



CLINICAL STUDY PROTOCOL

Protocol no.: SMR-3395

Title: Evaluation of implementation of pre-exposure prophylaxis (PrEP) in subjects at particular risk of infection with human immunodeficiency virus (HIV).

Indication: Pre-exposure prophylaxis (PrEP) for HIV

Investigational medicinal product: Emtricitabine/tenofovir disoproxil combination tablet (FTC/TDF)

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Sponsor:

Oslo University Hospital (OUH)

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PROTOCOL OUTLINE

Working title		Implementation of pre-exposure prophylaxis (PrEP) in subjects at particular high risk for human immunodeficiency virus (HIV) acquisition - an evaluation study.
Study objectives		<ul style="list-style-type: none">Assess the impact of PrEP on the sexual and psychological health of PrEP usersIncidence of sexually transmitted infections (STIs) in PrEP users compared to those not taking PrEPAssessment of drug complianceIncidence of HIV seroconversion despite PrEPFrequency and development of drug resistance in subjects who HIV-seroconvert (if any)
Selection criteria (abbreviated)	Inclusion	<ol style="list-style-type: none">Male, female or transgender persons aged \geq 18 years who are offered or have started PrEP in routine clinical practice, and 2, 3, 4, 5, 6 or 7 (below).Men who have sex with men (MSM) and transgender persons;<ol style="list-style-type: none">who have had unprotected anal sex with two or more partners during the last six months and/orwho have had bacterial sexually transmittable infection(s) during the last twelve months and/orwho have used post-exposure prophylaxis(PEP) during the last twelve months and/orwho use recreational drugs when having sexIndication for PrEP is present according to the assessment of the health care providerMen and women who are at high risk of HIV according to their sexual practicesHIV-negative partner of a HIV-positive person not yet virologically suppressed by antiretroviral therapy (ART)Sex workers with inconsistent condom usePersons with inconsistent condom use with sexual partners in / from countries with a high prevalence of HIV (COHP)
	Exclusion	<ol style="list-style-type: none">HIV positive subjectsSubjects who cannot take FTC/TDF due to contraindications
	Control group	<ol style="list-style-type: none">Enrolled patients will be regarded as their own control when it comes to their sexual health and quality of life reported for period prior to inclusion in the study.Subjects diagnosed with HIV in general clinical practice and referred to the out-patient clinic at the Dept. of Infectious Diseases, OUS, for details, see 3.3.2.Frequency of STI reported to the National Institute of Public Health (MSIS) will be compared with the frequency of STIs in the study cohort.
Methods & procedures		<p>PrEP assessment occurs on designated clinic days at The Olafia clinic and will be performed by a team of doctors and nurses specifically trained in PrEP assessment. Persons may be self-referred or referred from other health providers for PrEP assessment. At other sites this will be organized according to the local resources.</p> <p>Subjects will be provided with written and oral information about the study and invited to sign an informed consent form. Subjects not consenting to participation in the study will still be offered PrEP (if indicated) and follow up according to national (NFIM) and local (Olafiaklinikken) guidelines.</p> <p>Subjects who sign the consent form will go through an enrolment procedure to ensure that the PrEP treatment is indicated according to inclusion/exclusion criteria (based on national and local guidelines). Study participants will be asked to complete a questionnaire with detailed information on demographics, medical history, sexual behaviour the last 6 months, perception of HIV risk at the last condomless sex, risk management strategies, personal history of STIs, HIV& STI testing frequency and drug/</p>



		<p>alcohol use.</p> <p>Subject will be screened for the following STIs during the enrolment visit: HIV, syphilis, hepatitis A/B/C, <i>Chlamydia trachomatis</i>, <i>Neisseria gonorrhoea</i>, and <i>Mycoplasma genitalium</i>.</p> <p>Participants will be asked to return approximately one week later to discuss their HIV result and whether they wish to proceed with initiation of PrEP.</p> <p>The decision regarding initiation of continuous or intermittent PrEP is based on a discussion with the subject and study team (doctor/nurse), subjects' personal preference, medical considerations and whether the expected use will surpass more than 15-20 tablets of FTC/TDF per month.</p> <p>HIV testing will be repeated at 2, 4 and 8 weeks from the most recent high risk exposure (for HIV acquisition) prior to initiation of PrEP. Thereafter participants are requested to visit the clinic every 3 months from PrEP initiation (for the next 24 months) for HIV & STI testing, evaluation of compliance (blood test for drug monitoring in continuous PrEP arm, drug diaries in both continuous and intermittent PrEP arms), assessment of clinical and/or biochemical adverse reactions and quality of life and sexual behaviour assessment. Subjects will be asked to answer the same questions regarding sexual behaviour and quality of life at follow up visits as at inclusion study visit.</p>
Statistics	Sample size	Not applicable
	Methods	Categorical variables will be described by means of absolute and relative frequencies, while continuous variables by means of mean, standard deviation, quartiles, min and max.



LIST OF ABBREVIATIONS

AE	Adverse Event
ART	Anti retroviral therapy
COHP	Country of high prevalence of HIV
CRA	Clinical Research Associate
CRF	Case Report Form
CSR	Clinical Study Report
CT	Chlamydia trachomatis
DM	Data Manager
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	The European Medicines Agency
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ITT	Intention-To-Treat
MG	Mycoplasma genitalium
MSM	Men who have sex with men
NG	Neisseria gonorrhoea
PI	Principal Investigator
PIS	Patient Information Sheet
PrEP	Pre-Exposure Prophylaxis
SAE	Serious Adverse Event
SD	Standard Deviation
SDV	Source Data Verification
SUSAR	Suspected Unexpected Serious Adverse Reaction
STI	Sexually Transmitted Infections
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil fumarate



1 INTRODUCTION

Pre-exposure prophylaxis (PrEP) is the pre-emptive use of drugs to prevent disease in people who have not yet been exposed to the disease-causing agent. In July 2016 the European Medicine Agency (EMA) recommended that the EU commission should grant a marketing approval for Truvada® (tenofovir disoproxil fumarate + emtricitabine) as PrEP in combination with safer sex practices to reduce the risk of sexually acquired HIV infections. The Committee for Medicinal Products for Human Use (CHMP) based their decision on clinical trials which show substantial reduction in risk for HIV infections when Truvada® was used as PrEP. Truvada® is approved for PrEP in USA since 2012.

The introduction of PrEP is mainly based on two studies, the IPERGAY (Molina JM. Et al., 2015) and PROUD studies (McCormack S et al., 2016). In these two studies Truvada® was given "on demand" or continuously, respectively. The protective effect was comparable in the two studies at 86%. In people who have high risk sex several times per week the risk for HIV acquisition is ongoing and continuous HIV protection is required. On the other hand individuals who have high risk sex on a predictable, yet infrequent basis may not need continuous PrEP. In the latter case intermittent ("on demand") PrEP may be more appropriate.

Intermittent PrEP should reduce cost and the risk of adverse drug reactions as drug exposure is minimized. The Norwegian National Guidelines on HIV management (NFIM) and European guidelines (EACS) recommend both intermittent and continuous PrEP as options based on the frequency of risk behaviour.

Descovy® (tenofovir alafenamide + emtricitabine) is a newer alternative to Truvada® with less risk of renal adverse effects. Many HIV physicians are replacing Truvada® with Descovy® as NRTI backbone. Studies are ongoing to evaluate Descovy® as PrEP.

The incidence of bacterial STIs appears to have increased in some settings where PrEP has been available, whilst others report a decreased incidence of bacterial STIs in PrEP users. It is important to see what implications PrEP will have on the incidence of STIs and sexual behaviour of PrEP users in Norway.

Drug resistance is an important factor in HIV treatment. Usually HIV drug resistance occurs in an individual as a result of poor adherence to ART. Alternatively, HIV drug resistance may be acquired at the time of transmission if infected by a person already harbouring a resistant virus, i.e. transmitted drug resistance. On a worldwide basis, three cases of HIV seroconversions despite good PrEP adherence have been reported [Knox D et al. 2016]. In one case, the PrEP user was infected by a virus resistant to tenofovir + emtricitabine. According to national surveillance data for drug resistance among newly diagnosed patients in Norway, the frequency of tenofovir and/or emtricitabine resistance is low: in 2015, two of the 149 samples tested were resistant to emtricitabine (1%), and none to tenofovir

In existing guidelines in Europe and US, there is a consensus that PrEP should be made available for those at highest risk of HIV infection. This particularly includes men who have sex with men (MSM) and male to female transgender persons, based on the incidence of HIV infection, individual risk behaviour and other factors affecting sexual behaviour.

The World Health Organization (WHO)'s guidelines for PrEP (from 2015) identify populations with a HIV infection incidence of 3 per 100 persons/ year. These include sub-populations of MSM, male to female transgender persons and heterosexuals with a HIV positive partner not virologically suppressed. The risk will vary and will be evaluated in each individual case.

The European AIDS Clinical Society (EACS) guidelines recommend that PrEP should be considered for HIV negative MSM and transgender persons who are inconsistent in their use of condoms when having sex with casual partners or HIV positive partners who are not on treatment. Centre for Disease Control and Prevention (CDC) in US recommend PrEP to MSM with high risk of HIV infection, based on individual risk. As in several other countries, e.g. the United Kingdom, The Netherlands and France, the Norwegian Associations for Infectious



Diseases has settled on a similar definition of risk and recommend PrEP to the similar target populations in its guidelines.

The number of sexually active homosexual, bisexual or other MSM in Norway is unknown. Based on previous national and international population studies, the proportion of MSM in the male population is estimated to be between 3-7%. Although MSM constitute a relatively small proportion of the male population, the group represent more than half of the annual HIV cases. This indicates a substantial risk of HIV among MSM.

In the UN's new political declaration about HIV and AIDS June 2016, MSM were estimated to have 24 times higher risk of HIV infection than other adults in the general population. Similarly, transgender persons were estimated to have 49 times higher risk of HIV than other adults in the general population. PrEP is mentioned in the declaration as one of several biomedical interventions that should be considered to reach the goal to eliminate HIV and AIDS within 2030.

In EU and EEA there has been an increase in new HIV cases among MSM. 53% of all new HIV cases are found among MSM and this group is the only group of the population that show an increase in new HIV cases.

Based on the national HIV surveillance figures, MSM are the obvious target group for PrEP in Norway as MSM constitute by far the largest single group that contract HIV infection. During the period 1986-2016 MSM constituted 32,8% of all HIV cases reported to the National Institute of Public Health (NIPH). In 2016 a total of 220 new HIV diagnosis were registered of whom 70 acquired their HIV infection in their country of origin prior to immigration and thus not eligible for preventive measures. Among the 150 new HIV cases in people residing in Norway and eligible to preventive measures, MSM were over-represented with 87 (58%) new HIV infections. The majority of new infections found in MSM occurred as a result of sex with a casual partners either in Norway or abroad. An increasing proportion of new infections among MSM occurred abroad in 2016 (59%) while new infections among MSM acquired in Norway remained stable.

Despite the significant preventive efforts to reduce HIV infections in the past decades, the incidence in MSM has plateaued at a higher level after the turn of the millennium. In 2015 a reduction in newly diagnosed HIV cases was reported for the first time. Early detection of HIV and treatment as prevention may have played a positive role in reducing HIV transmission, however, numbers increased again in 2016. Over 90% of HIV positive MSM in Norway are treated and virologically suppressed and thereby considered not infectious.

Since the early days of the HIV epidemic, changes in sexual behaviour and increased use of condoms have been advocated and the only tools available to prevent HIV transmission. Later, frequent testing and treatment of STIs (including HIV) have been added to the preventive measures available. Still, this does not seem to be sufficient for all MSM. The use of PrEP is therefore likely an important supplement to prevent HIV infections in MSM at high risk for HIV acquisition.

In 2016 the incidence of HIV dropped by 30-40% among MSM in London. Participation in PROUD and the availability of PrEP (for those who can purchase it privately) has been proposed as the main reason for this substantial drop in the incidence [press release 56 Dean Street].

1.1 Aim of Present Study

The main objective of this study is to monitor the impact of PrEP on the subject's psychological and sexual health. It is also important to monitor the adherence to PrEP, development of drug resistance (in the case of undetected HIV infection at initiation of PrEP), frequency of other STIs, changes in sexual behaviour, recreational drug use and quality of life. PrEP has proven to be effective in reducing the sexual acquisition of HIV, however this requires that the medication is taken as prescribed, whilst the subject is exposed to high risk of infection.



2 OBJECTIVES

This study is designed to evaluate implementation of PrEP treatment as a part of the general HIV preventive program in Norway. The target groups are mainly MSM and transgender persons at high risk of HIV infection, as well as other subjects at risk of HIV infection due to their sexual practices.

Objectives include assessment of the following:

- Assess the impact of PrEP on the sexual and psychological health of PrEP users
- Incidence of sexually transmitted infections (STIs) in PrEP users compared to those not taking PrEP
- Assessment of drug compliance
- Incidence of HIV seroconversion despite PrEP
- Frequency and development of drug resistance in subjects who HIV-seroconvert (if any)

3 POPULATION

3.1 Inclusion Criteria

In order to participate in the PrEP arm of this study the subjects must meet all of the following inclusion criteria:

1. Male, female or transgender persons aged ≥ 18 years who are offered or have started PrEP in routine clinical practice, and 2, 3, 4, 5, 6 or 7 (below).
2. Men who have sex with men (MSM) and transgender persons;
 - a. who have had unprotected anal sex with two or more partners during the last six months and/or
 - b. who have had bacterial sexually transmittable infection(s) during the last twelve months and/or
 - c. who have used post-exposure prophylaxis(PEP) during the last twelve months and/or
 - d. who use recreational drugs when having sex
3. Indication for PrEP is present according to the assessment of the health care provider
4. Men and women who are at high risk of HIV according to their sexual practices
5. HIV-negative partner of a HIV-positive person not yet virologically suppressed by antiretroviral therapy (ART)
6. Sex workers with inconsistent condom use
7. Persons with inconsistent condom use with sexual partners in / from countries with a high prevalence of HIV (COHP)

Subjects who are included in the PrEP arm will act as their own controls regarding possible changes in psychological and sexual health. At the screening visit they will complete questionnaire requesting information related to last 6 months prior to study start. Individuals who seroconvert during the observational period will be transferred to the out-patient clinic for Infectious Diseases as is already standard of care.

Patients diagnosed with HIV in general clinical practice and referred to the out-patient clinic at the Dept. of Infectious Diseases, OUS, will be asked to act as controls to assess their past psychological and sexual health. They will be asked to sign the consent form and answer the same questionnaire as those in the PrEP arm but not followed further in this study.

Frequency of STI reported to the National Institute of Public Health (MSIS) will be compared with the frequency of STIs in the study cohort.

3.2 Exclusion Criteria



In order to participate in the study subjects must not meet any of the following exclusion criteria:

1. HIV positive subjects
2. Subjects who cannot take FTC/TDF due to contraindications

3.3 Control Group

Subject to be included in the control group:

1. Enrolled patients will be regarded as their own control when it comes to their sexual health and quality of life reported for period prior to inclusion in the study.
2. Subjects newly diagnosed with HIV in general clinical practice and referred to the out-patient clinic at the Dept. of Infectious Diseases, OUS, who meet the following inclusion and exclusion criteria:
 - a. Inclusion criteria in the control group:
 - i. Confirmed positive HIV-test, AND
 1. Confirmed negative HIV-test < 12 months ago, OR
 2. Self-reported assumed time of infection < 12 months ago, AND
 - ii. Resident for > 6 months in a country of one of the following regions (EU/EFTA, North America or Australia/New Zealand) at the time of confirmed or assumed infection.
 - b. Exclusion criteria in the control group:
 - i. Confirmed positive HIV-test > 12 months ago, OR
 - ii. Self-reported assumes time of infection > 12 months ago.
3. Frequency of STI reported to the National Institute of Public Health (MSIS) will be compared with the frequency of STIs in the study cohort.

3.4 Recruitment and Screening

Individuals attending the clinic for PrEP assessment are either referred from other health care providers or referred by themselves (self-referral).

Those who have commenced PrEP elsewhere (abroad, purchased themselves, another provider) and attend for "PrEP follow-up" either at Olafiaklinikken or a corresponding venereological clinic/study site in Norway, may also be included in the study.

Eligible subjects will have the study explained to them, and will receive the written informed consent form (ICF). After having had the time to review the nature of the study, they will have the opportunity to ask questions to the investigating team. If the subject agrees to participate, they will be asked to sign and date one original written informed consent form (ICF). The subject will then receive a copy of the signed and dated patient information/informed consent form. The original signed ICF will be filed in the Investigator Site File (ISF). The PIS will contain site contact information in case of any questions or medical emergency.

Newly diagnosed HIV positive individuals referred to the out-patient clinic of the Dept. of Infectious Diseases, OUS, will be invited to participate as controls. The inclusion and exclusion criteria for the control group aim at including newly infected individuals (< 12 months) residing in a country for > 6 months where PrEP might have been available, and excluding individuals infected long time ago in a country where PrEP was inaccessible; i.e. mostly countries with high HIV-prevalence outside the EU/EFTA-region, North America and Australia/New Zealand. They will be presented with the same consent form and questionnaire on sexual and psychological health prior to the HIV diagnosis.

Any written information given to potential subjects will be submitted to, and approved by, the Ethics Committee(s) prior to implementation.



3.5 Subject Withdrawal

In accordance with the Declaration of Helsinki, the Investigator must explain to the subject that they have the right to withdraw from the study at any time, and that this will in no way prejudice their future treatment. The reason for any kind of withdrawal should be recorded on the appropriate CRF.

If a subject is proven HIV positive when using PrEP, the treatment should be stopped immediately to prevent development of resistance, registered as a PrEP failure, and referred to the Dept. of Infectious Diseases for regular follow-up of their HIV infection and checked for resistance to tenofovir disoproxil fumarate and emtricitabine (as is already standard clinical practice).

4 TREATMENT PROCEDURES

4.1 Study plan

The observation will begin after the subjects have signed the informed consent form. PrEP treatment should then be initiated when the HIV antibody/antigen test (4th generation test) taken at the first visit is confirmed negative.

However, the window period to rule out HIV infection is 12 weeks. It is not desirable that participants are undergoing HIV seroconversion when they commence PrEP, however the study population is per definition at high-risk for HIV acquisition. It is likely that the majority of the participants will not be in a position to abstain from sex or use condoms effectively for a 12 week period. Therefore it is NOT recommended to delay PrEP pending a negative HIV test results 12 weeks from the last high risk exposure. International and national guidelines do not recommend delaying PrEP initiation in this high risk group for HIV acquisition. Per definition, those in need for PrEP are at high risk for HIV acquisition justifying PrEP initiation even at first visit.

For those who have had high risk exposure within 14 days prior to screening, a HIV-DNA provirus test should be requested and the serum test for HIV should be repeated at 2 weeks, 4 weeks and 8 weeks and 12 weeks from the day they commenced PrEP.

Subjects that have already commenced PrEP treatment can be included in the study. These subjects will be requested to consent to collection of historical medical information from the date when the PrEP treatment was initiated.

Follow-up visits are according to clinical practice, clinical judgement and standard patient management described in SmPC. For those outside the window period for HIV infection a standard visit at 4 weeks and 12 weeks post initiation of PrEP and thereafter every 3 months during the PrEP treatment for 24 months. Where clinically indicated the subject may attend the clinic between 3 months' follow-up visits. Data from these visits will be collected as Extra Clinical Visits.

4.2 Variables

Subjects will be treated according to local prescribing information and clinical judgement and assessments performed according to site clinical practice. The inclusion period will last from final approval from The Regional Ethical Committee and until end of 2018.

Data on demographics, sexual health including sexual behaviour, HIV infection status, STIs, compliance and recreational drug use will be collected at the baseline visit, 3 months' follow-up visits, end of study visit and relevant extra visits. HIV-tests will also be taken at weeks 2, 4 and 8 in order to identify people in the seroconversion phase at inclusion to reduce risk of development of drug resistance. For subjects at particular high risk for HIV infection prior to PrEP treatment, HIV-DNA provirus testing will be assessed at the first visit according to the doctor's clinical judgement. As a measure of adherence blood samples will be drawn and the tenofovir disoproxil fumarate (TDF) concentration in plasma will be measured as well as a self-reported drug protocol.



Investigators are asked to report the requested data in the electronic Case Report Form (eCRF).

Table 1 Data collection and visit structure

Study Visits ¹	Visit 0 (evaluation)	Visit 1(start of treatment)	Visit 2 (week 2)	Visit 3 (week 4)	Visit 4 (week 8)	Follow-up visits (approx. every 3 months)	Extra visits	End of study visit (24 months after start of treatment)
Clinic visits	x			x		x ¹	x	x
Informed consent	X							
Assess eligibility criteria	x	x						
Demography	X							
HIV test ²	x		x	x	x	x	x ³	x
HIV-DNA provirus ⁴	x ⁴	x ⁴						
History of STI	x							
STI screening	x					x	x ³	x
Bloodsample for TFV-PD plasma concentration				x		x ⁵	x ^{3,5}	x ⁵
Questionnaire sexual behaviour (start of treatment)	x					x		x
Questionnaire sexual behaviour (follow-up)	x					x		x
Compliance				x		x	x	x
Adverse events				x		x	x	x
Subject diary				x		x		x

¹ clinic visits to be schedule to fit with PrEP treatment guidelines and local clinical practice. At each visit assessments as indicated in table should be captured in the database if they are conducted.

² If a subject is infected with HIV during PrEP treatment resistance of the HIV virus for emtricitabine and tenofovir disoproxil fumarate should be checked.

³ If clinically indicated

⁴ If high risk sexual contact within the last 14 days

⁵ only applicable for subject on continuous PrEP treatment

4.3 Adverse Events and Serious Adverse Events

4.3.1 General

The Investigator should ask the subject questions during the clinic visits in order to ensure that appropriate adverse event information is recorded in the subject's source notes and is then subsequently entered into the CRF. Adverse events will be recorded in response to the following question - "Since you were last asked have you felt unwell or different from usual in any way?" All relevant responses from the subject will be recorded in the CRF on an adverse



event form and graded on severity, seriousness and relationship to study medication. For further details regarding the classification of adverse events see below.

Subjects will be questioned regarding any signs and symptoms occurring in the screening period and for baseline signs and symptoms prior to the first dose of study medication on Day 1. Subjects will subsequently be questioned regarding adverse events throughout the study. All adverse events are to be reviewed by the Investigator while on-going and subsequently documented at the point of resolution. All adverse events classified as serious are to be immediately brought to the attention of the Investigator by site staff for review and action in accordance with Section 4.4.5 below.

All on-going adverse events will be followed up by the Investigator until subject discharge or resolution. Additional clinic visits may be scheduled by the Investigator to follow-up on adverse events according to their clinical judgement.

4.3.2 Seriousness

- Adverse Events (AE): any untoward medical occurrence in a subject or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. This includes clinically significant laboratory abnormalities as judged by the Investigator.
- Serious Adverse Events (SAE) are defined as: any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. Events otherwise considered serious by the Investigator should also be reported as SAEs. Malignancy would in most cases fall into that category. The medical occurrence or effect does not need to be related to the study medication.

4.3.3 Severity

Severity is classified according to the Common Terminology Criteria for Adverse Events (CTCAE v.4.03):

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

4.3.4 Relationship to study medication

- Unrelated: This category is applicable to those adverse events which, after careful medical consideration at the time of evaluation, are judged to be clearly and incontrovertibly due to extraneous causes (disease, environment, etc.) and do not meet the criteria for study medication relationship listed under remote, possible or probable.
- Unlikely: In general, this category is applicable to those adverse events that, after careful medical consideration at the time they are evaluated, are judged to be remotely related to the test study medication. An adverse event may be considered remote if, or when, for example: (i) it does not follow a reasonable temporal sequence from administration; (ii) it could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (iii) it does not follow a known response pattern to the suspected study medication; (iv) it does not reappear or worsen when the study medication is re-administered.
- Possible (must have first two criteria): This category is applicable to those adverse events which, after careful medical consideration at the time they are evaluated, the connection with the test study medication administration appears unlikely but cannot be ruled out with certainty. An adverse event may be considered possible if, or when: (i) it follows a reasonable temporal sequence from administration; (ii) it could readily have been



produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (iii) it follows a known response pattern to the suspected study medication; (iv) it does not reappear or worsen when the study medication is re-administered.

- Probable (must have first three criteria): This category is applicable to those adverse events, which, after careful medical consideration at the time they are evaluated, the connection with the test study medication administration appears to, with a high degree of certainty, be related to the test study medication. An adverse event may be considered probable if: (i) it follows a reasonable temporal sequence from administration; (ii) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (iii) it disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the study medication, yet study medication-relatedness exists; e.g. bone marrow depression, fixed study medication eruptions, and tardive dyskinesias; (iv) it follows a known response pattern to the suspected study medication; (v) it reappears upon rechallenge.
- Not assessable: When it is not possible to assign the event to any of the criteria above categories.

4.3.5 Serious adverse reactions and unexpected adverse reactions

Definitions

Adverse Reaction: all untoward and unintended responses to an investigational medicinal product related to any dose administered.

Unexpected adverse reaction: an adverse reaction, the nature or severity of which is not consistent with summary of product characteristics for Truvada® (http://www.ema.europa.eu/docs/no_NO/document_library/EPAR_-_Product_Information/human/000594/WC500043718.pdf).

Suspected Unexpected Serious Adverse Reaction (SUSAR): any serious adverse reaction that might be related to the study medication and is unexpected according to the definition above.

4.3.6 Reporting of suspected unexpected serious adverse reactions by Investigator

Suspected unexpected serious adverse reactions (SUSARs) will be reported by the investigator according to appropriate Competent Authority and Ethics Committee requirements. SUSAR reporting to the Competent Authorities and Ethics Committees will be performed in writing using CIOMS forms, according to local regulations.

Fatal and life-threatening SUSARs should be reported as soon as possible to the Competent Authorities and Ethics Committees according to local regulations, and in any case no later than seven calendar days, after knowledge by Investigator of such a case. Relevant follow-up information on the case will be subsequently communicated within an additional eight days. All other SUSARs shall be reported to the Competent Authorities concerned and to the Ethics Committee concerned according to local regulations as soon as possible but within a maximum of fifteen days of first knowledge by Investigator.

In addition to the first evaluation of an adverse event that is performed by the investigator, a second evaluation with respect to seriousness, causality and expectedness and a risk-benefit assessment is performed by ISCR to process safety evaluation according to a four-eye principle.

5 INVESTIGATIONAL MEDICINAL PRODUCT

5.1 Investigational Medicinal Product and Comparator

The following medication supplies will be used in the study:



IMP:

Truvada® 200 mg/245 mg film-coated tablets. Each film-coated tablet contains 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (equivalent to 300 mg of tenofovir disoproxil fumarate or 136 mg of tenofovir).

Excipients

Tablet core:

Croscarmellose sodium, Lactose monohydrate, Magnesium stearate (E572), Microcrystalline cellulose (E460), Pregelatinised starch (gluten free).

Film-coating:

Glycerol triacetate (E1518), Hypromellose (E464), Indigo carmine aluminium lake (E132)
Lactose monohydrate, Titanium dioxide (E171).

Marketing authorisation holder and manufacturer:

Gilead Sciences Intl Ltd. Cambridge CB21 6GT, UK

After the study protocol was sent to The Regional Committees for Medical and Health Research Ethics (REC South East), a parallel generic combination tablet (Emtricitabine/tenofovir disoproxil Sandoz®) became available in Norway. REC South East has been informed about this in an amendment.

Marketing authorisation holder and manufacturer of Emtricitabine/tenofovir disoproxil Sandoz®:

Sandoz A/S, Edvard Thomsens Vej 14, 2300 København S, Danmark

Subject included in the control group will not receive any study specific treatment.

5.2 Supply, Packaging, Labelling, Handling and Storage

The subject will receive a prescription on FTC/TDF 200 mg/245 mg for a maximum of 3 months that will be collected at a regular pharmacy.

Labelling will be done by the pharmacy according to the prescribed dose and local regulations.

The subject will bring their remaining medication to the next visit to the clinic for the investigator to verify the used number of tablets.

The subjects will report their intake of medication in a paper diary received at the clinic or by an app on their phone (Viedocme). The subject should bring their paper diary to the clinic for every visit. In addition, plasma levels of either tenofovir or emtricitabine or both will be measured on every visit for those subjects enrolled for continuous PrEP as an objective tool to assess compliance.

5.3 Dosage and Administration

The subjects are enrolled in this study because they will receive FTC/TDF as PrEP treatment. FTC/TDF has a marketing approval in Norway and will be prescribed by the investigator as continuous treatment in accordance with the SmPC or intermittently according to the regime in the IPERGAY-study (ref) and The National Guidelines for the management and prevention of HIV.

Dosing continuous treatment: 1 tablet per day

Dosing intermittent treatment: 2 tablets 2-24 hours prior to sexual contact, and 1 tablet 24 and 48 hours after sexual contact, but max. 15-20 tablets per month. If in need of more tablets per month, national guidelines recommend continuous PrEP.



In accordance with the SmPC each subject will together with their physician decide whether they will take FTC/TDF every day or intermittent (on demand). Adherence should be closely followed during the study period.

Patients with a contraindication to FTC/TDF as a result of e.g. renal dysfunction, will be assessed according to standard of care. These patients may be referred to the Dept. of Infectious Diseases, Oslo University Hospital, for second opinion and may be included in this study if put on FTC/TDF, but not if offered an alternative regimen.

The subjects should be informed that PrEP treatment does not give full protection against HIV and offers no protection against other bacterial STIs and therefore should be used in combination with condom.

5.4 Duration of Treatment

Subject will be followed up for a period of up to 24 months.

5.5 Methods for Assigning Subjects to Treatment

There is no randomisation in this study. The subject will be prescribed PrEP as continuous or intermittent treatment as agree with the investigator according to their needs.

5.6 Concomitant Medication

Any medication (prescription as well as over the counter (OTC) drugs) or therapeutic intervention deemed necessary for the subject, and which, in the opinion of the Investigator, do not interfere with their safety, may be continued unless they are listed in 4.5 Interaction with other medicinal products and other forms of interaction of the SmPC.

Any medications, herbal medicines, natural health remedies and nutritional supplements used at Screening until Follow-up visit (24 months) are to be recorded in the Concomitant medication module in the eCRF system. The generic name of the medication (i.e., not local trade names), along with start date, stop date, dose, route, regimen and indication shall be recorded as applicable in the eCRF system.

Any new medications or changes to the dose or regimen of pre-existing medications will be updated on a routine basis during the study.

5.7 IMP Accountability

Medication will be prescribed on a reimbursable prescription and collected at their regular pharmacy. Subject will bring their remaining tablets to the clinical visits for the clinic to verify their compliance.

6 VARIABLES

- Demographic information (age, gender, race, height, weight, sexuality, education, work situation, relationship status)
- Sexual behaviour (number of partners, condom use, HIV positive partners)
- Sexual transmittable infections (history and current status for infections with syphilis, hepatitis A/B/C, *Chlamydia trachomatis*, *Neisseria gonorrhoea*, and *Mycoplasma genitalium*).
- Compliance (days tablets taken, days tablets missed, compliance (%), compliance in connection with exposure to infection, reason for poor compliance, serum concentration of FTC/TDF).
- HIV infection status (positive, negative, resistance)
- Quality of Life using attached questionnaire
- Adverse reaction related to PrEP treatment



7 STATISTICAL METHODOLOGY AND DATA MANAGEMENT

7.1 Statistical Analysis Plan

All analyses will be performed by the Sponsor after the study is completed and the database is locked. Statistical programming and analyses will be performed using SAS and/or other validated statistical programs. A detailed statistical analysis plan (SAP) will be described in a separated document.

7.2 Study Populations

Data will be described on enrolled subjects undergoing PrEP treatment. Subjects who do not satisfy inclusion criteria will not be included in the analysis. A summary table reporting reasons for exclusion will be provided.

7.3 Descriptive statistics

Categorical variables will be described by means of absolute and relative frequencies, while continuous variables by means of mean, standard deviation, quartiles, min and max. Analyses will consider data collected at variable observational points, according to clinical practice and clinical judgement. In order to summarize data by time point the nearest available evaluation measurement will be considered (acceptable range).

7.4 Missing data

Subjects missing data values will not be excluded from the analysis, but their data will not be replaced; frequency of missing data will be given for all analysed variables.

7.5 Data Collection / Case Report Forms

Data will be collected using an electronic data capture (EDC) solution. Electronic Case report forms (eCRFs) will be utilised for recording data from each subject meeting the eligibility criteria but will not be completed for subjects who fail to meet eligibility criteria. The eCRF system, VieDoc™, will be available on an internet portal accessible through any standard computer with internet access. A personal log-in will be provided for all responsible personnel to allow for an audit trail relating to the study data to be maintained.

For the subject questionnaire at 3 months follow-up and the subject diary there will be an option to complete these electronically through the app ViedocMe™ on a smart phone.

The data in the eCRFs should be consistent with the relevant source documents. The Investigator will sign the designated signature fields of the eCRF data entry screens to confirm that the information on each screen is accurate and complete. All data must be stored in an unidentifiable form treated with strict confidentiality in accordance with applicable data protection regulations.

7.6 Data Management

Data will be transmitted electronically into the web based EDC system. Upon receipt, data will be coded according to pre-specified dictionaries. The handling of data, including data quality control, will comply with all applicable regulatory guidelines.



8 REGULATORY AND ADMINISTRATIVE PROCEDURES

8.1 Institutional Review

The study will be conducted in accordance with the Fortaleza, 2013 amendment to the Declaration of Helsinki 1964.

The Protocol and the Patient Information Sheet / Informed Consent Form will be approved by the relevant Competent Authorities and Ethics Committees, and possibly other public bodies according to local requirements before commencement. If a protocol amendment is necessary, this will be prepared with the agreement of the Principal Investigator, and signed by the relevant parties. If the amendment is considered to be substantial, it will be submitted to the Competent Authorities and Ethics Committees, and possibly other public bodies according to local requirements for review and approval. The protocol amendment will not be implemented before the required approvals are obtained. Minor amendments which do not affect the safety or physical or mental integrity of the clinical trial participants or the scientific value of the trial (i.e. non-substantial amendments) will not be submitted to Competent Authorities or Ethics Committees.

8.2 Patient Information / Informed Consent

The Investigator is responsible for giving the study subject full and adequate verbal and written information about the nature, purpose, possible risk and benefit of the study. Study subjects must also be notified that they are free to withdraw from the study at any time. The subjects should have reasonable time to read and understand the information before signing. The Investigator is responsible for obtaining signed informed consent from all subjects before including the subject in any study related procedures.

A signed copy of the patient information and of the Informed Consent Form in local language, will be given to the subjects, [Appendix 12.1](#).

8.3 Subject Confidentiality

The Investigator must ensure that subject's confidentiality will be maintained. eCRFs should only identify subjects by their initials and study number. The Investigator should keep a separate log of subject codes and names. Documents not for submission to the Sponsor, e.g., subject's completed Consent Forms, should be retained by the Investigator in strict confidence.

The Investigator is required to record primary efficacy and safety data, concomitant medication and subject progress in the subject's file/notes/medical record.

8.4 Subject Treatment Plan

It will be possible for the subject to continue with the PrEP treatment after end of the study. Subject withdrawing their consent will be offered to continue with the PrEP treatment independently of their study participation.

8.5 GCP

The study will be managed and conducted according to the latest International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP). A copy of these guidelines can be found in the Investigator Site File (ISF).

8.6 Record Retention

eCRFs and all medical records upon which the eCRF are based (source data) must be kept for at least 15 years after completion of the study. Image carriers or other data carriers may be used for this purpose. The documentation should be easily retrievable and readable during the entire archiving duration.



8.7 Quality Assurance

During or after the study is completed, sponsor representatives or regulatory authorities may wish to carry out an audit or an inspection. These representatives must have the access to all study data and subject source data.

8.8 Insurance and Liability

Liability for IMP-induced injury will be according to local requirements. The sponsor will indemnify the Investigator in accordance to national regulations.

8.9 End of Trial

The end of the trial is defined as the last visit of the last subject included in the trial. Within 90 days of the end of the trial, the Sponsor will notify Competent Authorities and Ethics Committees the regular termination of the study as required according to national law and regulations.

8.10 Study Report

A study report SR will be prepared covering clinical and statistical aspects and summarising all findings of the clinical study. The content has to be treated as strictly confidential. The study report will be sent to the Investigators, the Competent Authorities and Ethics Committees according to local requirements.

8.11 Publication and Data Rights

It is envisaged that the findings of the study will, in due course and by mutual agreement, be published in a scientific journal and/or presented at a scientific meeting

The published international guidelines for authorship (International Committee of Medical Journal Editors, 1997) will be adhered to; i.e. 'All persons designated as authors should qualify for authorship. Each author should have participated sufficiently in the work to take public responsibility for the content.'

Authorship credit will therefore be based only on substantial contributions to 1) conception and design, or analysis and interpretation of data; and to 2) drafting the article or revising it critically for important intellectual content; and on 3) final approval of the version to be published. Conditions 1), 2) and 3) must all be met. Participation solely in acquisition of funding or the collation of data does not justify authorship. General supervision of the research group is not sufficient for authorship. It is intended that information on what each author has contributed will be published.

It is emphasised however, that only those who entirely meet the above mentioned criteria will be listed as authors.



9 REFERENCES

ECAS guidelines, October 2016.

National guidelines for infectious medicine 2017.

Knox, D. and others. HIV-1 infection with multiclass resistance despite preexposure prophylaxis (PrEP). CROI, 2016. Abstract 169LB.

McCormack S., Dunn DT., Desai M., et.al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. Lancet 2016; 387: 53–60.

Molina JM., Capitant C., Spire B., et al., for the ANRS IPERGAY Study Group. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. N Engl J Med 2015;373:2237-46.



10 SIGNATURES

The protocol has been approved by:

Name and function	Signature	Date
Anne Olaug Olsen Principal Investigator		



11 SIGNATURE PAGE FOR INVESTIGATORS

By signing this page, the Investigator confirms having read the entire protocol and its appendices, and agrees to conduct this study in accordance with the protocol, GCP, the Declaration of Helsinki and national regulations.

The signature also confirms that the Investigator agrees that the results of this study may be used for submission to national and/or international registration and supervising authorities. The authorities will be notified of the Investigators name, address, qualifications and extent of involvement.

Name	Signature	Date



12 APPENDICES

12.1 Patient Information Sheet /Informed Consent Form

12.2 Questionnaires