ATN 170

Hybrid Type 2 Effectiveness-Implementation Trial of Status Neutral, Integrated Behavioral Activation and Risk Reduction Intervention for Stimulant Use Among Sexually Active Young Gay/Bisexual Sexual Minority Men (Project IMPACT)

A Multi-Center Study of the Adolescent Medicine Trials Network for HIV Interventions (ATN)

Funded by

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

With Co-Funding from:

The National Institute on Drug Abuse (NIDA)

The National Institute of Mental Health (NIMH)

Clinical Trial Registry Identifier: NCT06444360

Version 3.0

03 October 2024

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PROTOCOL SIGNATURE PAGE

I have read the protocol, appendices, and accessory materials related to the ATN 170 protocol and agree to the following:

- To conduct this study as described by the protocol and any accessory materials.
- To protect the rights, safety, and welfare of the participants under my care.
- To provide oversight to all personnel to whom study activities have been delegated.
- To conduct the study in accordance with Office of Human Research Protection (OHRP) regulations (45 Code of Federal Regulations [CFR] Part 46), and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines [ICH E6(R2)], all applicable local and national regulations, and the requirements of all applicable regulatory authorities (single Institutional Review Board and relevant local Institutional Review Boards [IRBs]).
- To obtain approval for the protocol and all written materials provided to participants prior to initiating the study at my Site Consortium (SC).
- To obtain informed consent, and updated consent in the event of new information or amendments, from all participants enrolled at my SC prior to initiating any study-specific procedures to those participants.
- To maintain records of each participant's participation and all data required by the protocol.

_____	_____
Site Consortium Number	Site Consortium Name

_____

Name of Site Consortium Project Lead

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Signature of Site Consortium Project Lead	Date

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ART	Antiretroviral Therapy
ATN	Adolescent Medicine Trials Network for HIV Interventions
BA	Behavioral Activation
CAS	Condomless Anal Sex
CBT	Cognitive Behavioral Therapy
CEPAC-AYA	Cost Effectiveness of Preventing AIDS Complications for Adolescents and Young Adults
CFR	Code of Federal Regulations
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
CM	Contingency Management
CSQ	Client Satisfaction Questionnaire
CRF	Case Report Form
DASH	Data and Specimen Hub
DBS	Dried Blood Spot
DSMB	Data and Safety Monitoring Board
EC	Executive Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ePRO	electronic Patient Reported Outcomes
ERIC	Expert Recommendations for Implementing Change
eSOC	Enhanced Standard of Care
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEE	Generalized Estimating Equations
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IATA	International Air Transport Association
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	Identification

Abbreviation	Definition
IRB	Institutional Review Board
LPC	Lab Processing Chart
LWHIV	Living with HIV
MAR	Missing at Random
MCAR	Missing Completely at Random
MDMA	Methylenedioxymethamphetamine
MOGO	Manual of General Operations
MOP	Manual of Procedures
MSM	Men who have sex with men
NICHD	*The Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NLWHIV	Not Living with HIV
OCC	Operations and Collaborations Center
OHRP	Office of Human Research Protection
PEP	Post-Exposure Prophylaxis
PHI	Protected Health Information
PII	Personally Identifiable Information
POCT	Point-of-Care Testing
PrEP	Pre-Exposure Prophylaxis
QNS	Query and Notification System
RCT	Randomized Controlled Trial
RR	Risk Reduction
SAE	Serious Adverse Event
SAMHSA	Substance Abuse and Mental Health Services Administration
SAP	Statistical Analysis Plan
SC	Site Consortium
SCID	Structured Clinical Interview for DSM
SD	Standard Deviation
SDMC	Statistical and Data Management Center
SOC	Standard of Care
STI	Sexually Transmitted Infection

Abbreviation	Definition
TasP	Treatment as Prevention
U.S.	United States
UP	Unanticipated Problem
YGBSMM	Young Gay/Bisexual Sexual Minority Men

PROTOCOL SYNOPSIS

Protocol Title	Hybrid Type 2 Effectiveness-Implementation Trial of Status Neutral, Integrated Behavioral Activation and Risk Reduction Intervention for Stimulant Use Among Sexually Active Young Gay/Bisexual Sexual Minority Men (Project IMPACT)
Protocol Short Title	Project IMPACT
Study Description	IMPACT is a Human Immunodeficiency Virus (HIV) status-neutral, behavioral intervention to reduce stimulant use and concurrent HIV sexual transmission risk. This study will evaluate the effectiveness of IMPACT and determine feasibility of implementing IMPACT across various settings for translation into real-world practice using a hybrid effectiveness-implementation design.
Study Design	Two-arm, multisite, and multiformat randomized controlled trial (RCT)
Study Objectives	Following the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework: <u>Primary Objective:</u> • To determine the effectiveness of IMPACT in reducing condomless anal sex (CAS) <u>Key Secondary Objective:</u> • To determine the effectiveness of IMPACT in reducing stimulant use <u>Secondary Objective:</u> • To determine the effectiveness of IMPACT by format of intervention (in-person vs. virtual) <u>Non-Clinical Implementation Objective:</u> • To evaluate the multifaceted implementation strategy in terms of adoption and accessibility, implementation, maintenance, and dissemination, including cost-effectiveness of IMPACT
Study Population	• Cisgender Young Gay/Bisexual Sexual Minority Men (YGBSMM), ages 16-24, of any HIV serostatus who report stimulant use in the context of CAS. • Participants will be enrolled nationally to ensure geographic variability; those not located near an ATN SC will participate virtually. • The aim is to randomize 360 participants, which may require enrolling up to 450 participants.

Main Criteria for Inclusion	• Age 16-24 years, inclusive, at enrollment; • Assigned male at birth; • Self-identifies as a cisgender boy or man; • Self-reports CAS with another boy/man—receptive or insertive—while using stimulants (1 hour prior to, or during, sex) within the last 4 months (s*timulants* is defined by crystal methamphetamine, cocaine, and methylenedioxymethamphetamine [MDMA] [e.g., ecstasy, molly]); and • Willing and able to provide written informed consent to participate in the study. **In addition, virtual participants <u>must meet all</u> the criteria listed below:** • Access to a computer/smartphone/tablet that can use video chat (e.g., Zoom or Google Meet); • Provide a mailing address where they can receive a package; • Access to stable internet that they can use for more than 2 hours at a time; • Have a private place (where no one else can see or hear) where they can complete visits online; and • Reside within the continental United States (U.S.).
Main Criteria for Exclusion	• Unable to provide informed consent due to severe mental or physical illness; • Concurrent enrollment in another HIV prevention or treatment study (enrollment in a substance treatment program is acceptable); • Non–English-speaking; • Is currently incarcerated or pending incarceration; or • Any other medical condition, medical/behavioral intervention, or other condition that, in the opinion of the SC Project Lead or designee, could interfere with the safety of participants or staff, adherence to study procedures, or compromise interpretation of study results.
Clinical Centers	Five SCs in the U.S. will participate in this study. Participants may also participate virtually through centralized administration of online assessments and video-based intervention sessions.
Study Duration	Estimated duration: 5 years
Length of Participation	Total participant duration: Approximately 12 months

Study Intervention	IMPACT is a status-neutral intervention that uses behavioral activation (BA)—an evidence-based, cognitive behavior therapy—as a treatment for stimulant use and sexual risk reduction (RR) counseling for YGBSMM. The IMPACT intervention includes 10 sessions: 2 intervention sessions of HIV RR, 1 session focused on orienting and rationale of BA, 6 sessions integrating BA and RR—including pre-exposure prophylaxis (PrEP) or antiretroviral therapy (ART) and HIV care—and 1 final session on relapse prevention. The enhanced Standard of Care (eSOC) group includes two HIV RR intervention sessions.
Criteria for Evaluation	<u>Primary endpoint:</u> • Distinct acts of CAS defined as anal sex acts without the use of a condom or without the protection of prevention-effective PrEP (for participants not living with HIV [NLWHIV]) or viral suppression (for participants living with HIV [LWHIV]) over the course of study follow-up <u>Key secondary endpoint:</u> • Stimulant use over the course of study follow-up (based on urine drug testing via Point-of-Care Testing [POCT] and/or self-report)

PROTOCOL SCHEMA

Figure 1 Flow Diagram of Study

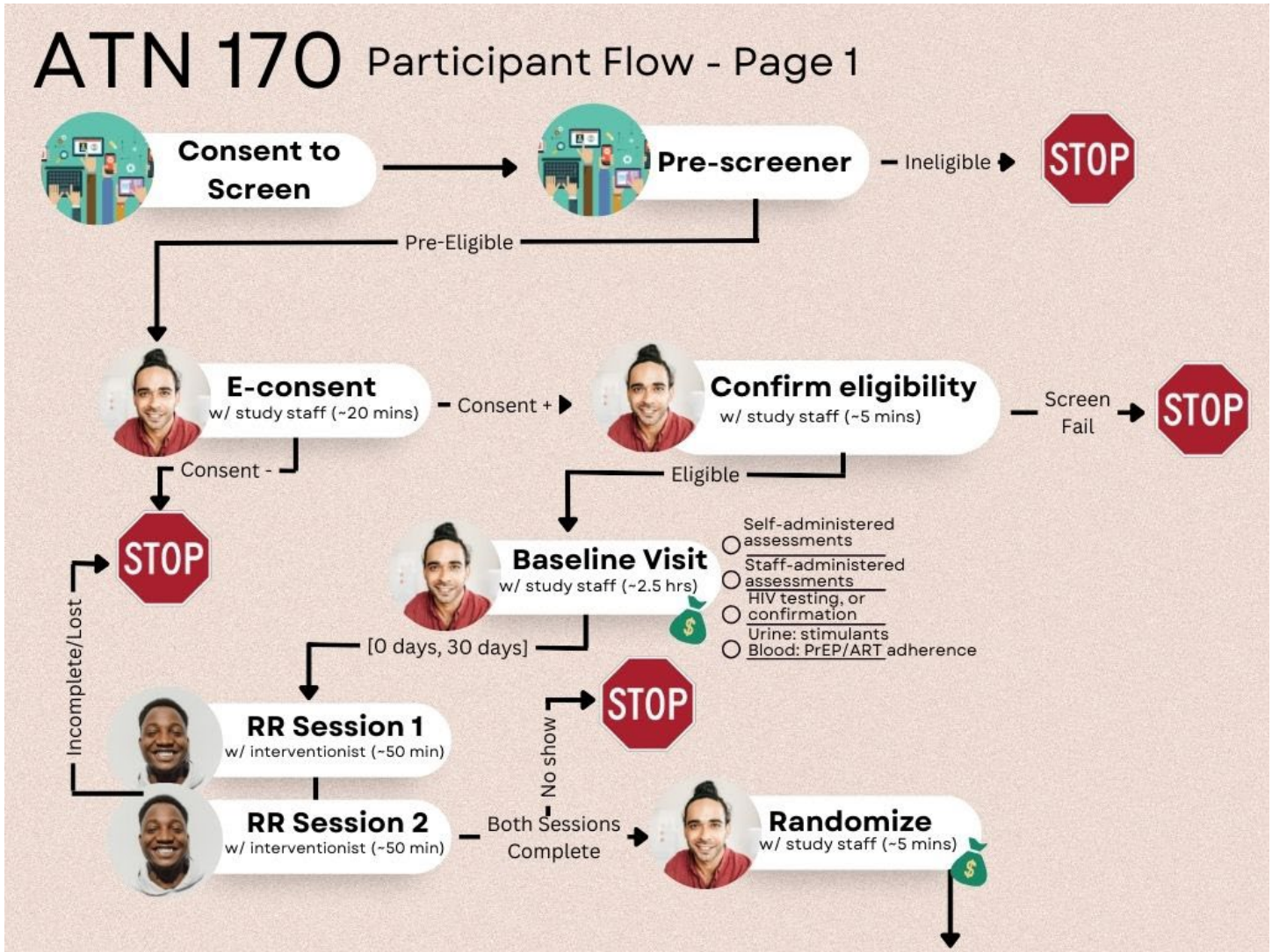
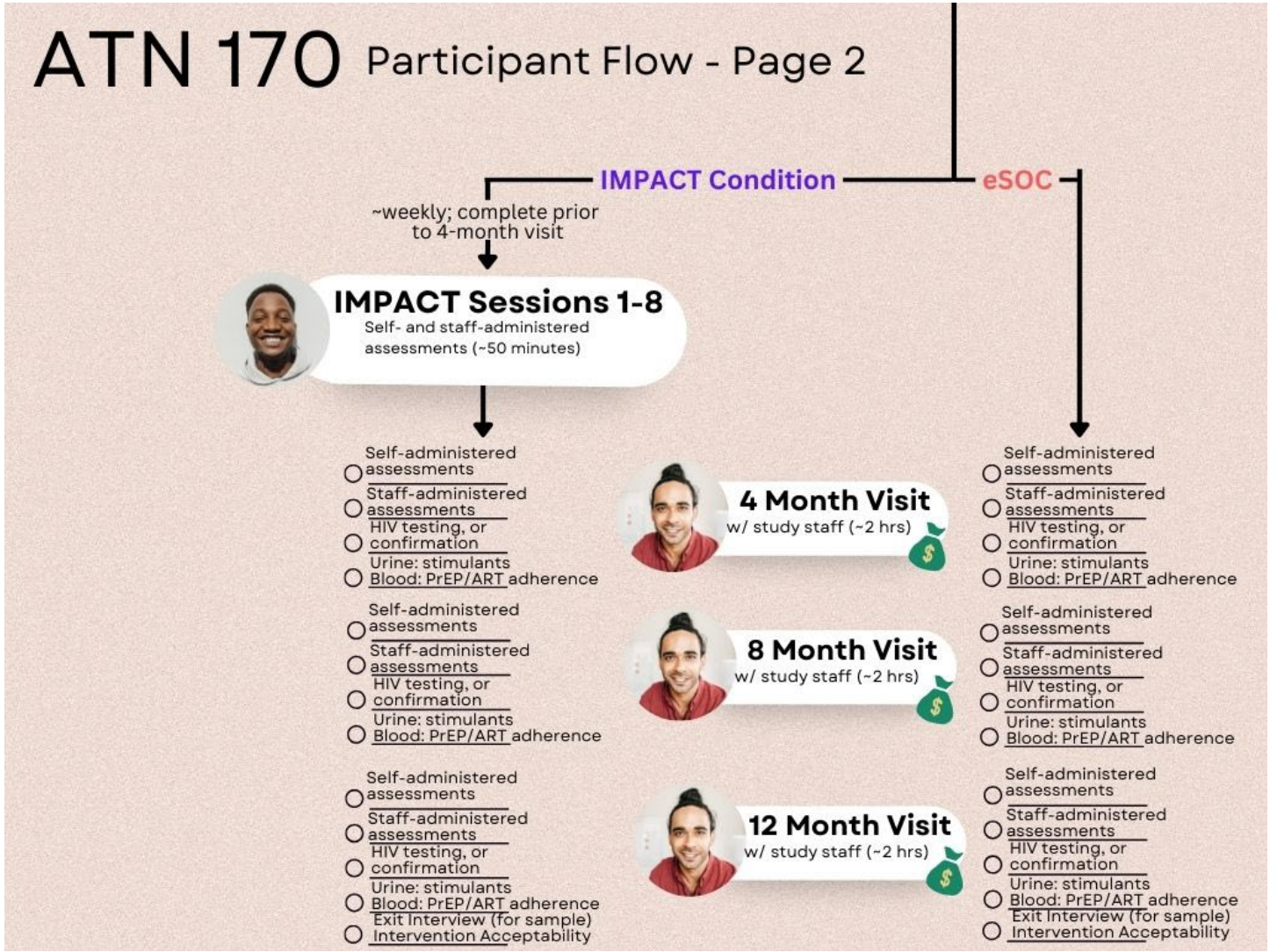


Figure 1 Flow Diagram of Study (continued)



1. Introduction

1.1 Study Rationale

Use of stimulants—crystal methamphetamine, cocaine, and MDMA (known as ecstasy or molly)—is a substantial public health problem among YGBSMM in the U.S. The prevalence of past-year use is two times greater among YGBSMM compared to their heterosexual counterparts.[1] Use of stimulants may lead to behavioral disinhibition and facilitate, prolong, and enhance sexual activity, contributing to increased engagement in sexual risk behaviors, CAS, and HIV and sexually transmitted infection (STI) acquisition and transmission.[2-5] In the U.S., as high as 33 percent of YGBSMM report having ever used stimulants in the context of sex.[1, 6] Stimulant use often co-occurs with other psychosocial problems (e.g., depression), further increasing HIV vulnerability among YGBSMM.[4, 7] Stimulant use also hinders the use of prevention services, such as uptake/adherence to PrEP. Similarly, for YGBSMM LWHIV, stimulant use leads to suboptimal ART adherence, poor retention in HIV care, and unsuppressed viral load, which impedes treatment as prevention (TasP) efforts[8] and leads to devastating HIV-related health outcomes.[9] Thus, targeted behavioral interventions to reduce stimulant use are likely to provide additive benefits to expanding PrEP and ART use/adherence, improving retention in PrEP care and HIV primary care, and reducing sexual transmission and acquisition of HIV and STIs.

This study aims to efficiently and rigorously prepare Project IMPACT—a status-neutral, modular intervention that uses BA as a treatment for stimulant use and sexual RR counseling for YGBSMM—for translation into real-world practice by harnessing the resources, geographic and site diversity, and multidisciplinary expertise of the ATN.

1.2 Background

Stimulant use remains a major public health problem among YGBSMM. Past-year use prevalence of methamphetamine is about four times greater among YGBSMM and about two times greater among YGBSMM ages 18-25 years compared to their heterosexual counterparts.[1] Use of cocaine and MDMA is also more than twice as common among sexual minority youth.[18] Moreover, although there has been a decrease in past-year use of methamphetamine, cocaine, and MDMA among heterosexual high school students (approximately ages 15-18) since 2005, numbers have remained stable among gay-identified youth.[19] Historically seen as more prevalent in the West Coast, stimulant use among men who have sex with men (MSM) has increased in the East Coast over the past decade.[20, 21]

Sexualized stimulant use greatly increases HIV risk among YGBSMM. Sexualized stimulant use is strongly associated with sexual risk behaviors, including engaging in sex work, CAS, having multiple sexual partners, and group sex, leading to increased HIV and STI transmission.[2-5, 22-24] Indeed, a recent meta-analysis showed a strong association between sexualized drug use and STI (odds ratio=2.83) and HIV transmission (odds ratio=3.55), particularly when stimulants were involved.[25]

YGBSMM LWHIV who use stimulants have suboptimal HIV treatment engagement, ART adherence, and viral suppression. Overall, YGBSMM LWHIV are about 50 percent more likely to remain undiagnosed and are less likely to achieve undetectable viral loads compared to MSM 25 years and older, contributing to continued HIV transmission.[26, 27] Barriers to engagement in

the HIV continuum of care are compounded among YGBSMM who use stimulants, who are five times as likely to miss HIV visits[28] and almost twice as likely to have a detectable viral load than individuals who do not use stimulants, jeopardizing TasP efforts.[29]

YGBSMM NLWHIV who use stimulants have difficulty accessing and adhering to PrEP. Although interest in HIV PrEP may be high among HIV-negative YGBSMM who use stimulants,[30] stimulant use poses substantial challenges to PrEP uptake[31] and maintaining adequate medication adherence.[30-33] Since medication adherence is crucial for the effectiveness of PrEP, stimulant use contributes to continued HIV transmission even among individuals being prescribed PrEP.[9, 34] YGBSMM who use stimulants may experience both age- and drug use-related barriers to PrEP, contributing to lower PrEP use among methamphetamine-using MSM under 30 years compared to those ages 30-54.[8] Therefore, treatment of stimulant use among YGBSMM can lower HIV transmission through reducing sexual risk behaviors and improving engagement in HIV treatment and prevention care, including PrEP.

Co-occurring polysubstance and problematic alcohol use and mental health problems potentiate morbidity related to stimulant use. Stimulant use co-occurs with a variety of mental health problems, such as depression and depressive symptoms,[22, 35-37] anxiety,[36] suicidality,[37] and problematic alcohol and polysubstance use.[2, 22] Moreover, early initiation of stimulant use is associated with misuse of other substances and injection drug use, and predicts stimulant use disorder later in life.[38-40] Previous work showed that anhedonia (i.e., loss of interest in previously enjoyed activities) and symptoms of depression and anxiety often follow cessation of use, a period during which individuals may lose the ability to enjoy non–drug-related activities previously considered to be pleasurable.[10] Given that stimulant use can be normative in some circles of MSM, interruption of use may also lead to disruption of one's social and sexual relationships, social isolation, and feelings of loneliness.[4, 10] Since stimulant use can itself be a coping mechanism for depressed mood and low social belongingness,[4, 35] experiencing these mental health and interpersonal consequences of cessation of stimulant use often leads to continued use or relapse after cessation.[10] This illustrates the challenges in treating stimulant use and underscores the urgent need for interventions to address stimulant use in the context of co-occurring psychosocial problems and HIV transmission/acquisition risk behaviors.

Currently, there are no Food and Drug Administration (FDA)-approved pharmacologic treatments for stimulant use disorder. A recent placebo-controlled trial showed that extended-release naltrexone-bupropion (an opioid receptor antagonist and an antidepressant, respectively) combination therapy led to an 11 percent reduction in methamphetamine use at 12 weeks ($p<0.001$), while also reducing methamphetamine cravings.[41] Additionally, an RCT with MSM and transgender women showed that mirtazapine (an antidepressant) reduced positive urine samples by 33 percent at 12 weeks and 27 percent by 36 weeks ($p=0.003$ and $p=0.02$, respectively).[42] This study also showed significant reductions in number of sexual partners (risk ratio=0.52, $p=0.04$) and CAS with serodiscordant partners (risk ratio=0.47, $p=0.04$) at week 24, which were not sustained at week 36.[42] In both trials, however, non-adherence to the experimental treatment (by participant report) was greater than 30 percent[41, 42] despite the use of pre-randomization run-in visits, raising concerns about real-world compliance with these regimens.[43] Given that not all patients will want to take medication and that at present

pharmacotherapy is limited, evidence-based behavioral interventions are needed to address the syndemic of stimulant use and HIV risk among YGBSMM.

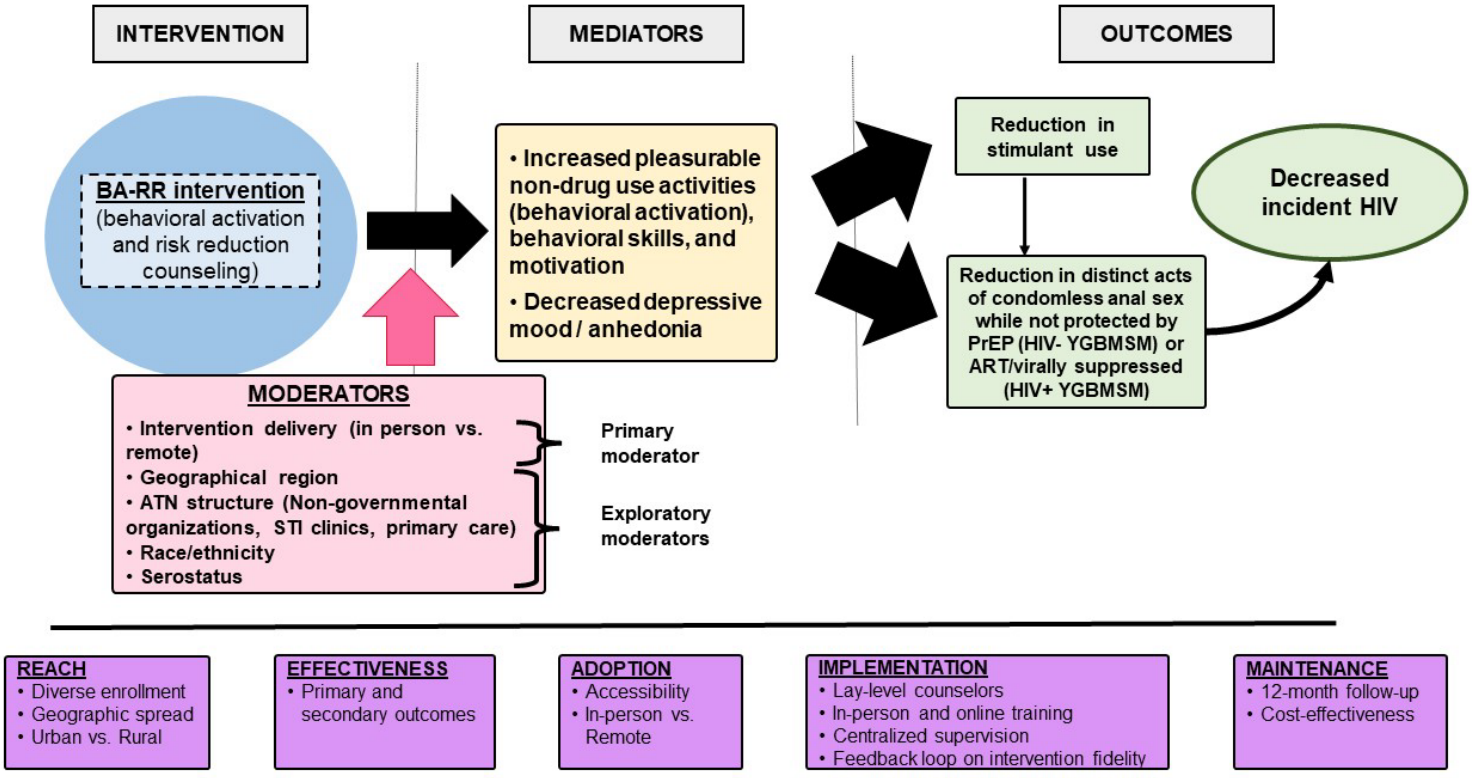
1.2.1 Behavioral Activation

Behavioral interventions can play a crucial role in mitigating stimulant use/HIV risk among YGBSMM. Behavioral interventions can promote retention in care, improve adherence to medications, and address concomitant issues to help improve these behaviors (i.e., problem-solving skills, social functioning).[44, 45] Currently, the two main behavioral approaches for stimulant use are contingency management (CM) and cognitive behavioral therapy (CBT). CM (i.e., monetary rewards for stimulant abstinence) is efficacious in reducing stimulant use, promoting drug abstinence, and reducing condomless sex acts among MSM in the U.S.[46-48] However, concerns remain about the sustainability of the initial gains achieved with CM interventions, and several studies have reported that effects greatly reduce or cease shortly after the interruption of the program.[47, 49] CBT is another approach used for stimulant use disorder, which emphasizes identifying problematic patterns of thought and behavior and working on problem-solving and coping skills[50] to reduce quantity and frequency of stimulant use and sexual risk behaviors[47, 51-53] and is recommended for stimulant use disorder by the Substance Abuse and Mental Health Services Administration (SAMHSA).[54] However, CBT has shown only mild improvements in reducing stimulant use, and sustainability of these mild improvements has been mixed.[47, 51, 52, 54, 55]

BA combined with RR counseling is an efficacious tool to reduce problematic stimulant use and related HIV risk behaviors among YGBSMM and has been tested for both face-to-face and virtual delivery. BA is a treatment for depressed mood that helps patients gradually increase goal-directed, potentially rewarding, and pleasurable activities. BA has been used successfully in the treatment of depression and anxiety,[56-58] including among youth.[59-61] In a dismantling study to identify the most effective ingredients in CBT approaches for depression, BA alone was as efficacious as the traditional CBT package.[62] Another major study comparing BA, traditional CBT, and antidepressant medication showed BA to be as efficacious as antidepressant medications and to have a slight advantage over traditional CBT in the treatment of moderate to severe depression.[63] Among adolescents and young adult gay, bisexual, and other men who have sex with men, BA interventions delivered in-person and virtually have demonstrated high acceptability and feasibility across studies.[11-13, 61, 64, 65] The BA model proposes that life events, which can include "specific trauma or loss, biological predispositions to depression, or the daily hassles of life," lead to individuals experiencing low levels of positive reinforcement in their lives.[66-69] Notably, self-defeating behaviors that perpetuate depression, such as stimulant use or behavioral avoidance more generally, may serve the function of coping with negative feelings and make the individual feel better in the short term. However, these behaviors may increase, exacerbating depression through negative reinforcement. The relevance to combining stimulant use and sex is that this combination can become addictive and result in "narrowing" of an individual's activities that derive any pleasure. Accordingly, individuals with problematic stimulant use/sex slowly narrow their pleasurable activities to this, and slowly reduce other enjoyable life activities. BA, therefore, is used as it has been developed, to help individuals re-engage (or engage) in healthy activities that derive pleasure or mastery. This reduces a major symptom of depression (loss of interest/anhedonia).

Formative work showed that an important consequence of continued stimulant use is anhedonia.[10] Accordingly, stimulant use becomes a central means for enjoyment in YGBSMM who routinely use stimulants.[10] The hypothesized mechanism of action is that BA will re-engage participants in pleasurable non–drug use activities (e.g., interests or hobbies that were enjoyable before stimulant use) that will serve as a natural reinforcement for functional behavior, improve depressed mood when not on stimulants by experiencing increases in pleasure and mastery, and decrease overall distress so that YGBSMM who use stimulants can better benefit from HIV RR counseling (see Figure below).

Figure 2 Mechanism of Action for Behavioral Activation



In prior studies with both MSM LWHIV and MSM NLWHIV, IMPACT (BA combined with HIV RR counseling [BA-RR]), had positive effects on reducing stimulant use and sexual risk, which was sustained at 6 months post-intervention (findings described in detail below).[11-13] We have also adapted and pilot tested all IMPACT procedures for virtual delivery, maintaining high fidelity and retention as well as participant acceptability.

Early identification of factors that influence intervention implementation is crucial to ensure real-world impact of efficacious interventions. Hybrid effectiveness-implementation designs can accelerate the implementation of evidence-based interventions into routine practice.[14] Using this type 2 hybrid design,[14] this study will simultaneously evaluate the effectiveness of IMPACT for YGBSMM and determine feasibility of implementation of the intervention across various settings (i.e., clinics and community-based sites and online). Informed by the RE-AIM framework (see Figure above),[15, 16] **Reach** (ability to enroll diverse groups of YGBSMM),

Effectiveness (with respect to stimulant use, HIV risk, and PrEP use), **Adoption** (characteristics of format, sites, and counselors that influence intervention uptake), **Implementation** (level of consistency in delivery of intervention across settings and time), and **Maintenance** (sustainability across sites, including its cost-effectiveness) will be assessed.

1.2.2 Preliminary Studies

1.2.2.1 Qualitative Developmental Work Guiding the Development of the IMPACT Intervention

Twenty formative qualitative interviews were conducted with adolescent and adult MSM who use stimulants in the context of engaging in CAS to inform the current intervention.[10]

Themes about loss of interest from stimulant use. Notably, almost every participant interviewed (95%) mentioned loss of interest in other activities as a side effect to coming off stimulants and, in some instances, men were drawn back to using stimulants because of this intense loss of interest/anhedonia. This pattern continued after each episode of using and, thus, became a driver for these men to relapse to additional stimulant use after each prior episode ended. As one participant noted: *"After using crystal, I had feelings of self-worthlessness, feeling that I'm a f***-up, feeling that I'm a failure, my life is sh**, and losing interest in everything."*

1.2.2.2 NIDA-Funded Open Pilot Trial of the IMPACT Intervention

Based on formative qualitative work, the IMPACT intervention was developed and pilot tested in an open trial with 20 MSM NLWHIV.[11] The intervention integrates BA for treating stimulant abuse and anhedonia with RR counseling for decreasing CAS. The study demonstrated participant acceptance, ability to recruit, feasibility of treatment delivery, adaptation of the treatment manual, and clinically significant participant improvement. Over 40 percent of participants were ethnic/people of color, and each reported engaging in CAS with a non-monogamous male partner while using stimulants in the month prior to enrollment. At 3- and 6-month follow-up assessments, participants reported significant reductions in both CAS and stimulant use. Participants also reported significant reductions in the number of sex partners while using stimulants over study follow-up. Improvements in RR skills, BA, and depression were observed. Mean unprotected anal intercourse episodes decreased significantly from baseline to acute postintervention (β=-4.86; 95% confidence interval [CI]=-7.48, -2.24; p=0.0015) and from baseline to 6 months postbaseline (β=-5.07; 95% CI=-7.85, -2.29; p=0.0017; test of fixed effects $\chi(2)$=16.59; DF=2,13; p=0.0002). On average, there was a significant decrease over time in the number of crystal methamphetamine episodes in the past 3 months ($\chi(2)$=22.43; DF=2,15; p<0.0001), and the number of days of crystal methamphetamine use in the past 30 days ($\chi(2)$=9.21; DF=2,15; p=0.010). Statistically significant reductions in depressive symptoms and poly-substance use were also maintained.

1.2.2.3 NIDA-Funded Pilot RCT of the IMPACT Intervention

In this pilot RCT, 41 participants NLWHIV (21 intervention, 20 control) were randomized across the two study arms: (1) BA-RR (BA and RR counseling), which lasted 10 sessions, and (2) the eSOC comparison arm, which included 2 equivalent RR counseling sessions without any additional intervention.[13] Participants were followed for 6 months. Main outcomes included the number of CAS acts without protection of PrEP and the number of stimulant use episodes. At

baseline, in the prior month, participants had an average of 11 sexual partners, had CAS 18 times on average, and had CAS while using stimulants 16 times on average. In longitudinal Poisson regression models, the main sexual risk outcome data showed fewer CAS acts overall between the intervention and comparison arm ($p<0.0001$). Similarly, fewer CAS acts were demonstrated while using stimulants (2.24 [0.2] vs. 6.94 [0.4] $p<0.0001$) and fewer CAS acts with a serodiscordant partner while using stimulants (1.0 [0.2] vs. 2.5 [0.4] $p=0.0005$), both at 6-month follow-up. Also, at 6-month follow-up, the intervention group reported a longer period of stimulant non-use in the past 90 days (50.10 [1.5] vs. 39.00 [1.4] $p<0.0001$] vs. standard of care (SOC)).

1.2.2.4 National Institute of Allergy and Infectious Diseases/Centers for AIDS Research Funded Pilot of IMPACT Intervention for MSM with HIV

An open pilot trial of the IMPACT intervention (approximately 10 BA sessions) was conducted for MSM with stimulant use disorder who were LWHIV (n=11).[12] This study provides preliminary evidence that the intervention for this population was feasible (100% retention at 6 months) and acceptable (100% of intervention sessions attended). Exit interviews indicated that the intervention was well received and acceptable. The mean change score in self-reported stimulant use within the past 30 days (within-person change; reduction in self-reported stimulant use) was 4.14 days at 3 months and 5.0 days at 6 months (Cohen's d=0.89). The mean change score in weekly toxicology screens (reduction in positive toxicology screens) was .71 at 3 months and 1.0 at 6 months (Cohen's d=1.05).

2. Objectives and Endpoints

2.1 Study Objectives

2.1.1 Primary Objective

- To determine the effectiveness of IMPACT in reducing CAS

2.1.2 Key Secondary Objective

- To determine the effectiveness of IMPACT in reducing stimulant use

2.1.3 Secondary Objective

- To determine the effectiveness of IMPACT by format of intervention (in-person vs. virtual)

2.1.4 Non-Clinical Implementation Objective

- To evaluate the multifaceted implementation strategy in terms of adoption and accessibility, implementation, maintenance, and dissemination including cost-effectiveness of IMPACT

2.2 Study Endpoints

2.2.1 Primary Endpoint

- Distinct acts of CAS defined as anal sex acts without the use of a condom or without the protection of prevention-effective PrEP (for participants NLWHIV) or viral suppression (for participants LWHIV) over the course of study follow-up

2.2.2 Key Secondary Endpoint

- Stimulant use over the course of study follow-up (based on urine drug testing via POCT and/or self-report)

2.2.3 Secondary Endpoints

- Distinct acts of CAS by intervention format
- Stimulant use by intervention format

2.2.4 Non-Clinical Implementation Endpoints

- Adoption and Accessibility*
  - Intervention uptake and completion rates by participant demographics, intervention format, site characteristics, and interventionist background
  - Client Satisfaction Questionnaire (CSQ)-8 scale scores and intervention satisfaction rates
    - *Satisfaction* is defined a priori by achieving standardized scores of 80 percent or greater on the CSQ-8 scale.[74]

*The following implementation measures are approved as an exempt component of this research: interventionist knowledge, self-efficacy, and skills pre- and post-training, by format, site, and timepoint

- Maintenance
  - Structured qualitative interview of individuals responsible for conducting the IMPACT intervention at each site
  - Coding of a select subset of participant and staff qualitative interview transcripts to identify themes related to intervention implementation and dissemination
  - Incremental cost-effectiveness of IMPACT versus eSOC estimated using the Cost Effectiveness of Preventing AIDS Complications for Adolescents and Young Adults (CEPAC-AYA) model

3. Study Design

We will use the RE-AIM Framework to inform the design, implementation, and evaluation of the IMPACT intervention to reduce stimulant use and concurrent HIV sexual transmission risk. Following best practices described in the Expert Recommendations for Implementing Change (ERIC) framework,[17] we will use a multifaceted training and implementation strategy for the Project IMPACT intervention across sites and formats (see details below). We will then enroll approximately 450 YGBSMM who report stimulant use in the context of CAS, who will be randomized using a 2:1 allocation ratio to either the IMPACT intervention or an eSOC control. Allowing for drop out prior to randomization, we aim to randomize 360 YGBSMM. To ensure geographic variability in our sample, we will enroll nationally. Those physically located near a participating ATN SC will participate in-person, while those not located near an ATN SC will participate virtually (i.e., online assessments and video-based counseling). We anticipate that about 50 percent of the randomized sample will participate virtually (n=180) and 50 percent in-person (n=180), and randomization will be stratified by site and format; the study is well-powered to detect differences in intervention effectiveness by format.

Participants will be followed for 1 year, with assessments at enrollment and Months 4, 8, and 12. Figure 1 (Flow Diagram of Study) provides a schematic of the study. At each time point, participants will provide a urine sample and a blood sample, and complete a self-report psychosocial and sexual risk assessment battery. Primary outcomes include the number of CAS acts while not protected by PrEP (YGBSMM NLWHIV) or while not virally suppressed (YGBSMM LWHIV) and stimulant use. We will also test our multifaceted implementation strategy by assessing adoption/accessibility and implementation using mixed-methods assessments that describe and examine characteristics of successful implementation (including differences by intervention delivery format). Finally, we will assess the feasibility of maintenance and sustainment of Project IMPACT by using the well-established CEPAC-AYA model to project its cost-effectiveness on HIV transmissions, quality-adjusted life years, and per-person lifetime costs.

3.1 Study Design Rationale

While attentive to the need for exportable, generalizable, brief interventions, it must be acknowledged that stimulant use is a highly complex and, generally, treatment-refractory problem. Hence, this study will evaluate an intervention approach that involves BA to re-engage YGBSMM in pleasurable non–drug use activities that will serve as a natural reinforcement for functional behavior, improve depressed mood when not on stimulants by experiencing an increase in pleasure, and decrease overall distress so that YGBSMM who use stimulants can better benefit from HIV RR counseling. Prior studies demonstrated that a 10-session intervention is acceptable and necessary for treatment and is a typical minimum length for CBT interventions for depression.

We also considered providing additional substance use treatment as part of the eSOC condition, but since there is no demonstrated efficacious intervention for stimulant use, we will not be withholding evidence-based treatment. Moreover, because we aim to assess effectiveness across multiple sites, we determined that allowing each site to determine its own SOC would be most appropriate and informative. Notably, we will document SOC at each site, tracking any changes over the study period.

3.1.1 Rationale for Study Endpoints

When conducting research on HIV prevention and treatment, it is essential to include study endpoints that capture relevant sexual risk behaviors and their relationship to preventive measures such as condom use, PrEP, and viral suppression. The rationale for incorporating a study endpoint that asks about CAS acts and whether they are protected by PrEP (for individuals NLWHIV) and/or viral suppression (for individuals LWHIV) includes:

1. **HIV transmission risk.** CAS is a high-risk behavior for HIV transmission. Understanding its occurrence and the level of protection provided by preventive measures is crucial for evaluating the effectiveness of the IMPACT intervention. By incorporating this study endpoint, we will collect data on actual anal sex acts and be able to determine the risk of transmission associated with CAS with and without the protection of PrEP/viral suppression.
2. **Monitoring progress.** Incorporating this study endpoint enables us to determine intervention effectiveness in reducing CAS acts and improving the level of protection provided by PrEP and viral suppression over time. Thus, it allows us to assess the effectiveness of the IMPACT intervention on improving additional HIV prevention approaches beyond condom use over study follow-up. For example, monitoring progress allows us to assess whether the IMPACT intervention improves PrEP adherence or ART adherence (viral suppression) in the context of ongoing CAS acts over the course of 12 months.
3. **Tailoring IMPACT intervention sessions.** For individuals NLWHIV, if CAS is not protected by PrEP, we initiate a conversation about either (1) PrEP uptake or (2) a need for enhanced adherence support or education. For individuals LWHIV, if CAS occurs without viral suppression, we initiate a conversation about either (1) initiating HIV treatment or (2) enhanced adherence support or education. As such, this endpoint allows for tailored IMPACT intervention sessions based on individual risk profiles.

Using a study endpoint that asks about CAS acts and their protection by PrEP (for individuals NLWHIV) and/or viral suppression (for individuals LWHIV) provides a comprehensive, real-world understanding of sexual risk among the participant population over study follow-up.

3.2 Study Definitions

3.2.1 Enrollment

A participant is considered enrolled in the study after consent is obtained, all eligibility criteria are met, the participant is entered in the electronic data capture (EDC) system, and a participant identification (ID) is assigned.

3.2.2 Screen Failure

A screen failure is defined as a participant who consented to participate in the study but does not endorse stimulant use or CAS in the Enrollment Visit. Enrolled participants who do not endorse inclusion criteria during baseline assessment should be reviewed with Protocol Co-Chairs on a case-by-case basis to determine and authorize screen failure criteria.

3.2.3 Premature Discontinuation

Participants may withdraw from the study at any point of their own choice. Participants may also be withdrawn from the study by the Protocol Team or SC following the study Manual of Procedures (MOP) should their participation pose an undue risk to themselves or study staff. Additionally, participants that do not return for any study activities after enrollment will be considered premature discontinuations.

3.2.4 Randomization

Participants will be randomized after completing the Enrollment Visit and the first two RR sessions. The first RR session is to be completed within 28 days of the last day of the Enrollment Visit, and the second RR session is to be completed within 14 days of the first session. Participants who do not attend the first RR session within 28 days after the last day of the Enrollment Visit or do not attend the second RR session within 14 days after the first RR session will not be randomized and will be considered a premature discontinuation from the study. Randomization must occur within 42 days of the last day of the Enrollment Visit. See Appendix 1 for specific visit windows.

3.2.5 Window Period

A window period is defined as the period of time allowable for a specific follow-up visit. See Appendix 1 for specific visit windows.

3.2.6 Lost to Follow-Up

Retention efforts will be employed throughout the entire duration of anticipated participation. Therefore, a participant is not formally lost to follow-up until 6 weeks after the anticipated Month 12 visit.

3.2.7 Study Completion

3.2.7.1 Participant Study Completion

A participant will be considered having completed the study if they participated in the two RR intervention sessions, were randomized, and completed the Month 12 visit.

3.2.7.2 End of Study

The end of study is defined as completion of the last visit or procedure shown in the Schedule of Events for the study across all SCs.

4. Study Population

4.1 Inclusion Criteria

To be considered eligible for enrollment, an individual must meet all the criteria listed below:

1. Age 16-24 years, inclusive, at enrollment;
2. Assigned male at birth;
3. Identifies as a cisgender boy or man;
4. Self-reports CAS with another boy/man—receptive or insertive—while using stimulants (1 hour prior to, or during, sex) within the last 4 months; s*timulants* is defined as crystal methamphetamine, cocaine, and MDMA (e.g., ecstasy, molly); and
5. Willing and able to provide written informed consent for study participation.

In addition, virtual participants must meet all the criteria listed below:

1. Access to a computer/smartphone/tablet that can use video chat (e.g., Zoom or Google Meet);
2. Provide a mailing address where they can receive a package;
3. Access to stable internet that they can use for more than 2 hours at a time;
4. Have a private place (where no one else can see or hear) where they can complete visits online; and
5. Reside within the continental U.S.

4.2 Exclusion Criteria

To be considered eligible for enrollment, an individual must not meet any of the criteria listed below:

1. Unable to provide informed consent due to severe mental or physical illness;
2. Concurrent enrollment in another HIV prevention or treatment study (enrollment in a substance treatment program is acceptable);
3. Non–English-speaking;
4. Is currently incarcerated or pending incarceration; or

5. Any other medical condition, medical/behavioral intervention, or other condition that, in the opinion of the SC Project Lead or designee, could interfere with the safety of participants or staff, adherence to study procedures, or compromise interpretation of study results.

5. Recruitment and Enrollment

5.1 Site Consortium Activation

Prior to implementation of this study, Sterling IRB, the single IRB of record for this study, will approve the protocol, including the master informed consent forms (ICFs). Subsequently, the local IRBs at participating SCs will cede review of this study to Sterling IRB through the execution of a reliance agreement. All site-specific participant-facing materials, including site-level ICFs, pre-screener, fact sheets, and recruitment materials, must then be reviewed and approved by Sterling IRB. The SC must receive confirmation of SC activation approval from the ATN Operations and Collaborations Center (OCC) prior to initiating any study-specific activities, including recruitment and screening of participants. The SC must maintain original approved regulatory documents. This study will follow the ATN procedures for SC activation that are outlined in the ATN Manual of General Operations (MOGO).

5.2 Recruitment and Pre-Screening

The ATN SCs that have been chosen for this study have a proven ability to enroll and retain participants, an astute awareness of the developmental and cultural issues experienced by youth, and outstanding productivity with previous clinical studies. In general, participants will be recruited from the SC's patient populations, SC partners and local advisory boards, community-based venues, referral-based methods, and through social media and/or other technology-based recruitment methods successfully used in previous HIV prevention and treatment studies for youth.

Potential participants may be recruited online or in-person. Pre-screening and referral will occur through a centralized utility (online pre-screener), which will help determine if a participant is a potential fit for the study. Information for potential participants will be forwarded to an ATN SC for screening and possible enrollment.

If the potential participant is referred to an ATN SC through the online pre-screener, the study staff at an ATN SC will contact the potential participant, review eligibility, and if relevant, schedule them for an in-person or virtual session during which informed consent for study participation will be obtained, eligibility criteria will be confirmed, and the participant will be enrolled in the study.

If the potential participant is recruited directly by an ATN SC, the study staff will assist the potential participant in completing the online pre-screener. Subsequently, the study staff will proceed with obtaining informed consent for study participation, confirm eligibility criteria, and enroll the participant in the study. Alternatively, the participant can be scheduled to return on a different day to provide consent and enroll in the study.

5.2.1 Screening Log

Each individual who is pre-screened eligible and contacted by SC site staff, whether consented for study participation or not, will have information entered on a Screening Log (an electronic file or a hard copy, depending on SC staff preference) that will be maintained securely at the ATN SC. Individual names and other personally identifiable information (PII) will remain on the Screening Log only. Throughout the study period, the ATN SC will submit tabulated information on individuals who were pre-screened eligible but not enrolled in the study via the Screening

Summary form in the EDC. No individual-level data will be submitted, only summary information. Summary information for reasons not enrolled in the study (e.g., specific inclusion/exclusion criteria not met, declined participation in the study) will be tabulated as well. This data will provide information that is required to ensure transparent reporting on recruitment, screening, and enrollment of participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities.

5.3 Informed Consent

Study details will be discussed, and questions will be answered during the informed consent process. Signed informed consent from the participant will be obtained before any study-related activities or procedures are performed.

For this protocol, an electronic consent (eConsent) developed using ClinOne, will be used. ClinOne is a secure, encrypted, web-based, Health Insurance Portability and Accountability Act (HIPAA) and 21 CFR Part 11 compliant platform. The ClinOne platform is compatible for use on various devices (website, tablet, or phone) and a paper ICF completion option will be available as necessary. A SC study staff member will conduct the consent process whether it is done in-person or virtually. Participant signatures should be obtained using electronic signature, however written signature is acceptable when a paper ICF is required. Upon completion of the consent process, participants will be provided with a copy of their signed ICF.

Those individuals who refuse to provide signed consent to participate in the study will be asked if they are willing to provide their reason for declining participation, and if answered, the response will be recorded on the Screening Log.

5.4 Participant Registration

After confirming that a participant is eligible for the study, the SC Research Coordinator or designee will enroll the participant in the study by completing an electronic case report form (eCRF) in the EDC system. A participant ID will be assigned upon signed ICF, confirmation that the participant is eligible for the study, and enrollment into the EDC (generated by the system).

5.5 Participant Contact Information

Once consented and enrolled, designated SC study staff will collect contact information from the participant on a Contact Information Worksheet (an electronic file or a hard copy, depending on SC staff preference). Participants will be asked to provide multiple forms of contact information through which they can be reached. Participants will also be asked to provide valid contact information for two family members or friends who can be contacted in the event the participant cannot be reached through the contact information they provided for themselves. Participants will be asked if voice and text messages can be left at the telephone numbers provided. Study staff will not leave messages unless expressly permitted to do so by the participant, which also will be documented on the Contact Information Worksheet. If permission is given to leave messages, study staff will assure participants that messages left with a family member or friend will only ask the participant to contact the study staff and will not include any protected health information (PHI) or information related to study participation.

The Contact Information Worksheet (paper or electronic) will be stored securely at the SC, separate from all study records, with access limited to designated SC study staff. Participants will be asked to update their contact information at subsequent study visits.

5.6 Randomization and Stratification

Randomization of participants to study arms will be performed through the EDC system's enrollment module. The study arm assignments will be generated by the statistician at the SDMC. The SC Research Coordinator or designee will complete an eCRF in the EDC system to verify participant eligibility. Upon completion of the randomization, relevant SC staff will receive immediate notification of the study arm assignment on the randomization screen in the EDC system, followed by email notification. The relevant SC staff will maintain records of the participant's study arm assignment in accordance with the ATN MOGO.

Participants will be allocated with a 2:1 representation to the two arms, with two-thirds randomized to the IMPACT intervention and one-third to eSOC group. Block randomization will be stratified by SC and intervention format (online vs. in-person) to ensure balanced representation in the two arms. This allocation ratio was chosen to ensure sufficient power to examine whether there are differences in intervention efficacy by delivery format. Participants will be randomized after completing the Enrollment Visit and the first two RR sessions.

A randomization assignment, once issued, will not be re-allocated. Details of the randomization process are described in the study-specific Randomization Plan.

5.7 Co-Enrollment Guidelines

Co-enrollment in other clinical studies may be considered at the discretion of the Protocol Team. Requests for "blanket" co-enrollment approvals into other relevant open protocols during the implementation of this protocol will be considered by the Protocol Team and, if meritorious, will be granted before implementation of this protocol. **ATN Protocol 164 (Screen to Prevent)** has obtained such a blanket approval for co-enrollment and does not require further permission to co-enroll participants in this protocol. Studies that open after this protocol is implemented can be considered for co-enrollment either by requesting a blanket, one-time approval from the Protocol Team, or by requesting case-by-case permission for co-enrollment in writing from the Protocol Team using the ATN Query and Notification System (QNS).

6. Study Intervention

6.1 Study Intervention Description

6.1.1 Intervention Arm: BA and RR Counseling (IMPACT)

The IMPACT intervention consists of 10 sessions: 2 sessions focused on HIV acquisition/transmission RR, 1 session focused on orienting and rationale to BA, 6 sessions integrating BA and HIV RR counseling (including PrEP or ART and HIV care), and 1 final session on strategies for slip-ups and recurrence management. These sessions are detailed below and are meant to be flexible so that only relevant material is covered and high-need content can be repeated if necessary. Each session lasts approximately 50 minutes.

Each session begins with a discussion of HIV risk and substance use over the prior week (since the last visit) and re-emphasizes the need for continuation in substance treatment.

NOTE: The intervention manuals contain a full description of session content. The content for the interventionists is semi-structured and will be used by the study interventionist as a guide for each of the individual sessions, presented in the form of a flip book. As with any therapeutic intervention, the exact content of the discussions will vary depending on the needs and context of each study participant. Minor changes or modifications will be discussed with the clinical supervisor at regular supervision meetings and revised as applicable per their discretion. Fidelity to the intervention manuals will be monitored regularly per the study protocol.

- **HIV sexual RR counseling (two sessions).** Adapted from our previous work with those LWHIV and those NLWHIV, we will begin the intervention with modules that focus directly on sexual RR, including discussion of one's sexual history, sexual "risk limits," and barriers (e.g., motivation or skills) to staying within their sexual risk limits, including topics such as PrEP, ART, TasP, and condomless sex. These sessions will also focus on enhancing motivation and behavioral skills for RR and, as needed, formulation of an individualized behavioral skills plan.
- **Introduction to BA: Orienting, rationale, and information gathering (one session).** In this session, the interventionist seeks to continue to build rapport with the participant, to introduce what BA is and its rationale, and to assess participant-specific needs and desires for RR.
- **BA integrated with RR counseling (six sessions).** Subsequent intervention components will focus on BA—re-learning how to enjoy previously enjoyed activities without stimulant use, and the continued integration of RR counseling. Each of these sessions, however, will begin with an assessment and discussion of stimulant use and sexual risk-taking; a review of skills learned in the prior sessions that target behavioral skill aspects of RR; and an assessment of the participant's mood over the past week. Consistent throughout the modules will be the use of motivational interviewing for change. Examples of activities include: discussing barriers to participating in activities that do not involve drug use, one's history of participating in interests that do not involve drug use, and the potential cycle between stimulant use, decreasing participation in and enjoyment from activities that do not involve stimulant use, and continued stimulant use; identifying times and situations when they are more and less likely to feel enjoyment from activities that do and do not involve stimulant use; problem-solving ways to re-engage in such

activities; and breaking down overwhelming tasks into manageable steps with the goal of reducing behavioral avoidance.

- **Review strategies for slip-ups and recurrence management (one session).** A final session will involve a review of previous sessions and skills with an emphasis on emphasizing the assets of YGBSMM, and a plan for slip-ups regarding stimulant use, high HIV transmission risk sexual behavior, PrEP or ART adherence, and continued engagement in enjoyable life activities that do not involve stimulants or other drugs. This session will involve differentiating a lapse from a relapse, anticipating difficult or stressful situations that may be triggers for lapses, and encouraging ways to use skills learned to maintain gains. The focus of this session, generally, is to transition participants to be their own interventionists.

6.1.2 Comparison Arm: eSOC with Sexual RR Intervention Sessions

The eSOC comparison arm will receive the same HIV sexual RR intervention sessions (n=2) outlined above and referrals to substance use and mental health treatment, per SOC for respective SCs.

6.2 Study Intervention Administration

The IMPACT arm consists of 10 sessions (approximately 50 minutes each) delivered over the course of approximately 10 weeks. The eSOC arm consists of two RR intervention sessions described in Section 6.1.

A participant is not required to finish all intervention sessions to complete a follow-up visit; it is acceptable to miss sessions and continue with follow-up visits. However, once the Month 4 visit is conducted, no further intervention sessions can occur.

Following best practices described in the ERIC framework,[17] a multifaceted training and implementation strategy for interventionists will be used for implementing the IMPACT intervention across sites and formats. A detailed description (including the Working Alliance Inventory-Therapist Report) of the intervention training and ongoing evaluation plan was acknowledged as an exempt sub study (ATN 170 Addendum: Interventionist Training and Evaluation, Study 11201) by Sterling IRB on August 8, 2023.

To enhance and maximize the adoption and accessibility of the IMPACT intervention, the intervention will be implemented in two separate formats: in-person at the selected ATN SCs and virtually, provided by the central research staff at Brown University and UCLA. This will allow for the intervention to be offered to a larger, broader, and more diverse population in terms of geography and physical ability status.

6.3 Study Intervention Fidelity

Intervention fidelity monitoring will consider interventionist adherence and competence. A rating checklist, called a Fidelity Form, will be used that includes whether the specific components of the modules of treatment were, in fact, delivered. The rating checklist will be completed by the Central Coordinating Research Team after reviewing the audio-recorded sessions. Competence will be ensured by weekly clinical supervision using the audio-recorded sessions and rating checklists. At least 10 percent of the sessions, and at least one session per week per interventionist, will be reviewed for adherence and competence and will have the rating

checklist applied. Although following the manual is important, flexibility in the timing of interventions, content emphasis, and the order of topics is important to keeping the treatment relevant to participants.

Once per year—while the intervention is being implemented—the Protocol Team will conduct qualitative interviews with study interventionists, as well as at least one site administrator at each SC, to obtain input on (1) strengths and challenges in implementing the IMPACT intervention; (2) ways to improve training, implementation, and content of the intervention; and (3) strategies for broad dissemination following study completion, including funding sources and potential partners.

6.4 Study Intervention Adherence

Intervention sessions will be scheduled approximately 1 week apart. At the end of each visit, the interventionist will schedule the next session to enhance adherence. If a participant misses a scheduled intervention appointment, study staff will attempt to reschedule the appointment for later in the week. If needed, two intervention visits may occur in the same week, with at least 2 days in between (e.g., Monday and Thursday or Tuesday and Friday).

To ensure adherence to the protocol, we will use tracking procedures that have proven effective in prior studies. Meticulous tracking procedures increase the likelihood that attrition will be random rather than systematic. Participants are enrolled in the study for approximately 12 months. During this time, in addition to their Enrollment Visit and at Month 4, Month 8, and Month 12 follow-up study visits, staff will contact participants monthly to review their most current contact information, address any concerns they have with the study, address scheduling issues or barriers to keeping study visit appointments (e.g., review train/bus routes and times, check for accuracy of plans), and stay connected with the participant (i.e., follow-up calls). Additionally, staff will contact participants to remind them of their appointments the week before their scheduled study visit and again the day before the scheduled visit (i.e., reminder call). All contacts and contact attempts will be recorded in the local contact tracking log.

When filling out the Contact Information Worksheet, staff will follow the instructions and ask for permission to send mail to a residential address, to leave a voicemail on contact phone lines, to send text messages, or to provide the name of the study to any person who is not the participant who may respond to telephone calls. Staff will ask how they should identify themselves when reaching out (e.g., *Calling from xxx regarding a research study*). In completing the Contact Information Worksheet, staff will obtain as much contact information as possible, including the participants' email addresses and phone numbers, social media contact information, and the contact information of at least two people (i.e., secondary contacts) who could help us locate the participant in the future. The staff will prompt participants to provide contact information for social service providers who may have regular and direct contact with participants. Investing time in gathering this contact information at the initial visit will pay off with higher retention at all study visits.

Staff will ask each participant for their preferred method of contact and use that preferred method first when attempting to contact them. If this method is unsuccessful, other available contact information will be used. If two consecutive attempts to reach the participant have been unsuccessful, progression to a secondary contact will be made. Staff will not attempt to contact any individual more than twice a day. Staff will refer to their local contact tracking log prior to

contacting the participant to ensure that other study staff have not already contacted them. All retention attempts, including follow-up calls, reminder calls, text messages, and emails should be entered into the local contact tracking log and should reference the outcome and any next steps to be taken. When participants are repeatedly nonresponsive via phone (or their preferred means of communication), staff should consider alternative methods including but not limited to their secondary contacts, social media, text messaging, email, and paper mail. Retention efforts following missed appointments should be conducted at least weekly per participant and up to twice a week as needed, depending on participant responsiveness. Old, inaccurate, or disconnected means of communication should be labeled as such. A participant should not be considered “lost to follow-up” until all avenues of outreach have been pursued to confirm the participant’s status. Staff will consult with the SC Project Lead and Study Manager prior to determining if the participant is considered lost to follow-up. If a participant re-initiates contact, a new Contact Information Worksheet with current information should be completed prior to the next scheduled visit.

7. Study Visits and Procedures

The following study assessments and procedures will be performed on each participant, after signed informed consent is obtained, as part of participation in this study. See Appendix 2 for a tabulated summary of the measures and assessments described below and Appendix 1 for their schedule of completion.

7.1 Pre-Screening

Pre-screening will occur through the online pre-screener (see Section 5.2). Potential participants found eligible based on the online pre-screener will be contacted by a Research Coordinator, Outreach Coordinator, or designee at a participating SC to provide them information about the study. Participants who pre-screen as eligible and agree to learn more about the study will be scheduled for the Enrollment Visit at a participating SC or via video conferencing.

7.2 Enrollment

In-person participants may complete the Enrollment Visit in 1 day or 2 separate days, based on site discretion. Virtual participants will complete this visit in 2 or 3 separate days. In both cases, the entire enrollment visit must be completed within 28 days of pre-screener completion.

All participants will complete items in Section 7.2.1 on the first day of the enrollment visit.

If the in-person visit is split into 2 separate days, participants should complete the items in biospecimen collected noted in Section 7.2.3 and the Measures and Assessments related to the primary outcomes in Section 7.2.2 on Day 1, with the remaining items being completed on Day 2, as needed.

For the virtual participants, only the items listed in Section 7.2.1 can be completed on Day 1. On Day 2, participants should complete, at minimum, the items in biospecimen collected noted in Section 7.2.3 and the Measures and Assessments related to the primary outcomes in Section 7.2.2. Remaining items can be completed on Day 3, as needed.

Regardless of the number of days for the Enrollment Visit, the primary outcome measures and assessments listed in Appendix 2 should always be completed on the same day as biospecimen collection.

7.2.1 General

- Administer informed consent
- Confirm eligibility
- Enroll participant
- Complete Contact Information Worksheet
- Evaluate for social harms, adverse events (AEs)/serious adverse events (SAEs), and unanticipated problems (UPs)

7.2.2 Measures and Assessments

(See Appendix 2 for a detailed list.)

- Staff-administered
- Self-administered

Virtual Participation – For the Enrollment and Follow-up Visits, participants will complete the self-reported questionnaires and specimen collection forms via an online secure link (that is unique to that study participant) sent to participants via electronic Patient Reported Outcomes (ePRO), a web-based, HIPAA-compliant platform for collecting data via direct data entry. Once the participant completes the self-reported questionnaires and specimen collection forms, they are asked to log out and close their browser to ensure confidentiality of their responses. The research staff will then verify completion of the self-reported questionnaires and specimen collection forms.

The staff-administered questionnaires will take place via video conferencing. A secure hyperlink to access the video conference will be sent to the participant via a HIPAA-compliant secure messaging email or texting platform. Special arrangements may be made to complete the surveys and questionnaires over the phone with research staff, as applicable.

7.2.3 Biospecimen Collection

- In-Person Participants
  - POCT:
    - All participants
      - Toxicology screening, urine (iCup®)
    - For participants who report NLWHIV, are unsure of their HIV status, or decline to answer:
      - HIV antibody test, saliva
  - Local Laboratory Testing (venipuncture)
    - For participants who report NLWHIV, are unsure of their HIV status, or decline to answer:
      - Instrumented HIV Ag/Ab test
      - Plasma storage
    - For participants who report LWHIV:
      - HIV viral load testing
      - Plasma storage
  - Central Laboratory Testing (venipuncture)
    - For participants who report NLWHIV, are unsure of their HIV status, or decline to answer)
      - PrEP adherence monitoring, dried blood spot (DBS); prepared within the clinic or by the local laboratory staff
- Virtual Participants
  - At-Home POCT (self-testing):
    - All participants
      - Toxicology screening, urine (iCup®)
    - For participants who report NLWHIV, are unsure of their HIV status, or decline to answer:
      - HIV antibody test, saliva
  - Central Laboratory Testing (fingerstick, self-collected by participant)
    - For participants who report NLWHIV, are unsure of their HIV status, or decline to answer:

- DBS - PrEP adherence monitoring
- For participants who report LWHIV:
  - HemaSpot blood collection device (or equivalent) - HIV viral load testing

Virtual Participation – After Day 1 of the Enrollment Visit, where the participant will consent to the protocol and contact information will be collected, self-administered lab evaluation kits will be mailed to participants. The toxicology screening and HIV antibody test will be done in real time and the participants will present their results to the study team via video conferencing and/or photo upload of results. The study team will then document results in the EDC system. The DBS and HemaSpot will be mailed to a central lab for analysis.

Section 11.1 contains additional information relating to biological specimens.

7.3 On-Study

The following assessments will be performed at Month 4, Month 8, and Month 12. Visit windows are defined in Section 3.2.5 and included in the Schedule of Events in Appendix 1.

If the follow-up visit is split into 2 days, the primary outcome measures and assessments listed in Appendix 2 should **always** be completed on the same day as biospecimen collection. The entire follow-up visit must be completed within 28 days of the initial follow-up encounter.

Please note, if randomized to the intervention arm, a participant is not required to finish all intervention sessions to complete follow-up visits; it is acceptable to miss sessions and continue in follow-up. However, once the Month 4 visit is conducted, no further intervention sessions can occur.

7.3.1 General

- Review/update Contact Information Worksheet
- Evaluate for social harms, AEs/SAEs, and UPs

7.3.2 Measures and Assessments

(See Appendix 2 for a detailed list.)

- Staff-Administered
- Self-Administered
- Brief qualitative exit interview (at Month 4 or Premature Discontinuation, for selected intervention participants only)

7.3.3 Biospecimen collection

See Section 7.2.3 as the On-Study biospecimen collection is identical to the enrollment biospecimen collection.

7.4 Premature Discontinuation

7.4.1 Assessments for Participants Discontinuing from Study Intervention

- Document reason for study intervention discontinuation.

- Those who request to stop participating in the study intervention will be asked for the reason(s) for stopping, and a subset will be asked to complete an exit interview.
- In addition, the participant will continue to complete all study follow-up visits, unless the participant decides to discontinue participation in the study entirely.

7.4.2 Assessments for Participants Discontinuing from the Study

- Document reason for discontinuing from the study.
- Those who request to stop participating in the study will be asked for the reason(s) for stopping and if they are willing to complete one final study visit.

7.5 Efficacy Assessments

All study assessments are listed in Appendix 2. In brief, primary efficacy will be determined by a combination of self-report and biomarkers at each follow-up visit. Participants will be asked to report the number of times (continuous) in the past 4 months they have engaged in CAS with a male partner. Those who report oral PrEP use will also provide blood samples for assessing PrEP adherence, and those who report injectable PrEP use will be asked to provide a medical record release to confirm receipt of their bimonthly injections. Similarly, those who are LWHIV will provide blood samples for viral load testing.

7.6 Safety Assessments

Reportable AEs/SAEs will be solicited from participants at enrollment and Months 4, 8, and 12. All events will be recorded using the designated form and will be reported in the data entry system.

See Section 13.3 for definitions of reportable safety events. Details regarding specific forms can be found in the Advantage eClinical® eCRF Completion Guide.

8. Description of Study Assessments and Measures

8.1 HIV Testing

The local laboratory will perform testing for HIV diagnosis at enrollment and other scheduled visits for in-person participants. SCs will follow local algorithms for HIV testing, and those algorithms should be shared with the Central Laboratory prior to site activation. For virtual participants, HIV testing will be performed using self-collected at-home rapid testing kits for participants NLWHIV and participants who are unsure of their status. Participants who test reactive on the rapid test will be referred to local HIV care services/resources in their respective areas. Linkage-to-care will involve one-on-one follow-up phone calls by trained study staff who will provide referral information for ongoing HIV treatment in their respective area.

8.2 HIV Viral Load Testing

For participants LWHIV, viral suppression will be assessed for in-clinic and virtual participants. For in-person participants, viral load testing should be done using an FDA-cleared assay with a limit of detection of 40 copies/mL or lower. For virtual participants, capillary (fingerstick) blood will be self-collected on a DBS card and sent for viral load testing at the Central Laboratory, or a laboratory designated by the Central Laboratory.

8.3 Pharmacology

DBS samples for pharmacology testing will be collected throughout the study from both in-person and virtual participants; however, this testing may be limited to a subset of samples. For participants reporting long-acting PrEP, plasma may be used to assess drug concentrations. Procedures for sample processing and shipping are outlined in the study Lab Processing Chart (LPC). The primary pharmacologic assessments will be performed using assays that have been appropriated validated and approved by the Central Laboratory, an external quality assurance group. Interpretation of pharmacologic results, including modeling, will be led by the Central Laboratory and the ATN Laboratory Diagnostics and Mobile Technologies Scientific Leadership Group, in collaboration with other groups, as needed.

8.4 Substance Use

For all participants (in-person and virtual), urine will be collected for substance use testing. The test will use a POC antibody-based methodology, and specific drug class speciation will not be performed.

9. Participant Management

9.1 Participant Tracking and Follow-Up

The SC study staff will reach out to participants at least every month between study visits to check in on how they are doing and obtain any changes in their contact information. Check-ins will be done using the participant's preferred means of contact (e.g., telephone call, email, text message, chat/WhatsApp) as provided on the Contact Information Worksheet.

The following actions will be taken if a participant fails to complete a required study visit:

- The SC study staff will attempt to contact the participant and reschedule the missed visit within the protocol-specified visit window. At least three attempts should be made to reach the participant to reschedule the missed visit.
- Before a participant is deemed lost to follow-up, the SC Project Lead or designee will make every effort to regain contact with the participant using the participant's preferred means of contact. These contact attempts should be documented in the local contact tracking log.
- Should the participant continue to be unreachable and the visit window closes, the study visit will be considered missed. The SC study staff will attempt to reach the participant for their next scheduled study visit when the visit window opens.
- The participant will be considered lost to follow-up if SC staff are unable to contact them for their final Month 12 visit within 6 weeks after the anticipated date.

9.2 Criteria for Premature Discontinuation from Study Intervention and/or the Study

9.2.1 Temporary Discontinuation of Study Intervention

The SC Project Lead or designee will decide whether a participant needs to temporarily discontinue the study intervention per SOC guidelines. Upon deciding to temporarily hold the study intervention, the SC Project Lead or designee will inform the Protocol Team via the QNS of the decision with the rationale for the decision and plan for re-starting administration of the study intervention.

9.2.2 Permanent Discontinuation of Study Intervention

Participants who are permanently discontinued from study intervention (as applicable) due to an AE, whether serious or nonserious, must be followed until the AE is resolved or considered stable (see Section 13).

9.2.3 Premature Discontinuation from the Study

The SC Project Lead has the authority to withdraw any participant at any time if, in their opinion, it would be in the best interest of the participant. They will inform the participant of the study withdrawal and explain the rationale behind it. The reason for the premature discontinuation or failure to provide a reason must be documented by the SC Project Lead and recorded within the EDC system.

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

- The participant withdraws consent;
- The participant develops a new medical condition or experiences a safety event such that continuing study participation is no longer in the best interest of the participant;
- The participant is noncompliant with study procedures; or
- Death of the participant.

Participants may withdraw from study participation at any time for any reason. Should a participant decide to withdraw from study participation, safety-related follow-up will be encouraged, but not mandated. If a participant withdraws consent, no further data collection will occur from the date consent is rescinded. Study data and specimens that have been recorded/collected prior to study discontinuation will be retained for use by the study.

It is possible that experiencing an AE/SAE may necessitate the participant's stopping or pausing the study intervention; any such participants will continue to be followed for safety until the AE/SAE is either resolved or considered stable, as determined by the SC Project Lead or designee. All safety-related follow-up will cease if the participant withdraws consent.

9.3 Participant Replacement

In cases of premature discontinuation, a replacement participant may be enrolled.

9.4 Participant Compensation

Participants will be compensated for each intervention visit and study visit with the amount as indicated in the SC-specific ICF as approved by Sterling IRB and the local IRB at the SC, where required. SCs will be encouraged to provide compensation commensurate with the time and effort required by the protocol and as per IRB guidelines.

9.5 Mitigation Plans for Social Harms

All SCs have specific policies governing the protection of human subjects. Medical and psychological assistance will be available in the immediate environment in the event a participant experiences any social harm resulting from participation in the study.

Measures to ensure safety will be taken if, at any time during the study, a participant divulges that they are at risk for harm, including being abused or experiencing violence, if harm is suspected or likely, or if the participant states they are suicidal/homicidal. Reporting will be done as appropriate to the situation and the legal statutes, including reporting to child protection agencies or other appropriate agencies, and referrals will be provided to appropriate support, counseling, or treatment resources. Social harms will be reported to the Protocol Team following the procedure for social harms reporting (see Section 12).

9.6 ATN QNS

The ATN QNS, established for notifications and queries from the ATN SCs to the Protocol Team, will be used for this study. SC study staff will use the ATN QNS to consult with the Protocol Team on any issues that may arise during study implementation, such as, but not limited to, participant management, study management, and safety reporting guidance. The ATN QNS is accessible via the ATN website (https://www.atnconnect.org). Upon receipt of a query, the

Protocol Team will discuss it as needed and formulate a response. The Protocol Team will respond to queries generally within 2 business days. If the Protocol Team anticipates that a response will take more than 2 business days to formulate, the Study Manager will inform the query requestor by email. Queries and responses will automatically be archived at the OCC. The Study Manager will post queries and responses deemed relevant to all SCs as Frequently Asked Questions on the ATN website, where they will be available to all SCs and the Protocol Team for future reference. Note that social harm/AE notification via the QNS does not meet the requirements to enter social harm/AE data in the EDC system.

10. Study Termination/Halting

10.1 Study or SC Termination Criteria

This study may be terminated at any time by NICHD. Reasons for study termination include if, in those organizations' judgment, there are no further benefits to be achieved from the study or if the intervention presents an unreasonable and significant risk to participants. If the study is terminated, notifications will be made to Sterling IRB, SCs and their local IRBs, and study participants in accordance with all applicable regulations governing the study and the SCs and their Project Lead. All participants will be informed, explained the rationale, and taken off the study. The SC Project Lead will discuss other options with participants.

Participation by an SC and/or an SC Project Lead may be terminated at any time by NICHD, Executive Committee (EC), or by a ruling of Sterling IRB. Possible reasons for termination of the study at an SC include:

- Noncompliance with signed agreements, statements, or undertakings;
- Safety concerns;
- Inaccurate or incomplete data collection;
- Falsification of records; and
- Failure to adhere to the protocol.

If participation by an SC or SC Project Lead is terminated, notifications will be made to Sterling IRB, the SC's local IRB, and other concerned parties in accordance with the applicable regulations governing the study and the SCs and their Project Lead.

10.2 Study Halting Rules

No halting rules are planned.

Individual participant stopping criteria are outlined in Section 9.2.

11. Study Management

11.1 Biological Specimens

Biological specimens will be collected during in-person or virtual visits. Laboratory testing will be conducted as specified in the Schedule of Events (Appendix 1).

11.1.1 Biological Specimens – In-Person Visits

The following types of specimens will be collected at in-person visits for testing/processing at the clinic or local laboratory:

- Blood
- Saliva
- Urine

Results from POCT at the SC will be recorded by SC staff into the EDC. Assay results generated via local laboratories will be reported to the SC and entered into the EDC.

Biological specimens (i.e., DBS and plasma) that are collected for centralized testing will be processed, labeled, and stored at the SC in accordance with SDMC requirements. The SC will enter specimens into GlobalTrace and ship specimens to the Central Laboratory or a laboratory designated by the Central Laboratory upon request. Specimens will be managed and shipped as per the study LPC.

11.1.2 Biological Specimens – Virtual Visits

The following types of specimens will be self-collected by study participants during virtual visits:

- Blood
- Saliva
- Urine

Specimens may be tested using POCT technologies. For urine and saliva, participants will enter information regarding collection and upload photos in ePRO. Results will then be directly entered into EDC by the study site staff. For blood, participants will enter specimen collection information into ePRO; once entered, the information will merge into GlobalTrace where the Central Lab can accept the shipment electronically.

Virtual participants will ship blood collected as dried blood spots to the Central Laboratory as per the study LPC and participant instructions included with the kits.

11.1.3 Specimen Storage (Including Long-Term Storage) and Possible Future Research Testing

Samples collected during this study may be stored at the local SC or at the Central Laboratory. Any specimens that remain after testing should be stored for at least 12 months after the last participant last visit. Long-term storage may be required based on study endpoints. If an SC does not have the capacity to accommodate long-term storage, the Central Laboratory should be contacted.

11.2 Protocol Deviations

A protocol deviation is any noncompliance or unplanned excursion from the approved investigational plan (e.g., protocol, study MOP, ATN MOGO), or ICH GCP guidelines. The noncompliance may be on the part of the participant, the SC Project Lead, or the SC staff. If a deviation occurs, a corrective action plan may need to be developed and implemented promptly by the SC.

For this study, missed assessments due to participant refusal, scheduling issues, difficulties attending the study visit, and related issues will not be considered protocol deviations in order to facilitate retention of participants for later study assessments. These issues will be tracked and reported to the Protocol Team, however.

SC Project Leads must adhere to the investigational plan as detailed in this protocol and associated study materials (e.g., study MOP, forms instructions, user guides) and only deviate from the protocol in order to prevent immediate harm to participants. SC Project Leads will ensure that all staff assisting with the study are adequately trained to perform the study-related duties and functions they have been delegated.

All protocol deviations must be recorded in the source documents and be promptly entered in the EDC system by the SC staff within 3 business days of SC awareness. It is the responsibility of the SC to use continuous vigilance to identify and report protocol deviations as outlined below.

Protocol deviations can be separated into two categories:

- A nonsignificant deviation is a deviation that affects only logistic or administrative aspects of the study and has no substantive effect on the safety or well-being of study participants; does not affect the value of the data collected; and does not result from willful or knowing misconduct on the part of the SC staff.
- A significant deviation is a deviation that affects the scientific design/integrity of the study; affects the rights, safety, or welfare of study participants; changes the risk/benefit ratio; or violates an ethical principle. Significant deviations for this study may include: 1) enrollment violation; 2) informed consent violation; or 3) failure to link distressed participants to care.

All protocol deviations are to be reported to the Protocol Team through the EDC system by SC staff within 3 business days of SC awareness.

Nonsignificant protocol deviations do not need to be reported to Sterling IRB unless the Sponsor requires that the SC Project Lead do so. Local institutional guidelines, if different, must also be followed.

Significant deviations must be reported within 10 business days of SC awareness to Sterling IRB. In addition, all significant deviations must be reported to appropriate local institutional officials or local IRB per institutional requirements.

Note that no special notification via the QNS is needed for nonsignificant protocol deviations, except in cases where the SC is unsure of how to define the event and/or has questions on participant management.

11.3 Site Monitoring

Participating SCs are monitored to ensure compliance with GCP guidelines, the currently approved protocol, and applicable federal and local regulatory requirements. The ATN employs a targeted site monitoring approach focusing on critical data elements and processes in its efforts to ensure the protection of human subjects and the integrity of study results. A study-specific site monitoring plan will be developed to meet the specific needs of the study prior to when the study opens for accrual.

Site monitors from the OCC will visit SCs (either virtually or in person) to review a selected portion of the individual participant records, including consent forms, data collection forms, and supporting source documentation, to ensure protection of study participants, compliance with the protocol, and accuracy and completeness of records. Regulatory files, as required, will also be inspected to ensure that regulatory requirements are being followed.

The SC Project Lead will make all study documents (e.g., consent forms, data collection forms) and pertinent clinic records readily available for inspection by the OCC site monitors for confirmation of the study data.

Site monitors, other authorized representatives of the Sponsor, representatives of the IRB, and regulatory agencies may inspect all documents and records required to be maintained by the SC, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study. The SC will permit access to such records.

11.4 Audits and Inspections

Authorized representatives of NICHD or the IRB may visit the site to perform audits or inspections, including source data verification. The purpose of the audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP guidelines, and any applicable regulatory requirements.

The SC Project Lead should contact Westat immediately if contacted by a regulatory agency about an inspection.

11.5 Quality Assurance and Quality Control

Investigators receiving Federal funding must adhere to the CFR to protect research participants and produce reliable study information. SCs participating in research funded by NICHD need to have an internal quality assurance plan that will identify problems and correct errors in research study records. SCs are responsible for following ATN data quality assurance procedures outlined in the ATN MOGO.

11.6 Safety Oversight

The ATN Data and Safety Monitoring Board (DSMB) will monitor this study for safety and conduct. DSMB members will be independent of the study investigators. DSMB members will be experts in the areas of infectious disease, statistical analysis, or other disciplines relevant to the study as required. The DSMB will monitor the implementation and progress of the study and

will review the accumulating safety data by study arm to detect evidence of early safety concerns while the study is in progress. In some cases, efficacy data may also be considered by the DSMB in evaluating the potential risks and benefits of the study product or intervention under study.

The DSMB will convene to review safety data as well as social harms data, as applicable, approximately three times a year following study opening. Meetings will be conducted virtually via secure video platform (e.g., Zoom, Teams, or WebEx). Flexibility is allowed regarding timing of meetings in relation to study milestones and/or study progress. Additional ad hoc meetings may be called by the Sponsor or the DSMB Chair. Following each DSMB meeting, the DSMB Recommendation Form will be submitted to the Sponsor. The written recommendations serve as an immediate action report if any of the DSMB findings are of a serious and immediate nature or if there is a recommendation to halt or discontinue all or part of the study. A synopsis of the DSMB report indicating whether there are safety or ethical concerns with the study and whether the DSMB has recommended the continuation of the study will be submitted to the Sponsor after each DSMB meeting. In the event the DSMB recommends modifying the study, temporarily halting the study, or terminating the study, Sterling IRB will be notified of the recommendation.

The SC Project Lead is responsible for ensuring that all social harms, UPs, AEs, and SAEs occurring in participants during the study are managed and reported in accordance with the protocol and all applicable Federal and local regulations and institutional policies. All social harms information will be reviewed and monitored by the Protocol Team. The Protocol Team will perform aggregate review of the social harms data as part of their regular study monitoring meetings and will make decisions about the need to modify the protocol and/or study procedures.

The SDMC Medical Monitor, in collaboration with the NICHD Representatives, will oversee the study and provide ongoing monitoring. This includes the following: promptly reviewing all reported AEs/SAEs; making determinations of their reporting status and need for follow-up; providing assistance to SCs with protocol implementation questions and participant management questions; leading safety evaluations, risk management, and mitigation processes; and other safety aspects of protocol implementation.

12. Social Harms and Unanticipated Problems Monitoring

The Protocol Team and SC Project Lead will work closely to monitor and respond to occurrences of all social harms and UPs in a timely manner.

NOTE: The SDMC Safety team will not have any responsibility to evaluate or to follow any reported social harms or unanticipated problems, as defined in this section.

12.1 Social Harms

12.1.1 Definition of Social Harms

Social harms are generally defined as negative consequences of study participation that may manifest in social, psychological, or physical ways. Participants may face social harms from having an increased likelihood of acquiring HIV, being perceived to have HIV, or for participating in research. A variety of factors, including cultural norms around sexuality and morality, local understandings of gender roles, previous experience of violence within intimate partner relationships, and stigma can contribute to and exacerbate social harm risk.

Monitoring the full impact of research studies includes evaluating the impact of the study on the welfare of:

- Study participants;
- Study staff; and
- The neighborhood/community in which the study is being conducted.

Reporting of study participant or staff-associated social harms to the Protocol Team will result in the examination of study procedures, as necessary, to address concerns about participant management, recruitment, enrollment, adequacy of training, and/or to modify procedures. Community-associated social harms reporting will facilitate understanding of the impact of the study on the community and will provide the opportunity to address community-level concerns and to intervene in a timely manner to correct misinformation or perceptions of practices that may cause community concern.

12.1.2 Social Harms Reporting

All social harms that are at least possibly related to the study must be reported to the Protocol Team through the EDC system by SC staff with 3 business days of SC awareness. If a site has any questions on whether or how to report the event, a query should be sent to the Protocol Team via the QNS.

Any event that is deemed to have negatively impacted a participant, staff member, and/or community to more than a minimal extent and is at least possibly related to study activity must also be reported to the Sterling IRB within 1 business day of SC awareness if the event is life-threatening or fatal, otherwise reported within 10 business days of SC awareness.

Regulatory Affairs at the OCC will review all social harms that are reported to have more than a minimal negative impact and work with the SC staff to submit these events to Sterling IRB. The SC Project Lead is responsible for ensuring that the local IRB at the SC is notified of the event, as required.

All social harms that are at least possibly related to study activity that occur during study implementation must be documented and entered into the EDC system.

Examples of more than minimal impact events for study participants that could be related to the study activity include:

- Disruptive or violent behavior during the scheduled study visit session;
- Information regarding personal harm that is disclosed or uncovered during interview sessions (e.g., current suicidal or homicidal ideation, physical or sexual abuse, depression);
- Significant visible distress or injury resulting from the research encounter may provoke emotional responses/distress and may require involvement of SC study staff to provide support/guidance to the participant; and
- Breach of confidentiality.

Study staff may encounter social harms during sessions that personally affect them. Training and guidance will seek to minimize this risk. The Protocol Team should be notified of these events via the EDC system so that they may be immediately addressed, evaluated, and guidance modified or expanded to minimize similar risk to other staff. These events will be catalogued and will be included in the assessment of the cost of conducting the study.

A critically important area any community-based study intends to evaluate is the impact, including social harms, of the study on the community. This will be evaluated informally with social harm being reported to the Protocol Team via the EDC system.

The SC Project Lead is responsible for acquiring as much information as possible to determine the root cause of the social harm. The Protocol Team will work with the SC Project Lead to determine any actions or changes that are warranted to prevent future recurrence.

12.2 Unanticipated Problems Involving Risks to Subjects or Others

12.2.1 Definition of Unanticipated Problems Involving Risks to Subjects or Others

UPs are any incident, experience, or outcome that meets **all** the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

12.2.2 Reporting Unanticipated Problems Involving Risks to Subjects or Others

All UPs that occur during study implementation must be documented and entered in the EDC system, either as a social harm or as an AE, within 3 business days of SC awareness. If the UP is

also an SAE, it must be entered in the EDC system within 3 reporting days of SC awareness (see ATN MOGO Chapter 8 Appendix B for the definition of "reporting day").

The SC Project Lead will report UPs to Regulatory Affairs at the OCC, to the Sterling IRB, and to their local IRB per institutional requirements. The UP report will include the following information:

- Protocol identifying information: protocol title and number, SC Project Lead's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

Reporting of UPs will follow the timeline below:

- UPs that are life-threatening or fatal must be reported promptly, within 1 business day of SC awareness, to Sterling IRB.
- All other UPs must be reported to Sterling IRB within 10 business days of the SC awareness.
- All UPs should also be reported to the appropriate local institutional officials or local IRBs per institutional requirements.

13. Assessment of Safety

This study will not involve any investigational drugs or devices; as such, it is considered low risk. Acute management of AEs will be according to best clinical practices and the judgment of the SC Project Lead.

For this study, the events specified in Section 13.3 are the only safety-related events considered reportable (i.e., the only events that will be documented and entered into the EDC system).

13.1 Definitions

13.1.1 Adverse Events

An AE is any untoward medical occurrence in humans, whether or not considered drug-related, which occurs during the conduct of a study. Any changes in clinical status, routine labs, physical examinations, etc. that is considered clinically significantly by the SC Project Lead is considered an AE.

An AE does not include the following:

- Medical or surgical procedures not associated with the study intervention, e.g., tooth extraction, transfusion, and surgery. (The medical condition that leads to the procedure is to be recorded as an AE.)
- Pre-existing conditions or procedures present or detected at the start of the study that do not worsen.
- Hospitalization for elective surgeries or for other situations in which an untoward medical event has not occurred.
- Overdose of concomitant medication unaccompanied by signs/symptoms. If signs/symptoms occur, the final diagnosis should be recorded as an AE.
- Pregnancy by itself, unless a complication occurs during pregnancy leading to hospitalization; in which case, the medical condition that leads to the hospitalization is to be recorded as the AE.
- A significant worsening of the disease under investigation which is captured as an efficacy parameter in this study and, thus, is not to be recorded as an AE.

13.1.2 Serious Adverse Events

An AE is a “serious adverse event (SAE)” if, in the view of the SC Project Lead, Protocol Team, or NICHD, it results in any of the following outcomes:

- Death;
- A life-threatening AE (An event is considered “life-threatening” if, in the view of the SC Project Lead or Protocol Co-Chairs, its occurrence places the participant at immediate risk of death, inclusive of suicide attempts);
- Inpatient hospitalization (admission) or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;

- A congenital anomaly/birth defect; or
- Important medical events that may not immediately be life-threatening, or result in death or require hospitalization, but require intervention to prevent one of the other outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

13.2 Classification of an Adverse Event

13.2.1 Severity Assessment

All reportable AEs and SAEs will be assessed for severity by the SC Project Lead. Inherent in this assessment is the medical and clinical consideration of all information surrounding the event including any medical intervention required. The current Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events with the ATN Preamble ("DAIDS AE Grading Table") will be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The eCRF for AEs will reflect only the highest severity for continuous days an event occurred. If an event is not found in the DAIDS AE Grading Table, the guidelines shown below will be used to grade severity.

Severity	Grade level	Description of symptoms
Mild	Grade 1	Asymptomatic or mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated
Moderate	Grade 2	Moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated
Severe	Grade 3	Severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated
Life-Threatening	Grade 4	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death
Fatal	Grade 5	Death

The terms "serious" and "severe" are not synonymous. As defined by the ICH guideline for GCP, the term "severe" is often used to describe intensity (severity) of a specific event (e.g., mild, moderate, or severe headache); the event itself may be of relatively minor medical significance (such as severe headache). This is **not** the same as "serious", which is based on a participant/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. Any AE that meets the criteria for seriousness must be reported as an SAE.

13.2.2 Expectedness Assessment

The SC Project Lead will be responsible for determining whether an AE is expected or unexpected. Only severe (Grade 3 or higher) AEs that are directly related to DBS collection/venipuncture are considered reportable for this study; as such, these will be the only events that will be graded for expectedness. An AE will be considered unexpected if the nature, severity, and/or frequency of the event is not consistent with the risk information previously described for DBS collection/venipuncture.

For example, using this definition, an infection that is judged to be a direct consequence of the DBS collection/venipuncture, requires antibiotic treatment, and causes a missed day of work may be considered "expected"; an infection that causes an extended absence from work or that leads to hospitalization for further treatment may be considered "unexpected." As previously noted, the SC Project Lead will determine expectedness; the Emmes Medical Monitor will be available to provide advice regarding such decisions, if necessary.

13.2.3 Relationship Assessment

The SC Project Lead will assess the relationship of each AE to the DBS collection/venipuncture. The SC Project Lead will use clinical judgment in conjunction with the assessment of a plausible biologic mechanism, a temporal relationship between the onset of the event in relation to the DBS collection/venipuncture, and identification of possible alternate etiologies including underlying disease, concurrent illness, or concomitant medications. Relatedness of an AE is often assessed by asking 'Is there a reasonable possibility that the DBS collection/venipuncture caused the event?' The relatedness between the AE and the DBS collection/venipuncture will be presumed unless a clearly recognized alternate etiology is identified. Alternative explanations for clinical or laboratory abnormalities must be sought before discontinuing study participation.

The following guidelines should be used to assess the relationship of an AE to the DBS collection/venipuncture and only a physician can make this determination.

Relationship	Description
Related	The AE is known to occur with DBS collection/venipuncture, there is a reasonable possibility that the DBS collection/venipuncture caused the AE, or there is a temporal relationship between the DBS collection/venipuncture and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the DBS collection/venipuncture and the AE.
Not related	There is not a reasonable possibility that the DBS collection/venipuncture caused the event, there is no temporal relationship between the DBS collection/venipuncture and event onset, or an alternate etiology has been established.

13.3 Safety Reporting Requirements

13.3.1 Adverse Event Reporting

The AE reporting period begins at the signing of informed consent and continues through the end of study participation.

A reportable AE for this study is defined as an event that is considered both related to the DBS collection/venipuncture and is severe (Grade 3 or higher).

If an AE also meets the definition of an UP (see Section 12.2.1), the AE must be entered in the EDC system within 3 business days of the SC staff becoming aware of the event.

NOTE: The SDMC Safety team will not have any responsibility to evaluate or to follow any reported social harms or unanticipated problems that do not qualify as AEs/SAEs.

If an AE meets the definition of an SAE (see Section 13.1.2), the SAE reporting procedure must be followed (see Section 13.3.2).

All other AEs must be entered in the EDC system within 7 calendar days of the SC staff becoming aware of the event. These AEs will be reviewed by the Protocol Team during their regular study monitoring meetings and by the DSMB as part of their routine DSMB reports/meeting. AEs will also be reported to Sterling IRB/local IRBs in the annual report.

The SC Project Lead is responsible for acquiring as much information as possible to determine the causality and outcome of a reportable AE and to determine whether a medical event meets criteria for an SAE. Follow-up of the AE is required until the event has resolved, returned to baseline, or has been deemed stable and is not expected to worsen, based on the judgment of the SC Project Lead. All events must be followed until resolution. Events that are unresolved at 30 days after the safety monitoring period ends will be documented using the last known status of the event.

13.3.2 Serious Adverse Event Reporting

Any event that meets the criteria defined in Section 13.1.2 is reportable as an SAE regardless of the determination of relatedness to the DBS collection/venipuncture.

The SAE reporting period begins at the signing of informed consent and continues through the end of study participation.

Grade 4 (life-threatening) or Grade 5 (fatal) SAEs must be entered in the EDC system within 3 reporting days of SC awareness (see ATN MOGO Chapter 8 Appendix B for the definition of "reporting day").

The primary means of reporting will be through completion of the SAE eCRF in the EDC system. If the eCRF is not available or data cannot be transmitted (e.g., internet not functional), a scanned copy of the paper SAE form can be submitted to the SDMC Safety Team via email (ATN_safety@emmes.com). The SAE eCRF must then be completed in the EDC system as soon as the system becomes available.

If an SAE is unexpected and has a reasonable possibility of being related to the study, the SC Project Lead will submit the SAE to Sterling IRB within 1 business day of SC awareness if the event is life-threatening or fatal, otherwise submit within 10 business days of SC awareness. Furthermore, the SC Project Lead will report SAEs to their local IRB per institutional guidelines.

Upon entry of an SAE eCRF in the EDC system, a notification will be automatically generated and sent to the Protocol Co-Chairs, Study Manager, NICHD Representatives, OCC Regulatory Affairs Unit, and the SDMC Safety Team, inclusive of the SDMC Medical Monitor. Within 24 hours of the event's entry in the EDC, the SDMC Medical Monitor will perform a preliminary assessment of the relationship of the SAE to the DBS collection/venipuncture and the expectedness of the event to determine the reporting status to the regulatory authorities and to other stakeholders. The SDMC Medical Monitor will prepare the SAE report and send it to the

NICHD Representatives for review and comment. The Protocol Co-Chairs and Study Manager will be copied on the communications between the medical monitor and representatives. The final assessment of the relationship of the SAE to the DBS collection/venipuncture and the expectedness of the event determines the reporting status to Sterling IRB and other regulatory agencies, as applicable. The DSMB Chair will be informed of all SAE reports in real time via email.

Additional information may need to be gathered to evaluate SAEs and to complete the appropriate eCRFs and the summary. This process may include obtaining hospital discharge reports, medical records, autopsy records and/or any other type records or information necessary to provide a complete and clear picture of the SAE and events preceding and following the event. If the SAE is not resolved or stable at the time of the initial report or if new information becomes available after the initial report, follow-up information must be submitted as soon as possible.

Like AEs, each SAE must be followed until the event has resolved, returned to baseline, or has been deemed stable and is not expected to worsen, based on the judgment of the SC Project Lead. If the event resolves during the study or follow-up period, a resolution date should be documented.

14. Statistical Considerations

This section summarizes the primary features of the statistical analysis for the study. A statistical analysis plan (SAP) will be prepared and finalized prior to database lock and will specify all analyses to be performed. Major changes in the analysis (e.g., redefinition of analysis methodology of a primary endpoint) should result in a protocol amendment. Minor changes, deviations, or changes from the statistical analyses specified in the protocol will be described and justified in the SAP and/or the final study report.

14.1 Statistical Hypotheses

The hypothesis for the primary objective of determining the effectiveness of IMPACT is:

Primary hypothesis: When compared to eSOC, IMPACT will result in a reduction of distinct acts of CAS from baseline to Month 12 post-intervention initiation.

- **Null hypothesis:** The rate of distinct acts of CAS will be the same between individuals assigned to the IMPACT intervention and those assigned to the eSOC arm.
- **Alternative hypothesis:** The rate of distinct acts of CAS among individuals assigned to the IMPACT intervention will be different from the rate among individuals assigned to the eSOC arm.

The hypothesis for the key secondary objective of determining the effectiveness of IMPACT on stimulant use is:

Key secondary hypothesis: When compared to eSOC, IMPACT will result in a reduction of stimulant use from baseline to Month 12 post-intervention initiation.

- **Null hypothesis:** The rate of stimulant use will be the same between individuals assigned to the IMPACT intervention and those assigned to the eSOC arm.
- **Alternative hypothesis:** The rate of stimulant use among individuals assigned to the IMPACT intervention will be different from the rate among individuals assigned to the eSOC arm.

14.2 Sample Size Considerations

Careful consideration was given to the effect size used in the power analysis and is estimated based on data from previous studies. In our pilot study, the mean difference in CAS acts between the intervention versus control arm at 6 months was 4.7 (>50% reduction). Although the pilot study had a large effect on reductions in sexual risk behaviors, effect sizes from small studies like the pilot study are less reliable and frequently inflated.[70] Additionally, in the present study, the eSOC comparison group will be receiving two RR sessions and, as such, they will likely also decrease their engagement in CAS. Therefore, the study is powered to detect a 20 percent (or greater) reduction in the number of CAS acts between groups in the 12-month follow-up period, expecting both groups to show improvements from baseline. This decision will account for the fact that in clinical trials in general, and HIV behavioral trials in particular, when the control group receives any of the intervention content, it is more difficult to find a between-group difference[71-73] as well as take into account the fact that the primary timeframe in the present study is 12 months instead of 6. Lastly, a 20 percent or greater reduction in the number of CAS acts has been previously described as a clinically meaningful change related to HIV sexual risk outcomes.

Moreover, to ensure sufficient power to assess whether intervention effectiveness differs between intervention delivery format (i.e., virtual vs. in-person) with a power of 90 percent, alpha level of 0.05, 291 participants will need to complete the proposed intervention in order to examine difference between IMPACT (n=194) and eSOC control (n=97). We plan to randomize 360 participants (n=240 in IMPACT and n=120 in eSOC) to account for 20 percent attrition at the month 12 visit.

14.3 Statistical Analysis Methods

14.3.1 General Analysis Considerations

All data collected will be summarized and/or listed. Analyses will be performed using SAS® software (SAS Institute Inc., Cary, NC) version 9.4 or higher.

Unless otherwise specified, descriptive statistics include the mean, SD, median, minimum, maximum for continuous variables, and the number and proportion in each group for categorical variables. Unless otherwise specified here or in the SAP, statistical tests and confidence intervals (Cis) will be computed using a two-sided 5 percent significance level. Exact Cis will be used for univariate summaries of dichotomous variables, and Wald- or score-based Cis will be used for mean/rate differences/ratios. All proportions will use as denominator the number of subjects contributing data at the specified time point within the specified group and analysis population. Summaries will be presented by intervention and by time point, where relevant.

For all summaries outlined in this section, the SAP will contain additional detailed descriptions of the analyses to be conducted.

14.3.2 Populations for Analyses

Intent-to-Treat Population

Analyses of primary and secondary endpoints will be conducted in an Intent-to-Treat population that includes all randomization participants. Participants will be analyzed according to the intervention to which they were randomized.

14.3.3 Analysis of Primary Endpoint

Estimands

The primary analysis of the primary endpoint will compare the rate of distinct acts of CAS over the course of follow-up between the IMPACT intervention arm and the eSOC comparison arm.

For this endpoint, the primary estimand is defined by the following attributes:

- **Intervention condition:** IMPACT intervention versus eSOC including the effects of intervention discontinuation and intake of additional interventions/therapies.
- **Population:** Cisgender YGBSMM as defined by the inclusion criteria to reflect the key population.
- **Variable:** Number of distinct acts of CAS without the use of a condom or without the protection of prevention-effective PrEP (for participants NLWHIV) or viral suppression (for participants LWHIV) over the course of follow-up.
- **Intercurrent events:** The following intercurrent events are anticipated:

  - Discontinuation of intervention due to any reason
    - Handling strategy: treatment policy (captured through the intervention condition definition)
  - Intake of additional interventions/therapies
    - Handling strategy: treatment policy (captured through the intervention condition definition)

Further intercurrent events are not anticipated at this time.

- **Population-level summary:** Rate ratio between intervention conditions

Analysis Models

For the primary endpoint, a marginal Poisson model will be used, with logarithmic link function, common intercept, linear fixed effect for intervention, and accounting for the length of the reporting period for each observation. A Generalized Estimating Equations (GEE) approach will be used to fit the model, assuming an unstructured working correlation structure. Given the possibility of missing data from participants who discontinue the study prior to the Month 12 visit, inverse probability weighting will be incorporated into the modeling procedure; more details will be described in the SAP. Substitute model specifications to be used in the event the primary model does not converge will be described in the SAP.

Least squares means will be used to estimate intervention-specific rates; the rate point estimates and standard errors will be reported. The intervention comparison will use the rate ratio comparing IMPACT to eSOC, which will be estimated along with its 95 percent CI from the model. The primary hypotheses will be tested via the Type 3 likelihood ratio chi-square test of the intervention fixed effect. The test statistic value and p-value will be reported.

Supplemental and Sensitivity Analyses

Primary model estimates and results will be accompanied by tabulated summary statistics of the endpoint data by intervention and visit. The primary model will also be used to assess the treatment effect at the Month 4 and Month 8 time points by incorporating a covariate for time point using appropriate contrasts.

Additional models that add a linear effect for a baseline/demographic factor as well as an (intervention * factor) interaction term will be used to assess the effect of intervention by factor. The factors that will be investigated (in separate models) will include geography, HIV status, and race/ethnicity.

Sensitivity analyses will also be performed for the primary endpoint. The SAP will describe the analyses in more detail.

14.3.4 Analysis of Secondary Endpoints

The primary analysis of the key secondary endpoint will compare the rate of stimulant use over the course of follow-up between the IMPACT intervention arm and the eSOC comparison arm.

For this endpoint, the primary estimand is defined by the following attributes:

- **Intervention condition:** IMPACT intervention vs. eSOC including the effects of intervention discontinuation and intake of additional interventions/therapies.

- **Population:** Cisgender YGBSMM as defined by the inclusion criteria to reflect the key population.
- **Variable:** Number of reported uses of stimulants over the course of follow-up.
- **Intercurrent events:** The following intercurrent events are anticipated:
  - Discontinuation of intervention due to any reason
    - Handling strategy: treatment policy (captured through the intervention condition definition)
  - Intake of additional interventions/therapies
    - Handling strategy: treatment policy (captured through the intervention condition definition)

Further intercurrent events are not anticipated at this time.

Population-level summary. Rate ratio between intervention conditions.

The analysis of the key secondary endpoint will follow the procedures outlined for the primary endpoint.

Secondary endpoints. For the secondary endpoints assessing effectiveness by intervention format, Poisson models will be fit. Additional models that add a linear effect for intervention format as well as an (intervention * intervention format) interaction term may be used to assess the effect of intervention by format.

14.3.5 Analysis of Non-Clinical Implementation Endpoints

Adoption and accessibility. Intervention uptake and completion rates will be summarized by intervention format (in-person vs. virtual), site characteristics (e.g., health center, academic research center, community-based organization), and interventionist background (e.g., specialized mental health training).

Study completion and early discontinuation will be summarized by intervention and baseline participant characteristics (e.g., age, stimulant use patterns, sexual behaviors, HIV serostatus).

Implementation. Fidelity checklist scores will be summarized for subjects on the intervention arm by format, site, and time, and compared using t-tests to identify any differences by format, site, and time (months since study initiation).

14.3.6 Safety Analysis

Number and type of reportable AEs/SAEs as defined in Section 13 will be summarized by group and overall, and by each Medical Dictionary for Regulatory Activities (MedDRA®) system organ class and preferred term.

14.3.7 Other Analysis

Individual and total (where applicable) survey and questionnaire item responses/scores will be summarized by intervention, domain/category (if applicable), and visit. Statistics of responses will be generated as appropriate for the type of response.

Descriptive summaries of laboratory evaluations will be generated by intervention.

14.4 Participant Characteristics

Descriptive statistics will be computed for:

- Sociodemographic and other initial participant characteristic data, which may include age, race/ethnicity, sexual and gender identities, education, and relationship status;
- Behavioral and reproductive health and medications history, such as substance use, sexual behavior, depression and anxiety, and HIV/STI history.

Participant disposition, including the number of participants screened, enrolled, eligible for randomization, randomized, completed each of the follow-up visits, and dropped out of the study early, will be summarized by intervention. The summaries will be supported by a CONSORT diagram.

PrEP and ART use and adherence will be summarized by time point and intervention.

Protocol deviations will be summarized by deviation category and intervention.

14.5 Planned Interim Analysis

No formal interim analysis is planned.

14.5.1 Temporary Halting or Early Termination Criteria

There are no study or individual halting criteria.

14.6 Procedures for Reporting Changes to the Planned Analysis

Any deviation(s) from the original planned analysis will be described and justified in the SAP and/or in the final study report, as appropriate.

14.7 Missing, Unused, and Spurious Data

As noted in Section 14.3.3, missing primary endpoint data will be handled via inverse probability weighting. The use of weighted GEE provides estimates that are consistent with data that are Missing at Random (MAR). Sensitivity analyses will address missing primary endpoint data in multiple ways: (1) ignoring missing data, which assumes the data are Missing Completely at Random (MCAR), and (2) imputing using multiple imputation, which provides consistent estimates when missing data are MAR.

Missing implementation endpoint, safety, and participant characteristic data will be assumed to be MCAR, and no imputation will be performed.

Planned explorations of outlying or influential data will be described in the SAP.

14.8 Modeling Core Analysis

We will collect resource use and cost data associated with the IMPACT intervention to understand resources needed for both start up and maintenance of the intervention when implemented in real-world settings. We will work with the SDMC and Modeling Core throughout the trial to identify the appropriate methods to project longer term clinical and economic benefits depending on the results of the study (i.e., the magnitude of changes in behavior that may impact HIV transmissions averted and change in stimulant-free days that may impact quality of life to a different degree than HIV acquisition). The SDMC and Modeling Core

meet quarterly to review progress. In Years 5-7 of the current ATN cycle, these groups will identify one ATN study amenable to model-based cost-effectiveness analyses using the published CEPAC-AYA model; if ATN 170 is selected in a given award year, we will estimate the projected lifetime clinical and economic outcomes for adolescent and young adult MSM who use stimulants based on the efficacy of the IMPACT intervention in the RCT phase, including number of HIV diagnoses averted, increase in number of stimulant-free days, and quality-adjusted life years saved. We will also describe the incremental cost-effectiveness ratios for the IMPACT intervention compared to eSOC. Model parameters will include data from the literature, participant-reported resource utilization, and staff-reported time and effort for conducting the IMPACT intervention. To ensure timely adaptation of our approach, we will meet biannually during the first 2 years of study initiation and adjust the frequency of meeting as needed, thereafter.

15. Human Subjects

This study will be conducted in compliance with the protocol, ICH GCP guidelines, and CFR applicable to research studies (45 CFR Part 46).

Children may participate in research if all the applicable requirements of 45 CFR Part 46 Subpart D and any local laws and regulations are met. All personnel involved in the conduct of this study will have completed Human Subjects Protection and ICH GCP training.

15.1 Participant Confidentiality

All research activities will be conducted in as private a setting as possible.

Participant confidentiality and privacy is strictly held in trust by all components of the ATN, including the participating SC Project Lead and their staff, Protocol Team members, and NICHD and their agents. This confidentiality is extended to cover testing of biological specimens in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No participant-level data that contains PII and/or PHI will be released to any unauthorized third party outside of the ATN without prior written approval of NICHD, the EC, and the participant.

All study-specific evaluation forms, reports, and other records will be identified by a coded number only, to maintain participant confidentiality. All records must be stored in a secured area at the SC when not in use, and with restricted access during work hours and/or when unattended. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written consent of the participant, except as necessary for monitoring by the OCC or NICHD.

15.1.1 Certificate of Confidentiality

To further protect the privacy of the study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). With this Certificate in place, the ATN researchers cannot be forced to turn over identifiable, sensitive information gathered during the study about a study participant in any Federal, state, or local criminal, administrative, legislative, or other proceedings. By protecting researchers and institutions from being compelled to disclose information that would identify study participants outside of the ATN, the Certificate of Confidentiality helps achieve the research objectives and promotes participation in studies by helping assure confidentiality and privacy to participants. This Certificate does not prevent study participants from voluntarily turning over their information nor does it prevent researchers from providing research-related information to others when requested by the study participant or when required by law, such as in cases of suspected or actual harm to or by the study participant.

15.1.2 Known Potential Risks and Benefits to Human Participants

15.1.2.1 Known Potential Risks

- Finger Prick: Participant may feel minor pain from pricking their finger. It is less likely that the participant could bruise where they prick their finger. It is rare that that the participant would get an infection where they prick their finger.
- Blood drawing: It is possible that the participant may feel discomfort during the blood draw. It is also possible there may be bruising, swelling, or bleeding where the needle

enters the skin. The participant may also feel dizzy or light-headed when blood is drawn. The total participant blood volume drawn will not exceed the maximum blood volume allowed for the study period.
- Discomfort with survey questions: All participants will be informed that they can decline to answer any question that makes them uncomfortable without consequence. They will also be reminded that all their responses are confidential.
- Potential risk of loss of confidentiality: There is a potential risk of loss of confidentiality. Every effort will be made to protect the participant's confidential medical information, but this cannot be guaranteed.
- Unforeseen risks: There may be other risks to the participant in this research that are not known or foreseeable at this time.

15.1.2.2 Known Potential Benefits

There is no guarantee of direct benefit to the participants in this study. However, previous interventions using behavioral skills enhancement that are individualized to participants' needs have shown success in helping participants reduce risky behaviors. Therefore, participants in this study may benefit from the study.

- Participants in the IMPACT intervention arm will receive BA-RR—including referrals to other medical, mental health services, or case management needs they require—to help them cope with and reduce the distress associated with sexual risk-taking and substance use.
- Participants in the eSOC comparison arm will receive the equivalent RR counseling, including referrals to other medical, mental health services, or case management needs they require. The BA-RR intervention has been pilot tested and found to be acceptable to all study participants. Participants in prior pilot studies also improved with respect to their stimulant use (decreased), sexual risk-taking (decreased), and depressive symptoms (decreased), so it is anticipated that these participants will improve as well.

The behavioral RR counseling approaches with BA therapy targets a host of complex issues within the YGBSMM population who are at great risk for HIV transmission. This study has public health implications in so far as it may help to curb new HIV transmission rates among YGBSMM.

15.1.3 Assessment of Potential Risks and Benefits

Risk Category: Research not involving greater than minimal risk (45 CFR §46.404 and 21 CFR §50.51)

Participation in this study poses no more harms or discomforts to research participants than they may experience in normal daily life or during routine medical or psychological examinations or tests.

15.2 Informed Consent

Informed consent is a process that is initiated prior to the participant agreeing to participate in the study and continuing throughout the individual's study participation.

Extensive discussion of risks and possible benefits of participation in this study will be provided to the participant. ICFs detailing the study procedures and risks will be given to the participant, and written documentation of informed consent will be required prior to enrolling in the study. ICFs will be IRB-approved, and the participant will be asked to read and review the document. Upon reviewing the document, the SC Project Lead or designee will explain the research study to the participant and answer any questions that may arise.

The Protocol Team will provide the SC Project Lead, in writing, any new information that bears significantly on the participant's risk to participating in the study. The SC Project Lead will communicate new information to participants who consent to participate in the trial in accordance with IRB requirements. The informed consent document will be updated, and participants will be re-consented, if necessary.

Per 21 CFR 50.3 (o) and 45 CFR 46.402 (a), persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations (or the research), under the applicable law of the jurisdiction in which the clinical investigation (or the research) will be conducted and so the legal age for consent may be different in different jurisdictions.

15.2.1 Waiver of Requirement for Parent/Legal Guardian Permission for Minor Participants

Sterling IRB, and local IRB at the SC where required, will be requested to grant a waiver of parent/legal guardian permission for minors under the age of majority to participate in this research study. Under 45 CFR 46.116 (e), 46.116 (f) and 46.408 (c), an IRB has the authority to waive parent/legal guardian permission if it determines that the proposed study meets the requirements, thus participants would consent for themselves within the context of Sterling IRB safeguards.

A waiver of parent/legal guardian permission for studies with sexual and gender minority youth has become common practice. This is done to avoid the selection biases operating in only recruiting youth whose parents/legal guardians are both aware of and comfortable with their sexual orientation. Commonly, these youth have explored their sexual orientation without their parent's/legal guardian's knowledge as the youth struggle with issues of disclosure and its consequences within the social, religious, and economic context of their families. If the purpose of requiring parent/legal guardian permission as stated in the CFR is to protect the minor participant, then requiring parent/legal guardian permission for youth in these circumstances is not a reasonable requirement (not practicable).

Of note, if a waiver of requirement for parent/legal guardian permission is not granted, this protocol will only enroll participants at the age of legal majority or those who could potentially meet the legal criteria of a "mature minor." No youth under the age of legal majority (or meeting the definition of "mature minor," where allowed) will be enrolled in this protocol if the waiver is not granted.

15.2.2 "Mature Minor" Participants

This study involves solely processes for which minors can give consent outside the research context under applicable state and local laws, i.e., research on STIs, pregnancy, and HIV. These "mature minors" would not meet the definition of children as defined at 45 CFR 46.402(a). Thus,

subpart D would not apply to the research and parental permission (or waiver thereof) is not a consideration. Under these circumstances, “mature minors” may provide their own informed consent.

Most states do not have a lower age limit on ability to consent for STI diagnostic and treatment care. In Illinois, New York, and California, for example, a provision exists for mature minors (usually defined by state law as a minor that is near the age of maturity, displays sufficient understanding of medical procedures, and can be medically emancipated in the treatment or diagnosis of certain conditions, including venereal disease, pregnancy, and drug abuse) to seek medical care without parent/legal guardian permission for the prevention (including PrEP), testing and treatment for HIV and other STIs. Based on where the selected SCs are located, discussion of a waiver of parent/legal guardian permission within the context of local laws will be pursued. In addition to local institutional and community consultation, the ATN 170 Protocol Team will also consult with the Bioethics Scientific Leadership Group.

15.2.3 Requirements for Consenting Participants Enrolled as Minors Who Reach Age of Majority While on Study

15.2.3.1 Studies Requesting Waiver of Parent/Legal Guardian Permission for Minor Enrollment

When an IRB has waived the requirement for parent/legal guardian permission for minors enrolling in an ATN study, the IRB, in effect, has judged that the study meets the criteria set out in 45 CFR 46.116 (e), 46.116 (f) or 45 CFR 46.408 (c) and has waived consent for participation in the study. Minor participants in these studies need not be re-consented when they reach legal majority.

15.3 Prisoner Participation

As per 45 CFR 46 Subpart C, there are additional protections pertaining to prisoners as study participants. A prisoner is defined as any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

The ATN and NICHD have concluded that this protocol does **not** meet Federal requirements governing prisoner participation in human subject research and should not be considered by IRBs for the recruitment of prisoners.

If a participant in the study becomes incarcerated or otherwise meets the 45 CFR 46 Part C definition of a prisoner during the study, all research interactions and interventions with, and obtaining identifiable private information about, the participant must be suspended immediately. No study visits can occur during the period of incarceration or detention. Upon the end of incarceration or detention, the participant may continue study participation if they are still within the study follow-up period.

16. Supporting Documentation and Operational Considerations

16.1 45 CFR Parts 160 and 164 Standards for Privacy of Individually Identifiable Health Information ("Privacy Rule" Pursuant to the Health Insurance Portability and Accountability Act - HIPAA)

The HIPAA Privacy Rule provides U.S. Federal protection for the privacy of PHI by implementing standards to protect and guard against the misuse of individually identifiable health information of participants participating in clinical trials. Authorization is required from each research participant (i.e., specific permission granted by an individual for the use or disclosure of an individual's PHI). A valid authorization must meet the implementation specifications under the HIPAA Privacy Rule.

All individuals within the ATN are required to adhere to the ATN networkwide Data Sharing and Management Plan that describes the various components of the ATN through which participant data will flow. The ATN will ensure that the use and disclosure of PHI obtained during this study complies with the HIPAA Privacy Rule.

The SC Project Lead is also responsible for adherence to their individual institution's HIPAA policies and procedures.

The HIPAA authorization will be combined with the ICF for this study and will outline data sharing within the ATN network and include study-specific disclosures for both PII and PHI. No information concerning the study, or the data will be released to any unauthorized third party outside of the ATN without prior written approval and formal data sharing agreements.

16.2 Pandemic Risk Mitigation

An infectious disease pandemic or other force majeure events may pose additional risks to the visit schedule and adherence to protocol-specified safety monitoring or laboratory assessments. Refer to the ATN MOGO for further details on the risks and risk mitigation strategy.

16.3 Future Use of Data

Data collected for this study will be analyzed and stored at the ATN SDMC. After the study is completed, information about the study, including de-identified study data, will be submitted to the NICHD Data and Specimen Hub (DASH) (https://dash.nichd.nih.gov). With NICHD approval, the data submitted to DASH may be used by other researchers for additional, unrelated research. NICHD will review any request prior to release of the data to ensure that all appropriate approvals have been obtained.

The study data submitted to DASH will be de-identified, meaning it will not include any information that can identify the participant. The Protocol Team may also share the de-identified study data with other researchers. When the participant's de-identified study data are provided to other researchers for the purposes of future research, it will be done without obtaining additional permission from the participant.

Submission of de-identified data to the NICHD DASH will be described in the informed consent.

16.4 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with used needles, blood, and blood products containing HIV, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention. All specimens will be shipped using packaging that meets requirements specified by the International Air Transport Association (IATA) Dangerous Goods Regulations for UN 3373, Biological Substance, Category B, and Packing Instruction 650.

16.5 Publication and Data Sharing Policy

Publication of the results of this study will be governed by ATN policies as outlined in the ATN MOGO. Protocol Team members will make any presentation, abstract, or manuscript available for review by the ATN leadership prior to submission. The NIH Public Access Policy ensures that the public has access to the published results of NIH-funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. Further, the policy stipulates that these papers must be accessible to the public on PubMed Central no later than 12 months after publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this study will be registered at ClinicalTrials.gov, and results from this study will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

Information about this study, including study results, will be published without further permission from the participant as detailed in the ICF. Participants will not be identified in any publications or presentations made about the study.

16.6 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this study will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this study. The ATN leadership, in conjunction with NICHD, has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

17. Data Handling and Record Keeping

The SC Project Lead is obligated to conduct this study in accordance with OHRP 45 CFR Part 46, ICH GCP guidelines, and all applicable Federal and state laws. The SC Project Lead is responsible for informing the IRB of any safety issues related to the study, as required by their local IRB.

17.1 Data Management

17.1.1 Case Report Forms

The SDMC, in collaboration with the Protocol Team, is responsible for the development of the CRFs needed to collect the information required to implement this protocol. The SDMC will develop an EDC system for remote data entry by staff at the SCs.

Study monitoring data, including information about eligibility, demographic data, and safety events, will be documented in the EDC system. Sample CRFs for this study will be available for download from the ATN SDMC website. The sample CRFs are for reference and should not be used as source documentation.

eCRFs must have corresponding source documentation on file at the SC to substantiate all submitted data (per Division of AIDS Source Documentation Guidelines, see ATN MOGO), unless via ePRO or questionnaires read to the participant by site staff, which are direct data entry. Each participating SC will maintain appropriate medical and research records for this study, in compliance with ICH E6 (R2), Section 4.9, 21 CFR 312.62, and regulatory and institutional requirements for the protection of confidentiality of participants. Each SC will permit authorized representatives of the Sponsor, its designees, and appropriate regulatory agencies to examine (and, when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. These representatives will be permitted access to all source data, which include hospital records, clinical and office charts, laboratory notes, memorandums, participants' memory aid or evaluation checklists, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, and participant files and records kept at the laboratories and medico-technical departments involved in the study. Data edits through range checks and field inconsistencies will be built into the EDC system to enable real-time correction of key entries and eCRF completion errors.

ATN SCs must follow guidelines for eCRF completion and entry that are specified in the ATN 170 eCRF Completion Guide. The SC Project Lead is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. For paper-based forms, permanent ink is required to ensure clarity of reproduced copies. When making a change or correction, the original entry should be crossed out with a single line, and the change should be initialed and dated. Staff should not erase, overwrite, or use correction fluid or tape on the original.

Data reported on the eCRF should be consistent with the source documents, or the discrepancies should be documented. ATN will provide guidance to SC study staff on making corrections to the eCRFs.

Each SC is responsible for entering data into the EDC system. All data must be entered into the EDC system according to timelines specified in the ATN 170 eCRF Completion Instructions.

17.1.2 Security for Electronic and/or Web-Based Data

Clinical data (including AEs/SAEs) will be entered into a 21 CFR Part 11-compliant web-based EDC system provided by the SDMC. The EDC system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

Some data will be collected via ePRO, a web-based platform for collecting data via direct data entry. The ePRO system can be used with an electronic device (computer, tablet, or phone). A detailed description of the ePRO system is available in the ePRO User's Guide.

Pre-Screening Data: The Qualtrics survey platform will be used to collect pre-screening information from potentially eligible participants. These systems will be developed to ensure that guidelines and regulations surrounding the use of computerized systems used in clinical trials are upheld.

eConsent Data: The ClinOne eConsent and Consent Management Platform will be used to obtain eConsent from potentially eligible participants. ClinOne is a secure, encrypted, web-based, HIPAA and 21 CFR Part 11 compliant platform compatible for use on various devices (website, tablet, or phone).

17.1.3 Data Records

All participant-related study information will be identified through the participant ID on all CRFs, laboratory reports, clinical assessments, and questionnaires (paper and electronic). Names and other personal identifiers will not be used on any of these study documents. Study documents will be kept locked in a limited access area accessible only to SC study staff and representatives from the NICHD and regulatory authorities (e.g., local IRB, Sterling IRB).

Original source documents for individual participants will be maintained at the respective site and will be accessible only to ATN study staff and representatives from the NICHD and regulatory authorities.

The participant's contact information will be securely stored at each SC for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by Sterling IRB, the local IRB, institutional policies, and/or Sponsor requirements. Both the SC Project Lead and the institution at which the study is conducted will hold responsibility to maintain custody of all study records until the Sponsor permits their destruction.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the SDMC. Individual participants and their research data will be identified by a unique participant ID. The study data entry and study management systems used by SCs and the ATN research staff will be secured and password protected.

See Section 5.2.1 for details on Participant ID tracking and screening data.

Individuals who consented to participate in the study but do not complete the screening process or who complete the screening process but do not enroll in the study will have information collected on the Screening Form, which will be entered into the EDC system using a method to maintain anonymity (as outlined in Section 5.2.1):

- Participant ID will not be assigned to these individuals;
- PII will not be collected on this form;
- Individuals will not be listed on any log that could link unique identifiers to individual names; and
- No source documentation will be maintained by the SC staff.

17.2 Data Handling

The SC Project Lead is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Permanent ink is required to ensure clarity of reproduced copies. When making a change or correction, the original entry should be crossed out with a single line, and the change should be initialed and dated. Do not erase, overwrite, or use correction fluid or tape on the original.

Data reported on the eCRF should be consistent with the data collection form/source documents, or the discrepancies should be documented. The Sponsor and/or its designee will provide guidance to the SC Project Lead and their study staff on making corrections to the data collection forms and eCRFs.

17.3 Data Management Responsibilities

All study data must be reviewed by the clinical team and data entry staff, who will ensure that they are accurate and complete. AEs must be graded, assessed for severity and causality by a licensed clinician, and reviewed by the SC Project Lead or designee. Data collection is the responsibility of the SC staff under the supervision of the SC Project Lead. During the study, the SC Project Lead must maintain complete, current, and accurate documentation for the study.

The SDMC for this study will be responsible for data management, quality review, analysis, and reporting of the study data.

17.4 Data Capture Methods

Clinical data (including AEs) will be entered into a 21 CFR Part 11-compliant web-based data capture system provided by the SDMC. The EDC system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents unless via ePRO or questionnaires read to the participant by site staff, which are direct data entry Some data will be collected via ePRO, a web-based platform for collecting data. The ePRO system can be used with any electronic device (computer, tablet, or phone). A detailed description of the ePRO system is available in the ePRO User's Guide.

17.5 Types of Data

Data for this study will include screening demographics, social determinants of health, behavioral and reproductive health, medical and medications history, enrollment, laboratory

evaluations, participants survey and questionnaires, assessments for participants discontinuing from the study or from study intervention, efficacy assessments, and safety assessments.

17.6 Timing/Reports

The DSMB will convene and make recommendations on study continuation based on the safety data collected periodically.

17.7 Study Records Retention

Records and source documents pertaining to the conduct of the study (including CRFs when used as source, medical records, consent forms, or laboratory test results), must be retained by the SC Project Lead for a period of at least 3 years after the date upon which the final study report has been sent to NICHD, or in accordance with the SC institutional requirements, whichever is longer. The date of filing the final study report will be published on the ATN website for the SC Project Lead's reference.

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Appendices

Appendix 1 Schedule of Events

Activity	Pre-Screening/ Enrollment[1]	On-Study		Premature Discontinuation
		Weekly	Months 4[2], 8[3], and 12[4]	
Online pre-screener	x			
General				
Administer informed consent*	x			
Confirm eligibility*	x			
Enroll participant*[,5]	x			
Review/update Contact Information Worksheet*	x		x	x
Evaluate for social harms, AEs, SAEs, and UPs	x		x	x
Measures and Assessments (See Appendix 2 for full list)				
Staff-administered	x		x	x
Self-administered	x		x	x
Exit interview			x[6]	x[6]
Behavioral Activation and Risk Reduction Counseling (all enrolled participants)				
HIV sexual RR (2 sessions)[7]		x[8]		
Randomization[9]		x		
Behavioral Activation and Risk Reduction Counseling (IMPACT arm only)[8]				
Introduction to BA: Orienting, rationale, and information gathering (1 session)		x		
BA integrated with RR counseling (6 sessions)		x		

Activity	Pre-Screening/ Enrollment[1]	On-Study		Premature Discontinuation
		Weekly	Months 4[2], 8[3], and 12[4]	
Review strategies for slip-ups and recurrence management (1 session)		x		
Measures and assessments (See Appendix 2 for full list)		x		
Study Intervention Administration and Fidelity				
Working Alliance Inventory-Therapist Report		x[10]		
Fidelity Form		x[11]		
Biospecimen Collection (See Section 7.2.3 and Section 11.1 for biospecimen sources)				
POCT testing	x		x	x
Local lab testing[12]	x		x	x
Central lab testing	x		x	x

[1]In-person participants may complete this visit in 1 day or 2 separate days. Virtual participants will complete this visit in 2 or 3 separate days. For the virtual participants, the items listed with a * will be completed on Day 1 of the Enrollment Visit, with the remaining items completed on Day 2 or Day 3 of the visit. The separate visit days do not need to be consecutive, as long as the last visit day is within 28 days of pre-screener completion.
[2]The Month 4 visit may be conducted as early as 21 days before or 60 days after the target date. If randomized to the intervention arm, a participant is not required to finish all intervention sessions to complete the Month 4 visit, however, once this visit is conducted, no further intervention sessions can occur.
[3]The Month 8 visit may occur ± 60 days of the target date.
[4]The Month 12 visit may occur 61 days before or 42 days after the target date.
[5]Must occur within 28 days of the completion of the pre-screener.
[6]This is completed at Month 4 or Premature Discontinuation, for selected intervention participants only.
[7]The first RR session is to be completed within 28 days of the last day of the Enrollment Visit; the second RR session is to be completed within 14 days of the first session.
[8]Scheduled approximately 1 week apart. If a scheduled intervention appointment is missed, study staff will attempt to reschedule the appointment for later in the week. If needed, two intervention visits may occur in the same week, with at least 2 days in between.
[9]Randomization must occur within 42 days of the last day of the Enrollment Visit, and after the first two RR sessions are complete.
[10]Completed one time by the interventionist immediately following the last weekly intervention session.
[11]Completed by the Central Coordinating Research Team for at least 10 percent of the sessions, and/or at least one session per week for each interventionist.
[12]For in-person participants only.

Appendix 2 Measures and Assessments

Survey or Questionnaire	Enrollment	Weekly[1]	Month 4	Month 8	Month 12
Staff-Administered					
1-Mini International Neuropsychiatric Interview (MINI) (select modules)	x				x[2]
2-Timeline Follow Back*	x		x	x	x
3-Substance Use*	x		x	x	x
4-Stimulant Use*	x		x	x	x
5-Penn Alcohol Craving Scale (PACS) – Adapted for Methamphetamine*	x		x	x	x
6-Behavioral activation for depression scale (BADS)*	x		x	x	x
7-Stimulant Use Motivation*	x		x	x	x
8-Post-Exposure Prophylaxis (PEP) Awareness and Use	x		x	x	x
9-Social Support (OSLO-3)	x		x	x	x
10-Sexual Minority Stress	x		x	x	x
11-Stimulant Use & Treatment*	x		x	x	x
12-Participant Resource Utilization Questionnaire	x		x	x	x
13a-Participant Cost Evaluation Questionnaire[1]		x			
13b-Patient Health Questionnaire-2 (PHQ-2)[1]		x			
13c-Behavioral Activation Questionnaire[1]		x			
Self-Administered					
14-HIV/STI Testing*	x		x	x	x
15-PrEP Use and Adherence*	x		x[3]	x[3]	x[3]

Survey or Questionnaire	Enrollment	Weekly[1]	Month 4	Month 8	Month 12
16-Adherence Self-Efficacy Scale for PrEP (PrEP-ASES)[3,*]	x		x	x	x
17-HIV Care Cascade[4,*]	x		x	x	x
18-HIV Treatment Adherence Self-Efficacy Scale (HIV-ASES)[4,*]	x		x	x	x
19a-Demographic and Baseline Characteristics*	x				
19b-Demographics Follow-up*			x	x	x
20-Perceived Stress Scale (*PSS-10*)	x		x	x	x
21-Sexual Behavior*	x		x	x	x
22-Sexual Risk*	x		x	x	x
23-Condom Use Self-Efficacy*	x		x	x	x
24-Center for Epidemiologic Studies Depression Scale Revised (CESD—R-10)	x		x	x	x
25-Childhood Sexual Abuse Scale (CSA)	x				
26-Client Satisfaction Questionnaire-8 (CSQ-8)[1]			x		
27-Resilience	x				
28-Stigma and Discrimination	x				
29-Acceptability Rating Profile[1]			x		
30-Working Alliance Inventory-Short Revised (WAI-SR)[1,*]		x[5]			

*Survey or questionnaire is related to the primary outcome.
[1]Intervention arm (IMPACT) only.
[2]Module J only – Substance Use Disorder (Non-Alcohol).
[3]Completed only by participants who report NLWHIV, are unsure of their HIV status, or decline to answer.
[4]Completed only by participants who report LWHIV.
[5]Completed one time immediately following the last weekly intervention session.