mLab App Plus:
A randomized controlled trial of an mHealth intervention for increasing access to HIV and syphilis testing and care among young men

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LIST OF ABBREVIATIONS

CDC	Centers for Disease Control
CFR	Code of Federal Regulations
CUIMC	Columbia University Irving Medical Center
DSMB	Data Safety and Monitoring Board
FDA	Food and Drug Administration
GLMM	Generalized linear mixed model
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IRB	Institutional Review Board
ISO	Information Security Office
mHealth	Mobile Health
MSM	Men who have sex with men
MTF	Male to female transgendered individual
NIH	National Institutes of Health
NYC	New York City
PI	Principal Investigator
PrEP	Pre-Exposure Prophylaxis
RCT	Randomized Control Trial
REDCap	Research Electronic Data Capture
SAE	Serious adverse event
SAS	Statistical Analysis System
STI	Sexual Transmitted Infection
TGW	Transgender women
US	United States
YMSM	Young men who have sex with men
YTGW	Young transgendered woman

mLab App Plus
SCHEMA

Purpose:	The purpose of this research study is to assess the feasibility of the "mLab App Plus," which provides an imaging algorithm that incorporates a duplex HIV/syphilis point-of-care (POC) test.
Design/ Evaluation:	We will conduct a randomized control feasibility trial (RCT) of participants randomized to two study arms: 1) the mLab App Plus and 2) standard of care (SOC).
Intervention:	• mLab App Plus • HIV/syphilis point of care test (DPP® HIV-Syphilis)
Study Duration:	This will be a 3-month study.
Population:	Men who have sex with men (MSM) and transgender women (TGW) who have sex with men ages 18-39 in New York City (NYC)
Sample Size:	40 YMSM and TGW (18-39 years)
Participating Sites:	Columbia University School of Nursing (Washington Heights, NYC)
Data Collection:	We will use self-report surveys to measure demographics, knowledge, attitudes, skills, and behaviors. We will measure testing uptake with data collected from the app and through survey collection.

Summary
MSM, especially young MSM (YMSM), and TGW have some of the highest rates of HIV and syphilis diagnoses in the United States. The goal of this proposed feasibility study is to pilot the mLab App Plus to assess YMSM's and YTGW's abilities to perform and interpret self-tests for HIV and syphilis and consequently increase the number of YMSM and YTGW who initiate self-testing for HIV and syphilis.

1.0 INTRODUCTION

1.1 Background Information and Prior Research

From 2018 to 2019, the rate of syphilis increased by 11.2% [1] It has increased steadily since 2000 especially among men, in which MSM bear a disproportionate majority of cases (47% of all cases were among MSM in 2019) [2, 3].

HIV and syphilis rates continue to rise among YMSM [2, 3]. While MSM account for only about 2% of the US population [4], they are most affected by HIV, constituting 56% of PLWH [2]. Moreover, the rate of syphilis among MSM is profoundly elevated, at least 100 times higher than that in men who have sex with women and even higher among YMSM [5, 6]. Importantly, syphilis makes it easier to both acquire and transmit HIV, and about half of MSM who have syphilis are co-infected with HIV [5].

The risk of syphilis and HIV continues to rise in YMSM in New York City, the study site [6]. Given these epidemiologic risk factors for HIV and syphilis, there is a strong scientific premise for this pilot study that proposes to test innovative and effective HIV and STI testing, prevention, and treatment models. Given that approximately 17% of MSM living with HIV in the U.S. are unaware of their status and significant comorbid syphilis in that population, both pathogens may be simultaneously transmitted [7]. The increasing number of syphilis diagnosed in MSM highlights the importance of STI control in this population, not just for the health of the patient, but also for prevention of HIV and syphilis in uninfected persons.

The number of youths living with HIV continues to rise, and they are disproportionately represented at each stage of the care continuum. Most relevant to this application, it is estimated that less than half of HIV-infected youth in the US have been diagnosed with HIV, and AIDS-related deaths among youth have increased over the past decade despite decreased death rates among all other age groups. Simply stated – youth unaware they are HIV+ cannot get the treatment they need to stay healthy and may infect others without knowing it. Thus, increasing access to HIV testing is a critical component to engaging and identifying YMSM and YTGW with undiagnosed HIV, linking them to care, and lowering forward HIV transmission [7-9].

YMSM and YTGW, and specifically Blacks and Latinos, are disproportionately infected with HIV. To illustrate, in 2015, youth comprised 22% of all new cases of HIV [10]. Of these youth, 81% of infections occurred among YMSM [10]. Among YTGW under the age of 29, limited data exists, but community-based samples suggest an HIV prevalence from 5% to 20% in this population [11]. These numbers are exacerbated in racial/ethnic minorities. Black men who have sex with men (MSM) have more HIV diagnoses than any other racial/ethnic group of MSM (38%) and Black YMSM comprise 39% of these HIV diagnoses [10]. Latino MSM comprise 27% of HIV diagnoses among MSM [7] and 7 out of 10 new HIV diagnoses among Latinos. YTGW have also been disproportionately affected by HIV with the highest percentage of HIV+ test results of any gender category [9].

There are a number of behavioral and social factors that likely account for the high rates of new and undiagnosed HIV infections among youth, and specifically YMSM and YTGW. Engaging in receptive anal intercourse and a higher likelihood of having partners who may be at increased risk for HIV are some of the behavioral factors that potentiate the HIV epidemic in youth [6, 12, 13]. Moreover, having never witnessed the devastating effect of HIV/AIDS in the early years of the epidemic, youth may perceive themselves to be at lower risk of HIV [12]. Social factors including stigma, homophobia, and racism may compound those factors; many YMSM and YTGW feel rejected, isolated, and/or lack social support [12, 14]. Healthcare system factors also contribute to the low HIV testing rates in youth. Many youths avoid contact with providers who offer HIV testing and care due to lack of health insurance, discomfort with facilities and services, fear of stigmatization, and concerns about confidentiality [15-17]. For these reasons, many YMSM and YTGW avoid HIV testing services, making them unaware that they may be infected with HIV [7].

Outreach is needed among YMSM and YTGW to engage them in HIV testing, which remains an important tool in the fight against HIV [18, 19]. There are large disparities in HIV testing rates in youth and ethnic and racial minorities. Among those HIV-infected, only 49% of YMSM aged 18-24 years compared to 66% of adults knew of their infection, highlighting the need for improved outreach for testing among high-risk youth [7, 20]. Among all MSM, 54% of

Black/African American men knew of their infection, compared with 63% of Hispanic/Latino men and 86% of white men [2, 7, 19]. This data reflects major racial and ethnic disparities and, therefore, the need for our proposed study that targets enrollment of Black and Latino YMSM and YTGW (NIMHD priority area) [21, 22]. Transgender women (TGW) of all ages are also immensely burdened by HIV. In one study, TGW were shown to have a lower prevalence of ever having been tested (35.6%) or having been tested in the past year (10.0%) for HIV compared to cisgender gay and bisexual men (61.8% ever tested; 21.6% tested in past year) [9]. TGW have consistently low HIV testing rates and a resultant high percentage of undiagnosed infection in comparison to the general population, pointing to the need for interventions to increase the uptake of HIV testing in this population [23-25]. YMSM and YTGW do not have adequate access to HIV prevention and testing [9, 19] and they have poorer access to healthcare, in general [15, 16]. The healthcare system is failing to test youth, contributing to the high percentage of youth with undiagnosed HIV; this is especially true for YMSM and YTGW who are often overlooked by the current healthcare system [15-17]. As a result, more Black and Latino men end up being tested in non-clinical settings than White men, pointing to the need for expanding non-clinical options, such as self-testing, especially among racial and ethnic minorities [18, 21, 26].

Though HIV self-testing may supplement gaps in healthcare provision, there are concerns regarding its potential to reduce contact with care providers or in healthcare settings where more sensitive tests may be warranted and other prevention approaches, such as pre-exposure and post-exposure prophylaxis, might be delivered [27, 28]. Another concern frequently cited about the HIV self-test is that individuals who receive a reactive or preliminary positive test result may be less likely to seek or to receive a confirmatory test and be linked to appropriate care [29]. Findings from a recent RCT suggests that when supported through a helpline, individuals with HIV that was identified through self-testing were adequately and appropriately linked to care [27]. Perhaps most importantly, there were no serious adverse events described in this study or in other HIV self-testing studies [27, 30]. While HIV self-testing kits can be purchased over the counter, we acknowledge that there has been low uptake of HIV self-testing among YMSM in the US, pointing to the need for technologies, such as the one proposed in this study, to promote the uptake of the HIV self-test (OraQuick test) [31].

The implementation of HIV self-testing for YMSM also provides an opportunity for self-testing of another STI prevalent in the MSM community: syphilis. MSM comprise approximately 46% of cases of concurrent HIV and syphilis infection in the US [3]. The biological nature of syphilis infection, specifically syphilitic ulcer proliferation, facilitates transmission of HIV, making it highly dangerous for PLWH. Syphilis infections in PLWH were also associated with higher HIV viral load and lower CD4 cell counts, and therefore worsen the severity of HIV-related symptoms [32]. Considering the increased harm caused by coinfection with syphilis amongst PLWH, there is a need for increased concurrent testing for HIV and syphilis. One study showed that uptake of concurrent HIV-syphilis testing in a healthcare setting was highest amongst people between the ages of 25-34, suggesting a strong acceptability of concurrent testing amongst youth [33]. Moreover, the study acknowledged the social barriers to concurrent HIV-syphilis testing acceptance within the healthcare setting and called for the development of interventions that circumvent decision-making burden between providers and high-risk patients [33].

1.2 Prior Research

In response to the need for interventions to increase HIV testing in youth, our study team developed

the mLab App, which affords advantages over existing self-test options to support the potential for higher uptake of the HIV self-test. The mLab App is a mobile app on a phone that is accessible using a login name and password. The app provides HIV prevention information, push notification reminders for testing, step-by-step instructions for using the OraQuick HIV tests, and an image upload function so individuals can send an image of their OraQuick HIV test to the study team. Individuals enter the results of the OraQuick test in the app. By using the app, we are asking individuals to help test the app's ability to interpret the results of the OraQuick tests. Individuals are not able see the results of this interpretation on the existing mLab application. If an individual tests HIV positive by the OraQuick HIV test, the mLab app provides information on how to set up follow-up confirmatory testing within the following 24 hours. All information that they provide within the app is stored on a secured server. The mLab App is derived from extensive participatory based research (focus groups, design sessions, usability testing) with young men (CDC U01 PS003715) (described in detail in APPROACH: preliminary study #1) [33-35]. Building on this extensive user-centered design work and the engineering work of Dr. Scherr (Co-I; see APPROACH: preliminary study #3), who developed the automated image processing algorithm to provide real-time interpretation of smartphone camera images of a lateral flow assays for malaria, [36] the mLab App extends the algorithm to interpret the HIV self-test (OraQuick).

The mLab App addresses many of the current barriers to self-testing kits through the integration with a smartphone to overcome ambiguous test interpretations, provides immediate results reporting, and helps support linkage to care. In addition, the mLab user interface promotes a holistic diagnostic experience because it provides step by step error-checking with clear picture directions. While in principle, rapid tests, such as the OraQuick, seem simple to interpret [37] with weak positive bands or weak control lines, it is all-too-often difficult for users to accurately interpret the test results, which we found in our own research on the OraQuick home test [31]. Beyond diagnosis, the mLab App provides information facilitating linkage to care for those who test HIV-positive and educates users on the importance of follow-up testing and prevention services for those who test HIV-negative.

We conducted preliminary studies to support the usage of this intervention for young men:

1) Dr. Schnall led a CDC cooperative agreement (U01 PS004975) using critical iterative end-user feedback to design a mobile app for promoting HIV prevention behaviors in high-risk MSM [35]. The methodological details, associated findings, and final Design Document have been widely disseminated [38]. Findings from this study guided the content of the mLab App, which is being refined in this proposed study.

   Dr. Schnall conducted a study using in-depth interviews, observations, and a think-aloud protocol to understand high-risk young adults' use of the rapid (HIV) self-test. Our study incorporated a performance record to carefully identify competency in self-administration of the test [31]. This study provided evidence of the perceived usefulness of the self-test by young adults, especially in light of their concerns about lack of privacy in medical settings. Notably, only one (of 21) participant followed all of the instructions for using the test. The policy implications of this finding are important since the Food & Drug Administration (FDA) Requirements for labelling and packaging are critical for the safe use of devices, but at the same time, end-users' abilities to understand and use these package inserts, especially in stressful situations, must be better considered [31]. To address this need, we developed the mLab App which provides step by step instructions on the smartphone screen and also an imaging algorithm for interpretation of test results so that the participants can be less burdened by the interpretation of fuzzy red lines, a common and well-known limitation to the self-test.

2) Dr. Scherr's team published its work on smartphone integration of a number of existing

technologies as an attractive tool for standardized detection and reporting of infectious diseases. Dr. Scherr demonstrated that using an unmodified mobile phone to photograph rapid detection lateral flow assays is superior to visual interpretation by inexperienced users. In short, the photo imaging algorithm has been successfully used with lateral flow assay tests for malaria with untrained users in non-clinical settings [(36)]. Dr. Scherr's work demonstrated that an automated image processing algorithm has an improved limit of detection over a commercially available lateral flow reader and reduced reporting errors inherent in visual test interpretation.

To understand high-risk YMSM and YTGW's plans for using the mLab App, barriers to use, and feasibility of using the imaging algorithm (the mLab), Drs. Schnall and Scherr conducted a mixed methods observational study among 18 YMSM and YTGW (mean age 24) who have all engaged in high-risk sexual behavior (unprotected anal sex) in the past 3 months. Participants used the mLab App and then completed a follow-up survey and an in-depth interview. Participants completed the Health-ITUES survey and rated the mLab App as Impact on health (4.3 out of 5), Useful (4.4 out of 5) and Easy to Use (4.4 out of 5). We collected paradata as part of our pilot study and collected time stamps, pages accessed, test image, type of Internet browser, operating system, and the smartphone device. Following the survey, we conducted in-depth interviews to understand high-risk youth's plans for using the mLab App and barriers to use. All of the participants reported this would be a very useful tool for high-risk youth and thought most youth would want to use the mLab App. They also all indicated they would seek follow-up care if they themselves tested positive and saw the principal advantages of the mLab App as being convenient and portable and an enabler for promoting uptake of HIV testing. In particular, participants noted that the mLab would be especially helpful to youth who did not have a close relationship with a provider or were concerned about potential stigma from a provider regarding their sexual behavior. Participants also provided useful feedback on the user interface with suggestions [(39)].

1.3 Rationale

In response to the mLab App study and the scientific evidence of need for at-home syphilis POC testing among YMSM and YTGW, we propose to implement the **mLab App Plus** to assess YMSM's and YTGW's abilities to perform and interpret self-tests for HIV and syphilis and consequently increase the number of YMSM and YTGW who initiate self-testing for HIV and syphilis.

We propose the following Specific Aims:

1**:** Examine the feasibility of using the DPP® HIV-Syphilis test as a self-test to improve uptake and access to STI testing.

2**:** Estimate the effect sizes for the mLab App Plus for improving testing uptake in YMSM and YTGW.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objective of this study is to pilot the use of added syphilis testing to mLab and determine its feasibility among YMSM and YTGW for further use and study, recruiting 40 YMSM and YTGW into the RCT. We will assess demand and a limited effect size to predict

usefulness for a larger study of the application. Because DPP® HIV-Syphilis tests are not yet approved by the FDA for self-administration, participants will complete their self-tests at our clinic in Washington Heights under the supervision of a trained clinician. The clinician will be qualified to use the device according to the approved Instructions for Use (IFU) and will complete the test in a manner consistent with the point of care (POC), non-CLIA waived label of the test. Thus, we will also be assessing participants' abilities to self-administer and interpret DPP® HIV-Syphilis tests. If participants are unable to self-administer, apprehensive, or incorrectly use the DPP® HIV-Syphilis test as per the IFU, the clinician will intervene and conduct the test on the participant.

3.0 STUDY DESIGN

3.1 Randomized Control Trial

We will conduct a small-scale digital RCT to evaluate the feasibility of the mLab App Plus and testing/linkage to care uptake as compared to the control arm (receiving SOC). We will enroll 40 YMSM and YTGW (ages 18-39) who report being negative for HIV and syphilis, or whose statuses are unknown, and randomize them into the intervention or control condition. The trial includes screening, a baseline appointment, and a 3-month follow-up appointment.

Intervention Condition: Participants randomized to intervention will be provided with the mLab App Plus, and a box of condoms. The intervention arm will also complete two HIV/Syphilis Ab Combo Rapid Tests (DPP® HIV-Syphilis Test) at their baseline (1st test) and 3-month follow-up (2nd test) appointments in the clinic (more details in section 5.4 Intervention/Investigation Procedures).

Control Condition: Participants randomized to standard care will be sent an email with links to mobile-optimized online prevention information, including PrEP and HIV/STI testing information found on the CDC website, and a box of condoms [40].

3.2 Study Randomization

After providing informed consent, participants will be randomized to study arms in a 1:1 ratio of intervention to control arms. To reduce opportunities for selection bias, we will use a variable permuted randomization block design where block size itself is randomly selected (i.e., blocks of four to eight). The advantage of a permuted block design is that treatment assignment is pre-determined before the trial begins and assignment remains static throughout the trial. Both groups will receive standard care HIV/STI testing-related risk reduction counseling, a box of condoms, and PrEP assessment. The intervention group will self-administer their first DPP® HIV-Syphilis Test under the supervision of a trained clinician at baseline and again at their 3-month follow-up. No control group participant will be offered HIV or Syphilis testing in order to observe intervention outcome.

4.0 Study Population

4.1 Inclusion Criteria for Aims

Individuals who meet the following initial criteria are eligible to proceed to the confirmatory study screening:

- 18-39 years of age (see justification below)
- Assigned male sex at birth and identify as (1) a man or (2) a trans woman

(e.g., MTF, YTGW)

- Understand and read English or Spanish

  - Self-identify as any race or ethnicity
  - Substantial risk for acquiring HIV infection per CDC guidance (e.g., Sexual partner with HIV and/or recent bacterial STD and/or high number of sexual partners and/or history of inconsistent or no condom use and/or commercial sex work) [1, 2, 41]
  - All participants must report having sex with a man/men
  - Smartphone ownership
  - Self-report being HIV-negative or unknown status
  - Self-report being negative for syphilis or unknown status
  - Not having been tested for HIV or syphilis in the past 3 months (e.g., therefore being somewhat outside of the current CDC testing recommendations for high-risk populations – see below)
  - Understand the limitations of the duplex lateral flow test and the mLab App Plus (e.g., a confirmatory test is needed and self-test must be performed in the presence of a qualified clinician)

4.1.1 Considerations of Age for Inclusion Criteria

The proposed inclusion ages of 18-39 captures the upper range of the greatest increase in new infections [42], and the youngest age is the average age when sexual initiation begins [43, 44].
-54).

4.2 Exclusion Criteria for Aims

Individuals who meet any of the following criteria will be excluded from the study:

- Persons who have a known diagnosis of HIV and/or syphilis
- Persons for whom the investigators determine that participation may be detrimental to the participant or to the study (e.g., severe cognitive deficit)
- Persons diagnosed with Systematic Lupus Erythematosus, as their medical condition could affect the results of the DPP HIV-Syphilis test
- Persons who are unable or unwilling to provide consent for study participation

4.3 Co-enrollment Criteria

Participants are ineligible for participation if they are currently enrolled in any other HIV or syphilis testing-related research study.

4.4 Recruitment Procedures

We will likely employ a multi-modal recruitment strategy. The research team has extensive experience recruiting YMSM and YTGW of color into research studies, including the pilot study of the mLab App, in which 12/18 participants (67%) were non-white and the preliminary study in which 70% were non-white (CDC U01 PS004975).

We have used a variety of recruitment venues for other similar studies and maintain strong working relationships with online advertising vendors and local community-based organizations. Although online venues are constantly evolving, in the past major categories of recruitment have included social network sites (e.g., Facebook, Instagram, Twitter); online sexual networking apps (e.g., Grindr, Scruff); and banner advertisements on other websites frequented by MSM (e.g., POZ). We will recruit young men through posting flyers and promoting the study through community partners. Those recruited through these flyers will be directed to an online web survey (e.g., REDCap) for eligibility screening.

4.4.1 Recruitment Limitations, Anticipated Problems and Alternative Solutions

Limitations

Some limitations or anticipated problems with recruitment may involve the efficacy of the utilized ads. In addition, participant interest may vary from population to population. There is always the possibility of restricted recruitment as it pertains to accessing and promoting studies in public spaces (i.e., schools, parks, etc.). We will also inform the study participants upon enrollment that the goal of the mLab App Plus is for self-testing and NOT for partner testing/sero-sorting. In order to ensure that DPP® HIV-Syphilis Tests are used only on the study participants themselves, participants will not be given DPP® HIV-Syphilis tests to take home. Participants will receive a test at our clinic in Washington Heights where a provider will be present and watch them self-administer the test. Because the DPP® HIV-Syphilis tests are not yet FDA approved as self-tests, it is possible that participants will be unable to perform the test on themselves, and will need the clinician to administer it for them.

Alternative Solutions

Some alternative solutions to participant recruitment may include, but are not limited to email blasts, posted flyers, and in-network recruitment. With regard to partner testing, we will suggest that participants who have partners who are interested in testing should contact the study team for more information on HIV testing. If participants are apprehensive about self-administering the DPP® HIV-Syphilis test, they will have the option to ask the clinician to administer it for them.

4.5 Screening Procedures

Interested participants will be sent a RedCap link to the mLab App Plus screener to fill out online. If found eligible, they will then have a visit at our clinic in Washington Heights with one of our investigators to answer questions and consent to enroll in the study. After receiving written consent, the study team will randomize participants to one of the two arms. After signing the consent and being randomized, they will be considered to be “enrolled” into the study.

4.6 Informed Consent

We will be using electronic online informed consent procedures for enrolling YMSM and

YTGW into the study. Interested participants will verbally consent to screening. If screened as eligible, participants will complete a consent form for enrollment into the study at the beginning of their baseline session. Prior to randomization, participants will read and sign the consent form provided to them by study staff onsite. The informed consent form provides details of the study procedure, risks, benefits, site contact information, and the nature of confidentiality and voluntary participation. The consent process also covers information on the study and compensation for time. The same consent form will be given to all study participants. Participants consent to be randomized to any of the two aims for study purposes. Before a participant signs the informed consent forms, staff will review the forms, ask if the participant understands the content of the consent forms, and answer any questions. Participants will be given a copy of the informed consent forms for their records.

5.0 Study Procedures

5.1 Enrollment Procedures

After successfully providing consent, the participant will be randomized to a study arm and then complete a computer self-administered baseline survey (further described in section 5.4). After completing the baseline survey, both groups will receive standard care HIV/STI testing-related risk reduction counseling, a box of condoms, and PrEP assessment. Participants who are randomized to the intervention arm will be given a DPP® HIV-Syphilis Test at their baseline appointment, which they will self-administer in the presence of a qualified clinician.

5.2 Locator/Contact Information

At the participant's baseline study visit, participants will be asked to provide contact information for follow-up assessments: this information will be entered into REDCap. We will collect each participant's cell phone number, email address, as well as encourage them to share their social media handles (e.g., Snapchat, Instagram, Twitter Facebook, WhatsApp, and/or Skype usernames). Participants will be asked if it is okay to mention the name of the project and method(s) of study communication preferred when sending reminder (e.g., text messaging, email, phone call, leave voicemail). Study staff will not send messages or leave voicemail messages unless explicitly permitted to do so by the participant. If permission is given to leave voice messages, site staff will assure participants that messages left will not include any protected health information or information related to study participation. Contact information will be maintained using the same confidential data management practices used for all study data.

5.3 Randomization Procedures

After providing informed consent, participants will be randomized to study arms in a 1:1 ratio of intervention to control arms. To reduce opportunities for selection bias, we will use a variable permuted randomization block design, where block size itself is randomly selected (i.e., blocks of four to eight). The advantage of a permuted block design is that treatment assignment is pre-determined before the trial begins and assignment remains static throughout the trial [55]. No control group participant will be offered HIV or Syphilis

testing in order to observe intervention outcome.

5.4 Intervention/Investigation Procedures

See Table 1 for baseline and 3-month follow-up schedule of events.

Table 1. Schedule of Events

	Intervention Arm		Control Arm	
	Baseline	3-Months	Baseline	3-Months
Standard-of-Care Counseling[a]	X		X	
Online Survey	X	X	X	X
mLab App Plus	X			
DPP® HIV-Syphilis Test	X	X		

a: Receipt of standard-of-care HIV/STI testing-related risk reduction counseling, box of condoms, PrEP assessment, and referral information for clinics that provide PrEP.

Baseline Visit

The *baseline survey* will include questions on demographics, health literacy [52], sexual risk behaviors including number of men (and other genders) they engaged in anal or oral sex with, condomless anal intercourse, and HIV/STI testing history and opinions regarding HIV/STI testing. The baseline survey will also include questions on PEP/PrEP use and adherence, drug and alcohol use, [51] and HIV Risk Index [54]. We are using REDCAP, a web-based survey software package with several benefits that have been cited including data being captured directly in electronic format and interactive data capture checks [56]. This approach will be especially beneficial in a multi-site study. REDCap is a secure web-based system that provides an intuitive interface, audit trails, and automated export. REDCap is a service offered through CUIMC Information Technology. Staff at Columbia University will have a link to the secure web-based data collection survey tool and will be present to assist the participant in completing the survey. Staff will be accessible during survey completion to address any technical problems or to answer questions participants may have. Staff may periodically check-in with the participant to inquire about any difficulties that may arise in completing the survey. However, to ensure privacy, the staff person will not directly observe the full process of completing the survey unless requested by the participant. Both the baseline and 3-month follow up surveys will be conducted in-person.

At the baseline study visit, following consent and completion of the baseline questionnaire, participants randomized to the intervention group will be instructed on how to use the mLab App Plus by the investigator, who will create an account for them during baseline. Next, they will verbally complete a DPP® HIV-Syphilis testing assessment so that study staff ensures they are aware of the functions and limitations of the test. Participants will be taken to the CUIMC Nurse Practitioners clinic where they will be instructed to self-administer their first DPP® HIV-Syphilis test under the supervision of a trained clinician. The clinician will ensure that the DPP® HIV-Syphilis test is administered correctly and test results are accurately interpreted. The participant will use the mLab App Plus and the DPP® HIV-Syphilis testing instructions to guide them through the DPP® HIV- Syphilis testing process and to help them understand their test results. Participants will be provided with all necessary materials to complete the test by the on-site clinician. In the event that the participant feels uncomfortable or unable to perform the DPP® HIV-Syphilis test as a self-

test, they may ask the clinician to administer the test for them.

Testing with a DPP® HIV-Syphilis kit requires that the participant obtain a small drop of blood using a sterile lancet and sample loop and insert it into the SampleTainer Bottle. Participants will then drop the blood sample on the test strip per the DPP® HIV-Syphilis test instructions. The participant will then attach the DPP Micro Reader, a device which interprets the test results, to the test strip. Once the DPP Micro Reader has finished running the test, participants will take a picture of the DPP Micro Reader display screen through mLab App Plus, which is then processed through automated image processing software. Participants then see their results on their smartphone screen. The test will likely take around twenty minutes to complete. For step-by-step instructions, please refer to the mLab App Plus Workflow. The mLab App Plus is unique in that it allows a person to test themselves. However, because DPP® HIV-Syphilis tests are not yet approved by the FDA as self-tests, participants will be required to complete the self-testing process at our clinic in Washington Heights, under the supervision of a qualified clinician. Test results are then stored on the participants' smartphones and also securely transmitted and stored on the REDCap Server. This will contribute to the validity of findings as participants' reports of testing themselves can be confirmed through this device. In addition, the mLab App Plus user interface can promote a more holistic diagnostic experience, particularly in self-testing because the interface provides step-by-step picture directions, and information on linking to follow-up testing and prevention services, as appropriate.

Upon receiving a test result, participants will be directed to another screen on their smartphone informing them that a study team member will be in contact with them shortly to discuss their test results. The study team member will meet with the participant at the clinic, immediately after they have completed their DPP® HIV-Syphilis test. They will discuss with the participant what their test result means and what it does NOT mean. In the event of a positive test result, the study team member will offer support and help the participant set up an appointment at our clinic for confirmatory testing. Participants will receive reminders on mLab App Plus for their next visit prior to the 3-month follow up visit.

3-Month Follow Up Visit

The *3-Month Follow Up survey* will include questions on demographics, health literacy [52] sexual risk behaviors including number of men (and other genders) they engaged in anal or oral sex with, and condomless anal intercourse, as well as questions on PEP/PrEP use and adherence, drug and alcohol use [51], and HIV Risk Index [54]. Participants randomized to both the control arm and intervention arm of the study will all participate in the questionnaire at the 3-month time point. The survey will also inquire about participants' opinions towards HIV/STI testing since the baseline visit and their experiences using the mLab App Plus, if they are randomized to the intervention arm.

Following completion of the survey, intervention arm participants will once again self-administer the DPP® HIV-Syphilis test at the clinic in the presence of a clinician. They will follow the same testing procedure as they did at baseline and a study team member will meet with them to discuss results and set up confirmatory testing, if necessary, once they have completed their DPP® HIV-Syphilis test. Results are stored on their smartphone through the mLab App Plus and securely transmitted and stored on the REDCap Server.

6.1 Study Evaluations and Measures

6.2 Study Outcomes and Measures

The primary outcome is the number of participants who are able to self-administer the DPP® HIV-Syphilis test with mLab App Plus (**Table 2**). A successful self-test is defined as having completed the DPP® HIV-Syphilis test by themselves and having accurately identified and interpreted their HIV and Syphilis statuses as determined by the supervising clinician. In the event that the clinician, rather than the participant administers the DPP® HIV-Syphilis test, the test is not recorded as a successful self-test. Secondary outcomes are also listed in Table 2, including information about linkage to health care and other support services.

Table 2. Outcome Data for Aim 3
YMSM/YTGW who completed testing for HIV/syphilis at Baseline and 3-Month Follow-up
YMSM/YTGW who self-administered the DPP® HIV-Syphilis test at Baseline and 3-Month Follow-up
negative/positive results
YMSM/YTGW referred for HIV/STI services (participants with HIV and/or syphilis only)
YMSM/YTGW linked to (attend one appointment) HIV/STI prevention or care services
YMSM/YTGW attending other HIV/STI prevention service appointments
YMSM/YTGW accessing HIV/STI prevention or social service appointments (e.g., PEP, PrEP, STI testing, mental health counseling, drug treatment, job assistance, education services, job skills training, housing assistance)
Outcome indicator data disaggregated by race/ethnicity, age, testing history and geographical area
Additional HIV-associated health outcomes (e.g., sexual behaviors associated with HIV transmission)

7.1 Data Collection and Site Monitoring

7.2 Data Records

All electronic data will be stored on a certified environment. The recordings will be stored securely after the data have been analyzed and the findings disseminated. The smartphone that is connected to the mLab App Plus will require a password. Data will be coded. The PI and Project Manager will have access to the identifiable data. Study data will be encrypted and stored on secure HIPAA- compliant servers at the CUIMC campus. mLab App Plus data will be stored at Vanderbilt University. All study data will be kept in password-protected computers or file cabinets in locked offices and will be maintained in a completely secure and HIPAA-compliant environment. All CUIMC servers have HIPAA-compliant security.

7.3 Data Quality Control and Quality Assurance

Routine data quality control assessments will identify and resolve data errors in both data collection (e.g., surveys) and study documentation (e.g., visit logs). Data quality resolutions will be documented for reference. As determined necessary by the PI, the study Data Safety Monitoring Board will advise resolutions for data quality concerns during Board meetings. Data validation tools available through the REDCap platform will be leveraged to ensure data quality assurance in study data collection and documentation such that data is checked against validation standards at the time of input. Quality assurance measures will be routinely reviewed with new measures added as necessary to address emerging data quality

concerns.

8.1 Participant Tracking and Clinical Management

8.2 Tracking Participants Follow-up

Contact (phone calls, text, email, or note as preferred by the participant) will be made by the site study staff 3 days and 1 day prior to the follow-up visit to confirm or reschedule an appointment. Participants in the intervention arm will also receive a 3-month follow-up visit reminder through the mLab App Plus. The discrete contact will thank the participants for being in the program, remind them of the date and time of their follow-up appointment, and note the telephone number that can be called if rescheduling is necessary. Participants who do not respond and cannot be located during the acceptable 1-month window period are coded as a missed assessment and attempts to contact them will resume for the next assessment. We will contact participants until they express the desire to be dropped from the study. These extensive procedures will be used to promote participant attendance at the follow-up visits and have been successful in previous HIV prevention studies conducted by our study team.

8.1.1 Retention

Participants will be asked at the end of the screening what would be the best way for us to remind them of the appointment (voice phone, text, e-mail). Participant retention during the intervention will be enhanced in several ways. We will offer multiple reminders via text, email, calls, or mLab App Plus, for participants randomized to the intervention arm. We will use several approaches that have shown success at reducing barriers, including: 1) clearly explaining the duration of the study; 2) collecting multiple contact points (phone number, e-mail, social media username) based on participants' preferences; and 3) implementing consistent study staff follow-up with participants to build rapport.

8.2 Intervening on "Social Harm"

If a study participant reports severe depressive symptoms or suicidal ideation, we will refer the participants to the local emergency room or mental health referral facility.

8.3 Acquisition of HIV and/or Syphilis Infection while on Study

If a participant receives a reactive or indeterminate result from the DPP® HIV-Syphilis test for their HIV and/or Syphilis status during the course of the study, the study team will link them to confirmatory testing on site at the clinic.

To facilitate these tasks, study staff must complete the HIV/Syphilis Confirmation Testing instrument in REDCap which should be updated with the information around the preliminary positive, confirmatory test, and linkage to care information as it is updated. Once HIV and/or syphilis status has been confirmed as positive, participants will be withdrawn from study.

9.1 Statistical/Analytic Considerations

9.2 Size Considerations and Power Estimates

Due to the small sample size (n=40), results will not be powered enough to be representative of the greater population. Our goal is to examine feasibility among participants and estimate the effect size of the intervention for a future RCT.

9.3 Data and Safety Monitoring

The Data and Safety Monitoring Plan (DSMP) outlined below will adhere to the protocol approved by the Single Institutional Review Board (IRB) which will oversee the study activities. A Data and Safety Monitoring Board will be established after a Notice of Award is granted.

9.3.1 Training on Human Subjects and Data and Safety Monitoring

All proposed staff have participated in the Department of Health and Human Services required trainings for conduct of studies that involve human subjects and any future study staff will do so upon hiring. Training for all staff includes (but is not limited to) Protection of Human Subjects, Informed Consent, Good Clinical Practice, Quality Management, Confidentiality, and Reporting of Adverse Events. If any study staff discovers any untreated condition (e.g., onset of physical or mental health condition), they will refer participants to appropriate treatment immediately.

9.3.2 Data Management and Data Quality

Columbia University will be responsible for computerized survey programming and data capture, management, and analysis. All study information will be identified through the Participant Identification Number on all forms and computerized files.

9.3.3 Data Monitoring

Biweekly reports for the study sites will be created by the data manager (i.e., data monitoring is done by both Columbia University staff and Vanderbilt University staff) to review relevant app engagement data, barriers with recruitment/enrollment and retention, laboratory and medical records, compliance with the protocol, and accuracy and completeness of the records. The investigative team will schedule biweekly conference calls, and these reports will be briefly reviewed by the team at these meetings. These regular reviews will ensure close communication between the research assistants, quickly identify missing data points, and ensure consistent management of any issues with the protocol across sites. Data quality will be examined before statistical analyses are conducted, including examination of missing data, assessment of distributional assumptions, and identification of outliers. In addition to data quality, the comparability between intervention and control groups will be carefully examined, including baseline balance and differential attritions at all waves of follow-up.

9.3 Adverse Events

9.3.1 Adverse event assessment

We anticipate that the Data and Safety Monitoring Board will define study-specific serious adverse events (SAE)s. While we do not anticipate any SAEs, we will carefully review safety and data security and study drop-out.

9.3.2 Adverse event reporting

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening but are clearly

of major clinical significance. They may jeopardize the participant's health and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

We will follow the guidelines of the IRB that require investigators to promptly notify the IRB (within 1 week from awareness of the occurrence) when an adverse event (AE) or serious adverse event (SAE) meets the definition of an Unanticipated Problem (UP).

The IRB requires that any event that is unexpected, related or possibly related to the research intervention, and suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized must be reported. Events that are unrelated to the research intervention do not have to be reported to the IRB; however, we will report these to the monitoringentity and Centers for Disease Control and Prevention (CDC). Risks that are described in the protocol and consent form do not have to be reported unless the expected event occurs more frequently or is more severe than expected. One exception to this rule is in the case of a death. All deaths must be reported whether or not the death was related to the research.

An unanticipated adverse device effect (UADE) is defined as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects" (In accordance with 21 CFR 812.3(s)).

In accordance with 21 CFR 812, UADEs will promptly be reported to the FDA and IRB, but no later than 10 working days after the investigator first learns of the event.

9.4 Data Analysis Plan

All multivariate analyses will be preceded by standard descriptive bivariate analyses to describe the key variables and relationships among them. These analyses will include means, frequency tables, histograms, and examination of distributions. Frequencies and rates of HIV/syphilis tests, as well as corresponding confidence intervals, will be calculated for each arm (mLab App Plus vs. Standard of Care (Control)). Logistic regression models will be used to compare in the likelihood of having HIV/STI tests between the mLab App Plus arm and the standard clinic-based testing arm.

9.5 Missing Data

Prior to performing any outcome analyses, we will evaluate the amount, reasons, and patterns of missing data. Missing data unrelated to the outcome of interest will be considered missing completely at random, and complete case analysis will still generate unbiased estimates. We will conduct sensitivity analyses to compare estimates of treatment effects with and without multiple imputation to assess the effect of missing data on statistical inference.

We propose a GLMM to analyze data, the main advantages being unbiased estimates when there are missing outcomes during the follow-up period if the probability of missing is not related to the outcome value. For the missing values at the baseline or partial baseline collected data, we will use a multiple imputation approach. Models will also be run on the raw, non-imputed data with full information maximum likelihood estimation. Inferences for the trial arm, wave, and interaction between trial arm and wave do not differ between the analyses of the raw and multiply imputed data. Rates of reduction will be calculated from population-averaged rates, which control for all other covariates in the multivariable model. Models will be calculated by using the GLIMMIX and MIANALYZE procedures in SAS, version 9.4, and model fit will be evaluated by diagnostic statistics and residual plots.

10.0 Human Subjects Protections

10.1 Informed Consent

The informed consent of each participant will be obtained in accordance with 21 CFR Part 50 and the Declaration of Helsinki before protocol-specified procedures are carried out. An investigator will obtain the participant's written informed consent prior to any study-related procedures. Consent will be documented by the dated signature of the subject. The signature confirms that the consent is based on information that has been understood. Each participant's signed informed consent form will be kept on file by the investigators for possible inspection by regulatory authorities.

The study plan, advertisements, or recruitment letters, lay description of the study, and all consent forms will be submitted to the IRB following proposal acceptance and prior to study initiation. Dr. Schnall will be responsible for obtaining IRB approval for this study. Recruitment for study participation will occur following IRB approval. The investigators will determine eligibility for inclusion, explain the purpose of the study, answer any questions, and obtain e-consent from the participants. Patients who agree to participate will sign a consent form. Potential risks and strategies for risk management will be carefully explained as part of informed consent procedures. All HIPAA requirements will be applied to this study.

We will assure potential participants in these study activities that their willingness to participate and/or to complete the study activities will not have an impact on their participation in other aspects of the study or on their employment or student status at study sites.

10.2 Vulnerable Subjects: Protecting Against/Minimizing Potential Risk

Ethnic and racial minority populations will be enrolled. While this group is considered a vulnerable population, the study team has considerable experience enrolling these participants. The study will be conducted according to Good Clinical Practice guidelines, the U.S. Code of Federal Regulations (CFR) Title 21 CFR (Part 50 – Protection of Human Subjects and Part 56 – Institutional Review Boards) and the Declaration of Helsinki.

10.3 Risks

10.3.1 General risks

There may be risks or discomforts in participating in this study. Participants may feel uncomfortable with completing some questions in the survey. Participants may skip any HIV/STI information or

questions that may make them feel uncomfortable or stop the research procedure. People around may observe participants using the mLab App Plus. If participants are concerned about people seeing them use of mLab App Plus, it is important that they access the application in private location.

10.3.2 Loss of confidentiality

A risk of taking part in this study is the possibility of a loss of confidentiality or privacy. Loss of confidentiality or privacy means having personal information shared with someone who is not on the study team and was not supposed to see or know about your information.

10.3.3 Venipuncture

There is a small risk of local hematoma or infection associated with blood sampling. On rare occasions, drawing blood can cause dizziness, presyncope, and even syncope.

10.4 Benefits

10.4.1 Potential Benefits of the Proposed Research to Research Participants and Others

The potential benefits to an individual participant in the study are not known. The potential benefits of the study to others could be considerable. If our hypotheses are true, this study will make a significant contribution towards preventing HIV and syphilis in YMSM.

This study has not been designed for the direct benefit of its participants; however, there are several ways in which they may derive benefit. The proposed research will increase knowledge of HIV and syphilis testing among YMSM. The knowledge gained will contribute to the body of knowledge regarding the use of health information technology for improving the lives of MSM at risk for HIV and syphilis. The avoidance of HIV and syphilis through study participation will be a significant personal benefit to participants.

10.4.2 Importance of Knowledge to be Gained

The knowledge gained from this research will enable the scientific community, clinicians, and high- risk populations to prevent new HIV and syphilis infections in the US.

10.5 Participant Privacy and Confidentiality

10.5.1 Access to individually identified private information about human subjects

Access to individually identified private information about human subjects will be limited to research team members who collect and manage the data, study staff, site principal investigators and the Principal Investigator. Coded data will be accessible to all members of the research team involved in the data analysis. Our study team is extremely prudent in keeping participant data secure and confidential. All laboratory specimens, evaluation forms, reports, and other records will be identified by a unique coded number to maintain participant confidentiality. The material, records, and data obtained through participation in the study will be specifically for research purposes. Existing health records may be used with the permission of the participants. Materials will be obtained by trained clinical staff at each study site. Data will

be stored using Research Electronic Data Capture (REDCap) at each respective performance site, and then the completely deidentified data will be merged at CUIMC. All laboratory specimens will be identified only by the identification number. The code linking the participant identification number to participant identifying information (name, address, etc.) is maintained at the clinical sites through REDCap, and only authorized site personnel have access to the code. Limited individually identifiable private information is collected that is essential for processing participant payments and for analysis purposes.

10.5.2 Confidentiality of the App

The App requires a password. All study data will be encrypted and stored on secure HIPAA- compliant servers at the CUIMC campus. All study data will be kept in password-protected computers or file cabinets in locked offices and will be maintained in a completely secure and HIPAA-compliant environment. All CUIMC servers have HIPAA-compliant security. Nonetheless, there is always the risk of a data breach, so we will make our study participants aware of this risk upon enrollment.

10.5.3 Confidentiality and privacy of the study data

All study data will be stored in password-protected computers or file cabinets in locked offices. Audio recordings of interviews or focus groups will be destroyed once data are transcribed and analyzed. All research team members will pass the protection of human subjects and HIPAA research exams and sign a protocol-specific conflict of interest. Risks will be minimized by not including personal identifying information on the forms, when possible, and by conducting interviews and collection of personal information in a private setting. All data will be collected using unique patient identification codes. All laboratory specimens, evaluation forms, reports, and other records will be identified by a coded number to maintain participant confidentiality. All records will be stored in a locked file cabinet. Study data from both sites will be collected and managed using REDCap. REDCap is a secure web application designed to support data capture for research studies, providing user-friendly web- based case report forms, real-time data entry validation (e.g., for data types and range checks), audit trails, and a deidentified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team. This iterative development and testing process results in a well- planned data collection strategy for individual studies. REDCap also includes a powerful tool for building and managing online surveys. The research team can create and design surveys in a web browser and engage potential respondents using a variety of notification methods. REDCap is flexible enough to be used for a variety of types of research and provides an intuitive user interface for database and survey design and data entry. Lastly, clinical information will not be released without written permission of the participant, except as necessary for monitoring by the IRB or the CDC.

10.5.4 Plan for privacy and data security

Beginning with the development process and throughout the research project, we will follow the privacy and security principles set forth at healthhit.gov. Our team is familiar with the importance of the privacy and security of personal health information to engender individual trust in the use of health IT applications. We have expertise and experience in this domain as we have developed several health IT systems funded through NIH and the Agency for Healthcare Research and Quality for persons living with HIV whose personal health information is usually held to higher security standards than traditional patients as HIV has historically been a stigmatized disease. We built the the mLab App Plus (NIMH

R01MH118151) which is housed on the CUIMC IT servers. Study data from mLab App Plus will be stored on the CUIMC servers. The CUIMC servers are in a secure datacenter, with necessary redundancies. Currently the network can be accessed remotely via Virtual Private Network with a Citrix solution being developed. All servers have HIPAA compliant security.

CUIMC has an Information Security Office (ISO) that facilitates all aspects of information security risk management at CUIMC, with a particular focus on threat management and HIPAA compliance. This includes administration and enforcement of information security policies on campus.

The Information Security Office also provides guidance to CUIMC schools and departments regarding any information security concerns they may have. The ISO collaborates with the entire CUIMC community to protect the confidentiality, integrity, and availability of critical information and computer resources. The ISO strives to implement secure computing infrastructure and practices with sensitivity to CUIMC's educational and research environment. Columbia University has an information security charter which is the foundation of all the work carried out by Dr. Schnall and her research team. In specific, Dr. Schnall will work with the CUIMC IT server group and the information security office to protect the confidentiality, integrity, and availability of participants' data. Confidentiality means that information is only accessible to authorized users. Integrity means safeguarding the accuracy and completeness of data and processing methods. Availability means ensuring that authorized users, such as research participants, have access to data and associated information resources when required.

Prior to consent, study participants will be informed as to what data the App will collect. Data will be encrypted and stored securely on the CUIMC IT servers. As a starting point for ensuring privacy and security, all smartphones will be password–protected. In addition, there will be an additional password for the App so that only study participants will be able to open the App.

10.6 Unexpected and Serious Adverse Event Reporting

A detailed monitoring plan will be included as part of the study protocol, submitted to the IRB, and reviewed and approved by the Centers for Disease Control and Prevention (CDC) before the study begins. Prior to initiation of the study, agreement about the data safety monitoring plan will be confirmed to ensure the safety of participants and the validity and integrity of the data. Study staff at each site will report serious adverse events (SAEs) that are unexpected and study-related immediately to the PI who will convey this information to the study team, IRB, and the CDC. All AEs and SAEs will be captured, reports will be completed, and information will be entered into the study database. A safety report will detail all serious and unexpected AEs or other unanticipated problems that involve risk to study participants or others and whether these appeared to be related to the study-based interventions or research assessment protocols. All SAEs will be reviewed every 6 months, or sooner, with the designated safety Data Safety and Monitoring Board.

10.7 ClinicalTrials.gov

This study will be registered on ClinicalTrials.gov.

11.0 References

1. Centers for Disease Control and Prevention. HIV Incidence: Estimated Annual Infections in the U.S., 2010-2016 2019 [cited 2022]. Available from: https://www.cdc.gov/nchhstp/newsroom/2019/HIV-incidence.html.
2. Centers for Disease Control and Prevention. HIV among Gay and Bisexual Men 2018 [cited 2022]. Available from: https://www.cdc.gov/hiv/group/msm/index.html.
3. Centers for Disease Control and Prevention. Sexually Transmitted DiseaseSurveillance, 2019 Atlanta, GA: Department of Health and Human Services; 2021. Available from: https://www.cdc.gov/std/statistics/2019/default.htm.
4. Purcell DW, Johnson CH, Lansky A, Prejean J, Stein R, Denning P, Gau Z, Weinstock H, Su J, Crepaz N. Estimating the population size of men who have sex with men in the United States to obtain HIV and syphilis rates. Open AIDS J. 2012;6:98-107. Epub 2012/10/11. doi: 10.2174/1874613601206010098. PubMed PMID: 23049658; PMCID: PMC3462414.
5. Braxton J, Carey D, Davis D, Flagg E, Footman A, Grier L, Harvey A, Kidd S, Kirkcaldy R, Llata E, Nelson R, Pitasi M, Presley R, Rivers F, Smith C, Stenger M, Su J, Torrone E, Weinstock H. Sexually Transmitted Disease Surveillance 2014. Atlanta, GA: 2015.
6. Pathela P, Braunstein S, Schillinger J, Shepard C, Sweeney M, Blank S. Men who Have Sex with Men Have a 140-Fold Higher Risk for Newly Diagnosed HIV and Syphilis Compared with Hetersexual Men in New York City. Journal of Acquired Immune Deficiency Syndromes. 2011;58(4):408-16.
7. Centers for Disease Control and Prevention. Estimated HIV Incidence and Prevalence in the United States, 2015-2019; HIV Surveillance Supplemental Report 2021. 2021.
8. Mayer KH, Grinsztejn B, El-Sadr WM. Transgender People and HIV Prevention: What We Know and What We Need to Know, a Call to Action. J Acquir Immune Defic Syndr. 2016;72 Suppl 3(Suppl 3):S207-9. Epub 2016/07/20. doi: 10.1097/qai.0000000000001086. PubMed PMID: 27429184; PMCID: PMC4969053.
9. Pitasi M, Oraka E, Clark H, Town M, DiNenno E. HIV Testing among Transgender Women and Men -- 27 States and Guam, 2014-2015. MMWR Morb Mortal Weekly Rep 2017;66:883-7.
10. Centers for Disease Control and Prevention. HIV among African Americans 2017 2017 [cited 2022]. Available from: https://www.cdc.gov/hiv/group/racialethnic/africanamericans/index.html.
11. Centers for Disease Control and Prevention. Daily Pill Can Prevent HIV 2015 [cited 2022]. Available from: https://www.cdc.gov/vitalsigns/hivprep/index.html.
12. Clements-Nolle K, Marx R, Guzman R, Katz M. HIV prevalence, risk behaviors, health care use, and mental health status of transgender persons: implications for public health intervention. Am J Public Health. 2001;91(6):915-21. Epub 2001/06/08. doi: 10.2105/ajph.91.6.915. PubMed PMID: 11392934; PMCID: PMC1446468.
13. Winetrobe H, Rice E, Bauermeister J, Petering R, Holloway IW. Associations of unprotected anal intercourse with Grindr-met partners among Grindr-using young men who have sex with men in Los Angeles. AIDS Care. 2014;26(10):1303-8. Epub 2014/04/24. doi: 10.1080/09540121.2014.911811. PubMed PMID: 24754563.
14. Brennan J, Kuhns LM, Johnson AK, Belzer M, Wilson EC, Garofalo R. Syndemic theory and HIV-related risk among young transgender women: the role of multiple, co-occurring health problems and social marginalization. Am J Public Health. 2012;102(9):1751-7. Epub 2012/08/10. doi: 10.2105/ajph.2011.300433. PubMed PMID: 22873480; PMCID: PMC3416048.
15. Dorrell C, Sutton M, Oster M, Hardnett F, Thomas P, Gaul Z, Mena L, Heffelginer J. Missed Opportunities for HIV Testing in Health Care Settings among Young African American Men who Have Sex with Men: Implications for the HIV Epidemic. AIDS Patient Care and STDs 2011;25(11):657-64.
16. Pharr JR, Lough NL, Ezeanolue EE. Barriers to HIV Testing Among Young Men Who

Have Sex With Men (MSM): Experiences from Clark County, Nevada. Glob J Health Sci. 2015;8(7):9-17. Epub 2015/01/01. doi: 10.5539/gjhs.v8n7p9. PubMed PMID: 26925893; PMCID: PMC4965686.
17. Veinot TC, Caldwell E, Loveluck J, Arnold MP, Bauermeister J. HIV Testing Behavior and Social Network Characteristics and Functions Among Young Men Who have Sex with Men (YMSM) in Metropolitan Detroit. AIDS Behav. 2016;20(11):2739-61. Epub 2016/10/21. doi: 10.1007/s10461-016-1296-y. PubMed PMID: 26837634; PMCID: PMC5234266.
18. Kurth AE, Lally MA, Choko AT, Inwani IW, Fortenberry JD. HIV testing and linkage to services for youth. J Int AIDS Soc. 2015;18(2 Suppl 1):19433. Epub 2015/03/01. doi: 10.7448/ias.18.2.19433
19433. PubMed PMID: 25724506; PMCID: PMC4344538.
19. White House Office of National AIDS Policy. National HIV/AIDS Strategy for The United States: Updated to 2020. 2015.
20. Centers for Disease Control and Prevention. HIV Testing and Risk Behaviors among Gay, Bisexual, and Other Men who Have Sex with Men -- United States 2013. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6247a4.htm.
21. Singh S, Mitsch A, Baohua Wu M. HIV Care Outcomes among Men who Have Sex with Men with Diagnosed HIV Infection -- United States, 2015. 2017.
22. UNAIDS. UNAIDS Report on The Global AIDS Epidemic 2010. Geneva, Switzerland: 2010.
23. Herbst JH, Jacobs ED, Finlayson TJ, McKleroy VS, Neumann MS, Crepaz N. Estimating HIV prevalence and risk behaviors of transgender persons in the United States: a systematic review. AIDS Behav. 2008;12(1):1-17. Epub 2007/08/19. doi: 10.1007/s10461-007-9299-3. PubMed PMID: 17694429.
24. Poteat T, Reisner SL, Radix A. HIV epidemics among transgender women. Curr Opin HIV AIDS. 2014;9(2):168-73. Epub 2013/12/11. doi: 10.1097/coh.0000000000000030.PubMed PMID: 24322537; PMCID: PMC5947322.
25. Schulden JD, Song B, Barros A, Mares-DelGrasso A, Martin CW, Ramirez R, Smith LC, Wheeler DP, Oster AM, Sullivan PS, Heffelfinger JD. Rapid HIV testing in transgender communities by community-based organizations in three cities. Public Health Rep. 2008;123 Suppl 3(Suppl 3):101-14. Epub 2009/01/27. doi: 10.1177/00333549081230s313. PubMed PMID: 19166094; PMCID: PMC2567010.
26. D'Angelo LJ. When will routine testing for human immunodeficiency virus infection be the routine for adolescents? Arch Pediatr Adolesc Med. 2012;166(4):385-6. Epub 2012/01/04. doi: 10.1001/archpediatrics.2011.1555. PubMed PMID: 22213604.
27. Jamil MS, Prestage G, Fairley CK, Grulich AE, Smith KS, Chen M, Holt M, McNulty AM, Bavinton BR, Conway DP, Wand H, Keen P, Bradley J, Kolstee J, Batrouney C, Russell D, Law M, Kaldor JM, Guy RJ. Effect of availability of HIV self-testing on HIV testing frequency in gay and bisexual men at high risk of infection (FORTH): a waiting-list randomised controlled trial. Lancet HIV. 2017;4(6):e241-e50. Epub 2017/02/22. doi: 10.1016/s2352-3018(17)30023-1. PubMed PMID: 28219619.
28. Stevens DR, Vrana CJ, Dlin RE, Korte JE. A Global Review of HIV Self-testing: Themes and Implications. AIDS Behav. 2018;22(2):497-512. Epub 2017/02/06. doi: 10.1007/s10461-017-1707-8. PubMed PMID: 28155039; PMCID: PMC5910655.
29. Martinez O, Carballo-Diéguez A, Ibitoye M, Frasca T, Brown W, Balan I. Anticipated and actual reactions to receiving HIV positive results through self-testing among gay and bisexual men. AIDS Behav. 2014;18(12):2485-95. Epub 2014/05/27. doi: 10.1007/s10461-014-0790-3. PubMed PMID: 24858480; PMCID: PMC4229402.
30. Eaton LA, Driffin DD, Smith H, Conway-Washington C, White D, Cherry C. Black men who have sex with men, sexual risk-taking, and willingness to use rapid home HIV tests. Prev Sci. 2015;16(2):321-9. Epub 2014/06/08. doi: 10.1007/s11121-014-0496-9. PubMed PMID:

24906999; PMCID: PMC4258525.
31. Schnall R, John RM, Carballo-Dieguez A. Do High-Risk Young Adults Use the HIV Self-Test Appropriately? Observations from a Think-Aloud Study. AIDS Behav. 2016;20(4):939-48. Epub 2015/11/01. doi: 10.1007/s10461-015-1240-6. PubMed PMID: 26518679; PMCID: PMC4799728.
32. Buchacz K, Patel P, Taylor M, Kerndt PR, Byers RH, Holmberg SD, Klausner JD. Syphilis increases HIV viral load and decreases CD4 cell counts in HIV-infected patients with new syphilis infections. Aids. 2004;18(15):2075-9. Epub 2004/12/04. doi: 10.1097/00002030-200410210-00012. PubMed PMID: 15577629; PMCID: PMC6763620.
33. Klein PW, Martin IB, Quinlivan EB, Gay CL, Leone PA. Missed opportunities for concurrent HIV-STD testing in an academic emergency department. Public Health Rep. 2014;129 Suppl 1(Suppl 1):12-20. Epub 2014/01/05. doi: 10.1177/00333549141291s103. PubMed PMID: 24385644; PMCID: PMC3862983.
34. Aliabadi N, Carballo-Dieguez A, Bakken S, Rojas M, Brown W, 3rd, Carry M, Mosley JP, Gelaude D, Schnall R. Using the Information-Motivation-Behavioral Skills Model to Guide the Development of an HIV Prevention Smartphone Application for High-Risk MSM. AIDS Educ Prev. 2015;27(6):522-37. Epub 2015/11/26. doi: 10.1521/aeap.2015.27.6.522. PubMed PMID: 26595265; PMCID: PMC4868035.
35. Brown W, 3rd, Carballo-Diéguez A, John RM, Schnall R. Information, Motivation, and Behavioral Skills of High-Risk Young Adults to Use the HIV Self-Test. AIDS Behav. 2016;20(9):2000-9. Epub 2016/02/18. doi: 10.1007/s10461-016-1309-x. PubMed PMID: 26885813; PMCID: PMC4988939.
36. Scherr TF, Gupta S, Wright DW, Haselton FR. Mobile phone imaging and cloud-based analysis for standardized malaria detection and reporting. Sci Rep. 2016;6:28645. Epub 2016/06/28. doi: 10.1038/srep28645. PubMed PMID: 27345590; PMCID: PMC4921854.
37. Paltiel AD, Walensky RP. Home HIV testing: good news but not a game changer. Ann Intern Med. 2012;157(10):744-6. Epub 2012/10/10. doi: 10.7326/0003-4819-157-10-201211200-00545. PubMed PMID: 23044643; PMCID: PMC3661188.
38. Schnall R, Rojas M, Bakken S, Brown W, Carballo-Dieguez A, Carry M, Gelaude D, Mosley JP, Travers J. A user-centered model for designing consumer mobile health (mHealth) applications (apps). J Biomed Inform. 2016;60:243-51. Epub 2016/02/24. doi: 10.1016/j.jbi.2016.02.002. PubMed PMID: 26903153; PMCID: PMC4837063.
39. Wood OR, Garofalo R, Kuhns LM, Scherr TF, Zetina APM, Rodriguez RG, Nash N, Cervantes M, Schnall R. A randomized controlled trial of an mHealth intervention for increasing access to HIV testing and care among young cisgender men and transgender women: the mLab App study protocol. BMC Public Health. 2021;21(1):1959. Epub 2021/10/31. doi: 10.1186/s12889-021-12015-w. PubMed PMID: 34715833; PMCID: PMC8554516.
40. Faulkner L. Beyond the Five-User Assumption: Benefits of Increased Sample Sizes in Usability Testing. Behav Res Methods Instrum Comput. 2003;35(3):379-83.
41. Centers for Disease Control and Prevention. CDC Fact Sheet: HIV among Gay and Bisexual Men 2017 [cited 2022]. Available from: https://www.cdc.gov/nchhstp/newsroom/docs/factsheets/cdc-msm-508.pdf.
42. Centers for Disease Control and Prevention. CDC Fact Sheet: New Infections in the United States 2016. Available from: https://www.cdc.gov/nchhstp/newsroom/docs/factsheets/new-hiv-infections-508.pdf.
43. Centers for Disease Control and Prevention. State Laws that Enable a Minor to Provide Informed Consent to Receive HIV and STD Services 2020 [cited 2022]. Available from: https://www.cdc.gov/hiv/policies/law/states/minors.html.
44. Donenberg GR, Emerson E, Bryant FB, Wilson H, Weber-Shifrin E. Understanding AIDS-risk behavior among adolescents in psychiatric care: links to psychopathology and peer relationships. J Am Acad Child Adolesc Psychiatry. 2001;40(6):642-53. Epub 2001/06/08.doi:

10.1097/00004583-200106000-00008. PubMed PMID: 11392341; PMCID: PMC1201503.
45. Ezennia O, Geter A, Smith DK. The PrEP Care Continuum and Black Men Who Have Sex with Men: A Scoping Review of Published Data on Awareness, Uptake, Adherence, and Retention in PrEP Care. AIDS Behav. 2019;23(10):2654-73. Epub 2019/08/30. doi: 10.1007/s10461-019-02641-2. PubMed PMID: 31463711.
46. Golub SA, Gamarel KE, Rendina HJ, Surace A, Lelutiu-Weinberger CL. From efficacy to effectiveness: facilitators and barriers to PrEP acceptability and motivations for adherence among MSM and transgender women in New York City. AIDS Patient Care STDS. 2013;27(4):248-54. Epub 2013/04/10. doi: 10.1089/apc.2012.0419. PubMed PMID: 23565928; PMCID: PMC3624632.
47. Whitfield T, Grov C, Rendina J, Parsons J. Adherence to Pre-Exposure Prophylaxis (PrEP) Among Gay and Bisexual Men: Prevalence and Predictors of Missed Doses. 10th Annual Meeting of the International Association of Providers and AIDS Care (IAPAC). 2015.
48. Giroir BP. The Time Is Now to End the HIV Epidemic. Am J Public Health. 2020;110(1):22-4. Epub 2019/11/15. doi: 10.2105/ajph.2019.305380. PubMed PMID: 31725312; PMCID: PMC6893354.
49. Lelutiu-Weinberger C, Golub SA. Enhancing PrEP Access for Black and Latino Men Who Have Sex With Men. J Acquir Immune Defic Syndr. 2016;73(5):547-55. Epub 2016/07/28. doi: 10.1097/qai.0000000000001140. PubMed PMID: 27454250; PMCID: PMC5110381.
50. Rivet Amico K, Bekker LG. Global PrEP roll-out: recommendations for programmatic success. Lancet HIV. 2019;6(2):e137-e40. Epub 2019/01/21. doi: 10.1016/s2352-3018(19)30002-5. PubMed PMID: 30660592.
51. Bradley KA, Bush KR, Epler AJ, Dobie DJ, Davis TM, Sporleder JL, Maynard C, Burman ML, Kivlahan DR. Two brief alcohol-screening tests From the Alcohol Use Disorders Identification Test (AUDIT): validation in a female Veterans Affairs patient population. Arch Intern Med. 2003;163(7):821-9. Epub 2003/04/16. doi: 10.1001/archinte.163.7.821. PubMed PMID: 12695273.
52. Mimiaga MJ, Reisner SL, Grasso C, Crane HM, Safren SA, Kitahata MM, Schumacher JE, Mathews WC, Mayer KH. Substance use among HIV-infected patients engaged in primary care in the United States: findings from the Centers for AIDS Research Network of Integrated Clinical Systems cohort. Am J Public Health. 2013;103(8):1457-67. Epub 2013/06/15. doi: 10.2105/ajph.2012.301162. PubMed PMID: 23763417; PMCID: PMC3752382.
53. Newcombe DA, Humeniuk RE, Ali R. Validation of the World Health Organization Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): report of resultsfrom the Australian site. Drug Alcohol Rev. 2005;24(3):217-26. Epub 2005/08/13. doi: 10.1080/09595230500170266. PubMed PMID: 16096125.
54. WHO Assist Working Group. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): development, reliability and feasibility. Addiction. 2002;97(9):1183-94. Epub 2002/08/30. doi: 10.1046/j.1360-0443.2002.00185.x. PubMed PMID: 12199834.
55. Liu AY, Vittinghoff E, von Felten P, Rivet Amico K, Anderson PL, Lester R, Andrew E, Estes I, Serrano P, Brothers J, Buchbinder S, Hosek S, Fuchs JD. Randomized Controlled Trial of a Mobile Health Intervention to Promote Retention and Adherence to Preexposure Prophylaxis Among Young People at Risk for Human Immunodeficiency Virus: The EPIC Study. Clin Infect Dis. 2019;68(12):2010-7. Epub 2018/09/22. doi: 10.1093/cid/ciy810. PubMed PMID: 30239620; PMCID: PMC6541706.
56. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-81. Epub 2008/10/22. doi: 10.1016/j.jbi.2008.08.010. PubMed PMID: 18929686; PMCID: PMC2700030.
57. Beauchemin M, Gradilla M, Baik D, Cho H, Schnall R. A Multi-step Usability Evaluation of a Self-Management App to Support Medication Adherence in Persons Living with HIV. Int J

Med Inform. 2019;122:37-44. Epub 2019/01/10. doi: 10.1016/j.ijmedinf.2018.11.012. PubMed PMID: 30623782; PMCID: PMC6369913.