ADOLESCENT MEDICINE TRIALS NETWORK FOR HIV/AIDS INTERVENTIONS

PROTOCOL

Adaptive Antiretroviral Therapy (ART) Adherence Interventions for Youth Living with Human Immunodeficiency Virus (HIV) through Text Messaging (SMS) and Cell Phone Support (CPS) Embedded within the Sequential Multiple Assignment Randomized Trial (SMART) Design

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PROTOCOL TITLE:

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
0	10.09.2019	Resubmission into new RAMP template	No
1	10.09.2019	Change of Study Specific Screener welcome script; updated Consent/Assent Form with audio recordings deletion timeline; updated Study Personnel with 5 new Research Assistants; added CITI refresher for Dilones; removed confirmation page from the Locator Form; updated call guides, email templates, and SMS templates with minor wording changes; and added OneFlorida approval letter	Yes

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		and estimate for utilizing OneFlorida research infrastructure for SMART recruitment.	
2	11.06.2019	Addition of data collection sheet (i.e. a list of variables with a brief description) to be used for the OneFlorida database. Updating procedures for using OneFlorida database for recruitment. See section 6.0 Procedures Involved on page 9 and section 13.0 Recruitment Methods on page 17-18.	No
3	01.03.2020	Reduced the N=90; increased the subject compensation; changed the compensation structure; added bonus incentives; addition of OneFlorida participant email script and provider letter; drafted email notification for currently enrolled participants RE revised compensation	Yes
4	01.30.2020	Revised the scripts drafted for OneFlorida providers and participants Addition of ATN 144b Project DABS sub-study	Addition of 2nd consent for new study
5	02.24.2020	Project DABS: addition of 4 new items (invitation call script; kit registration form; test kit ID card; and sharing VL result script) and minor edits on consent/assent (added end of consent script); locator form (added 1 question and end of contact script, reformatted some items); and measures (added 2 discrimination scales)	No
6	04.03.2020	Provided COVID updates and plans; added COVID update email script for SMART participants; revised SMART email templates to include language for splitting VL+ART submission forms; revised SMART email templates to temporarily remove clinic visits and Quest options; revised DABS invitation email script to provide temporary contact information due to office closure from COVID outbreak; revised DABS kit registration form; addition of DABS QR code; and revised CASI measures to change terminology and addition of "Everyday Discrimination" scales for sexual orientation and race	No
7	04.23.2020	SMART: added email notification about NO clinical visits during COVID; revised email templates to include language for full	No

		compensation despite of missing VL due to COVID DABS: Added 4 new items – CASI completion reminder email with office phone number; CASI completion reminder email with temporary phone number due to COVID; Exit interview with office phone number; Exit interview with temporary phone number due to COVID	
8	05.22.2020	SMART: Added COVID-related measures to CASI; expanded 12-month window due to COVID-19 (see page 16 track changes)	No
9	07.02.2020	SMART: Resume recruitment and enrollment in July; increase sample size from 90 to 120; Added pandemic stress index to screening measure; revised CASI measures with formatting language	No
10	07.23.2020	DABS: Added 2 new items – a study screener and short version of the locator form.	No
11	10.28.2020	SMART: Piloting new social media platform, Reddit as a recruitment strategy, a final push to enrollment of youth with HIV (see page 25). We will be using the currently existing recruitment materials.	No
12	11.25.2020	SMART and DABS: Addressed modifications requested on parental consent of minors (see page 42-49). Modified study-specific screener, assent, and locator forms.	Yes
13	12.08.2020	SMART: Added updated assent and consent for those who will be enrolled in Jan-Feb 2021 as they will be able to participate in the study only up to 9-months. However, we will continue to use the existing assent/consent for those enrolled in the study by December 2020.	Yes
14	06.17.2021	SMART: Added 1 new item: Email template for unpausing Quest appointment. DABS: Replaced the Clinical Microbiology Lab at the SUNY Downstate Medical Center with the Caliendo Molecular Lab at the Miriam Hospital (see page 18).	No

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Study Summary

Study Title	Adaptive Antiretroviral Therapy Adherence Interventions for Youth Living with HIV through Text Messaging and Cell Phone Support Embedded within the Sequential Multiple Assignment Randomized Trial (SMART) Design
Study Design	This study will use a Type 1 effectiveness-implementation hybrid design to adapt adherence interventions to improve self-management and maintain VL suppression, and enhance the potential for scale up. A Sequential Multiple Assignment Randomized Trial (SMART) will be utilized to maximize real-world implementation and identify effective sequences of treatments and their cost-benefit ratio. For the sub-study, to collect pilot data on the development and implementation of DBS procedures, this study seeks to conduct a mixed-method analysis to examine suitability, feasibility and acceptability of utilizing DBS to obtain viral load (VL) data.
Primary Objective(s)	• Compare Cell Phone Support (CPS) versus Text Messaging (SMS) for youth living with HIV (YLH) who are not virally suppressed. • Understand the benefit of incentives for non-responders, identify how to taper interventions for responders, and describe potential moderators of treatment effect.

	• Study the barriers and facilitators to wide-spread implementation as well as cost-effectiveness of treatment sequences. Sub-study: Assess the suitability, feasibility and acceptability of using dried blood spot (DBS) collection to obtain timely data on VL monitoring for human immunodeficiency virus (HIV)-positive youth between 15-24 years old.
Secondary Objective(s)	• Conduct an exploratory evaluation of tapering the intensity of CPS and SMS (among responders) vs. termination after completion of the 3-6 month intervention to determine if this improves the durability of intervention effects. • Explore the relative effectiveness and cost-effectiveness of the individual intervention sequences embedded within the SMART design for responders and non-responders. • Assess the five components of the Self-Management Model and how these components vary over time, are directly improved by the intervention, and mediate intervention effects. • Assess barriers and facilitators to the implementation and sustainment of intervention sequences in adolescent HIV care settings using mixed methods (Exploration, Preparation, Implementation, and Sustainment [EPIS] surveys, qualitative interviews, fidelity measurements and sequential analysis). **Sub-study:** 1. Examine barriers and facilitators of using DBS collection for VL monitoring and expand access to VL monitoring for HIV-positive youth between 15-24 years old. 2. Adapt VL collection methods (i.e., construction and distribution of at-home testing kits and surveys, tracking and monitoring testing kit completion, tracking and monitoring at-home survey completion) for DBS in this population. 3. Use a central laboratory to measure VL and evaluate the accuracy and lower limit of detection of a DBS. Currently, the lower limit is estimated at 500 to 800 copies/mL. This is not consistent with the latest definition of VL below detection (e.g., 200 copies/mL). Explore utilizing DBS collection to screen and monitor VL for ATN 144 SMART and future protocols.
Research Intervention(s)	The intervention will consist of CPS or SMS. CPS will be provided by an adherence facilitator (AF) who will assess if participants have taken their antiretroviral therapy (ART) medication(s) and provide brief problem solving support. SMS will act as a reminder to participants to take their

	medication and participants will text back a confirmatory response. The CPS intervention will occur on weekdays, excluding holidays. The SMS intervention will occur every day. The tapered intervention will occur on two weekdays per week, excluding holidays. Incentives will be added to the intervention for those participants who do not meet viral suppression requirements at 3 months. Sub-study: Project DABS does not implement any interventions.
Study Population	The study population will consist of HIV-positive youth (15-24 years old, inclusive) who have: a VL ≥200 copies/mL within 12 months prior or self-reported adherence (SRA) ≤ 80% in the past 4 weeks after being on a prescribed ART medication regimen for three months prior to eligibility VL; a cell phone and service plan; and the ability to understand written and spoken English. Sub-study: Youth (15-24 years of age) living with HIV (YLH) who are willing to provide DBS specimens for HIV VL measurement and have the ability to understand written and spoken English.
Sample Size	We will enroll 120 HIV-positive youth living with HIV aged 15-24. Sub-study: 50

Study Duration for individual participants	The total duration of the study for participants is approximately 12 months for both groups.
	• Baseline Assessment
	• Follow Up Assessment (post baseline)
	  ○ 3-Month Follow Up
	  ○ 6-Month Follow Up
	  ○ 9-Month Follow Up
	  ○ 12-Month Follow Up
	Sub-study: approximately 1 month

Study Specific Abbreviations/ Definitions	Adherence Facilitator (AF) Adolescents Medicine Trials Network (ATN) Cell Phone Support (CPS) Cell Phone Support + Incentives (CPS-I) Cell Phone Support Tapered (CPS-T) Sequential Multiple Assignment Randomized Trial (SMART) Text Messaging (SMS) Text Messaging + Incentives (SMS-I) Text Messaging Tapered (SMS-T) Youth living with HIV (YLH) ART – antiretroviral therapy CASI – computer assisted self-interviewing

	DBS – dried blood spot HIV – human immunodeficiency virus PI – principal investigator VL – viral load

1.0 Objectives*

Specific Aims:

1. To compare CPS versus SMS for youth living with HIV who are not virally suppressed.
2. To understand the benefit of incentives for non-responders, identify how to taper interventions for responders, and describe potential moderators of treatment effect.
3. To study the barriers and facilitators to wide-spread implementation as well as cost-effectiveness of treatment sequences.

Secondary Aims:

1. Conduct an exploratory evaluation of tapering the intensity of CPS and SMS (among responders) vs. termination after completion of the 3-6 month intervention to determine if this improves the durability of intervention effects.
2. Explore the relative effectiveness and cost-effectiveness of the individual intervention sequences embedded within the SMART design for responders and non-responders.
3. Assess the Five Components of the Self-management Model and how these components vary over time, are directly improved by the interventions, and mediate intervention effects.
4. Assess barriers and facilitators to the implementation and sustainment of centralized national recruitment, enrollment, intervention delivery, and retention using mixed methods (EPIS surveys, qualitative interviews, fidelity measurements and sequential analysis).

The proposed project is highly innovative because it focuses on a critical area for intervention, adherence to ART in YLH, and goes beyond what has been done previously in several key ways:
1. It directly compares two successful, potentially sustainable, and youth-friendly modes of mobile health (mHealth) youth adherence intervention delivery.
2. The project uses a SMART design to explore a number of key issues surrounding sequencing mHealth interventions in a cost effective manner that would be practical in clinical settings.
3. The CPS intervention uniquely addresses multiple barriers to antiretroviral therapy (ART) adherence in real-time using a social support framework.
4. The study will explore the clinical and public health costs of sequencing of interventions based on viral suppression and sexual transmission risk.

Sub-Study:
The primary aim of this sub-study “ATN 144b Dried At-Home Blood Science” (Project DABS) is to leverage our current ATN 144 SMART recruitment and screening methods and patient population to develop and test DBS implementation procedure to promote home-based DBS collection and change the landscape of adherence research in youth living with HIV. Additionally, if feasible, DBS collection implementation may enhance ATN 144 SMART protocols for obtaining VL, both at enrollment and follow-ups. DBS

collection has the potential to help identify additional youth who are eligible for ATN 144 SMART, thereby increasing enrollment in this difficult patient population, and aid in improving retention for those who do not provide VL via a clinic or testing facility.

Specific Aims:

1. Assess the suitability, feasibility and acceptability of using DBS collection to obtain timely data on VL monitoring for HIV-positive youth between 15-24 years old.
2. Examine barriers and facilitators of using DBS collection for VL monitoring and expand access to VL monitoring for HIV-positive youth between 15-24 years old.
3. Adapt VL collection methods (i.e., construction and distribution of at-home testing kits and surveys, tracking and monitoring testing kit completion, tracking and monitoring at-home survey completion) for DBS in this population.
4. Use a central laboratory to measure VL and evaluate the accuracy and lower limit of detection of a DBS. Currently, the lower limit is estimated at 500 to 800 copies/mL. This is not consistent with the latest definition of VL below detection (e.g., 200 copies/mL).
5. Explore utilizing DBS collection to screen and monitor VL for ATN 144 SMART and future protocols.

2.0 Background*

Adherence to ART is a critical factor contributing to low rates of viral suppression among YLH. At the end of 2015, there were approximately 60,300 YLH ages 13-24 in the U.S., and this number continues to increase. In 2016, YLH made up 21% of new HIV diagnoses—the equivalent of 8,451 new cases in that year alone. National treatment guidelines recommend initiating treatment with ART as soon as an individual is ready. Even with simpler, more potent, and better tolerated medications, viral suppression is difficult to achieve in youth. Only 41% of YLH in 2014 received HIV-related care, 31% were retained in care, and 27% were virally suppressed, the lowest percentage of any age group.

Adherence to ART is critical to sustain health, reduce transmission, and minimize the development of ART resistance. Non-adherence has both public health implications and personal health risks. High viral load (VL) increases the likelihood of viral transmission, and non-adherent individuals may be more likely to transmit drug-resistant strains of the virus. Conversely, treatment adherence decreases the pool of infectious individuals when condom use is poor, even among youth aware of their HIV status.

The Centers for Disease Control and Prevention (CDC) released a statement in 2017 that further underscored the importance of ART adherence and VL suppression. The CDC's statement acknowledged that individuals living with HIV who have an undetectable viral load are not able to transmit HIV. This is commonly known by the slogan launched by the Prevention Access Campaign: Undetectable=Untransmittable, or U=U, and has

ushered in a new era of treatment as prevention for HIV, as well as contributed to reduced stigma for those living with HIV.

While it has been abundantly clear for over two decades that adherence to ART is a critical problem, the field has identified only a limited number of modestly successful interventions available for YLH, including motivational interviewing, directly observed therapy, multisystemic therapy, and cell phone reminder calls. These failed to demonstrate lasting impact on VL beyond the intervention. All of the interventions, except the cell phone reminder pilot studies, require in-person sessions, which may be difficult for non-adherent youth to complete. Interventions that reach youth more frequently, using modern and youth-friendly means of intervention delivery, such as cell phones, may hold promise for improving both short and long-term adherence.

Cell phones may be a powerful tool for HIV prevention and treatment intervention. Interventions delivered via cell phone may offer an advantage over traditional, in-person interventions in cost, flexibility, and ease of adapting the intervention to the participant. Our pilot study found that daily phone call reminders were both acceptable and feasible for non-adherent youth. Cell phone intervention delivery allows for tapering of the frequency of calls or texts in response to the needs of each participant, which could help sustain the impact of the intervention over a longer period of time for a lower cost. However, few interventions utilizing cell phones as a stand-alone mode of intervention (vs. as part of a larger intervention) have been tested, and even fewer have targeted YLH.

Supportive Accountability: A theoretical rationale for CPS to improve medication adherence. The intervention is guided by the conceptual model of supportive accountability. This model was developed to guide research into human support components of mHealth interventions. The model is based on the premise that human support increases adherence through accountability to a coach (in the intervention, an Adherence Facilitator or AF) who is perceived as trustworthy, knowledgeable, and benevolent. Accountability should involve clear, process oriented expectations that the patient is involved in determining (e.g., reporting adherence, problem-solving). The effect of accountability may be moderated by patient motivation so that patients with higher intrinsic motivation may actually require less support.

The process of support is also mediated by the mode of communication (e.g, phone, text messages, computer), with different advantages and disadvantages for each mode. There is evidence that “lean media,” or those modes of communication with less face-to-face contact and fewer visual social cues, may be associated with more positive, even idealized, attributions of communication partners. This is because people tend to form stronger impressions based on more limited social and interpersonal cues. Interactions via lean media, including CPS and text messages, have the potential to foster social accountability towards improved adherence.

Multiple studies have demonstrated that social support is a strong predictor of good adherence to ART, and retention to HIV care is predicted by clients' perceptions of

providers as engaging and validating. While overall social support was predictive in these studies, specific aspects such as instrumental support (i.e., practical assistance) and informational support (advice or problem-solving) were found to be predictive of adherence in adults with HIV. The content of conversations in the CPS study were designed to validate the importance of adherence, prompt problem solving (through informational support), and provide instrumental assistance (through referrals) to address barriers as they emerge. This intervention utilizes social support constructs to provide tailored conversations to improve both short- and long-term adherence.

Sub-Study:
Use of DBS technology, a method introduced by the World Health organization (WHO) guidelines in 2015 for routine VL monitoring of HIV-positive individuals on ART[1,2] is currently underutilized in the United States. HIV biomarker, VL testing, has been increasingly recognized as the gold standard for monitoring treatment efficacy and detecting treatment failure.[3] According to a systematic review of 13 articles evaluating the performance of DBS samples, DBS is still an emerging method for monitoring VL and has been mostly used for detecting HIV.[3] Only two studies have found the lower detection limit to be 550 and 800 copies/mL.[3] More recently, a study of 205 young adults with HIV living in the Chicago metropolitan area reported a significant percent (34%) of subjects with a detectable VL at the time of study visit self-reported an undetectable VL at their last medical visit.[4] However, performing traditional serological testing requires youth to schedule an appointment either with their primary care provider or a laboratory such as Quest Diagnostics to extract the serum from blood specimens. In the context of a research study such as ATN 144 SMART, this requires a release of information. In addition, youth often fail to make or keep these appointments. ATN 144 SMART has faced multiple challenges to enrollment, primarily difficulty obtaining VL and/or youth who are ineligible due to self-reported VL level.

3.0 Study Endpoints*

The ultimate goal of this study is an adaptive adherence intervention designed to improve self-management and achieve and maintain VL suppression while understanding the context for wide-scale implementation in an effectiveness-implementation Type 1 Hybrid trial.

Sub-study:
The use of traditional treatment methods for engagement and retention to care may not be well-suited for YLH. The ultimate goal of this pilot study is to develop and test DBS implementation procedure for obtaining VL and promote self-management.

4.0 Study Intervention

Cell Phone Support. Each participant randomized to CPS will be assigned a lead and back up Adherence Facilitator (AF). At the time of study entry, the AF and the

participant will choose a start date and arrange a call time that is after their daily ART dosage time and within office hours. For those participants taking their medication after dinner/before bed, the AF will call in the morning to confirm they took their ART the night before. While the study allows flexibility in planning for the timing of taking the medication and the phone call that follows it based on the participant's schedule, the call time should be mutually agreeable to the AF and the participant. All calls must take place during the agreed upon time range.

Preferably, calls should begin the next Monday following the baseline visit and/or within two weeks of study entry. Calls from the AF will occur Monday through Friday, once a day, and continue for three months, except for major holidays. While the initial call will last 10-15 minutes, it is expected that most calls will last less than five minutes. AFs will take an additional five minutes to document the content of the call. To protect the confidentiality of the participant, the AF will confirm that the person who answered the cell phone is the participant enrolled into the study. Voice recognition can be used as the primary confirmation; however, participants will also be offered the use of a code word for identification purposes to further protect their privacy. AFs will use cell phones to conduct the daily calls, send/receive texts, and have voice messages

On each call, AFs will assess if the participant has taken their medication for that day and if medication was taken during days when calls to participants are not completed (i.e., weekends and holidays). If the participant has not yet taken their ART medication(s), the AFs will wait for the participant to retrieve and take their medication, if available. If the participant usually takes their ART the night before, then the AF will not request that the participant take their medication during the call. If the participant is non-adherent, the AFs will assess reasons for non-adherence and will engage the participant in brief problem solving around these identified barriers. The AFs will also discuss any new or ongoing problems in the participant's life (e.g., related to housing, transportation, or food), and provide support around problem-solving to address these issues. In addition, they will reinforce prioritizing medications, remind participants about scheduled appointments, and suggest scheduling any relevant referrals (e.g., case management, mental health services, substance use counseling) through their healthcare providers. Youth needing more intensive assistance will be referred to their care team using the information provided on the participant's locator form, and with the youth's permission, the AF will contact the care team to share the concerns.

Text Message Support. Participants enrolled in the SMS intervention will receive daily personalized SMS adherence reminders for three months. Participants will be able to choose the timing and the wording of the text message. Participants will be asked to text back if they did or did not take their ART medications. The texts will be sent through Trumpia, a robust, customizable technology to deliver text messages to participants and track their responses. Trumpia is compliant with HIPAA laws as all personal identifiable data are encrypted.

Incentives and Tapering. After three months of either the CPS or SMS intervention, participants will be sorted into new intervention arms depending on their VL. Participants

will submit proof of VL and complete a computerized survey. Participants whose VL is <200 copies/mL are categorized as "responders," because they were able to successfully reduce their VL by adhering to their ART medication during the past three months. Participants whose VL is ≥200 copies/mL are categorized as "non-responders."

All responders will be randomized into the tapered intervention arm or into standard care, where no interventions (calls or texts) will be made. Those originally in the CPS group will receive the CPS tapered (CPS-T) intervention; likewise, those in the SMS group will receive the SMS tapered (SMS-T) intervention. In the tapered interventions, calls and texts will be reduced to two days a week. CPS-T and SMS-T will last for three months until the six month follow-up, after which participants will go into standard care. At this point, all responders will be in standard care, and will continue throughout the nine- and twelve-month follow-ups.

Participants who were non-responders after the first three months will be re-randomized to CPS or SMS, but with the addition of an incentive. They will receive incentives for text messaging or cell phone support participation. Those participants who answer the cell phone support call or respond to the text messages 75% of the time or more each month will receive an additional $50 during the incentive phase. This will be implemented for three months until the six month follow-up, after which the intervention will be tapered to two times per week. Those in CPS-I will enter CPS-T, and those in SMS-I will enter SMS-T. After the nine-month follow-up, participants will enter standard care until completion of the study at the last twelve-month follow-up.

The three-, six-, nine-, and twelve-month follow-up assessments for all participants include a viral load and a computerized survey.

Sub-Study:
Project DABS does not implement any interventions.

5.0 Procedures Involved*

Enrollment Procedures. Enrollment in this study may occur at any time during the recruitment period. Potential participants recruited utilizing the OneFlorida Data Trust will receive a "text-in" number, in which interested persons will be able to text-in to receive instructions for screening and enrollment. Potential participants through the OneFlorida Data Trust who do not "opt-out" of being contacted could also be directly contacted by the study team to be inform of the study and screening/enrollment options for preliminary eligibility.

Screening and enrollment may occur on the same day, as long as the appropriate VL and ART regimen data are appropriately obtained. If a participant is determined to be eligible for the study, a unique Qualtrics link will be sent to the participant for submitting proof of HIV VL ≥200 copies/mL and ART regimen. After final eligibility is determined, study staff sends the potential participant the SMART enrollment link, which contains the study

consent/assent form, HIPAA Authorization form, and the baseline web-based survey. These are programmed in Qualtrics by the REC. The baseline survey can be completed at the participant's convenience (ideally within 14 days before and 28 days after their scheduled assessment date). Upon completion of all portions of the enrollment link, participants are considered enrolled in SMART. Study staff will then randomize and stratify the participants into their respective intervention arms (CPS or SMS) for the first period of the study. Stratification is based on method of contraction: Perinatal vs Behavioral (and other).

Participants randomized to the CPS intervention group will speak with the AF to determine the start day and call time for intervention phone calls. This phone call should be completed within 30 days from entry. Participants randomized to the SMS intervention will speak with the Project Coordinator (PC) to identify the start day, timing, and content of the text messages they will begin receiving daily.

At each follow-up, participants will complete web-based surveys programmed in Qualtrics by the REC. A link to these computerized surveys will be sent to each participant by the REC and can be completed at the participant's convenience (ideally within 14 days before and 28 days after their scheduled assessment date). Participant VL data will need to be obtained before the study procedures for the respective assessment period is considered complete and the participant is compensated. Data files will be downloaded via Qualtrics by the Data Management Team of the REC. The REC will maintain a linkage of PID and subject name, and these will be stored in password protected files. These web-based surveys will take approximately 60-90 minutes to complete.

Randomization Process/Systems. Participants will be randomized at the end of their baseline assessment into one of two intervention conditions: (1) CPS or (2) SMS. Both intervention conditions will receive 3 months of intervention (i.e., 3 months of CPS or SMS). Each participant's condition will be tracked in REDCap. At the 3-month follow-up, a second stratified randomization will occur in blocks with 8 possible intervention trajectories as follows:

- CPS responders (VL <200 copies/mL) will be randomized to either 9 months of standard care (SC) or 3 months of CPS-T followed by 6 months of SC;
- CPS non-responders (VL ≥200 copies/mL) will be randomized to 3 months of CPS-I or SMS-I followed by 3 months of CPS-T or SMS-T, respectively, and then 3 months of SC for both groups thereafter;
- SMS responders (VL <200 copies/mL) will be randomized to either 9 months of SC or 3 months of SMS-T followed by 6 months of SC; and
- SMS non-responders (VL ≥200 copies/mL) will be randomized to 3 months of CPS-I or SMS-I followed by 3 months of CPS-T or SMS-T, respectively, and then 3 months of SC for both groups thereafter.

Participants who are unable to provide a valid HIV VL result at the 3-month time point have approximately 30 days to obtain a HIV VL performed at Quest Diagnostics or have a physician release this information to PRIDE. Participants who are unable to provide this

information within the timeframe i.e. 30 days after their 3 month follow-up assessment will be treated as non-responders to the intervention and will be re-randomized to an incentive arm. The 30 day window follows the same timeframe as the 30 day window for calls to begin following baseline.

Retention and Follow-up. The REC will have automated procedures to communicate with participants about remembering to complete their surveys, and also to complete VL testing. Participants will be reminded of upcoming study procedures, including VL blood draw logistics. The locator form will be reviewed with the participant during these reminder calls, and any changes will be noted. Multiple contact methods will be used for difficult to reach youth (e.g., alternate phone numbers, email, text messaging, family members, or friends and healthcare providers). We will have a mechanism in place for troubleshooting text-message bounce-backs and retaining hard to reach participants.

All participants are retained in the intervention regardless of their missing the 75% monthly requirement or missing several consecutive weeks. The incentive is provided only for the months that participants reach the 75% target. This is expected to increase the overall number of calls and SMS completed over the 3-month CPS-I and SMS-I interventions.

Study staff will use Trumpia to text participants during the duration of their participation in the study to remind them of upcoming follow-up visits. Participants will receive both an email and a text message reminder simultaneously. The text message will inform a participant that an email reminder was sent and will ask the participant to respond accordingly with a number notifying staff that they received the email, or if there are any problems. (e.g., “text back ‘1’ if you received the email or ‘2’ if you DID NOT receive the email.”). Study staff will utilize an Access database using an Application Program Interface connected to Trumpia’s secure server to track responses and respond to participants accordingly.

Specimen Collection. VL will be collected for baseline and follow-up assessments (i.e., months 3, 6, 9 and 12) for all participants. This is the only study component that cannot be completed by the participant online or by phone. Participants have several options for how they would like this data submitted to the REC.

VL measurements collected during screening or after will be used for the baseline assessment, as long as the remaining components of the baseline assessment are completed no later than 1 month from the VL collection date (exceptions to this must be approved by the REC).

Participants may submit VL test results from their standard care providers (at both SRV and non-SRV clinics) as long as they were measured using a level of detection of <200 copies/mL or below and the VL collection dates are within 6 months prior to screening or the baseline assessment, and within 2 weeks prior to or 4 weeks after all other study follow-up assessments. VL measurements using a level of detection ≥200 copies/mL will not be accepted. If participants have a standard care provider, but no VL test results

within the required window period, they may request a new VL test from their usual provider and invoice the REC.

If participants decide to obtain a copy of their standard care VL test results, they will be given two choices on how to submit their VL test results. The REC will inform the participant that they may take a picture of their newly obtained standard care VL test result using their personal cell phone and submit the picture through a secure Qualtrics online submission form. Participants may also request their providers directly send their newly obtained lab results to the REC. This option may require youth to provide a release of information (ROI) if one is not already in place.

If standard of care results are not available, participants who have access to a clinical SRV, but have not completed a VL test within the required window period may request a new VL test for research purposes. The REC will refer participants to a clinical SRV; participants do not need to be an existing patient or establish care at this clinic in order to complete this study component. This new test will be invoiced to the REC and not billed to the patient's insurance. Clinical care VL measurements can be used as long as they were measured using a level of detection of <200 copies/mL or below. VL measurements using a level of detection ≥200mL will not be accepted. Participants should complete this VL test within 1 month of screening before the baseline assessment, and within 2 weeks of each follow-up assessment. The REC will contact providers to submit VL measurements via fax or Qualtrics.

Participants who cannot or do not wish to visit a medical provider may be referred to local Quest Diagnostics labs for VL testing. The REC will order and pay for these labs, and receive VL data directly via online.

One way the Privacy Rule protects the privacy of protected health information (PHI) is by generally giving individuals the opportunity to agree to the uses and disclosures of their PHI by signing an authorization form for uses and disclosures not otherwise permitted by the Rule.

The Privacy Rule establishes the right of an individual, such as a research subject, to authorize a covered entity to use and disclose their PHI for research purposes. This requirement is in addition to the informed consent to participate in research required under the Department of Health and Human Services (HHS) Protection of Human Subjects Regulations and other applicable Federal and State law.

Incentives and Compensation. Participants will be compensated up to $500 total for completing all study assessments, not including compensation for completing the intervention. Participants will be compensated $60 after completing the baseline survey and providing the proof of viral load. A $10 increased compensation will be offered over time each time participants complete the survey and submit viral load results. We will also offer a $10 bonus for participants who complete the survey within one week of the date is sent out and a $10 bonus for participants who submit the viral load results within two weeks of the date link is sent out. See table below for a summary of the

compensation amounts for each study assessment. At the end of each month for participants in the CPS-I and SMS-I interventions, those participants who reach the 75% monthly adherence to calls/text responses will receive $50. Compensation will be provided via electronic gift cards (e.g., Amazon, Target, or Walmart).

Baseline Assessment Compensation	**$ 80.00**
Submission of the viral load result	$ 30.00
Completion of the survey	$ 30.00
Submitting the viral load result within two weeks of the screened eligible date (bonus)	$ 10.00
Completing the survey within one week of the date is sent out (bonus)	$ 10.00
3-Month Assessment Compensation	**$ 90.00**
Submission of the viral load result	$ 35.00
Completion of the survey	$ 35.00
Submitting the viral load result within two weeks of the date link is sent out (bonus)	$ 10.00
Completing the survey within one week of the date is sent out (bonus)	$ 10.00
6-Month Assessment Compensation	**$ 100.00**
Submission of the viral load result	$ 40.00
Completion of the survey	$ 40.00
Submitting the viral load result within two weeks of the date link is sent out (bonus)	$ 10.00
Completing the survey within one week of the date is sent out (bonus)	$ 10.00
9-Month Assessment Compensation	**$ 110.00**
Submission of the viral load result	$ 45.00
Completion of the survey	$ 45.00
Submitting the viral load result within two weeks of the date link is sent out (bonus)	$ 10.00
Completing the survey within one week of the date is sent out (bonus)	$ 10.00
12-Month Assessment Compensation	**$ 120.00**
Submission of the viral load result	$ 50.00
Completion of the survey	$ 50.00
Submitting the viral load result within two weeks of the date link is sent out (bonus)	$ 10.00
Completing the survey within one week of the date is sent out (bonus)	$ 10.00
Total Compensation (upon completion of all 5 assessments)	**$ 500.00**

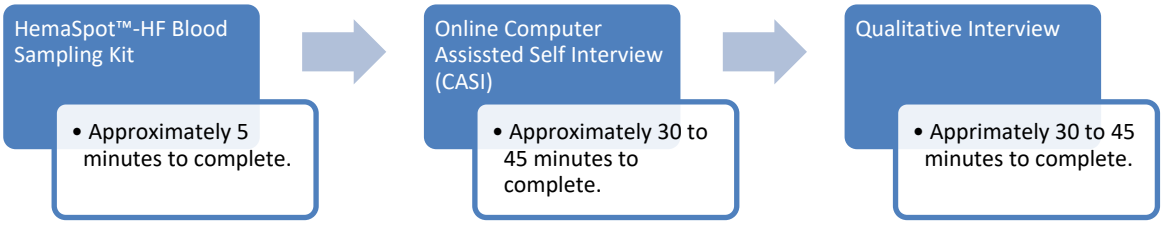
Measures. Baseline data collections should be completed all within the same day, and ideally no later than 7 days after the beginning of the baseline. Follow-up data collections should be collected up to 14 days prior to target date and up to 28 days after the target date. Due to COVID-19 pandemic, 12-month assessment window will be extended to 90 days. Those who are overdue for 12-month assessment will be allowed to complete the CASI and submit the VL after their window is closed. These participants will receive 90 days extension to complete the last component of the study. The REC Data Management Team will monitor reports of when participants are due for follow-up assessments. Self-report measures will be collected via a link to Qualtrics which can be accessed via smartphone, laptop, or PC. Site characteristics, including resources and supports available for non-adherent youth living with HIV, will be recorded into a Qualtrics survey and managed by the REC.

Web-based CASI Measures	Baseline	Follow-Up
Demographics		
Demographics/Socioeconomic Characteristics (ATN)	X	
Primary Outcomes		
HIV Positive Cascade: Medication Adherence Variables	X	X
Viral Load	X	X
Other Self-Reported Measures		
HIV Positive Cascade: Other Participant Characteristics	X	X
Self-Efficacy for Medication Adherence	X	X
Sexual Risk Behavior Questionnaire (harmonized + additional questions)	X	X
Additional Self-Management Measures		
Substance Use: ASSIST	X	X
PHQ-8 (Depression)	X	X
GAD7	X	X
PROMIS: Emotional Support, Informational Support, Instrumental Support, Companionship, Social Isolation	X	X
BRIEF-A: Plan/Organize and Task Monitor Scales; Plan/Organize and Shift Scales; Behavioral Regulation Subscales (Inhibit, Self-Monitor)	X	X
PAM (Patient Activation Measure)	X	X
Modified Healthcare Access Measure	X	X
HIV Positive Cascade Biomedical Data – Chart Abstraction		
HIV Positive Cascade Biomedical Data (harmonized + ART Regimen)	X	X
Supplement Measures		
HIV Stigma Scale	X	X
Knowledge of HIV Treatment Scale	X	X
Internalized Homophobia Scale	X	X

Sub-Study:

Study Design. To collect pilot data on the development and implementation of DBS procedure, this study seeks to conduct a mixed-method analysis to examine suitability, feasibility and acceptability of utilizing DBS for obtaining VL data. We will conduct recruitment for this study by reaching out to contacts who have been previously screened and not currently enrolled in SMART due to enrollment criteria or those who were unable to complete the components of the enrollment phase. We will develop survey measures and structured interview guide to collect both quantitative and qualitative data.

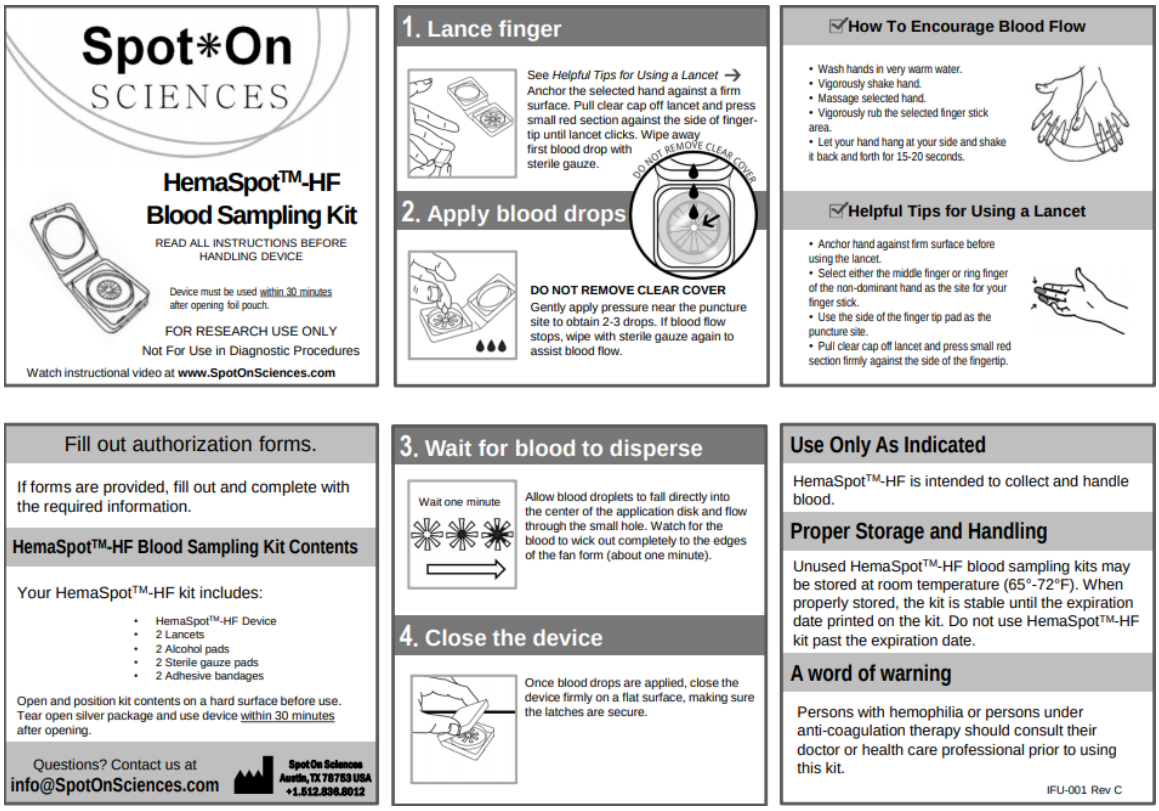
Figure 1. Project DABS' three study components.



Study Assessments

Hemaspot™-HF Blood Sampling Kit. Once the protocol team has received the subject's consent/assent to participate, the protocol team will mail the HemaSpot™-HF blood sampling kit to the address provided by the participant. The HemaSpot-HF collection kit is a cartridge with absorbent paper covered by a surface with a small spot to direct blood onto the paper. After drawing 3 drops of blood, the paper is sufficiently saturate; a desiccant within the cartridge rapidly dries the blood to preserve it for transit to the laboratory, which can occur at ambient temperature. The HemaSpot cartridge will be placed within appropriately labeled specimen packaging and returned to the PRIDE Health Research Consortium at Hunter College with prepaid mailing labels. After receiving kits, study staff will store samples to be sent to the laboratory for testing in batches. The kit contains instructions on how to perform the blood collection and properly store and handle the kit (see below). Participants will also receive a brief survey that contains an instructional video along with the kits received and sent dates to allow for more accurate tracking and monitoring of the samples in transit. The Caliendo Molecular Laboratory at the Miriam Hospital in Rhode Island will then perform a quantitative analysis of VL using the participant's DBS sample. We will use the AmpliPrep/COBAS TaqMan HIV-1 Test, v2.0 assay to analyze samples collected.

Figure 2. Spot*On Sciences' HemaSpot™-HF blood collection sampling kit instructions.



Online Computer Assisted Self-interviewing (CASI). The protocol team will send an online CASI questionnaire, supported by the Qualtrics platform, via a hyperlink to the email and phone number provided by the subject. The online CASI will ask questions pertaining to the following: demographics, modules on suitability, feasibility, and acceptability of using DBS, social determinants of health, HIV cascade, and the last section focused on feedback for future trials.

Web-based CASI Measures	Baseline
Section A: Demographics (Aims 1, 2, and 5)	
ATN Standard Domain: Demographic Characteristics	X
Section B: Suitability, Feasibility, and Acceptability (Aim 1)	
Module 1: Suitability	
Intervention Appropriateness Measure (IAM)	X
Module 2: Feasibility	
Feasibility of Intervention Measure (FIM)	X

At-Home Dried Blood Spots Testing Usability Scale	X
Psychometric Analysis of the Perceptions of At-Home DBS Testing Questionnaire	X
Module 3: Acceptability	
Post-test Questionnaire on Acceptability and Preference of HIV Self-testing	X
Acceptability of Intervention Measure (AIM)	X
Section C: Social Determinants of Health (Aim 2)	
Module 1: Economic Stability	
Module 2: Education	
Module 3: Health and Health Care	
Health Care Utilization	X
Medical Research Distrust Scale	X
Module 4: Neighborhood and Built Environment	
Module 5: Social and Community Context	
HIV Stigma Scale	X
Experiences of Discrimination Scale	X
Section D: HIV Cascade (Aims 2 and 5)	
ATN Standard Domain: HIV Positive Cascade Participant Characteristics	X
SMART Self-Efficacy for Medication Adherence	X
Section E: Feedback for Future Trials	

Qualitative Interview. After the protocol team has received both completed HemaSpot™-HF blood collection sampling kit and online CASI from the subject, the protocol team will invite the subject via email, phone, or text, to participate in a qualitative phone interview aimed to gather the subject's thoughts on the suitability, acceptability and feasibility of the at-home blood sampling kit to determine the kit's utility as a VL monitoring and self-management tool for YLH. Completion of the qualitative interview concludes the subject's participation in this study.

Qualitative Interview Measures. Qualitative interview measures assess the suitability, acceptability, and feasibility of the adoption and use of the at-home DBS; anticipated barriers and facilitators of receiving at-home DBS collection kits; perspectives on implementation and recommendations on the delivery and pickup methods; cost and compensation; perspectives on implementation and engagement of participants; and

suggestions for future trials (see Appendix for the qualitative interview guide). The PRIDE Hunter Team will be responsible for conducting the qualitative interviews, audio recordings, and coding the data.

Referral to ATN 144 SMART. Subjects that produce an unsuppressed VL (≥ 200 copies/mL) could potentially join ATN 144 SMART as a subject. The protocol team will notify the subject of their lab result via phone and/or email and offer them the opportunity to enroll in ATN 144 SMART, a study aimed to assist YLH adhere to their ART so that they may achieve a suppressed VL (< 200 copies/mL). The subject will then follow ATN 144 SMART's study procedures if enrolled, which includes providing VL lab results every 3 months. If viable, the HemaSpot™-HF blood sampling kit could potentially serve as a mechanism for collecting VL data for these subjects during ATN 144 SMART's retention phase. This referral will be offered at the end of their participation in this study. A participant cannot be concurrently enrolled in DBS and SMART.

Compensation. Subjects will receive $20.00 compensation for successfully completing and mailing the DBS sampling kit and $20.00 compensation for completing the online CASI and the qualitative phone interview. Subjects can therefore receive up to $40.00 total compensation for completing all study assessments. Subjects will receive compensation in the form of an electronic gift card sent directly to the email they provide.

6.0 Data and Specimen Banking*

Data for Future Use
Participants consent to these procedures as part of the consent/assent process.

The research team, authorized staff, and government agencies that run this type of research may have access to research data and records in order to check on the research. Research records given to approved researchers will be de-identified. If a researcher requests the data, they will be special permission from the Research Compliance Administrator. Data collected during this research study may be used for future research purposes. The data stored will be de-identified.

Data that cannot be linked to participants (i.e., de-identified data) will be kept indefinitely; this data will be saved for future use and may be shared with other researchers.

Biological samples collected for the purposes of this study will not be used to conduct any future research. They will be destroyed after analysis is completed

At the end of the study data collected will be made available, in accordance with the NIH Data Sharing Policy (http://grants.nih.gov/grants/policy/data_sharing). These data will be saved for future use and may be shared with other researchers. By participating in this study, you are agreeing to allow us to save and share your data anonymously.

Sub-Study:
Data Banking. Participants consent to these procedures as part of the consent/assent process. Data collected during this research study may be used for future research purposes. The data stored will be de-identified. Data that cannot be linked to participants (i.e., de-identified data) will be kept indefinitely; this data will be saved for future use and may be shared with other researchers without additional informed consent. The research team, authorized staff, and government agencies that run this type of research may have access to research data and records in order to check on the research. Research records given to approved researchers will not have identifying data. Publications and/or presentations that result from this study will not include the identifying data.
At the end of the study data collected will be made available, in accordance with the NIH Data Sharing Policy (http://grants.nih.gov/grants/policy/data_sharing). These data will be saved for future use and may be shared with other researchers. By participating in this study, participants are agreeing to allow us to save and share their data anonymously.

Specimen Banking. This study will not bank the DBS specimens for future use. Biological samples collected for the purposes of this study will not be used to conduct any future research. They will be destroyed after analysis is completed.

7.0 Sharing of Results with Subjects*

If participants go to Quest Diagnostics for VL testing, the research team will share with them the lab results produced by Quest. These results are not shared with any other individuals.

Sub-Study: The research team will share with subjects their VL lab results produced from the HemaSpot™-HF blood collection device. The protocol team will not share these results with any other individuals. Participants will receive their VL results by phone and may request a written copy be emailed to them. The protocol team will develop phone/email templates for sharing both detectable and undetectable results. The templates will include a brief introduction of the research staff delivering the results followed by either detectable or undetectable VL results and the meaning of those results. For those who had undetectable VL, no further step is needed. For those who had detectable VL, referral to SMART as well as any necessary referrals will be provided. Participants will also be recommended to follow up with health care provider.

8.0 Study Timelines*

Individual participants are in the study for 12 months (baseline assessment, 3 months of the intervention, and follow-up assessments at 3, 6, 9, and 12 months post-baseline).

All study subjects will be enrolled over the course of 15 months.

Sub-Study:

Participation Duration. The HemaSpot™-HF blood collection device takes approximately 5 minutes to complete. The online CASI takes approximately 1 hour to complete. Lastly, the qualitative interview will take approximately 45 minutes to complete. The duration of an individual subject's participation in this study depends on multiple factors, such as the delivery time of the DBS collection kit to the subject's desired address and delivery time to the lab. Assuming a subject manages to complete the study's components in a timely manner their participation should not exceed more than a month.

Study Duration. Project DABS expects to begin enrolling study subjects by January 2020 and to complete enrollment of all study subjects by November 2020. The protocol team aims to enroll 5 subjects per month to achieve the enrollment goal of 50 study subjects.

9.0 Subject Population*

Inclusion Criteria. To be considered eligible for enrollment, an individual must meet the following criteria:

- A youth living with HIV (ages 15 years and zero days through 24 years and 364 days, inclusive, at the time of signed informed consent or assent) ;
- Willing to provide proof of VL ≥200 copies/mL or blood specimens for HIV VL measurement within 12 months prior to baseline enrollment or self-reported adherence (SRA) ≤80% in the past 4 weeks;
- Prescribed an ART medication regimen for a minimum of 3 months prior to eligibility VL;
- The sole owner of a device capable of sending and receiving calls and text messages;
- Able to provide consent for research team to communicate with participant's HIV care provider team

Exclusion Criteria. Exclusionary criteria includes:

- Participants whose mental, physical or emotional capacity does not permit them to complete the protocol as written;
- Inability to understand written or spoken English;
- Concurrent participant in any behavioral research intervention designed to impact medication or care adherence, as indicated in screener.

We will include individuals who are not yet adults:
Study procedures involve no more than minimal risk. The nature and scope of the proposed research study, communication skills training and the CHTC intervention do not pose more than "minimal risk" to participants as defined in 45 CFR Part 46.102, "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves that those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests".

We will not include individuals who are adults unable to consent, pregnant women, and prisoners.

Sub-Study:
Inclusion Criteria. This study will include individuals who are not yet adults and pregnant women. Subjects must meet the following study criteria:

- YLH ages 15-24.
- Willing to provide DBS specimens for HIV viral load measurements.
- Living in the U.S.

Exclusion Criteria. This study will exclude prisoners and those who are unable to consent. This sub-study also excludes subjects that meet the following criteria:

- Subjects whose mental, physical or emotional capacity does not permit them to complete the protocol as written.
- Inability to understand written or spoken English.
- Subjects with hemophilia or on anti-coagulation therapy.

10.0 Vulnerable Populations*

We will enroll research participants 15-24 years of age. The nature and scope of the proposed research study and SMART intervention do not pose more than “minimal risk” to participants, as defined in 45CFR Part 46, 102, “the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.” Given that some participants will be under the age of 18, adequate provisions will be made for soliciting informed assent.
We will not require parental consent for study enrollment. Parental consent may decrease participation rates because some youth will fear that they may be "outed" as a result of participation. Disclosure of HIV status may place participating youth at risk for parental harassment, abuse or expulsion from the home.
The intervention and measures utilized in this study are standard in this population, as are waivers of parental permission for survey and interview studies. Additionally, consistent with national policy recommendations from the Society for Adolescent Medicine, requiring parental permission for the proposed study would have a number of possible negative effects, including: (1) reducing the validity of the findings by effectively eliminating potential participants unwilling to share permission forms with their parents/guardians; (2) increasing risk to some youth whose parents have a negative response to the material in the permission forms that would suggest their child has a minority or alternative sexual orientation; and (3) adding little in the way of actual subject protection, given the minimal risk of study participation. Our procedures for the waiver of parental consent are consistent with the guidelines provided by the Department of Health and Human Services: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartd.

We will obtain assent from participants who are under 18 years of age.

This research does not include neonates, prisoners, or cognitively impaired adults.

(same as sub-study)

11.0 Local Number of Subjects

We will enroll 120 HIV-positive youth living with HIV aged 15-24.

Sub-Study:
This study aims to enroll 50 YLH, ages 15-24, nationally.

12.0 Recruitment Methods

A number of recruitment strategies previously utilized by the Hunter College Center for HIV Educational Studies and Training (CHEST) will be implemented by the Scale It Up Recruitment and Enrollment Center (REC). To ensure the desired sample of 120 participants is reached, both site referrals and national media campaigns will be used. The following are methods through which recruitment will take place: (1) referrals from Scale It Up clinical subject recruitment venues (SRVs), (2) social media ad campaigns, (3) geosocial networking data application ads, (4) nationwide flyers and recruitment material distribution, and (5) indirect recruitment through CHEST's Online Master Screener (OMS).

Clinical SRVs involved in Scale It Up will refer potentially eligible patients to the Text-In option or provide the REC screening phone number. Flyers and other recruitment materials will be distributed to SRVs to inform patients about the study. SRV staff will not screen patients directly, but will discuss the study and refer interested patients to complete the Study Screener online or by phone.

REC team will run national ad campaigns on social media sites (e.g., Facebook, Instagram, Reddit, etc.). Filtering features will be used during the ad set-up to target social media users who indicated in their profiles that they are between 15-24 years old and live within the United States. Other "Interest" categories will be used to target individuals based on Facebook algorithms, which will identify young men who have sex with men or young men and women who have interacted with HIV-related pages and status messages on Facebook. Similar to Facebook and other social media platforms, Reddit's ad platform will be utilized to target individuals by demographics and regions. Both free and paid advertising methods will be used to recruit participants through Reddit. Paid advertising enables the study to be promoted post pinned to the top of a given subreddit to boost its reach and engagement to targeted audiences. Users subscribed to the communities of HIV related discussion forums within the Reddit platform will learn about the study. Interested participants will click the ad and will be routed to an online Study Screener to determine eligibility.

REC team will also recruit through ads on geosocial networking dating applications (apps). Two methods of ads will be used to recruit participants: (1) a pop-up message shown when a user first logs in, encouraging users to click through to determine eligibility for the study, and (2) a message sent by the app directly to the user's inbox. Similar to Facebook, once a participant clicks the ad, they will be taken to the Study Screener and will be provided with more information on how to enroll in the SMART study. Although the REC team is unable to use filters to target users who fit within study age restrictions and HIV status, they will be able to use geo-targeting, similar to those used with social networking websites, to target potential participants within the United States.

Flyers and other recruitment materials with a text-in number will be distributed to AIDS service organizations (ASOs) and other clinics that provide care for youth living with HIV. In order to diversify recruitment and reach individuals outside of an online setting, the REC will identify ASOs/clinics including Ryan White funded recipients and other community-based organizations (CBOs) where potential participants can learn about the study. The REC team will set up a keyword through Trumpia™, a popular text-messaging marketing service. Interested individuals will text a keyword (e.g., "RESEARCH") to a five-digit number (e.g., 99-000) to learn about how to screen for the study. Once a potential participant sends the keyword to the five-digit number, they will receive an automated text-message with a link to a landing page where they may complete the preliminary screener specific to this study (e.g., chestnyc.org/SMART).

REC team will download the list-serve from the Health Resources & Services Administration (HRSA) website (https://data.hrsa.gov/data/download?data=HAB#HAB). By accessing the HRSA website, email address of Ryan White recipients will be filtered using Ryan White as the Grant Program Name on the Active Grants Data Downloads page. REC team will also launch a website where providers outside of the ATN network can learn about the SMART study and request recruitment materials or further information (http://chestnyc.org/smart-provider). Outreach emails will be sent to Ryan White funded recipients with links to the website and recruitment materials order form. Our plan is to send emails in batches of ~50 providers at a time and follow up with all engaged sites 2 weeks after recruitment materials are shipped to ensure materials are delivered and to answer any additional questions.

Potential participants can also be routed to the SMART study through the PRIDE OMS. The OMS determines potential eligibility for several PRIDE studies. If the interested individual is potentially eligible for SMART, a screen will be displayed informing them that they might be eligible for the study, followed by a separate online form, which will collect contact information.

Recruitment Strategy Utilizing OneFlorida Data Trust. We would like to utilize the OneFlorida Research Infrastructure to assist with recruitment for the SMART study. An initial Data Trust query was conducted and resulted in identifying at least 127 youth that fit the inclusion criteria of the SMART study. Following approval from the OneFlorida

Executive committee and IRBs, we would like to use the OneFlorida Honest Broker system to re-identify this data and provide us with information on those clinicians and sites that are interested in participating in this project, and that are providing services to the identified youth. Additional requested data from the Honest Broker, which will be outlined in the data release cover sheet, includes: Patient Demographics, contact information (address), Clinical encounter details , Diagnosis, Procedures, Lab Results, Medications, Provider ID (provider NPI info), Geographical location, i.e. Facility location (3 digit zip), and Numbers of eligible adolescents at each site.

Prior to data release, the PI and study team will need permission from OneFlorida partners to receive the re-identified data from the Honest Broker. After identifying which partners would like to participate, we would proceed to engage these OneFlorida partners in the SMART study by informing them of study objectives and recruitment plan. Additionally, we will seek permission from partners and providers for the study team to send letters to potential participants on behalf of their clinical providers, approval typically provided at the clinic or department level. The letter sent to participants will include study information and an opportunity to "opt-out" of being contacted by the study team. Additionally, letters will include a "text-in" number, in which interested persons will be able to text-in for enrollment, and receive instructions for enrollment screening. After the warm hand-off via letters process, the study team will directly contact potential participants (those that did not opt-out of being contacted) to inform them of the study and screening/enrollment options for preliminary eligibility.

Prior to reaching out to potential participants, we will receive permission from interested OneFlorida partners and the potential participant's healthcare providers. Initial outreach without partner and provider permission will not be conducted.

Should recruitment rates fall below an acceptable threshold, the study team will work with the providers and their clinical staff to add a recruitment process wherein patients will be referred for the study during clinic visits, representing a direct and in-person warm handoff.

Sub-Study:
ATN 144b At-Home DBS Recruitment Methods. The protocol team will recruit subjects from the United States beginning in January 2020 until November 2020. The protocol team will send an invitation email to potential subjects that screened ineligible for ATN 144 SMART or those who were unable to complete the procedures to be enrolled in SMART and consented to being contacted for other studies. This email will contain a link to a locator form where the subject can provide their contact information if they wish to participate in Project DABS. The electronic locator form will also include items on whether a participant will be willing to receive DBS collection kit and mail it back to us along with the exclusion criteria. In addition, they will be asked to provide their preferred mailing address which maybe home address or USPS/UPS pick up/drop off locations. Upon submitting their contact information, the Qualtrics software will generate a unique subject ID (PID) number for the subject. The protocol team will then send the consent/assent, with the PID embedded within the electronic form, to the subject via email to begin the consent/assent process.

ATN 144 SMART Recruitment Methods. To achieve this sub-study's aims, we will use ATN 144 SMART's recruitment and screening methods, to enroll 50 YLH aged 15-24 years old living in the United States. A number of recruitment strategies previously utilized by Hunter College will be implemented[5-7] by the Scale It Up Recruitment and Enrollment Center. Both site referrals and national media campaigns will be used. The following are methods through which recruitment will take place: (1) referrals from Scale It Up clinical subject recruitment venues, (2) social media ad campaigns, (3) geosocial networking data application ads, (4) nationwide flyers and recruitment material distribution, and (5) indirect recruitment through Hunter College's Online Master Screener (OMS).

ATN Subject Recruitment Venues (SRVs). Clinical subject recruitment venues involved in Scale It Up will refer potentially eligible patients to the text-in option or provide the REC screening phone number. Flyers and other recruitment materials will be distributed to SRVs to inform patients about the study. SRV staff will not screen patients directly, but will discuss the study and refer interested patients to complete the study screener online or by phone.

Table 1. Scale it Up SRVs.

Subject Recruitment Venue	Location
Johns Hopkins University	Baltimore, MD
University of Alabama at Birmingham	Birmingham, AL
State University of New York Downstate	Brooklyn, NY
Children's Hospital Los Angeles	Los Angeles, CA
St. Jude Children's Research Hospital	Memphis, TN
University of Miami	Miami, FL
Children's Hospital of Philadelphia	Philadelphia, PA
University of California San Diego	San Diego, CA
University of South Florida	Tampa, FL
Children's National Health System	Washington, D.C.

Social Media. REC team will run national ad campaigns on social media sites (e.g., Facebook, Instagram, etc.). Filtering features will be used during the ad set-up to target social media users who indicated in their profiles that they are between 15-24 years old and live within the United States. Other "Interest" categories will be used to target individuals based on Facebook algorithms, which will identify young men who have sex with men or young men and women who have interacted with HIV-related pages and status messages on Facebook. Interested subjects will click the ad and will be routed to an online Study Screener to determine eligibility.

Geosocial Networking Apps. REC team will also recruit through ads on geosocial networking dating applications (apps). Two methods of ads will be used to recruit subjects: (1) a pop-up message shown when a user first logs in, encouraging users to click

through to determine eligibility for the study, and (2) a message sent by the app directly to the user's inbox. Similar to Facebook, once a subject clicks the ad, they will be taken to the Study Screener and will be provided with more information on how to enroll in the SMART study. Although the REC team is unable to use filters to target users who fit within study age restrictions and HIV status, they will be able to use geo-targeting, similar to those used with social networking websites, to target potential subjects within the United States.

Short Message Service. Flyers and other recruitment materials with a text-in number will be distributed to AIDS service organizations (ASOs) and other clinics that provide care for youth living with HIV. In order to diversify recruitment and reach individuals outside of an online setting, the REC will identify ASOs/clinics including Ryan White funded recipients and other community-based organizations (CBOs) where potential subjects can learn about the study. The REC team will set up a keyword through Trumpia™, a popular text-messaging marketing service. Interested individuals will text a keyword (e.g., "RESEARCH") to a five-digit number (e.g., 99-000) to learn about how to screen for the study. Once a potential subject sends the keyword to the five-digit number, they will receive an automated text-message with a link to a landing page where they may complete the preliminary screener specific to this study (e.g., chestnyc.org/SMART).

REC team will download the list-serve from the Health Resources & Services Administration (HRSA) website (https://data.hrsa.gov/data/download?data=HAB#HAB). By accessing the HRSA website, email address of Ryan White recipients will be filtered using Ryan White as the Grant Program Name on the Active Grants Data Downloads page. REC team will also launch a website where providers outside of the ATN network can learn about the SMART study and request recruitment materials or further information (http://chestnyc.org/smart-provider). Outreach emails will be sent to Ryan White funded recipients with links to the website and recruitment materials order form. Our plan is to send emails in batches of ~50 providers at a time and follow up with all engaged sites 2 weeks after recruitment materials are shipped to ensure materials are delivered and to answer any additional questions.

Online Master Screener. Potential subjects can also be routed to ATN 144 SMART through the Hunter College OMS. The OMS determines potential eligibility for several Hunter College studies. If the interested individual is potentially eligible for SMART, a screen will be displayed informing them that they might be eligible for the study, followed by a separate online form, which will collect contact information.

13.0 Withdrawal of Subjects*

Criteria for Premature Discontinuation

These are the categories of "dropping" participants along with their definitions.

Category: Definition	Procedure	Notes
Ineligible prior to BL (Prior to Consent): **Screened eligible, but finally ineligible after proof of suppressed viral load (VL) test result within the past 12 months due to necessary VL eligibility confirmation**	Remove from reminder call lists and mark as "Do Not Contact" in Access.	Counted towards screened number only.
Refused baseline (BL) (Prior to Consent): **Screened eligible, but never provided consent during BL assessment and/or no longer wishes to be contacted.**	Remove from reminder call lists and mark as "Do Not Contact" in Access.	Counted towards screened number only.
Withdrew during BL (After Consent): **Provided consent but refused to finish BL assessment.**	Remove from reminder call lists and mark as "Do Not Contact" in Access.	Counted up to and including magic number; these participants get marked as "Withdrew from Study" for IRB purposes.
Withdrew after BL (After Consent): **Participant completed the BL but asked to be removed from the study thereafter.**	Remove from Follow-Up Call Lists; should be Tracked as enrolled and have a condition assigned.	Counted up to and including randomized/enrolled and stays in all denominators for Follow-Up retention; these participants get marked as "Withdrew from Study" for IRB purposes.
Ineligible after BL (After Consent): **Participant either completed the BL OR both BL and follow-ups but was found ineligible for enrollment at a later date (e.g., found to have psychiatric conditions while collecting BL data)**	Remove from Follow-Up Call Lists; should be Tracked as enrolled and have a condition assigned	Counted up to and including randomized/enrolled and stays in all denominators for Follow-Up retention; these participants get marked as "Withdrew from Study" for IRB purposes.
Refused intervention (if applicable), Still Enrolled: **Participants who are no longer interested in the intervention, but have**	Remain in Database to be called for Follow-Up visits	Treated as other enrolled participants except they wouldn't receive any future randomization or intervention.

indicated a willingness to continue to be followed for Follow-Up Visits		
Passed away: **Participant was enrolled but later passed away**	Notify Recruitment and Enrollment Center (REC) immediately with details regarding the situation (i.e. Date of Death, Date Notified, Cause of Death, Participant Age and Sex); Remove from Follow-Up Call Lists	Counted up to and including randomized/enrolled and stays in all denominators for Follow-Up retention; these participants get marked as "Withdrew from Study" for IRB purposes.
Other	If a participant withdraws for any other reason not listed here, please contact the REC immediately to discuss how to proceed.	

Sub-Study:
All subjects that have signed the consent form have enrolled in the study; however, a variety of scenarios may require discontinuation of participation and removal from the study. Removal from the study simply means we have stopped following them, but they remain enrolled. Anyone marked as "withdrew from study" for sIRB purposes should be included in the sIRB continuation, SIU Data Safety Monitoring Plan (DSMP) report, and the Research Performance Progress Report.
Below are the categories of removing subjects along with their definitions. These categories should be accurately used in the site's tracking materials if one of the conditions below occurs.

- **Refused to participate prior to consent**: Invitation email sent out, but never completes the locator form and/or no longer wishes for further contact.
- **Withdrew after consent**: Provided consent, but refused to complete study-related components afterwards or subject asked to be removed from the study.
- **Ineligible after consent**: Subject either completed the consent, DBS kit, CASI, and/or exit interview, but was found ineligible for enrollment at a later date (e.g., found to have psychiatric conditions).
- **Passed away**: Subject enrolled, but later passes away.
- **Withdrawn from the study by the research team**: Subject enrolled, but later dismissed from the study by the Protocol Lead.

14.0 Risks to Subjects*

The SMART Protocol Team has determined that this study does not involve greater than minimal risk (45 CRF Part 46.404 and 21 CFR Part 50.51). Participation in this study does not involve any physical risk above and beyond that which would ordinarily be

encountered in daily life, standard clinical practice, or physical or psychological evaluations and tests. However, there is some risk of emotional discomfort or distress due to the personal nature of some questions asked in behavioral assessments as well as by the AF during intervention phone calls and risk of breaching confidentially during the calls or text messages. Feedback from the AF is designed to be very respectful, but there is a chance that the AF and the participant may find parts of the phone calls distressing. Participants will be informed that they are free to decline to answer any questions, or withdraw from participation at any time without penalty. AFs will make every effort to ensure that the person who answers the cell phone is the participant enrolled into the study. This will be primarily conducted through voice recognition. If requested by the participant, the use of a code word can also be employed.

The HIV VL measurement will be collected for participants who do not have a record of a VL result obtained within the specified timeframes. The collection requires venipuncture 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.

Sub-Study:
The protocol team has determined that this study does not involve greater than minimal risk (45 CRF Part 46.404 and 21 CFR Part 50.51). Participation in this study does not involve any physical risk above and beyond that which would ordinarily be encountered in daily life, standard clinical practice, or physical or psychological evaluations and tests. This study utilizes the HemaSpot™-HF blood sampling kit from Spot*On Sciences, who warns that persons with hemophilia or persons under anticoagulation therapy should consult their doctor or health care professional prior to using their kit; however, the protocol team will exclude subjects that indicate themselves as a person with hemophilia or under anticoagulation therapy. Furthermore, due to the personal nature of some questions asked in the CASI and/or exit interview, these study components do present some risk of emotional discomfort or distress.

15.0 Potential Benefits to Subjects*

This study includes assessment and monitoring of medication adherence and behavioral functioning. An assessment of these areas is considered standard of care for individuals infected with HIV, but is not always easily available in clinical settings. Thus, this study has the potential to provide participants (and their care providers, with participant permission) with clinical data that may be valuable in monitoring effects of HIV and its treatments.

Sub-Study:
Subjects do not receive any direct benefits for participating in this sub-study.

16.0 Data Management* and Confidentiality

Data Management and Data Quality. The first randomization involves allocation to CPS vs. SMS using a 1:1 allocation ratio. This step will use stratified randomization in permuted blocks to achieve balance in distribution of behaviorally and perinatally infected youth. The REC data team will program the randomizer in Qualtrics and will not participate either in the intervention delivery or in the adherence reinforcement steps. The protocol team will monitor race, ethnicity, and gender to ensure balanced distribution at the first stage. After 6 months, stratified randomization will occur with permuted blocks within each trajectory. Since second stage randomization is dependent on first stage response status, we will only maintain the balance within each first stage treatment outcome when randomizing at the second stage.

Following the Analytic Core's (AC) standard quality assurance, including checking for outliers and abnormal values using graphical methods, we will verify that the distributions of measures meet the assumptions of the statistical tests to be used, applying a formal test such as the Shapiro-Wilk's test [60]. Transformations will be used when distributional assumptions are not fulfilled. Tests will be conducted to identify potential relationships among baseline demographic and clinical variables and our dependent variables and to see whether they are balanced between groups. If a baseline variable is not balanced between groups and is correlated with the dependent variable ($r>.30$), we will include this variable as a covariate in subsequent analyses. Since we will test more than one primary hypothesis with one primary outcome variable (VL suppression), the Hochberg step-up multiplicity adjustment will be used with a two-tailed family wise alpha-level of .05 [61]. All other tests described below will each have a two-tailed alpha-level of 0.05. Outcome analyses will be based on the principle of intention-to-treat [62].

Quantitative Analysis Plan. The AC's primary analysis will be a comparison of the VL suppression rate (primary outcome) between the CPS and the SMS group at the first stage of randomization (see Study Design). This will be performed using anχ^2test. We will also compare the drop in VL (measured in logarithmic scale with base 10) between the two groups. Since this is a continuous measure, we will use two-sample t-test to conduct this analysis. We will also compare medication adherence rate (secondary outcome) between the two groups using an χ^2 test. All the primary analyses will be based on initial assignment to groups, using the intention-to-treat (ITT) principle. Each of the primary hypotheses will be tested using linear mixed-effects (LMEs) regression analyses [63]. For testing primary hypothesis 1, the model will include up to 4 repeated assessments of VL suppression (months 0, 3, 6, 12) as the dependent variable. For primary hypothesis 2, we will only focus on non-responders (for both CPS and SMS at stage 1) and compare the VL suppression as dependent variable using a repeated measure LME (months 0, 3, 6, 12). Each LME model will include a random intercept and slope and fixed effects for adherence intervention group, and time, as well as the stratification variables: clinical site, age, gender. A likelihood ratio test will examine the incremental contribution of the group by time interaction, which represents the interaction of interest for Primary Hypothesis 1 and Primary Hypothesis 2, testing for a differential adherence intervention effect over time. The decision rule for each primary hypothesis calls for

rejection of null hypothesis if this interaction is statistically significant using the Hochberg's step-up alpha adjustment [61]. A site by group interaction will be also examined and included in each model (above) if significant at the .05 level. In addition, likelihood ratio tests will be used to compare the model fit with that having a first order autoregressive (AR1) covariance structure, as described by Hedeker and Gibbons [63].

We will also conduct similar models as above however predicting adherence to ART (secondary outcome), which is measured at every time point. Each model will be a two-level model in which time points (Level 1) are nested within participants (Level 2). This approach accounts for the non-independence of repeated measurements within individuals. The purpose of the LME based [64] analysis for the primary aim is to determine which of the first-stage intervention, CPS or SMS, is associated with the most improvement in VL and adherence, regardless of which second-stage treatment participants received. Also note in SMART design, we compare combinations of subgroups (as in two Specific aims), but not individual subgroups. The study is designed and powered to test the two primary hypotheses with one primary outcome. However, we expect that data based on SMART design will yield valuable information for hypotheses generation involving high quality embedded interventions, which can guide the design of subsequent confirmatory studies.

SMART Secondary Aims. The first of the secondary aims is to compare the effect of tapering with termination at the second randomization among those who received CPS and those who received SMS and achieved VL <200 copies/mL. The AC will compare viral suppression rates among the two groups (tapering vs. termination), followed by more refined analysis using LME modeling. We will first perform a χ^2 test between the two viral suppression rates, followed by mixed-effects modeling.

The purpose of the second secondary aim is to determine which of the adaptive intervention arm leads to the greatest improvement in VL and adherence over the entire study period. To perform this, we will estimate the viral suppression and adherence rates following each of the 8 embedded interventions, and conduct a χ^2 test. Since both responders and non-responders are re-randomized, there is no need to use inverse-probability weighting [65]. However, in order to account for the correlation induced by subjects shared between any two embedded interventions, we will use robust (sandwich) standard errors as in the generalized estimating equations approach [66].

Additionally, we will study the moderators of treatment effect. This is a potentially impactful goal, given the gradual but assured paradigm shift in behavioral interventions from "one-size-fits-all" approach to the modern personalized medicine. Potential moderators in the current context are subject's demographics and the level of motivation – these can be incorporated in the analysis of the SMART data to deeply personalize the adaptive intervention for future patients. Because of the two-stage nature of the adaptive interventions, a straightforward regression analysis including potential moderators in the model as interaction terms is not suitable due to the possibility of unmeasured confounding induced by selection bias (also known as "collider-stratification bias") that can be present in time-varying settings, even in presence of randomization [67]. To avoid

this bias, one needs to employ 2 separate regressions corresponding to the 2 stages of SMART, and carefully move backward through the stages; such a state-of-the-art approach is known as Qlearning [68]. Each regression will contain interaction terms between the stage-specific treatments and the appropriate stage-specific moderators. If any come out significant, then patient characteristics can be used to deeply tailor the interventions for future patients. This will be performed using the R software package qLearn [69]. As customary, secondary aims are not powered and exploratory in nature.

Site Clustering Effects. Although some of the participants will be recruited via a site referral, we do not anticipate substantial site effects. A group identifier for each participant will be included in the merged analytic dataset, and the intra-class correlation (ICC) for each outcome within sites will be calculated prior to conducting multivariate analysis. If no significant variance (<0.05) is carried at the group level, we will reduce the model to a traditional two-level model (only clustering due to repeated measure). If significant group-level variance does emerge, dummy codes to control for site-specific variance will be used to enhance statistical power using a 3-level LME model. In other words, ICC will be included in the model at three-level to control for the clustering effect by design, provided third level is significant. The significance test is always at 0.05. We did not recommend a three-level model all the time as power analysis is conducted considering two-level models only i.e. ignoring site effect.

Sample Size and Power. Statistical power analyses examined the sample size requirements to detect greater than chance group differences on primary outcome (Primary Hypotheses 1 and 2). Because two primary hypotheses have been proposed, the Hochberg alpha adjustment will be used in hypothesis testing. The smaller of those sequential alpha-levels of .025(=0.05/2) was used in our estimates of the multiplicity-adjusted sample sizes. Preliminary data have traditionally been used for this purpose, but the small sample of the pilot data to provide estimates that are too imprecise for sample size calculations [70]. The power analyses examined the sample sizes required to detect clinically meaningful group differences in the VL suppression rate over time (i.e., the slope). Statistical power was estimated in a Monte-Carlo simulation study using SAS PROC MIXED over 1000 iterations. This represents the differential course for the two interventions over time. Based on the results, the protocol requires recruitment of 190 participants (≈95/group at 1st stage) with ≈50% non-responder in 2nd stage. The power table above shows the statistical power to detect standardized interaction effects of various magnitudes (0.45 to 0.55) for the Ns and a two-tailed alpha-level of 0.025. The intra-class correlation coefficient within subjects varied (ICC: .30, .40, .50, based on pilot data). The sample size of 95/group provides sufficient statistical power to detect differences in slopes that results in endpoint differences of _0.45 sd. units with ICC=.30 or .40 and 0.50. In the power analysis it is assumed about 50% responder state at the end of stage 1, thus resulting about 95 subjects in responder and non-responder group.

Strategies for Attrition. Attrition introduces bias and reduces power, precision and generalizability [71]. In keeping with the Intent-to-Treat principle we distinguish between intervention and study termination (complete withdrawal). Accordingly, we will make every effort to continue assessments for the entire course of randomized intervention,

even among those who do not continue with randomized group [72]. The mixed-effects models will incorporate all available data, even from subjects who do not complete the study. Mixed-effects models yield valid inferences assuming ignorable attrition [73]. For conducting descriptive and two-group comparison Multiple Imputation will be used to replace missing values in the outcomes and other measures. Point estimates, standard errors, and all tests will be calculated using Rubin's rules for combining the results of identical analyses performed on each of the imputed data sets [74].

Additional Secondary Aims. Self-management model analysis will be conducted based on the exploration, preparation, implementation, sustainment (EPIS) model. For the implementation aim, we will explore provider perceptions of the centralized implementation intervention and of the intervention as an evidence-based practice, through qualitative interviews and quantitative assessments based on the EPIS model. Data coding and analysis will proceed in a three-phase process with the EPIS Team. First, consistent with Morgan's [75] recommendations for qualitative content analyses and Hsieh and Shannon's [76] directed qualitative content analytic approach, standard definitions of the concepts to be coded in the text will initially be developed by the ISC based on the EPIS model. We will first systematically review each interview at each time point for all thematic mentions of EPIS model constructs, initially using existing theory to guide categorization, but also allowing themes to emerge from the data through open coding procedures [77, 78]. This combined inductive and deductive coding approach will allow us to both validate and extend the EPIS framework through our analysis. Revision of our initial coding categories will occur iteratively until we reach saturation in the identification of new codes. During this iterative process, categories and their definitions will be refined and sub-categories of codes consolidated, consistent with an axial-coding process. At this point, we will return to each interview and systematically apply the final, revised set of codes. In addition, case codes will be applied to each interview to reflect clinic role, site, cluster, and relevant demographic characteristics of the respondent. All coding will be conducted using NVIVO Version 10. For reliability, a random selection of 30% of the interviews will be independently coded. Coding will be monitored to maintain a kappa coefficient of .90 or higher [79, 80]. Any discrepancies will be discussed and resolved. We will work closely with the EPIS team and then ISC to develop an Intervention Profile and Implementation Resources for replication and sustainment of the intervention. The Profile will synthesize intervention components and implementation analyses into intervention-specific practical guidance for further scale up. Additional resources to facilitate uptake, quality implementation, and sustainment of effective interventions are described in the ISC.

Cost-Effectiveness Analysis Plan. Detailed resource use for the interventions will be collected for the initial randomization and subsequent treatment assignment. These data will be assigned standard cost weights developed by the AC for the purpose of performing incremental cost effectiveness analyses across studies. The use of resource use measures with standard cost values will assure that the economic analyses associated with the clinical trial meet the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Good Practices for Economic Evaluation Alongside Clinical Trials [81]. We will use a modification of the approach described by Kim and

colleagues (2015) and used in the economic evaluation of the Positive Charge multisite program aimed at linking HIV-infected youth to care in five states [82]. Data collection will be completed for this component by having each site's financial management contact fill out a standard Excel spread sheet which contains resource use categories relevant to calculation the cost of the intervention. The personnel cost data collected through this method will be combined with study contract and expenditure records to estimate the cost of the CPS and SMS conditions. The personnel data are collected using a standardized Excel spreadsheet to estimate the economic cost of alcohol and other drug treatment programs (e.g., personnel, facilities, supplies). Client case flow data is incorporated to determine the average weekly and annual cost/client for each service type, average cost per intervention episode, and marginal cost per contact. We will also collect data on resources used for tapering and incentives, which will be factored into calculating costs of the interventions. Data on sexual activity will be collected to be used with recent national estimates [54] of cost per HIV infection avoided, and/or on cost per HIV-infection delayed, a more conservative measure. This will allow the estimation of potential cost savings in reduction in new HIV infections. If warranted by study findings, we will use a previously validated Markov decision analysis model [83] to estimate the expected treatment cost savings resulting from the increase in time with suppressed VL. The resource use measures and cost data collected will be used to develop budget impact scenarios to help inform "scale up" and diffusion planning for the most cost-effective intervention combinations.

Intervention Monitoring/Quality Control. It is critical to maintain consistency in the intervention delivery for all participants across all phone calls and the AFs at the REC. As previously described, the AFs will be trained to carry out the intervention. A fidelity evaluation will be conducted to assess whether the AF is collecting the correct information and providing an appropriate level of support. This is to ensure fidelity to intervention delivery and to detect areas of the AF training that need to be improved. A Clinical Coordinator will conduct this fidelity evaluation.

All intervention phone calls between the AF and participant in this study will be digitally recorded utilizing the amplifier and recorder provided by the REC team. AFs will save all digital recordings in a secure network or review. The Clinical Coordinator will review 20% of all audio files for each AF during the initial three months. The audio files will be randomly selected from all audio files saved by the AFs. If 90% of reviewed files are found to be adherent to the requirements listed above, the Clinical Coordinator will only review 10% of all audio files after the initial three months. The recordings will be assessed for: Adherence to the phone call script;

- Appropriate responses/advice/referrals;
- Centering of participants in discussion;
- Order of content discussed;
- Appropriate length of call

The Clinical Team will share any discrepancies and provide critical feedback to the AFs as soon as possible, and other feedback will be provided during the monthly AF

meetings. This ongoing feedback process will assist in ensuring the integrity of the intervention.

Documentation regarding follow up with the HIV care provider team will be reviewed to ensure that follow-up activities occurred when needed and follow up was conducted in a timely manner. Quality assurance activities will confirm that data captured on study forms are complete and accurate per source documentation. In addition, source documentation or forms will be compared to the data entered into the database to ensure that they match.

Participants' Confidentiality. All laboratory specimens, questionnaires, evaluation forms, reports, and other records will be identified by a coded number only, to maintain participant confidentiality. All records with personally-identifying information will be kept in a locked, limited access area (such as a locked file cabinet). 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 (and parent or legally authorized representative, when applicable), except as necessary for monitoring by the ATN SIU or NICHD.

Certificate of Confidentiality. To further protect the privacy of the study participants, the ATN SIU has obtained a Certificate of Confidentiality from the U.S. Department of Health and Human Services (DHHS). With this Certificate in place, the ATN SIU researchers cannot be forced to turn over identifying information about a study participant in any Federal, State, or local criminal, administrative, legislative, or other proceedings. This Certificate does not prevent a study participant from volunteering to turn over their research information, nor does it prevent researchers from providing research-related information to others when requested by the study participant.

Sub-Study:

Data Management. The CASI data will be entered directly by the participant into Qualtrics. Data will reside on a secure server with firewall protection and SSL encryption. Only the Protocol Leads, Data Management and Statistical Team will have administrator privileges enabling them to download these data. The database, data structure, and data quality will be routinely reviewed by the Data Management and Statistical Team. Data will be downloaded into Dropbox Business account which will be used as the study's file sharing site. Lab Manager and Project Manager will be creating specific folders for the Wayne State Statistician to have access to those folders. Dropbox provides secure shared folders for storing, sharing, and accessing files across sites. In order to allow others to access Dropbox files, the Lab Manager/Project Manager will deliberately share these folders. These folders will be accessible once an invitation sent by Lab Manager/Project Manager is accepted and Dropbox is installed by the site. Dropbox accounts and folders are password protected. At Dropbox, a dedicated security team using the best tools and engineering practices available to build and maintain Dropbox, and has implemented multiple levels of security to protect and back up files. There is also a two-step verification, a login authentication feature which one can enable to add another layer of security to the account. Other Dropbox users can't see our files in Dropbox unless the Lab Manager/Project Manager deliberately share links to files or

share folders. Dropbox employees are prohibited from viewing the content of files stored in the Project DABS folder. Employees may access file metadata (e.g., file names and locations) when they have a legitimate reason, like providing technical support. Like most online services, a small number of Dropbox employees will be able to access user data for the reasons stated in their privacy policy (e.g., when legally required to do so). But that's the rare exception, not the rule. Dropbox has strict policies and technical access controls that prohibit Dropbox employee access except in these rare circumstances. In addition, Dropbox employ a number of physical, technical, and heuristic security measures to protect user information from unauthorized access.

Data Quality. Data quality will be examined before statistical analysis can be conducted, including examination of missing data, invalid responses, assessment of distributional assumptions, and identification of outliers.

Data Analysis Plan. To assess the feasibility of using DBS we will examine descriptive data to determine how many participants returned the DBS specimen. Descriptive statistics, frequencies, means and standard deviations, will be used to describe the samples' demographic characteristics as wells as perceptions of their suitability, feasibility and acceptability. To identify potential barriers and facilitators of testing response rates we will conduct exploratory analyses comparing differences in demographics and perceptions in youth who did return the DBS specimen versus those who did not. We will examine proportional differences using chi-square tests for categorical variables and mean differences using t-tests for continuous outcomes (alpha = 0.05). For the suitability, feasibility and acceptability scales we will calculate Pearson correlation coefficients to examine the relationship between these variables and potential barriers and facilitators. Point bi-serial correlations will be used when comparing the scales and dichotomous variables.

Confidentiality. All laboratory specimens, questionnaires, evaluation forms, reports, and other records will be identified by a coded number only, to maintain participant confidentiality. All records with personally-identifying information will be kept in a locked, limited access area (such as a locked file cabinet). 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 (and parent or legally authorized representative, when applicable), except as necessary for monitoring by the ATN SIU or NICHD.

To further protect the privacy of the study participants, the ATN SIU has obtained a Certificate of Confidentiality from the U.S. Department of Health and Human Services. With this Certificate in place, the ATN SIU researchers cannot be forced to turn over identifying information about a study participant in any Federal, State, or local criminal, administrative, legislative, or other proceedings. This Certificate does not prevent a study participant from volunteering to turn over their research information, nor does it prevent researchers from providing research-related information to others when requested by the study participant.

17.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

This research involves no more than Minimal Risk to subjects.

The protocol has a Data Safety Monitoring Plan and is reviewed semiannually by a Study Monitoring Committee.

The Scale-It-Up (SIU) U19 Data Safety and Monitoring Plan will utilize a single monitoring system for all SIU protocols (including SMART) in order to harmonize review standards across protocols. The review process of the most vulnerable protocol will be applied to all SIU protocols thereby ensuring adequate oversight. We propose utilizing an independent study monitoring committee (SMC). A SMC was selected as the Clinical Research Management (CRM) as it is the highest level CRM needed for the most vulnerable SIU protocol. The proposed SMC will be composed of three independent experts who possess the relevant expertise (e.g., HIV-related research and prevention, adolescent medicine, and sexual health) to evaluate each SIU protocol and whom do not have a conflict of interest. Mary Velasquez, Jim (Xinguang) Chen, and Dushyantha Jayaweera have formally agreed to serve on the SIU SMC. Together, they represent an academically diverse and highly experienced team capable of providing the necessary foresight and oversight to ensure data safety monitoring plans are diligently designed and implemented. SIU has the appropriate funding available to financially support the activities of the SMC. The SMC will review each research protocol and plan for data and safety monitoring every 6 months, with additional ad-hoc reviews as necessary. All SMC meetings and reviews will be held via telephone conference.

Adverse Events Reporting. Data for monitoring participants' safety will be captured within the Access database as part of the required study data. There are no additional study-specific reporting requirements. Information on unexpected events including serious adverse effects will be reported to the sIRB.

Sub-Study:
This study does not involve more than minimal risk to subjects.

18.0 Provisions to Protect the Privacy Interests of Subjects

We protect the privacy interests of participants in several ways. The team of research staff working on this study is trained and committed to advancing the rights, regard, and sexual health of youth living with HIV. We utilize sex-positive and non-judgmental approaches in developing standard operating procedures, surveys, and intervention guides. Staff training in contacting participants highlights creating a comfortable interaction for the participant, having good listening skills, adopting non-judgmental approach, paying close attention to detail, being very knowledgeable about the study so as to answer questions participants may have, and being sensitive and flexible to participant's personal situations that may impede completing a study assessment within their window. The research team is permitted to access participants' information only

after completion of a comprehensive training followed by post-training mocks and feedback.

19.0 Compensation for Research-Related Injury

The research and the sub-study do not involve more than Minimal Risk to subjects.

20.0 Economic Burden to Subjects

Research subjects are responsible for co-pays that may be incurred during any medical visits to a healthcare provider for viral load testing.

Sub-Study: The protocol team expects enrolled subjects to incur no financial costs as a result of their participation in this study.

21.0 Consent Process

Once it is determined that a potential participant may qualify for the study, study details will be discussed and all questions answered by phone. During this screening process, potential participants will be asked if they verbally consent to being screened and complete a phone screener. Electronic informed consent/assent and HIPAA authorization will be obtained from each participant before any study-related procedures are performed. Since this is a nation-wide study, the consent process is not done in person. Instead participants receive the consent/assent form via an emailed link from Qualtrics. The electronic consent/assent form contains a set of "True or False" statements at the end of the form to verify that the participant understands the study and its components. The consent/assent form asks the following questions:

1. True or False: Participating in the study is my choice and I can choose to stop participating at any time, even if I agree today.
2. True or False: Every participant will be asked to complete online surveys and provide HIV viral load results or complete HIV viral load testing every three months for the full year of this study.
3. True or False: If I ask, the SMART research team may contact my provider to share information such as whether I need a refill of my medications or other quality of life matters.
4. True or False: The HIV viral load testing performed for this study is free. I am not responsible for the cost of a study related HIV viral load test.
5. True or False: If I already have HIV viral load results I can provide these to the research team if the results are recent.

If one response is incorrect, the form redirects to a page that contains all of the correct responses to the above statements for the participant's review.

Non-English Speaking Subjects. Eligibility includes criteria that participants must speak English. No separate plan for obtaining consent is needed for non-English speakers.

Sub-Study:
Informed Consent. Once it is determined that a potential subject may qualify for the study, study details will be discussed through the online consenting process and all questions answered by email/phone. During this consenting process, potential subjects will be asked if they consent to complete an online survey, complete the at-home DBS testing component, and complete an exit qualitative interview. Electronic informed consent/assent will be obtained from each subject before any study-related procedures are performed. Additional electronic consent/assent will be provided for audio recordings as part of the qualitative exit interviews. Since this is a nation-wide study, the consent process is not done in person. Instead subjects receive the consent/assent form via an emailed link from Qualtrics. The electronic consent/assent form contains a set of "True or False" statements at the end of the form to verify that the subject understands the study and its components. The consent/assent form asks the following questions:

- True or False: Participating in the study is my choice and I can choose to stop participating at any time, even if I agree today.
- True or False: Every subject will be asked to complete a one-time online survey and provide DBS specimen for the participation of this study.
- True or False: The HIV viral load testing performed for this study is free. I am not responsible for the cost of a study related HIV viral load test.

If one response is incorrect, the form redirects to a page that contains all of the correct responses to the above statements for the subject's review.

22.0 Process to Document Consent in Writing

Consent will be obtained electronically using a consent or assent form which details all study procedures and expectations for participation. The participant will electronically sign the consent/assent form, which is then stored on Qualtrics. The consent and assent forms were written using the template consent document (HRP-502).

Sub-Study:
Consent will be obtained electronically using a consent or assent form which details all study procedures and expectations for participation. The subject will electronically sign the consent/assent form, which is then stored on Qualtrics. The consent and assent forms for this study comply with Florida State University's template consent document (HRP-502).

Waiver or Alteration of Consent.
For children, age 15-17, whose parents or legal guardians already know about the children's HIV status and who if told would not place the children at risk of harm, parental permission for these children will be obtained. We are requesting a waiver of parental consent for youth who indicate that involving their parent or guardian may put them at risk of harm.

We are requesting a waiver of parental consent for participants aged 15-17. Our research protocol is designed for conditions or for a subject population for which parental or

guardian permission is not a reasonable requirement to protect the YLH, age 15 – 17. Youth will be completing daily phone calls and online surveys that discuss sensitive topics such as their sexual behavior, sexual orientation, etc. It is also expected that there will be participants who have not disclosed their HIV status to parents/legal guardians, and the parents/legal guardians will not be aware of the subject's sexual orientation or risk behaviors. 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 HIV-related research with youth. Parental permission would put those youth whose parents do not already know about their sexual behavior and/or HIV status, infrequency of HIV-related care, at risk of their parents learning about this by the nature of requesting their permission to participate in a study of this kind. This may then place these youth at risk for parental harassment, abuse or expulsion from the parental home. Requiring parental permission could not only place these youth at increased risk of harm, but it would also substantially limit the generalizability of our research.

Our justification for this waiver is informed by prior research with the target population, which has demonstrated risks of parental victimization during coming out or discussions of sexual orientation. Most young men who have sex with men (YMSM) are unwilling to ask their parents' permission to be in an HIV-focused study and those who are willing are significantly different on key variables. In addition, research suggests that YMSM have the capacity to make an informed decision regarding participation (e.g., appreciation of risks/benefits to themselves, understanding research components such as randomization) despite this not meeting the legal definition of consent. As shown in prior research, parents with LGBT-identified children appreciate the rationale for waivers of their permission when the study and its purpose are explained. This evidence supports the fact that YMSM are a population for whom parental or guardian permission is not a reasonable requirement to protect the participants and a waiver of parental permission is appropriate under 45 CFR 46.408(c). This determination was further supported by the fact that this study does not expose participants to greater risk than encountered in everyday life, and therefore the waiver could also be approved under 45 CFR 46.116(d) based on the evidence described above that the research is not possible if parental permission is required. Additionally, consistent with national policy recommendations from the Society for Adolescent Medicine, requiring parental permission for the proposed study would have a number of possible negative effects, including: (1) reducing the validity of the findings by effectively eliminating potential participants unwilling to share permission forms with their parents/guardians; (2) increasing risk to some youth whose parents have a negative response to the material in the permission forms that would suggest their child has a minority or alternative sexual orientation; and (3) adding little in the way of actual subject protection, given the minimal risk of study participation.

Under 45 CFR Part 46.4116 (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." The study procedures involve research on individual on perspectives

through collection of data from individual interviews. Foreseeable harms from participating in this study are not greater than those encountered in everyday life or during the performance of routine physical or psychological examinations or tests. In addition, in all 50 states and the District of Columbia, minors are explicitly permitted to consent for STI services without parental permission.

For children whose parents or legal guardians do not know about the children's HIV status and who if told would place the children at risk of harm, a waiver of parental permission for these children is requested. For children whose parents or legal guardians are aware of HIV status, but knowledge of participation in study would place the children at risk of harm, a waiver of parental permission for these children is requested. For children whose parents or legal guardians already know about the children's HIV status and who if told would not place the children at risk of harm, parental permission for these children will be obtained.

Procedures to Obtain/Waive Parental permission for YLH, age 15- 17.
The study team will put the following steps in place to ensure that parental permission for youth stakeholders, 15 – 17, is obtained or waived as set forth by the Institutional Review Board.

Screening procedures.

- The study screener will inform interested participants under the legal age (18) will need parental or legal guardian consent to be part of this study
- The study screener will inform prospective youths that although their parent's permission is usually required before children under the age of 18 may take part in the study, this permission will not be obtained for children who will be placed at risk of harm if their parents were told about their children's participation in this study.
- The screener will ask youth under 18 whether their parents or legal guardians know about their HIV status, and whether if told would will be placed at risk of harm.
- Youth who report that their parent is aware of their HIV status, they will be asked whether they will be placed at risk of harm if their parents were told about their participation in the study.
- Youth that indicate that they will *not* be at risk for harm, will be told that parental consent is required to participate in the study, and they must be able to comply with that requirement.
- Key study team members will review these youth's responses in the screener to ensure and document that only for children who indicated risk of harm was parental permission not obtained.

Consenting Procedures.

- The youth consent/assent form include a section to obtain parental consent for youth under 18 who will be not placed at risk of harm
- This section on the consent/assent form will inform youth under 18, who will not be placed at risk of harm that parental permission is required to take part

in the study and includes 2 questions to allow parental permission to be obtained.

The study team will ensure that youth whose parents or legal guardians already know about the children's HIV status and who if told would not place the children at risk of harm, parental permission for these children will be obtained.

The study team will review and document youth stakeholders' who whose parents or legal guardians do not know about the children's HIV status and who if told would place the children at risk of harm, a waiver of parental permission for these children is requested. For children whose parents or legal guardians are aware of HIV status, but knowledge of participation in study would place the children at risk of harm, a waiver of parental permission for these children is requested.

Additionally, the study team will ensure to review and document that study screener information and consent/assent forms are completed appropriately for all youth and document youth that indicate they would be at risk for harm.
For every jurisdiction in which the study will be conducted and for which parental permission will not be obtained for one or more of the youth under the age of 18, waiving parental permission for these youth is not inconsistent with the state law in those jurisdictions in which the study will be conducted.

23.0 Setting

This research is being conducted at the PRIDE Health Research consortium at Hunter College, New York, NY. All research procedures will be performed in the offices of the research facility.

Potential Participants are identified through healthcare provider referrals (e.g., Ryan White clinic or ATN clinic referrals), online social media, and dating apps. Please see recruitment sections for more information.

The Community Advisory Board for this protocol is a part of the national Youth Community Advisory Board for the Scale It Up program of research. They meet on a quarterly basis via skype to discuss study progress, recruitment strategies, and recommendations for youth engagement.

Sub-study:
Potential subjects are identified through the pool of subjects that screened ineligible for ATN 144 SMART or those who were not able to complete the study components to be enrolled in the SMART trial. These subjects were recruited from healthcare provider referrals (e.g., Ryan White clinic or ATN clinic referrals), online social media, and dating apps. Please see recruitment sections for more information. PRIDE Health Research Consortium at Hunter College, New York, NY, will perform all research procedures, excluding quantitative analysis of VL (to be performed by a third party lab) and the study data analyses to be performed by the Wayne State University Team in the offices of the research facility.

The Community Advisory Board for this protocol is a part of the national Youth Community Advisory Board for the Scale It Up program of research. They meet on a quarterly basis via skype to discuss study progress, recruitment strategies, and recommendations for youth engagement.

24.0 Resources Available

A number of recruitment strategies previously utilized by the Hunter College will be implemented by the Scale It Up REC. To ensure the desired sample of 120 participants is reached, both site referrals and national media campaigns will be used. The following are methods through which recruitment will take place: (1) referrals from Scale It Up clinical subject recruitment venues (SRVs), (2) social media ad campaigns, (3) geosocial networking data application ads, (4) nationwide flyers and recruitment material distribution, and (5) indirect recruitment through Hunter College's OMS.

The duration of this study is 43 months. During Months 1-4, the research team will focus on finalizing protocols, hiring/training staff, and completing IRB-related documents. For Months 5-19, the REC will recruit and enroll participants. After closing recruitment and enrollment, Months 20-31 are dedicated to completing the follow-up assessments. Finally, Months 32-43 are devoted to data analyses and dissemination.

Hunter College's Promoting Resilience, Intersectionality, Diversity, and Equity in Health Research Consortium was created to serve as a hub for Hunter's expanding work in sexual and gender minority health and broader focus on sexuality, gender, and health. The PRIDE Consortium supports research at the nexus of psychology, public health, and the health and helping professions that is relevant to understanding and addressing the health needs of diverse SGM individuals. A major focus of studies supported by the PRIDE Consortium has been to understand the structural, social, and psychological determinants of health disparities for SGM communities and to design and implement empirically-supported interventions to reduce disparities in the pursuit of health equity. The research center is located in midtown Manhattan and all services are research-related; no clinical services are provided at PRIDE.

Since this is a nation-wide study, youth needing more intensive assistance (medical or psychological) will be referred to their care team using the information provided on the participant's locator form, and with the youth's permission, the AF will contact the care team to share the concerns. Any adverse events reported by the participant to the AF will be triaged by the REC Clinical Team and appropriate procedures will be followed.

The MPIs of Scale It Up, and the MC, maintain responsibility for the overall conduct and implementation of the study; the MC is also responsible for management of recruitment and retention including enrollment and retention. The REC will also be responsible for Data Management while the AC will be responsible for analysis and reporting. The Protocol Leads are responsible for scientific leadership and dissemination. Protocol meetings are held bi-weekly to keep all assisting personnel informed about the protocol

and its procedures. Moreover, Dropbox is utilized to facilitate the storage and sharing of study-related documents, which further informs protocol personnel about any updates to research procedures.

Sub-Study:

A number of recruitment strategies previously utilized by the Hunter College will be implemented by the protocol team. To ensure the achievement of the desired sample size of 50 subjects, the protocol team will contact all of ATN 144 SMART's ineligible subjects or those who did not fulfill the enrollment components. These subjects were recruited using the following methods (1) referrals from Scale It Up clinical SRVs, (2) social media ad campaigns, (3) geosocial networking data application ads, (4) nationwide flyers and recruitment material distribution, and (5) indirect recruitment through Hunter College's OMS.

The duration of this study is 17 months. During Months 1-5, the research team will focus on finalizing protocol, study instruments, identifying the central lab for analyzing DBS specimens, and completing IRB-related documents. For Months 6-11, the PRIDE Team will recruit and enroll subjects. In addition, Months 7-12 are also dedicated to data analyses and dissemination.

Hunter College's PRIDE Health Research Consortium was created to serve as a hub for Hunter's expanding work in sexual and gender minority health and broader focus on sexuality, gender, and health. The PRIDE Consortium supports research at the nexus of psychology, public health, and the health and helping professions that is relevant to understanding and addressing the health needs of diverse SGM individuals. A major focus of studies supported by the PRIDE Consortium has been to understand the structural, social, and psychological determinants of health disparities for SGM communities and to design and implement empirically-supported interventions to reduce disparities in the pursuit of health equity. The research center is located in midtown Manhattan and all services are research-related; no clinical services are provided at PRIDE.

The principal investigator of Scale It Up and the Protocol Leads maintain responsibility for the overall conduct and implementation of the study. The Management Core, as well as the Recruitment and Enrollment Center, are responsible for management of recruitment, enrollment, and retention. The Recruitment and Enrollment Center will also be responsible for programming surveys in Qualtrics and databases as well as protocol development, and IRB submissions while the Wayne State University Team will be responsible for data management and analysis. The protocol leads are responsible for scientific leadership and dissemination. Protocol meetings are held as necessary to keep all assisting personnel informed about the protocol and its procedures. Moreover, Dropbox is utilized to facilitate the storage and sharing of study-related documents, which further informs protocol personnel about any updates to research procedures.