ATN 152

Triggered Escalating Real-time Adherence Intervention to Promote Rapid HIV Viral Suppression among Youth Living with HIV Failing Antiretroviral Therapy: The TERA Study

A Multi-Center Study Randomized, Controlled Trial of the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN)

Version 3.1

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Contents

Protocol Version History

Version	Date	Major Changes
1.0	21 Jul 2017	
1.1	10 Aug 2017	• Clarified that text messages will not use the clinic name or any reference to the participant's health status or diagnosis • Added Locator Form to Schedule of Evaluations to be collected at Baseline and Weeks 4,12, 24, 36, 48
1.2	18 Aug 2017	• Updated Site Roster to include Carrie Chambers, study coordinator at the University of Colorado-Denver. • Added pregnancy as an exclusion criteria. Pregnancy test (either blood or urine) will be performed to determine eligibility after consenting to study participation. • Modified screening procedures to include rescreening at a later date if a participant either did not return for enrollment within 45 days of latest VL assessment or if HIV VL was <200 copies. • Increased information collected in medical chart abstraction to include: VL, CD4, and pregnancy test. • Modified which visits have a required VL testing as part of the study rather than as chart abstraction to include Weeks 12, 24, 36, and 48 visits. VL testing at Week 4 can be abstracted from medical chart if done as standard of care, if not, it is not required at this visit. • Added pregnancy test (either blood or urine) prior to enrollment to the informed consent and parental permission informed consent and assent
1.3	06 Nov 2017	• Added Michael Hudgens as the ATN Coordinating Center Investigator • Updated Site Roster to include Maureen Garcia, study coordinator at UCLA • Replaced Site PI at Children's Diagnostic and Treatment Center, Inc. with Dr. Lisa-Gaye Robinson on the Site Roster. Removed all study coordinators except Amy Inman from this site. • Replaced study coordinators at St. Jude with Ryan Heine and Colin Quillivan on the Site Roster. • Added Ayanna Walters as study coordinator at Wayne State University on the Site Roster. • Changed timeframe for study enrollment to allow for an HIV VL test with HIV RNA ≥200 copies/m from 28 days prior to 45 days prior to enrollment. • Renamed 'Locator Form' to 'Contact Form.' • Lengthened time window from screening to enrollment visit from 28 days to 45 days

		• Modified VL testing windows for study visits to state: For follow-up study visits at Weeks 12, 24, 36, and 48, HIV-VL can be +/- 14 days from the Week 12 follow-up visit and +/- 28 days from the Weeks 24, 36, and 48 due date • Changed visit windows for Weeks 24, 36, and 48 Visits from a 14 day to a 28 day window • Changed Secondary Outcome Measures (from ± 14 to ± 28 days): HIV-1 RNA < 50 copies/ml. Participants with HIV-1 RNA ≥ 50 copies/ml or with no HIV-1 RNA measurement within ± 28 days of the scheduled visit will be classified as failures • Changed Secondary Outcome Measures (from ± 14 to ± 28 days): HIV-1 RNA < 200 copies/ml. Participants with HIV-1 RNA ≥ 200 copies/ml or with no HIV-1 RNA measurement within ± 28days of the scheduled visit will be classified as failures • Increased the number of efficacy analyses to take place after at least 60 participants have Week 12 HIV-1 RNA results available. • Requested a waiver of consent for the coaches and site staff interviews.Verbal consent will be given if the waiver is not granted. • Reported clinicaltrials.gov Identifier Number: NCT03292432
1.4	15 Nov 2017	• Modified language to include 'written' in the waiver of written consent for all coach and clinic staff interviews. • Added the Contact Form information to be collected at screening visit and removed this form from the Week 48 Visit. • Added the Verbal Consent Form for Staff Interviews.
2.0	21 May 2018	• Modified language of the 'boot camp' approach of the intervention • Added details for the secure audio recording software and subsequent audio storage. • Updated tables 1 and 2 (Triggered Two-way Outreach and Check in Outreach contacts) to reflect the dash functionality. • Updated timeline for contacting participants who have been out of contact to a 7 day period. • Added Protocol Deviation reporting and tracking • Modification to inclusion criteria to allow for inclusion of youth failing on any line ART regimen provided regimen is once daily. Daily can involve more than one ARV medication. • Removed option for TERA arm particpants to disable the 1-way reminder text near their dose time. • Updated protocol team roster and site personnel
3.0	06 Mar 2019	• Edited Monitoring Untoward Events section to refer to monitoring both Safety Events and Untoward Events. The section

		also refers to using Chapter 10 of the ATN Manual of Policies and Procedures for Safety Event/Untoward Event definitions, reporting, and grading requirements. • Removed UCLA and UAB from Site Roster. • Added Emory University to Site Roster. • Clarified in Enrollment visit procedures that pregnancy test must occur on day of enrollment. • Added sIRB approved telephone script as recruitment method. • Clarified that the enrollment visit may not be a split visit.
3.1	12 Jan 2020	• Updated protocol team roster and site roster. • Updated email address for Barbara Heckman. • Specified location of UNC sIRB SOP 1401: Reporting New Safety Information on the ATN secure website. https://sites.cscc.unc.edu/atn/tera-grouped • Made minor punctuation, spacing, header, and formatting changes. • Revised 9.4.3 to reflect that staff will only complete interviews and not surveys • Revised 11.6.3.6 to clarify that the coaches and site staff will be interviewed at the end of the intervention phase.

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List of Abbreviations

ADMQ	Adolescent Decision Making Questionnaire
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Transaminase
ART	Antiretroviral Treatment/Therapy
ARV	Antiretroviral
ASSIST	Alcohol, Smoking and Substance Involvement Screening Test
AST	Aspartate Aminotransferase
ACASI	Audio Computer-Assisted Self-Interview
ATN	Adolescent Medicine Trials Network for HIV/AIDS Interventions
ATN MOPP	ATN Manual of Policies and Procedures
BID	Twice per Day
cART	Combination Antiretrovial Treatment/Therapy, cART and ART will be used interchangeably
CBC	Complete Blood Count
CC	Coordinating Center
CE	European Conformity (Conformité Européene)
CEPAC	Cost Effectiveness of Preventing AIDS Complications
CES-D	Center for Epidemiologic Studies Depression Scale
CFR	Code of Federal Regulations
CRF	Case Report Form
CRF	Case Report Form
CSQ-8	Client Satisfaction Questionnaire
DHHS	Department of Health and Human Services
DNA	Deoxyribonucleic Acid
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDM	Electronic Dose Monitoring Device
EQ-5D-Y	EuroQol 5 Dimensions Questionnaire – Youth
ERQ	Emotional Regulation Questionnaire
FAQ	Frequently Asked Question
FDA	Food and Drug Administration
FSTRF	Frontier Science and Technology Research Foundation
FTE	Full Time Equivalent
GCP	Good Clinical Practices
GMS	Global System for Mobile
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HIV-VL	HIV Viral Load
HX	History

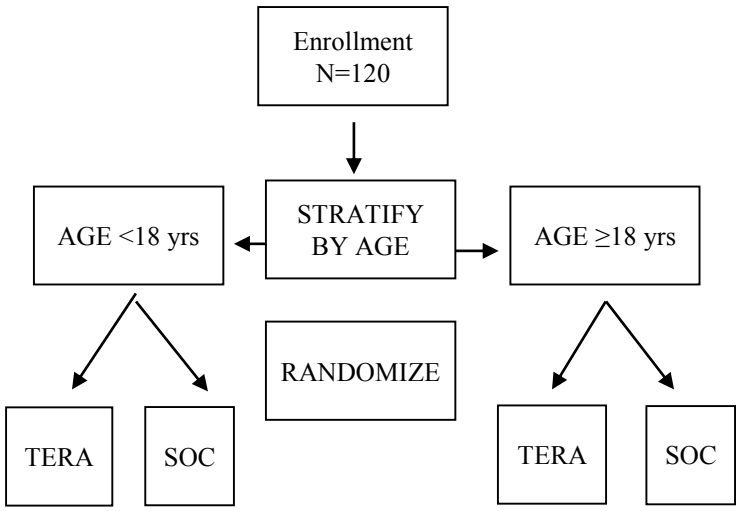
IATA	International Air Transport Association
ICF	Incofmed Consent Form
ICH	International Conference on Harmonization
ICH E6	International Conference on Harmonization Section E6 – Good Clinical Practice
ID	Identification
IDI	In depth interview
IMB	Information, Motivation, Behavioral Skills Model
IMB-AAQ	Information Motivation Behavioral Skills ART Adherence Questionnaire
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Network
IRB	Institutional Review Board
IND	Investigational New Drug
IoR	Investigator of Record
ITT	Intent-to-Treat
LES	Life Events Scale
LPC	Laboratory Processing Chart
MI	Motivational Interviewing
MOP	Manual of Procedures
MOS	Medical Outcomes Study
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Development
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NIMHD	National Institute on Minority Health and Health Disparities
OHRP	Office of Human Research Protections
OI	Opportunistic Infections
PCR	Polymerase Chain Reaction
PID	Participant Identification Number
QA	Quality Assurance
QNS	ATN Query and Notification System
RE	Regulatory Entity
RNA	Ribonucleic Acid
RX	Prescription
SAP	Statistical Analysis Plan
SDAC	Statistical Data Analysis Center
SES	Subject Enrollment System
SID	Study Identification Number
sIMB	situated-application of the Information Motivation Behavioral Skills Model
sIRB	single Institutional Review Board
SJCRH	St. Jude's Children's Research Hospital
SMC	Study Monitoring Committee
SMS	Short Message Service
SOC	Standard of Care

SOP	Standard Operating Procedures
SSL	Secure Sockets Layer
TERA	Triggered Escalating Real-time Adherence Intervention
UNC-CH	University of North Carolina at Chapel Hill
US	United States
VL	Viral Load
VLS	Virologic suppression (HIV-1 RNA at <50 copies/mL or <200 copies/mL as specified)
YLWH	Youth Living With HIV

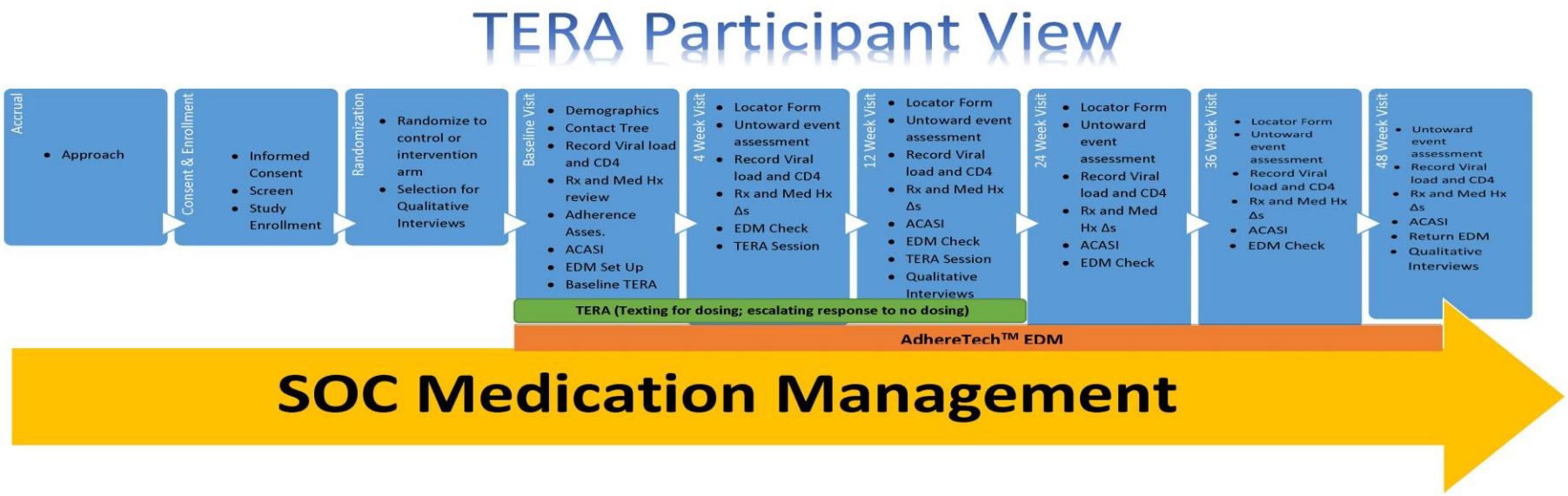
Study Abstract

DESIGN:	Phase II, two-arm, randomized, open-label study. Participants will be stratified by age (<18 vs. ≥18 years of age) and randomized with equal probability to receive either the TERA intervention or standard of care (SOC). Participants will be followed for 48 weeks.
DURATION:	Approximately 96 weeks total. Participants will be followed for 48 weeks.
SAMPLE SIZE :	120 youth living with HIV (YLWH)
POPULATION:	The study will enroll HIV infected youth 13-24 years of age (inclusive) failing antiretroviral therapy (ART) defined as HIV RNA PCR ≥ 200 copies/mL at least 24 weeks or more since being prescribed ART.
STUDY INTERVENTION:	The triggered, escalating, real-time adherence (TERA) intervention is a time-limited (12 weeks) approach that includes education and motivational skills building from an adherence coach, and monitoring with wireless electronic dose monitoring (EDM) for identification of delayed and missed doses and related alerts and coach phone-based outreach.
STRATIFICATION:	Age (<18 years vs. ≥18 years)
DATA COLLECTION:	Data will be collected through EDM, ACASI, chart abstraction, eCRFs, project implementation dashboard, AdhereTech (EDM), secure audio program recordings , and ATN Query & Notification System (QNS).
PRIMARY OBJECTIVES:	To estimate and compare HIV virologic suppression rates in YLWH 12 weeks after initiating TERA or continuing SOC.
SECONDARY OBJECTIVES:	To estimate and compare virologic suppression rates in YLWH at 24, 36 and 48 weeks after initiating TERA or continuing SOC. To estimate and compare proportions of participants initiating TERA or continuing SOC who achieve virologic suppression by 12 weeks and maintain virologic suppression though 48 weeks. To summarize and compare ART adherence patterns in YLWH initiating TERA or continuing SOC during the intervention period (weeks 0-12) and the post intervention period (weeks 12-48).
RISK/BENEFIT CATEGORY:	Minimal
MONITORING SAFETY EVENTS	Routine team monitoring of any events of potential impact to participant's health or wellbeing are recorded as safety events. The study will rely on the ATN Query & Notification System (QNS), a real-time, web-based interactive reporting system. The protocol chair, study team, protocol manager, and program officials will review all new safety events.

Overview of Study Design and Randomization



Overview of Intervention and Data Collection



Requirements for Site Participation in Protocol

This study is open to US International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) and Adolescent Medicine Trials Network (ATN) for HIV/AIDS Interventions sites with the following minimum requirements in order to participate:

Ability to enroll in a one-year period a minimum of five youth (13-24 years of age inclusive) with human immunodeficiency virus (HIV) infection failing antiretroviral therapy (ART) defined as plasma HIV RNA PCR ≥ 200 copies/mL at least 24 weeks or more since being prescribed an effective ART regimen and meeting other inclusion criteria.

Have adequate private space for administration of Audio Computer Assisted Self-Interview (ACASI) and an internet-connected, web-cam enabled computer in a private location for remote intervention counseling through a two-way video conferencing software program.

Site Roster

Site PI	Study Coordinator(s)
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Study Management

Before the recruitment and enrollment of participants, the participating study sites must have local Institutional Review Boards (IRBs) enter into reliance agreements with the single IRB (sIRB) at the University of North Carolina at Chapel Hill (UNC-CH). All procedures and forms will be approved by the sIRB and additional steps required by their local IRBs should be completed as appropriate. In addition, study sites must receive protocol registration approval from the ATN Coordinating Center (CC). All original approved documents must be maintained at the clinical site.

All queries for this protocol should be sent to the ATN 152 project team using the ATN Query Notification System (QNS) accessible via the ATN secure website (https://sites.cscc.unc.edu/atn/). The appropriate team member will address the query generally within 2 business days via the ATN QNS and copy the other team members. The Protocol Manager, with the help of other ATN CC personnel, FSTRF staff and/or NICHD, if necessary, will answer general protocol implementation, eligibility, and CRF completion questions. The Protocol Chair or her designee will respond to study and participant management, exemptions and/or safety event queries. Queries and replies will automatically be archived through the ATN QNS at the CC. The protocol manager will post queries and responses deemed relevant to all sites as a frequently asked questions (FAQs) on the ATN secure website, where they will be available for future reference.

This study will use the Audio Computer-Assisted Self-Interview (ACASI) to collect study data. All questions related to the ACASI should be directed to the FSTRF user support group usersprt@fstrf.org. FSTRF User Support is available 24 hours a day, 365 days a year with the exception of the holidays which will be provided to sites to ensure no research activity on those days and/or appropriate back-up plans as needed. Please contact User Support and provide a detailed description of the problem encountered. Phone: 716-834-0900 x7302
Email: user.support@fstrf.org.

For protocol registration issues, contact the ATN CC at ATN152CC@unc.edu.
For remote data capture issues, contact Barbara Heckman at bheckman@frontierscience.org.

1 INTRODUCTION

1.1 Background

Of the 35 million people living with HIV worldwide, 7 million are below the age of 24. With the concerted efforts to increase viral suppression globally and through strategic national plans, the unique sequela of youth living with HIV (YLWH) requires specific attention. Successful progression through the continuum of HIV care is poorer among adolescents than adults in the US, with as many as 43% failing to reach and sustain HIV viral suppression (VLS).[1] A sizable minority of adolescents and adults who start antiretroviral therapy (ART) fail their first-line ART and require transition to second-line ART, while others are re-started on their first-line regimen if that regimen is still effective. The odds for continued failure is significantly higher for those who fail first-line, particularly those moved to second-line ART due to non-adherence.[2-3] Moreover, evidence suggests that second-line ART failure is not explained by resistant virus for many.[4] Thus, without intervention, failing on ART signals increased potential for on-going failure. For YLWH in the US, there are multiple second- and third-line ART options, however the costs and burden are often high and without intervention, repeated failure due to ongoing adherence problems is not uncommon. Recent international work found a higher first-line ART failure rate among middle, versus early, adolescent Thai youth, 10.8 versus 7.4 per 100 patient years[5]; each higher than the average adult rate. Some 31% of adults demonstrate poor adherence to second-line ART regimens,[3] which is likely even more dramatic in youth. The call for interventions to improve adherence, particularly among YLWH failing first-line ART,[6] is well understood but remains largely unanswered.

Despite considerable advances in promotion of adherence and factors associated with it (e.g., retention in HIV care) in adult populations, the evidence base for interventions to promote adherence in YLWH remains sparse and largely inconclusive.[78] Skills building may offer promise,[9] and previous pilots with YLWH have supported problem-solving counseling using cell phones.[10] Specific to adherence to second- or third-line ART, interventions are near absent from the evidence base. International work with adults living with HIV reported null findings for a partner-administered directly observed therapy approach[11] while a multi-component intervention approach including problem-solving counseling[12] was effective on viral suppression. Given that youth are in developmental phases that are known to challenge the kinds of skills needed for adherence-related motivation and skills, we propose combining evidence-informed strategies (e.g., phone based problem solving counseling[10]; wireless drug monitoring with texts on delayed dosing [found effective for improving adherence in adults][13]) in an escalating intensity, triggered intervention approach.

To support YLWH failing ART due to non-adherence, this study will evaluate a novel, evidence-informed triggered, escalating, real-time adherence intervention (TERA) that leverages contemporary technology to address a key area of need as it relates to the care continuum of YLWH. TERA is a time-limited (12 weeks) intervention approach that (a) uses wireless electronic dose monitoring (EDM) to identify dose-times passing with no bottle opening, (b) sends a text

asking about the delay, (c) evaluates response to text and (d) initiates follow-up by an adherence coach depending on response and if the bottle remains unopened for a designated period post dosing. Phone based outreach will use problem solving discussion with an adherence coach, who can use an agreed-upon contact tree to reach the youth through other individuals. With the vast majority of youth on once-daily dosing (single-tablet formulations for first line and multiple tablets per dose for second-line), the intervention is tailored to youth prescribed once-daily dosing regardless of number of tablets in the regimen. The TERA intervention will be compared with standard of care (SOC) on HIV VLS at 12, 24, 36, and 48 weeks, EDM rates of ART adherence at the same time points, and patterns of adherence over time.

1.2 Prior Research/Current Evidence Base

1.2.1 Research and Care Sites

Among the sites participating in the TERA project, a diverse population of YLWH are served, with a sizable minority of youth failing ART therapy each year. A review of SOC for YLWH failing therapy suggests that all sites implement a medication management approach, where youth are advised on the importance of adherence, have a medication-taking plan developed or reviewed, and most are encouraged to use their cell-phones for alarm setting; some sites offer uni-directional text reminders sent at user-defined dose times automatically. Even in this context, optimal outcomes for YLWH failing ART are not realized for the majority of youth at 12-months. Our detailed exploration of progression from second line therapy to viral suppression at the St. Jude Children's Research Hospital (SJCRH), International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) site, identified that only 61% (53/87) of YLWH initiating second-line therapy achieved VLS at 3-months, and only 46% (40/87) at 1-year. Further, among youth who achieved VLS at 3-months, a progressive loss of suppression occurred at 6-months (15% lost VLS), 9-months (30% lost VLS) and 12-months (38% lost VLS). Durable VLS from 3-months through 12-months was obtained by only 38%.

Selected sites are well-positioned to implement the proposed research. Each site has a demonstrated history in the implementation of high quality/high rigor research protocols. Moreover, our polling of sites indicates a high interest in developing effective strategies for YLWH who fail to achieve or maintain VLS on daily dosed, effective regimens.

1.2.2 Technology Enhanced and Delivered Interventions

Evidence supports the use of technology enhanced interventions to promote medication adherence among those living with HIV.[14] Recent work with adults in Cape Town, South Africa evaluated an intervention approach that used text messages to signal late doses according to a Wisepill ™ device for first-line therapy ART.[15] Messages were received for 48 weeks and were the same selected message each time a dose was delayed by more than 30 minutes. These text messages included "Have you forgotten something," "Just take it!," gave the time, or sent just a study number. A slight reduction in treatment interruptions was reported, although overall adherence, retention in care, and viral suppression did appear improved for this cohort. Other

text-based strategies[16 17], that are not yoked to monitoring but are systematically sent, require a response from participants, and also seem to suggest that an interactive component is particularly beneficial.[18-19] Garofalo and colleagues recent work in this area with 105 adolescents and young adults where two-way daily texts were provided to non-adherent youth demonstrated a significant improvement in self-reported adherence and high satisfaction scores.[20] Furthermore, a pilot study using personalized, interactive, daily text messages demonstrated significant improvement among 14-to-29 year olds living with HIV with poor self-reported adherence rates.[21] Texting yoked to known delays in dosing, however, has not been rigorously evaluated with YLWH in a randomized, controlled trial.

The TERA study will utilize the AdhereTech™ smart wireless pill bottles to monitor participant medication adherence in real-time for those in the TERA intervention arm during the active implementation phase of TERA (12 weeks), and to document adherence over 48 weeks of study participation in all arms [AdhereTech Inc, 2015]. The smart pill bottle system was designed to address previous electronic monitoring tool shortcomings by simplifying the setup process, designing a bottle to be used like a regular bottle with a standard child-resistant cap, having flexible reminder options, and a long (6 month or more) battery life per charge. The AdhereTech™ device is a pill bottle that contains a worldwide cellular communication chip to allow for the bottle to passively send real-time adherence data when opened. The smart pill bottle sends an electronic medication event record to a central server that is stored on a secure server. AdhereTech's™ system also includes optional adherence promoting tools, including on-bottle lights and chimes as well as text and phone calls to participants that are delivered in real-time. Monitoring of dosing events is included for TERA participants for 12 weeks of active intervention implementation followed by data collection with the EDM for the remaining 36 weeks of study participation. During the project, participants in both arms will receive the pill bottle with the light-feature activated. The on-bottle light feature is a small band near the bottom of the pill-bottle (see Figure 1) that emits soft-blue light pulses 15 minutes prior to dose time if the bottle has not yet been opened around a dose-time and continues for a period of time after the dose time if the bottle remains unopened. This is intended to act as a 'soft' reminder. This feature is left active for all participants to enhance engagement with the EDM device. Youth in our advisory group noted this feature specifically as engaging and attractive. As one aspect of our work focuses on dose monitoring patterns over time, youth in each arm are encouraged to dose from the device for the duration of their participation. Allowing the dose-light feature across arms may help with engagement with the device and refines the active intervention to the components under evaluation – eHealth facilitated coaching in real time.

Other features of the pill-bottle EDM are available only to TERA intervention arm participants-which include a one-way text at dose time when the device was not opened around dose time and an outreach two-way text if the device remains unopened 1.5 hours past the expected dose time. Participants have the option of disabling the one-way text but cannot disable the SMS two-way (interactive) outreach text. These text messages will not use the clinic name or any reference to the participant's health status or diagnosis.

Dosing from the bottle is actively monitored only for TERA intervention arm participants only for their 12 weeks on the TERA intervention. Post-intervention for TERA intervention participants and for the full study for control arm participants electronic dose monitoring data is collected for analysis at end of study. Functionality of the bottles is monitored regularly for all participants throughout their 48 weeks of participation.

Available since 2013, AdhereTech™ (Figure 1) is currently being used by multiple industry and clinical research trials across a variety of disease and age groups including HIV. Aggregate data from AdhereTech™ Inc. suggest high levels of acceptability and feasibility across a diversity of treatment regimens (including HIV). Patient surveys among those using AdhereTech™ have also demonstrated an 88% satisfaction rate (e.g., satisfied or very satisfied) with the entire smart pill bottle system. Additionally, 92% of AdhereTech™ users reported the smart pill bottle was "easy to use." The bottle communicates wirelessly through cellular networks. Regulated by the FDA as a class 1 medical device, the entire system is HIPAA-compliant. The data display for aggregate and individual data is customized per project and can be used as well to send texts to adherence coaches when certain conditions (such as dose delays) occur. The device has received positive review from our youth advisory board, which is particularly important given our experiences with use of other EDM devices that did not receive positive reviews and had related issues in our use of them in clinical trials. We are confident that this EDM will avoid the user-fit issues we encountered with other larger devices.

Figure 1

1.2.3 Evidence for Phone-Based Outreach Problem Solving

Evidence has supported the utility of phone-based outreach using a problem solving approach.[10,12] In a recent review, harnessing mobile phone technology was identified as a promising area for future interventions encouraging optimal adherence among YLWH.[20] Furthermore, evidence suggests using phone-based technology to engage adolescent social support networks may promote optimal engagement in care and adherence to medications.[22] [22-23] A recent study of a phone-based support intervention among non-adherent YLWH found that it was acceptable and feasible among youth and clinic staff.[24] The TERA intervention will uniquely combine these aspects (distance counseling at the clinical research site on a site computer from an adherence coach using HIPAA compliant VSee (https://vsee.com/) remote counseling 'room' and phone-based problem solving from adherence coach linked to a real-time electronic adherence monitoring device) to promote optimal adherence among YLWH. Although phone-based outreach has been supported in pilot work, it has not been rigorously evaluated, nor has triggered outreach been evaluated, as evaluations to date have implemented the phone outreach based on time (e.g., daily, weekly) and not tethered to actual dosing patterns or potential problems. Additionally, the adherence coaches that will implement the phone-outreach are centrally located and are not part of the clinical care team at sites. This allows for dedicated counselors/coaches, may offer an elevated sense of privacy among youth,

and assures an on-call system for complete coverage during the intervention arm participants' 12 week engagement in the intervention. All correspondence is through VSee, calls, texts, or other approved media. The project requires coaches have a strong command of the English language- fluency in other languages is not required. Using a central 'coach' has a number of implementation and generalizability benefits, and fits well with the most common forms of communication use among youth presently (texting and cell-phone). Criteria for adherence coaches include past counseling experience and advanced training, history of working with youth, demonstrate high cultural humility and will engage in advanced MI training and supervision while coaching TERA participants.

1.2.4 Evidence for Theory-Based Drivers of ART Adherence in YLWH

The protocol team has considerable experience in social-behavioral modeling of adherence, as well as engagement in HIV-care- known to impact adherence and persistence. The protocol chair has co-developed the Information, Motivation, Behavioral Skills (IMB) model of ART adherence,[25] which has been used extensively in interventional adherence enhancement research.[26-27] Through a series of studies, the strength of the model, its core constructs, and structural relationships have been established through structured equation modeling in diverse groups.[27-29] Although the IMB-model and the situated-application of the model (sIMB)[30] were developed to speak to adherence and persistence across populations, the TERA study will be the first to apply a sIMB model to YLWH in the context of previous adherence failure. The study is well positioned to offer new insights on youth and the impact of their adherence-related information, motivation and behavioral skills on VLS, as well as patterns of dose-taking over the first 48 weeks.

1.3 Rationale

YLWH are at elevated risks for failure to achieve HIV viral suppression (VLS). Recent reviews suggest that a subset of youth achieve VLS post 48 weeks of ART at alarmingly low rates (27% to 89%).[31] Progression through the continuum of care for YLWH in the US suggests that only 6% are durably virally suppressed.[1]

The evidence base for strategies to support adherence and successful VLS in YLWH is lacking. The current evidence base is generally lacking in effective adherence improvement interventions for YLWH. Despite the fact that youth failing ART because of non-adherence are clearly at higher risk for repeated failure, the evidence base remains relatively silent on the issues, approaches, and facilitators/barriers for this at-risk group. For YLWH more generally, recent reviews provide limited evidence for effective interventions for adherence support. This study is responsive to this need specific to YLWH, exceeds standards for rigorous design, harnesses contemporary wireless technology and contributes to a higher quality evidence base.

Interventions developed specifically for YLWH are needed. With a limited evidence base dominated by pilot interventions for effective strategies to use when intervening with YLWH to support ART adherence, pulling from the adult intervention literature to guide approaches is not uncommon. However, considerable evidence suggests that youth are a unique cohort with unique needs. Although literature specific to adults failing first-line ART therapy suggests that gender (female) and delayed start of second-line therapy predict lack of suppression by 24-weeks,[32] research unpacking the complex socioecological factors influencing patterns of adherence to second-line therapy specifically focused on YLWH is sparse. The evidence base in characterizing first- or second-line ART failures and outcomes in resource limited settings[33] is growing, however such correlates may not generalize to YLWH in the US, nor do surface-level demographic factors provide direction of intervention opportunities. Thus, despite nearly two-decades of available effective ART, drivers of adherence for YLWH and how to best intervene to optimize adherence remain poorly understood.

From a developmental perspective, youth would likely benefit most from strategies that specifically bridge the gaps common during adolescence cause by normal neuro-cognitive development.[34] Enhancing salience of dosing through text cues, interactive texts, and ultimately human outreach as and when needed matches well with the added desired for autonomy characteristics in youth and concomitant need for connection and guidance (see Young and colleagues[35] for example). Challenges in executive functioning and cognitive abilities are common among infected youth, even prior to ART initiation.[36] Other factors, such as social support, impulsivity constraining prospective planning, lability, increased needs for autonomy, and identity development support an approach where intensive involvement in adherence is appropriate for a time-limited period. A time intensive approach allows for heavy involvement with youth failing ART in developing strong problem solving skills during the first 12 weeks of continuing, restarting or starting new ART regimens. A 'boot camp' approach offers the opportunity to develop strong skills and motivation, and autonomy through emphasis on problem solving (versus solution-giving) and self-efficacy in completing a time-limited intensive program, which is well-aligned to the developmental processes of youth.

The TERA study addresses gaps in our evidence-base and interventions for youth and will dramatically further the scientific understanding of critical factors in the pathway to ART adherence and success for YLWH on ART. The TERA study will considerably advance scientific understanding of the theory-based dynamics that influence ART adherence in youth. This work advances the number of options for highly generalizable strategies to optimize adherence among youth living with HIV (YLWH) known to have struggled with ART in the past. Interventions that are matched to maturational issues and demands of youth are critically needed. Further, TERA contributes to the understanding of ART adherence and non-adherence in this population at considerable risk for continued ART failure. We are well positioned to advance both science and practice and address ART adherence - a key component of the continuum of care for YLWH. Our research has identified an overall lack of rigorous adherence enhancing research, which has been echoed in a number of recent research syntheses.[722] Evidence for effective interventions for YLWH failing first-line ART regimens is even less well

represented in the literature. Although agencies and service providers are advised to adopt evidence-based adherence support strategies, there are no strong, rigorously tested interventions to consider. Three main strategies, well matched to the developmental and social context of adherence among youth, leveraged in the TERA intervention include electronic dose monitoring with real-time response, engaging youth in a short-term high-intensity program, and centralized adherence coaches.

Electronic dose monitoring, real time triggered interventions, and interactive and real-person phone-based outreach with use of a contact-tree are all novel components to adherence support that promise high impact. The existing evidence base will be leveraged to create a high-intensity, responsive, time-limited intervention approach. While texting has a strong evidence base for adults,[16,18,25] use with youth, while intuitively appealing given the widespread use of texting, remains supported largely with only pilot studies.[21] Similarly, phone-based problem solving discussion with adherence coaches has preliminary evidence[10] demonstrated in a pilot study. Our work leverages the wealth of pilot evidence to create an intervention approach with demonstrated promise but not yet rigorously evaluated. Of particular interest, our goal is to mesh together an evidence-informed approach that can also be generalizable. Given that sites and clinics working with youth will have limitations in resources, we adapted interventions implemented over extended periods of time to a discreet, intensive approach implemented over a 12-week period and intensified in report to delayed or missed doses. This creates a more generalizable program as resources required are similarly time-limited. The key pieces that make up the TERA intervention are largely in place; YLWH overwhelmingly have cell phones and clinic team members already use or will be trained in problem solving. A system for sending and receiving texts can be automated, with costs allocated towards building the system and minor costs for maintenance of system. If the intervention is effective, it could have an immediate impact on care services provided to YLWH failing ART who are continuing or restarting on a once-daily regimen and future applications to other points in the continuum of HIV prevention and care that depend on youth adhering to the applicable interventions.

Adoption of a time-limited high-intensity “boot camp” approach is innovative. Short but intensive health promotion approaches are now common in descriptions of professional training,[37-38] weight loss, and even diabetes control.[39] Present day sentiment among our youth towards the approach is largely positive, as associations with the term have moved from older and unsuccessful applications of correctional boot camps to wilderness and health/fitness boot camps. Review by our youth advisory group suggests support for the time-limited, intensive approach. For YLWH, a boot camp approach may offer the kind of assurance needed to allow for full engagement in an approach that is both demanding and involves monitoring, review and guidance. Autonomy is a high priority for many of our youth. Programs that allow youth to consider their involvement to be time-limited and the assistance to be similarly time-limited may arguably facilitate greater involvement than a program with no visible end. Moreover, there is a sense of accomplishment and success with completing an intensive course or “training” which can build efficacy and pride. Single session and brief interventions using motivational interviewing with youth have been effective in risk reduction in other health areas,

such as alcohol use.[40] While a longer intervention may be needed for YLWH failing ART, the appeal of a short yet intensive intervention that seeks to establish skills and the development and use of adherence promotion strategies that will persist beyond the intervention is clear.

Centralization of adherence coaches is also intended to uniquely apply to youth, where coaches may be considered more neutral and also can be available when needed. For the TERA intervention, while EDM devices are issued at point of clinical care and research activities (e.g., survey) are completed at clinic, the intervention itself is centralized and is not dependent on clinic staff or resources at clinic. Adherence coaches can be located anywhere geographically, as intervention components do not use in-person contact. Texting and phone-calls can be placed from any location. This allows for the intervention to be "stand alone", making it highly generalizable and replicable for youth throughout the US. However, because coaches can access and communicate with site staff, local resources for unmet needs and establishing referrals can be accomplished. Interventions using phone and web-based applications, versus face-to-face, are a growing area in mHealth technologies.

1.4 Hypotheses

- Youth in the TERA arm will be more likely to achieve viral suppression at weeks 12, 24, 36 and 48 compared to youth in the SOC arm
- Youth in the TERA arm will be more likely to achieve and sustain VLS than those in SOC arm
- Youth in the TERA arm will have higher rates of weekly dosing as measured by EDM over 48 weeks than those in SOC arm
- VLS and adherence will be associated with gains in adherence-related information, motivation and behavioral skills, which will be higher in youth in the TERA arm than those in the SOC arm
- Youth will report positive attitudes and experiences with the intervention content with themes emerging relative to adherence support that are unique from those in the control arm

2 STUDY OBJECTIVES

2.1 Primary Objective

- To estimate and compare HIV virologic suppression rates in YLWH 12 weeks after initiating TERA or continuing SOC

2.2 Secondary Objectives

- To estimate and compare virologic suppression rates in YLWH 24, 36 and 48 weeks after initiating TERA or continuing SOC
- To estimate and compare proportions of participants initiating TERA or continuing SOC who achieve virologic suppression by 12 weeks and maintain virologic suppression up to 48 weeks
- To summarize and compare adherence patterns (EDM) in YLWH initiating TERA or continuing SOC during the intervention period (weeks 0-12) and the post intervention period (week-12 and week-48)

2.3 Other Objectives

- To evaluate and compare changes in survey collected social-psychological factors by study arm, and establish the extent to which these changes are associated with adherence and viral load outcomes
- To identify profiles (phenotypes) of adherence based on EDM data
- To describe the resource requirements and costs of the TERA intervention, including the AdhereTech™ bottles, virtual coaching software, SMS messages, and personnel time and salaries
- To characterize through qualitative interviews, the main themes youth report for adherence support needed, received, and valued at 12 and 48 weeks
- To evaluate acceptability and feasibility of participation in the intervention with mixed methods (interviews and ACASI survey)
- To gather feedback from intervention coaches and clinic staff on experiences implementing the intervention with YLWH

3 STUDY DESIGN

This is a phase II, two-arm, randomized, open-label study. Eligible participants will have failed ART, defined as having detectable HIV virus (HIV-1 RNA ≥200 copies/ml) within 45 days of enrollment despite having been on ART for at least 24 weeks. They may be continuing the same ART regimen or starting a new once daily regimen. Participants will be stratified by age (<18 vs. ≥18 years of age) and randomized in equal proportions to receive the study intervention (TERA) or standard of care (SOC), with no enrollment limits in each stratum. Institutional balancing will ensure roughly equal numbers of participants in each study arm at each site. After being randomized to study arm, a second procedure will randomly select a subset of participants to engage in the qualitative interviews. To promote ART adherence, participants in the TERA intervention arm will receive an intensive, time-limited EDM-based intervention for a 12-week period. This "boot camp" strategy is used to unsettle or disrupt established non-adherence behaviors and factors promoting ongoing non-adherence. Participants will be followed for 48 weeks. Both arms will have data collected through the EDM throughout the study. Provided below is a brief description of main components of the trial with specific details provided in appropriate sections in the remaining sections of the protocol.

YLWH failing antiretroviral therapy (defined as having plasma HIV RNA PCR ≥ 200 copies/mL at least 24 weeks on ART) who are either continuing or restarting a once-daily ART regimen will be recruited from participating sites. Those who consent to screening and potential study participation and who meet the eligibility criteria will be enrolled and randomized. Participants will be issued an EDM bottle with training on use and charging provided. Those assigned to the TERA intervention will receive additional education about the intervention components they will be receiving for the next 12 weeks and will engage in the introduction session with the adherence coach via VSee in a private location at the clinic.

There will be six study visits (see Appendix I) -- baseline, 4, 12, 24, 36 and 48 weeks. Audio computer assisted self-interview (ACASI) survey data includes adherence related information, motivation and skills, with an emphasis on social support and perceived efficacy, depression assessment, mental and physical health functioning, and substance use. ACASI surveys occur at baseline, 12, 24, 36 and 48 weeks (section 3.3.6). The EDM device is issued at baseline. Only one medication will be stored and dispensed from their study assigned AdhereTech™ EDM bottle. For those on a one-pill daily ART regimen, the EDM will contain their complete ART regimen but for those on a multi-pill once-daily regimen, only one of them will be stored and dispensed from the EDM. Viral load data at weeks 12, 24, 36 and 48 will be collected; HIV viral loads done at these time points as per the site's SOC will be used but in the case that a SOC HIV VL is not done, site staff will order one specifically for ATN 152. In addition to granular data (e.g., exact time and date of all opening events) collected from EDM daily dosing, social-behavioral data will be collected via ACASI in 12-week intervals.

All youth (both the TERA and SOC arms) will be asked to dose from their AdhereTech™ EDM over the full 48 weeks of the study and therefore will be provided training on use of the EDM. A clinic team member will issue the device, assist participants who take multiple ARVs to identify

the one that will be stored in the device (participants are encouraged to pick the ART medication they anticipate most difficulty with), and record the dose time. Per protocol, participants will be on once-daily dosing. The decision to limit the intervention to youth on a once-daily dose schedule was based on information suggesting that youth in participating clinics are largely on once-daily regimens, even when on second-line regimens, and to streamline the intervention which has multiple active features linked specifically to dose-time. If the intervention is effective linked to the once-daily schedule, future work will consider impact when youth are negotiating multiple dose-times (eg., those on salvage regimens). FSTRF support phone line will be used to collect the data needed to activate a device and FSTRF staff will then enter the information on the AdhereTech™ dashboard. The device will likely be fully active for the next dose and at the longest 24-hours from set-up. The ATN 152: TERA Manual of Procedures (MOP) will detail the exact process the sites will use.

For YLWH who do not have their medication available for loading into the EDM at baseline, they will receive training and set-up but will be asked to load the device within 24-hours. These situations will be attended to on a case by case basis, however site-staff will call each YLWH who self-loaded the device outside of clinic within 24-48 hours to confirm the bottle is filled and answer questions. The EDM will collect dose (device opening) data for all participants centrally; only participants in the TERA arm will have their data automatically reviewed in real-time to identify delays or potential missed doses during the 12-week active intervention period. For youth in both the SOC arm and TERA arm after the 12-week intervention, data will be collected and stored for analyses. For all youth, the EDM data is not intended for use by the clinic site - rather, the data will be maintained centrally, and adherence coaches - also remote from the clinic site – working with youth in the intervention arm during the first 12 weeks of their participation will actively review and respond to EDM data. As such, the intervention will be evaluated as a “stand alone” approach. The research team will monitor EDM functionality and work with sites to replace or repair any EDMs that appear to be malfunctioning. The study project manager will monitor for malfunctioning devices on the dashboard throughout the study.

In addition to the TERA and standard of care control arm procedures, a subset of participants (20 in each arm) will be randomly selected to engage in in-depth interviews about their experiences at week-12 and week-48. Confirmation of desire to participate in the qualitative portion is requested at baseline (when randomly selected). The participant is expected to engage in both the week-12 and week-48 interview. Selection probabilities will be increased during accrual if refusal rates at week-12 are higher than expected. Every effort to engage week-12 interview participants in the week-48 interviews will be made- including phone based interviewing. Strategies to add new participants to the week-48 interviews will be considered if loss to follow-up reduces the originally selected sample size. To facilitate feasibility of collecting interviews, participant interviews can occur any time in the week-12 visit and week-48 visit windows after completion of study visit. (See Appendix I for visit window timeframes.)

Participants remain on-study for approximately 48 weeks with a window of ±28 days.

3.1 Study Population

This study will be conducted among approximately 120 YLWH at ATN and IMPAACT sites in the US. Each of these sites has existing populations of YLWH and will continue to receive new referrals over the course of the study through linkages to their communities. These sites are located in key cities around the US, representing areas of high rates of newly infected and high-risk youth. Participants will be selected for the study according to the criteria in Sections 4.1 and 4.2 and the guidelines in Section 4.3.

4 SELECTION AND ENROLLMENT OF STUDY PARTICIPANTS

4.1 Inclusion Criteria

Potential participants must meet all of the following criteria in order to be included in this study:

1. Age 13 through 24 years (inclusive)
2. Confirmation of HIV-1 Infection as documented in the participant's medical record by at least two of the following criteria:
    a. Reactive HIV screening test result with an HIV antibody or HIV antibody/antigen-based, Food and Drug Administration (FDA)-licensed assay followed by a positive supplemental assay (e.g., HIV-1 Western Blot, HIV-1 indirect immunofluorescence, HIV-1/HIV-2 discriminatory immunoassay)
    b. Plasma HIV-1 quantitative ribonucleic acid (RNA) assay >1,000 copies/mL
    c. Positive HIV-1 deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) assay
    d. Positive plasma HIV-1 RNA qualitative assay
3. Participant aware of his or her HIV infection, as determined by site staff
4. Documented plasma HIV-1 RNA plasma ≥200 copies/mL within 45 days of the date of the enrollment visit
5. Prescribed antiretroviral therapy for at least 24 weeks or more prior to documented plasma HIV-1 RNA plasma ≥200 copies/mL.
6. Prescribed a once-daily (one or more pills once a day) ART regimen with at least two active agents (per clinician judgment or genotype evidence) at enrollment
7. Able to communicate in spoken and written English
8. Currently has a cellular phone that is also able to send and receive text messages
9. Willing and able to provide at least one additional contact phone number (preferably two) to contact participant
10. Able and willing to provide written informed assent/consent and able to obtain written parental or guardian permission (if required as specified by the site, by state law, and/or IRB policy, and detailed in each site's Protocol Implentation Plan [PIP])to be screened for and to enroll in this study

4.2 Exclusion Criteria

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

1. Gross cognitive limitations, acute emotional instability, or medical or mental health illness that in the opinion of site personnel would impair the individual's ability to provide informed consent and/or interfere with the protocol's objectives.
2. Concurrent participation in interventional studies addressing adherence unless approved in advance by study team

3. Positive pregnancy test at the time of enrollment. If participant becomes pregnant while on study, they may continue on study
4. Currently using or planning to use an electronic dose monitoring and reminder device outside of the study

4.3 Recruitment

Sites will generate a list of potentially eligible participants based on medical chart review. Potential participants will be approached for the study through the clinics by trained clinic staff, research staff or other means, as the per the site's recruitment strategy. Sites may also use the sIRB-approved recruitment flyers to identify interested participants. To contact current clinic patients who have been out of care for some time, sites may use the sIRB-approved telephone scripts to gauge potential interest in the study and conduct a few pre-screening procedures. Potential participants will need to visit the site to complete a formal screening.

Potential participants will be informed of the nature of the study, the information to be collected, and the evaluations and assessments that are involved. No procedures, other than preliminary verbal assessment of eligibility or medical chart review to assess potential eligibility, are included in initial screening.

Those who are approached for participation, outcomes of approach (accept, decline, reasons for decline) will be recorded in the ***recruitment log***. This log may include name or initials, date of birth or age, birth sex, race, and ethnicity and will be stored in a secure location at site. See the appendix of the current MOP for the recruitment log. When study accrual ends, site study staff will remove all names or initials and dates of birth belonging to individuals who did not consent to participate in the study. The protocol team may request tabulated information on individuals who participated in the recruitment process, but did not provide informed consent and the reasons these individuals refused to participate. These data will provide general information on the population that is recruited at the study site.

Those who are approached and express interest may lack viral load data in their charts that are within the acceptable time interval for eligibility. In these cases a viral load test supported by the study will be obtained. In addition, a pregnancy test (blood or urine) supported by the study will be obtained, if not included in standard of care. Consent for study participation must be obtained prior to study-supported viral load test and/or pregnancy test.

4.4 Study Informed Consent and Screening

Potential participants meeting study criteria will engage in full consent procedures for study participation. Study details will be discussed, and questions answered during the informed consent process. Signed informed consent from the individuals or assent with signed parental permission, as determined by the sIRB (and local IRBs where required), will be obtained before any study related medical chart data are recorded or study procedures are performed.

A waiver of parental/legal guardian consent will be requested from the sIRB given that minor

individuals often seek HIV care and treatment without parental/legal guardian permission, depending on each site's state laws.

After consent, the site uses one of its participant identification numbers provided by the study to enter all screening data into the Subject Enrollment System (SES). At the end of screening, eligible participants are enrolled (see section 7.1 and 7.2). If a participant fails screening for any reason, the ATN152 ***Screening Failure form*** is completed using the screen number provided by SES and the PID used is retired from the site's list of available TERA participant IDs, unless this participant is rescreened at a later time.

4.5 Contact Information

Once consented, designated study staff will complete the ATN 152 Contact Form with the participant. Participants will be asked to provide contact information where they can be reached. Participants will also be asked to provide valid contact information for a family member and/or friend who can be contacted in the event the participant cannot be reached. Participants will be asked if voice and/or text messages can be left at the numbers provided. Study staff will not leave any messages unless expressly permitted to do so by the participant, which will also be documented on the contact form. If permission is given to leave messages, site staff will assure participants that messages left with a family member and/or friend will only ask the participant to contact study staff and will not include any protected health information or information related to study participation. We will also ask participants what message they would like for us to leave and how we should identify ourselves.

The ATN 152 Contact Form will not contain any study data and will be securely maintained at the study site, separate from all study records, with access limited to designated site research personnel.

4.6 Participant Retention

Once a participant is enrolled in this study, study staff will make every effort to retain him or her for the protocol-specified duration of follow-up, thereby minimizing potential biases associated with loss to follow-up. Each site must establish and outline study specific procedures in their Protocol Implementation Plan (PIP) that target retention rates that are sufficient to allow the primary study outcomes to be reliably estimated (a maximum 10% loss to follow-up). Refer to Section 9.5 for more information on monitoring participant retention in this study.

4.7 Participant Withdrawal or Termination from the Study

Regardless of the participant retention procedures referenced above, participants may voluntarily withdraw from the study. Participants may also be terminated from the study by the site investigator or designee under the following circumstances:

- Participant re-locates away from the study site or is otherwise determined to be lost to follow-up
- Investigator or designee determines that continued participation in the study would be

unsafe or otherwise not in the best interest of the participant, after consultation with the protocol team

- The study is stopped or canceled by the sponsors, government or regulatory authorities, or sIRB.

For any participant who withdraws/is withdrawn or is terminated from the study prior to scheduled completion of follow-up, study staff will document the reason for the withdrawal or termination in detail and will make every effort to complete final evaluations as described in Section 7.7. In the event that the circumstances that led to a participant's withdrawal or termination change (e.g., he or she returns to the study site area after having re-located previously), the site investigator or designee should contact the protocol team to discuss options for resumption of follow-up.

4.8 Co-enrollment Guidelines

Concurrent participation in studies addressing adherence interventions is not permitted. 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 prior to implementation of 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 chair using the ATN Query and Notification System (QNS) located on the ATN website (https://sites.cscc.unc.edu/atn/).

5 STUDY PROCEDURES

The Schedule of Evaluations (Appendix I) provides a timeline of when each study visit/activity/etc. is to be performed.

5.1 Enrollment Procedures

Enrollment must occur no more than 45 days after the screening visit. Screening and enrollment can occur (and is preferable) on the same visit, conditional on availability of an HIV VL ≥ 200 copies/mL within the prior 45 days[1].

The Frontier Science Data Management Center Subject Enrollment System (SES) will be used to assist with tracking the screening and enrollment process. When informed consent is obtained for the study, a participant identification number (PID) is assigned by the site using a study specific PID list and is used to enter all screening information into the SES. This PID remains with the participant and is only reused if a potential participant rescreens. If the same potential participant is rescreened at a later time the same PID should be used and a different screening number should be obtained Successful screens generate a Study identification number (SID) that is used for internal data management procedures and is linked to the PID for study procedures detailed below. For participants who are found to be ineligible for the study, or who do not enroll in the study for any reason, an eCRF (screening failure form) will be completed to record the screening outcome using the screen number provided by SES as an identifier.

5.2 Randomization Strategy and Procedures

Participants will be randomized to the TERA or SOC study arms using the Frontier Science Data Management Center's SES. Immediately after randomization to study arm and using the SES, 40 participants (20 in each arm) will be randomly selected to participate in in-depth interviews within 14 days after their week 12 visit and 28 days from their week 48 visit. Refer to Section 11.3 for details.

5.3 Intervention and Standard of Care Procedures

5.3.1 TERA Intervention

The TERA intervention is a sequence of adherence support strategies implemented as needed and in increasing intensity on the basis of monitoring of dose-taking from the AdhereTech™ EDM device. Components of the intervention implemented over the 12-week intervention period include: (1) remote education/preparation through counseling and planning with the assigned adherence coach (on computer at clinic site at baseline and weeks 4 and 12, as needed and as-available between visit coaching sessions); (2) one-way text alert at dose time when bottle has not yet been opened for that dosing window; (3) missed dose two-way interactive outreach text asking "What's the plan?"; and (4) implementation of the coach-outreach (phone, text, remote counseling) triggered by missed doses or as a check-in. Text

[1] Sites can request study specific funding to perform a viral load test for any youth that appears to qualify on other criteria but is missing viral load within the timeframe required. Note that consent for participation in the study is needed prior to this viral load testing and confirmation of entry into the study cannot be provided until detectable virus criteria is met.

messages will not use the clinic name or any reference to the participant's health status or diagnosis. Each component is implemented for 12 weeks total for intervention arm participants and is described below.

5.3.1.1 Face to Face Remote Counseling

When youth are assigned to the TERA intervention condition at baseline, they meet with their assigned adherence coach in a private location via web-enabled virtual counseling (VSee) at clinic. These trained coaches are not part of the clinic team; rather they are centrally located at the University of Michigan. The first session is anticipated to last up to 60 minutes, and includes building rapport, discussing roles and expectations, explaining the intervention components, and building engagement. The coach works with the youth to develop a personal adherence plan, contact tree and preferences, and problem solving around previous challenges with adherence. Specific details about the EDM bottle may be reviewed and how texts are prompted will be explained. Details for phone contact tree, black-out times (times when the participant does not want to be called), preferred name and appropriate pronouns, and other important aspects of the participant's life that need to be considered throughout the interactions with coaches will be documented through "notes" and entered by the coach in a profile area on the TERA implementation dashboard for later use. A secure audio recording program records all sessions and stores this data on a HIPAA compliant secure website at the University of Michigan. Coaches can review their sessions for training purposes and to confirm notes.

When coaches (counselors with training in Motivational Interviewing) review the intervention with youth, they will intentionally emphasize intensity, difficulty and short-duration as a way to mobilize pride in engaging in and 'succeeding' in the program. Motivational interviewing (MI) strategies will be used to work through ambivalence and garner support for engaging in the intervention. Because the coaches have set face-to-face meetings only three times (baseline, week-4 and week-12) and the week-12 visit focuses on termination and transition off of active intervention, the need for baseline to function as a single session is critical and well-suited to MI approaches. Counseling strategies are detailed in the TERA Coach's Manual.

5.3.1.2 **Triggered Outreach**

The sequential escalation of adherence support follows a set pattern, where late and no dosing prompts increased efforts to connect and work with youth. AdhereTech's™ algorithm identifies each opening event as an early, on-time, or late dose for a given expected dose. An opening event may be counted as an early dose from an expected dose time that has passed or an early dose for an upcoming expected dose based on a computation of time elapsed and remaining for doses not yet 'taken'. 1.5 hours elapsed without an opening event prompts interactive outreach. From the moment the two-way outreach is sent, a "ticket" is opened for the event with all implementation procedures from that point forward are tracked on the study specific implementation dashboard.

Potential outcomes of the two-way outreach text are detailed below in Table 1 and include: (1) there is no response within 1-hour; (2) the participant replies he or she is not taking it (each

participant has 1 pass-reply per week where a report of not intending to take the dose is permissible with no follow-up); (3) participant replies that the dose is being taken now; (4) participant response that says he/she has taken the dose; or (a plan for taking the dose later is reported); or (5) reply that dose will be taken later. Note that events such as the dose monitoring capturing an opening event between the outreach text and coach involvement may occur and negate the need for follow-up. Finally, the response may be uninterpretable and require follow-up.

For participants who fail to respond to the two-way outreach text within an hour, the event is investigated by the monitor on call and then escalated to **coach outreach** as needed. The adherence coach team member monitoring alerts at that time will escalate the ticket and make contact with the participant's assigned coach when possible or address the ticket as needed him or herself if the specific coach is not available.

Table 1. Triggered Two-way Outreach

Participant response	**Action**	**MONITOR**
a) taking now	Text alert sent to Monitor 30 minutes after receipt of reply	Checks dashboard to see if an opening event was registered in past 30 minutes Yes→ Closes ticket No→ Escalate to coach
b) took already	Text alert sent to Monitor	Check dashboard to see if an opening event was registered that may represent the dose already taken Resolved→ Closes ticket Not resolved→ Escalate to coach
c) taking later	Text alert sent to Monitor	Get more information regarding planned time. Check dashboard to see if an opening event was registered at planned time. Resolved→ Closes ticket Not resolved→ Escalate to coach
d) other	Text alert sent to Monitor	Get more information regarding plan →Escalate to coach as needed
e) pass [only when a pass is available]	Ticket is moved to closed automatically by the dashboard	No action required by monitor

Participant response	**Action**		**MONITOR**
"e" or "pass" when no pass is available	Automated text from dishboard sent to participant "A pass is not available. Please respond with a)Taking Now b)Took Already c)Taking Later d) Other"	Different Selection "corrects" response and loops into appropriate row above	NA
		No change in response or no response is handled as no reply	NA
Uninterpretable	Automated text from dishboard sent to participant "Please reply with available options"	Different Selection "corrects" response and loops into appropriate row above	NA
		No change in response or no response is handled as no reply	NA
No reply after 1 hour	Text alert sent to Monitor		Monitor sends inquiry text to participant. Resolved→ Closes ticket Not resolved→ Escalate to coach

Note: The ticket monitor on-duty creates tickets and determines need for escalation to coach. Monitors watch the system during active hours 7-days a week.

The adherence coach contacting the participant documents the situation, contact attempts and successes, plan, and content of discussion or text for each ticket. Coaches are trained to follow site-provided (local) protocols for suicidality or discourse suggesting that the participant is a threat to self or other(s). Any interactions that include threat to self/other(s) will also be documented as a safety event in the ATN QNS tracking system.

Discourse between participant and coach will be documented in the notes section of the TERA implementation dashboard, as will the strategic plan result from the conversation which can vary between participants and within participant over time (from dose-taking, to accessing other services or using referrals). Documentation is marked with PID and appropriate ticket number. Our implementation database will maintain lists of all tickets sent. Related details and tickets are "closed" only when coaches submit documentation and submit tickets for closure= which can be closed by approved supervisory staff. In the event that coaches cannot reach youth via any agreed upon modality (phone, text, social media), the **phone tree** will be used in the order in which the youth listed contacts. The coach will implement all agreed upon forms of outreach to contact the youth, with the final attempt being outreach to the clinical-care team. Tickets that are open and unresolved for over a week will be dealt with by the team on a case by case basis. While sites are engaged by coaches to resolve contact issues when needed, and also to identify appropriate referrals and local resources as needed, sites do not have access to EDM monitoring dashboards. It is not possible to blind sites completely on assignment to condition, however, because coaches may need to discuss referrals for a given participant. Any communications of this nature will be documented.

5.3.1.3 Additional Outreach

Additional outreach in the form of a texted check in (Checking in. All good?) will be used when there has been no contact with the participant for a 7-day period. This is to keep participants engaged with the intervention and to offer assistance from a coach *before* a potential dosing delay or skip occurs. Thus, these are not triggered by a no- or late-dosing event. Rather, they are gentle check-ins for participants who have not triggered outreach in 7-days. The "ticket" approach used in the TERA implementation dashboard will be used for these check-ins where the text check-in represents a ticket that must be closed and documented in the dashboard, like other tickets. The process is depicted in Table 2 below.

Table 2: Check in outreach contacts "Checking in. All good? Y) yes N) no"

Participant response	**Action**		**MONITOR**
Yes	Ticket is moved to closed automatically by the dashboard		NA
No	Text alert sent to Monitor		→Escalate to coach →Provide follow-up to participant as needed
No Reply after 24 hours	Automated text from dishboard sent to participant "Checking in again. All OK? Y) Yes N) No"	Different Selection "corrects" response and loops into appropriate row above	NA
		Ongoing no reply after 24 hours of second text sends an alert text to Monitor	Monitor investigates dashboard data and gathers information as needed. Resolved→ Closes ticket Not resolved→ Escalate to coach

5.3.1.4 **Participant Requested Contact**

Participant requested contact is possible and will be tracked throughout the 12-week intervention. A participant in the TERA condition can text questions or requests for contact to the study specific cell phone. Coaches have training in ART related content, but will assist participants in linking to their care team should questions center on side-effects, medications, or other medical issues best addressed by the clinical care team.

5.3.1.5 Adherence Coaches

Adherence Coaches will have advanced skills in motivational interviewing and working with youth. All coaches will participate in two days of concentrated training and an additional one-week of practice before starting with youth. Monitoring of skills and implementation will be conducted in collaboration with the Protocol Chair. Procedures will be documented in TERA Coach's Manual.

5.3.1.6 SMS

All text messages are received, reviewed and replied to using the SMS platform located on the secure TERA implementation dashboard. Text messages will not use the clinic name or any reference to the participant's health status or diagnosis.

5.3.2 Standard of Care

Per the eligibility criteria, all youth in both the SOC and TERA arms will be continuing or restarting with a once-daily regimen with at least two active agents (per clinician judgment or

genotype evidence) as per their primary care providers prior to randomization. We intentionally leave the decision of whether the YLWH are on an "effective" regimen to the primary care provider recognizing that these clinical SOC decisions are informed by a number of clinical factors including a discussion with the patient and are best individualized and not standardized or protocol driven.

SOC relative to adherence support each participant is receiving will be enumerated in detail at study start and updated at each study visit. In previous work we have developed a SOC measure for ART adherence support[41] that follows international recommendations for strategies[42], as well as strategies known to have positive effects[43] in some populations. We anticipate, based on polling of IMPAACT sites, that use of cell-phone reminders, patient-education, adherence planning (medication management), and checking-in on adherence at clinical care visits, as well as VL monitoring with patient feedback on VL, are used at sites. Less common, but available as a general service at some sites, on several websites, and at many pharmacies, youth may also receive text messages at dose times, for appointment reminders, and for refill reminders. Given that these are automated and not generally interactive, and are not in response to non-dosing, these do not 'compete' with the TERA intervention components.

5.3.3 Research Staff Training

The protocol chairs and project manager assume primary responsibility for training the adherence coaches and the sites regarding the project and TERA intervention. The adherence coaches will have training in therapeutic/counseling strategies, have previous experience facilitating behavioral interventions with youth, and receive additional formal training and supervision in Motivational Interviewing.

5.3.4 Intervention Monitoring/Quality Control

The intervention facilitators will be trained centrally to carry out the intervention protocol, thus providing consistency in training experience. Intervention facilitators will engage in group supervision. In addition, intervention facilitators will complete session checklists at the end of each interaction with a participant to document the elements of the intervention that were delivered and to record unique issues that arise. This method has proven successful in assisting interventionists in monitoring their adherence to the protocol and preventing the use of proscribed intervention in prior studies. By providing multiple layers of clinical oversight and ongoing feedback, deviations from fidelity will be easily detected and addressed.

6 STUDY MEASURES

6.1 Computer Assisted Surveys

Audio computer assisted surveys (ACASI) will be collected at baseline, week-12, week-24, week-36, and week-48, during scheduled visits. Table 3 describes each measure used in the ACASI as well as the schedule for data collection and a brief description of each measure. The ACASI should take approximately 30 minutes or less to complete.

Table 3. ACASI Measures and Collection Time-Points

Measures	Time Point	Description
Adherence Support During Participation	Week-12, Week-48	Check list of receipt of specific kinds of support during first 12 weeks and at week-48
Information Motivation Behavior Skills ART Adherence Questionnaire[44,45]	Baseline, Week-12, Week-24, Week-36, Week-48	Measure of adherence barriers identified by the Information, Motivation, Behavioral Skills Model of Adherence.
The HIV Adherence Self-Efficacy Scale[46]	Baseline, Week-12, Week-24, Week-36, Week-48	Measures self-efficacy for adherence to HIV treatment plans, including, but not limited to taking HIV medications. The overall self-efficacy scale score as well as integration and perseverance subscales will be used for study purposes.
Adolescent Decision Making Questionnaire (ADMQ)[47]	Baseline, Week-12, Week-24, Week-36, Week-48	Revised version of the ADMQ that measures decision making patterns in adolescence. Four subscales will be used for this study: avoidance, self-confidence, panic, and impulsive/thoughtless
CESD-10[48]	Baseline, Week-48	Self-reported 10 item screening instrument designed to measure symptoms of depressed mood in respondents. Higher scores indicate increased depressive symptomology.
Demographics	Baseline	Study developed and ATN harmonized items assessing socio-demographic characteristics
Emotional Regulation Questionnaire (ERQ)[49]	Baseline, Week-12, Week-24, Week-36, Week-48	10-items scale designed to measure respondents' tendency to regulate their emotions in two ways: cognitive reappraisal and expressive suppressive. Higher scores indicate greater use of emotion regulation strategy.
EQ-5D-Y (Overall health status)[50]	Baseline, Week-12, Week-24, Week-48	Standardized measure of overall health status designed to provide a simple measure of health for clinical appraisal. Provides a descriptive score for 5 dimensions: mobility, looking after myself, doing usual activities, having pain/discomfort, and sad or

Measures	Time Point	Description
		happy). A visual analogue scale item records respondent's self-rated health on a vertical scale to quantitatively measure respondents' self-reported overall health status.
HIV Cascade Measure (U24)	Baseline	ATN harmonized items related to engagement in HIV related care.
HIV Stigma Mechanisms[51]	Baseline, Week-12, Week-24, Week-36, Week-48	Measures stigma mechanisms defined by the HIV Stigma Framework including measures of internalized, anticipated and enacted HIV stigma. Higher scores indicate greater stigma.
Life Events Survey (LES)	Baseline, Week-12, Week-48	Study adapted measure of significant or traumatic life events
Satisfaction Scale (Developed for study)	Week-12, Week-48	Study developed measure of TERA arm participants' satisfaction with the TERA intervention.
Self-Reported Adherence[52]	Baseline, Week-12, Week-24, Week-36, Week-48	3-item self-reported measure of adherence to HIV medications - Doses taken (0 to 30), frequency of doses taken in last 30 days (Likert response), and rating of how good of job taking medications (Likert response).
Sex Behavior	Baseline, Week-12, Week-48	Brief item set to assess rates of condomless sex
Social Support Scale (MOS)[53]	Baseline, Week-12, Week-24, Week-36, Week-48	Measure designed to assess overall functional social support as well as four separate social support subscales: emotional/information support, tangible support, affectionate support, and positive social interaction. A higher score for an individual scale or for the overall support index indicates more support.
Substance Use (ASSIST)[54]	Baseline, Week-12, Week-48	Screening measure designed for use in primary care settings to screen for problem or risky use of tobacco, alcohol, cannabis, cocaine, amphetamine-type stimulants, sedatives, hallucinogens, inhalants, opioids and "other drugs" that do not fall into the previous categories. Higher scores for each substance use category indicate greater risk of experiencing severe problems as a result of substance use as well as greater risk for substance dependence.

6.2 Dose Real-Time Adherence Monitoring

An AdhereTech™ smart pill bottle will be provided to participants randomized into both study

arms, the TERA intervention and SOC arm. The AdhereTech™ device has a global system for mobile (GSM) communication chip and a wireless signal is sent to a central management system (AdhereTech™ web server) whenever the device is opened. AdhereTech™ data (unique identifier and time/date stamp) will be received on a continual basis and stored on the secured AdhereTech™ server. Data from the AdhereTech™ device will be used to assess medication adherence and persistence. AdhereTech™ data will be maintained centrally for adherence coaches and will not be made available to site clinical staff.

6.3 Biomarkers

HIV-VL and $CD4^+$ count and percentage will be abstracted from participant medical records. If a recent HIV-VL test is not available, it must be collected. For screening of eligible participants, HIV-VL can be up to 45 days before the enrollment (week 0) study visit. For follow-up study visits at weeks 12, 24, 36, and 48, HIV-VL can be ±14 days from the week 12 follow-up visit and ±28 days from the week 24, 36, and 48 due date. All HIV-VL and CD4+ data outside of study visit time-points but within the time of participation on study will be abstracted.

The frequency of HIV-VL testing in the study is intended to align with what is the sites' standard of care and hence not require a separate HIV-VL to be done exclusively for the purpose of the TERA study. HIV-VL testing done as part of the standard of care should not be labeled or billed as a TERA study test. If SOC HIV-VL is not available or planned within the study visit window, then it should be done (and billed) within the study visit window as per the TERA study schedule of evaluations.

6.4 Medical History/Health Status

Date of HIV diagnosis, route of HIV transmission, previous experience with HIV medications, AIDS defining illnesses and opportunistic infections (OIs) since diagnosis, and current co-morbidities and concomitant medications will be abstracted from participant medical records.

6.5 Demographics

Descriptive information about participants will be collected including, but not limited to, gender assigned at birth, subject's identified gender, age, and race/ethnicity.

6.6 Intervention Acceptability and Feasibility Measures

This satisfaction scale will be completed by participants randomized to the intervention arm via ACASI at their week-12 and week-48 visit. Items are rated on a 5-point Likert scale.

A semi-structured interview will also be used to collect information on acceptability and feasibility of the TERA intervention. The interview guide has interviewer prompts that inquire about overall experiences with the intervention and with adherence services offered as standard of care. (see section 8.2 data collection)

7 STUDY EVALUATIONS

An overview of the study visits and evaluation schedule is provided in Appendix I. Presented in this section is additional information on visit-specific study procedures. Each site will provide detailed study specific procedures in their PIPs for review and sign-off by the ATN CC prior to site activation. The PIPs must reflect the required expected procedures as specified in the ATN 152: TERA MOP.

Although split visits should be avoided as much as possible, the MOP includes guidance for strategies for split visits and off-schedule visits. All visits and procedures must be documented in accordance with the NICHD policies for source documentation; refer to Section 8 for more information on documentation requirements and completion of CRFs.

In addition to the procedures listed in this section, study staff may complete other tasks consistent with the site's standard operating procedures for conducting research and providing care, including but not limited to collecting, reviewing, and updating demographic and contact information; reviewing elements of informed consent; scheduling telephone contacts and visits; providing instructions for contacting study staff between visits; providing visit reminders; and following up on missed visits. All such tasks should be documented consistent with each site's PIP. Study staff should inform participants of clinically meaningful physical exam findings and laboratory test results when available.

7.1 Screening

Refer to Section 4.3 for a description of the study recruitment, screening, and enrollment process. Screening procedures may be performed up to 45 days prior to enrollment. Multiple visits may be conducted to complete all required screening procedures if necessary. For potential participants who do not meet the eligibility criteria, screening may be discontinued once ineligibility is determined. Potential study participants who did not meet study eligibility criteria for reasons such as the latest HIV VL was < 200 copies/ml or who did not return to the clinic within the 45 day window from HIV VL assessment to study entry, can be rescreened.

Before screening a potential participant, site staff will conduct a medical record review to determine if a VL ≥200 copies/mL within 45 days before the enrollment visit has been or needs tobe performed. As previously noted (Section 5.1), study sites may perform a viral load test as needed once consent for study participation is obtained. Enrollment/Entry visit can only be started once the viral load requirement for participation is confirmed. As stated earlier in section 4.3, no procedures, other than preliminary verbal assessment of eligibility or medical chart review to assess potential eligibility, may be done before the informed consent process is complete.

Screening Visit Procedures (up to 45 days prior to enrollment)	
Administrative and Regulatory	• Preliminary evaluation of potential eligibility • Obtain written informed consent • Assign PID from list • Obtain screening number from SES

7.2 Enrollment/Entry

Refer to Section 4.3 and 4.4 for a description of the study recruitment, screening, and enrollment process. The Enrollment/Entry visit should ideally be conducted on the same day as the Screening visit. However, if this is not possible (e.g., a pre-screening VL≥200 copies/mL within the previous 45 days is not available in the subject's medical record and needs to be collected for study purposes), the enrollment visit must occur no more than 45 days after the screening visit.

The enrollment visit may not be a split visit. All Enrollment Visit procedures must be performed on the day of enrollment; procedures that may provide information relevant to eligibility for the study (e.g., pregnancy test and medical history), should be performed first, prior to final eligibility determination. If not included as standard of care, site staff will perform a pregnancy test (blood or urine), once consent for study participation is obtained.

Enrollment Visit Procedures *(Day 0)*	
Administrative and Regulatory	• Complete final eligibility determination and confirmation • Enter checklist data into SES, print and file a copy of the confirmed enrollment file to retain as paper or electronic file at site • Generate randomization for treatment assignment • Generate randomization for offering participation in qualitative interview • Complete Contact form
Clinical Data	• Chart abstraction for VL, CD4, and pregnancy test[1] • Medical history • Medication history
Participant Surveys and Data	• Demographics • ACASI survey • Adherence service utilization form
EDM (AdhereTech™ Bottle)	• EDM set up and training • Activation of EDM (FSTRF call line) • EDM device check and charging • Issue EDM • Complete EDM tracking log

Behavioral and Counseling	• Adherence counseling per SOC
TERA Intervention Arm	• Baseline TERA remote coaching session

[1]Pregnancy test must be performed on day of enrollment visit

7.3 Week-4 Visit

The Week-4 Visit is targeted to take place on Day 28, counted from the date of enrollment as Day 0, with an allowable window of ± 14 days.

Visit Procedures *(Day 28)*	
Administrative and Regulatory	• Check Contact form • Safety event assessment • Confirm and schedule participants for qualitative interviews for those randomized to qualitative interview subset
Clinical Data	• Chart abstraction for VL and CD4 (as available) • Medication history and changes
EDM (AdhereTech™ Bottle)	• EDM device check and charging
Behavioral and Counseling	• Adherence counseling per SOC
TERA Intervention Arm	• TERA remote coaching session in clinic (visit 2)

7.4 Week-12 Visit

The Week-12 Visit is targeted to take place on Day 84, counted from the date of enrollment as Day 0, with an allowable window of ± 14 days.

Visit Procedures *(Day 84)*	
Administrative and Regulatory	• Check Contact form • Safety event assessment
Clinical Data	• Chart abstraction for VL and CD4 • Medical history and changes • Targeted Medication History
Participant Surveys and Data	• ACASI survey • Adherence service utilization form • Qualitative interviews (schedule at or within 14 days of Week-12)
EDM (AdhereTech™ Bottle)	• EDM device check and charging
Behavioral and Counseling	• Adherence counseling per SOC
TERA Intervention Arm	• TERA remote coaching clinic session (visit 3/final visit)

7.5 Week-24 Visit

The Week-24 Visit is targeted to take place on Day 168, counted from the date of enrollment as Day 0, with an allowable window of ± 28 days.

Visit Procedures (Day 168)	
Administrative and Regulatory	• Check and/or update Contact form • Safety event assessment
Clinical Data	• Chart abstraction for VL and CD4 • Medical history and changes • Targeted Medication History
Participant Surveys and Data	• ACASI survey • Adherence service utilization form
EDM (AdhereTech™ Bottle)	• EDM device check and charging
Behavioral and Counseling	• Adherence counseling per SOC

7.6 Week-36 Visit

The Week-36 Visit is targeted to take place on Day 252, counted from the date of enrollment as Day 0, with an allowable window of ± 28 days.

Visit Procedures (Day 252)	
Administrative and Regulatory	• Check and/or update Contact form • Safety event assessment • Confirm and schedule participants for qualitative interviews for those randomized to qualitative interview subset
Clinical Data	• Chart abstraction for VL and CD4 • Medical history and changes • Targeted Medication History
Participant Surveys and Data	• ACASI survey • Adherence service utilization form
EDM (AdhereTech™ Bottle)	• EDM device check and charging
Behavioral and Counseling	• Adherence counseling per SOC

7.7 Week-48 Visit (Off-Study Visit)

The Week-48 Visit is targeted to take place on Day 336, counted from the date of enrollment as Day 0, with an allowable window of ± 28 days. At this visit, participants will be informed of how to contact study staff with any post-study questions and how to learn about the results of the study when available.

Visit Procedures *(Day 336)*	
Administrative and Regulatory	• Safety event assessment • Enter off-study form in Rave when all evaluations are complete
Clinical Data	• Chart abstraction for VL and CD4 • Medical history and changes • Targeted Medication History
Participant Surveys and Data	• ACASI survey (final) • Adherence service utilization form • Qualitative interviews (schedule at or ±28 days of Week-48)
EDM (AdhereTech™ Bottle)	• Return EDM
Behavioral and Counseling	• Adherence counseling per SOC

7.8 Premature Discontinuation from the Study

Participants who discontinue from the study after baseline but prior to their Week-48 visit, will have all evaluations scheduled for the Week-48 visit completed at the time of their study discontinuation.

7.9 Off-schedule Visits

Sites should make every effort to engage participants within the study window. When not possible and a participant who has missed a visit(s) can be contact, an off-schedule visit should be performed. Sites should query the protocol team for specific instructions on which assessments should be prioritized for these off-schedule visits.

8 DATA COLLECTION AND SITE MONITORING

8.1 Data Records

Data on screening and enrollment in this study will be collected using the FSTRF Subject Enrollment System. Study sites must maintain adequate and accurate research records containing all information pertinent to the study for all screened and enrolled participants, including supporting source data. Electronic CRFs (eCRFs) are completed and keyed using a remote data entry system managed by FSTRF known as Rave. In this system, computerized checks are applied to the data and when required, data queries are issued for resolution by site staff. All data must be keyed and transferred to FSTRF within 21 days. Queries must also be resolved within 14 days.

Participant-related study information will be identified through the Patient Identification Number (PID) on all participant CRFs and ACASI files. Participant names or other personally-identifying information will not be used on study documents with the exception of (1) a linking sheet located at site that links PID to contact information which is stored in a secure location at the local siteand (2) first names or nick names and contact tree information to be used by the coaches kept in the TERA implementation dashboard on a secure server. Information required to activate the EDM device will include contact phone number and PID, as well as dose times for the EDM alerts and optional features. All study-related information at site will be kept in double-locked, limited access areas. The log that links the names of participants to their PID numbers are accessible only to the study staff, site monitors, and representatives from the NICHD. Original source documents for individual participants will be maintained at the respective clinic site and will be accessible only to the study staff. Data from original source documents will be transcribed into Rave as applicable.

Individuals who do not complete the screening process are reflected in summary data the sites will collect and report on to the core team in the form of the recruitment log. Those who complete the screening process but screen fail will have anonymous information collected on the *ATN 152 Screening Failure Form* which will be entered into the study database- screening numbers are used in data entry, no personally identifying information is collected, there is no log that links the screening ID to personally identifying information, and no source documentation on incompletely screened or screen failed individuals will be maintained by the site staff.

8.2 Data Collection

8.2.1 Case Report Forms

Study monitoring data, including information about eligibility will be collected on eCRFs. All eCRFs and tools for this study will be available for download from the FSTRF portal (https://www.frontierscience.org/). eCRF completion guidelines will be made available to sites.

8.2.2 AdhereTechTM Electronic Dose Monitor (EDM)

An AdhereTech bottle will be provided to participants in both arms of the study. This device is a

pill bottle that electronically monitors whenever the bottle is opened and sends an electronic medication event record to a central server for real-time medication adherence monitoring. These medication event records are stored as data on the secured AdhereTech server and will be downloaded by FSTRF as .CSV files to the FSTRF study database per institutional secure standards. Interventionists will be provided unique user IDs and passwords to log into the AdhereTech server so that they can set up or modify participant specific dose monitoring times as well as review any text message responses that are stored when participants' reply to the AdhereTech survey text if they do not take their dose during the specified study dose window.

8.2.3 Audio Computer Assisted Self-Interview (ACASI)

All ACASI data will be collected on a portable laptop computer or tablet. ACASI responses will remain confidential; sessional responses are identified by the participant identification number (PID). Data is not shared with clinical team or intervention coaches. The PID will be used in order to link the survey responses to the participant's CRF data. Detailed instructions on the operation of the ACASI will be provided to the sites in the ATN 152 TERA MOP.

Table 4. ACASI Individual Measure Schedule

ACASI Measure	BL	W12	W24	W36	W48
DEMOGRAPHICS/BACKGROUND INFORMATION	X				
MENTAL/PHYSICAL HEALTH FUNCTIONING (EQ-5D-Y)	X	X	X		X
EMOTIONAL REGULATION QUESTIONNAIRE (ERQ)	X	X	X	X	X
SOCIAL SUPPORT SCALE (MOS)	X	X	X	X	X
CES-D	X				X
HIV STIGMA MEASURE	X	X	X	X	X
SUBSTANCE USE (ASSIST)	X	X			X
SEX BEHAVIOR	X	X			X
HIV CASCADE MEASURE (Adapted from U24 Harmonized Items)	X				
SELF-REPORTED MEDICATION ADHERENCE	X	X	X	X	X
ADHERENCE (IMB-AAQ)	X	X	X	X	X
ADHERENCE SELF EFFICACY	X	X	X	X	X
ADOLESCENT DECISION MAKING QUESTIONNAIRE (ADMQ)	X	X	X	X	X
LIFE EVENTS SURVEY (LES)	X	X			X
SATISFACTION WITH INTERVENTION (CSQ-8)		X			X
ADHERENCE SUPPORT DURING PARTICIPATION		x			X

8.2.3.1 ACASI Data Security

Web-based data collection will be collected via a commercial software tool designed by DatStat, Inc. for online data collection instruments. The DatStat software tool (Illume) uses secure HTTPS connections that adhere to the Food and Drug Administration (FDA) guidelines for secure electronic data capture. The collected data will be stored on DatStat's server and periodically

copied to the FSTRF database. Access to the database will be limited to those designated by the principal investigator.

8.2.3.2 ACASI Data Transmission

DatStat secure servers are registered with site certificates provided by VeriSign Internet Trust Services that provides for advanced encryption over the wire. As users move through the data entry forms, the responses are encrypted while in transit between the browser and DatStat's server using SSL (Secure Sockets Layer) and Public Key Encryption.

8.2.3.3 Data Access

Physical access to DatStat servers and data backup is restricted to a minimal number of IT professionals. Access to data stored on the server is available only to designated Illume users who log in with specified usernames and passwords. Users are logged out after a period of time. A listing of the named users with a description of their access privileges is available within the application.

8.2.3.4 Participant Confidentiality

To ensure an even greater level of security and confidentiality, participants/study staff are required to enter a Personal Identification Number (PID) to gain access to the data entry forms. It is ONLY the PID that is stored with the collected survey data, thus ensuring that under no means may the collected survey data reveal a participant's identity. Participants will also complete the ACASI survey in a private clinic room further ensuring their answers remain confidential.

8.3 Qualitative Interviews

Qualitative interviews will be conducted for 20 randomly selected participants in each arm (N=40). The interview will be scheduled by the site team and conducted via Vsee's remote face-to-face platform by a study team member not involved with the implementation of the trial but well versed in qualitative methodology. Interviews will not exceed 60-minutes and will be recorded on the secure audio recording program and stored on the HIPAA-compliant University of Michigan Box. All audio will be de-identified and transcribed verbatim by a qualified transcription service. Analyses (see section 11) will generate main themes and coded data. De-identified transcripts will be shared with study team members. Original audio recordings will be shared only with the transcription service and will be maintained on the secure server until data destruction post trial.

8.4 TERA Dashboard

Metrics collected from the TERA implementation dashboard include :
Date, time, and/or occurrence for:

- Ticket opening and closing—with reason for ticket opening and conditions surrounding closure
- Escalation

- All Coach contact via SMS and all following texts
- All Coach contact via phone
- Use of contact tree
- Participant requested contact
- Coach or monitor who handled the event

Tracking can then be summarized for producing summed counts of any of the listed events, overall and in specific time intervals, qualitative evaluation of overall themes emerging from outreach notes, time elapsing between events (alert, contacts, ticket closure), reasons for alters (tickets) and specific outcomes and reasons for closing tickets, and all texts sent and received for length, duration of exchange, and content.

8.5 Remote Counseling Data

Vsee and a secure audio recording program are used to collect all face to face remote counseling data. VSee and the audio recording program are both hosted on a secure server and are HIPAA compliant. Per the vendor's website https://vsee.com/telemedicine/, *"VSee uses end-to-end 256-bit AES, FIPS 140-2 certified encryption to guarantee that no servers have access to the decryption keys."* Documentation for HIPPA compliance can be found at vsee.com/hipaa.

The interaction will be audio recorded unless a participant specifically declines audio recording. Audio recording is done through *Audacity* which is an open source software program that stores directly to a secure server. The adherence coach controls start and end of recording and saving it to the secure server. The research team conducting the qualitative evaluation of coaching session content will retrieve the audio recording from the secure server for transcription. De-identification of the session will occur during transcription.

8.6 Costing Data

To characterize costs associated with the implementation of the TERA intervention, several sources of information/data collection will be used. As indicated in Table 5, several data sources are used to generate costing data.

Table 5. Costing Data Sources

Critical Components of Intervention Implementation	Method of collection	Timing of assessment
Electronic Dose Monitoring Device		
Cost per unit	Study budget	End of study
Unit replaced over the trial (loss, malfunction)	EDM tracking log	End of study
Time required for profile set up	Clinic Staff Qualitative Interview item 2d	Collected during semi-structured interviews end study
Devices identified as	EDM tracking log (retired or	End of study

Critical Components of Intervention Implementation	Method of collection	Timing of assessment
malfunctioning	returned devices)	
Time required to address	Project Manager self-report	End of study
Device identified as out of battery	Project manager report (study log non-source document)	End of study
Time required to address	Project Manager self-report	End of study
Remote Counseling Visits		
Vsee software cost	Study budget (weighted if needed by average minutes for per participant costs)	End of study
Prep for scheduled patient session	Coach self-report: 1-week log	Within 3-months of study start During final weeks of implementation of intervention phase
Session length in minutes	Extracted from audio transcription data	End study
Charting/documentation	Coach self-report: 1 week log	Within 3-months of study start During final weeks of implementation of intervention phase
Alerts and follow-up		
Average minutes per monitor shift spend watching alerts	Monitor self-report- 1 week log Dashboard data for number of events	Within 3-months of study start During final weeks of implementation of intervention phase
Coach time allocated to outreach	Time between escalation and ticket close-out Coach self-report- 1 week log Dashboard data for number of events	Within 3-months of study start During final weeks of implementation of intervention phase
SMS fees	Project budget	End of study
Staffing		

Critical Components of Intervention Implementation	Method of collection	Timing of assessment
Project manager FTE adjusted to implementation activities/Salary Coach FTE/Salary MI specific training MI supervision Supervisory meetings Supervisory recording reviews	Self-report and study budget	End of study

8.7 Data Submission

All forms and data collection are electronic. There are no paper forms submitted.

8.8 Case Report Forms/Data Collection Forms

Study sites must follow the study CRF/DCF completion and entry that are specified in ATN 152 MOP. Once the study database is developed, the Rave screens are available for data entry, and protocol training has been completed, research staff at the sites will be responsible for ensuring that CRF data is entered into Rave within the timeframe specified on the CRF.

Each clinical site is responsible for entering data into Rave. CRFs must be completed and entered into Rave within 21 days from the date of the study visit. CRFs must have corresponding source documentation on file at the clinical site to substantiate all submitted data. Data edits through range checks and field inconsistencies will be built into the Rave system to enable real time correction of key entries and CRF completion errors.

8.9 AdhereTech™ EDM Data Transmission

Data from the AdhereTech™ bottle will be received on a continual basis (the wireless signal with unique identifier and date/time stamp is activated when the container is opened) and stored on a secure server at AdhereTech™ Inc. The AdhereTech device is a FDA Class I approved medical device. The entire AdhereTech system (e.g., bottle, dashboard) is HIPAA-compliant and all bottles are CE marked. The AdhereTech device operates on a worldwide cellular data network.

Data captured by the AdhereTech bottle and dashboard will be downloaded to the FSTRF study database as CSV files. Participants names will not be included in the AdhereTech data. Instead, PIDs will be entered in the database.

8.10 Data Quality Assurance

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

8.11 Study Site Monitoring and Record Availability

Site monitors from the ATN coordinating center will visit participating study sites to review a selected portion of the individual participant records, including assent/consent forms, CRFs and supporting source documentation to ensure the protection of study 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 site investigator will make study documents (e.g., consent forms, case report forms) and pertinent hospital or clinic records readily available for inspection by the local IRB, the site monitors, the NICHD, the Office of Human Research Protection (OHRP), or the sponsor's designee for confirmation of the study data.

9 PARTICIPANT MANAGEMENT

9.1 Tracking Participants/Follow-up

Study site staff will track participant study recruitment and retention for the intervention and follow-up visits. Study interventionists will also track intervention sessions completed by participants.

9.2 Study Visit Management

Ideally, all study visit related evaluations should be completed on the same day. If a n individual is unable to complete their study visit evaluations in one day, he/she will have 7 calendar days to complete all evaluations, with the exception of the baseline/enrollment visit which must be conducted in one day (see section 7.2). If the evaluations cannot be completed within 7 days, the study visit evaluations should be considered missed. Study visit windows are included in the schedule of evaluations in Appendix I. Sites should submit a query via the ATN QNS to conduct study evaluations outside of the protocol window unless otherwise allowed per protocol documentation.

9.2.1 Completing the ACASI

Study staff should follow the following procedures at each site:

- Participants should be reminded they may discontinue at any time with no penalty, and that they have the right to choose to leave any questions unanswered
- Participants should be given headphones and a laptop or desktop computer in an accommodating, private and quiet area
- Site staff must assist particiants with ACASI tutorials
- If the participant requires a break, site staff must make sure the computer program is exited and re-entered properly so that participant confidentiality is maintained

If the ACASI is discontinued for any reason, during the follow-up visits only, the participant can plan to return to finish the survey another time, up to 7 days from the start of the survey.

9.2.2 ACASI Debriefing and Referral Procedures

Participants will be debriefed about possible reactions to answering questions of a sensitive nature, such as short-term feelings of sadness or anxiety. Participants will be instructed to contact study personnel or to consult the list of referrals provided if feelings persist or worsen after several days. Referrals for mental health services will be provided to all participants if warranted.

Study staff should follow the following debriefing procedures following each ACASI survey:

- The site staff member facilitating the session will ask “Is there anything else about the interview that you would like to discuss?” If the respondent says *“no,”* she or he should

be thanked for participation. The respondent will be given contact information for mental health personnel available at the site and informed that she or he can also contact study personnel in the event that issues or concerns arise later.

- If the response indicates the participant is in urgent need of mental health assistance, site staff should follow their individual site procedures for acute mental health referrals. Site staff should contact a supervisor immediately and stay with the study participant until the supervisor, mental health professional or emergency services, if needed, arrives.
- All such events should be reported in the QNS as a safety event.

9.3 Participant Reimbursement

Reimbursement will be provided for participants at each study visit. The amount of such reimbursement will be determined by the local study site staff and will be confirmed with the single IRB and will be reflected in the site-specific consent form and the recruitment flyers.

9.4 Intervening on “Social Harms"

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

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

9.5 Criteria for Premature Discontinuation

9.5.1 Premature Discontinuation from Intervention

If there is a concern that a participant may need to be discontinued from the study intervention, the site must notify the Protocol Team via the ATN Query Notification System (QNS). The Protocol Team will make a decision on whether the participant is discontinued from the study or only discontinued from the intervention. Site staff will then complete the Permanent Study Treatment Discontinuation eCRF.

9.5.2 Premature Study Discontinuation

Participants may request to discontinue their study participation at any time, and in so doing will be considered off-study. Site staff must complete the Study Discontinuation Log eCRF. Otherwise, participants may be discontinued prematurely from the study if any of the following occurs:

- The participant fails to comply with the study requirements that may seriously interfere with the validity of the study results;
- The site investigator determines that further participation would be detrimental to the health or well-being of the participant;
- The participant becomes incarcerated or detained impeding the ability to adhere to the study intervention and causing more than one study visit to be missed;
- The participant withdraws consent;
- The participant moves out of the area or is lost to follow-up;
- The study is stopped by a government agency such as the National Institutes of Health or the FDA;
- The study has to be stopped for other administrative reasons.

10 MONITORING SAFETY EVENTS

ATN protocols administratively managed by the CC, such as TERA, follow the ATN Manual of Policies and Procedures (MOPP) for safety event reporting, including untoward events (UEs). All study staff should report safety events/UEs using the definitions and guidelines stated in Chapter 10 Safety and Adverse Event Reporting of the MOPP located on the ATN secure website at: https://sites.cscc.unc.edu/atn/.

Events that meet the criteria for New Safety Information will be reported to the UNC sIRB by ATN CC Protocol Manager within the designated reporting period. The safety criteria is found in the UNC Office of Human Research Ethics's SOP 1401: Reporting New Safety Information that is available on the ATN secure website in the ATN Manual of Policies and Procedures, Appendix 10-6: https://sites.cscc.unc.edu/atn/policies-procedures-grp

11 STATISTICAL/ANALYTIC CONSIDERATIONS

11.1 Study Design

This is a Phase II, randomized, open-label study designed to assess the effectiveness of using a Triggered Escalating Real-time Adherence (TERA) intervention for 12 weeks, in YLWH failing ART. Success of the intervention will be assessed by subsequent viral suppression and adherence to the ART regimen being taken at entry to this study.

120 YLWH will be randomized with equal probability to the TERA intervention or continuing standard of care (SOC), with stratification by age (<18 years vs. ≥ 18 years). At entry, 40 participants (20 from each arm) will be randomly selected to engage in additional in-depth interviews about their experiences at weeks 12 and 48.

The primary outcome of virologic suppression is assessed at Week-12. Results for the primary outcome are required to be entered into ClinicalTrials.gov within one year of the last participant reaching Week-12, which may occur before the full 48 weeks of follow-up is complete on all participants. Since this could compromise the integrity of the study, a request will be made to ClinicalTrials.gov to delay results entry until one year after the last participant completes their 48 week follow-up.

The study will enroll a relatively small number of participants at a large number of sites with varying SOC. Power to detect differences may be impacted by variability in SOC across sites, although it will increase generalizability of the conclusions. However, even if statistically significant differences in virologic suppression rates are not found, the study will provide information on feasibility of the TERA intervention and preliminary data on its effectiveness. It will also provide information about adherence and its association with behavioral characteristics that will inform a predictive model of virologic suppression. This will contribute to the overarching goal of increasing numbers of YLWH with sustained virologic suppression.

11.2 Sample Size and Power Estimates

11.2.1 Sample Size

The primary study outcome is percent of participants in each arm with virologic suppression at week-12. Prior experience drawn from YLWH initiating second-line ART with SOC adherence monitoring indicates that about 60% would likely achieve the primary outcome of HIV-1 RNA < 200 copies/ml. With 120 participants (60 in each group) and a Type I error of 5%, there will be 85% power to show a difference of 25% (an 85% success rate in the TERA arm) and 62% power to show a difference of 20% (an 80% success rate in the TERA arm). Table 7 shows the power to detect differences of 20% to 30% in outcome rates in the two arms with varying success rates in the SOC arm. Since participants who are lost to follow-up are inherently likely to have poor adherence (an example of informative missingness), calculations assume that participants with missing HIV-1 RNA measurements at Week-12 for any reason (lost to follow-up, missed visit, etc.) are classified as failures.

A key secondary outcome is sustained virologic suppression defined as HIV-1 RNA <200 copies/ml at weeks 12, 24, 36 and 48. Prior experience indicates that approximately 38% of YLWH initiating second-line ART achieve and maintain controlled viral load over 48 weeks on SOC. Assuming a 40% success rate in the SOC arm, there will be 89% power to show a difference of 30%, and 75% power to show a difference of 25% in success rates between the two arms out to Week-48. As for the primary outcome, these calculations assume that participants with missing HIV-1 RNA measurements are classified as failures.

Table 7. Sample Size and Power

Sample size	% with HIV-1 RNA < 200 cp/ml at Week-12		Difference in outcome rates	Power
120	**60%**	**85%**	**25%**	**85%**
		80%	20%	62%
	50%	80%	30%	92%
		75%	25%	77%
		70%	20%	62%
	40%	70%	30%	89%
		65%	25%	75%
		60%	20%	61%

11.2.2 Accrual

Accrual of 120 participants is expected to require about 12 months after the first participant is enrolled.

11.3 Randomization

A dynamic permuted block system will be used to randomize approximately 120 participants equally to TERA or SOC. Randomization will be stratified by age (<18 vs. ≥ 18 years) to ensure balance in treatment assignments, with no enrollment limits on either age stratum. Institutional balancing will be used to help ensure roughly equal balance in intervention assignments within each site.

Immediately after randomization to study arm, enrolled participations will be randomly selected by the FSTRF Randomization system to participate in in-depth interviews at weeks 12 and 48, implemented until 40 participants (20 in each intervention arm) are identified. If refusal rates at Week-12 are higher than expected, probabilities of selection will be increased during accrual. Every effort to engage week-12 interview participants in the week-48 interviews will be made, including phone based interviewing. Strategies to add new participants to the week-48 interviews will be considered if loss to follow-up reduces the originally selected sample size.

11.4 Study Outcome Measures

11.4.1 Primary Outcome Measures

Primary Objective #1. To estimate and compare HIV virologic suppression rates in YLWH 12

weeks after initiating TERA or continuing SOC

Primary Outcomes:

- HIV-1 RNA <50 copies/ml. Participants with HIV-1 RNA ≥ 50 copies/ml or with no HIV-1 RNA measurement within the Week-12 window (± 14 days) will be classified as failures
- HIV-1 RNA < 200 copies/ml. Participants with HIV-1 RNA ≥ 200 copies/ml or with no HIV-1 RNA measurement within the Week-12 window (± 14 days) will be classified as failures

11.4.2 Secondary Outcome Measures

Secondary Objective #1. To estimate and compare virologic suppression rates in YLWH 24, 36, and 48 weeks after initiating TERA or continuing SOC

Outcomes:

- HIV-1 RNA < 50 copies/ml. Participants with HIV-1 RNA ≥ 50 copies/ml or with no HIV-1 RNA measurement within ± 28 days of the scheduled visit will be classified as failures
- HIV-1 RNA < 200 copies/ml. Participants with HIV-1 RNA ≥ 200 copies/ml or with no HIV-1 RNA measurement within ± 28 days of the scheduled visit will be classified as failures

Secondary Objective #2. To estimate and compare proportions of participants initiating TERA or continuing SOC who achieve virologic suppression (HIV-1 RNA < 200 copies/ml) by 12 weeks and maintain virologic suppression through 48 weeks

Outcome:

- HIV-1 RNA < 200 copies/mL at weeks 12, 24, 36 and 48. Participants will be classified as virologic successes if both the Week-12 (± 14 days) and 48 (± 28 days) HIV-1 RNA measurements are < 200 copies/mL and at least one of the Week-24 (± 28 days) or Week-36 (± 28 days) HIV-1 RNA measurements is < 200 copies/mL.

Secondary Objective #3. To summarize and compare adherence patterns in YLWH initiating TERA or continuing SOC during the intervention period (weeks 0-12) and the post intervention period (weeks 12-48).

Outcomes:

- Electronic dose monitored adherence: Percent of days with all doses taken per week.
- Electronic dose monitored on-time adherence: Percent of days with all doses taken within the defined acceptable windows (±4 hours) per week.
- Electronic dose monitored non-persistence: Number of gaps (at least 7 consecutive days (168 hours) between doses) in the intervals: week 0-12, 12-24, 24-36 and 36-48.

11.4.3 Other Outcome Measures

Other Objective #1. To evaluate and compare changes in survey collected social-psychological

factors by study arm, and establish the extent to which these changes are associated with adherence and viral load outcomes.

Outcomes:

- Emotional Regulation Questionnaire (ERQ)
- Social Support Scale (MOS)
- CES-D
- HIV Stigma Measure
- Self-reported Medication Adherence
- Adherence (IMB-AAQ)
- Adherence Self Efficacy
- Adolescent Decision Making Questionnaire (ADMQ)
- EDM measures listed in Secondary Objective #3
- VL measures listed in Secondary Objective #2

Other Objective #2. To identify profiles (phenotypes) of adherence based on EDM data. Outcome: Adherence phenotypes that highlight temporal patterns of use and overall adherence.

Other Objective #3. To describe the resource requirements and costs of the TERA intervention, including the AdhereTech™ bottles, virtual coaching software, SMS messages, and personnel time and salaries.

Outcomes:

- Adherence counsellor staff time associated with the intervention through activity logs translated into dollar terms using loaded salary data of the personnel involved and transformed into a per participant fixed and variable cost estimates
- Cost of the AdhereTech™ bottle and replacements.
- Staff time required to maintain the process flow of the TERA intervention translated into dollar terms using loaded salary data of the personnel involved and transformed into a per participant fixed and variable cost estimates

Other Objective #4: To characterize through qualitative interviews, the main themes youth report for adherence support needed, received, and valued at 12 and 48 weeks.

Outcomes: Thematic content of interview inquiries about

- Facilitators and barriers to adherence
- Perceptions of received (types of support and value) support for adherence
- Unaddressed adherence related needs

Other Objective #5: To evaluate acceptability and feasibility of participation in the intervention with mixed methods (interviews and ACASI survey).

Outcomes: Acceptability

- Satisfaction Survey at week-12 ACASI (all TERA arm participants)
- Semi-structured interview with a subset of participants in TERA.
- Thematic content of interview inquiries about
- Satisfaction with TERA intervention
- Experiences with specific components of the intervention
- Recommendation of intervention to others
- Perceptions of needs met, unmet needs, and impact
- Recommendations for changes

Outcomes: Feasibility

- Ability to enroll: number of youth enrolling in study compared to total number approached for enrollment
- Drop-out rate: number of participants lost to follow-up prior to Week-12 clinic visit compared to total enrolled
- Adherence coach contact failure rate: number of failed attempts to contact participants compared to total number of contact attempts made [TERA study arm only]
- Adherence coach ratings on quality of interactions and contacts [TERA study arm only]
- AdhereTech™ bottle replacement rate: number of AdhereTech™ bottles requiring replacement due to loss, theft, or breakage
- Participant reported problems with the AdhereTech™ device or any aspects of TERA intervention [TERA study arm only]

Other Objective #6. To gather feedback from intervention coaches and clinic staff on experiences implementing the intervention with YLWH.

Outcomes: Semi-structured interview with TERA coaches and discussions with site staff after completion of intervention phase of research generating thematic content for:

Coaches/Monitors

- Advantages of TERA
- Challenges with TERA
- Skills required from coaches
- Experiences with monitoring tickets and assigning escalations
- Experiences with youth in sessions and in outreach
- Reactions to use of Smart-Bottle
- Case examples (best and worst)
- Recommendations for changes
- Estimation of hours/time allocations for specific activities

Site Staff/team members

- Advantages of TERA

- Challenges with TERA
- Skills required for site-level procedures
- Perceived impacts, facilitators and barriers to youth adherence
- Perceived impacts, facilitators and barriers to TERA implementation
- Estimation of hours/time allocations for specific site-level study-related activities
- Reactions to use of Smart-Bottle
- Recommendations for changes

11.5 Study Monitoring

Implementation of the study will be monitored by the Protocol Team and by an independent Study Monitoring Committee (SMC) that provides this oversight for other on-going ATN protocols.

11.5.1 Monitoring by Study Team

Full details of the proposed monitoring reports will be described in a separate Study Progress Data and Safety Monitoring Plan (SPDSMP). Accrual and retention based on reports generated by FSTRF in collaboration with the Statistical and Data Analysis Center (SDAC) will be presented monthly. If there are any problems with accrual or retention rates at specific sites, the Protocol Team will work with the sites to identify operational issues or problems and take appropriate action.

The Protocol Team will review other key indicators of study quality monthly, based on reports generated by SDAC. These reports will include information on baseline characteristics as well as data completeness. All reports for the Protocol Teams will present data combined across the TERA and SOC arms. The Protocol Team will also be responsible for reviewing any safety events, including untoward events, as they are reported from the ATN QNS.

Protocol deviations will be reported in the Rave data management system and reviewed by the Protocol Team on a regular basis. Protocol related tests, procedures or labs not performed as scheduled due to malfunctioning equipment, patient non-compliance, patient need or preference (i.e. vacation), patient condition or due to falling on a weekend or holiday will be noted in the patient study record but will not be reported as deviations.

Protocol deviations that are required to be reported to the sIRB within 7 days, such as ones that harm a participant or others, must also be reported in the ATN QNS for immediate review. The list of these deviations is included in the Manual of Procedures (MOP).

11.5.2 Study Monitoring Committee

An independent SMC will review this study at scheduled, planned points, or as otherwise determined by the SMC. Reports for the SMC will include accrual, baseline characteristics, data quality and completeness, participant retention, study implementation issues, safety events, and summaries of the primary outcome by masked intervention arm.

The primary consideration at any interim review is avoidance of harm to participants. At any point, should the SMC or Protocol Team become aware of major unexpected findings that impact participant safety or study research integrity, then it may be necessary for the SMC to consider recommending prematurely stopping enrollment and/or participant follow-up.
As this is a Phase II study, there are no a-priori statistical stopping guidelines. At every interim review the SMC should consider the totality of evidence including feasibility assessed by rates of enrollment, losses-to-follow-up, and implementation issues using the AdhereTech™ device. Efficacy analyses will take place at each interim review after at least 60 participants have Week-12 HIV-1 RNA results available. Efficacy analyses will focus on the proportions of participants with HIV-1 RNA < 200 copies/mL at Week-12 in the TERA and SOC arms and whether the 95% confidence intervals for the two proportions overlap. Non-overlapping confidence intervals would indicate large efficacy differences between the two arms. For example, if one third of participants had reached Week-12 (20 in each arm), the difference in proportions between the two arms (depending on outcome rates) might need to be as large as 0.5 for the 95% confidence intervals to be non-overlapping. With half the participants reaching Week-12 (30 in each arm), the difference could be as large as 0.4. If the SOC arm is superior to the TERA arm based on Week-12 data, the SMC might consider recommending termination of the study. However, even if the TERA arm is superior to the SOC arm at Week-12, it is possible the benefit of the TERA intervention would not be sustained in the post-intervention phase, so the SMC's discussion should include consideration of recommending continuing enrollment and participant follow-up until evidence of the durability of the intervention effect is available. An additional consideration will be outcome rates in the SOC arm, upon which sample size calculations are based. If outcome rates are very different from anticipated, the sample size of the study may need to be reassessed.

At each review the SMC may recommend that the study proceed as currently designed, proceed with design modifications, or be discontinued. The SMC may also provide specific operational recommendations to help address any study implementation challenges identified during their reviews.

11.6 Statistical Analysis Plan

The primary and secondary goals of this study are to estimate and compare virologic suppression rates and adherence over 48 weeks between the TERA and SOC arms. Analyses will be intent-to-treat (ITT) using all participants as randomized. Categorical outcomes will be summarized using proportions (95% confidence intervals) and continuous outcomes will be summarized using means/medians as appropriate. In adjusted analyses, the number of covariates used in the models will be limited because of the relatively small sample size. A significance level of $p < 0.05$ will be used with no adjustments for multiple comparisons or interim analyses.

Full details of the proposed analyses will be described in separate statistical analysis plans (SAPs). The primary SAP will include primary and secondary objectives and outcomes. This will

form the basis of the primary manuscript. Analyses of the other objectives and outcomes will be summarized in separate SAPs, grouped together to form separate manuscripts. These secondary SAPs will be finalized once the primary analysis is complete as the primary findings will inform priorities for the additional analyses.

11.6.1 Primary Outcome

The primary unadjusted analysis will estimate and compare proportions of participants with virologic suppression (HIV-1 RNA < 50 copies/ml and < 200 copies/ml) at Week-12 in the TERA and SOC arms. Participants lost-to-follow-up before 12 weeks or with no HIV-1 RNA measurement within ±14 days of the Week-12 visit will be classified as failures. Adjusted analyses will use logistic regression models adjusted for study arm and may use other covariates measured at study entry that differ between arms and associate with outcome (such as route of HIV infection, years living with HIV, age, motivation and behavioral skills, mental health, substance use, ARV regimen, and others). Adjusted analyses will explore the resilience of the intervention effect after adjustment for other covariates, as well as identifying other factors associated with the primary outcome.

11.6.2 Secondary Outcomes

11.6.2.1 To estimate and compare virologic suppression rates (<50 and <200 copies/ml) in YLWH 24, 36, and 48 weeks after initiating TERA or continuing SOC.

The analytic approach for this secondary outcome will be similar to that used for the primary outcome, with unadjusted comparisons at each time point and using logistic regression for adjusted analyses.

11.6.2.2 To estimate and compare proportions of participants initiating TERA or continuing SOC who achieve virologic suppression (HIV-1 RNA < 200 copies/ml) by 12 weeks and maintain virologic suppression through 48 weeks.

The analytic approach for this secondary outcome will be similar to that used for the primary outcome, with unadjusted comparisons of the proportions of participants achieving and maintaining documented viral suppression through 48 weeks, and using logistic regression for adjusted analyses.

11.6.2.3 To summarize and compare adherence patterns in YLWH initiating TERA or continuing SOC during the intervention period (weeks 0-12) and the post intervention period (weeks 12-48).

The EDM will provide daily information on adherence in each participant. Two outcomes (percent of days correctly dosed per week and percent of days dosed within the targeted time frame per week) will be summarized by arm by week, in 12-week intervals, and during and post-intervention. Differences may be largest during the initial 12 weeks, since that is when the

intervention is administered, with differences waning over time. To address the issue of informative censoring induced by losses-to-follow-up, analyses will include (i) available data and (ii) imputing weekly adherence of 0% after a participant has been lost-to-follow-up. Interventions will be compared using repeated measures rank sum tests.

Alternative outcome definitions may need to be used if there is insufficient variation in percent adherence. For example, it might be necessary to define a binary outcome (adherent, not-adherent) if the majority of percent adherence measures are >95%, in which case analyses would be based on comparisons of proportions and logistic regression.

An incidence rate (95% confidence interval) of the number of gaps between dosing of > 7 days in each 12-week interval will be calculated and compared between intervention arms.

11.6.3 Other Outcomes

Analyses of other outcomes will be initiated after results of the primary and secondary objectives are known, so the analyses listed below are subject to change.

11.6.3.1 To evaluate and compare changes in survey collected social-psychological factors by study arm, and establish the extent to which these changes are associated with adherence and viral load outcomes.

Each social-psychological outcome of interest and changes from baseline will be summarized at each measured time point by arm. Correlations among survey measures will be summarized. Depending on observed patterns, survey measures may be grouped or combined and used in regression models to determine their association with the VL and EDM adherence outcomes.

11.6.3.2 To identify profiles (phenotypes) of adherence based on EDM data
This will be an exploratory analysis based on doses taken per day. Daily and weekly summaries of the data will be explored to see if there are distinct patterns of adherence, such as weekend holidays, regular periods of good and poor adherence, extended periods with no doses etc.

11.6.3.3 To describe the resource requirements and costs of the TERA intervention, including the AdhereTech™ bottles, virtual coaching software, SMS messages, and personnel time and salaries.

Cost and resource use as well as efficacy data from Secondary Objective 1 will serve as inputs for model-based analyses to project the longer-term clinical outcomes, costs, and cost-effectiveness of the TERA intervention. Each resource will be multiplied by its unit cost (e.g., coach minutes spent as a proportion of FTE * coach salary; number of SMS messages * per-message cost) to calculate total costs for the intervention. As data permit, costs will be stratified by key participant characteristics, such as demographics and adherence level.

Outcomes will be examined not only for the intervention as implemented in the trial, but also under a range of relevant scenarios, including use of alternative virtual coaching and adherence monitoring software, as well as if implemented in different populations with different duration and magnitude of effectiveness. If resources are available, model-based analyses will be conducted in collaboration with the Cost-effectiveness of Preventing AIDS Complications (CEPAC) research team, at Massachusetts General Hospital, Boston, MA.

11.6.3.4: To characterize through qualitative interviews, the main themes youth report for adherence support needed, received, and valued at 12 and 48 weeks.

Transcripts from qualitative interviews using semi-structured interview guides will be reviewed by a qualitative coding team iteratively to identify main themes emerging within specific areas. A hybrid approach using framework analysis methodology to sort discourse text into content captured in response to specific question areas (eg., questions asking about facilitators of adherence, barriers to adherence, perceptions of support received, adherence related needs) and thematic content analysis to identify main themes emerging from their areas of inquiries will generate the basic coding structure. This also allows for examination of specific content codes across the frames, Dedoose (an online coding software program) will be used to import the transcript documents and creating coding structures- first with the frames and then thematic content. Inter-coding reliability for application of frame themes will be established through the testing/training function of Dedoose. Coders will continue training until perfect agreement is obtained on initial transcripts. Frames will be iteratively reviewed to identify the main themes which will be summarized with sample quotes. Potential differences in themes from specific groups of participants (eg., age group, route of HIV infection, gender) and over time (12 versus 48-week interviews) will be considered. Quantitizing will be considered, although the main focus of these analyses will be on detailing nuanced experiences.

11.6.3.5 To evaluate acceptability and feasibility of participation in the intervention with mixed methods (interviews and ACASI survey).

All aspects of TERA implementation will be summarized including: ability to enroll to the study (both study arms), drop-out rates by Week-12 and throughout the study (both study arms), numbers of participants escalating to different alerts and outreach at least once and numbers of alerts per participant (TERA arm only).

Feasibility of using the AdhereTech™ device will assessed by summarizing bottle replacement rates (with reasons) and participant-reported problems.

The qualitative data contributing to participant perspectives of the acceptability and feasibility of the TERA intervention will come from the interviews specifically with individuals in the TERA intervention condition at weeks 12 and 48. The same procedures noted above (11.6.3.4) are used for these analyses.

11.6.3.6 To gather feedback from intervention coaches and clinic staff on experiences implementing the intervention with YLWH.

The same procedure for identification of themes emerging from specific interview guide questions and narratives that cut across frames will be used with the interviews of coaches and clinic staff. Coaches and clinic staff are free to decline participation. Interviews will take place at the end of the intervention phase for coaches and site staff. Interviews are conducted by an interviewer trained in qualitative interviewing and will be audio recorded for transcription. Transcription will de-identify the data and the qualitative team will code the transcripts according to the previously detailed procedures.

12 HUMAN SUBJECTS

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

12.1 Participants' Confidentiality

All adherence records, questionnaires, including the ACASI, evaluation forms, reports, and other research-related records will be identified by a coded number only, to maintain participant confidentiality. All records with personally-identifying information will be kept in a locked, limited access area (such as a locked file cabinet or secured electronic folder). All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant (and parent or legal guardian, when applicable), except as necessary for monitoring by the ATN CC or NICHD.

12.2 Certificate of Confidentiality

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

12.3 Risks and Benefits

12.3.1 Risks

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

However, there are some risks of emotional discomfort or distress due to the personal nature of some questions asked in the behavioral assessments as well as by the Adherence Coach during intervention phone calls and risk of breaching confidentiality during the calls and/or the text reminders that the participant receives. Participants will be informed they are free to decline to answer any questions, or withdraw from participation at any time without penalty. Participants will be instructed to contact study personnel or to consult the list of referrals provided if feelings persist or worsen after several days. If the response indicates the participant is in urgent need of mental health assistance, site staff should follow their individual site procedures for acute mental health referrals. Site staff should contact a supervisor immediately and stay with the study participant until the supervisor, mental health professional or emergency services, if needed, arrives.

Participants will undergo a debriefing interview after completing the behavioral assessments

and will be offered referrals to speak with mental health professional staff that is available at the study site if needed.

The biomarker measurements that are involved in this study requiring a venipuncture to collect blood samples are all considered part of SOC and not an additional study specific requirement. This procedure may cause local discomfort, bleeding, or bruising; rarely small clot or infection can occur at the blood draw site. This measurement should not be considered greater than minimal risk in and of itself given its routine use in general health care delivery.

Finally there is a risk of breach of confidentiality related to disclosure of participant information as part of the communications (text message, phone call, email) with the participant or attempts to reach them through the contacts they provided on the TERA Contact Form. Every effort to avoid an inadvertent breach of confidentiality will be taken. Participants will be asked if messages can be left at the contact numbers they provided. Study staff will not leave messages unless expressly permitted to do so by the participant. If permission is given to leave messages, site staff will assure participants that messages left with a family member or friend will only ask the participant to contact study staff and will not include any protected health information or information related to study participation.

12.3.2 Benefits

Information from this study may benefit other youth, now or in the future, by understanding methods to motivate HIV-positive young people to start and adhere to their prescribed HIV treatments. Possible participant benefits may include: (1) improvements in HIV medication adherence and thus, health status, and (2) assisting in identifying a potential intervention to improve HIV medication adherence and health outcomes for YLWH.

12.4 Institutional Review Board (IRB) Review and Informed Consent

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

Signed informed consent (or assent as applicable) will be obtained from the participant (or parent, legal guardian, or person with power of attorney for participants who cannot consent for themselves). The study team is requesting the waiver of parental permission for minor participation based on 45 CFR 46.408. If waiver of parent consent is not granted, then a signed informed consent from the parent and the minor's assent will be required. The signed original consent/assent form will be kept on file at the site and a copy of the consent/assent form will be given to the participant and to the parent or legal guardian, if applicable. Sample informed consent/assent forms are included in Appendix 2.

The study team is also requesting waiver of written consent for the interviews with coaches and

clinic staff. Verbal consent will be requested from all staff participants; therefore, no documentation of participation will be recorded, which will enhance participant confidentiality. The qualitative interviews will take place at the end of the intervention phase for coaches and at the end of the study for clinic staff. They will be asked for feedback regarding their experiences implementing the study intervention. The interviews will not contain questions regarding sensitive data or protected health information. Their answers will be kept confidential and de-identified by the transcription service as previously described. Coaches and clinic staff are free to decline participation.

12.5 Risk Category: Minimal Risk

Permission will be sought from at least one parent or guardian in accordance with IRB approved procedures unless the IRB/EC has waived the requirements for obtaining parental or guardian permission in accordance with 45 CFR §46.408 (c).

The study team is requesting the waiver of parental permission for minor participation based on 45 CFR 46.408, which provides that the single IRB may waive parental permission under the same circumstances that it may waive individual consent, as described in 45 CFR 46.116 (d): (1) the research involves no more than minimal risk to participants; (2) the waiver or alteration will not adversely affect the rights and welfare of the participants; (3) the research could not practicably be carried out without the waiver or alteration; and (4) whenever appropriate, the participants will be provided with additional pertinent information after participation. This research clearly meets requirements 1 & 2. Since many YLWH access medical care services independently of parental involvement, the requirement to involve parents may adversely affect the minor's decision to participate and thereby potentially bias the sample.

Assent of the children involved in this study will be sought in accordance with the regulations at 45 CFR §46.408(a) or 21 CFR §50.55 and IRB-approved policies and procedures.

12.6 Waiver of Requirement for Parental Consent for Special Circumstances

The single IRB will be requested to grant a waiver of parental/legal guardian consent to participate in this research study under the age of legal majority based on state or local laws.

Under 45 CFR Part 46.4116 (c), an IRB has the authority to waive parental permission if it determines that "a research protocol is designed for conditions or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects" and "an appropriate mechanism for protecting the children who will participate as research subjects is substituted" and "that the waiver is not inconsistent with Federal, state, or local law."

The Protocol Team would submit that:

- This study is not considered greater than minimal risk. Participants will complete surveys, use an electronic pill bottle, and undergo routine HIV viral load monitoring. None of the content of this study is beyond what would be covered during routine

medical or psychological visits or procedures related to improving medication adherence. The probability of harm from participating in this study is no greater than that occurring in routine care.

- Participating clinic sites and most other community agencies offering HIV-related services are confidential and do not require parental/legal guardian notification or permission to treat under most state regulations.

- Contacting the parent/legal guardian could constitute a breach of confidentiality for these HIV-positive participants at risk for abuse or ousting from the home if parents/legal guardians are not aware of their HIV status.
- It is expected that there will be subjects who have not disclosed their HIV status to parents/legal guardians, and the parents/legal guardians will not be aware of the subject's gender identity or risk behaviors. A requirement for parental permission in this type of study could not only affect a person's willingness to participate, but could also potentially impact the ability of researchers to engage in this type of HIV-related research with youth.
- Adequate protection has been substituted by the mechanisms in place to protect the privacy and confidentiality of subjects and by the treatment referrals offered if needed.

12.7 Prisoner Participation

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 for the recruitment of prisoners. Participants enrolled who subsequently become incarcerated or are placed in detention may not continue study participation during incarceration. Study visits cannot be conducted during the period of incarceration or detention.

12.8 45 CFR Parts 160 and 164 Standards for Privacy of Individually Identifiable Health Information ("Privacy Rule" Pursuant to the Health Insurance Portability and Accountability Act - HIPAA)

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

12.9 Study Discontinuation

This study may be discontinued at any time by the NICHD.

13 ADMINISTRATIVE PROCEDURES

13.1 Regulatory Oversight

This study is sponsored by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the National Institute of Mental Health (NIMH), the National Institute on Drug Abuse (NIDA) and the National Institute on Minority Health and Health Disparities (NIMHD), which are parts of the United States National Institutes of Health (NIH).

The ATN CC is responsible for the oversight of this study and for providing funding support to the clinical research sites at which this study will be conducted. ATN clinical site monitors will perform on-site monitoring for visits as described in section 8.11. As part of these visits, monitors will inspect site files to ensure compliance with both U.S. and local regulatory requirements.

13.2 Protocol Registration

Before the recruitment and enrollment of subjects, sites must have their local IRBs cede to the UNC single IRB, which will review the protocol and any subsequent full version amendments, and the protocol informed consent form(s). Sites are required to work closely with their IRBs to coordinate approval of UNC as the single IRB and submit any material (i.e., approved informed consent forms, protocol registration documents) to their IRBs as needed/as requested by their local IRB. Staff at the CC will review the submitted protocol registration documents to ensure that all of the required materials have been received. Original documents must be maintained at the study sites.

For additional information about the initial protocol registration and subsequent protocol registration process, please refer to the current version of the study MOP.

13.3 Study Implementation

This study will be conducted in accordance with the protocol, international good clinical practice guidelines (ICH E6), and all applicable U.S. and local regulations. Study implementation at all sites will also be guided by the study-specific procedures and other implementation material, which will be available on the ATN website: https://sites.cscc.unc.edu/atn/

Study implementation at each site is based on the study MOP and is articulated by each site in a Protocol Implementation Plan and Delegation of Authority and Master Signature Log which will describe roles, responsibilities, and procedures for this study.

13.4 ClinicalTrials.gov

The trial is registered with ClinicalTrials.gov under Identifier Number: NCT03292432.

13.5 Publications

NICHD and ATN policies will govern publication of the results of this study. Publication of the results of this trial will be governed by the ATN Publications Policy, from the ATN Manual of

Policies and Procedures. Any presentation, abstract or manuscript will be made available for review by the core protocol team prior to submission. Scientific publications or presentations that result from the study will not mention participants by name or reveal any personal information that could potentially compromise participant confidentiality. All publications and presentations must clearly report funding source, ATN protocol number, and supporting agencies.

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APPENDIX I: SCHEDULE OF EVALUATIONS

Event	Screening[1]	Entry/ Baseline	Week-4	Week-12	Week-24	Week-36	Week-48 (Off Study)
Window			+/- 14 days	+/- 14 days	+/- 28 days	+/- 28 days	+/- 28 days
Eligibility checklist	X						
Informed Consent	X						
Confirm eligibility		X					
Contact Form[2]	X	X	X	X	X	X	
Enrollment and Randomization		X					
Demographics/Medical History[3]		X					
ACASI Surveys		X		X	X	X	X
Safety Events			X	X	X	X	X
Viral Load	X[4]		X[5] (as available)	X[6]	X[6]	X[6]	X[6]
CD4 if available	X	X[7]	X	X	X	X	X
Pregnancy Test[8]		X[8]					
Medication History & Changes Log		X	X	X	X	X	X
Adherence Support Service Utilization Check list (past 30 days at baseline; since last visit at follow-up)		X		X	X	X	X
EDM Device Issue, Follow-up, or return		X	X	X	X	X	X
Remote Coaching In Clinic Session Visit (intervention arm)		X	X	X			
Qualitative Interviews [subset]				X			X

[1] Entry/Enrollment visit should be within 45 days of screening; [2] Contact information is a site tool and is not collected in Rave; [3] Baseline medical history covers previous 30 days; [4] Documented laboratory results may be used if available within 45 days of study enrollment visit. This is part of study eligibility criteria; [5] Abstract from medical record if done for standard of care; not required to be done for research study purpose only; [6] Collect for research study purpose if not already planned/available for standard of care; [7] At baseline record most recent CD4 value; [8] Pregnancy test (urine or blood; research test if not also planned for standard of care) result required for study entry, pregnancy tests at study visits other than study entry based on site's standard of care.

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