstration project of 2 different HIV prevention strategies (daily or intermittent PrEP), as part of a comprehensive HIV prevention program.

Study population: Men who have sex with men at increased risk for HIV (i.e. diagnosed with syphilis, urethral or rectal chlamydia or gonorrhoea within the last six months, reporting unprotected anal intercourse (UAI) with casual partners within the last six months, received PEP within last six months or having a HIV positive partner with unknown or detectable viral load in the last six months).

Intervention: Demonstration project with two arms: one group will receive daily PrEP and the second group will be provided with intermittent PrEP (i.e. 2 tablets between 24 and 2 hours before sexual contact followed by one tablet every 24 hours until 48 hours after the last sexual contact). After counselling, participants can choose an intervention. In addition, participants are allowed to switch between arms.

Main study parameters/endpoints: We will investigate uptake, acceptability, and usability of daily and intermittent PrEP, medication adherence, adverse events, behavioural disinhibition (i.e. increase in risk behaviour and in incidence of STIs), HIV infection and resistance.

Timeline: Start inclusion 1 May 2015. End of inclusion: 1 November 2017. End of study interventions: 1 June 2018. End of follow-up: 1 December 2018.

1. INTRODUCTION AND RATIONALE

1.1 HIV in the Netherlands

For people to become infected by HIV, they must first be exposed to an HIV infective person, then the virus must invade their immune system and subsequently viral shedding will take place in blood, genital fluids and other compartments which causes infectiveness to others. Exposure can occur by sharing injecting equipment among people who inject drugs but mostly happens by unprotected sex in the Netherlands. HIV prevalence in Western countries is highest among MSM (1). In the Netherlands MSM account for 71% of the new HIV diagnoses and an estimated 24% of the total HIV infected people in the Netherlands is unaware of being infected (1, 2). This adds up to an estimated 14,000 MSM living with HIV, of whom 3500 men are not aware of their infection. Another group is not in care for several reasons and an estimated 10% of the HIV positive MSM are diagnosed and in care, but have detectable virus levels because they are not treated or have not reached undetectable load (2).

HIV has been transformed from leading to imminent death due to AIDS in the 1980s towards a well manageable chronic disease. This has implications for the MSM community as a whole, as MSM living with HIV could provide a reservoir for further transmission.

HIV Monitoring Foundation and SOA AIDS Netherlands (3) estimated that around 6000 men still have a detectable viral load resulting in an increased risk to infect HIV negative sex partners (Figure 1).

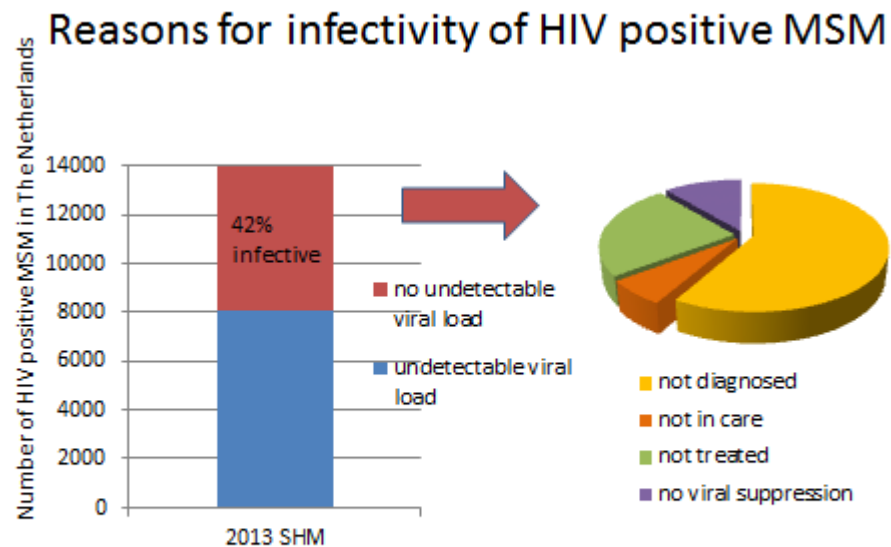


Figure 1. Reasons for infectivity (detectable viral load) of HIV positive MSM in the Netherlands (2, 3).

By 2013 HIV incidence (number of new infections per 100 person years) has stabilised but is not decreasing among MSM (3, 4), despite numerous HIV prevention interventions like motivational interviewing, condom provision at STI clinics and in gay bars and clubs, online tailored prevention advice, as well as informing prioritised populations about safe sex and offering free, anonymous and low-threshold STI and HIV screening. New prevention strategies are needed to limit the ongoing HIV transmission in the Netherlands.

1.2 Risk Factors for HIV infection

Research data from observational studies (from the Amsterdam Cohort Study and elsewhere) and prospective trials identified risk factors for new HIV infections (5-7). Risk factors for MSM include having an STI (syphilis, rectal or urethral chlamydia or gonorrhoea), reporting unprotected anal intercourse (UAI), especially receptive UAI with casual partners, having sex with an HIV positive partner and having more sexual partners.

Several scoring systems have been described (8, 9) to identify MSM at high risk for HIV. These scoring systems are based on risk ratios of various risk factors from observational

data from US cohorts, and include, among others, drug use, age, number of partners and STI. An observational study among MSM (10) conducted in San Francisco, USA, reports that 2 episodes of proctitis due to chlamydia or gonorrhoea resulted in an 8-fold risk for HIV infection.

In the Netherlands, risk for HIV among MSM has recently been studied in the long-standing Amsterdam Cohort Studies (ACS) (6). Risk factors that were significantly associated with incident HIV in multivariate analysis were UAI with casual partners and gonorrhoea.

Moreover, a study among MSM who needed PEP in Amsterdam showed that individuals who have been prescribed post-exposure prophylaxis after a sex incident, have an increased risk for HIV infection (11).

1.3 Risk behaviour

Unprotected sex

UAI, especially receptive and with casual partners, is the most important risk factor for HIV infection. At the beginning of the HIV epidemic, 78% of MSM participating in the ACS was not using condoms (6), followed by a strong decrease in response to the HIV epidemic (5, 12). The proportion of MSM in the ACS reporting UAI with casual or steady partners increased from 38% in 1991 to 60% in 2013. The proportion of MSM that has UAI with casual partners also increased, from 12% in 1991 up to 32% in 2013 (2, 13). The introduction of cART has led to an increase in risk behaviour (5). From these data we conclude that sexual risk behaviour is increasing, although it is not as prevalent as at the start of the HIV epidemic.

1.4 STI prevalence

Since October 2008, all MSM participating in the ACS are routinely screened for chlamydia, gonorrhoea and syphilis. In 2013, the overall positivity rate of any STI was 5.9% (66/1110). The prevalence of STIs was significantly higher among HIV positive MSM compared to HIV negative MSM (2).

A similar tendency of high STI prevalence among MSM can be demonstrated from data from the STI clinic of the Public Health Service in Amsterdam. In 2013, an STI was diagnosed in 5104 (14.6%) of the almost 35,000 consultations; this percentage was 18% among HIV negative MSM and 31% among HIV positive MSM (4).

1.5 Drug use during sex

Data from the ACS indicate that alcohol use and sexual encounters under the influence of alcohol have decreased in the period 1995 to 2012. However, during the same time period, the use of ecstasy, cocaine, and poppers increased both in general and during sexual encounters (14). Sex-related drug use is common and is associated with high-risk sexual behaviour among clients of the STI clinic in Amsterdam. Recreational drugs during sex were used by 25% of the visitors in the 6 months preceding their visit, among MSM this was 31%. Sex-related drug use was associated with high-risk sexual behaviour and both were associated with STI. After adjusting for high-risk sexual behaviour, sex-related drug use was still associated with STI (15).

1.6 Antiretroviral-based biomedical Interventions for HIV prevention

Introduction

Early achievements in HIV prevention included barrier protection (condoms), blood product screening, and clean needle use. In more recent years, on combination antiretroviral therapy (cART) based biomedical approaches for HIV prevention have been developed. Among the first cART based biomedical prevention approaches were prevention of mother-to-child transmission with antiretroviral therapy and post-exposure prophylaxis (PEP). However, the HIV epidemic among MSM is not responding to currently available HIV prevention approaches. Recently, early treatment as prevention of transmission (TaSP) and pre-exposure prophylaxis (PrEP) for HIV negative persons were added to the cART based biomedical prevention tool kit.

Prevention of mother-to-child transmission and treatment as prevention are beyond the scope of this protocol and will not be discussed.

Pre-exposure prophylaxis for HIV prevention

Pre-exposure prophylaxis (PrEP) for HIV prevention means providing (daily) antiretroviral medication, usually a combination of tenofovir disoproxil fumarate and emtricitabine (Truvada ®) to HIV negative people who are regularly exposed to HIV. PrEP is a discrete user-controlled protection against HIV infections. In the past, gels containing antiretroviral

therapy have been studied as well; injectable antiretroviral medications for pre-exposure prophylaxis are in the pipeline.

Six randomized controlled trials (RCTs) that studied oral pre-exposure prophylaxis to prevent HIV infection have been published to date (September 2014). Two focused on women only (VOICE, South Africa, Uganda and Zimbabwe (16); and FEM PrEP, South Africa, Kenya, Tanzania (17)), one on heterosexual men and women (TDF2, Botswana) (18), one on people in a heterosexual serodiscordant relationship (Partners PREP, Uganda and Kenya) (19), one on injecting drug users (Bangkok tenofovir study) (20) and one on MSM (iPrEX, United States and several other countries) (21). The results are summarized in Table 1. The overall efficacy ranged from 0% to 67%, increasing to >90% in subgroups with good adherence.

In the US, after the completion of the iPrEx study, an open label extension cohort study was performed (22). Uptake of PrEP in this extension study was 76%, the hazard ratio for HIV infection in the group that choose PrEP was 0.51 (95% CI 0.26-1.01) compared to those who chose not to use PrEP.

Quite often the effectiveness of medication is lower in routine clinical settings compared with research conditions (23). Therefore demonstration studies are warranted to investigate feasibility of PrEP in a real-world clinical setting.

Recently finalized PrEP studies

In Europe, two large trials investigating PrEP among MSM were stopped early because of efficacy. One is the PROUD study in the United Kingdom, a multi-center, open label randomized design to immediate or deferred inclusion of a daily tablet of fixed-dose tenofovir and emtricitabine as part of HIV reduction interventions. The purpose of this study was to determine the feasibility of a larger trial powered for cost-effectiveness and clinical effectiveness. However in October 2014, after the enrollment of 546 participants from 8 UK study sites, they stopped the deferred arm because of effectiveness (24). Results will be presented in February 2015 at CROI. The second study is the Ipergay study. This study is a collaboration of study sites in France and Canada, investigating intermittent PrEP use (2 fixed-dose tablets containing tenofovir and emtricitabine between 24 and 2 hours before the sexual encounter, followed by one tablet every 24 hours until 48 hours after the last sexual encounter). The placebo arm of this study also was stopped early because of effectiveness (25) (ipergay.fr/un-grand-succes-dans-la-lutte-contre-le-vih-sida.html).

PrEP guidelines

Centers for Disease Control and Prevention (CDC) published an interim guidance for the prescription of PrEP in January 2011 (26) and an update in 2014 (27). In the update, they state that PrEP with fixed-dose tablets containing tenofovir and emtricitabine is now considered one of the standard available prevention options for populations disproportionately affected by HIV.

The World Health Organization (WHO) published their guidance in July 2012, urging for demonstration projects to be started (28). They stated that PrEP is a promising new approach for HIV prevention and demonstration studies are needed. In July 2014 WHO took the issue further by publishing their consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations (29). In these guidelines, based on published evidence of PrEP effectiveness in HIV prevention, PrEP is recommended for risk groups as an additional HIV prevention choice within a comprehensive HIV prevention package. A third guideline is published by the New York State department of Health AIDS institute (hivguidelines.org). This guideline is a clinical guidance document with information for health care providers.

In the Netherlands, the NGOs SOA AIDS Netherlands and AIDS foundation advised in October 2014 to not only start a pilot project on PrEP in high risk MSM but also start planning implementation of PrEP in the Netherlands (30). Lastly, in December 2013 the Public Health Service of Amsterdam (PHSA) published a position paper on antiretroviral-based biomedical interventions in The Netherlands, based on a review of the scientific literature, a situational assessment and discussions with stakeholders, partners and community (12). In this report it is recommended that the Public Health Service of Amsterdam prepares and implements a demonstration or experimental project in which publicly funded state-of-the-art HIV exposure prophylaxis is made available to high risk MSM for the prevention of HIV infection.

Trial	Population	Countries	Intervention	Relative reduction of HIV incidence	Other remarks
iPrEx	2499 MSM	Peru, Ecuador, South Africa, Brazil, Thailand, USA	Daily oral TDF/FTC or placebo	44% (95% CI 15-63%, p=0.005	92% if detectable drug levels in blood samples; 58% in group reporting receptive UAI (21)
Partners PrEP	4747 heterosexual men and women with HIV positive partner	Uganda, Kenya	Daily oral TDF, TDF/FTC or placebo	TDF 67%, FTC/TDF 75% (95% CI 55-87%, p<0.0001)	86% if detectable drug levels in blood samples (19)
TDF2	1219 heterosexual men and women	Botswana	Daily oral TDF/FTC or placebo	63% (95% CI 22-83%, p=0.01)	(18)
FEM PrEP	2056 heterosexual women	Kenya, South Africa, Tanzania	Daily oral TDF/FTC or placebo	6% (95% CI 34-41%, p=0.79)	stopped early for futility, 38% had detectable blood levels of TDF (17)
VOICE	5029 heterosexual women	South Africa, Uganda, Zimbabwe	Daily oral TDF, TDF/FTC, placebo, vaginal gel or placebo	HR 1.04 (95% CI 0.75-1.49)	<30% of samples had detectable blood levels of TDF (16)
Bangkok Tenofovir Study	2413 people who inject drugs	Thailand	Daily oral TDF or placebo	49% (95% CI 10-72%, p=0.01)	(20)

PROUD study	545 MSM	UK	Direct or deferred TDF/FTC	86%	(24)
IPERGAY study	MSM	France and Canada	On demand TDF/FTC or placebo	86%	(25)

Tabel 1. Summary of randomized controlled trials on PrEP

Cost-effectiveness of PrEP

Several cost-effectiveness studies for PrEP have been done, in the US (31-34), Australia (35), South Africa (36, 37) and Peru (38) among others. We will focus on the studies in high income countries and on studies among MSM.

Based on different assumptions, studies report different outcomes. The models assume PrEP will be given to high risk men with HIV incidence rates between 0.75 and 2.3 per 100 person years. PrEP costs in the studied models are similar to the assumed costs in the Netherlands: approximately 750-1000 USD per person per month. The models differ in time span, ranging from 5 years to lifetime, costs for HIV testing and treatment costs in case of incident HIV infection (which was not modelled in every study). Costs per QALY range from 31,000 USD for a 5 year time period (39) to 298,000 USD based on lifetime risk (32). In the Netherlands no official cut-off for cost-effectiveness has been established, however € 20,000 up to € 50,000 (27,000-68,000 USD) per QALY gained is generally taken as limit for cost-effectiveness. Key factors in PrEP cost-effectiveness are PrEP effectiveness, which is strongly dependent on adherence, and the HIV risk of the group taking PrEP.

The number needed to treat (NNT) per year is 62 in the iPrEx trial, however the NNT is lower for people reporting unprotected receptive anal intercourse (36) or cocaine use (40).

Adherence

Adherence is the weakest link in PrEP efficacy. In the iPrEx trial, overall HIV protection was 44%, however in the group with detectable drug levels, protection was 92% (21). Risk perception seems to be a potent driver of adherence: men who practiced unprotected receptive anal intercourse, had higher adherence and better HIV protection (58% in

subgroup efficacy). Men who did not have sex were least likely to take PrEP. On the other hand, the FEM-PrEP trial among young women in southern Africa, was stopped prematurely due to lack of effect (17). In this trial, 70% of the participants considered themselves to be at a low risk of HIV infection. Self-reported adherence and pill-counts were high, but the drug was detected in serum in only 26% of blood samples. The VOICE trial, which also enrolled southern African women, did not show an HIV protective effect for either oral PrEP or oral PrEP combined with vaginal application of tenofovir containing gel. More than 50% of the women in the active arm of this trial had never tenofovir detected in blood samples (16). The IPERGAY study on intermittent PrEP reported that 53% used PrEP as scheduled during the last sexual encounter, 28% used PrEP but not according to the schedule and 19% did not use PrEP(25).

Based on the results of these studies, we may conclude that effectiveness of PrEP is highly dependent on adherence. In a successful demonstration project, adherence is thus of great importance and participants should be offered intensive adherence support. Participant's self-reports of adherence have limited accuracy and tend to overestimate actual adherence; social desirability may play a role in this.

Information is needed on factors influencing PrEP adherence, including knowledge about PrEP, personal beliefs and attitudes, perceived risk of HIV infection, self-efficacy in risk reduction and barriers and facilitators of PrEP adherence.

Safety

There are concerns that availability of PrEP can reduce commitment to primary prevention strategies and consequently will result in increased high-risk behaviour (i.e. risk compensation or safety offset). In the past, a low perception of HIV threat after the availability of cART lead to more risk behaviour (41). However, several recent trials and observational studies among MSM provide evidence of similar or lower frequency of risk behaviour and STI after PrEP (i.e. prevention synergy) (21, 42, 43). Results from outside research settings or reporting longer follow-up periods are not yet available.

Viral resistance in incident HIV infections while someone is using PrEP, is another concern. As PrEP involves only two antiretroviral agents instead of the usual three in HIV treatment, resistance may occur. In the iPrEx study, among the ten subjects who appeared to have had acute HIV infection upon enrolment, 3 had FTC-resistant infections and no one had TDF-resistant infections. Among the subjects who became infected during the trial, no FTC or TDF resistance was detected.

Intention to PrEP use and PrEP acceptability

Most PrEP trials use medication adherence as a measure of acceptability. Willingness to start PrEP among MSM has been evaluated in several countries but mainly in the US (44). Although important, adherence and willingness alone are not sufficient for efficient use of PrEP: the broader social context must be taken into account, including social, cultural and structural factors (45). In the Netherlands, willingness to PrEP use has been evaluated among MSM (article under review) in 2013. Of Dutch MSM participating in the ACS, 54% was aware of PrEP. Only 13% reported a high intention to use PrEP: predictive factors were a steady relationship with an HIV positive partner or partner with unknown HIV status and reporting high risk sexual behaviour. Psychosocial determinants such as high perceived self-efficacy and high perception of relief (defined as feeling liberated, relieved and receiving hope) due to PrEP, resulted in a higher intention to use PrEP. Of all participants, 39% anticipated that they would decrease their condom use during anal intercourse while using PrEP. This percentage was higher among those with a high intention to use PrEP and those reporting higher risk behaviour. More than half (55%) of the MSM interviewed stated they would be willing to pay € 50 per month for PrEP.

Co-operation

This *Biomedical interventions for HIV prevention among MSM* project is part of the H-team. H-team stands for HIV towards Transmission Elimination in AMsterdam. Several organisations work together to try to reach this ambitious goal. Five working packages are formed which are linked and which closely cooperate. The working packages are, besides the project of this protocol, a project that focusses on increasing HIV testing including provider-initiated testing in addition to testing in outreach settings, at general practitioner practices and at the PHSA. A third working group will construct a new awareness campaign among MSM about acute HIV infections (symptoms related to recent risk behaviour) and the importance of testing if an acute infection is suspected. Another project is testing attitudes and assessing barriers about Treatment as Prevention among HIV care providers, and the last project is about functional cure. This functional cure project aims to start a cohort of patients with acute HIV infections, to assess the viral reservoir and start early treatment. Monthly meetings take place to set common goals and keep on track.

2. OBJECTIVES

Primary Objective: To investigate the uptake, acceptability and usability of a comprehensive HIV infection prevention program for high-risk MSM through 2 different intervention strategies: daily PrEP and on demand PrEP, combined with intensified standard care at the PHSA.

Secondary Objectives:

A. Adherence

To assess the adherence of the participants to medication schedules and follow-up regimes

To assess factors predicting adherence

To assess barriers for adherence

To assess the number of attended scheduled clinic visits

B. Adverse events

To assess the incidence of serious adverse reactions attributable to the antiretroviral medication

To assess the incidence of adverse events that lead to interruption or cessation of antiretroviral medication

To assess changes in renal function

C. HIV infection

To assess the HIV incidence rate in the two project arms

D. Viral resistance

To assess HIV-drug resistance in case of incident HIV infection

E. Risk behaviour

To assess trends in self-reported risk behaviour

F. STIs

To determine trends in incidence rate of STIs

G. Barriers and motives of choice of intervention

To identify barriers and motives of choice of intervention and participant satisfaction with their choice

H. General well-being

To assess self-perceived health and psychosocial well-being including sexual health

3. PROJECT DESIGN

3.1 Introduction

We will perform an evaluation study of a demonstration project of 2 different HIV prevention strategies: daily PrEP and on demand PrEP, both combined with intensified standard care. We aim to include a group that is at high risk for HIV (incidence, 3.7-6.7/100 person years according to previous data) (6, 11).

3.2 Recruitment and enrolment

We will recruit participants among the visitors of the STI clinic of Amsterdam and through advertisements online and offline. Screening and enrolment will take place at the STI clinic of Amsterdam. Figure 2 illustrates the enrolment process. Inclusion criteria are described in chapter 5.

At **pre-screening**, eligibility will be checked and the project will be explained. The patient information will be provided. If the person is interested and possible eligible, a standard STI and HIV testing will be planned (if not done within the last 3 weeks) followed by a **screening** consultation during which the project will be explained, questions will be answered and informed consent will be obtained. The next step is to order serum creatinine and urineanalysis. Approximately one to two weeks later the project staff will give the results of the tests at a scheduled visit. If the person is eligible and wants to take part in the project, the project team will proceed with enrolment. At this **enrolment visit**, final questions will be answered and the participant will decide in which project arm he will be enrolled, using shared and informed decision making. A blood sample for hepatitis C and HIV PCR, and for HIV 4th generation combo test will be taken; medication will be provided.

Switch from project arm during follow-up is allowed at each project visit, as people need different HIV prevention options for periods in their lives whenever their personal circumstances change.

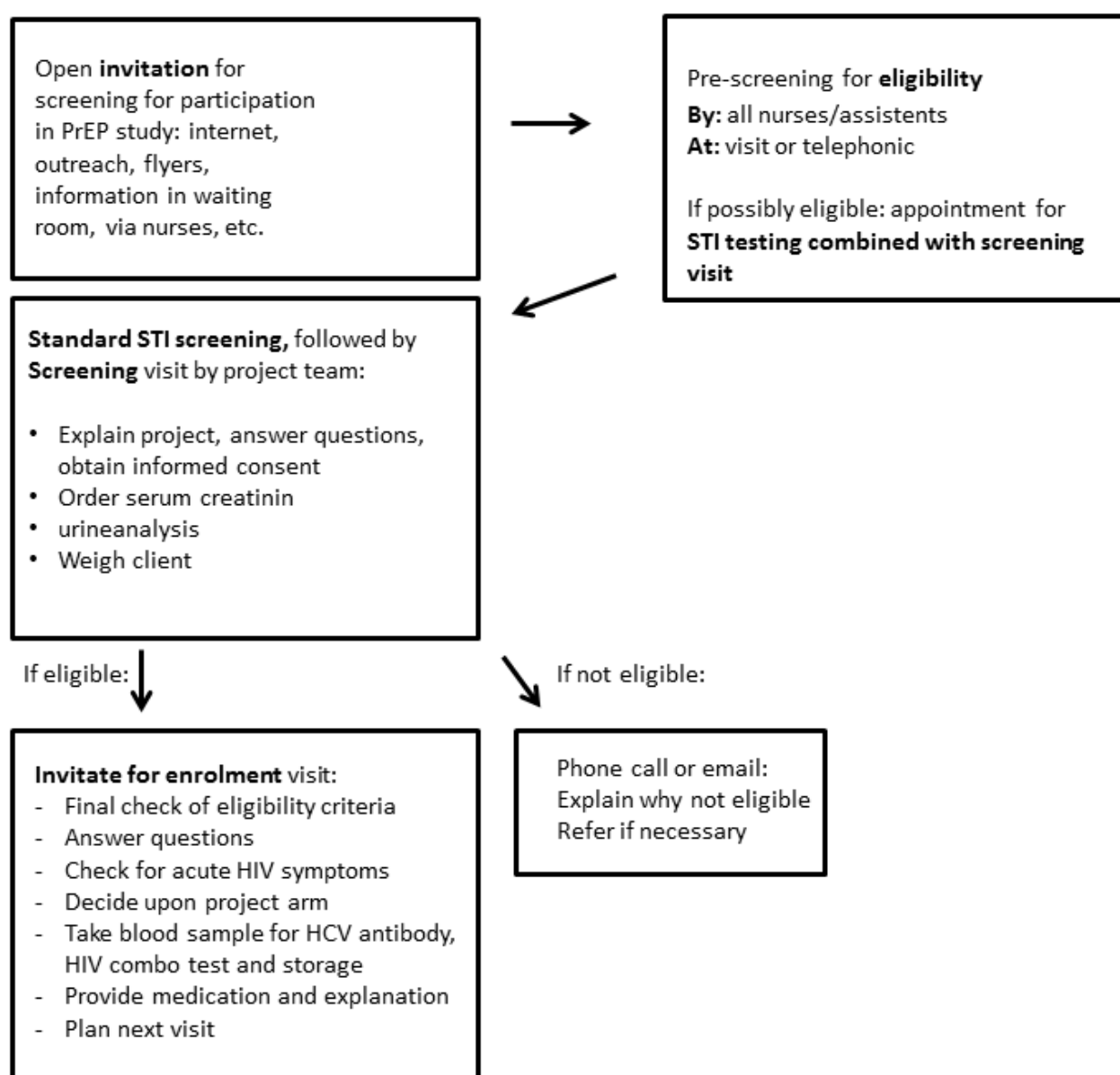


Figure 2. Flow chart of the enrolment process.

3.3 Follow-up and assessments

Follow-up visits and assessments are in detail described in chapter 6.2 and in figure 3. In short: at enrolment a self-administered questionnaire needs to be completed, involving demographic information, rationale for choice of intervention, sexual risk behaviour, lifestyle and quality of life, followed by 3-monthly questionnaires about sexual risk behaviour, quality of life and adherence. Yearly, an extended version of the 3-monthly questionnaire will be requested. In a subgroup, in-depth interviews will be performed. Each participant is asked to complete an incident-driven diary, online or as application for mobile phone, about adherence and risk behaviour.

Enrolment will stop 1 November 2017. Until 1 June 2018 the project will be continued and all medication will be provided. After 1 June 2018, the provision of PrEP medication as part of the project will be stopped, and standard Dutch rules for financing medication will apply. Participants will be invited to have 3-monthly HIV and STI checks and be asked to complete the above-mentioned questionnaires until the end of the project at 1 December 2018.

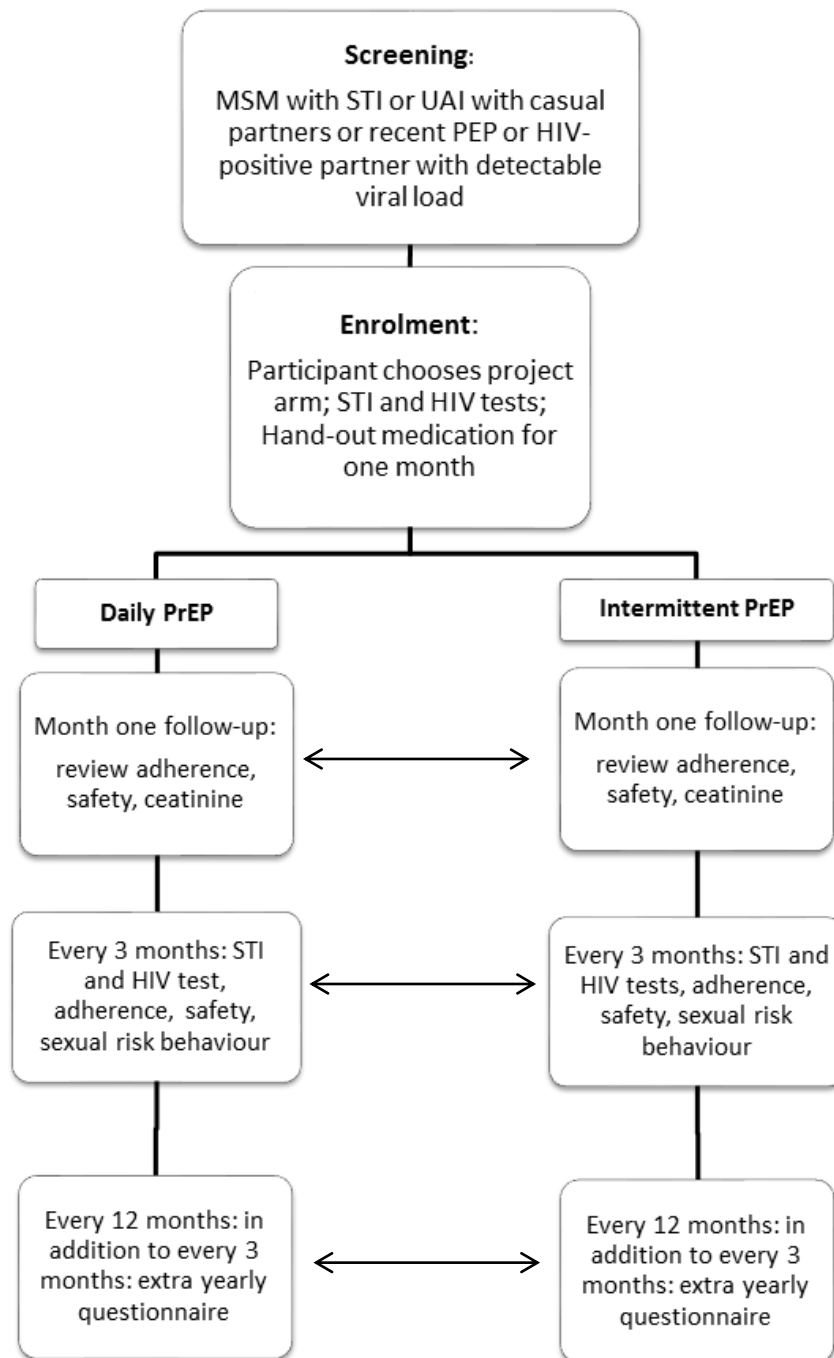


Figure 3: Flow chart summarising project design

4. Prioritised POPULATION

4.1 Population

The population to be studied are HIV negative men who have sex with men (MSM) at increased risk for HIV infection.

4.2 Participant inclusion criteria

All of the following:

1. Male or transgender, age 18 years or more
2. MSM
3. Completed HIV and STI screening
4. HIV negative by 4th generation Elisa antigen/antibody test.
5. Willing and able to comply to project visit schedule and procedures
6. Willing and able to give written informed consent
7. Sufficient understanding of Dutch or English

AND at least one of the following:

1. One or more documented STI (urethral or anal chlamydia or gonorrhoea, primary or secondary syphilis) in the last 6 months (either at STI clinic or a documented infection diagnosed elsewhere)
2. UAI with casual partners in the last 6 months
3. Received PEP after sexual risk incident in the last 6 months
4. HIV positive partner with unknown or detectable viral load

4.3 Participant exclusion criteria

One of the following:

1. Signs or symptoms of acute HIV infection¹
2. Hepatitis B infection (i.e. HbsAg positive)
3. Creatinine clearing (using cockroft gault formula) < 60 ml/min
4. Concurrent use of nephrotoxic medication (aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2)

5. Hypersensitivity for one of the components of fixed combination tablet containing tenofovir and emtricitabine²
6. Unlikely, in the opinion of the clinician, to comply with trial schedule

¹ Signs suspected for acute HIV infection are: fever, rash, diarrhoea, pharyngitis, lymphadenopathy, fatigue, night sweats, unexplained weight loss

² Components of: fixed combination tablet containing tenofovir and emtricitabine: Tablet core: Croscarmellose sodium, Lactose monohydrate, Magnesium stearate (E572), Microcrystalline cellulose (E460), Pregelatinised starch (gluten free); Film-coating: Glycerol triacetate (E1518), promellose (E464), Indigo carmine aluminium lake (E132), Lactose monohydrate, Titanium dioxide (E171)

5. Interventions

5.1 Arm 1 of demonstration project: daily PrEP

Intervention

The intervention in this project arm is Truvada (containing emtricitabine 200 mg and tenofovir disoproxil fumarate 245 mg), to be taken orally once daily from inclusion until the end of the demonstration project, or until the participant decides to stop participation in the project. Truvada is licenced for HIV treatment since 2003 and for HIV pre-exposure prophylaxis in 2011, however for the latter only in the United States of America. In Europe, Truvada is licenced for HIV treatment only. Most common (10%) side effects are headache, diarrhoea, nausea, abnormal dreams, insomnia, dizziness, decreased renal function. For further information, please refer to the SPC, the Investigator Brochure and Investigational Medical Product Dossier IMPD.

Standard care

All participants will receive standard sexual health care. Hepatitis B is checked at first clinic visit. Vaccination is offered if the participant is core-antibody negative. STI checks will be performed according to PHSA protocols. If the participant is asymptomatic, the study nurse or doctor will take a swab from the pharynx and the participant or the doctor/nurse will take an anal swab for chlamydia and gonorrhoea Nucleic acid amplification test; a blood sample will be taken for syphilis serology and HIV testing with 4th generation combo test (Liason®). If he is symptomatic, further examination is performed depending on the complaints, according to PHSA protocols.

All STI clinic visitors have access to condoms and lubricant. Sexual health and risk reduction counselling is part of the standard consultation.

Participant information

Every participant will be fully informed, both by oral instructions and by use of written material about PrEP: mechanism of action, importance of adherence, actions to take after missing one or more doses, side effects and additional primary prevention methods.

Dispensing procedures

The medication will be delivered to the STI clinic by a GCP-licensed pharmacy (Slotervaart apotheek) in bottles containing 30 tablets. The bottles will be labelled according to regulations. The study medication will be kept at a locked cupboard at the STI clinic and storage conditions will be according to local guidelines. The medication will be dispensed at the STI clinic following standard dispensing procedures. Daily PrEP clients will receive 90 pills for every 3 months.

Medication interruption

In case of a serious adverse event possibly due to tenofovir with emtricitabine, or if renal function is abnormal, tenofovir with emtricitabine must be interrupted pending further investigation. Reintroduction at the discretion of the clinician is allowed.

Medication discontinuation

In case of the following, tenofovir with emtricitabine must be discontinued: incident HIV infection, toxicity or adverse event. The participant is free to interrupt or discontinue tenofovir with emtricitabine. However, if he practices UAI, he should be counselled about the risks of discontinuation.

Overdose of medication

An overdose is defined as 2 or more tablets a day for three or more consecutive days, or more than 3 tablets in one day. In case of an overdose, tenofovir with emtricitabine will be discontinued and the participant will be monitored for renal or other toxicity. After resolving, tenofovir with emtricitabine can be restarted.

Adherence

Adherence will be supported by providing the participants with pill boxes and by motivational interviewing.

Adherence will be checked at every visit by pill counts and counselling. Moreover, all participants are asked to keep an online incident-driven diary, which will give additional data on PrEP adherence and sex acts (number of partners, condom use). Blood samples for drug levels will be taken at 1 month, 3 months, followed by 6-monthly samples in a subset. The PHSA is considering a randomised approach of adherence interventions in this study arm, involving feedback of drug level results to half of the participants, compared to standard adhering support in the other participants. If the decision is made to proceed with this, approval from the METC will be requested beforehand and a sub-study protocol will be submitted.

Post-exposure prophylaxis

In the event that a participant has had UAI that is not protected by tenofovir with emtricitabine, post-exposure prophylaxis can be prescribed according to local guidelines (PHSA protocol).

Interacting medication

For every participant who uses concurrent medication, an interaction check will be performed via www.epocrates.com or www.hiv-druginteractions.org.

For reasons of interactions with tenofovir with emtricitabine, co-use of the following medication is not permitted:

- Drugs containing lamivudine
- Adefovir
- Cidofovir
- Non-steroidal anti-inflammatory medication (NSAIDs) in chronic use or high doses.

Treatment and referral after HIV seroconversion

Participants who become HIV infected during follow-up will stop tenofovir with emtricitabine immediately and will be referred the same day for consultation to an HIV treatment center for further disease management including resistance testing. This is standard procedure at the PHSA.

5.2 Arm 2 of demonstration project: intermittent PrEP

Intervention

The intervention in this project arm is Truvada (containing emtricitabine 200 mg and tenofovir disoproxil fumarate 245 mg), to be taken orally if the participant regards himself at risk for having condomless sex with a partner with an unknown hiv status. The dosing schedule for intermittent PrEP is as follows: 2 Truvada tablets between 24 and 2 hours before the sexual encounter, followed by one tablet every 24 hours until 48 hours after the last sexual encounter (figure 4). This intervention will be applied by participants who choose this option from inclusion until the end of the demonstration project, or until the participant decides to stop participation in the project

Truvada is licenced for HIV treatment since 2003 and for HIV pre-exposure prophylaxis in 2011, however for the latter only in the United States of America. In Europe, Truvada is licenced for HIV treatment only, not for prevention. Most common (10%) side effects are headache, diarrhoea, nausea, abnormal dreams, insomnia, dizziness, decreased renal function. For further information, please refer to the SPC, the Investigator Brochure and Investigational Medical Product Dossier IMPD.

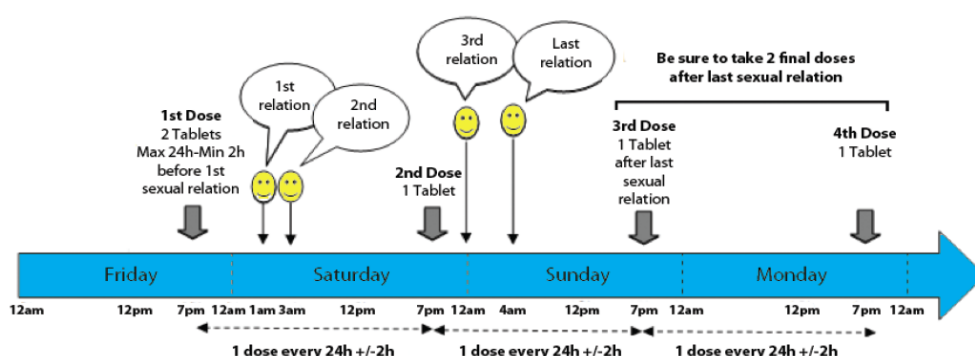


Figure 3: dosing scheme intermittent PrEP

Standard care

All participants will receive standard sexual health care. Hepatitis B is checked at first clinic visit. Vaccination is offered if the participant is core-antibody negative. STI checks will be performed according to PHSA protocols. If the participant is asymptomatic, the study nurse or doctor will take a swab from the pharynx and the participant or the doctor/nurse will take an anal swab for chlamydia and gonorrhoea Nucleid acid amplification test; a blood sample will be taken for syphilis serology and HIV testing with 4th generation combo test (Liason®). If

he is symptomatic, further examination is performed depending on the complaints, according to PHSA protocols.

All STI clinic visitors have access to condoms and lubricant. Sexual health and risk reduction counselling is part of the standard consultation.

Participant information

Every participant will be fully informed, both by oral instructions and by use of written material about PrEP: mechanism of action, importance of adherence to schedule, actions to take after missing one or more doses, side effects and additional primary prevention methods.

Dispensing procedures

The medication will be delivered to us by a GCP-licenced pharmacy (Slotervaart apotheek) in bottles containing 30 tablets. The bottles will be labelled according to regulations. The study medication will be kept at a locked cupboard at the STI clinic and storage conditions will be according to local guidelines. The medication will be dispensed at the STI clinic following standard dispensing procedures. Intermittent PrEP clients will receive at least 60 Truvada pills for 90 days.

Treatment after HIV seroconversion

Participants who become HIV infected during follow-up will be referred the same day for consultation within a week, to an HIV treatment center for further disease management including resistance testing. This is standard procedure at the PHSA.

6. METHODS

6.1 Endpoints

Primary endpoints

1. Uptake of each prevention intervention strategy

- a. Uptake per strategy among men who presented for screening
- b. Proportion of retained interventions, defined as proportion of enrolled people still in care and in intervention group of first choice, at 6, 12, 18 and 24 months, per strategy
- c. Proportion of enrolled people that switched project arm, per strategy
- d. Proportion of missed visits and proportion of participants that missed (definition: more than 2 weeks late for visit) one or more visits, per strategy

2. Acceptability

- a. Score on perceived and experienced agreeability of the chosen intervention as a personal HIV protection strategy (Likert scales) at base line and follow-up
- b. Score on the perceived usefulness and effectiveness of the chosen intervention as a personal HIV protection strategy (Likert scales) at base line and follow-up
- c. Score on the perceived and experienced disturbance by the chosen intervention as a personal HIV protection strategy (Likert scales) at base line and follow-up
- d. Proportion of participants that disclosed to others that they participate in this project

3. Usability

- a. Score on perceived and experienced ease of use of the chosen intervention as a personal HIV protection strategy (Likert scales) at base line and follow-up
- b. Score on perceived and experienced clarity /complication of use of the chosen intervention as a personal HIV protection strategy (Likert scales) at base line and follow-up

Secondary endpoints

A. Adherence

- a. Daily PrEP group: proportion of correctly taken doses according to self-report, diary and pill-counts. Level of drug in blood samples
- b. Intermittent PrEP group: proportion of correctly taken doses according to self-report, diary and pill-counts; median number of PrEP episodes per participant per

year, proportion of correctly started PrEP episodes, proportion of correctly finished PrEP episodes.

B. Side effects

- a. Both project arms: proportion of participants having adverse events
- b. Both project arms : serious adverse events attributable to tenofovir or emtricitabine; adverse events that lead to interruption or cessation of tenofovir with emtricitabine; yearly change in renal function

C. Number of incident HIV infections

D. Viral resistance

- a. Proportion of participants with incident HIV infection that has HIV drug resistance
- b. Type of resistance mutations, proportion associated with tenofovir or emtricitabine

E. Changes in risk behaviour

- a. Changes in number of sexual partners and type of sexual partner (steady or casual)
- b. Changes in number of sex acts protected by condom
- c. Changes in number and proportion of UAI sex acts with steady and with casual partners

F. Incidence rate of STIs (i.e., chlamydia, gonorrhoea, syphilis, hepatitis B and C)

G. Barriers and motives of choice

- a. Anticipated barriers and motives per proposed strategy by open-end questionnaires at baseline
- b. Experienced barriers and motives per proposed strategy, including rationale behind low scores of usability and acceptability (open end questionnaires; qualitative interviews in subsets), at follow-up
- c. Rationale behind personal choice of intervention strategy by open end questionnaires, at baseline and at switch
- d. Scores on anticipated and experienced level of self-efficacy per intervention strategy at baseline and follow-up
- e. Scores on anticipated general satisfaction with chosen intervention regimen at baseline and actual satisfaction scores at 12 and 24 months

H. General well-being

- a. Self-perceived health including sexual health, by questionnaire

6.2 Assessments

A schedule of all assessments is available in table 1. At each visit, a case report form (CRF) will be filled out. This CRF is added to the protocol (annex 1).

Screening

Screening procedures are described in chapter 3.

Enrolment visit

The enrolment visit will take place between one and five weeks after pre-screening visit. After a final check of eligibility and after answering remaining questions by the project doctor/nurse, written informed consent should be obtained. A blood sample is taken for hepatitis C and HIV PCR and for repeated HIV testing (4th generation combo test). STI check will be repeated if more than 1 month has passed since the previous STI check. The participant can now decide in which project arm he wants to be enrolled. The project doctor or nurse will ask for motives of choice by open end questionnaires; the answers will be recorded in the words of the participant by the investigator and the appropriate choice will be ticked (from several pre-defined possible options) by the investigator. Participants will be requested to complete a self-administered questionnaire on demographic information, sexual risk behaviour, lifestyle, general well-being, drug and alcohol use.

Month 1 visit

Side effects will be checked and a blood sample will be taken for creatinine and HIV test (4th generation combo test) and drug level. Urine analysis will be performed. Adherence will be addressed with pill counts and counselling.

Month 3,6,9,15,18, 21, 27, 30, 33 (3-monthly) visit

STI check and a 4th generation HIV test will be performed. Urine analysis will be performed and blood will be collected for drug levels at 1 month (serum), 3, 6, 9, 12 and 24 months (dried blood spot). Adherence will be addressed with pill counts and counselling. A short self-administered questionnaire on adherence and sexual risk behaviour will be completed.

Month 12, 24, 36 visit

Assessments as above mentioned, with additionally serum creatinine, hepatitis C antibodies and an extended self-administered questionnaire on usability, acceptability, behaviour, adherence and general wellbeing.

	screening	enrolment	month 1	month 3, 6, 9, 15, 18, 21, 27, 30, 33	month 12, 24, 36
Eligibility check	x	x			
Obtaining written informed consent	x				
STI check	x	x ¹		x	x
HIV 4th generation ELISA	x	x	x	x	x
Urine analysis for protein	x		x	x	x
Serum creatinine analysis	x		x		x
Hepatitis C antibody test					x
pooled PCR for HIV and Hepatitis C RNA		x			
Baseline questionnaire		x			
3-monthly questionnaire				x	
Yearly questionnaire					x
Pill count			x	x	x
Blood sample collection for drug level, dried blood spot will be obtained from this sample ³			x ²	x ²	x ²
Clinical Research Form (CRF)	x	x	x	x	x
AE and SAE assessment			x	x	x
online diary ⁴			x	x	x

¹ If more than 1 month between STI check and enrolment visit

² in subset

³ On month 3,6,9,12,24 time points

⁴ Daily records by participant

Table 1: Demonstration Project Assessments Schedule

7. SAFETY REPORTING

Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

AEs, SAEs and SUSARs

Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the project, whether or not considered related to PrEP. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

Adverse events in this project include: any events that lead to interruption or discontinuation of PrEP, any event considered important for safety by the investigator including renal function changes (eGFR decrease of more than 25%), any bone fractures and gastrointestinal disturbances (e.g., nausea, vomiting, diarrhoea) of grade 3 or higher according to the “DAIDS table for Grading the severity of Adult and Pediatric AEs”.

Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that at any dose: results in death; is life threatening (at the time of the event); requires hospitalisation or prolongation of existing inpatients' hospitalisation; results in persistent or significant disability or incapacity. Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

The investigator will determine SAEs and SUSARs during the project period. Severity will be graded according to the standard toxicity grading system “DAIDS table for Grading the severity of Adult and Pediatric AEs” (46). Likelihood for causality will be recorded. HIV infection and STI will not be reported as SAE, because these are study outcomes.

The investigator will report the SAEs through the web portal ToetsingOnline to the METC, within 15 days after the investigator has first knowledge of the serious adverse reactions.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered. Unexpected adverse reactions are SUSARs if the following three conditions are met: 1. the event must be serious; 2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to PrEP medication, regardless of the administered dose; 3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in the Farmacotherapeutisch kompas.

The investigator will report expedited the following SUSARs through the web portal ToetsingOnline to the METC: SUSARs that have arisen in the clinical trial that was assessed by the METC; SUSARs that have arisen in other clinical trials of the same investigator and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC. The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern. The expedited reporting of SUSARs through the web portal ToetsingOnline is sufficient as notification to the competent authority. The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

Exclusion criteria for Adverse event reporting

Adverse events do not include: pre-existing diseases or disorders present before treatment that have not worsened or hospital visit or hospitalisation for elective procedures such as cosmetic surgery.

Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC. This safety report consists of: a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study; a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of project within the Netherlands, as defined in the protocol

8. STATISTICAL ANALYSIS

8.1 Sample size calculation

Sample size

- Potential participants based on inclusion criteria: The proportion of HIV negative MSM with an STI at the STI clinic of the PHSA is 18% (4). So in the first year we will see 810 ($=4500 \times 0.18$) men who meet the first inclusion criterion (HIV negative MSM with STI) in one year. We provide approximately 120 PEP courses per year, of which around 100 in MSM. Data from the Amsterdam Cohort Studies showed that 28% of MSM practice UAI with casual partners. This would mean 1260 patients ($=4500 \times 0.28$) in the first year. At the STI clinic the percentage of UAI with casual partners is probably higher, but overlap (estimated at approximately 50%: $1260/2 = 630$ among men reporting UAI) among men who have an STI, who have UAI and who need PEP will also occur. In conclusion, we postulate that in the first year 1540 men ($=810 + 100 + 1260 - 630$) are eligible.
- In the second year, we postulate that we see 50% new unique MSM and 50 new unique MSM requesting PEP. After taking overlap into account, this results in 770 eligible MSM ($=1540 \times 0.50$).=
- So in the first 2 years we will see in total 2310 MSM ($=1540 + 770$) eligible for inclusion.
- We think that we will offer project participation to 80% (1848) of eligible MSM in a 2-year period.
- Potential participants in the PrEP arm based on data on willingness to use PrEP: At the STI clinic in Amsterdam, more than 6000 STI checks are performed yearly in 4500 unique HIV negative MSM (in 2012, personal correspondence data manager STI clinic). In a project about willingness to use PrEP among MSM from the ACS in Amsterdam, 13% had a high intention to use PrEP. Of the men with high intention to use PrEP, 55% would still use PrEP if they had to pay 50 euro per month (J. Bil, article in preparation). This adds up to around 322 ($=4500 \times 0.13 \times 0.55$) potential PrEP participants in the first year.
- We think, although we have no further data on this, that 20% ($1848 \times 0.20 = 370$) of eligible MSM will agree to participate.

- Considering our experience with longitudinal cohort studies, we estimate a yearly loss to follow-up of 15%, resulting in 85% still in care at 12 months and 72% at 24 months.
- Inclusion will start 1 March 2015 and end 1 September 2017. Participants will continue to have access to PrEP until 1 June 2018. All participants will be screened 3-monthly until 1 December 2018.

However, inclusion could be different than expected, considering the fact that PrEP uptake has been slow in the USA (47).

Person years

Total number of person years

First year: 185 participants in the first year: $185 * 0.5 = 93$ person years

Second year: 185 additional participants in the second year: $(185 * 1) + (185 * 0.5) = 278$ person years

Third year: $370 * 1 = 370$ person year

Fourth year: $370 * 0.75$ (9 months) = 278 person year

Total person years: $93 + 278 + 370 + 278 = 1019$

Loss to follow-up of 15% per year: $0.15 * 1019 = 152$ person years

Total number of person years in project after taking loss to follow-up into account: 866

8.2 Statistical testing

Baseline data analysis

Descriptive statistical analyses will be performed to describe uptake, choice of intervention strategy, acceptability, usability, baseline characteristics and barriers and motives of choice. This will be done for both all participants together and for the two intervention groups separately. The distribution of the characteristics of the two intervention groups will be compared by Chi-squared tests for categorical data and student t-test or rank sum tests for continuous data. Choice of intervention strategy will be further analysed by using univariate and multivariate logistic regression analyses to investigate the association between choice of intervention strategy and potential determinants (demographic variables, risk behaviour, acceptability, usability and barriers). Multivariate model building will be done using a step-wise backward procedure, including all variables with a univariate p value of less than 0.10. Variables will only be kept in the final multivariate model if they have a p value of less than 0.05.

Follow-up data analysis

Analyses will be performed by intention to treat and per protocol. Both quantitative and qualitative analysis will be performed.

1. Adherence will be determined and compared within groups by using different methods: self-reports, pill-counts, drug levels in blood.
2. Retention in care at 6, 12, 18 and 24 months (yes/no), switched (yes/no) and adherence (>80% versus <80%) will be further analysed by using regression methods to analyse the role of demographic variables, risk behaviour, acceptability, usability and barriers and motives as determinants of the outcomes. Variables with a p-value <0.05 in univariate analysis will be considered for inclusion in the multivariable model. These analyses will be performed for the two intervention groups separately.
3. Changes over time will be described for the following parameters: adverse events, risk behaviour, incidence of STIs. We will use appropriate univariate and multivariate statistical methods (poisson, logistic regression), corrected for repeated measurements within individuals to investigate changes over time and associated determinants. These analyses will be conducted within the two intervention groups.

4. The observed incidence rate of HIV and the occurrence of HIV resistance within the two different groups will be described using person time techniques, and modelled using poisson regression methods.
5. Changes between baseline and follow-up visits will be described within the two intervention groups for the following parameters: acceptability, usability and barriers and motives of choice. Time trends and determinants will be investigated using univariate and multivariate regression analyses.
6. Determinants of acceptability and usability will be computed by using regression analysis methods.

Sample size calculation on changes in UAI

We have several different types of endpoints, that differ from each other in type of data analyses and statistical tests that are applicable. For the outcome UAI, we performed a sample size power calculation.

If we consider 40% of all participants report UAI in the previous 6 months and in the PrEP arm we will have 250 participants, the study will have a power of 0.81 to show a significant increase in UAI prevalence to 53%, and a power of 0.85 to show a significant decrease in UAI to 27%.

9. ETHICAL CONSIDERATIONS

Regulation statement

The project will be conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

Community engagement

The MSM community in Amsterdam is involved in developing the study design. A community engagement group is formed in June 2014. It consists of individuals of the MSM community, the outreach prevention coordinator of the PHSA and the main co-investigator. This group meets regularly to give input on plans and procedures.

Recruitment and consent

Recruitment will take place at the STI clinic Amsterdam by the local team of nurses and physicians. If a person is interested in the demonstration project, he will receive further information from one of the project doctors or nurses. Information will be given in both oral and written form. The information for study participants written by the Dutch ministry of Health (<http://www.rijksoverheid.nl/ministeries/vws/documenten-en-publicaties/brochures/2014/09/01/medisch-wetenschappelijk-onderzoek-algemene-informatie-voor-de-proefpersoon.html>), will be made available to participants. No person will be obliged to participate in the project. Interested persons will be given ample opportunity to enquire about details of the project. The information should make clear that refusal to participate or withdraw from the project at any stage is without any prejudice to the subject's subsequent care. Interested persons will be allowed sufficient time to decide whether or not they wish to participate. The project coordinator is responsible for ensuring that the project team informs the participant correctly and fully, and that the team members check whether the participant understands the nature and purpose of the project.

The participant needs to give written informed consent before start of any project-related procedure. The signed informed consents will be retained by the investigator in the investigators' file and made available (for review only) to the project monitor, auditor and inspector, upon request. A copy of the signed informed consent will be given to the patient.

Confidentiality

Individual subject medical information obtained as result of this project is considered confidential and disclosure to third parties is prohibited.

Data generated as a result of this project are to be available for inspection on request by the participating physicians, the METC and the regulatory health authorities, including external site audits and inspections. All patient data are anonymised: all data are recorded with a patient identification number.

Benefits and risk assessments

Medication of choice for PrEP is a combination tablet containing emtricitabine 200 mg and tenofovir 245 mg (Truvada). Tenofovir with emtricitabine PrEP has been shown to effectively prevent HIV infection in research settings. The FDA has subsequently registered tenofovir with emtricitabine (Truvada) for this indication, but the European Medicines Agency (EMA) has not yet done so. PrEP is not considered standard care in Europe. However, performance of a placebo-controlled trial would not be ethical in the light of the available evidence. Several concerns about PrEP in a routine public health care setting need attention. The main fields of concern are risk behaviour, resistance and cost-effectiveness. Compensation of risk behaviour could potentially outweigh the protective effect of PrEP, if more unprotected sex acts would take place and more STIs would occur. Adherence is crucial in PrEP effectiveness and sub-optimal adherence leads to reduction in protective effect to HIV infection and may lead to drug-resistance in case of incident HIV infections. The financial costs of a PrEP program are high, however when prioritised to the highest risk groups, cost-effectiveness may be possible (33, 34, 34). If HIV infections are prevented, this will have a knock-on effect on the epidemic as a whole.

A strong ethical component of this project is choice. Participants will make their own decision of project arm, after being informed by a professional. This could result in better adherence and consequently in better HIV protection.

Treatment with medication inevitably involves side effects. However, tenofovir with emtricitabine has mainly mild side effects such as nausea, diarrhoea, and vertigo. Less common, but more severe side effects are elevated serum creatinine levels and renal failure. Therefore, kidney function will be checked regularly throughout the observation period.

Compensation for injury

The PHSA has a liability insurance which is in accordance with article 7, subsection 6 of the WMO.

The PHSA (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the project.

10. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

Handling and storage of data

Demographic data will be recorded at enrolment. Clinical data and information from questionnaires will be collected at each visit. Each participant will be given a unique project ID. The key code will be safeguarded and kept in a locked place by the project coordinator. Blood samples will be collected at enrolment for retrospective HIV viral load measurements in case of emergent HIV infection after enrolment, to distinguish between infection before or after enrolment. These samples will be kept until 1 year after the end of the project. All other patient samples will be stored according to the STI clinic procedures. All data will be kept until 15 years after the completion of follow-up.

Amendments

Amendments made to the research will only happen after a favourable opinion by the accredited METC has been given. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the investigator.

Annual progress report

The investigator will submit a summary of the progress of the study to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the study, serious adverse events / serious adverse reactions, other problems, and amendments.

Monitoring

Monitoring will be performed by a team from the Clinical Research Unit from the Academic Medical Center. A monitoring plan is submitted. The final and signed version will be sent to the METC after completing.

End of study report

The investigator will notify the METC of the end of the study within a period of 90 days. The end of the study is defined as the last participant's last visit. In case the study is ended prematurely, the sponsor will notify the METC within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator will submit

a final study report with the results of the study, including any publications/abstracts of the study, to the METC.

Publication policy

At the start, the project will be published at Nedtrial.nl and/or clintrials.gov.

The study outcomes will be considered for publication or presentation at scientific symposia or congresses. Authorship will follow the guidelines defined by the International Committee of Medical Journal Editors (<http://www.icmje.org>). Since participant data are recorded anonymously, privacy will be guaranteed.

11. STRUCTURED RISK ANALYSIS

Truvada (containing emtricitabine 200 mg and tenofovir 245 mg) is registered by FDA and EMEA for treatment of HIV infection since 2004 and is the most commonly used backbone of HIV treatment in many countries including the Netherlands. After the publication of HIV protective effects when used in HIV negative people at risk (21), it was registered for the indication of pre-exposure in the US in 2012. In Europe Truvada is only registered for HIV treatment, not yet for prevention.

a. Mechanism of action

Medication of choice for PrEP is Truvada (containing emtricitabine 200 mg and tenofovir 245 mg). This is a combination pill containing two different drugs of the group of the nucleoside reverse transcriptase inhibitors (NRTIs). NRTIs are developed for treatment of HIV infection. The mechanism of action is inhibition of transcription of viral RNA into DNA, which is the usual mechanism of the virus to incorporate its DNA into the DNA of the human cell, by which replication can occur. Adequate drug levels in blood and tissue can prevent the virus from transcribing its RNA into human DNA, and thus prevent a persisting HIV infection.

b. Previous exposure of human beings to the medication

Tenofovir in combination with emtricitabine is being used for HIV treatment since 2004, and the individual components emtricitabine and tenofovir since 2001 and 2003. Tenofovir with emtricitabine PrEP has been shown to effectively prevent HIV infection in research settings (21). The FDA has subsequently registered tenofovir with emtricitabine for this indication, but the EMEA has not yet done so.

c. Previous investigations in animals or ex vivo.

Before registration, tenofovir with emtricitabine has been tested both in animals and ex-vivo. Since registration in 2003, tenofovir with emtricitabine has been used extensively in HIV positive people. This has resulted in many clinical data on effectiveness and safety.

d. Selectivity of the mechanism to target tissue in animals and/or humans.

This point is not applicable, as anti-HIV effectiveness has already been proven in clinical trials

e. Analysis of the potential effect

Tenofovir with emtricitabine use is safe. It is the most-used antiviral drug in many high-income countries, including the Netherlands. Risk-benefit analyses for tenofovir with emtricitabine have previously turned out positive. Treatment with medication inevitably involves side effects. Tenofovir and emtricitabine have mainly mild side effects such as nausea, diarrhoea, and vertigo. Less common, but more severe side effects are elevated serum creatinine levels and renal failure. Therefore, kidney function will be checked regularly throughout the project.

f. Pharmacokinetic considerations

Tenofovir and emtricitabine pharmacokinetics are well known and described in the *farmacotherapeutisch Kompas* (<http://www.farmacotherapeutischkompas.nl>).

g. Project population

The project population will consist of healthy, HIV negative MSM with a high risk of HIV seroconversion.

h. Interaction with other products

Interactions of tenofovir and emtricitabine with other medication have been described in chapter 5.

i. Predictability of effect

Several randomised controlled trials, described in table 1, demonstrated protection against acquisition of HIV by tenofovir with emtricitabine in HIV negative people with a high risk of HIV seroconversion.

j. Can effects be managed?

In case of serious side effects such as decreased renal function, it is sufficient to stop the medication. Renal function will improve. Previously, tenofovir with emtricitabine could be restarted without problems in these cases.

In conclusion, safety of tenofovir with emtricitabine is good and risks are negligible. Side effects are rare, mostly non-severe and well-manageable.

12. REFERENCES

Reference List

1. van Veen MG, Presanis AM, Conti S, Xiridou M, Stengaard AR, Donoghoe MC, *et al.*
National estimate of HIV prevalence in the Netherlands: comparison and applicability of different estimation tools. *AIDS* 2011; **25**:229-237.
2. Stichting HIV monitoring. **Monitoring report 2014.** Published in 2014.
3. SOA AIDS Nederland. **Onder controle: strategie voor de aanpak van soa's en hiv onder MSM in Nederland, 2013-2018.** Published in 2013.
4. STI clinic Amsterdam. **Yearly report 2013.** Published in 2014.
5. Bezemer D, de WF, Boerlijst MC, van SA, Hollingsworth TD, Fraser C. **27 years of the HIV epidemic amongst men having sex with men in the Netherlands: an in depth mathematical model-based analysis.** *Epidemics* 2010; **2**:66-79.
6. Jansen IA, Geskus RB, Davidovich U, Jurriaans S, Coutinho RA, Prins M, *et al.*
Ongoing HIV-1 transmission among men who have sex with men in Amsterdam: a 25-year prospective cohort study. *AIDS* 2011; **25**:493-501.
7. Beyrer C, Baral SD, Weir BW, Curran JW, Chaisson RE, Sullivan PS. **A call to action for concentrated HIV epidemics.** *Curr Opin HIV AIDS* 2014; **9**:95-100.
8. Menza TW, Hughes JP, Celum CL, Golden MR. **Prediction of HIV acquisition among men who have sex with men.** *Sex Transm Dis* 2009; **36**:547-555.
9. Smith DK, Pals SL, Herbst JH, Shinde S, Carey JW. **Development of a clinical screening index predictive of incident HIV infection among men who have sex with men in the United States.** *J Acquir Immune Defic Syndr* 2012; **60**:421-427.

10. Bernstein KT, Marcus JL, Nieri G, Philip SS, Klausner JD. **Rectal gonorrhea and chlamydia reinfection is associated with increased risk of HIV seroconversion.** *J Acquir Immune Defic Syndr* 2010; **53**:537-543.
11. Heuker J, Sonder GJ, Stolte I, Geskus R, van den Hoek A. **High HIV incidence among MSM prescribed postexposure prophylaxis, 2000-2009: indications for ongoing sexual risk behaviour.** *AIDS* 2012; **26**:505-512.
12. F.van Griensven. **Going Dutch: towards a new Amsterdam Level; About reducing the capitol's HIV events.** Published in 2013.
13. Heijman T, Geskus RB, Davidovich U, Coutinho RA, Prins M, Stolte IG. **Less decrease in risk behaviour from pre-HIV to post-HIV seroconversion among MSM in the combination antiretroviral therapy era compared with the pre-combination antiretroviral therapy era.** *AIDS* 2012; **26**:489-495.
14. Kelly BC, Mustillo SA, Stolte IG, Prins M, Davidovich U. **The Impact of the Introduction of Combination Antiretroviral Therapy on Substance Use within the Gay Community: A Longitudinal Analysis.** *abstract* for AIDS impact conference 2013.
15. Heiligenberg M, Wermeling PR, van Rooijen MS, Urbanus AT, Speksnijder AG, Heijman T, *et al.* **Recreational drug use during sex and sexually transmitted infections among clients of a city sexually transmitted infections clinic in Amsterdam, the Netherlands.** *Sex Transm Dis* 2012; **39**:518-527.
16. Marrazzo J Ramjee G NGPTMB. **Pre-exposure Prophylaxis for HIV in Women: Daily Oral Tenofovir, Oral Tenofovir/Emtricitabine, or Vaginal Tenofovir Gel in the VOICE Study (MTN 003).** Published at CROI in 2013.

17. Damme van L, Corneli A, Ahmed K, Agot K, Lombaard J, Kapiga S, *et al.*
Preexposure prophylaxis for HIV infection among African women. *N Engl J Med* 2012; **367**:411-422.
18. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, *et al.* **Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana.** *N Engl J Med* 2012; **367**:423-434.
19. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, *et al.*
Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med* 2012; **367**:399-410.
20. Choopanya K, Martin M, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, *et al.* **Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial.** *Lancet* 2013; **381**:2083-2090.
21. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, *et al.*
Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010; **363**:2587-2599.
22. Grant RM, Anderson PL, McMahan V, Liu A, Amico KR, Mehrotra M, *et al.*
Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. *Lancet Infect Dis* 2014; **14**:820-829.
23. Volberding PA, Deeks SG. **Antiretroviral therapy for HIV infection: promises and problems.** *JAMA* 1998; **279**:1343-1344.

24. PROUD investigators. **PROUD study interim analysis finds pre-exposure prophylaxis (PrEP) is highly protective against HIV for gay men and other men who have sex with men in the UK.** Published in 2014.
25. Fonsart J, Capitant C, Spire B, Cotte L, Pialoux G, Lorente N, *et al.* **High Adherence Rate to Intermittent Oral PrEP with TDF/FTC among High Risk MSM (ANRS Ipergay).** Published in 2014.
26. Smith DK, Grant RM, Weidle PJ, Lansky A, Mermin J, Fenton KA. **Interim Guidance: pre-exposure prophylaxis for the prevention of HIV in Men who have sex with men.** Published in 2011. pp. 65-68.
27. US public health service. **Pre-exposure prophylaxis for the prevention of HIV infection in the United States - 2014.** Published in 2014.
28. WHO. **Guidance on pre-exposure oral prophylaxis (PrEP) for serodiscordant couples, men and transgender women who have sex with men at high risk of HIV: Recommendations for use in the context of demonstration projects.** Published in 2012.
29. WHO. **Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations.** Published in 2014.
30. SOA AIDS Nederland, Aids fonds. **Advies biomedische preventie van hiv in Nederland 2013.** Published in 2013.
31. Juusola JL, Brandeau ML, Owens DK, Bendavid E. **The cost-effectiveness of preexposure prophylaxis for HIV prevention in the United States in men who have sex with men.** *Ann Intern Med* 2012; **156**:541-550.

32. Paltiel AD, Freedberg KA, Scott CA, Schackman BR, Losina E, Wang B, *et al.* **HIV preexposure prophylaxis in the United States: impact on lifetime infection risk, clinical outcomes, and cost-effectiveness.** *Clin Infect Dis* 2009; **48**:806-815.
33. Schackman BR, Eggman AA. **Cost-effectiveness of pre-exposure prophylaxis for HIV: a review.** *Curr Opin HIV AIDS* 2012; **7**:587-592.
34. Desai K, Sansom SL, Ackers ML, Stewart SR, Hall HI, Hu DJ, *et al.* **Modeling the impact of HIV chemoprophylaxis strategies among men who have sex with men in the United States: HIV infections prevented and cost-effectiveness.** *AIDS* 2008; **22**:1829-1839.
35. Schneider K, Gray RT, Wilson DP. **A cost-effectiveness analysis of HIV pre-exposure prophylaxis for men who have sex with men in Australia.** *Clin Infect Dis* 2014.
36. Cremin I, Alsallaq R, Dybul M, Piot P, Garnett G, Hallett TB. **The new role of antiretrovirals in combination HIV prevention: a mathematical modelling analysis.** *AIDS* 2013; **27**:447-458.
37. Pretorius C, Stover J, Bollinger L, Bacaer N, Williams B. **Evaluating the cost-effectiveness of pre-exposure prophylaxis (PrEP) and its impact on HIV-1 transmission in South Africa.** *PLoS One* 2010; **5**:e13646.
38. Gomez GB, Borquez A, Case KK, Wheelock A, Vassall A, Hankins C. **The cost and impact of scaling up pre-exposure prophylaxis for HIV prevention: a systematic review of cost-effectiveness modelling studies.** *PLoS Med* 2013; **10**:e1001401.
39. Desai K, Sansom SL, Ackers ML, Stewart SR, Hall HI, Hu DJ, *et al.* **Modeling the impact of HIV chemoprophylaxis strategies among men who have**

sex with men in the United States: HIV infections prevented and cost-effectiveness. *AIDS* 2008; **22**:1829-1839.

40. Buchbinder SP, Glidden DV, Liu AY, McMahan V, Guanira JV, Mayer KH, *et al.* **HIV pre-exposure prophylaxis in men who have sex with men and transgender women: a secondary analysis of a phase 3 randomised controlled efficacy trial.** *Lancet Infect Dis* 2014; **14**:468-475.
41. Stolte IG, Dukers NH, Geskus RB, Coutinho RA, de Wit JB. **Homosexual men change to risky sex when perceiving less threat of HIV/AIDS since availability of highly active antiretroviral therapy: a longitudinal study.** *AIDS* 2004; **18**:303-309.
42. Schechter M, do Lago RF, Mendelsohn AB, Moreira RI, Moulton LH, Harrison LH. **Behavioral impact, acceptability, and HIV incidence among homosexual men with access to postexposure chemoprophylaxis for HIV.** *J Acquir Immune Defic Syndr* 2004; **35**:519-525.
43. Marcus JL, Glidden DV, Mayer KH, Liu AY, Buchbinder SP, Amico KR, *et al.* **No evidence of sexual risk compensation in the iPrEx trial of daily oral HIV preexposure prophylaxis.** *PLoS One* 2013; **8**:e81997.
44. Young I, McDaid L. **How acceptable are antiretrovirals for the prevention of sexually transmitted HIV?: A review of research on the acceptability of oral pre-exposure prophylaxis and treatment as prevention.** *AIDS Behav* 2014; **18**:195-216.
45. Kippax S. **Effective HIV prevention: the indispensable role of social science.** *J Int AIDS Soc* 2012; **15**:17357.

46. Division of AIDS. **DAIDS table for Grading the severity of Adult and Pediatric AEs**. Published in 2004.
47. Kirby T, Thornber-Dunwell M. **Uptake of PrEP for HIV slow among MSM**. *Lancet* 2014; **383**:399-400.