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ATN 138 - Connecting Youth and Young Adults to Optimize ART Adherence: Testing the Efficacy of the YouTHrive Intervention

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SIGNATURE PAGE

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

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Print/Type

Signed: _____ Date: _____

Role: SRV Site Principal Investigator

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AC	Analytic Core
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretoviral Therapy
ATN	Adolescent Medicine Trials Network for HIV/AIDS Interventions
CASI	Computer Assisted Self-Interview
CFR	Code of Federal Regulations
CRF	Case Report Form
DHHS	U.S. Department of Health and Human Services
EC	Ethics Committee
GCP	Good Clinical Practices
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
IRB	Institutional Review Board
MC	Management Core
MSM	Men who have Sex with Men
NICHD	National Institute of Child Health and Development
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
PI	Principal Investigator
OHRP	Office for Human Research Protections
QNS	Query and Notification System
RCG	Radiant Creative Group
RCT	Randomized Controlled Trial
RDC	Remote Data Capture
SID	Study Identification Number
SRV	Subject Recruitment Venue
SSL	Secure Sockets Layer
TC	Technology Core
TWM	Thrive With Me
UMN	University of Minnesota
VL	Viral Load
YLWH	Youth Living With HIV
YO	Years Old
YT	YouTHrive

STUDY ABSTRACT

DESIGN:	*YouTHrive* (*YT*) is a two-arm randomized controlled trial (RCT) to test the efficacy of an adapted version of the Thrive With Me intervention for youth living with HIV (YLWH).
DURATION:	YLWH are enrolled for 5 months.
SAMPLE SIZE:	Total study sample is 368 of which the following will be enrolled for each aim: 1) 48 participants for focus groups to inform intervention adaption; 2) 12-20 participants for usability testing to finalize intervention components; 3) 300 participants for a randomized controlled trial of YT, with participants randomized to either YT (n=150) or control (n=150).
POPULATION:	Participants for all aims of the study will include YLWH inclusive of all genders and all races/ethnicities. Focus group participants will be recruited from SRVs in Bronx, Chicago, and Houston. Usability participants will be recruited from SRVs in Bronx, Chicago, Houston, Philadelphia, Tampa, and Atlanta. RCT participants will be recruited from SRVs in Bronx, Chicago, Houston, Philadelphia, Tampa, Atlanta, Raleigh/Durham/Chapel Hill and Charlotte area. Usability participants must have had a detectable VL in the past 12 months. RCT participants will be required to meet eligibility criteria.
STRATIFICATION:	Focus group discussions will be stratified by age (50% 15-19 yo; 50% 20-24 yo). We will stratify by SRV (i.e., city) site for the RCT.
DATA COLLECTION:	Focus group discussions will be conducted in-person, digitally recorded, and professionally transcribed. There will be three data collection (screening, baseline, and 5-month) time points for the RCT. Visits are conducted in-person at the SRV or remotely. Surveys will be completed using online survey tools (Alchemer and Qualtrics). VL measure collection will occur in-person at the participant's SRV or remotely. Urine screen will happen at in-person visits only. Process data of participant activity on *YT* and control interventions will include log-in activity, tasks completed on the website, and number of written posts.

OBJECTIVES:	1) In a 2-arm RCT (n=300), assess the efficacy of YouTHrive (YT) to sustain suppressed viral load (VL) among YLWH, compared to an HIV information-only control condition. 2) Assess whether YT is more beneficial for substance-using than non-substance-using YLWH.

INTRODUCTION

1.1 Background

Fifty thousand persons are estimated to be infected with HIV in the United States each year,[1] of whom one-quarter were youth between the ages of 13 and 24 years in 2010.[2] Young gay and bisexual men accounted for 72% of all new HIV infections in the same year, with the majority of those being black youth.[2] Despite elevated risk for HIV infection, it is estimated that only 6-16% of youth/young adults living with HIV (YLWH) are virally suppressed.[3-5] Sufficient and sustained adherence to antiretroviral therapy (ART) reduces excess morbidity and mortality among people living with HIV (PLWH)[6] and lowers the probability of forward transmission to sexual partners.[7] Advancing targeted and innovative ART adherence interventions for YLWH is an urgent priority.[3]

Technology-supported ART adherence interventions have proliferated in recent years[8-10] due to the widespread adoption of technology across sociodemographic groups,[11] their ability to reach a broad audience, rapid scalability, and low implementation costs.[12,13] In the US, nearly all teens (between 12-17 years of age) use the Internet[14] and 78% own a cell phone.[15] Smartphone ownership among 18-29 year olds is high (86%).[16] ART adherence interventions that leverage software on PCs or through the internet[10] capitalize on consistency in delivery of content and long-term cost savings; however, to date the peer-to-peer interactivity that has come to symbolize Web 2.0[17] remains underutilized in technology-based ART adherence approaches. Peer-to-peer support is a recommended strategy to improve ART adherence,[18] is widely used by PLWH,[19] and has an evidence-base for in-person approaches (especially with adults[20]). However, youth in the US are increasingly accustomed to technology-mediated peer-to-peer interactions, suggesting that intervention approaches that specifically leverage high-use channels of interpersonal communication and support are needed.

The “Thrive with Me” (*TWM*) intervention leverages enhanced peer-to-peer interaction, ART adherence reminders and self-monitoring, and ART and HIV informational content[21] to improve ART adherence. In a pilot study of 123 adult MSM (average age = 43 years), those randomized to the *TWM* intervention showed improvements across all ART adherence outcomes compared to control participants, with greatest benefits for current drug-using MSM. Currently, our research team is funded to conduct an efficacy trial of an extended (5-month intervention period) and enhanced (tailored informational content; multi-dimensional self-monitoring; and gamification components, such as leveling and badges) version of the *TWM* intervention for adult MSM. Given youth’s broad acceptance and adoption of many of the components of the *TWM* intervention, and the critical need for novel and scalable ART adherence interventions for this population, the next logical step is to adapt the *TWM* intervention for YLWH.

As part of the UNC/Emory Center for Innovative Technology (iTech), we propose to test the efficacy of an adapted version of the *TWM* intervention, called YouTHrive (*YT)*, for YLWH. In this 4-year study, 300 YLWH between the ages of 15-24 with detectable viral load (VL) will be randomized to the *YT* or an HIV information-only control intervention for a 5-month period. A target of 50% of YLWH participants with self-reported alcohol and/or illicit drug use will be enrolled. The primary endpoint is VL post-intervention.

1.2 Rationale

There is a clear need to develop effective ART adherence interventions that meet the needs of YLWH. Although young MSM – especially racial and ethnic minorities – are at high risk for acquiring HIV and, if HIV-positive, having poor ART adherence, relatively few ART adherence interventions exist that are tailored to the needs of this population. For this reason, The TWM online peer-to-peer support intervention will be adapted for YLWH and assessed for effectiveness in a 2-arm randomized controlled trial (RCT) called YouTHrive (YT).

1.2.1 Focus groups with youth (ages 15-19 years old) and young adults (20-24 years old)

Focus groups will provide insights into what features and functions of the current TWM study youth like and dislike to assist intervention adaptation. Focus groups will be conducted at 3 SRVs (Bronx, Chicago, and Houston), and stratified by age (15-19 years old & 20-24 years old), to ensure that a geographically and demographically diverse sample of youth and young adults provide input to guide intervention adaptation. In addition, age stratification is intended to help younger participants (15-19 years old) to feel more comfortable sharing their opinions and feedback.

1.2.2 Usability Testing

The purpose of usability testing is to gain feedback about the intervention once a functional version of the intervention is available and to give SRV staff experience in implementing all procedures associated with intervention arm participation. It is primarily intended to get feedback from the target population about any technical issues they encountered, as well as to obtain any feedback about the look and feel of YT. As we have done in prior technology-based studies, we will recruit up to 12-20 youth total across the 6 SRVs where the RCT will occur: Houston, Bronx, Chicago, Tampa, Atlanta, and Philadelphia to use the *YT* intervention for a 2-week period. In order to ensure diversity in the sample, each SRV site will recruit two total participants, one male and one female from the younger (15-19 years old) and older (20-24 years old) age categories. We also will recruit at least one perinatally infected female, one perinatally infected male, and at least one behaviorally infected gay or bisexual male (these targets will be across all sites, not per site). SRV research staff will briefly introduce participants to the intervention and provide instruction on how to log their impressions and feedback about the intervention. After the 2-week period, participants will participate in an online interview using VSee to interact with *YT* research staff to provide their feedback about *YT*. The information will be placed in summary form, and provided to our technology development partner to guide any final changes to the *YT* intervention.

1.2.3 RCT of *YT*

A 2-arm RCT of *YT* will be conducted, comparing the full version of the *YT* intervention to a control group. The control group will consist of weekly e-mails with a link to a webpage containing information about topics of interest to YLWH, but not addressing ART adherence. A RCT was chosen since it is the gold standard for assessing the effectiveness of an intervention under tightly controlled conditions. The intervention and control group will have access to intervention content for 5 months, with CASI performed at baseline and 5-month (i.e., immediate post intervention). VL will be assessed at baseline and 5- month time points to assess primary hypotheses (i.e., more participants in the *YT* group will have undetectable VL at the 5-month and assessment and, among those in *YT*, a greater proportion of substance-using participants will demonstrate sustained virally suppression than non-substance-using participants). Up to twenty purposively selected participants from the intervention group will also take part in a short, semi-structured interview over VSee or Zoom about their experiences on the site with study staff at their 5-month follow-up.

STUDY OBJECTIVES

2.1 **Primary Objective:** In a 2-arm RCT (*n*=300), assess the efficacy of YouTHrive (YT) to sustain suppressed viral load (VL) among YLWH, compared to an HIV information-only control condition.

2.2 **Secondary Objective**: Assess whether YT is more beneficial for substance-using than non-substance-using YLWH.

2.3 Study Hypotheses/Research Questions

- *H1: A higher proportion of participants in the* YT *intervention arm than in the information-only control arm will have undetectable VL at the 5-month follow-up time point.*
- *H2: Among YLWH in the YT intervention arm, a higher proportion of substance-using YLWH will demonstrate VL suppression at the 5-month follow-up time point compared to non-substance-using YLWH.*

STUDY DESIGN

3.1 Study Phases/Aims

We will evaluate the *YT* intervention in a randomized controlled efficacy trial (see *YT* Schema) YLWH will be recruited from the 8 SRVs (Bronx, Houston, Chicago, Philadelphia, Tampa, Atlanta, Raleigh/Durham/Chapel Hill, and Charlotte), screened, and randomized to receive either the *YT* intervention or HIV-information only control condition. VL will be collected at the enrollment visit and 5-month follow-up assessment time point.

Phase/Aim 1: YT Intervention Adaptation
We will conduct six focus groups with approximately 8 youth (15-19 years old) and young adults (20-24 years old) each at 3 SRVs to obtain: 1) feedback from YLWH about the "look and feel" and content of the original *TWM* intervention; 2) suggestions for adapting the intervention for YLWH similar to themselves; 3) information about barriers to ART adherence and other challenges of living with HIV. Focus groups will be transcribed verbatim and a content analysis will be assisted by the Analytic Core (AC).

Phase/Aim 2: YT Adaptation and Build
Information and feedback gathered from the focus groups will inform the adaptation of the *TWM* intervention for YLWH. The ADAPT-ITT model will be used to guide the adaptation process. Briefly, the ADAPT-ITT model follows 8 steps- each contributing to the acronym; **A**ssessment of target population needs and local resources; **D**ecision making on components to leverage and adapt from TWM; **A**daptation of components to target group and pre-testing; **P**roduction of intervention draft; **T**opical experts review adaptations; **I**ntegration of feedback leading to second draft; **T**raining for implementation; and **T**esting.

Dr. Horvath and the research team will partner with Radiant Creative Group (RCG) in order to update the *TWM* intervention to include those features and functionality that arise during the aforementioned adaptation process. Usability testing with 12-20 participants at 6 SRVs (Bronx, Chicago, Houston, Philadelphia, Tampa, and Atlanta) will be conducted to finalize all features and components of the intervention (i.e., ensure that all features are working properly and function in a way that users can easily navigate).

Phase/Aim 3: Randomized Controlled Trial to Test Efficacy of YT
YLWH will be recruited from 8 SRVs (Bronx, Houston, Chicago, Philadelphia, Tampa, Atlanta, Raleigh/Durham/Chapel Hill, and Charlotte). Persons interested in the study will be screened to determine if they meet the eligibility criteria. Prospective participants can screen remotely or in person, and can be recruited within the SRV clinic or in the community, as long as they meet inclusion criteria. YLWH who meet all inclusion criteria will be invited for either an in-person or virtual enrollment visit. Screening and enrollment may also happen during one visit, when possible.

At the enrollment visit, participants will complete an in-office or online baseline CASI, complete a viral load test if one was not performed in the past 60 days, a urine screen for recent drug use, and will be randomized at survey outset to either intervention or control. The randomization sequence will be stratified by city and use random permuted blocks of size 2 and 4. YLWH assigned to the *YT* intervention will be shown example webpages of the intervention, will be given basic training on how to navigate the intervention, and will be given the opportunity to ask questions they have about the website. Control condition assigned participants will be shown example webpages they will receive during the intervention period.

The intervention period lasts five months. During this time, intervention participants will have continuous access to the *YT* website (mobile enhanced and available on all devices with internet connection). Participants in the control condition will receive an email with HIV-related information once per week.

Follow-up assessments will be conducted at the 5-month (i.e., immediate post-intervention; follow-up 1 in the clinical setting or online via a teleconferencing platform such as VSee of Zoom) time point. The 5-month follow-up visit will include an in-office or online administered CASI, a blood draw or self-administered finger prick to test for detectable viral load, and a urine screen for drug use. At the 5-month follow-up visit, up to 20 intervention participants will be offered additional compensation (as specified in each SRV's informed assent/consent form) to take part in an additional semi-structured interview with SRV staff or via Zoom with a member of the study team.

3.2 Study Population

We propose to enroll 368 HIV-positive individuals for the purposes of this study. Approximately 48 participants will be recruited for focus group discussions (with the goal of 8 per group), 12-20 participants will be recruited to conduct usability testing of the *YT* intervention, and 300 participants (n=150 YT and n=150 control) will be recruited to participate in the *YT* RCT. An enrollment target of 50% for illicit drug use and/or problematic alcohol use in the past 6 months is set for each SRV. Participants who are pregnant at the time of screening or who become pregnant during the study period will not be excluded from the study.

3.3 Study Randomization, Stratification, or Description of Non-Random Assignment Procedures

3.3.1 Focus Groups

Focus groups will be stratified by age such that 2 focus groups (1 consisting of youth 15-19 year olds and 1 consisting of young adults 20-24 years old) will be conducted at each of the 3 SRVs. Study staff at each SRV will oversee that approximately 8 participants (with a minimum of 5) are recruited for each of the 2 focus groups conducted at that site. SRV study staff will have at least weekly check-ins with the AC lead and the *YT* protocol chair to provide updates about recruitment successes and challenges, and to brainstorm recruitment strategies that may be used should recruitment goals not be met.

3.3.2 Usability Testing

Usability testing participants will be recruited from 6 SRVs (Bronx, Chicago, Houston, Philadelphia, Tampa, and Atlanta) without stratification or random assignment. However, participant demographics for this aim should be closely monitored to ensure that diversity in ages, genders, and race/ethnicity is achieved at each site. Management Core will work with sites to recruit a diverse sample for usability testing. Each SRV will recruit two participants for

usability testing. One participant will be from the younger age group (15-19) and one from the older age group (20-24). SRV recruitment staff will be asked to recruit one male and one female at each site. In addition, across all SRV sites, we will recruit at least one perinatally infected female and at least one perinatally infected male to ensure that YouTHrive is relevant for youth infected through different transmission routes.

3.3.3 RCT

At outset of the survey, participants will be randomized 1:1 to YT intervention or control group, based on a randomization sequence developed by the AC lead statistician and loaded into DFexplore via SAS. The randomization sequence will be stratified by city and use random permuted blocks of size 2 and 4.

SELECTION AND ENROLLMENT OF STUDY PARTICIPANTS

4.1 Inclusion Criteria

Inclusion Criteria for Aim 2 Usability Testing

- 15-24 years of age at the enrollment visit
- HIV-positive status (medical chart-verified)
- In HIV clinical care in the Chicago, Houston, Bronx (NYC), Philadelphia, Atlanta, or Tampa area
- Currently prescribed ART (medical chart verified)
- Medical chart-verified detectable VL (above the lower limit of detection for the clinical assay) within 52 weeks of enrollment date and an ART prescription for at least 90 days prior to this VL test date
- English-speaking (since the intervention will be in English)
- Internet and SMS messaging access for the usability testing period (approximately two weeks)
- Available to meet with SRV staff in person for the first research appointment
- Availability to meet with UMN research staff for a remote (i.e., telephone or video-conference) feedback interview

Inclusion Criteria for Aim 3 Randomized Control Trial

- 15-24 years of age at the enrollment visit;
- HIV-positive status;
- Residing in Chicago, Houston, NYC, Philadelphia, Atlanta, Tampa, Raleigh/ Durham/Chapel Hill, or Charlotte areas and available to meet with SRV staff for visits at baseline and 5-month follow-up assessment. Participants who are unable to attend in-person session will be given the option to complete assessments online;
- English-speaking (since the intervention will be in English);
- Anticipated continuous internet access and SMS messaging for the intervention period (approximately 5 months);
- Not enrolled in another ART adherence intervention research study at the time of screening;
- Has or is willing to create an e-mail address to use during the study period;
- Did not attend an iTech YAB (Youth Advisory Board)/YAC (Youth Advisory Council) meeting where the YouTHrive study was presented or YouTHrive study materials were discussed;

4.2 Exclusion Criteria

Exclusion Criteria for Aim 2 Usability Testing

- Aged younger than 15 years or older than 24 years
- HIV-negative
- Is not in HIV care in the Chicago, Houston, Bronx (NYC), Philadelphia, Atlanta, or Tampa area
- Not currently on ART medication (does not have an active ART prescription by a health provider)
- Does not have medical chart-verified detectable VL (above the lower limit of detection for the clinical assay) within 52 weeks of enrollment date and an ART prescription for at least 90 days prior to this VL test date
- Non-English speaking (since the intervention will be in English)
- Anticipate not having access to the internet or SMS messaging during the usability period (approximately two weeks)
- Not available to meet with SRV staff in person for first research appointment
- Not available to meet with UMN research staff for a remote (i.e., telephone or video-conference) feedback interview

Exclusion Criteria for Aim 3 Randomized Control Trial

- Aged younger than 15 years or older than 24 years
- HIV-negative
- Does not reside in Chicago, Houston, NYC, Philadelphia, Atlanta, Tampa, Raleigh/Durham/Chapel Hill, or Charlotte areas or is not available to meet with SRV staff for visits at baseline, and 5-month and follow-up assessment
- Non-English speaking (since the intervention will be in English)
- Anticipate not having access to the internet or SMS messaging for the intervention period (approximately 5 months)
- Enrolled in another ART adherence intervention research study at the time of screening
- Planning to move out of study area during the study period and unwilling to participate in virtual visits
- Unwilling or unable to comply with protocol requirements
- Participated in Aim 2 of the study (Aim 1 participants may be included if they meet other criteria)
- Does not have or is not willing to create an e-mail address
- Attended an iTech YAB (Youth Advisory Board)/YAC (Youth Advisory Council) meeting where the YouTHrive study was presented or YouTHrive study materials were discussed

All genders may participate in the study. Women who are pregnant at study onset or become pregnant during the study period are eligible and can be included as participants.

4.3 Recruitment

Participants for all aims of this study may be approached and recruited in one of three ways: 1) in the clinic, 2) in the community; and 3) online. Recruitment procedures may vary slightly depending on the SRV and study aim, which will be negotiated prior to the beginning of each aim of the study. In order to enroll approximately 8 participants per focus groups (minimum of 5 and no more than 10), SRVs where focus group recruitment will occur should over-recruit (12-15 potential participants) for each focus group to account for persons who express interest in the study but fail to show for the focus group. Over enrollment is not required for usability

testing (Aim 2) or the RCT (Aim 3), as enrollment will continue until the target recruitment goals are met.

For the Aim 3 RCT, we will follow respondent-driven sampling (RDS) methods and use a long-chain referral method to supplement recruitment, especially with the adolescents (15-17) who may be harder to reach than young adults (18-24).

Clinic Recruitment: Individuals in care at the clinic may be screened and enrolled in one of two ways. First, those who have had their medical chart reviewed to assess potential eligibility (e.g., age, HIV status, on ART, clinic appointment attendance) and who are referred to the study by a provider will be approached for recruitment either in the clinic before or after a medical visit or remotely (e.g., telephone or email). Potential participants will be informed of the nature of the study, the information to be collected, and the evaluations and assessments that are involved. Those who express interest in the study will be required to be screened electronically to determine if they meet all inclusion criteria. If the individual meets all eligibility requirements, research staff will inform them of their eligibility and will initiate the enrollment visit immediately or schedule the enrollment visit if the potential participant cannot complete the procedures at that time. Second, any individual in care may be screened for eligibility without reviewing their medical chart to assess for potential eligibility, as they may be eligible for the study based on self-reported criteria. These individuals may be approached for recruitment either in the clinic before or after a medical visit or remotely (e.g., telephone or email). If the prospective participant screens eligible remotely, research staff will initiate a follow-up call, text, or email that will inform them that they are preliminarily eligible and to schedule the enrollment visit. If the prospective participant screens in the clinic and meets all eligibility requirements, research staff will inform them of their eligibility and will initiate the enrollment visit immediately or schedule the enrollment visit if the potential participant cannot complete the procedures at that time.

Individuals who do not consent to participate will be asked if they are willing to provide their reason for declining participation; responses will be recorded. Individuals assessed as ineligible for enrollment will have the reason(s) for ineligibility recorded.

The Protocol Team may request tabulated information on individuals who participated in the recruitment process, but did not provide informed consent and the reasons these individuals refused to participate. These data will be de-identified and will not include PHI. These data will provide general information on the population that is recruited at the study sites into the study.

Community and Online Recruitment: SRV staff will identify YLWH in the surrounding community. This may be accomplished through RDS, the use of outreach workers to community venues where YLWH not in care spend time, through targeted ads on widely used websites and social media channels (such as but not limited to Facebook; Grindr), or by posting flyers in high traffic areas where these youth may frequent. These individuals may be approached for recruitment either in the community or contacted remotely (e.g., telephone or email), and asked to complete the online screener. If the prospective participant screens eligible remotely, research staff will initiate a follow-up call, text, or email that will inform them that they are preliminarily eligible and to schedule the enrollment visit. If the prospective participant screens in person in the community and meets all eligibility requirements, research staff will inform them of their eligibility and schedule a time for the enrollment visit. The receipt of outside community or clinic services will not depend on expressing interest or enrolling in the YT study (i.e., the receipt of services will be based on usual clinic requirements). Other processes described above under Clinic Recruitment, where appropriate, will apply to participants who are recruited from the community or online.

Those recruited online will be directed to a website to complete an online screener to determine eligibility. The self-administered screener will also include a brief online consent to screen.

Screeners will only be conducted via a secure online platform. Personal contact information will be obtained from potential participants who meet eligibility criteria. This includes screener's name, email address, and phone number.

4.4 Informed Consent

Informed consent/assent. For Aim 3 – RCT, those recruited online and/or who will complete the enrollment virtually will be shown an abbreviated consent/assent form to screen and to obtain a VL measure. Those who consent/assent to these procedures will be screened and, if eligible, potential participants will complete a VL test. This test will be performed by drawing potential participant's blood during an in-person visit to a lab (such as but not limited to Quest or LabCorp) or during an in-person visit at the SRV site, or by using a self-collection VL kit mailed to the potential participant's home. Potential participants may also log into their online health portal and show SRV staff the viral load test results in person or over a secure, HIPAA-compliant, videoconferencing platform. SRV staff may also obtain the VL test result from the participant's medical record if one has been performed within 60 days prior to the study visit. Participants will be asked to sign a HIPAA release form at the SRV site. SRV site staff will virtually consent participants to the study using complete consent/assent forms and procedures.

For individuals who are able to meet in person, the informed consent process will occur on the day the enrollment visit is held. Interested persons will be guided through the informed assent/ consent process by SRV study staff, who will explain all study procedures, answer questions concerning the study and assent/consent process, and offer a copy of the informed consent/ assent form. The research staff member will give the participant as much time as needed and will address any questions or concerns they may have. The participant will be allowed to take the consent/assent form home or have an electronic body emailed to them to review it before enrolling in the study if the participant needs more time to review the form. The research staff member will ask the participant questions to gauge comprehension. The consent/assent form describes all study procedures, including confidentiality and privacy, information about potential risks, discomforts, benefits of participation, and information regarding who they can contact with further questions. It also states that participation is voluntary, that participants may decide not to take part or to withdraw from the study at any time without penalty or loss of any benefit to which they might otherwise be entitled, and that study participation is in no way related to being able to access or continue getting care or services at any participating study site. Participants can refuse to answer any question, and can withdraw from the study at any time. The PIs, Co-PIs, or designee at each SRV site will review all informed consents and assents.

Assessing for decisional capacity. For all participants, the research assistant (RA) reviews the informed consent/assent to make an assessment of the youth's decisional capacity and ability to provide consent/assent prior to signing, using a 2-step process. First, the RA determines if the person understands the study goals by asking a question such as "Can you tell me what this study is about?" In step 2, potential participants will be asked questions designed to assess their capacity to understand, appreciate, reason with, and express a choice about participation in our specific protocol. Participants will be asked to: name things they will be expected to do during the study; explain what they would do if they no longer wished to participate in the study**;** explain what they would do if they experienced distress during the study; and identify potential risks for participating in the study. For youth who cannot answer these questions, the RA will go back and review the relevant elements of assent/consent with

the participant again and repeat the process. Youth who appear not to understand after repeated review will not be enrolled in the study.

Waiver of parental consent. We will request that the UNC-CH IRB as the single IRB (IRB of Record) grant a waiver of parental consent to participate in this research study for youth participants who are 15 to 17 years of age. The research team has been granted waivers of parental permission for prior studies with sexual minority youth. Under 45 CFR 46.408 (c), an IRB has the authority to waive parental permission if it determines that "a research protocol is designed for conditions or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects" and "an appropriate mechanism for protecting the children who will participate as research subjects is substituted" and "that the waiver is not inconsistent with Federal, State, or local law." A waiver of signed consent and parental/legal guardian permission will be sought given that minor individuals can often seek sexually transmitted infection (STI) and HIV testing without parental/legal guardian permission, depending on each site's state laws, and given that many of the youth in our study are likely to be gender and/or sexually fluid or have an attraction to persons of the same gender, but may not be out to their parents; requiring parental permission may place participants at risk for outing themselves as part of the LGBT community or being at risk for HIV infection. A waiver of parental permission for studies with LGBT youth that do not involve greater than minimal risk is a common practice among researchers working in the area of gay and lesbian health/mental health. This is done to avoid the selection biases operating in only recruiting youth whose parents are both aware of and comfortable with their sexual orientation. Commonly, these youth have explored their sexual orientation without their parents' knowledge as the youth struggle with issues of disclosure and its consequences within the social, religious, and economic context of their families. A requirement for parental permission in this type of study could not only affect a person's willingness to participate, but could also potentially impact the ability of researchers to engage in this type of research with sexual minority youth.

If the purpose of requiring parental permission as stated in CFR is to protect the minor subject, then requiring parental permission for youth in these circumstances is not a reasonable requirement. Additional privacy protections are provided in that all assessments, notes, reports, and other records will be identified by only a coded number to maintain participant confidentiality. These records and any forms that do contain identifying information (e.g., consent/assent forms, contact information) will be kept in a locked, limited access area (such as a locked file cabinet) at the participating site.

Consent/assent may be obtained up to 30 days prior to or on the day of enrollment, prior to implementing any study activities. If more than 30 days has elapsed, consent/assent must be reaffirmed on the day of enrollment.

4.5 Screening

Once a potential participant has been identified online, through the community or clinic-based recruitment, they will be sent a link to the online screening survey or taken into a confidential room to complete the online screening survey on a computer or tablet. The online survey is hosted on Alchemer, which will include the eligibility script, consent/assent to be screened, and questions. For those who meet eligibility criteria, the survey will record the name, e-mail, and phone number of the participant. We use SSL encryption for transfers of information online and data will be stored in the secure, HIPAA-compliant servers of Alchemer. The Emory AC team maintains a business partner HIPAA agreement with Alchemer.

STUDY PROCEDURES

5.1 Enrollment Procedures

Screening procedures are explained above in section 4.5. YLWH who meet all inclusion criteria will be invited for an enrollment visit within 60 days after screening. If a participant is eligible for the study and interested in participating, they will complete an enrollment visit. Screening and enrollment may happen during one visit if possible. The enrollment visit may be conducted in person or online. Online enrollment visits will be conducted via a HIPAA-compliant videoconferencing software, such as but not limited to Zoom.

Participants who elect to complete their enrollment visit virtually will be asked to complete a VL test. This test will be performed by drawing potential participant's blood during an in-person visit to a lab (such as but not limited to Quest or LabCorp) or during an in-person visit at our site, or by using a self-collection VL kit mailed to the potential participant's home. Participants may also log into their online health portal and show SRV staff the viral load test results in person or over a videoconferencing platform. SRV staff may also obtain the a VL test result from the participants medical record if one has been performed within 60 days prior to the study visit. Participants will be asked to sign a HIPAA release. SRV staff will contact potential participants and obtain their consent to mail the VL test either to the participant's address or to an alternate address provided by the potential participant. SRV will virtually consent participants to the study and email participant a secure link to complete the computer-assisted baseline survey, created by AC staff and hosted on Alchemer, a secure, HIPAA-compliant platform. Once the assessment is complete, SRV staff will contact the participant to schedule a virtual enrollment visit.

During the enrollment visit for Aims 2 and 3, SRV staff will confirm the participants' eligibility. YLWH who are eligible for the study will be guided through an informed consent process by research staff. Next, participants completing will complete a computer-assisted baseline survey, created by AC staff and hosted on Alchemer, a secure, HIPAA-compliant platform. During the RCT, participants will then be randomized 1:1 to *YT* intervention or control group, based on a randomization sequence developed by the AC lead statistician and loaded into DFexplore via SAS. The randomization sequence will be stratified by city and use random permuted blocks of size 2 and 4. The time between screening to enrollment must not exceed 60 days. If more than 60 days lapses between the screening and enrollment visit, then a person must be re-screened (see section 4.5). Participants will be considered enrolled upon signing the enrollment RCT consent form, completing the CASI, completing either an in-person or virtual enrollment visit, and being randomized to YT intervention or control.

5.2 Locator/Contact Information

Once consented and enrolled, designated site study staff will complete a Locator/Contact Information Worksheet with participants and/or enter the participant's contact information directly into SMART Web during the enrollment visit. Participants will be asked to provide a working phone number or valid email address through which they can be reached. Participants will also be asked to provide social media contact information, if the participant is willing. Participants will also be asked to provide valid contact information for a family member and/or friend who can be called in the event the participant cannot be reached by phone or email. Participants will be asked if messages can be left at the numbers provided. Study staff will not leave messages unless expressly permitted to do so by the participant which also will be documented on this form. If permission is given to leave messages, site staff will assure participants that messages left with a family member or friend will only ask the participant to contact study staff and will not include any protected health information or information related to study participation.

5.3 Randomization Procedures

Participants in the RCT will complete a computer-assisted baseline survey at or before the enrollment visit, created by AC staff and hosted on Alchemer, a secure, HIPAA-compliant platform. After completion of the survey, participants will be randomized 1:1 to *YT* intervention or control group, based on a randomization sequence developed by the AC lead statistician and

loaded into DFexplore via SAS. The randomization sequence will be stratified by city and use random permuted blocks of size 2 and 4.

5.4 Intervention/Investigation Procedures

5.4.1 Focus Groups

Focus groups will be conducted in person and at 3 SRVs (Bronx, Chicago, and Houston). Two focus groups will be conducted at each of the 3 SRVs, and focus groups should not be scheduled more than 3 days apart (so that they can be conducted in one visit by the Protocol Chair). Focus groups are anticipated to last approximately 90 minutes, and light refreshments and food will be served at each group (Focus Group Discussion Guide). The Protocol Chair and potentially 1 additional research staff member will conduct the focus groups. All focus groups will be audio recorded (equipment provided by the Protocol Chair). The Protocol Chair will coordinate with SRV staff to have cash/gift cards available (as determined by each SRV) to disperse at the end of each focus group.

5.4.2 Usability Testing

Twelve to twenty (2-3 per SRV) YLWH will be recruited at 6 SRVs (Bronx, Chicago, Houston, Philadelphia, Tampa, and Atlanta) to participate in usability testing (Usability Testing Checklist for site study staff). Usability testing will involve identifying potential participants at the SRV clinic/site, briefly describing the study, and screening for eligibility using an online survey accessible on a clinic/site computer or tablet in a confidential room. Once determined eligible, participants take the baseline CASI and then will be taken through a brief tutorial of the *YT* intervention (Usability Testing Script), and asked to use the intervention daily for the following 2 weeks. Participants will be scheduled to return for the follow-up visit in approximately 2 weeks. During the follow-up visit, the participant will be given access to software on the clinic/site computer to conduct a secure video session with the project coordinator from the University of Minnesota remotely. Participants will be asked to provide feedback about all aspects of the *YT* intervention (Usability Debriefing Interview Guide). The interview is anticipated to take 30-45 minutes. Clinic/site research staff will provide participants $25 at the first study visit and $25 at the conclusion of the debriefing interview at the second study visit ($50 total).

5.4.3 RCT

Recruitment for the RCT will occur via community and online outreach and at all eight SRVs. Once enrolled (i.e., eligibility is confirmed and the participant provides consent, completes the baseline survey, is randomized, and completes a urine screen [as described in the Baseline Checklist for Research Assistants]) they will be walked through a brief description of their respective study arm (Control Group Script and YT Intervention Group Script). To end the enrollment visit, participants will be compensated as specified in Section 8.2 and as outlined in each SRV's informed assent/consent form, and reminded that they will be asked to complete a study visit in 5 months. Participants who are unable to attend the in-person 5 month visit will be able to complete a virtual visit.

In order for the earliest participants to have peer interaction on the site as intended, 5 YLWH will receive compensation for being active on the site until 15-20 participants have been enrolled. Once the target of 15-20 has been reached the study team will re-evaluate the need for these peer advocates.

The *YT* site and control pages (although there are no interactive features on the control pages) will be monitored by research staff at the San Diego State University to ensure that participants are following established community guidelines (YT Intervention Community Guidelines).

Therefore, any concerns (e.g., hostile interactions, suicidal ideation) or comments that are evident on the YT site will be addressed by San Diego State University research staff and, if relevant, will activate the YT Clinical Protocol for User Postings.

At the follow-up assessment (5-month) time point, SRV staff will contact participants to either schedule a follow-up appointment or to complete an online survey at a confidential place of their choice. Follow-up appointments may be scheduled 30 days prior to *or* as late as the date of enrollment. Participants who do not have a confidential space to complete the survey will be encouraged to complete the survey at a computer or tablet located at the clinic. Participants will receive compensation once they have completed a follow-up survey.

In addition to the assessments undergone by all study participants, up to 20 intervention participants will be offered additional compensation to take part in an additional optional semi-structured interview remotely via Zoom or a comparable HIPAA-compliant videoconferencing platform with study staff at their 5-month follow-up visit. Participants that were particularly active on the site based on activity reports tracked by study staff will be offered the opportunity to interview.

5.4.4 Research and Training Staff

Research staff at individual SRVs who interact with *YT* participants at assessments do not need to be clinicians. A research assistant (RA) level position should be sufficient to obtain informed consent, be available for questions during the CASI, collect the urine sample for drug testing, and explain the YT intervention or control websites. A certified phlebotomist will be required to collect blood samples. RAs will also receive training on the use of self-administered VL testing to assist participants who may have questions about the specimen collection. The *YT* intervention is delivered online and will be accessible on multiple devices (computer, tablet, or smartphone). Research staff at SRVs will be trained via videoconferencing on the intervention components and will be given a script and checklist to review with participants. Along with reviewing components of the website, research staff will also explain community guidelines/ rules of site use and explain when researchers may intervene. If a participant asks a question that the RA does not feel equipped to answer, the RA will contact research staff at the San Diego State University and then follow-up with the participant. Research staff at the San Diego State University will monitor the site daily. Since this is a social networking site, users may post information (such as suicidal ideation) which would require involvement from the clinical team at the SRV, as described in the Clinical Protocol for User Postings.

5.4.5 Intervention Monitoring/Quality Control

Because the *YT* intervention and the Control webpages are fully online and available on computers, tablets, and smartphones, intervention fidelity is assured (i.e., all participants will receive the intervention in the same way and have access to all of the same resources). Study visit checklists will be used during study visits to ensure that study procedures are followed in the same steps for each participant.

EVALUATIONS AND MEASURES

Overviews of the administration of clinical and behavioral measures are shown in the Schedule of Evaluations. Presented below is additional information on visit-specific measure administration and procedures.

6.1 Screening

See Section 4.5 for screening details. Enrollment is to be completed within 60 days of the screening. Below is a summary of screening procedures and laboratory screening tests used for in-person visits.

6.1.1 Administrative and Behavioral Procedures

- Screening assessment using CASI
- HIPAA and/or medical record release authorization

6.1.2 Clinical Procedures

- None

6.1.3 Laboratory Procedures

None

6.2 Enrollment

The enrollment visit will only occur if potential participants meet the eligibility criteria. For those who are eligible, an appointment time will be scheduled for the enrollment visit that will include the following procedures listed below. Participants must be scheduled for an enrollment visit within 60 days of screening; otherwise they will need to be re-screened. Participants will be considered enrolled upon meeting all SMART eligibility criteria, signing the enrollment SMART consent/assent form, being randomized, completing the baseline CASI, and onboarding to their respective study arm.

6.2.1 Administrative and Behavioral Procedures

- Consent to verify eligibility
- Eligibility verification using CRF
- Informed Consent
- HIPAA and/or medical record release authorization
- Baseline Assessment using CASI
- Randomization to intervention or control
- For intervention participants, training on the *YT* intervention/procedures
- For control participants, training on control intervention/procedures
- Collection of locator/contact information
- Medical record abstraction

6.2.2 Clinical Procedures

- Urine collection (in-person visits only)
- Blood collection or self-administered VL test (if no VL test result in medical chart within 60 days of enrollment date)

6.2.3 Laboratory Procedures

- Urine test for presence of illicit drugs (if available in-person)
- Viral Load testing (if no VL test result in medical chart within 60 days of enrollment date)

6.3 5-month Assessment (Immediate Post-Intervention)

Participants will have access to intervention content (either the YT intervention or weekly control pages) for a total of 5 months. The 5-month assessment should occur as soon after their 5-month enrollment period as possible. However, the assessment may occur 30 days prior to or up to 60 days after (inclusive of the 60th day) the ideal 5-month assessment time point. Remote 5 month follow up will be offered to participants who reside outside of any participant who expresses an inability to make an in-person visit in an effort to reduce the number of participants who are lost to follow-up. In-person visits are the preferred method of follow-up. Participants will receive a phone call, e-mail, or text (as deemed appropriate for that site) from research staff at their respective SRV, and an appointment for this visit scheduled to complete the following procedures listed below. Blood collection should only be conducted if the participant does not have a measure of VL in their medical record or cannot provide proof of a VL test within the past 60 days. If a VL test has been conducted in the past 60 days, the results of that test should be recorded and no blood drawn for VL. Participants whose 5 month follow-ups visit are conducted remotely will have a VL test conducted either in a SRV clinic, external laboratory, or a mailed self-administered test.

At the 5 month visit, up to 20 participants randomized to the intervention arm will participate in a remote interview conducted by study staff over VSee or Zoom. The purpose of this interview is to elicit feedback on their experiences using the YT site, any technical difficulties encountered, and how the site could be further improved. Participants will be selected for interviews using purposive sampling based on level of engagement with the site (i.e., high engagement vs. low engagement relative to other users). All interviews will be audio recorded for transcription and analysis. Participants who are invited to interview and choose to do so will be provided an additional compensation payment. Study staff will track activity levels and select participants for the interview.

In-person 5-month visit:

6.3.1 Administrative and Behavioral Procedures

- 5-month assessment using CASI
- Feedback interview for up to 20 youth in the YouTHrive intervention arm
- Medical record abstraction

6.3.2 Clinical Procedures

- Blood collection (if no VL test result in the past 60 days is available in the participant's medical record or electronic health record)
- Urine collection (in-person visits only)

6.3.3 Laboratory Procedures

- Viral Load Testing (either from medical record, blood draw conducted in an SRV clinic, at an external laboratory, or self-administered VL test)
- Urine test for presence of illicit drugs (if available in-person)

DATA COLLECTION AND SITE MONITORING

7.1 Development of Protocol and Case Report Forms

The Management Core, in collaboration with the Protocol Team, is responsible for the development of this protocol as well as the Case Report Forms (CRFs) needed to collect the information required to implement this protocol.

7.2 Data Records

Participant-related study information will be identified through a study ID number (SID) and a participant code comprised of the first initial of the participant's first name and their two digit day of the month born on all participant CRFs, audio and video files, transcripts, and CASI files. Participant names or other personally-identifying information will not be used on any study documents and should be redacted from focus group and usability interview transcripts. All study-related information will be kept in double-locked, limited access areas at each study site. Participant names and their SIDs and participant code will be stored separate from other study information in SMART, accessible only to designated study staff, iTech site monitors, and representatives from the NICHD. Original source documents for individual participants will be maintained at the respective SRV and will be accessible only to the study staff. Data from original source documents will be transcribed on CRFs as applicable.

7.3 Data Collection

7.3.1 CRFs

Study monitoring data, including information about eligibility, demographic data, and monitoring untoward effects will be collected on CRFs. All CRFs for this study will be available for download from a secure Box or Microsoft OneDrive account.

7.3.2 CASI Survey Data

Self-administered surveys at the screener, usability testing first visit, enrollment and 5-month assessment time points will be completed by participants on a clinic computer or tablet. Participants completing the enrollment and 5-month assessment virtually will in a confidential setting of the participant's choosing via a computer, tablet or smartphone. Surveys will be hosted on Alchemer. We use SSL encryption for transfers of information online and data will be stored in the secure, HIPAA-compliant servers of Alchemer. The Emory AC team maintains a business partner HIPAA agreement with Alchemer.

All data collected using CASI will remain confidential; no personal identifying information will be collected during the computer session. The participant's unique SID# will be used in order to link the interview responses to the participant's CRF data.

7.3.3 CASI Data Security

<u>CASI Data Security</u>
Only authorized users with a login name and password will be able to access and open the survey through the internet site. To ensure data privacy, as soon as data is entered (in real-time), it will be encrypted during transmission to the AC using Secure Socket Layer technology. The data will then be immediately stored in a secure database on an AC server within the AC data center.

7.3.4 VSee Platform Description

For many of the interviews with participants, the AC and study staff will rely on VSee platform or a comparable HIPAA compliant videoconferencing platform. When using VSee, participants will have the option to use VSee in several formats: face-to-face video chat, video chat in which

they can see the interviewer but the interviewer cannot see them, audio chat only, or a text based conversation. The consent form for each research project will include a full description of VSee, their options for using VSee, and will also make it clear what they can opt not to do. VSee is compatible on PCs, tablets, and smartphones. Unlike other video-chat platforms (e.g. Skype), VSee is HIPAA-compliant. VSee includes the following functions to protect users:

*End-to-end encryption without a man-in-the-middle listener***.** In WebEx, Vidyo, Tandberg, and Polycom architectures, media is sent to a server (also called a video relay or MCU). Although encryption is applied from the user's computer to these servers, the servers still have full access to the user's media. In contrast, VSee uses end-to-end encryption where no server, including VSee servers, has the decryption key. VSee uses public/private RSA keys to exchange a 256-bit AES session key with the property that only the endpoints have the AES session key. VSee uses FIPS 140-2 certified 256-bit AES encryption.

*One port***.** VSee uses a single port for call signaling and media. The VSee protocol is structured so that only the outgoing port needs to be open because return traffic is always structured as responses to outgoing traffic. This allows administrators to set a policy where if users inside their network are using VSee, then their firewall lets VSee traffic securely cross the firewall; however, if users inside their firewall stop using VSee, then the firewall will block external port scans.

*Automatic HTTP/SSL tunneling***.** VSee prefers to use UDP since it allows higher performance video. However, if the firewall does not allow UDP, VSee will automatically switch to HTTP/SSL tunneling.

*Cloud Control***.** VSee's cloud solution allows enterprises to maintain central control of their security policies to a large number of end points even though the service is hosted by VSee. It does this by having VSee clients always connect first to VSee servers in the cloud, where the policies are controlled. The cloud servers determine whether any of these security policies should be applied and enforces them as the VSee client. This allows us to set our own security settings and to record the sessions.

*No-install client***.** Video conferencing software clients tend to be large and to leave a big footprint on the user's system. Almost all of them require administrator permissions to install. Once the client software gains administrator permissions, they can severely compromise computer security. VSee is a lightweight client that does not require administrator permissions or installation.

VSee offers the HIPAA-required Business Associate Agreement (BAA) where VSee agrees to be responsible for keeping all patient information secure and to immediately report any breach of personal health information. In this study, the iTech Technology core will enter into a BAA with VSee, and this will be extended to cover the proposed activities. The VSee sessions will include identifying information (e.g. images of the participant, voice recordings). All identifying information will be stripped from the recorded VSee sessions before they are sent to the analysis team for content analysis.

7.3.5 Zoom Platform Description

In addition to VSee, Zoom may be used to conduct qualitative interviews remotely. Participants will have the option to conduct face-to-face video chat, video chat in which they can see the interviewer, but the interviewer cannot see them, or audio chat only. Zoom is compatible on PCs, tablets, and smartphones; as well as maintains the option to conduct an audio conference without the video component. Emory University has entered into a BAA with Zoom, where Zoom agrees to be responsible for keeping all patient information secure and report any breaches of

protected health information (PHI).

End-to-end encryption. Zoom encrypts all presentation content at the application layer using the Advanced Encryption Standard (AES) 256-bit algorithm. Zoom end-to-end (E2E) chat encryption allows for a secured communication where only the intended recipient can read the secured message. Zoom uses public and private keys to encrypt the chat session with Advance Encryption Standard (AES256), and session keys are generated with device unique hardware ID to avoid data being read from other devices. This ensures that the session cannot be eavesdropped or tampered with.

Cloud Control Infrastructure. A distributed network of low-latency multimedia routers (software) resides on Zoom's communications infrastructure. With these low-latency multimedia routers, all session data originating from the host's device and arriving at the participants' devices is dynamically switched — never stored persistently through the Zoom communications infrastructure. Zoom's communications infrastructure for real-time video, audio, and data communications resides on Zoom dedicated servers, which are housed in SSAE 16 SOC2 compliant datacenters on opposite sides of the US. Zoom sessions are completely temporary and operate analogously to the popular mobile conversation over the public mobile network. In addition to unique security benefits, Zoom's communications infrastructure also enables an extremely scalable and highly available meeting infrastructure unrestricted by the limitations of physical data centers.

The Zoom client communicates with the multimedia router to establish a reliable and secure connection. At the time of instantiation, the Zoom client will determine the best method for communication, attempting to connect automatically using udp and tcp port 8801, 8802 and 8804 or HTTPS (port 443/TLS).

The Zoom sessions will contain identifying information, as in VSee above, but this information will be stripped form the recorded Zoom sessions before they are sent to the analysis team for content analysis.

7.4 Data Submission

7.4.1 CRFs

Although the iTech projects will involve substantial online follow-up, CRFs will be used to collect key study visit data (e.g., enrollment and randomization assignment), study milestones such as completion or discontinuation, study laboratory results, and adverse events (AE). AC staff will work with study investigators and the MC to develop and design the CRFs. During study conduct, the SRVs will maintain the CRFs in secured locations, and transmit CRF data to the AC either electronically using DFexplore or by submitting scanned paper forms using DFSend. DFexplore and its DFdiscover platform is a leading multi-site database environment for HIV RCT that can receive and transcribe CRF data via scanned PDFs, or allow for direct electronic data entry. It provides for monitoring form completion and data quality, and a system for data querying and resolution with SRVs, while maintaining an audit trail. The AC uses DFexplore for MSM studies and RCTs and data is maintained by the parent company DF/net on a cloud-based server with Microsoft Azure.

7.4.2 Audio/Video Data

Audio-recorded data for the focus groups and audio and video data for exit interviews will initially be stored as a digital file on a secure encrypted server. Focus group discussions will be transcribed verbatim from the digital audio-recording and de-identified by assigning unique numerical codes. All qualitative interviews will be transcribed. Transcripts of the interviews will not use the names of the participants, only their pseudonyms for FGs or study ID for the IDIs.

After transcripts are verified by the research team and one year after the study is over, audio and video files will be destroyed.

All qualitative interviews may also be recorded using a back-up digital audio recorder. Audio files will be erased after being transcribed and transcripts will be de-identified. All audio files will be kept confidential and stored in a locked/limited access folder on secured servers, which is only accessible to designated study staff. All members of the research team will be trained in confidentiality and have signed confidentiality agreements. A professional transcription service, experienced in the handling of confidential data, will be used to fully transcribe verbatim all audio files. Prior to receipt of the first audio file, the transcription service will be instructed to exclude from the typed transcript identifying information (e.g., a name) that may have been verbalized during the course of the focus groups.

All CASI data will only be identified with a unique study number and stored on a secure encrypted server by the AC team. Only SRV research staff, the AC team, and the research team at the San Diego State University will have access to the data.

7.4.3 CASI Data Transmission

Only authorized users with a login name and password will be able to access and open the survey through the internet site. To ensure data privacy, as soon as data is entered (in real-time), it will be encrypted during transmission to the AC using Secure Socket Layer technology. The data will then be immediately stored in a secure database on an AC server at Emory University.

7.4.4 Retention data

The study will use a HIPAA-compliant web-based platform entitled Study Management and Retention Toolkit (SMART), which is a SaaS (Software as a Service) based mobile application aiding studies with various aspects of participant recruitment, study implementation, and retention. The application has the ability to securely manage participant information across multiple studies and customers simultaneously, stratifying participant information by study and site. SMART includes an admin web portal and a participant facing mobile app (optional), which allows for secure messaging, study calendar management, self-scheduling by participants, secure photo uploads, and longitudinal tracking of participants from screening to study completion. The ability to designate specific roles to all SMART users allows for greater control around permissions and accessibility to participant information. Users can even be limited to a reporting only role, which allows for study oversight through real time aggregate reporting, but no access to PHI. SMART is a licensed service of the Center for AIDS Research (CFAR) at Emory University, Prevention Science Core. Utilization of the mobile app is optional and the admin web portal will fully function without it.

The following information outlines the security of the three SMART components: (1) the admin web portal, (2) the participant app, and (3) a web service that acts as a liaison between the mobile app and the study database.

Admin Web Portal. The admin web portal is a web-based application developed using Microsoft .NET technologies. It uses SQL server as backend database. The application requires two servers to host: (1) Web server [Windows server with IIS] and (2) SQL server [Standard or

Enterprise version]. Both these servers are to be placed behind a firewall. Web server will have a public IP to access the server using VPN. SSL certificate is to be installed on the web server. The admin website will be rendered over SSL (https).

The application uses form authentication (no integrated authentication such as AD). All passwords are stored encrypted within the database. System will also be using database level encryption, which will prevent any copying of information from one database to another. Web application also uses an automatic logout feature after a certain period of inactivity. By default, the inactivity duration is set to three minutes.

Study staff can only first gain access to the admin web portal if granted by a study or site administrator. Their assigned user role will determine their permissions to perform different actions and even view PHI. Email notifications are sent from the system (without the need to login) when: (1) a staff member requests to reset their password, (2) role assignments to a study are made, (3) an event/visit staff are scheduled to work is nearing, (4) a new task is assigned to a staff member, or (5) they are designated as a staff member to receive alerts of positive test results. All participant communications are performed using secure messaging through the message center (inbox) implementation within the mobile app. If the mobile app is not utilized by a study, communications are sent as standard email or text messages to participants.

Mobile App. The mobile app, developed natively for iOS and Android platforms and available for free in the App Store and Google Play Store, is an optional feature the study can utilize for self-scheduling, communication, photo uploads, and updating contact information. The study will indicate during the initial setup within the admin web portal whether the participant mobile app is utilized or not. If the app is utilized, participants will receive download instructions after their information is entered into the admin web portal. Only participants listed in an active study who validate their email or phone number against the contact information listed in the admin web portal will be able to proceed into the app. For validation, the app uses both traditional form authentication as well as social login (Facebook and Google). The social login feature will only work if the email associated with either social account matches the contact information within the admin web portal. The app does not request anything other than basic information from these authentication services. Participants cannot “remember” their password on the mobile device for automatic logins to ensure privacy. All participant data and activity status is maintained within a secure and encrypted SQL Server database. To create the connection between the admin web portal and the mobile app, each participant is assigned a unique ID within the application, which is associated with their login credentials. When a participant has been successfully authenticated through the mobile app, the admin web portal will send their specific information to their phone through the established secure session (web APIs using SSL). The app will not store the information presented locally on the phone. Local data storage is used only for storing some minimal non-PHI information, such as app settings. The mobile app implements an automatic logout when there is inactivity for more than three minutes. If a participant should need to re-download the app on a new device, login and password authentication will be required again.
The mobile app has push notifications that are primarily used for reminders and notifications of new messages. Push notifications displayed on the participant’s phone will be generic in nature and not contain any PHI. Reminders and notifications within the mobile app inbox will also be generic in nature, with any message containing sensitive information requiring a pin, established during registration as a secondary authentication, to open within the mobile app. Firebase cloud messaging service is used as a communication channel for these notifications. No PHI is passed through Firebase. Push notifications are customizable in the study setup, and samples of system notifications include: “You have a new message in your inbox,” “You have an upcoming event for March 7, 2018,” and “You have a pending task.”

Web Service. A web service will also be hosted on the web server. This service is used by the mobile application to retrieve and store data. The service will utilize secure socket layer (SSL) for communication.

7.5 Data Quality Assurance

Investigators receiving federal funding must adhere to the Code of Federal Regulations (CFR) to protect research participants and produce reliable study information. Sites participating in research sponsored by the NICHD need to have an internal quality assurance (QA) plan that will identify problems and correct errors in research study records.

7.6 Role of Data Management

The MC will provide instructions concerning the recording of study data on the CRFs, entry of the data into RDC, and administration and transmission of CASI data.

7.7 Study Site Monitoring and Record Availability

Site monitors from the MC will visit participating study sites to review a selected portion of the individual participant records, including assent/consent forms, CRFs, and supporting source documentation to ensure the protection of study subjects, compliance with the protocol, and accuracy and completeness of records. Regulatory files, as required, will also be inspected to ensure that regulatory requirements are being followed.

The site investigator will make study documents (e.g., assent/consent forms, case report forms) *and pertinent hospital or clinic records* readily available for inspection by the local IRB, the single IRB, the site monitors, the NICHD, the Office for Human Research Protections (OHRP), or the sponsor's designee for confirmation of the study data.

PARTICIPANT MANAGEMENT

8.1 Tracking Participants / Follow-up

All subjects will be contacted before each follow-up study visit/assessment (i.e., enrollment and 5-month time points). Multiple contact methods will be used for youth who are difficult to reach (e.g., mail, alternate phone numbers, e-mail, text message, social media contact information). Subjects will be asked whether or not messages can be left for each of the phone numbers that they provide. They will be informed that messages will not contain any information regarding the nature of the project.

8.2 Compensation

The method for compensation will be determined separately by each site, listed in the site's informed consent/assent form, and approved by the single IRB (the UNC-CH IRB).

If a subject is unable to go into the clinic to complete a follow-up study visit, the web-based CASI survey could be completed on their own. Site study staff will be notified when a subject has completed a CASI survey on their own and the compensation will be provided to the subject. Additional compensation will be provided for participants who are asked to return to clinic site for laboratory/clinical testing or asked to complete a self-administered VL test. Site study staff will determine the appropriate amount of compensation. Compensation can be provided in person, or sent to participants electronically or via mail, if allowed at the site.

8.3 Intervening on “Social Harms"

(*Describe potential harms that may occur as a result of participating in the study, and what steps will be taken to reduce or counteract the negative effects. These measures can be preventive or reactive.*)

We identified the following 6 items as possible risks to subjects and described how we plan on addressing those risks:

1. Protecting against going to the site by mistake. We have a secure site (https:) with an introductory page clearly specifying the nature of the study. Sensitive survey or intervention content is protected behind screening questions and a username/password, and therefore in the opening study webpage, we could not think of anything that would be deemed offensive by any persons or those who might be vulnerable. In this way, we have minimized the risk to a level that is negligible.
2. Protecting against others finding out about their sexual behavior, sexual orientation identity, or HIV status. Participants will be alerted to this and provided basic information on how to best protect themselves. Specifically, those who qualify for the study will have access to an informational page describing how we protect their confidentiality and what steps participants can take to protect their confidentiality during the study. The description of the purpose of the study will clearly state that the study is designed so that participants are encouraged to interact with one another virtually, and we will recommend that persons who are highly uncomfortable with such exchanges may be better served by not enrolling in the study. Once enrolled, we also minimize this risk of identification to participants in the following ways: a) participants will be required to create usernames that do not contain personally identifying information and the site will be continuously monitored to maintain high levels of confidentiality and b) participants may utilize the features of the intervention that they choose, although we will encourage the exploration of all features. Thus, although we cannot guarantee their anonymity, we will take appropriate safeguards to minimize this risk.
3. Protecting against discomfort in answering personal questions during the focus group discussions, the assessments, and/or revealing aspects of themselves during the intervention period with other participants. This risk is similar to #2 above, and we will use comparable safeguards to protect against it. Thus, we intend to fully inform participants of the purpose and nature of the study prior to their participation. Participants in all of the protocols are informed that they are free not to answer questions or utilize study features, and they may stop participation at any time. Since a “refuse to answer” option is provided to every self-report question in the study surveys, there is a constant reminder of their participant rights throughout the study. Internet-based studies may be less invasive than conventional study methodologies, as it provides users total control over their participation and they may opt out of the study by simply exiting the study website. We believe the risk to participants is minimal and we have adequately anticipated and set into place protocols to address potential risks that may arise.
4. Protecting against hostile interactions and inaccurate information from one participant to another. Participants will be informed during the consent process of the “group rules” regarding interactions with one another (e.g., “Honesty is important; however, hostile or abusive language will not be tolerated and may be grounds for immediate removal from the study”). These “rules” will also be available with a link on all intervention web pages for review by participants at any time. The project coordinator will manually review an automated compilation of posts participants make on a daily basis to flag hostile interactions and inaccurate information. Hostile interactions between participants will be handled by, first, reminding the participants in the interaction of the “group rules” regarding appropriate interactions. If the hostility continues, the offending participants

will be given a warning that the continued hostility will result in withdrawal from the study if it continues. On the third offense, the offending participant will be withdrawn from the study. Text containing hostile exchanges will be removed from the study website and unavailable to view. In cases in which inaccurate information is found, project staff be guided by experts on the team to post a comment that provides accurate information on the topic. In extreme cases, the PI's may decide to withdraw a participant before the third offense. We will ensure all clinic sites have a clear clinical protocol to address major issues that may come up at study visits or in online interactions. The major issues addressed in the procotol will be suicidal ideation, homicidality or violent ideation, emotional and cognitive disregulation, violent/aggressive or disruptive behavior, and intoxication. If research staff from San Diego State University see concerning comments or messages online from participants regarding self-harm or harm of others, they will contact clinicians at the site and take immediate precautions.

5. Protecting against concerns about the security of their data. Well-established security protocols will be followed, that include the following:
    1. Participants' identifying information is kept separate from the data set, in a separate file on a separate computer in the offices of the PI's, accessible only by authorized study staff.
    2. All data will be encrypted and stored on a password-protected computer behind a firewall to ensure access is provided only to those involved directly in data collection or analysis.
    3. Payment to subjects will be administered by research staff during the baseline, and immediate post-intervention follow-up.
    4. At the end of the study, the identifying information (participants' names and contact information) is destroyed. The original data records will be archived for 7 years (in accord with good data practices), and three copies of the de-identified dataset will be maintained (a working one and two archived at different sites).
    5. All project staff will be required to complete the NIH online training in research ethics. Further training and supervision will focus research staff on confidentiality concerns both during and after the study. The project coordinator in conjunction with the PI are responsible for ensuring that all research staff involved in this study document their NIH training.
6. Minimizing the risk and discomfort from phlebotomy and VL testing. Trained and certified phlebotomists will perform all blood draws done in person in order to minimize the risk of bruising or infection. In order to minimize discomfort, an experienced and/or certified medical assistant will perform these procedures. They are routinely done in medical settings, and therefore potential risks are no greater than those encountered during routine medical exams. SRV staff will make every effort to align participants' data collection time points with standard clinic viral load measures. When these do not align, an additional blood draw or self-collected VL testing will be needed. For both standard VL testing and self-administered VL testing, physical harms are minimal. The type of safety lancet selected for use in the study was designed to minimize the potential for infection or significant injury. Cleaning the area with an alcohol pad first lowers the already low infection risk further; pads are included in every kit. The spring-loaded lancet retracts fully after one firing, and thus does not pose a risk for "needle stick" injury to anyone after the device has been used. Subjects could experience dizziness, diaphoresis and nausea associated with the procedure but in prior clinical studies using self-administered testing, adverse events have been rare.

All sites have specific policies governing the treatment of human subjects. These policies specify that medical and psychological assistance will be available in the immediate environment in the event a participant should experience any adverse reactions resulting from study procedures.

While participants will be informed that they may refuse to answer any question at any time, responses or reactions to certain questions may indicate distress on the part of the participants. If at any time during the study, a participant divulges that they are at risk for harm, including but not limited to being abused or experiencing violence, if harm is suspected or likely, or if the participant states they are suicidal/homicidal, measures will be taken to ensure their safety. Reporting will be done as appropriate to the situation and the legal statutes, including reporting to child protection agencies or other appropriate agencies, and referrals will be provided to appropriate support, counseling, or treatment resources.

8.4 Criteria for Premature Study Discontinuation

Subjects will be prematurely discontinued from the study if any of the following occurs:

- The subject withdraws consent/assent;
- The subject becomes incarcerated or placed in detention
- The participant is unwilling or unable to comply with study procedures
- The investigator believes that ongoing participation may cause harm to the participant or study staff
- The investigator believes that ongoing participation may impact the integrity of the study data
- The study is cancelled by the *NIH (or iTech, or other administrative entity)*;
- The study is cancelled for other administrative reasons;
- The subject becomes incarcerated or placed in detention during the study; or
- Death of the subject.

The *Study Stop CRF* will be completed when participants are study stopped. No medical record data on participants will be abstracted past the date of study discontinuation.

Subjects who are prematurely discontinued from the study may be allowed to re-enroll into the study on a case-by-case basis. The Protocol Team will review the number of slots opened for replacements on a monthly basis, or more frequently, as needed.

MONITORING UNTOWARD EFFECTS ASSOICATED WITH OR RESULTING FROM STUDY

Site research staff must first follow their own IRB's procedure for reporting and managing untoward effects.

There are three types of untoward effects to be identified: (1) those related to the participant, (2) those related to the study staff, and (3) those related to the neighborhood/community *(if applicable).*

First, the study will catalogue any untoward effect related to the participant. Reporting is required for occurrences including social harms, psychological distress, and serious life-threatening events such as suicide attempts. These may be immediately apparent to the study staff, such as the participant's emotional upset state requiring referral for counseling; or they may be delayed and reported later to study staff, such as physical harm to an individual for having participated in the study. Study staff will notify the iTech team of any untoward effects using the iTech QNS accessible through the iTech website (www.itechnetwork.org) within 24 hours of becoming aware of these untoward effects. Study staff will be briefed during the training on the scope of possible untoward effects and instructed to report events.

Second, study staff may encounter untoward events during sessions that personally affect them. Training and guidance will seek to minimize this risk. Nonetheless, an assessment of the cost of conducting this study must include cataloguing these events as well. The protocol chairs should be notified of these events so that they may be immediately addressed, evaluated, and guidance modified or expanded to minimize similar risk to other study staff.

Third, a critically important area any community-based study intends to evaluate is the impact, including untoward effects, of the project on the community. This will be done informally for this protocol with untoward events being reported to the protocol team.

All untoward effects/adverse events/unanticipated problems will also need to be reported to the UNC IRB if they meet all three of the following criteria:

"Unanticipated problems involving risks to subjects or others" (UPIRSO) refers to any incident, experience, or outcome that:

1) is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2) is related or possibly related to a subject's participation in the research; and
3) 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.

Events that meet the criteria for an UPIRSO and are also serious adverse events should be reported to the UNC IRB within one (1) week of the investigator becoming aware of the event. Any other events that meet the criteria for a UPIRSO should be reported to the IRB within two (2) weeks of the investigator becoming aware of the problem.

If the report cannot be completed in its entirety within the required time period, a preliminary report should be submitted. The report should be amended once the event is resolved and/or more information becomes available.

STATISTICAL/ANALYTIC CONSIDERATIONS

10.1 Introduction

10.1.1 Focus Groups Overview

We will conduct six focus groups with approximately 8 youth (15-19 years old) and young adults (20-24 years old) each at 3 SRVs (Chicago, Houston, and New York) to obtain: 1) information about barriers to ART adherence and other challenges of living with HIV; 2) feedback from YLWH about the "look and feel" and content of the original *TWM* intervention; 3) suggestions for adapting the intervention for youth/young adults similar to themselves. Focus groups (as opposed to in-depth quantitative interviews) were chosen to gain feedback in these areas because this setting will allow participants to explore together the ways in which the *TWM* intervention meets their needs and how the intervention can be adapted to be community appropriate.

10.1.2 Usability Testing

A total of 12-20 YLWH across 6 SRVs (Bronx, Chicago, Houston, Philadelphia, Tampa, and Atlanta) will be recruited to provide feedback on the first full version of the *YT* intervention.

Usability testing is done to identify any technical problems with the program and any design features that are likely to impede engagement with the program.

10.1.3 RCT Overview

We propose to evaluate the *YT* intervention in a randomized controlled efficacy trial of 300 YLWH at 8 SRVs. YLWH will be recruited from the 8 SRVs, screened, and randomized to receive either the *YT* intervention or HIV-information only control condition. VL testing will be assessed at the enrollment visit and immediate post-intervention (5-month follow-up). We will evaluate interviews with up to 20 active users to obtain: 1) information about barriers to ART adherence and other challenges of living with HIV; 2) feedback from YLWH about the YouTHrive intervention; 3) suggestions for adapting potential future iterations of the intervention.

10.2 Power Estimates

10.2.1 Focus Groups Power Considerations

The purpose of focus groups is not to obtain generalizable data, but rather to obtain collective qualitative information to inform adaptation of the *TWM* intervention for youth. We are balancing feasibility with the need to obtain information from a spectrum of YLWH. As such, we will conduct 6 focus groups, targeting younger (15-19) and older youth (20-24) at 3 different SRVs with the goal of reaching 48 YLWH. Given our prior experience and best practices for the conduct of focus groups, this will provide us with information from enough youth to inform the adaptation process.

10.2.2. Usability Testing Power Considerations

Power is not a concern for usability testing as it is performed to collect feedback from a small number of members from the target population about a preliminary version of the intervention.

10.2.3 RCT of YT Power Considerations

We will continue to collect as much biologic data on viral load at baseline and month 5; however, given the difficulty in obtaining viral load measurements due to COVID, we will also utilize measures contained within our surveys to assess the impact of the intervention on self-reported HIV care continuum outcomes and possible mediating (social support) and moderating (depression) factors. We are already collecting this data, and thus will not need to modify our measures. We have been in discussions with SRVs about how many participants per month they believe that they could enroll. On average, sites reported that they would be able to recruit 4 participants per month each. If we begin the new inclusion criteria in April, then sites could potentially recruit up to 288 additional participants by ….. The study statistician (Dr. MacLehose) conducted a power analysis to ensure our proposed changes will still allow for meaningful detection of primary study outcomes. Assuming approximately 85% follow-up, we based our updated power calculations on 240 participants. The primary outcome, self-reported adherence is a continuous measure. A study by Belzer et al. suggest a standard deviation of 43; assuming a type 1 error of 5% and equal allocation of participants between the 2 arms, we have 80% power to detect a difference of 15.6 points between the two groups. For instance, if the control arm had an adherence of 48% (as seen in Belzer et al.), we could detect a significant difference of 63.6% adherence in the intervention arm. This is a clinically meaningful difference. We have also assessed the impact of these proposed study changes on important secondary outcomes that have been shown to impact ART adherence among YLH (including depression

and social support). Based on a literature review, depression is estimated to have a prevalence between 25% and 40% in this population. Using the same assumptions as above, we have 80% power to detect a difference of 13.9% (if the prevalence is as low as 25% in the control arm) or 16.7% (if the prevalence is as high as 40% in the control arm). We are also assessing social support as measured by the PROMIS-ES scale. A study by Shensa et al allows estimation of a standard deviation of 0.63 for this score, giving us 80% power to detect a different of 0.23 units. For example, if the control arm indicates a mean social support of 4, we could detect a difference if the intervention arm had a social support scale of 4.23.

10.3 Statistical Analysis Plan

10.3.1 Analyses of Focus Group Data.

Focus group discussions will be transcribed verbatim from the digital audio-recording, de-identified by assigning unique numerical codes, and entered into Dedoose software to assist with theme identification, coding textual data, and describing relationships among codes (via code co-occurrence and memoing functions). Following established focus group analysis guidelines, we will create a codebook of a priori and emergent themes including operational definitions of all codes and sample quotations to illustrate how to apply each code. Two study team members will then use the codebook to independently code the compiled user profiles while a third team member will review these sections of coded data and resolve discrepancies. We will draw a random sample of 20 instances for the coders to begin with and calculate an inter-rater reliability score based on their code assignments. If this score is <95%, we will refine the codebook definitions and retrain the coders. Coders will then complete the coding of the remaining instances and we will calculate an inter-rater reliability score. Discrepancies will then be reviewed and resolved by the research team. Coding and analytic activities will be discussed during weekly team meetings.

10.3.2 Primary Analyses for Usability Testing

A usability report will be compiled by Protocol Chair and reviewed by the investigator team and the AC. The report will include: a) a list of common problems like navigation problems; and b) recommended design-improvements that will be used in the final iterative stages of intervention adaptation.

10.3.3 Primary Analyses for RCT of YouTHrive

Stata version 15 (StataCorp) and SAS version 9.4 (SAS Institute) were used for power calculations and will be used for all analyses. The primary study outcome is HIV viral suppression at 5 months, measured as undetectable VL based on the standard level of detectability. The primary statistical test of intervention efficacy for YT will be the comparison between intervention and control arms of the proportion of participants with undetectable VLs at the 5-month follow-up, using a chi-square test. If there is evidence of baseline imbalance between intervention arms for important predictors of viral suppression, we will fit logistic regression models that adjust for those covariates.

10.3.4 Secondary Analyses for RCT of YouTHrive

As a secondary aim, we will investigate whether there is greater benefit from the YT intervention for substance-using participants compared with nonsubstance-using participants. We will use the same modeling approach described above to address this aim. First, we will examine the association between the intervention and viral detection separately among those who did and did not self-report current (since the last visit) substance use (i.e., yes/no for problematic alcohol use and/or illicit drug use). Second, to formally test whether there is an interaction between intervention arm and substance use, the models described above will be refit including an interaction term between substance use and interaction arm. Interactions will be evaluated on the additive scale. We will carefully examine the distribution of potential confounders of the substance use and VL association and adjust for them as necessary. As mentioned previously, we will adjust for covariates where appropriate.

The models described use logistic regression to model the outcomes. We will use estimates from these models to report prevalence differences and ratios. However, alternative (log-linear and Poisson) models may be explored to allow easy interpretation of parameters in the presence of common outcomes. In the event of loss-to-follow-up among study participants, we will perform sensitivity analyses of an alternative outcome. We will define an additional outcome where a failure is defined as either detectable VL or loss-to-follow-up. The analyses described above will be repeated with this alternative outcome. All of the models mentioned above can be modified to accommodate missing values in the outcome or covariates over time without dropping participants. Although attempts will be made to limit missing data, in the event that this occurs, we will carefully examine patterns of missingness. Multiple imputation will be implemented, as needed, to deal with missing covariate data.

Finally, we will examine models that include covariates that quantify the degree of site usage and which components were used. The additional outcome of self-reported ART adherence will be examined. The outcome will be defined as the percentage of ART taken in the past 30 days. Differences in this proportion by study arm will be evaluated using the same approach as described above. To explore the effects of the YT intervention on the intermediate theory-based processes of change, we will use the IMB-AAQ informational and motivational scales, adherence self-efficacy, and social support measures at each time point. These scales will be included as outcome variables in linear regression models to test the main effect of intervention arm.

Note: Any deviations from the analysis plans outlined above or in the sections that follow will be documented and justified in the Statistical Analysis Plan developed for this protocol.

10.4 Missing Data

Several procedures will be used to conduct data analysis when data for either outcomes or covariates are missing. The first step will be to assess the extent and pattern of missing data. If data are missing for only a few cases, then data analysis will be conducted only on study participants with complete data. However, when such a strategy would result in loss of data from a substantial proportion of participants, or if this approach would lead to biased or inaccurate results, then some form of imputation will be performed. The form of imputation used will depend on the nature of the data that are missing. For example, data that are collected repeatedly might be imputed using the “last value carried forward” method; and in some instances, interpolation between neighboring points might also be used.

When the primary endpoint is missing, one data analysis will be conducted using only cases with the endpoint. Subsequent analysis will be done where missing endpoints are imputed. Hot-deck imputation or regression imputation may also be used in this context.

HUMAN SUBJECTS

This study will be conducted in compliance with the protocol, ICH Good Clinical Practice (GCP) guidelines, and 45 CFR Part 46.

11.1 Participants' Confidentiality

All laboratory specimens, questionnaires, evaluation forms, reports, transcripts, and other records will be identified by a coded number and participant code to maintain participant confidentiality. All records with personally-identifying information will be kept in a locked file cabinet in a limited secure access area at each SRV site. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the MC or NICHD.

Every effort will be made to ensure that study participants are protected from risks. The main risk specific to the role of the AC is breach of confidentiality.

Breach of Confidentiality: A potential risk to participants is violation of confidentiality. We will take the utmost caution to protect the confidentiality of all responses. We will minimize this risk by maintaining confidentiality and discretion throughout all iTech research procedures and data management and analysis.

Participants may be concerned about the security of their data, particularly since it is collected and stored electronically. The AC has significant experience developing security protocols for Internet-based studies, and we will take a variety of steps to ensure participant security, including using a dedicated server behind a firewall, encryption of data, separation of identifiers from responses, and password-protected access to data. Therefore, we believe that this risk will be minimal. All of the apps and websites included in the iTech have features to ensure app security and privacy.

For the YT intervention in Aim 3 - RCT, participants will create a unique username that does not contain any identifying information but will be their social media handle on the YT website. Intervention participants will have the option to upload a profile picture in keeping with the site guidelines or select an anonymous avatar to represent themselves on the site. Participants are told at the enrollment visit and in multiple places on the YT website that it is a violation of community guidelines to reveal identifying information including name, address, phone number, email address, social media handles, places of employment, or locations to meet for personal or business use. Participants will not be able to privately communicate with each other on the YT website - all conversations are viewable on the main feed. Trained research staff at the San Diego State University (SDSU) will monitor the website daily to ensure violations to privacy, even through self-disclosure, are addressed. Participants will also be able to flag others' postings if they feel they have violated community guidelines. The YT website will use an "htpps" URL and entry into the website that is also password-protected.

11.2 Certificate of Confidentiality

This research specifically targets a vulnerable population, children - YMSM ages 15-17. We will take every available step to minimize the risk of identifying/linking data being subpoenaed, stolen, or inadvertently released. First, the iTech will request a Certificate of Confidentiality from the NIH. Second, all research staff members are required to complete ethical clearance certification regarding protection of human subjects through their relevant IRBs. Third, all

studies will have documented procedures to safeguard against the risk of the linking information being stolen by keeping such information in locked spaces to which only essential study personnel who have completed CITI certification for human subjects research ethics training (http://citiprogram.org) will have access.

A Certificate of Confidentiality for the iTech will be sought prior to enrolling participants. As noted on the NIH website (http://grants.nih.gov/grants/policy/COC/faqs.htm#187), a Certificate of Confidentiality will help the research team "...avoid compelled 'involuntary disclosure' (e.g., subpoenas) of names and other identifying information about any individual who participates as a research subject (i.e., about whom the investigator maintains identifying information) during any time the Certificate is in effect." We have applied for and received Certificates of Confidentiality for other NIH-funded research projects, and given the sensitive nature of the data collected for this project, do not foresee difficulty securing one for this study.

11.3 Risks and Benefits

11.3.1 Risks

Risks to participants in this research study may include:

By misspelling a web address or "surfing" the net, some individuals may unintentionally go to the study website. We deem this unlikely as we will use the prefix "https:" to prohibit persons from coincidentally viewing the site. Nonetheless, if someone were to mistakenly view the study website home page, we anticipate that the information contained on the homepage will be benign to viewers.

Potential participants or participants enrolled in the study may have concerns about others finding out about their HIV status or other personal behavior (e.g., sexual behavior or substance use). We anticipate that the likelihood of this occurring is high given that a major feature of the intervention is for participants to network with one another and that eligibility for enrollment in the study requires participants to identify as a HIV-positive. We anticipate these concerns to be even higher for focus group participants as well, since they will be meeting in-person with other YLWH. Subjects will be informed of the inclusion criteria and general questions that will be asked during focus groups during the recruitment period. Since subjects will be recruited directly within clinics, they will have the opportunity to discuss with clinic staff whether they feel comofrtable being a part of such discussions. Clear consent procedures and an introduction from the PI will also give opportunities for subjects to withdraw if they no longer feel comfortable participating in focus group discussions. For those in the RCT, subjects will be informed during the consent process of the basic features of the intervention and those who are not comfortable interacting with other HIV-positive persons will be encouraged to not participate in the study. Those who do enroll will be given the option of utilizing intervention features with which they feel comfortable, although utilization of all features will be encouraged.

The measurements that are involved in this study require venipuncture and self-administered finger pricks to collect blood samples. This procedure may cause local discomfort, bleeding, or bruising; rarely small clot or infection can occur at the blood draw site. This measurement should not be considered greater than minimal risk in and of itself given its routine use in general health care delivery.

To minimize the risk of participants feeling uncomfortable about answering personal questions, we will use CASI methods for the study's surveys. In CASI, participants read survey questions on a laptop computer or mobile phone and use a combination of mouse click and keyboard/ touchscreen entry to input the answers themselves. Study staff may be available to assist participants with questions or technical difficulties on the CASI. Participants will also be able to refuse to answer any question that makes them uncomfortable.

Participants may receive hostile communications or incorrect information from other participants during the course of the intervention. It is possible that some participants may respond aggressively or with hostility to other participants. Likewise, although well-intended, participants may provide inaccurate information about adherence or its risk factors to other participants by interactions through the website message boards/social networking wall. The *YT* intervention website includes a clear section on Community Guidelines and will be monitored daily by research staff. Users have the option to "flag" objectionable content. We have protocols in place for addressing hostile interaction in the site up to and including termination of participation in the study.

To minimize risks to confidentiality, we will secure study data with all appropriate physical, electronic, and operational protections. Data will be stored in a physically secure environment. All data files will have encryption and strong password protection. Any identifiable data will either be stored on Emory University's secure servers or will be on fully encrypted laptops. CASI surveys and online eligibility screening will take place on an encrypted commercial survey website, Alchemer. This site has been used by the investigators for thousands of online surveys with MSM with no data security breaches. Access to data will be on a role-based standard; only those study staff who require access to each type of data to complete their study-related roles will be allowed access. All study staff will be trained in security and confidentiality procedures, and will sign a confidentiality agreement before receiving access to any participant data.

We will also develop procedures to minimize indirect disclosure that a participant is participating in an HIV-related research study, or a study that enrolls MSM. For each mode of contact information, we will ask specifically whether anyone else potentially has access to that mode of communication, and if it is acceptable to leave a non-specific message about participation in a health study. No study-related messages will ever mention HIV prevention or the nature of the research study. Additionally, all scripts for email, text message, and telephone contact with participants will be reviewed and approved by the UNC IRB before being used for contact with participants.

We use SSL encryption for transfers of information online, and Alchemer has a business partner HIPAA agreement with Emory. Alchemer's servers are HIPAA compliant.

The AC will use Dedoose software to perform all qualitative analyses. Dedoose is a web-based application for organizing and analyzing textual, audio, and video data (qualitative) along with outstanding functionality for their integration with survey, test score, ratings, and demographic data (quantitative). Dedoose employs the highest levels of data encryption available for a web application in all data storage, back up, and transmission. Dedoose allows for project specific encryption feature. When using this feature, only Dr. Kate Muessig or her designee will hold the additional encryption key needed to be entered in order to view the project. This gives Dr. Muessig exclusive control over who can view the project under any circumstances.

In addition to a Certificate of Confidentiality, we will protect participants in the following ways (which correspond to the potential risks described earlier):

1. Breach of confidentiality. We will take every precaution to minimize risks to study participants. All AC research staff members are required to complete ethical clearance certification regarding protection of human subjects through UNC-CH or Emory University. We also have a strong data and safety monitoring plan in place to protect participants. Adverse events will be reported to the UNC-CH and Emory IRBs, individual research PI institutional IRBs, and SRV site-specific IRBs per each institution's IRB reporting requirements using Adverse Event Reporting Forms created by the AC. When possible, reports will be sent within 24 hours of notification by the PIs. Annual updates on enrollment and retention will also be sent to the IRBs.

All data collection will take place in secure and supervised clinical settings. All study personnel have completed training and received certification in Human Subjects Research Protection (CITI Program) and HIPAA regulations. They will continue to renew this training in compliance with institutional policies.

11.3.2 Benefits

Participation in the *YT* arm may provide participants with information and exercises that help them build peer social support, monitor their medication adherence and HIV-related care appointments, and develop skills. Participants in the control group may gain basic knowledge about medication adherence and links to outside resources. In either the experimental or control condition, the primary benefit is access to health information that may assist participants to improve ART adherence and quality of life. Secondary benefits include positive feelings related to having assisted in the development and testing of a novel internet-based adherence intervention, and if proven effective, the future availability of this intervention to others.

Compensation for participation is not considered a benefit, because we are simply reimbursing participants for their time, effort, and expenses (e.g., Internet access).

11.4 Institutional Review Board (IRB) Review and Informed Consent

This protocol, the informed assent/consent documents, and any subsequent modifications will be reviewed and approved by the UNC IRB who is responsible for the oversight of the study. The informed assent/consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation.

Consent/assent will be obtained to explain the nature, significance, and risks of the study.

11.5 Waiver of the Requirement for Parental Permission for Special Circumstances

The site IRBs and the UNC IRB as the single IRB will be requested to grant a waiver of parental permission to participate in this research study for youth participants under (not inclusive of) the age of 18.

Under 45 CFR 46.408 (c), an IRB has the authority to waive parental permission if it determines that “a research protocol is designed for conditions or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects” and “an appropriate mechanism for protecting the children who will participate as research subjects is substituted” and “that the waiver is not inconsistent with Federal, State, or local law.”

A request for a waiver of the requirement for parental permission is requested for 2 reasons: 1) many youth would be reluctant to participate in this study – which focuses on HIV and risks for poorer medication adherence – if they are required to get parental permission; and 2) many of the youth in our study are likely to be gay, bisexual, or have an attraction to persons of the same gender, but may not be out to their parents; requiring parental permission may place participants at risk for outing themselves as part of the LGBT community or having HIV. For these reasons, we believe it is important to be granted a waiver for parental permission for this study population.

11.6 Waiver of the Requirement for Signed Consent Form

1. For Study Participation

In order to maintain the anonymity of the survey and fully protect the privacy of the volunteer study participants, the UNC IRB will be requested to waive the requirement for a record of a signed consent form. A written consent form will be reviewed with each potential study participant and provided to each consenting one. This form describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation.

Under 45 CFR §46.117 (c) (1) and (2), an IRB may waive the requirement for the investigator to obtain a singed informed consent for some or all of the subjects if it finds either: (1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each participant will be asked whether they want documentation linking them with the research, and the participant's wishes will govern; or (2) that the research presents no more than minimal risk of harm to the participants and involve no procedures for which written consent is normally required outside the research context."

The protocol team believes that both #1 and #2 applies to this study and, both combined, justify a waiver of written consent.

11.6.2 For Eligibility Screening

An online consent process for the eligibility screening is proposed. The introduction to the screening interview includes all the required elements for consent (45 CFR 46.116). No identifying information on volunteers is recorded during the online screening until a participant is determined eligible (i.e., by marking "I do consent to be screened for eligibility.". Therefore, there will be no identifying link of who agreed to be screened or not screened for the study. In addition, the screening presents minimal risk to participants and involves no procedures that would require written consent outside of a research context. Under these conditions the IRB is authorized to modify the requirements to obtain a signed consent form for some or all subjects (45 CFR 46.117 [c]).

11.7 Prisoner Participation

NICHD has concluded that this protocol does NOT meet Federal requirements governing prisoner participation in human subjects research and should NOT be considered by local IRBs for the recruitment of prisoners. Subjects enrolled who subsequently become incarcerated or are placed in detention may not continue study participation. Study visits cannot be conducted during the period of incarceration or detention.

11.8 45 CFR Parts 160 and 164 Standards for Privacy of Individually Identifiable Health Information ("Privacy Rule" Pursuant to the Health Insurance Portability and Accountability Act - HIPAA)

Each site is responsible for adherence to their individual institution's HIPAA policies and procedures.

11.9 Study Discontinuation

This study may be discontinued at any time by the UNC IRB, NICHD, or other government agencies as part of their duties to ensure that research participants are protected.

PUBLICATION OF RESEARCH FINDINGS

Any presentation, abstract, or manuscript will be made available for review by the study sponsor(s) prior to submission.

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