

Project Title

A multicenter, observational cohort to study the characteristics of individuals asking for pre-exposure prophylaxis (PrEP) and the incidence of HIV and other STIs: 'The SwissPrEPared Study'

Research legislation: Ordinance on human research with the exception of Clinical trials (HRO) [1].

Type of Research Project: Research project involving human subjects

Risk Categorisation: Category A

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PROTOCOL SIGNATURE FORM

Study Title A multicenter, observational cohort to study the characteristics of individuals asking for pre-exposure prophylaxis (PrEP) and the incidence of HIV and other STIs: 'The SwissPrEPared Study'

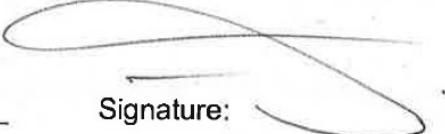
The project leader (main center) and the investigator (at the local center/site) have approved the protocol version **[1.0 (dated 24.10.2018)]**, and confirm hereby to conduct the project according to the protocol, the Swiss legal requirements [1,2], the current version of the World Medical Association Declaration of Helsinki [3] and the principles of Good Clinical Practice.

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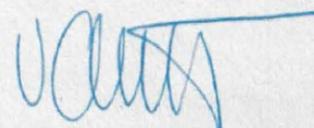
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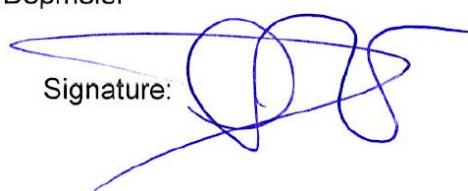
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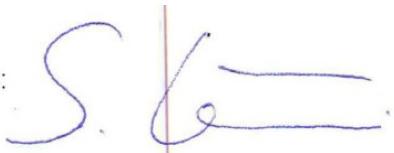


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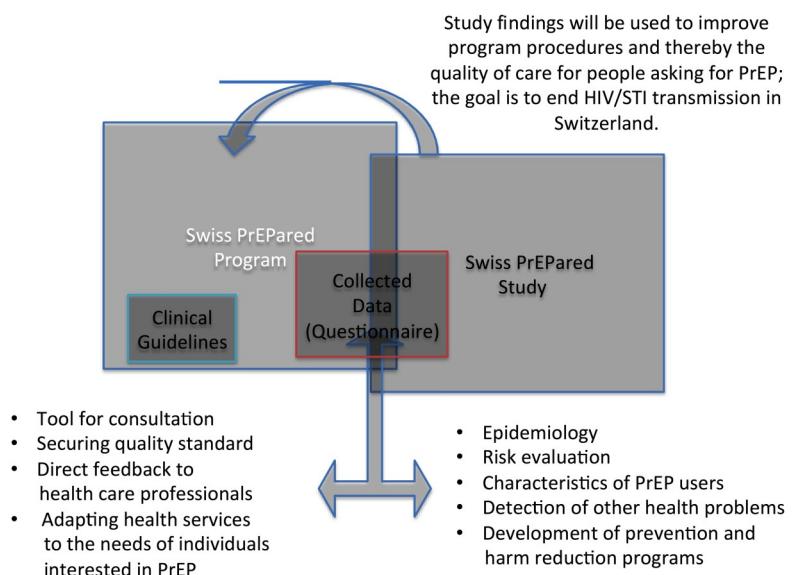
GLOSSARY OF ABBREVIATIONS

<i>ART</i>	<i>Antiretroviral Therapy</i>
<i>BASEC</i>	<i>Business Administration System for Ethical Committees</i>
<i>CRF</i>	<i>Case report form</i>
<i>ECDC</i>	<i>European Centre for Disease Prevention and Control</i>
<i>EMA</i>	<i>European Medicines Agency</i>
<i>FCSH</i>	<i>Federal Commission for Sexual Health</i>
<i>FDA</i>	<i>Food and Drug Administration</i>
<i>FOPH</i>	<i>Federal Office of Public Health</i>
<i>FSW</i>	<i>Female Sex Worker</i>
<i>HIV</i>	<i>Human Immunodeficiency Virus</i>
<i>HRA</i>	<i>Human Research Act</i>
<i>HRO</i>	<i>Ordinance on Human</i>
<i>MSM</i>	<i>Men having Sex with Men</i>
<i>PrEP</i>	<i>Pre-exposure prophylaxis</i>
<i>SHCS</i>	<i>Swiss HIV Cohort Study</i>
<i>STIs</i>	<i>Sexually Transmitted Diseases</i>
<i>TDF/FTC</i>	<i>Tenofovir/emtricitabine</i>
<i>UNAIDS</i>	<i>Joint United Nation Program on HIV/AIDS</i>
<i>STIs</i>	<i>Sexually Transmitted Diseases</i>

1 BACKGROUND AND PROJECT RATIONALE

Preliminary note: the "SwissPrEPared Study" is nested within the "SwissPrEPared Program" (Figure 1). The "SwissPrEPared Program" is a nation-wide program for the surveillance and the exchange of experiences related to HIV pre-exposure prophylaxis (PrEP) consultations. The goal is to ensure the best care for individuals asking for PrEP. Data generated by the program will be used to explore specific research questions, hereinafter referred to as the "SwissPrEPared Study". A comprehensive description of the SwissPrEPared Program procedures (program guidelines, visits, screening tests) is provided in a separate document (see "SwissPrEPared program description").

Figure 1: Relationship between the SwissPrEPared program and the SwissPrEPared study.



The Swiss HIV prevention program, under the auspices of the section 'prevention and promotion' of the Federal Office of Public Health (FOPH), has achieved a stabilization of the HIV epidemic in the past decade. Yet, each year, there is still a considerable number of newly detected HIV infections.¹

Pre-exposure prophylaxis (PrEP) is an effective measure to complement existing HIV prevention strategies among populations at risk of HIV infection (e.g. men having sex with men (MSM) or female sex workers (FSW)) for whom classic prevention tools (such as condom use for anal sex) are not sufficient. PrEP refers to the use of antiretroviral medication (ART) to prevent HIV negative individuals from acquiring HIV. Large trials have shown high efficacy of continuous^{2,3} or intermittent⁴ PrEP with tenofovir/emtricitabine (TDF/FTC) in MSM at very high

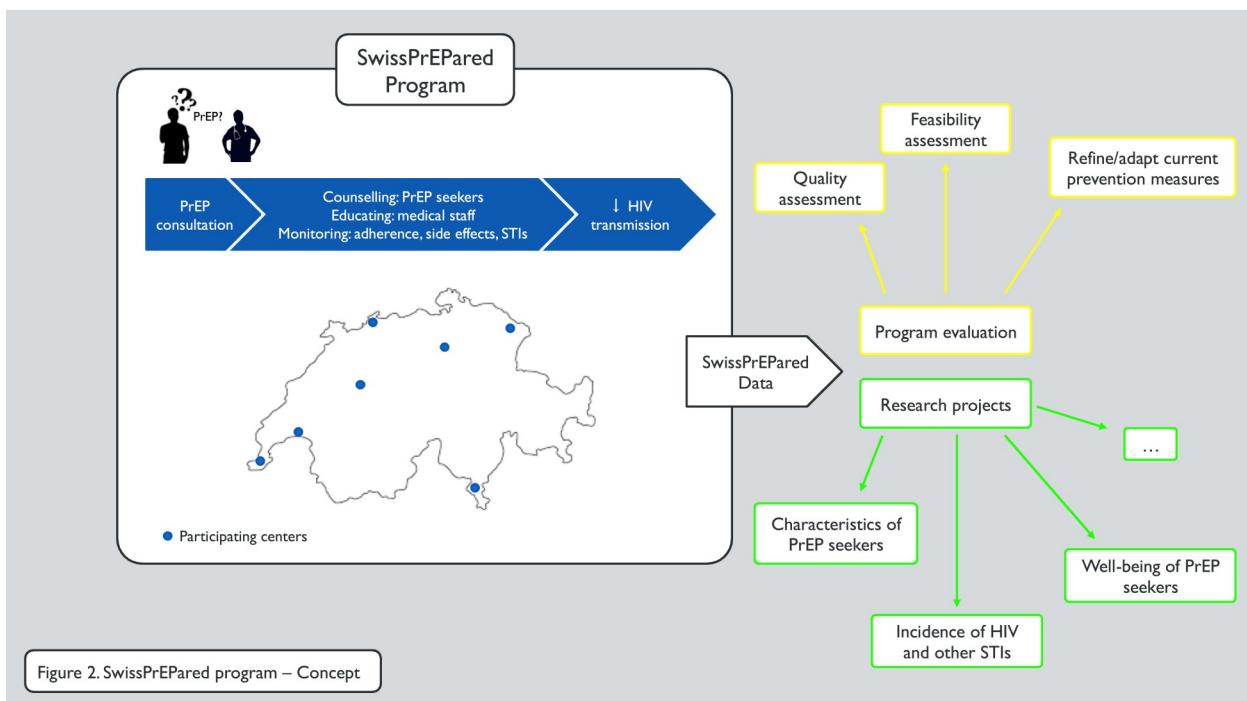
risk of HIV who adhere to the regimen. In these studies, MSM at very high risk were defined as having a large number of sexual partners with whom they engage in condomless sex, often under the influence of psychoactive substances, including alcohol. TDF/FTC was approved for PrEP by the United States Food and Drug Administration (FDA) in 2012 and the European Medicines Agency (EMA) in 2016. There is significant evidence that the introduction of PrEP helped further reduce the number of HIV transmissions in groups at high risk for HIV: in San Francisco, California, newly diagnosed HIV infections decreased from 453 in the year 2012 to 255 new infections in 2015;⁵ in London, the number of new HIV diagnoses in MSM was 40% lower in 2016 than in 2015.⁶ In a recently published study, the introduction of PrEP in New South Wales, Australia, led to a rapid decline in HIV diagnoses by 35%.⁷ Although a causal link cannot be formally established, it is plausible that the use of PrEP substantially contributed to these reductions.

Despite its lack of approval in Switzerland, PrEP use needs to be monitored carefully: data from social media (such as Facebook®, Grindr® or planetromeo®), from the European Centre for Disease Prevention and Control (ECDC), and from the European PrEP surveys (www.eatg.org) suggest that a growing number of people in Switzerland already use generic TDF/FTC. PrEP users were found to buy TDF/FTC through online pharmacies, often without medical supervision. Studies conducted in Switzerland confirm these findings. Hampel *et al.* performed an online-survey on the MSM geosocial networking application Grindr® to collect data on the acceptance of PrEP among sexually active MSM in Switzerland.⁸ The authors identified a high proportion of MSM with a positive attitude towards PrEP. Out of 1'893 survey participants, 944 individuals (50%) were considering starting PrEP within the next six months, and 1'474 (80%) at some point in the future. Eighty-two participants (4.3%) reported that they were currently taking PrEP, of whom 18 (22%) said that they were taking PrEP without medical supervision, and seven PrEP-users (9%) had not had an HIV test within the previous 12 months. Overall, 575 (30%) of all participants reported that their last HIV test was performed more than 12 months ago. Although some existing health care structures (such as Checkpoints, infectious disease clinics and Swiss HIV Cohort Study (SHCS) centers) already started offering counselling for individuals interested in taking PrEP, many PrEP users from the Grindr® survey were unaware of these services.

The lack of medical supervision in individuals taking PrEP remains also a relevant issue: aside from drug-related side effects (such as kidney failure), subsequent viral resistance may arise in those taking PrEP despite a latent, undiagnosed HIV infection.⁹ Almost one third of the Grindr®-survey participants and nearly 10% of PrEP users did not undergo HIV testing in the previous 12 months.

Furthermore, there have been concerns about the potentially harmful effects of PrEP on sexual behaviour and other sexually transmitted diseases (STIs). PrEP has been introduced in the context of a longstanding reduction in condom use,¹⁰ and many countries are experiencing an alarming increase in STIs such as syphilis, gonorrhoea and chlamydia.^{1,11,12} The PROUD trial showed evidence of sexual behavioural risk compensation, with 21% vs. 12% (p=0.03) of immediate vs. deferred PrEP recipients reporting non-condom sex with 10 or more partners.³ In demonstration projects monitoring PrEP implementation in the US, the mean number of condom-protected episodes of receptive anal sex decreased over the first 48 weeks.¹³ HIV-uninfected MSM using PrEP and HIV-infected MSM with undetectable viral load on ART can disclose and use this information on geosocial networking apps to choose partners for condomless sex (biomed-matching).¹⁴ PrEP may therefore result in changes in sexual practices, which might ultimately facilitate STI transmission. On the other hand, studies modelling the impact of a PrEP program (i.e. regular STI screening and subsequent treatment) revealed an overall decline in the incidence of STIs, even if the probability of condom use was reduced.¹⁵ Finally, participation to a PrEP program has been found to yield other health-related benefits for marginalized groups, such as more frequent screenings for depression, tobacco or diabetes, and an increased vaccination rate.¹⁶

There is thus an urgent need to build up a comprehensive PrEP program in Switzerland, serving as an official platform for the surveillance and the exchange of experience related to PrEP prescription, and offering targeted prevention measures to individuals at higher risk of HIV infection (Figure 2).



Ultimately, the “SwissPrEPared Study” intends to provide a better understanding of the needs, expectations and vulnerabilities of individuals asking for PrEP. Study findings are expected to yield more efficient and better-targeted prevention measures directed at individuals at high risk of HIV infection.

The “SwissPrEPared Study” has been deemed “category A” research project according to art.7 (HRO), as data collection only entails minimal risks and burden. The ethical rationale is described under section 6 of this document.

1 PROJECT OBJECTIVES AND DESIGN

Nested within the SwissPrEPared Program, the “SwissPrEPared Study” – a large, multicentric, nation-wide cohort study – aims to longitudinally follow individuals asking for PrEP prescription over a period of 3 years.

The main aims of the study will be:

1. To obtain *epidemiological data* on individuals asking for PrEP in Switzerland. We are particularly interested in:
 - Determining *the extent of PrEP use* in Switzerland;
 - Assessing and monitoring the *occurrence of STIs* in this particular population.
2. To assess *sexual health and sexual well-being* in individuals asking for PrEP using a questionnaire specifically designed for the SwissPrEPared program.

2.1 Hypothesis and primary objectives

The “SwissPrEPared Study” is based on the following hypotheses:

1. We expect a considerable number of individuals in Switzerland to be interested in starting PrEP. For those already taking PrEP, we assume there is a need for proper medical counselling and follow-up.
2. We expect that a large nation-wide program providing regular counselling and follow-up will improve the retention in care of individuals at high risk of HIV and other STIs.
3. We expect the SwissPrEPared program to lead to a better detection of new HIV cases in Switzerland through regular testing among a high-risk population.

4. We assume that systematic STI screening and appropriate clinical management will result in a decline of STIs rates, since there is a high prevalence of STIs in the population asking for PrEP.
5. We expect individuals at high risk of HIV to have higher rates of psychiatric disorders (depression, substance abuse); we assume that the SwissPrEPared questionnaire will be able to detect cases and to improve clinical management (i.e. early referral to specialist, appropriate therapy).

The primary objectives of the SwissPrEPared study are to:

1. Explore *the extent of PrEP use* in Switzerland, using the following endpoints:

- Number of individuals asking for PrEP
- Proportion of individuals qualifying for PrEP according to current guidelines
- Demographic characteristics of individuals asking for PrEP
- PrEP regime used
- Mode of drug supply (pharmacy *versus* online)
- Adherence rates
- Occurrence of side effects

2. Assessing and monitoring the *occurrence of STIs* in this particular population:

- Prevalence and incidence of HIV
- Prevalence and incidence of other STIs (syphilis, HBV/HCV, gonorrhoea and chlamydia, and mycoplasma genitalium)

3. To assess *sexual health and sexual well-being* in individuals asking for PrEP using a questionnaire specifically designed for the SwissPrEPared program. The following aspects will be explored:

- Sexual behaviour
- Factors associated with increased sexual risk taking (recreational drug use, number of sex partners, condomless sex with occasional partners)
- Presence of psychiatric disorders (depression, substance abuse)
- Influence of geosocial networking apps on sexual well-being of individuals asking for PrEP

2.2 Primary endpoints

Time points and methods of measurement for endpoint assessment are described under section 3.3 "study procedures". The following variables will be collected:

- Number of individuals asking for PrEP
- Proportion of individuals qualifying for PrEP according to current guidelines
- PrEP regime used (daily, intermittent, on-demand)
- Mode of drug supply (pharmacy *versus* online)
- Adherence rates (to PrEP and to program follow-up)
- Occurrence of side effects
- Prevalence and incidence of HIV
- Prevalence and incidence of other STIs (syphilis, HBV/HCV, gonorrhoea, chlamydia, mycoplasma genitalium)
- Using the SwissPrEPared questionnaire:
 - Demographic characteristics of individuals asking for PrEP
 - Sexual behaviour
 - Factors associated with increased sexual risk taking (recreational drug use, number of sex partners, condomless sex with occasional partners)
 - Presence of psychiatric disorders (depression, substance abuse)
 - Influence of geosocial networking apps on sexual well-being of individuals asking for PrEP

2.3 Project design

Nested within the SwissPrEPared Program, the "SwissPrEPared Study" is a large, multicentric, nation-wide cohort study that aims to longitudinally follow individuals asking for PrEP prescription over a period of 3 years.

The SwissPrEPared program has been described elsewhere (see document "SwissPrEPared program description"). In brief, seven large centers (i.e. Swiss HIV Cohort Study (SHCS) centers: Basel, Berne, Geneva, Lausanne, Lugano, St. Gallen and Zurich), four smaller health care structures (Checkpoints Bern, Geneva, Lausanne, and Zurich) and private facilities in Zurich (Medical center Kalkbreite, dermatological center) will be participating to the

SwissPrEPared program. The program will not be restricted to these centers, i.e. other centers may apply for participation after the start of the program.

2 PROJECT POPULATION AND STUDY PROCEDURES

3.1 Project population, inclusion and exclusion criteria

These aspects are detailed in the SwissPrEPared program description (section 3.1). In brief, all individuals aged 18 years asking for PrEP prescription at one of the participating centers will be asked to participate to the SwissPrEPared program (consecutive ongoing recruitment). Only HIV-negative individuals will be deemed eligible. Participants for whom PrEP is not indicated or individuals declining PrEP will still be offered to participate in the program (i.e. to receive regular counselling and undergo STIs monitoring).

According to the European MSM Internet Survey 2010 (EMIS-CH), approximately 80'000 MSM between 15 and 65 are currently living in Switzerland.¹⁷ Defining a “high risk of HIV infection” as 3 episodes of condomless anal intercourse in the last 12 months, we estimate 4'000 MSM to qualify for PrEP in Switzerland. Exact estimates of the full program population cannot be drawn up, since it remains unclear how many non-users (either not indicated or declining PrEP) might be willing to participate in the program.

3.2 Recruitment, screening and informed consent procedure

These aspects are detailed in the SwissPrEPared program description (section 3.2). To facilitate reading, a copy of this section is provided here:

The MSM community will be informed about the SwissPrEPared program by advertising in print and online magazines, and in geosocial networking apps like Scruff®, Grindr® or Planetromeo®. Potential participants will also be identified at local participating centers by their physician during consultation for PrEP prescription. Although not restricted to MSM, we expect only a small number of non-MSM individuals to participate in this program.

All individuals willing to participate in the program will be asked to provide consent regarding the use of their personal health-related data for research purposes (general consent allowing data collection for the SwissPrEPared Cohort Study). The rationale underlying general consent is that the SwissPrEPared program is expected to generate highly relevant data regarding individuals seeking PrEP in Switzerland and has the potential to address a considerable number of research questions. Participants will be informed orally and in writing by trained medical staff working at the participating centers. Participants will be free to withdraw their consent at any time during the program. Individuals unable to follow program procedures (e.g. language barriers, mental or psychiatric disorders) will not be considered eligible for health-

related data collection. More importantly, written informed consent will not be considered as a prerequisite for program participation, i.e. those declining personal data use will still be welcome to participate in the SwissPrEPared program (i.e. will benefit from regular counselling and STIs monitoring). Refusal will be consigned in personal records and no further data collection will be undertaken.

Eligibility criteria - SwissPrEPared Study	
Inclusion criteria	Exclusion criteria
Participation in the SwissPrEPared program	Individuals unable to follow program procedures (e.g. language barriers, mental or psychiatric disorders)
Aged ≥18 years	
HIV negative	

The enrolment procedure will be conducted as follows:

- At every local participating center, potential study participants will be identified by screening the PrEP consultation schedule
- One day prior to PrEP consultation, local study staff will contact potential study candidates on the phone. They will:
 - Inform them about the SwissPrEPared Program
 - Inform them about the possibility to participate in the nested SwissPrEPared cohort study
- If the candidate expresses interest for the study, the local study staff will send her/him via email:
 - The SwissPrEPared participant information
 - A link giving him access to the SwissPrEPared Questionnaire (secured web-portal)
- The local study staff will also inform participants that:
 - The questionnaire needs to be completed before the appointment at the PrEP consultation
 - All questions he/she might have will be answered at the PrEP consultation
- At PrEP consultation:
 - All remaining questions will be clarified
 - The informed consent form will be signed by the participant and the local investigator

- *If the candidate is not interested to participate in the study, the study staff will ask if the candidate allows them nonetheless to document the reason for refusal and his/her PrEP status (i.e. currently taking PrEP: yes/no):*
 - *If yes, an identification number will be generated and the reason for refusal + PrEP status documented*
 - *If not, an identification number will be generated and no data will be collected. The identification number is needed for an accurate enrolment log (e.g. whenever the participant reconsiders participating in the study at some point later, no new identification number will be generated).*

3.3 Study procedures

3.3.1 PrEP prescription:

Guidelines on PrEP prescription are detailed in the SwissPrEPared program description and in the Appendix 1 of this document.

3.3.2 Monitoring adherence, drug-related side effects and STIs

Regular follow-up visits (i.e. approximately every 3 months) to assess PrEP adherence and drug-related side effects (clinical assessment and labs, i.e. full blood count, liver tests (ALT), proteinuria, creatinine, and glomerular filtration rate) will be recommended.

Additionally, regular HIV and other STIs screening will be recommended to program participants, i.e. before starting PrEP and during follow-up (approximately every 3 months).

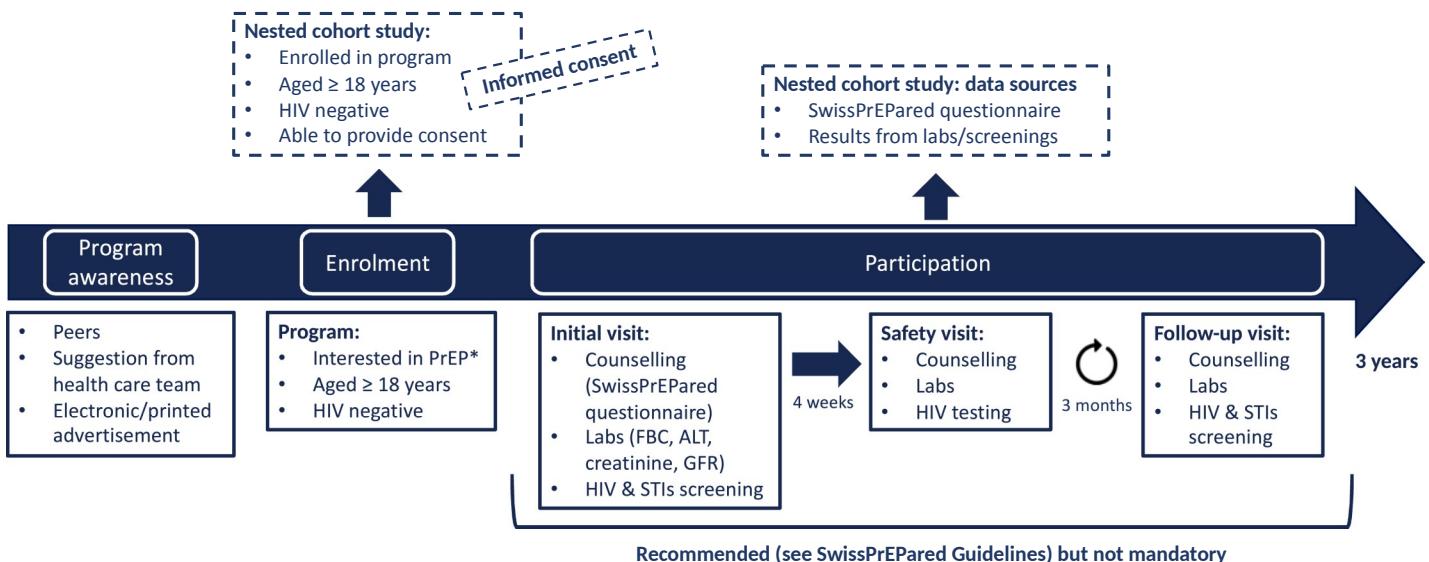
A full description of study visits is provided in Appendix 2.

3.3.3 Individualized counselling and follow-up using the "SwissPrEPared questionnaire"

Counselling and follow-up will be standardized throughout centers using an online, web-based questionnaire specifically designed for the SwissPrEPared program (see SwissPrEPared program description section 3.3.3 and Appendix 3 at the end of this document). The SwissPrEPared questionnaire shares similarities with questionnaires used by the SHCS to facilitate future research projects (data linkage).

Figure 3 outlines the procedures performed in the SwissPrEPared program and nested cohort study.

Figure 3. SwissPrEPared Program and nested cohort study – Design



* PrEP intake not mandatory for program/study participation

Plain boxes indicate processes related to the SwissPrEPared Program; **dashed boxes** indicate processes related to the nested SwissPrEPared cohort study.

ALT: alanine aminotransferase; FBC: full blood count; GFR: glomerular filtration rate; HIV: human immunodeficiency virus; PrEP: pre-exposure prophylaxis; STI: sexually transmitted disease

The following table illustrates the differences between the procedures carried on in the SwissPrEPared program versus the SwissPrEPared study.

	SwissPrEPared Program	SwissPrEPared Study
Overall objectives		
Official platform for the surveillance and the exchange of experience related to PrEP consultation	✓	✗
Improving the quality of care of individuals asking for PrEP (i.e. PrEP counselling, STI screening)	✓	✗
Targeted prevention measures to individuals at higher risk of HIV infection	✓	✓
Monitor the safety of PrEP use in uninfected individuals	✓	✓
Assess the extent of PrEP use in Switzerland	✗	✓
Assess and monitor the occurrence of STIs	✗	✓
Assess sexual health and sexual well-being	✗	✓
PrEP consultation		
Counselling about PrEP, HIV- and STI-prevention/-transmission	✓	✗
Assess PrEP-indication, -contraindications, -regime	✓	✓
Identify potential side-effects of PrEP	✓	✓
Assess concomitant medication	✓	✓
Assess vaccination status	✓	✓
Identify acute HIV-infection symptoms	✓	✓
Screen for depression and substance abuse	✓	✓
Processes of care		
Provide recommendations on laboratory testings	✓	✗
Monitor long-term safety of PrEP in HIV-negative individuals	✗	✓
Provide recommendations on HIV/STI screening	✓	✗
Assess STI-/HIV-incidence	✗	✓
Assess overall adherence to SwissPrEPared recommendations	✗	✓
PrEP: pre-exposure prophylaxis; STI: sexually transmitted infection		

3.3.4 Expected biases:

Selection bias may arise in several ways:

- Individuals interested in taking PrEP may seek counselling outside participating centers (e.g. general practitioner, hospital not participating to the SwissPrEPared program).
 - > Since PrEP prescription remains a relatively recent and rather specialized procedure, we expect consultations for PrEP prescription occurring outside the program to be rare. Additionally, the program will not be restricted to these centers, i.e. other centers may apply for participation after the start of the program.
- Vulnerable populations (low income, younger age, MSW, substance abuse) may renounce to program participation due to the comprehensive costs related to drug purchase or regular HIV and STI screenings.
 - > Financial support to reduce program-related costs is currently being discussed with several stake-holders.
- Loss to follow-up or drop-outs have to be expected when enrolling a healthy population.
 - > Measures designed to improve retention will be applied (regular reminders for follow-up visits, participant feedback actively sought to improve program procedures).

3.4 Withdrawal and discontinuation

Participants will be free to withdraw their consent to data collection at any time during the SwissPrEPared program. Whenever this occurs, the identification key will be destroyed and data will be fully de-identified.

Data from participants lost to follow-up, unable to further attend follow-up visits or deceased during program course are expected to be used for research purposes.

3 STATISTICS AND METHODOLOGY

4.1. Statistical analysis plan

4.1.1 Primary analyses

Since the aim of this cohort study is mainly descriptive (i.e. to obtain representative estimates from individuals asking for PrEP in Switzerland), a power analysis was deemed not relevant.

> Descriptive statistics: continuous data following a normal distribution will be expressed as mean and SD, categorical data as number and proportion. Standard methods for longitudinal studies (i.e. survival methods) will be used to describe HIV and STI incidence.

> Inferential statistics: regression analyses will be performed to explore the association between predefined risk factors (such as recreational drug use, number of sex partners, or condomless sex with occasional partners) and the occurrence of HIV/STI infection. Whenever the data allows it (i.e. appropriate control group size), we will compare the HIV/STI incidence and sexual behavioural factors between individuals on PrEP and those not taking PrEP.

4.1.2 Interim analysis:

Since participation and retention rates remain a relevant issue in longitudinal studies, we will conduct an interim analysis after 6 months with the aim to assess the demand, acceptability and resources related to the conduct of the SwissPrEPared cohort study. More specifically, we are interested in:

- Recruitment rates: number of participants enrolled compared to total number of potential candidates (i.e. total number of individuals asking for PrEP prescription)
- Acceptability of the SwissPrEPared questionnaire: behavioural (uptake, adherence and completion of questionnaire) and self-reported (questionnaire part C) assessment.
- Retention rates: number of participants loss to follow-up.
- Reasons for loss to follow-up: self-reported assessment (questionnaire, part B).
- Costs related to study conduct: estimation of time and resources needed to conduct the study over 6 months.

We will conduct quantitative (i.e. recruitment and retention rates, behavioural component of questionnaire acceptability) and qualitative (i.e. self-reported component of questionnaire acceptability, reasons for loss to follow-up) analyses. For qualitative data, content analysis will be performed using a conventional approach (identification of themes, open coding, combination/stratification).

4.2. Handling of missing data

In the case of dropouts or incomplete dataset, we will collect information to determine the nature of missing data (data missing completely at random (MCAR), data missing at random (MAR) or

data missing not at random (MNAR)). In case of missing randomness we will use multiple imputations for analyses where complete data are needed. We will also perform a *complete case analysis* (assuming that all data are MCAR or MAR) and compare findings from both methods.

5 REGULATORY ASPECTS AND SAFETY

5.1 Local regulations / Declaration of Helsinki

This research project will be conducted in accordance with the protocol, the Declaration of Helsinki [3], the principles of Good Clinical Practice, the Human Research Act (HRA) and the Human Research Ordinance (HRO) [1] as well as other locally relevant regulations. The Project Leader acknowledges his responsibilities as both the Project Leader and the Sponsor.

5.2 Notification of safety and protective measures (HRO Art. 20)

The project leader is promptly notified (within 24 hours) if immediate safety and protective measures have to be taken during the conduct of the research project. The Ethics Committee will be notified via BASEC of these measures and of the circumstances necessitating them within 7 days.

5.3 Serious events (HRO Art. 21)

If a serious event occurs, the research project will be interrupted and the Ethics Committee notified on the circumstances via BASEC within 7 days according to HRO Art. 21¹.

5.4 Amendments

Substantial changes to the project set-up, the protocol and relevant project documents will be submitted to the Ethics Committee for approval according to HRO Art. 18 before implementation. Exceptions are measures that have to be taken immediately in order to protect the participants.

5.5 End of project

Upon project termination, the Ethics Committee is notified within 90 days.

¹ A serious event is defined as any adverse event where it cannot be excluded, that the event is attributable to the sampling of biological material or the collection of health-related personal data, and which:

- a. requires inpatient treatment not envisaged in the protocol or extends a current hospital stay;
- b. results in permanent or significant incapacity or disability; or
- c. is life-threatening or results in death.

All biological materials collected during the SwissPrEPared Program will be processed according to protocols of local laboratories participating in the program (standard procedure not related to the conduct of the study). Health-related data collected during the SwissPrEPared Program and further used for study purposes will be anonymized upon termination of data analysis.

5.6 Insurance

Non-clinical/non-interventional research projects belonging to category A do not require an insurance.

6 FURTHER ASPECTS

6.1 Overall ethical considerations

The “SwissPrEPared Study” has been deemed “category A” research project according to art.7 (HRO), as data collection only entails minimal risks and burden (i.e. health-related data routinely collected in the setting of a large prevention program). Whilst we recognise that sexual health research may raise some ethical concerns, we believe that the 4 ethical principles are well embedded in our project:

- **Autonomy:**

The following measures ensuring self-determination will be taken: informed consent will be sought orally and in writing by trained study staff; study information will be provided in an understandable language; participants will be free to withdraw their participation at any time during the study; individuals unable to follow or understand study procedures will be excluded; subgroups in which the administration of TDF/FTC has not been studied extensively (such as individuals aged <18 years) will not be considered eligible; and finally, potentially eligible individuals will not be offered personal benefits for study participation (such as financial support for PrEP medication).

- **Beneficence:**

Risks and burden are deemed minimal: study participants will be expected to complete a self-administered questionnaire (SwissPrEPared questionnaire) at each visit, but full completion will not be mandatory for study participation.

Benefits: compared to non-participants, those taking part to the study will benefit from regular follow-up, screening for STIs and medical counselling. In the case of a positive STI diagnosis, state-of-the-art management will be proposed.

- **Non-maleficence:**

Because research related to the SwissPrEPared program targets individuals engaged in high-risk behaviour and because of the highly sensitive nature of the data collected, several measures will be taken to ensure confidentiality, such as: a self-administered questionnaire, data collection in a secured database, data deidentification, and publication of findings as aggregated data.

- **Justice:** the main goal of this study is to yield more efficient and better targeted prevention measures for individuals at high risk of HIV infection. In this respect, participants will be the direct beneficiaries of the study findings, either during the study itself (through regular follow-up, screening for STIs and medical counselling) or in the near future.

7 QUALITY CONTROL AND DATA PROTECTION

7.1 Quality measures

Data generated by the SwissPrEPared program will be collected using an electronic Case Report Form (eCRF), i.e. the SwissPrEPared questionnaire. Quality checks will be performed already on entry, and by the coordinating study center (Zurich).

For quality assurance the Ethics Committee may visit the research sites. Direct access to the source data and all project related files and documents must be granted on such occasions.

7.2 Data recording and source data

Data generated by the SwissPrEPared program will be collected using an eCRF providing custom access for each participant and researcher, based on a web application written in Python and a PostgreSQL database. The eCRF is based on the already-existing data collection web application of the SHCS. This eCRF does comply with the latest data safety requirements (e.g. audit trail, encryption of data at rest and in flight). Data sources will consist of routinely collected data from the SwissPrEPared program, i.e. original records (clinical assessment or labs) either in a paper or electronic version (depending on the system used by participating centers). Data will then be entered by the participants themselves and by health care professionals participating in the SwissPrEPared Program.

7.3 Confidentiality and coding

Health-related data collected during the SwissPrEPared Program and further used for research purposes will be handled with utmost discretion and is only accessible to researchers who require the data to fulfil their duties within the scope of the research project (need-to-know basis). On the SwissPrEPared questionnaire and other project-specific documents, participants are only identified by a unique participant number. This number will be generated by the eCRF upon enrolment in the program. All personal data will be deidentified during data collection. The participant identification list will be stored in a password-secured database generated by local participating centers.

Biological material (e.g. blood sample for HIV testing) collected during the course of the SwissPrEPared program will be handled following procedures specific to each participating center and their laboratories (standards of care). No biological material will be stored for study purposes (no use of Biobank).

7.4 Retention and destruction of study data and biological material

Health-related data collected from the SwissPrEPared program for research purposes will be stored 10 years after research findings publication. No biological material will be stored for study purposes (no use of Biobank).

8 FUNDING / PUBLICATION / DECLARATION OF INTEREST

So far funding for the SwissPrEPared program and related research has been obtained from the following sources:

- Swiss HIV Cohort Study
- Federal Office of Public Health

The funding organisations play no role in the design and conduct of the study; in the collection, management, analysis or interpretation of the data; or later in the preparation, review, or approval of the scientific manuscript.

The SwissPrEPared Research Team has no conflict of interest to declare.

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10 APPENDIX

Appendix 1: Recommendations regarding PrEP use – The “SwissPrEPared guidelines”

These recommendations were developed to help the PrEP-prescribing health care professionals participating to the SwissPrEPared program. They will be adapted at least once a year based on growing scientific knowledge and on quality assessment from the SwissPrEPared Program. The study physicians are not bound to these recommendations, but will be asked in collegial discussions for their reasons if not. The following recommendations are in line with the current recommendations by the Federal Commission for Sexual Health (FCSH),¹⁸ the International Antiviral Society (IAS),¹⁹ and the European AIDS Clinical Society (EACS).²⁰

A1.1. Who to prescribe PrEP

The final decision to take PrEP is always made by program participants. PrEP is recommended for populations whose annual HIV incidence is at least 2% (evidence rating AIII). In Switzerland this is mainly the case for some subgroups of the MSM population. However, individual risk might be contextual: for instance, individuals not considered at risk in Switzerland may have a higher risk when travelling abroad; alternatively, behavior may change over time and those not benefitting from PrEP at first may benefit later in the future. Using PrEP as an HIV prophylaxis is a personal and highly individual decision. Health care professionals are not supposed to make this decision for participants, rather they should provide them with the best information and guide them in the decision-making process. Health care professionals should also rule out contraindications for PrEP and assess the existence of other medical conditions (such as anxiety disorders), since this could affect the decision-making process. Individuals who might benefit from PrEP, individuals who do not need PrEP and contraindications for PrEP are listed in Table 1.

Table 1: Indications and contraindications for PrEP	
	Group with high prevalence of HIV (mainly: MSM)
	<u>AND:</u>
Individuals who may benefit from PrEP	<ul style="list-style-type: none">• anal sex (receptive or insertive) with inconsistent use of condoms or aim to have condomless sex in the future• any recently reported STI• use of drugs in combination with sex, including alcohol• repeated prescription of post exposure prophylaxis
Individuals who do not need PrEP	HIV negative MSM in monogamous HIV serodiscordant relationship, if HIV+ partner under antiretroviral therapy with undetectable viral load for at least six months
	Monogamous relationship with partner recently tested HIV-negative
Contraindications for PrEP	Acute or chronic HIV infection
	Presence of significant proteinuria
	Kidney function with a clearance of less than 50 mL/min (Cockcroft formula)
	History of chronic kidney disease

> Other individuals at risk:

Although PrEP is in Switzerland mainly indicated for subgroups of MSM, other individuals may also be at risk of HIV infection: heterosexuals frequently having unprotected vaginal or anal sex (specifically when abroad, i.e. sex-tourism), intravenous drug users or transgender individuals may also benefit from PrEP. It is worth to note, though, that daily dosing is the only regime recommended for women and transgender people, since levels of tenofovir have been found 10 times lower in vaginal tissue than in rectal tissue and clearance is faster.

A1.2 Medication

So far, the combination of 300mg TDF and 200mg FTC is the only recommended drug that should be used as PrEP. TDF/lamivudine, Tenofovir alafenamide /FTC, and TDF alone are not recommended for PrEP (evidence rating BIII).

Of note, in certain countries TDF is labelled as 245 mg rather than 300 mg to reflect the amount of the prodrug (tenofovir disoproxil) rather than the fumarate salt (tenofovir disoproxil fumarate). Studies with other drugs are ongoing and might lead to more possibilities in the future.

A1.3. Mode of PrEP

We currently recommend two regimes, which are well-studied and showed high efficacy in large clinical trials. The daily PrEP (= intake of 1 pill FTC/TDF every day) and the on-demand PrEP (according to the IPERGAY (Intervention Préventive de l'Exposition aux Risques avec et pour les Gays) protocol).⁴ Daily PrEP taken for a limited time-period (e.g. holidays) with long phases without PrEP intake is described as "holiday-PrEP" or "intermittent PrEP". The advantages, disadvantages and target population groups are listed in Table 2. Other regimes, such as continuous PrEP for four days a week, are not recommended until further evidence is made available (studies still on-going).

> Daily regime:

- Daily TDF/emtricitabine is the recommended regimen for men, women (evidence rating Ala), transgender individuals (evidence rating Alla) at risk of sexual exposure (evidence rating Ala) and for individuals injecting drugs (evidence rating Bla).
- A 1-week lead-in time is recommended with daily dosing for rectal, penile, and vaginal exposures with daily TDF/emtricitabine to ensure that adequate tissue levels are achieved (evidence rating CIII).

- If PrEP is to be discontinued, TDF/emtricitabine should be stopped 1 week after the last sexual exposure at the earliest (evidence rating CIII).

> On-demand regime:

On-demand TDF/emtricitabine PrEP, also known as “2-1-1” dosing may be considered as an alternative to daily PrEP for MSM with infrequent sexual exposures (evidence rating Ala).

The IPERGAY study assessed on-demand PrEP with TDF/emtricitabine given as 2 doses 2 to 24 hours before sex, 1 dose 24 hours after the first (double) dose, and 1 dose 24 hours later (“2-1-1” dosing). For consecutive sexual contacts, men were instructed to take 1 pill per day until 2 days after the last sexual encounter. With each new sexual encounter, PrEP was to be initiated with a double dose, unless the last PrEP dose had occurred within 7 days, in which case only 1 preexposure dose was recommended.

- This regimen is not recommended in other risk groups than MSM, especially not in women, since tenofovir levels were found 10-times lower in vaginal tissue than in rectal tissue and since clearance is faster.
- This regime is not recommended in patients with active HBV infection because of the risk of hepatitis flare and hepatic decompensation (evidence rating BIIa).
- If intercourse is planned in the context of 2-1-1 PrEP regimen, the first (double) dose of TDF/emtricitabine should be taken closer to the 24-hour precoital time than the 2-hour time (evidence rating CIII).

Table 2: Advantages and disadvantages of different PrEP regimes and possible populations.

	Daily PrEP	Intermittent PrEP	On-demand PrEP
Advantages	<ul style="list-style-type: none"> ➤ Best evidence ➤ Good protection, even when adherence is not optimal 	<ul style="list-style-type: none"> ➤ Less long-term side effects than daily regime ➤ Probably better protection than on-demand-regime in people with drug-adherence problems. 	<ul style="list-style-type: none"> ➤ Less long-term side effects ➤ Lower costs
Dis-advantages	<ul style="list-style-type: none"> ➤ Highest risk for long-term side-effects ➤ Costs 	<ul style="list-style-type: none"> ➤ No evidence from clinical studies ➤ No protection during PrEP-free periods, but possible change in risk-behavior due to "PrEP-experience". 	<ul style="list-style-type: none"> ➤ Less evidence than the daily regime ➤ No protection during PrEP-free periods, but possible change in risk-behavior due to "PrEP-experience"
People that might benefit from this regime	<ul style="list-style-type: none"> ➤ Individuals having frequent sexual exposure (more than once a month) ➤ Individuals having spontaneous sexual contacts ➤ Individuals who might have problems with drug-adherence ➤ Women or individuals born female 	<ul style="list-style-type: none"> ➤ Individuals having a higher risk of HIV during specific times periods. 	<ul style="list-style-type: none"> ➤ Individuals having only infrequent sexual exposure ➤ Individuals having planned sex (not spontaneous)
Not recommended for	<ul style="list-style-type: none"> ➤ Individuals having general contradictions for PrEP 	<ul style="list-style-type: none"> ➤ Individuals having general contradictions for PrEP ➤ Individuals having spontaneous sexual contacts 	<ul style="list-style-type: none"> ➤ Women or individuals born female ➤ Individuals having spontaneous sexual contacts ➤ Individuals who might have problems with drug-adherence

Appendix 2: SwissPrEPared program – Recommended visits

Individuals asking for PrEP will first be assessed at baseline visit (see description below). For those deciding to start PrEP, a second visit is recommended 4 weeks after PrEP initiation to evaluate early side-effects and to rule out an acute HIV-infection missed out at baseline visit (HIV test window period). After that second visit, a 3-monthly plan is recommended for all participants using PrEP, and a 6 to 12-monthly plan for participants at risk of HIV who decided not to start PrEP.

Each PrEP prescription should be for a period of maximum 3 months (90 tablets) to ensure appropriate monitoring.

A2.1 General recommendations for every visit:

Besides the recommended laboratory- tests, each visit should be used to:

- Evaluate the knowledge of the participant about PrEP, HIV and STIs transmission
- Remind the participant that condoms are required to prevent acquisition of non-HIV STIs, especially hepatitis C.
- Inform participants that PrEP does not protect 100% against HIV, and that regular HIV testing (every 3 months) is necessary to prevent resistance in the case of undiagnosed HIV.
- Screen participants for depression and substance abuse
- Evaluate counselling adherence
- Assess potential side effects related to TDF/FTC
- Assess if participants expectations regarding counselling are met

A2.2 Baseline visit

The following should be performed at baseline visit:

- Assessing the indication for PrEP, ruling out contraindications (i.e. medical history, current medication (especially nephrotoxic drugs), osteoporosis, kidney and liver diseases, previous STIs, previous post-exposure prophylaxis (PEP), symptoms or signs consistent with an acute HIV-infection within the last six weeks, sexual behaviour, drug use in combination with sex).
- The advantages and disadvantages of the different PrEP regimes should be discussed with each person.
- Assessment of serum creatinine level, alanin-aminotransferase (ALT, GPT) and full blood count

- HIV screening using 4th generation HIV-Combo test to avoid resistance in the case of an undiagnosed HIV infection. People who experienced high risk situations in the 6 weeks prior to starting PrEP should either have an additional HIV-PCR test or should be tested again using a 4th generation HIV-Combo test 4 weeks after starting PrEP (i.e. at safety visit).
- Hepatitis B status should be evaluated before starting PrEP but should not delay PrEP initiation. HBs-Antibody negative individuals should be recommended a full course of 3 Hepatitis B vaccinations and a vaccination titer control one month after the third vaccine. People with an incomplete vaccination status (HBs-antibody less than 100 but more than 10) should be recommended a single Hepatitis B Booster vaccination with a vaccination titer control 4 weeks after. For individuals with active HBV infection (detectable HBsAg), discontinuation of TDF/FTC PrEP could lead to acute HBV flares or hepatic decompensation, particularly for patients with hepatic cirrhosis; careful monitoring of HBV infection and liver function is recommended after discontinuation of TDF/FTC (evidence rating Alla). On-demand PrEP is not recommended for individuals with an active Hepatitis B infection.
- Assessment of Hepatitis A-vaccination status.
- Individuals asking for PrEP should be screened for other STIs, even when they decide not to take PrEP or show no symptoms. *Syphilis* should be screened using serological tests (TPHA, RPR), *Hepatitis C* should be tested using serological tests or blood PCR, and pooled PCR from rectum, pharynx and urethra should be performed for *chlamydia* and *gonorrhoea*. Individuals with symptoms of urethritis, proctitis or pharyngitis should be also screened for *mycoplasma genitalium*.
- HPV vaccination should be discussed with every participants, especially, those aged 26 years or younger.

In case of a contraindication for PrEP, the participant should be rescheduled within 7 days. If a participant is already taking PrEP at baseline, the interventions will be adapted accordingly. If a participant qualifies for PrEP but decline starting PrEP, a follow up every 6 to 12 months is recommended to perform STI and HIV testing.

A2.3. Safety-visit, 4 weeks after PrEP start

The following should be performed at safety-visit:

- Assessment of side effects
- Re-assessment of PrEP indication and PrEP-regime
- Assessment of PrEP adherence

- HIV 4th generation test
- Assessment of new medication (especially nephrotoxic drugs),
- Measurements of serum creatinine level, ALT, GPT and full blood count

A2.4 Follow-up visits, 3 months after safety-visit and then every 3 months

- Re-assessment of PrEP indication and PrEP-regime.
- HIV 4th generation test.
- STI tests (Syphilis, Gonorrhea, Chlamydia) are usually recommended every 3 months but the frequency should be adapted, if the participant had no or very few sexual intercourses since the last visit
- Assessment of sexual risk behaviour (for instance drug use in combination with sex)
- Assessment of creatinine, glomerular filtration rate and proteinuria (urine dipstick), ALT, full blood count
- Every 6 months: anti-HCV-Ig.

Table 3: Appointment schedule and key clinical assessments

	Baseline visit	Safety visit	Follow-up visit (every 3 months)
PrEP counselling which includes:			
<ul style="list-style-type: none"> • medical history and clinical examination • information on PrEP • conception/ pregnancy • short and long-term side effects • risk of developing resistance in the case of undiagnosed HIV 	x		
(Re-)Assessment of PrEP indication, regime and adherence	x	x	x
Assessment of side effects, including interaction with existing medications or supplements	x	x	x
Behavioral risk assessment	x		x
Symptoms of acute HIV infection (<1 month)	x	x	x
Adherence to counselling	x	x	x
Participant's feedback on counselling	x	x	x
HIV test	x	x	x
STI screening (Syphilis, Gonorrhea, Chlamydia)	x	x	x
Hepatitis C serology	x		Every 6 months or if clinically indicated
Hepatitis B Serology	x		
Assessment of vaccination status	x		
Labs: serum creatinine level, ALT, GPT, full blood count	x	x	x

Appendix 3: SwissPrEPared Questionnaire

Part A: baseline visit

1.	Year of birth	
2.	Postal-code (first two characters)	
3.	What is your current gender identity	1= male,2= female, 3= transgender; 9= I do not categorize myself
4.	What sex were you assigned at birth	1= male,2=female,3=intersex, 9=not stated
5.	Which of the following options best describes how you think of yourself	1= homosexual,2= heterosexual, 3=bisexual; 5= I don't usually use a term
6.	Do you consider yourself a member of an ethnic or racial minority in Switzerland?	Yes/No; if Yes <i>free text</i>
7.	Which country were you born in?	<i>List, if not Switzerland</i>
7a	(If 7= any other country than Switzerland), Since when do you live in Switzerland?	1= Since always; 2= Less than 12 months; 3= 1-5 years; 4= 5-10 years; 5=More than 10 years
8.	What level of education did you reach?	1=no completed school or professional education; 2=mandatory school (9 years in Switzerland); 3=finished apprenticeship; 4=bachelor; 5=higher professional education; 6=higher technical or commercial school; 7=university; 9=no information; 0=other
9.	Which of the phrases would you say comes closest in your feelings about your income these days:	1= Living really comfortable on present income; 2= living comfortable on present income; 3= Neither comfortable nor struggling on present income; 4 = Struggling on present income; 5= Really struggling on present income
10	Do you take any other medication (other than PrEP) at the moment	<i>Free text</i>
11	Do members of your close family (parents, grandparents) suffer from osteoporosis (bone disease)?	1=Yes 2= No
12	Have you ever taken PrEP?	1= Yes 2= No
13	If 12=yes, when have you started?	(Month/Year)

14	Have you ever used post exposure prophylaxis (PEP)?	Yes/No
15	Have you ever been diagnosed with an STI?	If Yes, 1=Syphilis; 2=Gonorrhea; 3=Chlamydia; 4=Hepatitis A; 5=Hepatitis B; 6=Hepatitis C; 7=Mycoplasma genitalium, 8=genital Herpes; 9= others (<i>free text</i>)
16	When was your last HIV test?	dd/mm/yy
17	When was your last anal or vaginal sex where you did not use a condom?	1= Last 48 hours 2= 3-15 days 3= 15 – 42 days 4= 42 – 90 days 5= More than 90 days.
18	Referring to your last condomless anal or vaginal sex: Did you know the HIV status of the partner?	1= unknown; 2=HIV positive, unknown if under antiretroviral treatment (ART); 3=HIV positive, under ART; 4=HIV positive not under ART; 5=HIV negative
19	Would you prefer another form of PrEP than the daily intake of a tablet, if it were available?	1= no 2= yes, a monthly injection 2 = yes, a 2-monthly injection 3= yes, a 3-monthly injection 4= yes, an implant 4 = other <i>free text</i>

Part B1: baseline and follow-up visit

This questionnaire will be sent to the program participant (text message or email) together with a reminder for the next appointment. Part A, questions 1 to 11, will be displayed as well and the participant will be asked to assess if the information is still valid or if changes need to be made.

#	Q	A
1.	Do you already have a new appointment?	1=yes;2=no
2.	If 1= no, Do you want to schedule a new appointment?	1= yes (please contact your health care provider after this survey) 2= no, because I do not have time at the moment, but I want to continue with the program 3= no, I want to stop the program because I stopped PrEP 4= no, I want to stop the program, but I continue with PrEP
3.	If 2=2 when shall we remind you for a new appointment	1= in 1 Week; 2 in 2 weeks; 3= in 1 months; 4=in 3 months
4.	If 2=4 please tell us why you want to stop the	<i>Free text</i>

	program.	
5.	Are you taking PrEP at the moment	1=yes;2=no
6.	If 5=1: Which mode do you use PrEP at the moment ?	1=daily (every day, including today) 2=daily, but only for certain periods 3=before and after planned sex, but not on a daily basis (2 pills 2-24 hours before planned sexual activity as well as one pill 24 hours and 48 hours after planned sexual activity) 4= I use a different regime than the described ones: please specify: <i>free text</i>
7.	If 6=2 how many days before a sexual risk situation do you usually start PrEP?	1-30
8.	If 6=2 how many days after your last sexual risk do you usually take PrEP?	1-30
9.	Do you think you can tell when you missed a dose?	1=Yes, I can always tell; 2=Not sure I can tell; 3=No, I can't tell
10.	If 6=2 or 3: how many days have you been on PrEP during the last 90 days	1-90 (estimated)
11a.	If 6=2 or 3 How often did you miss a dose in the last 3 months?	1= never; 2= once or twice; 3=3-5; 4=6-10 4=more than 10
11b.	If 6=1 How often did you miss a dose in the last 3 months? (Assuming 1 pill a day if taken daily)	1=never; 2=more than once a week, 3=once a week, 4=once every second week, 5= once a month,
12.	If 6= 1 Did you miss more than one dose in a row?	1=yes, (how many days) 2=No
13.	Where did you purchase your PrEP	1= online pharmacy (outside Europe); 2=online pharmacy (Europe); 3= in a regular pharmacy outside Switzerland; 4= in a pharmacy in Switzerland; 5= got it from someone I know; 6=other
14.	Did you experience any side effects or other health problem?	1=no; 2=yes, I experienced stomach/digestive problems, 3=yes, I experienced headaches, 4=yes, I experienced other problems: (<i>free text</i>)
15.	Are you in a relationship with a steady partner at the moment?	1=yes, 2=No; 3= I am not sure/ it is not defined
16.	If 15=1, do you know your HIV status of your partner	1= no; 2=HIV positive, I don't know if he/she is under antiretroviral therapy (ART); 3=HIV positive, he/she is under ART; 4=HIV positive, he/she is not under ART; 5=HIV negative
17.	(Not asked if 15=2) With your steady partner, do you use condoms for	1=always;2=mostly;3=sometimes;4=never

	anal or vaginal sex?	
18.	How many sexual partners have you had since your last visit?	Absolut number (estimated)
19.	In the last 3 months, how often have you used condoms with occasional partners for anal or vaginal sex?	1=always;2=mostly;3=sometimes;4=never;5=no anal or vaginal sex with occasional partners in the last three months
20.	Do you currently have any of these symptoms?	1=genital discharge; 2= pain or burning when urinating; 3= pain or swelling of the testicles; 4= genital ulcer, vesicles, rash, or swelling; 5= abdominal pain; 6= pain at defecation; 7= rectal pain or discharge; 8= rectal ulcer, vesicles, rash or swelling; 9=sore throat;
21.	How happy are you with your sexual life at the moment	Scale 1 to 10, where 1 = very dissatisfied; 10 is very happy.
	Over the last 2 weeks, how often have you been bothered by the following problems:	
22.	Feeling nervous anxious or on the edge	1= not at all; 2= some days; 3= more than half the days; 4= nearly every day
23.	Not being able to stop or control worrying	1= not at all; 2= some days; 3= more than half the days; 4= nearly every day
24.	Little interest or pleasure in doing things	1= not at all; 2= some days; 3= more than half the days; 4= nearly every day
25.	Feeling down, depressed, or hopeless	1= not at all; 2= some days; 3= more than half the days; 4= nearly every day
26.	Have you used any of the following substances in the last three months?	1= Alcohol; 2= poppers (nitrite inhalants); 3= Sedative or tranquilizers (Valium®, Rivotril®, Rohypnol®, Xanax®, Seduxen®, Phenazepam); 4=Cannabis; 5=Ecstasy/MDMA; 6=Cocaine; 7= Crack cocaine; 8=GHB/GBL; 9=Ketamine; 10= Amphetamine/Speed; 11=Mephedrone; 12= Synthetic stimulants other than mephedrone (eg. MXE, bathsalts, 3MMC, 4MEC, 4_FA, XTClight); 13 =Crystal Meth/Tina, 14= Heroin or other opioids, 15= LSD (acid), 16= I took drugs, but I don't know which drugs , 17= I have not taken any drugs or alcohol
27a.	<i>If 27 is any other than 17: Have you used any</i>	1= Alcohol; 2= poppers (nitrite inhalants); 3= Sedative or tranquilizers (Valium®, Rivotril®,

	of these substances in combination with sex in the last three months?	Rohypnol®, Xanax®, Seduxen®, Phenazepam); 4=Cannabis; 5=Ecstasy/MDMA; 6=Cocaine; 7= Crack cocaine; 8=GHB/GBL; 9=Ketamine; 10= Amphetamine/ Speed; 11=Mephedrone; 12= Synthetic stimulants other than mephedrone (eg. MXE, bathsalts, 3MMC, 4MEC,4_FA, XTClight); 13 =Crystal Meth/Tina, 14= Heroin or other opioids, 15= LSD (acid), 16= I took drugs, but I don't know which drugs; 17= I have not taken any drugs or alcohol in combination with sex
27b.	<i>If 27 was 6, 9, 10, 13 or 14: Have you injected any of these substances?</i>	1=Cocaine, 2=Ketamine, 3=Amphetamine, 4=Crystal meth, 5=No intravenous use
28.	Do you worry about your recreational substance use? (for example: did you encounter problems in your social life, at work or with your health due to these substances?)	1=yes; 2=no
29.	How many cigarettes do you smoke per day	0-99
30.	Since your last visit do you take any new medication?	<i>"list of last visit should be shown"</i>
31.	Do you want your doctor/ health care provider to see the answers of your questionnaire? It will help her/him to address specific topics, that might be important for you.	1= yes 2= no
31.	Is there something specific you want to discuss with your doctor on this visit?	

Part B2 (optional): baseline and follow-up visit

After finishing Part B1, participants will be given the possibility to answer additional questions. Alternatively, they may exit the online questionnaire and proceed to the next follow-up visit.

1.	Since your last negative HIV test, did you think your pill intake was good enough to protect you from HIV when you were at risk?	1=yes, 2=No
2.	If 1=2, was this because you	1=I forgot to take pills; 2=I had an unexpected risk

	(Please tick all that apply)	when not taking pills before; 3=I lost pills; 4=I did not have pills during a period of risk; 5=I ran out of pills; 6=Other reasons (free text)
3.	If B1,15=1 and B1, 5=1: does your partner know that you take PrEP?	1=yes; 2>No
4.	If B1,15=1 How good can you talk with your partner about the sexual relationship you have with each other?	1-10, 999= We are not in a sexual relationship
5.	Did you engage in fisting in the last 3 months?	1=no; 2=yes active and passive; 3= yes only active; 4=yes only passive
6.	Do you use dating-apps? (planetromeo®, grindr®, Scruff®, hornet® etc.)	1=Yes; 2>No
7.	If 6=1 how often do you approximately switch on a dating app	1=several times a day; 2= once a day; 3=several times a week; 4= once a week; 5= every couple of weeks; 6= Less frequently
8.	If B1,5=1 and 6=1, do you state on your dating-profile that you use PrEP?	1=yes, 2>No
9.	Does using a dating app improve your sex life?	1= yes, my sex life improved a lot, 2= yes, my sex life improved a bit; 3=My sex life hasn't changed due to dating apps; 4=no, my sex life got a bit worse; 5=no, my sex life got much worse; 9= I don't know/can't tell
10.	If 8=1: Have people made abusive comments on dating apps regarding your PrEP use in the last three months?	1=yes, 2>No
11.	Have you been discriminated against on a dating app in the last three months	1= no; 2= yes because of my skin color, 3 = yes, because of my age; 4= Because of my body features.
12.	In the last three months, have you used dating apps for sexdates only?	1=Yes; 2>No
12a.	If 12=2, for what else have you used them?	1=To meet someone, hoping that a relationship would develop; 2: To meet someone for social activities, without being on a date or having sex. 3= to chat only
13.	Have you felt ashamed of your behavior against others on a dating app in the last three months?	1=yes; 2=no
14.	Does the use of Dating Apps impair your other daily activities?	1=yes; 2=no
15.	Where have you received health/medical information in the last 3 months	1=physician/health care professional, 2=friends, 3=internet (also in chat/dating apps)

16.	If 15= 3: Which internet sources have you used	1= search engines (google, yahoo..), 2= social media (facebook) 3=Chatrooms (gayromeo, grindr) 4=specific health pages, 5= original medical journals, 6=forums
17.	If 16=4 or 5	Please specify
18.	Do you want your doctor/health care provider to see the answers of your questionnaire? It will help her/him to address specific topics, that might be important for you.	1= yes 2= no

Part C (Feedback): baseline and follow-up visit

1.	How satisfied have you been with your last visit?	1-10 (1=worst 10=best)
2.	Is there anything you want to tell us?	<i>Free text</i>

Part D (to be completed by health care providers): baseline and follow-up visit

1.	Reason for the visit today	1=information on PrEP;2=start PrEP; 3=regular PrEP follow-up; 4=unplanned visit (STI); 5=unplanned visit (other) (please specify: free text)
2.	Does the patient qualify for PrEP according to the current SwissPrEPared recommendations?	1=No 2=Yes
3.	Side effects of PrEP	1= No, 2=Nausea; 3= Diarrhea;4=Headache, 5= other
4.	Has the patient reported symptoms of a primary HIV infection?	1=No; 2=Yes
5a.	Screening for Gonorrhea	1=positive 2=negative 3=not performed
5b.	Screening for Chlamydia	1=positive 2=negative 3=not performed
5c.	Screening for M. gen.	1=positive 2=negative 3=not performed
5d.	Screening for Syphilis	1=positive 2=negative 3=not performed
5e.	Screening for Hep C	1=positive 2=negative 3=not performed
6.	HIV test performed	1=No; 2=yes 4th generation Combotest; 3=yes pcr; 4= yes, other than 4th generation or pcr;
6a.	If 6=yes, result?	1=reactive 2=not reactive
6b.	If 6a=reactive, was an infection proven?	1=No 2=Yes
7.	If 5a-d=no, please explain why no STI-screening was performed	Free text
8.	Creatinine/GFRUnit
9.	GPT	...Unit
10.	Prot/creat Quotient	...Unit
11.	Last HBV screening?	Date: XXX
11a.	Anti-Hbs ag	1=Neg 2=Pos, Titer if available (show last value)
11b.	Hbsag	1=Neg 2=Pos
11c.	If Hbsag=Pos HBV DNA PCR:	XXX copies/ml
11d.	Anti-Hbc	1=Neg 2=Pos
12.	Medical history	Sub-questions
12a.	Depression	1=No 2=Yes
12b.	Renal disease	1=No 2=Yes
12c.	Osteoporosis	1=No 2=Yes
12d.	Other relevant	Free text
13.	Any Co-Medication <i>Show list, patient filled out</i>	Free text
14.	Any new medical problems/diagnosis since last visit <i>Show list of diagnosis</i>	Grouped by organ systems
15.	Vitamin D supplementation?	1=Yes; 2=No
16.	Vaccinations <i>Show list of vaccinations from last visits</i>	1= Gardasil®9; 2=Engerix; 3=Haverix;4=Twinrix;5=other (free text)
17.	Assessment of existing knowledge about PrEP done?	1=No; 2=Yes
18.	Information provided on Adherence issues, risk on resistance, STI including HCV and HIV, side-effects of TDF/FTC?	1=No; 2=Yes
19.	Information provided about signs and symptoms of an acute HIV infection	1=No; 2=Yes

Part E (to be completed by study participants): unplanned visit

1.	What was the reason for your visit today	1=sexual transmitted disease, 2=PrEP related problem; 3=other acute illness
	Continue with C	