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Feasibility and impact of online HIV/STI screening addressed to men who have sex with men and transgender women users of pre-exposure prophylaxis (PrEP) in Spain (TESTATE PrEP): a study protocol for a non-blinded randomised controlled trial

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ABSTRACT

Introduction The objectives of the study are: to design and implement a pilot intervention to offer self-sampling kits to detect HIV, *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG) and *Treponema pallidum* (TP) among gay, bisexual and other men who have sex with men and transgender women users of pre-exposure prophylaxis (PrEP) as part of PrEP follow-up. To evaluate if the pilot intervention causes a reduction of the retention to PrEP follow-up among the target population. To analyse the capacity of the intervention to reduce the healthcare burden on the PrEP service. To evaluate the acceptability of the intervention among PrEP users and PrEP service healthcare workers and; to validate dried blood samples for treponemal and non-treponemal antibody detection using the Dual Path Platform syphilis screening and confirmatory assay compared with blood drawn by venous puncture.

Methods and analysis We will perform a non-blinded randomised controlled non-inferiority trial among PrEP users on follow-up. Participants on the control arm will follow the usual follow-up protocol with quarterly face-to-face visits where they will be tested for HIV and sexually transmitted infections (STIs). Participants in the experimental arm will alternate face-to-face meetings with online screening of HIV and STIs. The website https://testate.org/ will include a module for online follow-up visits of participants. Participants of the experimental arm will order self-sampling kits for HIV, CT, NG and TP through the website, will send the samples to the laboratory and check their results online. We will compare the retention to follow up and the healthcare burden in both arms. The acceptability of the intervention among participants and healthcare workers will be assessed.

Ethics and dissemination The project has been approved by the CEIC-HUGTIP (Reference: PI-22-051). Subjects will be included after giving their informed consent. Final conclusions and recommendations will be shared with stakeholders. Two publications in peer-reviewed journals are expected.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The TESTATE pre-exposure prophylaxis (PrEP) study encompasses a range of objectives, including designing a pilot intervention, evaluating its impact on retention in PrEP follow-up, analysing its potential to reduce healthcare burden, assessing acceptability among users and healthcare workers, and validating a novel testing method.

⇒ TESTATE PrEP study employs a non-blinded randomised controlled non-inferiority trial design, allowing for a robust assessment of the intervention's effectiveness compared with the standard approach.

⇒ The integration of an internet-accessed e-HIV/sexually-transmitted infection (STI) screening for follow-up visits and self-sampling kits enhances accessibility and convenience for participants, potentially increasing engagement in the intervention.

⇒ The TESTATE PrEP intervention is based on the website https://testate.org/, a self-sampling strategy for HIV and STIs with a demonstrated high level of acceptability in Spain.

⇒ The study is addressed to gay, bisexual and other men who have sex with men and transgender women, the populations most impacted by the HIV and STI epidemics in Spain.

Trial registration number NCT05752643.

INTRODUCTION

Background

In 2021, 2786 new HIV diagnoses were reported in Spain, representing a rate of 5.89 per 100 000 inhabitants, 86.1% were men and the median age was 36 years (IQR: 29–46). Gay, bisexual

and other men who have sex with men (GBMSM) accounted for the majority (56.3%) of transmissions, and 49.8% of new diagnoses presented a late diagnosis.[1]

Although HIV testing and condom promotion remain essential for risk reduction, these numbers reflect the need for a more radical approach for people not living with HIV and those with inconsistent condom use. One such approach is pre-exposure prophylaxis (PrEP), providing antiretroviral drugs before HIV exposure to prevent infection. The biological efficacy of daily oral tenofovir-based PrEP regimens in reducing HIV acquisition has been confirmed in randomised placebo-controlled trials, including GBMSM,[2 3] heterosexual individuals[4 5] and people who inject drugs.[6] PrEP has also proved to be cost-effective[7] and also supports the strategy of promoting early diagnosis of HIV and other sexually-transmitted infections (STIs) in populations at higher risk of contracting them, as well as early treatment in positive cases detected.[8]

PrEP is an intervention recommended by Joint United Nations Programme on HIV and AIDS to contribute to ending the HIV epidemic, as a complementary strategy to others already underway and framed in the 95-95-95 objectives for 2030.[9]

In those people who start PrEP, it is essential to carry out a correct clinical follow-up to quickly detect possible complications/events that might require additional actions. The clinical follow-up of PrEP users consists of 4 face-to-face follow-up visits per year in which participants receive a 3-month supply (90 tablets for those participants on daily PrEP or the required amount for those having PrEP on demand) of emtricitabine and tenofovir disoproxil (TD-FTC) and 3-monthly STI (*Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG) and syphilis) and HIV testing is conducted to minimise prolonged use of PrEP in the presence of a new HIV infection and to detect asymptomatic infections.[10] Furthermore, hepatitis A, B and human papilloma virus vaccines are offered and hepatitis C is screened annually.

The COVID-19 pandemic has had a considerable impact on testing for HIV, viral hepatitis and STIs in the WHO European Region.[11] Social distancing and community containment measure protocols implemented to prevent and contain the spread of COVID-19 affected the HIV prevention and care continuum; with reduced access to HIV testing, linkage to prevention and care services and antiretroviral therapy or PrEP initiation and maintenance.

Complementary testing modalities for existing testing strategies such as self-testing (for HIV) and self-sampling (for HIV, viral hepatitis and STIs), had not been widely implemented before the pandemic.[12] They constitute innovative options to diversify and optimise access to testing that should be regulated and made available as part of policy and practice at a national level.

Digital technologies are increasingly used to deliver sexual health interventions (e-sexual health),[13] including internet-accessed STI testing (e-STI testing). It enables users to order a test kit on-line, collect their own samples, return samples to a laboratory and be notified of their results by text message, phone or email.[14] e-STI testing may bypass the inconvenience and stigma associated with face-to-face services; and it could expand access to populations who do not use these services. Shifting tasks to patients via virtual services has proven cost-effective.[15] Prior research has shown that e-STI testing services increase uptake of STI testing, including HIV, for all groups, including high-risk groups.[16–18] Previous studies highlighted the crucial role that community-based organisations[19–21] in this context.

This study is based on the TESTATE project, launched in 2018 and aimed to design and implement an online self-sampling intervention for HIV, STI and hepatitis C testing and online result consultation among GBMSM and transwomen users of gay dating apps in Spain.[22]

Objectives

The general objective of the study is to design, implement and evaluate the feasibility, acceptability and impact of an innovative internet-accessed HIV and STI screening intervention (TESTATE PrEP) addressed to GBMSM and TW users of PrEP in Spain as part of PrEP follow-up.

New approaches are needed for a better management and Syphilis screenings, especially in hard-to-reach populations. One potential solution is using dried blood spots (DBS) as a convenient sample collection method for expanding syphilis screening programmes. Our study aims to assess the effectiveness of DBS samples for syphilis diagnosis as a secondary objective.

Specific objectives

1. To design and implement an e-HIV/STI testing pilot intervention (TESTATE PrEP) to offer self-sampling kits to detect HIV, CT, NG and *Treponema pallidum* (TP) among GBMSM and TW users of PrEP in Spain as part of PrEP follow-up.
2. To evaluate if the pilot intervention causes a reduction of the retention to PrEP follow-up among the target population.
3. To assess the potential impact of the intervention in reducing healthcare burden associated with PrEP provision and monitoring.
4. To assess the acceptability of the intervention among the target population and PrEP service healthcare workers.

Secondary objective

To validate the use of dried blood samples to detect treponemal and non-treponemal antibodies using the Dual Path Platform (DPP) syphilis screening and confirmatory assay compared with blood drawn by venous puncture.

METHODS AND ANALYSIS

Study design

We will carry out a non-blinded randomised controlled non-inferiority trial (figure 1). Participants will be randomly allocated either to alternate face-to-face follow-up visits with online screening for HIV, CT, NG and TP every 3 months (experimental arm) or have four

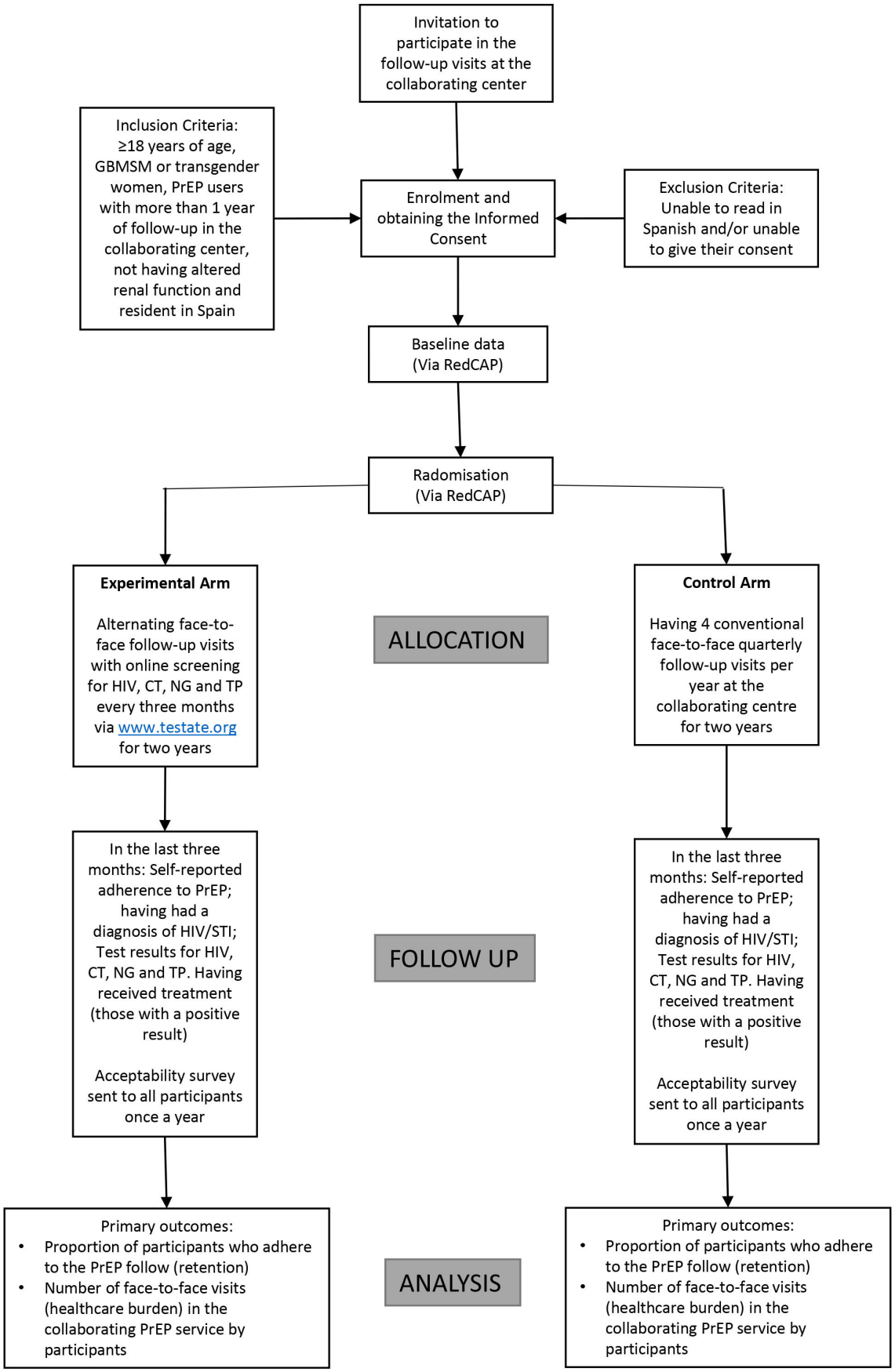

Figure 1 Flow diagram of study enrolment, randomisation, intervention arms, follow-up and analysis. CT, *Chlamydia trachomatis*; GBMSM, gay, bisexual and other men who have sex with men; NG, *Neisseria gonorrhoeae*; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection; TP, *Treponema pallidum*.

conventional face-to-face quarterly follow-up visits per year (control arm).

Eligibility

Inclusion criteria will be: ≥18 years of age, cisgender GBMSM or TW, PrEP users with more than 1 year of follow-up at the collaborating centre (The Drassanes Vall d'Hebron Centre for International Health and Infectious Diseases, Barcelona), no altered renal function, understanding of Spanish, signing the informed consent and resident in Spain.

Exclusion criteria for participants will be: <18 years of age, not being cisgender GBMSM or TW, PrEP users with less than 1 year of follow-up in the collaborating centre (same as above), having altered renal function, not understanding Spanish, not signing the informed consent, and not resident in Spain.

Recruitment and consent

Eligible individuals will be invited to participate during the PrEP follow-up visits at the collaborating centre. Additionally, the centre will display an informational poster about the study, encouraging potential participants to communicate their interest to the healthcare staff. Healthcare professionals will assess eligibility, provide verbal and written information about the study, and collect participants' consent via an online form (online supplemental material). A hotline and an email will be available for participant inquiries.

Allocation

Participants will be randomly assigned 1:1 to the experimental or the control arm. Block randomisation will be used to maintain a balance between the intervention and control groups.

After obtaining the informed consent the health professional will enter the name, surname and CIP code (Personal identification code of the Catalan Public Heath Care system) of the participant into an independent computer-based randomisation programme (REDCap (REDCap Systems, Vanderbilt University, USA)) that will generate a unique research number and allocate participants to either the intervention or the control group. The randomisation process will guarantee that neither front-line care providers, nor investigators or participants will be aware of whether the next eligible participant will be allocated in the control or experimental arm. Due to the nature of the intervention, it is not possible to blind either the participants or healthcare professionals.

Control arm

Participants will continue the conventional PrEP follow-up in the same service. In each follow-up visit, participants will receive a 3-month supply of TD-FTC and will be tested for HIV, CT, NG and Syphilis in the same service. Every 6 months, hepatitis C will be tested and renal function monitored. Those with a positive result will follow the circuits of the collaborating centre.

Experimental arm

Participants will alternate face-to-face visits with online screening every 3 months, having two face-to-face and two online screenings per year. The face-to-face biannual follow-up visits will be performed as usual. For the online follow-up, participants will receive a self-sampling kit for HIV and STIs (CT, NG and Syphilis) and 3-month supply of TD-FTC to their homes by certified mail. The online follow-up visits will be based on the TESTATE project (https://testate.org/). At the baseline visit, participants will be asked to register and enter the postal address where the self-sampling kits and medication will be sent. Test results of the online screening will be consulted through the project website. Participants will receive an email and an Short Message Service (SMS) with result availability and a link to consult them. Brief pretest information and post-test counselling will be provided according to the European and Spanish guidelines for HIV and STI screening. When a participant of the experimental arm has a positive result, the PrEP service will be alerted by email.

The website will include a follow-up module with an online survey that will be self-answered by participants at each online follow-up visit.

Measures to ensure adherence to the experimental intervention

If participants do not submit samples within 15 days of their PrEP follow-up due date, the field coordinator will call and prompt them to send samples to the reference lab. For unconsulted test results, automated email and SMS reminders will be sent from the project website. Positive results trigger reminders within 1 week. If positive participants do not request a service appointment within a week, PrEP service staff will contact them for an in-person visit and treatment.

Self-sampling Kits

Kits will include an oral swab to detect HIV antibodies (ORACOL Saliva Collection Device, Malvern Medical Developments, Worcester, UK), a pharyngeal and an anal swab (Deltaswab, DELTALAB, Rubí, Spain), and a urine pot (Biogen Diagnostica, Sant Cugat del Vallès, Spain) to collect samples for CT and NG detection. A lancet and a Whatman card (Biosample Card, ACEFESA, Gavà, Spain) to obtain DBS to determine TP will be included. The DBS samples will be sent in resealable barrier envelopes for 903 protein saver cards.

A prepaid envelope to post the samples to the reference laboratory at no cost will be included. The kit will include brochures with detailed instructions with pictures explaining how to get the samples. A video with the instructions of sample collection will be available on the project website and YouTube. The video will be accessible through a QR code included in the brochure.

A hotline will assist participants on self-sampling performance.

Laboratory analysis

All samples in the online HIV and STI screening will be analysed by the reference laboratory (Microbiology Service of Hospital Germans Trias i Pujol, Metropolitan Nord Laboratory). Samples taken in the PrEP service will be analysed by the Vall d'Hebron Microbiology department as usual.

HIV: Oral fluid samples for HIV testing will be collected using the Oracol saliva collection device (Malvern Medical) and will be tested with the LIAISON XL HIV Ag/Ab chemiluminescence assay (Diasorin, Vercelli, Italy) for the detection of antibodies against HIV1+2 and antigen p24 HIV1.

CT and NG: Pharyngeal and rectal samples will be collected with flocked swabs (Deltalab, Rubí, Spain), urine will be collected in a tube (Biogen Diagnostica). We use the Alinity m STI assay (Abbott Molecular) to detect CT, NG, *Trichomonas vaginalis* and *Mycoplasma genitalium* (only CT and NG results will be reported). Validation of DBS for syphilis diagnosis: Previous to the recruitment of participants, a validation study of DBS samples for microbiological syphilis diagnosis will be carried out, and it will be compared with the result obtained from serum samples. For the validation study, we will randomly select 62 serum samples from 62 patients from the Germans Trias i Pujol Hospital (Badalona, Spain) with a positive result for the treponemal test TREP SCREEN (Diasorin, Vercelli, Italy) and for the reaginic test with several titres (Beckton Dickinson, New Jersey, USA) processed in the Serology Section of the Microbiology Service and 62 serum samples from 62 patients with negative treponemal and reaginic test. Additionally, a total of 102 serum positive samples for treponemal and reaginic tests and 57 negative serum samples will be randomly selected in order to evaluate the performance of DPP syphilis screening and confirmatory assay e (Chem-Bio, Hauppauge, EEUU) to detect treponemal and non-treponemal antibodies. The DBS samples will be stored with the remaining whole blood sample collected to perform the haemogram in EDTA-containing tubes. Fifty microliters of whole blood will be blotted onto Whatman 903 filter paper (ACEFESA) in four separate spots. Spots will be dried at room temperature overnight. For DBS testing, the DBS will be punched from the filter paper into a Falcon tube and will be eluted in 500 µL of buffer solution. The evaluation process will be performed for 4 hours at room temperature on a rotation table. After centrifuging, the eluate will be directly used for DPP assay.

Data collection

Baseline visit

The following data will be collected during the visit: participant's study ID number, date and country of birth, sex at birth, gender identity, sexual orientation, level of education, monthly salary, sex work, drug use, chemsex and modality of PrEP used (daily or on demand) in the last 3 months. Tests for HIV and STIs will be performed.

During the baseline visit, participants will be asked to enter their baseline data directly into the RedCAP database (control arm) or onto the project website (experimental arm).

Follow-up visits

Follow-up visit (face-to-face and online visits): At each visit the following information will be collected: date and type of visit (PrEP follow-up visit, emergency visit, sample extraction, delivery of test results, other), modality of PrEP used in the last 3 months (daily or on demand), having had a diagnosis of HIV, CT, NG, TP or other STI in the last 3 months, having had any side effects of PrEP in the last 3 months, self-reported adherence to PrEP. Test results for HIV, CT, NG and TP. Having received treatment (for those with a positive result for HIV/STIs).

Participants will be asked to enter their follow-up data directly into the RedCAP database (at face-to-face visits of both arms), or the project website (at online screening visits of the experimental arm). A tablet will be provided by the PrEP service staff during the face-to-face visits to enter data into the REDCAP database and the project website.

Clinical data will be extracted monthly from the electronic medical records of the PrEP service. Test results of online screening will be uploaded to the project website by the lab staff. Participants will receive an email and an SMS informing them about the availability of their results and the link to consult them once they are available.

Outcomes

The primary outcomes will be the proportion of participants who adhere to the PrEP follow-up in each study arm (retention), and the number of face-to-face visits (healthcare burden) in the collaborating PrEP service by participants in each study arm. Box 1 shows the secondary outcomes .

Box 1 Secondary outcomes

- ⇒ Proportion of participants diagnosed with HIV in each arm.
- ⇒ Proportion of participants diagnosed with *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *Treponema pallidum* infections in each arm.
- ⇒ Proportion of participants who are prescribed treatment for HIV/sexually transmitted infection in each arm.
- ⇒ Adherence to pre-exposure prophylaxis (PrEP) in each arm.
- ⇒ Number of participants of the experimental arm who send the samples to the laboratory, and consult the results.
- ⇒ The proportion of participants in the intervention group who agree that the online follow-up combined with the face-to-face follow-up at the PrEP service is acceptable.
- ⇒ The proportion of participants in the control group who agree that face-to-face follow-up at the PrEP service is acceptable.
- ⇒ The proportion of healthcare professionals of the PrEP service who agree that the online follow-up combined with the face-to-face follow-up at the PrEP service is acceptable.

Retention will be defined as the proportion of PrEP users who have not missed any follow-up visit: Number of participants who have not missed a follow-up visit/total number of participants in follow-up for PrEPx100 (%).

We will define participants as having a missed visit if they miss one of the quarterly visits (independently of the study arm) and do not reschedule it in a period of 30 days after the expected face-to-face visit date (control arm), or those who do not send the samples and answer the online follow-up survey in a period of 30 days after the expected online visit date (experimental arm). If a spontaneous visit occurs between 15 and 30 days before a face-to-face visit for PrEP follow-up, this visit will be used as a visit for PrEP follow-up.

Healthcare burden will be defined as the median number of face-to-face visits at the collaborating centre per participant per year. A comparison between the median number of face-to-face visits for each participant per year in both study arms will be conducted.

Adherence to daily PrEP will be assessed using the Simplified Medication Adherence Questionnaire (SMAQ),[23] adapting the questionnaire to assess the adherence to PrEP on demand. We will analyse the global SMAQ score and one specific item referring to the number of missed doses during the previous week.

Acceptability

Annually, participants of both arms and health workers will be contacted by email and invited to answer a brief online and anonymous self-administered acceptability survey. Variables: Level of satisfaction with the intervention (experimental arm) and the PrEP service follow-up protocol (both arms) (Likert scale), perceived advantages and disadvantages of the online screening, aspects to improve (open field).

Focus group with staff of the PrEP Service: A focus group will be held at the end of the implementation period with a subset of 6 healthcare workers from the PrEP Service. The topics of discussion will include impact of the online screening on their professional practice, identification of potential measures to improve the implementation of online follow-up of PrEP users and measures to facilitate participant retention to the follow-up. Focus group sessions will be recorded and the records will be later transcribed for analysis. The transcripts will undergo qualitative content analysis facilitated by the Atlas.ti software (Atlas.ti Scientific Software Development, Berlin, Germany).

Sample size

Evaluation of the feasibility and impact of the intervention: The sample size calculation was based on the percentage of participants who exhibited non-adherence to the PrEP follow-up within the same STI clinic as our trial.[24] To obtain a power of 80.0% to reject the null hypothesis from a one-sided proportion non-Inferiority test for two independent samples, taking into account that the ratio of patients control-treated is 1:1, and the significance level is 5.00% and assuming that the proportion in the control arm is 12.70%, the proportion in the experimental arm is 10.0%, the proportion of participants in the control group with respect to the total is 50.0%, and the non-inferiority limit is 8.0%, therefore, it will be necessary to include 109 experimental units in the control arm and 109 units in the experimental arm. The total number of participants in the study will be 218.

Validation of DBS samples for microbiological syphilis diagnosis: To obtain a power of 80.0% to reject the null hypothesis from a one-sided proportion non-inferiority test for two related samples, taking into account that the ratio of patients control-treated is 1:1, and the significance level is 5.00%, and assuming that the proportion in the reference group is 99.9%, the proportion of participants in the control group with respect to the total is 99.0% and the non-inferiority limit is—5.0%, therefore, it will be necessary to include 62 matches of experimental units in the study. The total number of participants in the study will be 124 individuals (62 positive syphilis and 62 negative syphilis).

Data analysis

Evaluation of the efficacy of the intervention (primary outcomes): Retention and level of acceptability of participants in both study arms will be compared using Pearson's χ^2 test. Healthcare burden in both study arms will be compared using Kruskal-Wallis. A descriptive analysis will be carried out, comparing epidemiological, clinical and sociodemographic characteristics between those who missed a follow-up visit and/or are lost to follow-up and those who are not. The proportion of participants diagnosed with HIV/STI in both arms will be compared. We will also compare the proportion of participants in both arms that received treatment after a positive result for HIV/STI. Qualitative variables will be compared using Pearson's χ^2 test, or Fisher's exact test if necessary. Regarding quantitative variables, comparisons will be made between two or more groups using non-parametric tests (Kruskal-Wallis). Subsequently, a multivariate logistic model will be used (stepwise methodology) to estimate the factors associated with follow-up losses (number of participants who missed a follow-up visit/number of participants in follow-up) and positive results for HIV and STIs (number of participants who had a positive result for HIV or STIs tests/number of participants in follow-up) in each study arm. For all analyses, a significance level of 5% will be considered.

Validation of DBS samples for syphilis diagnosis: We will compare the frequencies of positive results of TP infection (*Treponema pallidum* haemagglutination and RPR) between the two samples (venipuncture and DBS) using the McNemar's 2 test. The sensitivity and specificity of the treponemal test and RPR for the DBS samples will be calculated assuming serum obtained through venipuncture as the gold standard. The inter-rater agreement will be determined using percent agreement and Cohen's kappa coefficient statistic (K) with corresponding 95%

CI. Additionally, for the chemiluminescence treponemal assay, receiver operating characteristic curves will be calculated to obtain the best value in terms of sensitivity and specificity for the DBS samples.

Data monitoring

Given the study's design and focus on non-treatment outcomes, a data monitoring committee (DMC) may not be necessary. The intervention involves low-risk online HIV/STI screening, reducing safety concerns compared with high-risk drug trials. This lessens the need for an extensive DMC safety mechanism.

Interim analyses

At 12 months of follow-up, an interim report will summarise data for each study group, including participant demographics, PrEP follow-up retention, new HIV/STI diagnoses and face-to-face visits. The report will be shared with the research team and made accessible to participants through newsletters and the project website.

Stopping guidelines

The trial would pause for safety assessment if adverse events related to self-sampling or online follow-up significantly increase. Similarly, if the experimental arm shows a substantial decrease in PrEP follow-up retention or if participants report dissatisfaction or challenges with online screening or self-sampling kits, the trial may be paused for intervention evaluation. Dissatisfaction or challenges reported by healthcare workers or unforeseen technical issues compromising data security may also trigger a trial review and potential halt.

Trial timeline

Recruitment of participants will start on month 18, June 2023. Participants' follow-up will be 24 months. A detailed trial timeline is shown in table 1.

Table 1 Trial Timeline

Timeline	Tasks
Months 1–6 (January–June 2022)	Trial setup
By month 13 (January 2023)	Validation of the DBS samples
	TESTATE website extended to include the offer of self-sampling kits to screen HIV and STIs for PrEP users
By month 17 (May2023)	Website and the established circuits piloted
Month 18 (June 2023)	Recruitment to the trial started
By month 20 (August 2023)	Recruitment to the trial completed
By month 29 (May 2024)	First interim report completed
By month 41 (May 2025)	Follow-up completed
By month 45 (September 2025)	Data analysis completed
	Final report developed
By month 48 (December 2025)	Paper submited for publication

DBS, dried blood spots; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection.

Patient and public involvement

While no patients were directly involved in the design and execution of this clinical trial, we are committed to assessing the acceptability and relevance of the intervention studied from a patient perspective. As one of the secondary outcomes of the trial, we plan to seek patient feedback on the acceptability of the intervention and its potential impact on their experiences and outcomes. Once the results of the trial will be published, participants will be informed of the main results through the project website (https://www.testate.org) and will be sent details of the results in a study newsletter suitable for a non-specialist audience.

Study limitations

The study uses a sample of PrEP patients with more than 1-year follow-up in the collaborating centre. We opted to exclude participants with less than 1 year of PrEP follow-up due to the challenges associated with conducting additional tests recommended by current guidelines during the initial year of PrEP usage. We recognise this approach's potential impact on result generalisability to a wider population. Self-reported data carry information bias risk due to potential memory lapses or misrepresentation. Using self-administered digital questionnaires on tablets or mobile phones could help reduce this bias. Titres of samples for the RPR test will be selected randomly with several titers. Unfortunately, higher titres are not as frequent as lower ones, so a lack in non-treponemal results will be assumed in the validation of DBS for syphilis diagnosis. An alternative strategy to self-collect finger blood to diagnose syphilis will be considered if we are not able to validate DBS. Finally, while transitioning from provider–patient interactions to more self-sampling and online consultations lessens the healthcare burden and boosts centre efficiency, there would be inherent disadvantages associated with this approach as well. We'll thoroughly explore these implications through annual participant and healthcare worker surveys and end-of-implementation focus groups.

ETHICS AND DISSEMINATION

Ethical aspects

The project has been approved by the CEIC-HUGTIP (Reference: PI-22-051) and CEIC-Hospital Universitari Vall d'Hebron (PR(AG)203/2022). Subjects will be included once they have given their informed consent. The ethical principles of the Declaration of Helsinki, the Standards of Good Clinical Practice, the legislation on biomedical research (Law14/2007) and the

obtaining and processing of biological samples and biobanks will be respected (RD1716/2011). The data processing will be done in accordance with the current regulations on data protection law (Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016; and the Spanish Organic Law 3/2018, of 5 December) to preserve the confidentiality of participants.

Information collected in this project will be confidential and no one but the researchers and healthcare professionals of the collaborating PrEP service will be able to see it. Data collected will be stored encrypted. The server will be protected by implementing the access control and registration of Microsoft's SQL database engines and the server will be hosted in the database server nest of the Catalan Institute of Oncology. No data transfer will be made to third parties.

All participants will be approached and given information regarding the study using a detailed informed consent document. Individuals expressing interest in participating will be provided with a copy of the informed consent document. Opportunities will be given to ask questions including the provision of contact details to allow potential participants to reach members of the study team after the clinical visit. The consent will be obtained, during the clinical visit and eligibility will be assessed. The consent process will continue throughout the study with confirmation of willingness to continue participation at each contact. Data collected will pertain to each patient and they will be informed of the means of requesting deletion of the data at any point.

The protocol has been registered at www.clinicaltrials.gov, identifier number: NCT05752643. Protocol version 1, 2 March 2023.

Publication plan

An annually report with preliminary results will be generated to give feedback to the stakeholders. The final analysis, conclusions, and recommendations will be shared with all the stakeholders and communicated to the general public. Results will be published in peer-review open-access journals; including one with the results of the validation of DBS to detect active infection of TP and another on the feasibility, acceptability and impact of the intervention. Journals in the first quartile will be prioritised.

Authorship for the two forthcoming publications will be based on substantial contributions, manuscript drafting or revisions, and unanimous approval by all listed authors. Professional writers are not anticipated.

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Contributors CA conceptualised and HMR, JG-P designed the study. CA, YD and MM-F developed the data analysis plan. VD, GF and AR-M developed the lab analysis contents. CA reviewed scientific literature and drafted the final version of the protocol. JC contributed to developing the overall TÉSTATE concept and implementation. EM, PR-d and JC contributed to improving the content in the sections of their expertise. All authors made a critical review and approved the final manuscript.

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