IMPAACT 2016

Evaluating a Group-Based Intervention to Improve Mental Health and ART Adherence Among Youth Living with HIV in Low Resource Settings

A Study of the International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Sponsored by:
National Institute of Allergy and Infectious Diseases
Eunice Kennedy Shriver
National Institute of Child Health and Human Development
National Institute of Mental Health

DAIDS ES #38506
Non-IND Study

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Version 1.0
29 August 2018

IMPAACT 2016

Evaluating a Group-Based Intervention to Improve Mental Health and ART Adherence Among Youth Living with HIV in Low Resource Settings

TABLE OF CONTENTS

IMPAACT 2016

Evaluating a Group-Based Intervention to Improve Mental Health and ART Adherence Among Youth Living with HIV in Low Resource Settings

DAIDS Study ID #38506

Version 1.0
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Protocol Signature Page

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

Signature of Investigator of Record	Date

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(printed)

IMPAACT 2016

Evaluating a Group-Based Intervention to Improve Mental Health and ART Adherence Among Youth Living with HIV in Low Resource Settings

ABBREVIATIONS AND ACRONYMS

ADAPT-ITT	Assess, Decide, Administer, Produce, Topical expert review, Integrate, Train, Pilot Test
AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ART	antiretroviral therapy
ARBA	AIDS Risk Behavior Assessment
CASI	Computer-Assisted Self-Interview
CFR	Code of Federal Regulations
DAIDS	Division of AIDS
DAERS	DAIDS Adverse Event Reporting System
EC	ethics committee
eCRF	electronic case report form
FDA	Food and Drug Administration
HIV	Human Immunodeficiency Virus
ICC	intra-cluster correlation
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Network
IPL	immediately post last group session
IRB	institutional review board
IoR	Investigator of Record
ILOM	Indigenous Leader Outreach Model
IYL	Indigenous Youth Leaders
LPC	laboratory processing chart
MOP	manual of procedures
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
PID	participant identification number
SES	Subject Enrollment System
SID	Study Identification Number
SOP	standard operating procedure
TI-CBT	Trauma-Informed Cognitive Behavioral Therapy
U.S.	United States

IMPAACT 2016

Evaluating a Group-Based Intervention to Improve Mental Health and ART Adherence Among Youth Living with HIV in Low Resource Settings

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IMPAACT 2016

Evaluating a Group-Based Intervention to Improve Mental Health and ART Adherence Among Youth Living with HIV in Low Resource Settings

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IMPAACT 2016

Evaluating a Group-Based Intervention to Improve Mental Health and ART Adherence Among Youth Living with HIV in Low Resource Settings

SCHEMA

Purpose: To evaluate whether an Indigenous Leader Outreach Model (ILOM) of trauma-informed cognitive behavioral therapy (TI-CBT) [referred to as TI-CBT delivered by Indigenous Youth Leaders (IYL)] is associated with improved mental health outcomes and ART adherence among youth living with HIV.

Design: Multi-site, two-arm, individually randomized controlled trial preceded by Focus Groups and Pilot Testing to adapt the intervention to the local context.

Study Population: 15-19 year old youth living with HIV and mental health distress, and their caregivers (if available and agreed to by youth participant).

Sample Size: Approximately 192 - 256 youth participants (96 - 128 per arm), plus their caregivers, in the Randomized Trial. Each arm will have 12 - 16 groups with an average of eight youth participants per group (range 6 – 10). Youth participants' caregivers will be assigned to the same arm as their youth participants.

Prior to the Randomized Trial, Focus Groups comprised of 5-8 youth participants and 5-8 caregivers will be conducted at selected sites. All sites will also conduct a Pilot Test with up to eight youth participants and up to eight caregivers.

Study Intervention: In the Randomized Trial, youth participants will be randomized in a 1:1 ratio with their caregivers to one of two study arms as shown in the table below.

Randomized Trial Arms	Youth Participants	Caregivers of Youth Participants
TI-CBT Intervention Arm	Six 2-hour TI-CBT group sessions led by IYL during Weeks 1 to 6 and One 2-hour booster TI-CBT group session at 6 months	Two 2-hour group sessions led by adult study staff during Weeks 1 to 6 and One 2-hour booster group session at 6 months
Discussion Control Arm	Six 2-hour discussion group sessions led by IYL during Weeks 1 to 6 and One 2-hour booster discussion group session at 6 months	Two 2-hour discussion group sessions led by adult study staff during Weeks 1 to 6 and One 2-hour booster discussion group session at 6 months

Study Duration: Approximately 22 months total.

Accrual into the Focus Groups and Pilot Testing is expected to be completed within three months with completion of the Pilot Testing and review requiring an additional three months for a total of six months. Accrual into the Randomized Trial is expected to be completed within four months (counted from the date of first enrollment) and each participant will be followed for 12 months.

Primary Objective

The primary objective of this study is to:

- Evaluate whether a TI-CBT Intervention is associated with improved depression, anxiety, and/or traumatic stress symptoms for youth living with HIV compared to a Discussion Control at six months.

Secondary Objectives

The secondary objectives of this study are to:

- Determine the feasibility, acceptability, and fidelity of a TI-CBT Intervention.
- Evaluate whether a TI-CBT Intervention is associated with improved depression, anxiety, and/or traumatic stress symptoms for youth living with HIV compared to a Discussion Control following the last group session and at 12 months.
- Assess whether a TI-CBT Intervention is associated with improved ART adherence (hair samples, self-report) and viral suppression (HIV RNA plasma) for youth living with HIV compared to a Discussion Control following the last group session and at six and 12 months.
- Assess whether a TI-CBT Intervention is associated with improved structural factors for youth living with HIV (HIV stigma and support for adherence; barriers to adherence; gender-based violence; gender roles) compared to a Discussion Control following the last group session and at six and 12 months.
- Assess whether a TI-CBT Intervention is associated with improved structural factors for caregivers (HIV knowledge, stigma, and support for adherence; barriers to adherence) compared to a Discussion Control following the last group session and at six and 12 months.
- Assess whether a TI-CBT Intervention is associated with improved behavioral risk outcomes for youth living with HIV (alcohol/drug use; sex-risk behaviors; caregiver report of youth behavior) compared to a Discussion Control following the last group session and at six and 12 months.
- Identify the individual, social, and structural barriers, and facilitators to implementation of a TI-CBT Intervention.
- Compare the rates of all targeted adverse events between a TI-CBT Intervention and a Discussion Control for youth living with HIV.

Other Objectives

The other objectives of this study are to:

- Evaluate whether a booster session at six months is associated with continued improvements in depression, anxiety and traumatic stress symptoms at 12 months.
- Assess whether youth and caregiver demographic and structural factors moderate the efficacy of a TI-CBT Intervention compared to the Discussion Control.

Exploratory Objectives

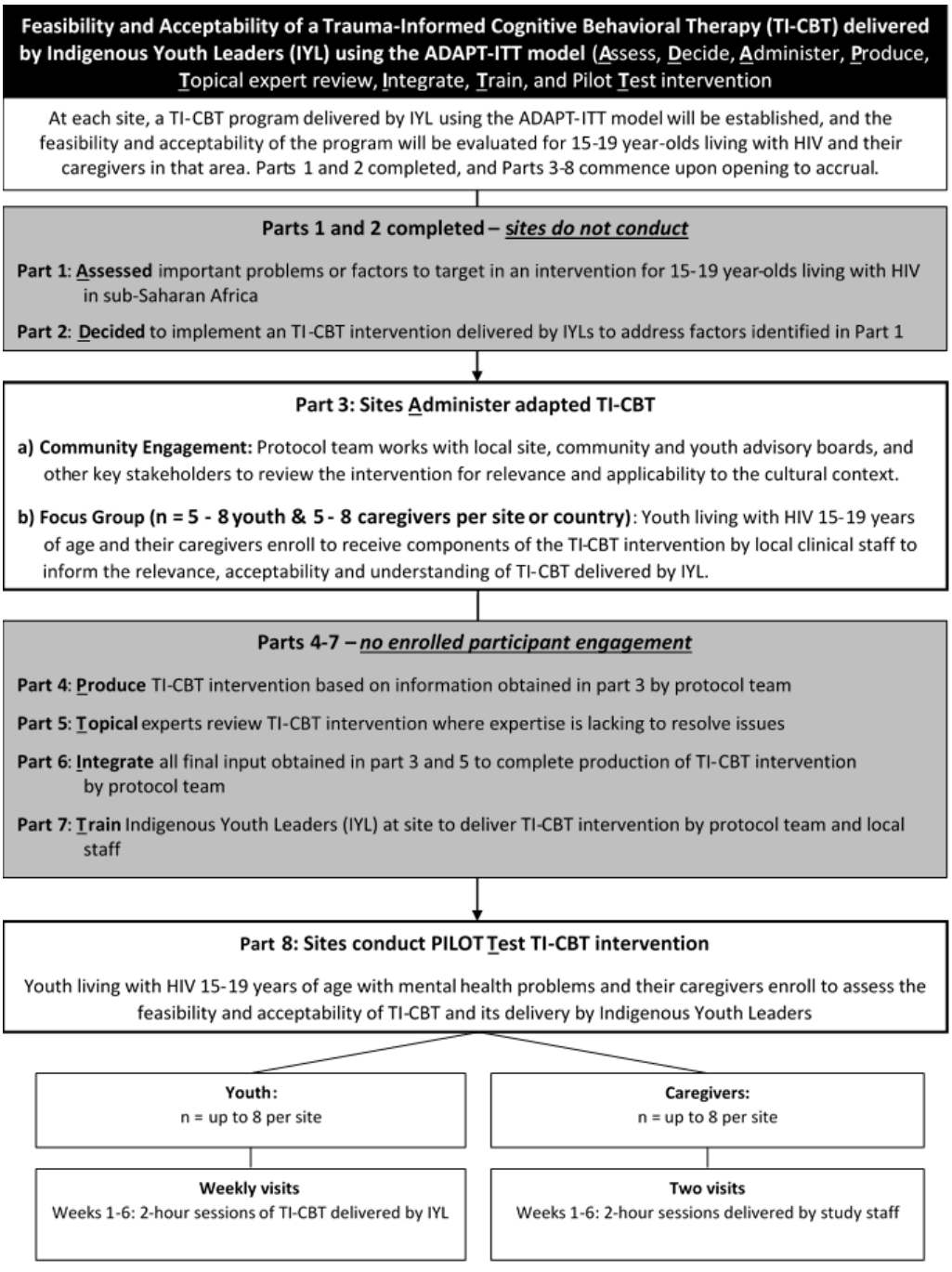
The exploratory objectives of this study are to:

- Examine whether a TI-CBT Intervention is associated with a decrease in plasma inflammatory biomarkers in youth from study entry to six and 12 months compared to a Discussion Control.
- Examine the moderating effect of inflammatory biomarkers in youth on the efficacy of a TI-CBT Intervention compared to a Discussion Control.

IMPAACT 2016

Evaluating a Group-Based Intervention to Improve Mental Health and ART Adherence Among Youth Living with HIV in Low Resource Settings

Figure 1: ADAPT-ITT Model (Focus Group and Pilot Test)

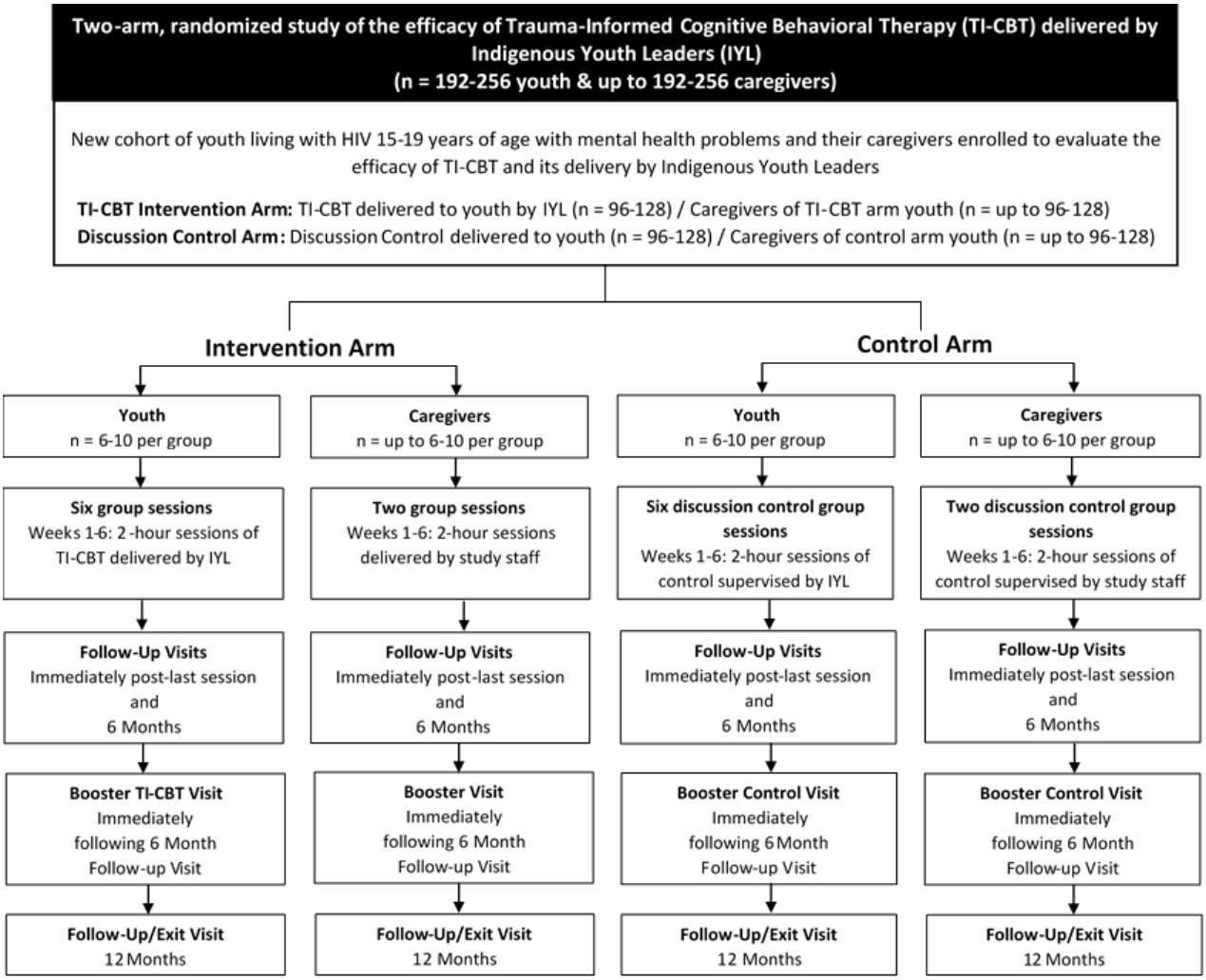


Accrual completed and data from a given site reviewed to inform the Randomized Trial.

IMPAACT 2016

Evaluating a Group-Based Intervention to Improve Mental Health and ART Adherence Among Youth Living with HIV in Low Resource Settings

Figure 2: Overview of Randomized Trial Design



1 INTRODUCTION

1.1 Background

Adolescence is a developmental period marked by awakening sexuality, identity formation, and the development of abstract thought (1). Adolescents living with HIV often struggle to cope with these normative developmental challenges in the face of having a chronic, life-threatening, stigmatized, sexually transmissible illness. This struggle is frequently marked by impulsivity, risk taking, and a sense of invincibility, and may be enacted through maladaptive health behaviors, such as antiretroviral therapy (ART) non-adherence, unprotected sex, and substance abuse (2). These high-risk behaviors have been found to be more likely among HIV-infected youth with a history of psychiatric diagnosis as compared to those without a psychiatric diagnosis (3). A high prevalence of mental health difficulties has been demonstrated among youth living with HIV, including anxiety, depression, emotional and behavioral difficulties, and post-traumatic stress symptoms (4-13) and these mental health difficulties have been associated with ART nonadherence and poor virologic outcomes (4).

Caregivers play a significant role in HIV-infected children's health behavior and emotional development. There is ample evidence that caregiver support, attentiveness, warmth and open communication can promote resilience and positive health outcomes and behaviors among children (14). Likewise, parental neglect and hostility are related to increased child and adolescent mental health problems. In the context of living with HIV, negative parent-adolescent relationships, caregiver stigma-related attitudes, and diminished support for adherence may prove essential barriers to positive mental health for youth living with HIV and may be an additional traumatic stressor. Evidence suggests that HIV-infected youth who were double orphans (both parents deceased) were more likely to be stigmatized by extended family caregivers and reported lack of adherence support and increased mental health difficulties compared to youth with one or both biologic parents alive (15). Family-based interventions have demonstrated efficacy for a broad range of child and adolescent mental health problems and may be helpful for youth living with HIV (16, 17). Strengthening the parent-adolescent relationship may protect against mental health problems and improve ART adherence for youth living with HIV.

Other structural factors impact both mental health and ART adherence for youth living with HIV. Three factors stand out as particularly relevant for youth living in sub-Saharan Africa: gender-based violence, traditional gender roles, and HIV stigma. Gender-based violence, including verbal, emotional, physical, and sexual abuse, is highly prevalent in sub-Saharan Africa. The culturally sanctioned gender roles, attitudes, and practices reinforce submissiveness among women and hegemony and coercion by men (18), creating power inequities that have given rise to high rates of forced sex, in turn increasing the risk of HIV infection and unwanted pregnancies. Data from large surveys of adolescent and young adults conducted in South Africa suggest that beliefs about traditional gender and relationship constructs have significant influence on behavioral patterns (18-22). Adolescent boys in South Africa are more likely than girls to view forced sex as a sign of love, an appropriate way to satisfy sexual urges, acceptable if the girl is financially dependent on the boy, and an effective way to punish female partners. Meanwhile, boys tend to be less knowledgeable than girls about the health and legal consequences of forced sex (20). Data also indicate heterogeneous views of gender roles and/or violence across males and females, or related behavioral patterns. For example, young men who consistently use condoms tend to hold less conservative gender role views, are less physically and/or sexually violent, and have fewer sexual partners than their peers who don't use condoms or use them inconsistently (19). While young women tend to conform to culturally sanctioned gender role expectations, young women use an array of strategies to negotiate their role (21). Young men and women's

views of gender roles are fluid and modifiable. For example, the Stepping Stones program, implemented in South Africa, showed efficacy in altering beliefs about gender and HIV-risk among young men and reduced intimate partner violence, while increasing behaviors that were healthy and culturally appropriate (22).

Stigma is known to affect mental health (23-26) and was highly associated with mental health in a study of Tanzanian youth living with HIV (4). HIV-positive adults and adolescents who perceive high levels of stigma tend to report less social support (23), exhibit mental health difficulties, and increased levels of incomplete ART adherence (4, 12, 27). A study among adolescent AIDS-orphans in South Africa also linked greater stigma with worse psychological outcomes (28).

The syndemic of HIV/AIDS and mental health problems among adolescents is particularly pervasive in the low-income countries where the majority of the world's two million HIV-infected 15 to 19 year-olds reside (29); however, few of these adolescents receive any mental health services. Lack of trained mental health practitioners and child psychiatrists make it difficult to offer mental health care to adolescents in these settings. Therefore, there is a critical need to develop and evaluate effective interventions that can be delivered by non-health care professionals to build in-country capacity and improve mental health and HIV outcomes in youth living with HIV.

Few mental health interventions specific for HIV-infected youth have been developed and evaluated to date. The *VUKA* pilot project in South Africa is a family-centered model that targets pre-adolescents age 10-14 years over 10 sessions and is delivered by trained mental health professionals (16, 17). *Sauti ya Vijana* (The Voice of Youth) is in the early stages of feasibility testing a mental health intervention developed to address mental health needs of HIV-infected youth (ages 12-24 years) in Tanzania and is delivered by lay-counselors (30, 31). The *Kigali Imbereheza Project* (KIP) includes youth in the target age range with supportive feasibility data and a complete training manual ready for scale up in additional countries. KIP uses trauma-informed cognitive behavioral therapy (TI-CBT) adapted to and delivered in Rwanda. In Rwanda, 350 youth 12 – 21 years old were enrolled in KIP. Preliminary outcome data suggest promising early results, including six-month follow-up reductions in depression, trauma, and anxiety and improved adherence to ART for males (32). In addition, caregivers who participated in the TI-CBT intervention reported greater HIV knowledge and less HIV stigma compared to baseline and compared to the control group (33). The KIP study in Rwanda used the Indigenous Leader Outreach Model (ILOM), where individuals from the target population, namely young adults (21-25 years old) living with HIV, were trained to deliver the intervention to younger youth living with HIV (34).

1.2 Prior Research

1.2.1 Indigenous Leader Outreach Model and Trauma-informed Cognitive Behavioral Therapy

This study will use the ILOM, which is founded on principles from social learning and social influence theories (35-37). In the ILOM, indigenous peers—defined as individuals with similar characteristics to the target population (e.g., age, behavior, experience, and cultural background) are trained to deliver health-related interventions (38-40) with the expectation of increased effectiveness (vs. non peer-led interventions), because peers can help establish new norms and are often viewed as more legitimate, knowledgeable, appealing, credible, responsible, and empathic to participants' life circumstances (40-43). According to the ILOM, communication during peer-led interventions is more egalitarian, as peer leaders engender trust and comfort among participants, and promote greater honesty and openness about sensitive topics (42, 44, 45). The

ILOM is promoted by NIH and WHO as effective in health-promotion, building leadership skills, and enhancing capacity to deliver programs in low-resource settings. An extensive research literature demonstrates that indigenous peer leaders can be trained to effectively deliver health-related interventions (46-53) with careful attention to high-quality preparation and ongoing coaching and technical assistance (36, 54-57), and that treatment fidelity can be achieved with timely feedback and continuous monitoring (56). Evidence in Rwanda supports the ability to train young adults living with HIV to deliver the manualized and low-tech TI-CBT to fidelity (58-60). However, the KIP study in Rwanda was not focused on youth with mental health issues and took place in a setting with strong mental health resources. Using TI-CBT with ILOM has not yet been evaluated in any other low-resource setting, nor with a focus on youth with symptoms of mental health problems. Of note, although mental health distress was not an inclusion criteria, youth participants reported high rates of distress, and there were no reports of adverse events.

TI-CBT is an empirically validated, resiliency-based mental health intervention that uses group psychoeducation to address the negative impact of stressful life or traumatic events (61). TI-CBT teaches relaxation techniques and new ways to manage distress through psychosocial health education, cognitive restructuring, and mastery of trauma. "Mastery of trauma" refers to the process by which survivors of psychological trauma work through the traumatic experience in a meaningful way, put it behind them (rather than to continue to re-live the trauma though mental health symptoms such as nightmares or flashbacks), and move on with life. The mastery of trauma component of TI-CBT addresses both the trauma of learning one has HIV and the trauma associated with managing a chronic and stigmatized illness. The psychosocial health education and cognitive restructuring components focus on the wide range of responses to learning one has HIV and identifying and problem-solving barriers to adherence. These components emphasize the long-term effects of trauma and stress on the body, common reactions to chronic stress, and ways to manage stress and stigma-related discrimination. The intervention highlights links between HIV and traditional gender roles, gender inequities, and gender based violence. Finally, the relaxation training teaches youth strategies to relax and these are integrated at the beginning and end of each session. TI-CBT provides a safe and supportive environment to achieve symptom mastery and improve wellness.

TI-CBT has been widely used in the United States, Europe, Asia, and Africa. In Uganda, TI-CBT was used to treat traumatic stress and depression in adolescent survivors of war (62). In Tanzania (63) as well as in Zambia (64), it was used to treat symptoms of grief and post-traumatic stress among child orphans. In Pakistan, TI-CBT was used to treat post-partum depression (65), and in the US to successfully treat youth victims of intimate partner violence (66, 67). Research indicates that CBT, if locally adapted, is feasible, acceptable, and effective in low resource settings (46, 49, 51). It can be delivered by local staff with limited prior counseling experience when provided adequate supervision and careful attention to fidelity monitoring (60). There is a functional TI-CBT Youth Intervention Manual for implementing TI-CBT, laying out approximately 12 contact hours divided into six, two-hour sessions.

1.2.2 ADAPT-ITT Model

The ADAPT-ITT model (the acronym is taken from the steps, as described below), consist of eight sequential steps. It is designed as a systematic approach to revise and contextualize an intervention for a local population, and will be an important component of the study as TI-CBT is implemented in multiple settings. The eight steps are: 1) ***A**ssessment* of the population's unique risk and protective factors based on previous literature, focus groups, and key informant interviews; 2) ***D**ecide* on the intervention to adapt for a new population based on findings from the assessment of the specific risk and protective factors; 3) ***A**dminister* components of the

intervention to small focus groups for feedback and identify new material/activities/content that will increase relevance for the local population; 4) ***P****roduction* or revising the curriculum based on feedback; 5) obtain feedback from ***T****opical experts* where the team lacks expertise; 6) ***I****ntegration* of the various inputs; 7) ***T****raining* personnel to deliver the intervention; and 8) ***T****esting* the final revised intervention in a pilot study (68).

ADAPT-ITT has been used in at least three NIH-funded studies, two in Cape Town, South Africa (69) and *South Africa STYLE* (70), and the KIP study in Rwanda for adolescents living with HIV. In both countries, there was an extensive evaluation of feasibility and acceptability, whereby participants reported the relevance of intervention content, activities, facilitator expertise, and general intervention characteristics. The process ensured that the chosen interventions incorporated unique cultural values, beliefs, and methodologies and recognized salient community-specific and socio-economic factors (71, 72). Furthermore, these feasibility and acceptability data informed final revisions to the intervention curriculum methods in preparation for larger randomized controlled trials. For IMPAACT 2016, a modified version of this ADAPT-ITT model will be used to ensure the TI-CBT intervention is relevant and acceptable to youth living with HIV in different countries in sub-Saharan Africa.

1.3 Rationale

Adolescents Living with HIV/AIDS

Despite improved access to effective ART, AIDS-related deaths among youth have tripled since the year 2000. AIDS is now the number one cause of death among adolescents in Africa and the second leading cause of death among adolescents globally (29). Although evidence indicates that stress and mental health-related symptoms significantly contribute to long-term morbidity, poor ART adherence, (26, 73) and ultimately, mortality, (74-76) evidence-based mental health interventions for this highly vulnerable group are lacking (77, 78). Similarly, few, if any programs address caregiver stigma and negative attitudes even though these factors may serve a central role in promoting or impeding mental health and medication adherence for youth living with HIV (15). Inclusion of caregivers in this intervention and evaluating caregiver attitudes is therefore an important component of this study.

Despite scale up efforts of effective ART, in the absence of evidence-based mental health interventions and the lack of resources to deliver effective programs, millions of adolescents living with HIV in low-income countries will remain disproportionately vulnerable to accelerated disease progression due to untreated mental health symptoms. The need for effective mental health interventions, especially those that can be administered by trained lay people in low-resource settings, to reduce mental health problems among youth living with HIV is a public health emergency. This study will test the effects of the ILOM of TI-CBT on depression, anxiety, and trauma symptoms among youth 15 - 19 years old living with HIV in low-resource settings. The study will also evaluate the impact of the intervention on youth adherence to ART.

Advances to the science and the evidence-base of HIV related outcomes

This study offers several scientific advances. First, there are currently no published evidence-based interventions that address mental health among adolescents living with HIV who are 15 to 19 years old in sub-Saharan Africa (73). Many African countries lack adequate mental health resources to provide effective programs. The only published pilot study addresses a younger age group (e.g., 10-14 year-olds) (16, 17). Two unpublished interventions do not restrict participating youth based on mental health symptoms and include a broader age range, namely 12-21 year-olds

in the *KIP* study in Rwanda; and 12-24 year-olds in the *Sauti ya Vijana* study in Tanzania (79). Indeed, none of the interventions are tailored to 15 – 19 year-olds specifically, even though this age group constitutes the vast majority of adolescents currently living with HIV, particularly in sub-Saharan Africa.

The 15-19 year-old age group represents a high-risk, yet underrepresented population in research. There are multiple reasons to focus on 15-19 year-olds and their mental health. One, mental health problems emerge during adolescence (80). Two, adolescence is a time when adherence to ART is tenuous at best (74, 76), producing HIV resistance mutations and virologic failure, thereby increasing the risk of HIV transmission to others (81). Changing health behavior during adolescence, a formative developmental stage, is easier than changing behavior in adulthood after habits are formed and entrenched. New behaviors (e.g., adherence) are more likely to be adopted and maintained if they are established at a younger age. Three, adolescence often marks the beginning of sexual activity and "romantic" involvement. It is an important developmental stage for the enactment of gender and power dynamics, including intimate partner violence. This intervention will provide an opportunity to address local gender norms and stereotypes in the context of sexual relationships, the importance of safer sex and delayed sexual debut, and the role of ART adherence in prevention of HIV transmission. Finally, the age group is still primarily connected to and reliant on their families and caregivers for support and care. Leveraging these caregivers in intervention efforts can increase the likelihood that adolescents will adopt positive behavior changes. For these reasons, the TI-CBT intervention, which addresses these high need areas, represents innovation over existing published interventions.

Another potential advancement to the science is the use of ILOM where older peers deliver TI-CBT to their younger peers. The ILOM has been used extensively in adolescent health promotion, (82) including school-based sexual health (83-85), but rigorous outcome research on peer-led interventions for youth is mixed (86). Studies have found positive effects of peer-led interventions with regard to HIV/AIDS knowledge (84-87), attitudes, beliefs and intentions about risky sex and condom use, (84, 88, 89) self-efficacy to refuse sex and delay sexual behaviors (90), condom use (91), and general health behaviors (92). However, other studies and reviews of peer-led programs report no impact on youth's risk reduction intentions, (93) sexual behavior (88, 94), condom use (93), or acquisition of sexually transmitted infections (84, 86). These contradictory findings are attributable in large part to an absence of methodological rigor, lack of equivalent comparison groups, inadequate sample details, no pre-intervention data, and weak study designs (38, 86, 88, 95-101). Indeed, a comprehensive meta-analysis of adolescent peer-led health promotion programs revealed that only 12 out of 210 studies were deemed methodologically sound (e.g., had an explicit theoretical framework, clear sample and methodology, stated aims and objectives) (38). Ten of the 12 were judged effective for one or more behavioral outcomes or non-behavioral outcomes (knowledge, beliefs, and attitudes). The poor methodological state of the field has led to numerous calls for more rigorous evaluations of peer-led programs (38, 41, 102), which this study will provide.

The role of inflammation in mental health symptoms, including depression, anxiety, and post-traumatic stress, is increasingly recognized (103-105). In both HIV-infected and HIV-uninfected individuals, elevated levels of high-sensitivity C-reactive protein (hsCRP), interferon α (IFNα), fibrinogen, sP-selectin, and interleukin 6 (IL6) have been associated with the development of depression and other neurocognitive disorders. Furthermore, in HIV-infected individuals, inflammation, measured by soluble cluster of differentiation 14 (sCD14), interleukin 1β (IL1β), IL6, D-dimer, tissue necrosis factor α (TNFα), chemokine C-C motif ligand 10 (CCL10), and vascular cell adhesion molecule 1 (VCAM1) in the blood compartment and at mucosal sites has been shown to be a major component of HIV pathogenesis (106-111). Thus, inflammation due to

HIV and mental health symptoms such as depression may synergize in HIV-infected individuals, further increasing morbidity. Inflammation may respond to interventions that improve adherence to and effectiveness of antiretroviral treatments.

Studies with non-HIV populations and animal experiments suggest that mental health and behavioral outcomes are also associated with markers of inflammation. Depressive symptoms such as fatigue, cognitive impairment, decreased social interaction and exploration, and loss of appetite may in part derive from chronic immune dysregulation and related cytokine activity (112). In two recent clinical trials, the level of C-reactive protein (CRP) in peripheral blood at pre-treatment baseline differentially predicted treatment responses to the antidepressants citalopram and nortriptyline (113), as well as treatment response to antidepressant augmentation with the TNF-α inhibitor infliximab (114) ,suggesting that a subset of depressive syndromes might be driven by inflammatory mechanisms. In healthy adult women, post-traumatic stress disorder (PTSD) due to childhood sexual abuse is associated with a significantly higher mean percentage of CD8+ T-cells expressing early activation marker CD45RA+; furthermore, the PTSD symptom severity is positively associated with the CD45RA+% (115). In vitro data suggest that an association between PTSD or trauma and immune outcomes may be driven by neuroendocrine and neuroimmune mechanisms. Dexamethasone (DEX)-induced inhibition of T-cell proliferation was significantly lower in cell cultures obtained from veterans with PTSD compared to veterans without PTSD and healthy controls. DEX-induced increase in LPS-stimulated IL-10 was less pronounced in traumatized veterans with and without PTSD compared to healthy controls. The results suggest that trauma exposure can induce changes in glucocorticoid receptor binding characteristics, while PTSD also induces resistance of T-cell proliferation to DEX (116).

Immune and inflammatory markers have been associated with certain psychological and behavioral outcomes in studies with HIV+ populations as well. In one IMPAACT-based study, CD4 nadir < 25% was associated with increased risk of incident depression in children with PHIV (117). In a US cohort of pregnant and postpartum HIV+ women, the risk of perinatal depression was independently associated with CD4+ nadir ≤200 cells/mL (103). In a cohort of low-income, urban African American adults with HIV, untreated depression was associated with current CD4 T cell counts <350 cells/mL, while depression treated with antidepressants or absence of depression were not associated with CD4 count, even after controlling for the mediating effect of non-adherence to ART (104). In a US-based cohort of 114 aviremic HIV+ adults, a positive screen for PTSD was associated with significantly higher total WBC count, total granulocytes, CD8%, and memory CD8%; lower naïve CD8%; and increased likelihood of having a hsCRP level >3 mg/L (105).

Recent studies of HIV-infected and ART adherent adults showed that the majority of adverse clinical outcomes with high morbidity and mortality were non-AIDS related (i.e., diabetes mellitus, non-AIDS malignancies, or severe cardiovascular, vascular or liver disease) (118-121). In the current treatment era, increased plasma inflammatory biomarkers appear to be valuable predictors of non-AIDS related morbidity and mortality among adults living with HIV (20, 122, 123). Thus, monitoring and exploring the impact of inflammatory biomarkers as part of this adolescent study will provide important scientific information regarding the effect of a neurobehavioral intervention on plasma inflammatory biomarkers in this age group.

Finally, this study will provide guidance on the most effective strategies to systemize the adaptation process of evidence-based programs to low-income settings and diverse cultural contexts. Although the ADAPT-ITT model has been used previously, this study will allow for careful documentation of key adaptation strategies that should be used to tailor TI-CBT to new

contexts, including methods for translation and back translation. In moving forward, these procedures can be used as the intervention is taken to scale.

Rationale for scale-up of chosen intervention and study design

This study will use the TI-CBT program developed for Rwanda (KIP) to evaluate replication, scale-up, and feasibility beyond Rwanda, a setting with relatively strong mental health services. Rwanda is unique because it has multiple trained psychologists in the country and the clinics where KIP was implemented provide extensive mental health care as part of their wrap-around treatment for adolescents and young adults living with HIV. For example, all youth participate in weekly "peer support groups" at the clinics, and these support groups served as the KIP study's standard of care (control) groups. The TI-CBT intervention replaced the weekly support group for 6 weeks, and then youth participants returned to the weekly support group following the intervention. Hence, it is unclear if KIP's study model will work in settings with less extensive mental health resources. The viability of the model can only be determined by additional research in low mental health resource settings with sufficient numbers of youth living with HIV.

Unlike previous research, this study will screen and enroll youth who meet pre-defined criteria on one or more of three well-validated mental health measures of depression, anxiety and/or trauma. This advancement of science has two important implications. First, no single site is likely to have a sufficient number of youth who qualify with mental health problems to conduct a rigorous 2-arm randomized controlled trial. Hence, to adequately test intervention effects with sufficient methodological rigor, access to the multiple sites within the IMPAACT network is essential. Second, because previous research included all interested youth living with HIV (i.e., *KIP* and *Sauti ya Vijana),* findings may have potentially obscured treatment effects for those who need it the most. Research indicates that screening youth using locally-validated mental health measures is feasible and has been done in other sub-Saharan African settings. In Tanzania, 25% to 45% of youth reported mental health difficulties that met criteria for significant distress (4, 124). Two studies in South Africa revealed similar rates of mental health problems as Tanzania. Among school-going youth in Gauteng Province, South Africa, 23% reported depression, 27% endorsed suicidal ideation in the last month, and 22% indicated lifetime suicide attempts (125). Similarly, among HIV-infected youth in Soweto, 20% met criteria for depression (major depressive disorder, minor depression, and dysthymia), 22% reported post-traumatic stress disorder, and 42% indicated suicidal ideation in the past two weeks (126).

Testing the intervention with youth who report clinical levels of mental health symptoms will provide a more robust evaluation of intervention efficacy.

In addition to mental health, this study will evaluate the intervention's impact on ART adherence and biomedical outcomes (e.g., quantitative ART drug concentration levels from hair samples (127-130) and viral loads that are systematically timed with follow-up evaluations). Current research typically relies on self-reported adherence or viral load and CD4 data from clinic medical records (e.g., KIP). These approaches have significant limitations in time matching and quality. Quantitative adherence measures using hair collection methods were performed at many IMPAACT sites as part of the PROMISE study, as well as among HIV-infected adolescents in Tanzania. Hair collection is non-invasive and has no special storage requirements. Data from hair demonstrated associations with ART adherence and drug exposure among children, adolescents, and adults (130-132). With these biologic markers of adherence and HIV outcomes, this study will be able to systematically link changes in adherence and virologic outcomes to changes in mental health symptoms and the impact of the TI-CBT intervention.

Engaging multiple sub-Saharan sites will increase the generalizability of findings. IMPAACT's access to numerous sites with minimal (if any) mental health resources will permit a strong and much needed evaluation of a mental health evaluation delivered by peers. This study will prioritize implementation in countries with high volumes of 15 - 19 year-olds living with HIV and minimal mental health care infrastructure in order to achieve the biggest impact and deliver the program in areas of greatest need. This study will build the capacity of these sites if the ILOM is found to be effective. Moreover, by adapting the intervention to several sites, the study will allow an evaluation of the potential for scale up across countries.

Lastly, this study has the potential to impact clinical mental health services for youth living with HIV. If the ILOM of TI-CBT is effective, it will provide data for policy and implementation in the clinics in which it was studied, as well as ways to expand the availability of mental health interventions in additional resource-poor settings. Proof of concept for training non-professional youth leaders to deliver evidence-based interventions may encourage other clinical settings to implement care that addresses both psychosocial and medical needs of youth living with HIV.

1.4 Hypothesis

The TI-CBT Intervention will result in reduced symptoms of depression, anxiety, and/or traumatic stress compared to the Discussion Control at six months.

2 OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to:

2.1.1 Evaluate whether a TI-CBT Intervention is associated with improved depression, anxiety, and/or traumatic stress symptoms for youth living with HIV compared to a Discussion Control at six months.

2.2 Secondary Objectives

The secondary objectives of this study are to:

2.2.1 Determine the feasibility, acceptability, and fidelity of a TI-CBT intervention.

2.2.2 Evaluate whether a TI-CBT Intervention is associated with improved depression, anxiety, and/or traumatic stress symptoms for youth living with HIV compared to a Discussion Control following the last group session and at 12 months.

2.2.3 Assess whether a TI-CBT Intervention is associated with improved ART adherence (hair samples, self-report) and viral suppression (HIV RNA plasma) for youth living with HIV compared to a Discussion Control following the last group session and at six and 12 months.

2.2.4 Assess whether a TI-CBT Intervention is associated with improved structural factors for youth living with HIV (HIV stigma and support for adherence; barriers to adherence; gender-based violence; gender roles) compared to a Discussion Control following the last group session and at six and 12 months.

2.2.5 Assess whether a TI-CBT Intervention is associated with improved structural factors for caregivers (HIV knowledge, stigma, and support for adherence; barriers to adherence) compared to a Discussion Control following the last group session and at six and 12 months.

2.2.6 Assess whether a TI-CBT Intervention is associated with improved behavioral risk outcomes for youth living with HIV (alcohol/drug use; sex-risk behaviors; caregiver report of youth behavior) compared to a Discussion Control following the last group session and at six and 12 months.

2.2.7 Identify the individual, social, and structural barriers, and facilitators to implementation of a TI-CBT Intervention.

2.2.8 Compare the rates of all targeted adverse events between a TI-CBT Intervention and a Discussion Control for youth living with HIV.

2.3 Other Objectives

The other objectives of this study are to:

2.3.1 Evaluate whether a booster session at six months is associated with continued improvements in depression, anxiety and traumatic stress symptoms at 12 months.

2.3.2 Assess whether youth and caregiver demographic and structural factors moderate the efficacy of a TI-CBT Intervention compared to the Discussion Control.

2.4 Exploratory Objectives

The exploratory objectives of this study are to:

2.4.1 Examine whether a TI-CBT Intervention is associated with a decrease in plasma inflammatory biomarkers in youth from study entry to six and 12 months compared to Discussion Control.

2.4.2 Examine the moderating effect of inflammatory biomarkers in youth on the efficacy of a TI-CBT Intervention compared to a Discussion Control.

3 STUDY DESIGN

IMPAACT 2016 is a multi-site, two-arm, individually randomized controlled trial of a TI-CBT Intervention for youth living with HIV delivered by IYL (refer to Figure 2). The Randomized Trial will be preceded by an adaption of the TI-CBT intervention at each site using the ADAPT-ITT model, which will include Focus Groups and Pilot Tests (refer to Figure 1, and Sections 1.2.2 and 3.1).

3.1 TI-CBT Adaptation using the ADAPT-ITT Model Prior to the Randomized Trial

Prior to the Randomized Trial (refer to Section 3.2), the TI-CBT Intervention will be adapted to ensure its relevance and acceptability at each study site, using the ADAPT-ITT model, as described in Section 1.2.2 and summarized in Table 1 (below). Steps 1 and 2 of the ADAPT-ITT Model have already been completed and have informed the development of this protocol. Steps 3-8 will be implemented as part of this protocol. A TI-CBT Youth Intervention Manual and Caregiver Intervention Manual will be developed for each site and will be updated to incorporate site-specific adaptations based on the Focus Groups and Pilot Testing, as described below.

Table 1. Adaptation of TI-CBT following the ADAPT-ITT model

Steps 1 and 2 have been completed.	
Step 1: Assessment	The most important issues to target in an intervention for 15-19 year-olds living with HIV were previously ***a****ssessed* using literature reviews, focus groups, and informant interviews. These sources highlighted the importance of mental health, trauma, gender-based violence and barriers to ART adherence as the key areas to address in an intervention (4, 10, 13, 124, 133). These topic areas will be further elucidated in Step 3 (focus group) at each study site.
Step 2: Decision	Using the data from Step 1, the protocol team ***d****ecided* to implement TI-CBT as the intervention for this study. TI-CBT has shown preliminary efficacy in a study in Rwanda, as described in Section 1.3, and has established feasibility for adaptation to address the issues identified in Step 1.
Steps 3-8 will be completed prior to the Randomized Trial.	
Step 3: Administration	***A****dministration* will first involve engaging study site community and youth advisory boards and other key stakeholders to identify components of the intervention that may require adaptation for the local context. This input will form the basis for the Focus Group conducted in each country having participating sites, whereby site staff will administer the components identified by stakeholders as needing adaptation to individuals from the target population (youth and caregivers). Site staff will request feedback from participants on whether the components of TI-CBT are relevant, acceptable, and well understood. Refer to Section 3.1.1 for more information about this step.
Step 4: Production	Minor ***P****roduction* modifications to the TI-CBT intervention are anticipated mainly to clarify mental health idioms.
Step 5: Topical Experts	Where expertise is needed beyond the protocol team, ***T****opical experts* outside the team will provide input into TI-CBT intervention.
Step 6: Integration	Site staff will ***I****ntegrate* feedback obtained in Steps 3-5 into the TI-CBT Youth and Caregiver Intervention Manuals that will be used in Step 8 to conduct the pilot test.
Step 7: Training	IYL will be recruited and **T**rained to deliver the TI-CBT intervention at each site. Refer to Section 5.2 for more information about this step.
Step 8: Pilot Test	For the *pilot* ***T****est*, IYL will deliver the complete TI-CBT intervention. Refer to Section 3.1.2 for more information on this step.

3.1.1 Focus Groups

The purpose of the Focus Groups is to test specific components of the TI-CBT Intervention identified by local stakeholders as potentially challenging to deliver in the local context. These components will be administered to Focus Group participants (youth and caregiver) reflective of the target population for the Randomized Trial. Feedback will be solicited from participants on the components' relevance, acceptability, and understandability. Focus Groups will be conducted in each study country. One youth Focus Group and one caregiver Focus Group will be conducted in Botswana, South Africa, and Zimbabwe. The sites in these countries share similar language and culture and therefore only one youth and one caregiver Focus Group is needed. In Malawi, the local context is sufficiently different and necessitates that Focus Groups be conducted at each site.

Youth 15-19 years old living with HIV and their caregivers will take part in separate Focus Groups. Youth who agree to participate in a Focus Group will be asked to invite their caregiver to participate; a youth's choice to not invite their caregiver will not impact the youth's participation. If this approach to caregiver recruitment does not yield an adequate number of caregivers to participate, caregivers may be recruited from other sources. As such, caregivers who take part in a Focus Group may or may not currently be caring for a youth who takes part in a Focus Group; however, all will be caregivers of youth 15-19 years old living with HIV. Written informed consent and assent for Focus Group participation will be obtained as described in Section 12.3; a sample form for this purpose is provided in Appendix III.

In advance of each Focus Group, study staff, community and youth advisory board members, and other stakeholders will review the TI-CBT Intervention and identify components that may require adaptation for the local context. Feedback will be documented in meeting notes and the components identified by these stakeholders will serve as the basis for the Focus Groups.

During Focus Groups, two adult study staff will deliver the components identified by the stakeholders to 5-8 youth and 5-8 caregivers (separately); the full intervention will not be delivered. The adult study staff will lead a discussion about the relevance and acceptability of the component in the local context. Questions, concerns, and recommendations for adaptation to fit the local context will be actively solicited. Feedback will be recorded in written notes and groups will be audio recorded for later reference if needed. This process will be repeated for each component identified as requiring review in the Focus Groups.

Designated protocol team members and site staff will meet and review feedback from the Focus Groups to determine if any changes are needed to the TI-CBT Intervention. A summary of the findings and recommended changes to the intervention will be prepared and final approval to implement the recommended changes will be provided by the protocol chairs and designated site staff. Agreed upon changes will be incorporated into the TI-CBT Youth and Caregiver Intervention Manuals at each applicable site in preparation for the Pilot Test.

Further detailed operational guidance on conducting and documenting Focus Groups will be provided in the study-specific MOP.

3.1.2 Pilot Tests

The purpose of Pilot Testing is two-fold: 1) to fine-tune the TI-CBT Intervention at each site, and 2) to practice and refine the logistics of recruitment, conducting Screening, Pre-Entry and Entry Visit procedures, and scheduling and conducting TI-CBT group sessions. Pilot Testing will be conducted with youth and caregivers. Written informed consent, and assent if applicable, is required for the Pilot Test; refer to Section 12.3 and the sample forms provided in Appendix IV and Appendix V.

In preparation for the Pilot Testing, IYLs will be recruited and trained to deliver the TI-CBT Intervention as described in Section 5.2. IYL supervision will follow the guidelines in Section 5.3 and intervention fidelity will be assessed as described in Section 5.4. Safety of participants will be monitored and managed throughout the Pilot Testing period as described in Sections 7, 8, and 12.

Youth and caregivers taking part in the Pilot Tests will complete Screening, Pre-Entry and Entry visits similar to the visits for the Randomized Trial as described in Sections 6.1 and 6.2, in order for study staff to practice procedures and refine the logistics of these visits. No blood or hair will be collected and no laboratory tests will be performed beyond the Screening Visit; however, participants will be asked to complete questionnaires (data from questionnaires will not be analyzed) and perform mock hair and blood collection to assess logistical feasibility. Youth and their caregivers in the Pilot Test will also participate in the TI-CBT group sessions as described in Section 5.1. At the end of each session, process information and feedback from Pilot Test participants will be documented, including participant perceptions of "how much they learned" and "how much fun they had," consistent with Section 5.5.5.

Following completion of the Pilot Test at each site, study staff and local stakeholders will review the process information and feedback from the Pilot Test participants and discuss final adaptations of the TI-CBT Intervention for the site based on interest among youth and caregivers in participating; session length, attendance, and timing; and acceptability of intervention topics and activities. The core constructs of the intervention and the questionnaires planned to be used in the Randomized Trial will not be changed, but the Pilot Test outcomes may alter how the intervention is delivered or the timing or sequence of procedures performed in the Randomized Trial. A summary of Pilot Test findings and proposed changes will be documented at the site, with final approval to implement the changes provided by the protocol chairs and designated site staff. Agreed upon changes will be incorporated into the site's TI-CBT Youth and Caregiver Intervention Manuals in preparation for the Randomized Trial.

Further detailed operational guidance on conducting and documenting Pilot Tests will be provided in the study-specific MOP.

3.2 Randomized Trial of TI-CBT

In the Randomized Trial, youth will be individually randomized to either the TI-CBT Intervention Arm or the Discussion Control Arm. Participants will meet as a group within their randomized arm and receive multiple group sessions within an eight-week period as described in Section 5. Each group will include an average of eight youth for an approximate total of 192-256 youth in the Randomized Trial (96-128 youth per arm). TI-CBT and Discussion Control groups in each arm will be mixed-gender unless it is determined necessary to have single-gender groups during the focus group.

Each youth group session may be conducted on separate days or an equivalent approach may be implemented in that multiple group sessions may be combined (e.g., group sessions 1 and 2 may be conducted during the same day) based on the Pilot Test and feedback during the adaptation stage (refer to Section 3.1). IYL's will facilitate the TI-CBT and Discussion Control group sessions; however, the IYLs delivering the TI-CBT group sessions will be trained in TI-CBT (refer to Section 5.2), and supervision of IYL will be conducted using the Cascading Supervision Model (refer to Section 5.3).

Caregivers (as available and with youth permission) will be assigned to the same study arm as their youth. Caregivers will meet as a group for two caregiver-specific sessions on two separate weeks and separate from their youth group sessions. Adult study staff will facilitate the TI-CBT and Discussion Control group sessions; however, the adult study staff delivering the TI-CBT group sessions will be trained in TI-CBT-related content (refer to Section 5.2).

Youth and caregivers will also receive one two-hour booster group session consistent with their assigned study arm immediately after the six-month evaluations. The booster sessions are meant to enhance treatment effect sustainability (refer to Section 5.1 for additional detail).

Youth and caregivers will complete a follow-up visit immediately after their last group session and two additional follow-up visits at six and 12 months (Refer to Section 6.3.5, 6.3.6, 6.3.8, 6.4.3, 6.4.4, and 6.4.6). At these visits, the following will be evaluated:

- Youth: targeted medical history, focused on mental health; self-reported ART adherence; plasma HIV-1 RNA; ARV concentrations in hair; HIV stigma; barriers to adherence; behavioral risks; gender roles; gender violence; and perception of caregiver behavior.
- Caregivers: HIV stigma, HIV attitudes, HIV knowledge, barriers to adherence, and perception of youth behavior.

Once all participants have completed their six-month evaluations, data from these evaluations will be analyzed to determine the short-term effects of the intervention. Additional analyses to assess the longer-term effects of the intervention, including the effects of the booster group session, will be performed after the completion of follow-up.

4 STUDY POPULATION

Section 4 applies to both the Pilot Test and Randomized Trial. Refer to the study-specific MOP for more information on the Focus Groups.

Youth participants will be selected according to the criteria in Sections 4.1, and 4.2; and their caregivers will be selected according to the criteria in Section 4.3 and Section 4.4. Co-enrollment guidelines are specified in Section 4.5. The study-specific approach to recruitment, screening, and enrollment is described in Section 4.6. Considerations related to participant retention and withdrawal/termination from the study are provided in Sections 4.7 and 4.8, respectively.

4.1 Inclusion Criteria: Youth Participants (Pilot Test/Randomized Trial)

All of the criteria listed below must be met in order for youth to be included in the Pilot Test and Randomized Trial.

4.1.1 At screening, 15-19 years old.

4.1.2 *If of legal age to provide independent informed consent as determined by site Standard Operating Procedures (SOPs) and consistent with site IRB/EC policies and procedures*: potential youth participant is willing and able to provide written informed consent for study participation.

If not of legal age to provide independent informed consent: Parent or guardian is willing and able to provide written informed consent for study participation and potential youth participant is willing and able to provide written informed assent for study participation.

4.1.3 Confirmed HIV-infection based on documented testing of two samples collected at different time points as documented in medical records or by confirmatory testing.

Sample #1 may be tested using any of the following:

- Two rapid antibody tests from different manufacturers or based on different principles and epitopes
- One enzyme immunoassay (EIA) OR Western Blot OR immunofluorescence OR chemiluminescence
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One HIV total nucleic acid test

Sample #2 may be tested using any of the following:

- Rapid antibody test. If this option is used in combination with two rapid tests for Sample #1, at least one of the three rapid tests must be FDA-approved, and the third rapid test must be from a third manufacturer or based on a third principle or epitope.
- One EIA OR Western Blot OR immunofluorescence OR chemiluminescence
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One HIV total nucleic acid test

All samples tested must be whole blood, serum, or plasma. If both samples are tested using antibody tests, at least one of the samples must be tested in a laboratory that operates according to Good Clinical Laboratory Practice (GCLP) guidelines and participates in an appropriate external quality assurance program. If nucleic acid testing is used, at least one test must be performed in a VQA-approved laboratory. For tests performed in other (non-GCLP-compliant or non-VQA-approved) settings, adequate source documentation including the date of specimen collection, date of testing, test performed, and test result must be available.

4.1.4 At screening, aware of his or her HIV infection, as confirmed by Investigator of Record or designee.

4.1.5 At screening, has been prescribed ART for a minimum of 24 weeks prior to screening based on medical record documentation.

4.1.6 At screening, meets at least one of the following indicators of moderate to severe mental health symptomology:

- Patient Health Questionnaire-9 (PHQ-9) score ≥ 10
- General Anxiety Disorder-7 (GAD-7) score ≥ 10
- UCLA Post-Traumatic Stress Disorder-Reaction Index (UCLA PTSD-RI) score ≥ 35

Note: Severe distress or suicidal ideation is not exclusionary.

4.2 Exclusion Criteria: Youth Participants (Pilot Test/Randomized Trial)

Youth who meet any of the following criteria will be excluded from the Pilot Test and Randomized Trial:

4.2.1 At entry, participating in a study delivering a mental health or ART adherence intervention.

4.2.2 For the Randomized Trial, prior participation in an IMPAACT 2016 Focus Group or Pilot Test

4.2.3 Any other condition, adverse social situation or cognitive impairment that, in the opinion of the site investigator, would preclude informed assent and informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

4.3 Inclusion Criteria: Caregiver Participants (Pilot Test/Randomized Trial)

All of the criteria listed below must be met in order for caregivers to be included in the Pilot Test and Randomized Trial.

4.3.1 Caregiver, defined as a biological parent, legal guardian, or person who provides emotional, psychological and/or informational care to a youth taking part in the Pilot Test or Randomized Trial, as identified by the youth, and for whom the youth has provided written permission to participate in the study.

Note: For youth not of legal age, caregiver may or may not be the parent or guardian who provided written informed consent for the youth to participate.

4.3.2 Of legal age to provide independent consent and willing and able to provide written informed consent for study participation.

4.4 Exclusion Criteria: Caregivers (Pilot Test/Randomized Trial)

Caregivers who meet following criterion will be excluded from the Randomized Trial (there are no exclusion criteria for caregivers in the Pilot Test):

4.4.1 For the Randomized Trial, prior participation in an IMPAACT 2016 Focus Group or Pilot Test.

4.5 Co-Enrollment Considerations (Pilot Test/Randomized Trial)

Participants should not take part in any concurrent research studies that deliver a mental health or ART adherence intervention. Co-enrollment in observational or other studies may be allowable with permission from the Protocol Teams of both studies. Requests for such approval should be emailed to the Core Protocol Team (refer to Section 7.1.2).

4.6 Recruitment, Screening, and Enrollment Process (Pilot Test/Randomized Trial)

Recruitment methods for this study may vary across sites. Sites will develop appropriate recruitment processes that are acceptable in their local communities. Advertising materials must be approved by each site's IRBs/ECs. All sites are expected to participate in both the Pilot Test and Randomized Trial (sites cannot participate in the Randomized Trial without prior pilot testing).

Upon identification of a potential participant, study staff will provide information about the study; each potential caregiver or youth participant (and parent/guardian as applicable) who expresses interest in learning more about the study will be provided additional information, education, and counseling as part of the study informed consent and assent process. The process will include detailed review of the study informed consent and assent forms (as applicable) and time to address any questions or concerns the youth, parent, or guardian may have, before proceeding to informed consent and assent decisions. Informed consent and assent processes will be fully documented, consistent with the Division of AIDS (DAIDS) policies referenced in Section 12.3.

Eligibility screening will be initiated after informed consent and assent (if applicable) are provided. As part of the youth informed consent/assent process, youth will be asked whether they are willing to identify a caregiver and provide written permission for the caregiver to participate in the study. Youth who cannot identify a caregiver or do not otherwise provide written permission for caregiver participation remain eligible to enroll as youth can benefit from participation in the intervention without caregivers. If the identified caregiver agrees to participate, he/she will be introduced to the study and asked to provide informed consent for his/her own participation. This can be done at any point between youth screening and the first caregiver group session.

Given that each TI-CBT and Discussion Control group should include 6-10 youth per group, sites will need to identify a pool of 12-20 eligible youth to be enrolled/randomized at one time (refer to Section 6.3.3). Enrollment/randomization must occur within 60 days of each youth participant initiating the screening process. Therefore, sites must screen a sufficient number of potential youth participants within this time period to ensure that 12-20 can be enrolled/randomized on a given day. The first TI-CBT Intervention and Discussion Control group sessions will be conducted on the day of enrollment/randomization.

Groups will be mixed gender unless a site determines that single gender groups are more appropriate for youth participants during the ADAPT-ITT process. Sites will develop appropriate SOPs accounting for the gender composition and related recruitment process as determined appropriate from the ADAPT-ITT process.

Once a sufficient pool of eligible youth has been identified, the site will schedule the Entry Visit and first group session (the first group session will occur on the day of the Entry Visit). Prior to the Entry Visit, eligible youth will be scheduled for a Pre-Entry Visit to complete baseline evaluations. This visit can occur on the same day or within 14 days prior to the Entry Visit. Youth who are screened more than 60 days prior to enrollment must be re-screened for all inclusion and exclusion criteria prior to enrollment. The youth will not be enrolled if deemed ineligible following repeat of screening evaluations. For details on randomization, refer to Sections 6.3.3 and 9.3.

Caregivers identified by youth to participate in the study will be contacted by study staff and invited to visit the clinic to learn more about the study and undergo an informed consent process for their study participation. Consenting caregivers will be enrolled and complete baseline evaluations at their Entry Visits. Caregiver Entry Visits may occur prior to or on the same day as the first caregiver group session.

When informed consent or assent is obtained, a unique participant identification number (PID) will be assigned to each of the youth and caregiver participants by the site. The IMPAACT Data Management Center (DMC) Subject Enrollment System (SES) will be used for both the screening and enrollment of youth participants and used only for enrollment of caregiver participants. Screening and enrollment processes will differ for youth and caregiver participants as follows:

- Youth: A study-specific screening number will be obtained through the SES for all youth for whom informed consent and assent (if applicable) is provided. Screening numbers will be generated by the SES upon successful entry of data into a study-specific screening checklist. For screened youth found to be eligible, enrollment will occur upon successful entry of required eligibility checklist data into the SES. Successful enrollment will generate a study identification number (SID) for youth in the Pilot Test and the Randomized Trial; the SES will also generate a random assignment — to either the TI-CBT Intervention or the Discussion Control arm — for youth enrolled in the Randomized Trial. Youth from the same household will be assigned to the same arm; the eligibility checklist will be used to determine the assignment for additional youth enrolled based on the first youth enrolled from the same household. The generation of the SID is the effective point of enrollment in the study.

- Caregiver: After successful enrollment of their youth, eligible caregivers will be enrolled through the same eligibility checklist that will link the PID numbers of the youth and caregiver through additional questions in the eligibility checklist. For the Randomized Trial only, the caregiver will receive the same random assignment as their youth upon the PID linkage. The generation of the SID is the effective point of enrollment in the study.

For youth who are screened and found to be ineligible, or who do not otherwise enroll in the study for any reason, limited demographic information and reasons for non-enrollment will be entered into an electronic case report form (eCRF). Refer to Section 9.5 for more information on monitoring participant accrual in this study.

4.7 Participant Retention (Pilot Test/Randomized Trial)

Once a youth and/or caregiver participant is enrolled in the study, study staff will make every effort to retain him or her for the protocol-specified duration of follow-up, thereby maximizing statistical power and minimizing potential biases associated with loss to follow-up. Each site must establish and implement SOPs that target retention rates that are sufficient to reliably estimate the primary study outcomes (10% loss to follow-up between evaluations is assumed in sample size calculations). Refer to Section 9.5 for more information on monitoring participant retention in this study.

Site SOPs should include measures taken to maintain current phone/text/email, and/or in-person contacts of participants and approximately three close contacts at each study visit to enable scheduling and remind participants of each evaluation and group session. Youth (and caregivers where relevant) will be contacted by study staff prior to each group session and evaluation to confirm attendance. Refer to the study-specific MOP for additional guidance on tracking procedures used in past studies to reduce attrition and sample size bias.

4.8 Participant Withdrawal or Termination from the Study (Pilot Test/Randomized Trial)

Temporary Hold from the Study

Disruptive youth will be removed from the current group session (TI-CBT or Discussion Control group session) at the discretion of the designated on-site study clinician as described in Section 8.1. The youth will be allowed to return to the following group session. The youth will be advised that the behavior is unacceptable and if the behavior is not resolved and continues, s/he will be removed from the study as indicated below.

Permanent Withdrawal or Termination from the Study

Youth participant/legal guardian and caregiver participants may voluntarily withdraw from the study. Participants may also be permanently terminated from the study by the site investigator or designee under the following circumstances:

- Participant re-locates away from the study site and is unreachable or is otherwise determined to be lost-to-follow-up, with no options for transfer to another site;
- The study is stopped or canceled by the sponsors, government or regulatory authorities, or site IRBs/ECs
- The participant fails to comply with study requirements and/or is disruptive, so as to cause harm to self or others, seriously interfere with the validity of the study results, or otherwise would not be in the best interest of the participants and study staff, after Investigator or designee consults with the Core Protocol team.

For any participant who withdraws 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. If 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 will contact the Core Protocol Team to discuss options for resumption of follow-up.
Youth participant withdrawal or termination does not impact their respective caregiver participation and vice versa.

5 STUDY INTERVENTION

Youth will be randomized to a study arm (TI-CBT or Discussion Control Arm), and caregivers will be assigned to the same study arm as their youth. Youth will receive TI-CBT group sessions described in Section 5.1.1 or Discussion Control group sessions described in Section 5.1.2, both delivered by IYL. Caregivers (as available with youth permission) will receive HIV knowledge and adherence-based group sessions described in Section 5.1.1 or Discussion Control group sessions described in Section 5.1.2, both delivered by adult study staff. No medications or other study product will be provided through the study. The adaptation of the intervention at each site involves Focus Groups and Pilot Testing as described in Section 3.1.

Youth and caregivers will receive the intervention or control in a group setting. Given the group-based nature of the intervention and control, youth and caregivers who miss a session will not have an opportunity to repeat the session. However, at the beginning of each group session, facilitators will review the main points of the previous session and address new content that is not contingent on previous sessions. As a result, the curriculum presented in each session can effectively stand alone. Support for transportation and snacks will be provided to the participants.

5.1 Study Arms

5.1.1 Trauma-Informed Cognitive Behavioral Therapy (TI-CBT) Intervention (Randomized Trial and Pilot Test)

Youth Participants

TI-CBT Sessions: Youth in the Pilot Test and those randomized to the TI-CBT Intervention Arm of the Randomized Trial will receive six 2-hour group sessions within eight weeks of session 1. Each session may be conducted on separate days or an equivalent approach may be implemented in that multiple sessions may be combined (e.g., sessions 1 and 2 may be conducted on the same day), depending on the adaption for local context. Refer to Table 2 for specific content to be delivered in a given session.

All sessions will be delivered by IYL who will follow a detailed TI-CBT Youth Intervention Manual (refer to Section 5.1.1.1) and receive general training on running TI-CBT groups (refer to Section 5.2 for detail on IYL training). TI-CBT teaches relaxation training and cognitive restructuring, as well as addressing barriers to ART adherence.

Booster Session: In the Randomized Trial only, a booster group session will be conducted after completion of the six-month follow-up evaluation - on the same day or within one month - to enhance sustainability of intervention effects. The session will consist of one 2-hour condensed review of the original TI-CBT material, emphasizing the intervention's primary goals. Content will address how feelings and thoughts drive behavior, coping effectively with stress and trauma, and the importance of relaxation. The session will offer opportunities for open discussion and questions from the youth participants.

Table 2. TI-CBT content delivered at each session to youth participants

Session	Content
Session 1	• How stress affects the body • Stresses of living with HIV • Coping with stress • HIV education
Session 2	• Stress related to HIV & adherence • Healthy/helpful or unhealthy/unhelpful coping strategies • Identifying alternatives and problem solving unhelpful responses
Session 3	• Connection between thoughts, feelings, and behaviors • Cognitive triangle • Learning about unhealthy/unhelpful patterns
Session 4	• Cultural gender roles and gender expectations • How gender and HIV influences thoughts, feelings, and behaviors
Session 5	• Interpersonal relationships in the context of pressure (peers & authority), medication logistics, and safe sex practices • Communication styles and solutions to difficult situations related to living with HIV
Session 6	• Review how stress affects the body, effective coping strategies, the connection between thoughts feelings and behaviors and the influence of thoughts on healthy/helpful choices or unhealthy/unhelpful choices while living with HIV • Problem solving skills
Booster Session (Randomized Trial only)	• Review original intervention material • Primary goals of the intervention (how feelings and thoughts drive behavior, coping effectively with stress and trauma) • Reflect on using learned strategies and skills • Problem solve barriers to skill and strategy implementation

Caregiver Participants

TI-CBT sessions: Caregivers of youth in the Pilot Test and of youth randomized to the TI-CBT Intervention Arm in the Randomized Trial will receive two 2-hour group sessions on two separate weeks within eight weeks of their youth's first group session. These sessions will occur separate from the youth sessions. Refer to Table 3 for specific content to be delivered in a given session.

All sessions will be delivered by adult study staff who will follow a detailed TI-CBT Caregiver Intervention Manual (refer to Section 5.1.1.1). Caregiver sessions are designed to improve caregiver's HIV knowledge, reduce caregiver stigma about HIV, educate caregivers about youth-reported obstacles to ART adherence, increase caregiver efforts to help youth adhere (e.g., attend clinic appointments, reminders to take medication), and strategies to improve caregivers' communication with youth about adherence. Role-play will be used to enact different adherence scenarios to teach caregivers how they may offer adherence support.

Booster session: In the Randomized Trial only, a booster group session will be conducted after completion of the six-month follow-up evaluation, on the same day or within one month, to enhance sustainability of intervention effects. This session will consist of one 2-hour condensed review of the original caregiver session material, emphasizing the importance of youth ART adherence and how caregivers can assist youth in their adherence efforts. The session will offer opportunities for open discussion and questions from the caregivers.

Table 3. Content delivered at each session to caregiver participants

Session	Content
Session 1	• HIV knowledge • HIV stigma • What is adherence and why is it important? • Obstacles to youth ART adherence
Session 2	• Why is adherence important? • How to help youth adhere to ART and healthcare • Caregiver communication about adherence
Booster Session (Randomized Trial only)	• Review original intervention material • Primary goals of the intervention • Emphasize the importance of youth ART adherence and how to assist youth in adherence efforts

5.1.1.1 TI-CBT Manuals

TI-CBT Training Manual

IYL and adult study staff designated to lead the TI-CBT group sessions during the Pilot Test and Randomized Trial will receive training to implement TI-CBT using a TI-CBT Training Manual. Refer to Section 5.2.2 for details on training. The TI-CBT Training Manual is the backbone to the TI-CBT intervention, providing an introduction to TI-CBT and the training modules, psycho-education and relaxation techniques.

TI-CBT Intervention Manuals

In addition to the TI-CBT Training Manual, a TI-CBT Youth Intervention Manual and TI-CBT Caregiver Intervention Manual are provided to IYL and adult study staff, respectively, and are each written in English, and will be translated into site-specific languages. The manuals will be refined/adapted for each site based on the local context and focus group feedback, and both are structured by session. Throughout the manual, sessions proceed as follows: 1) an overview of the main goals and activities; 2) language is provided for facilitators to deliver the curriculum; and 3) each session begins and ends with a relaxation exercise. The expected timing of each activity is provided so facilitators can abide by time constraints. Two IYL will be designated to co-lead each session, and the TI-CBT Manual specifies the text delivered by each facilitator (e.g., Facilitator 1 and Facilitator 2).

Refer to Section 5.2.2 for details on training.

5.1.2 Discussion Control

For the Randomized Trial only, there will be a Discussion Control Arm. Youth and caregiver in the Discussion Control Arm will meet separately, but in a group setting consistent with the TI-CBT Intervention Arm. Discussion Control group sessions will mimic the environment, transport, compensation, reimbursement, and refreshments of the TI-CBT group sessions, but facilitators will not be trained in TI-CBT nor have a particular agenda for the discussion group.

Youth Participants

Discussion Control group sessions: Youth randomized to the Discussion Control Arm will receive the same number and timing of group sessions as the TI-CBT Intervention Arm (Refer to Section 5.1.1). Each session will be led by IYL who will receive training on running Discussion Control groups (refer to Section 5.2 for detailed information on the IYL training). Discussion topics will be selected by youth in the group. Discussion Control group session will take place at a separate time from TI-CBT youth group sessions in attempt to minimize contamination.

Booster session: A booster group session will be conducted following the six-month evaluation on the same day or within one month. This session will consist of one 2-hour open discussion of a topic chosen by the youth participants.

Caregiver Participants

Discussion Control group sessions: Caregivers of youth randomized to the Discussion Control Arm will receive two 2-hour sessions on two separate weeks within eight weeks of their youth's first group session. These sessions will occur separate from the youth sessions. Each session will be led by adult study staff who will receive training on running Discussion Control groups (refer to Section 5.2 for detailed information on the staff training). Discussion topics will be selected by caregivers. Discussion Control group sessions will take place at a separate time from TI-CBT caregiver group sessions in an attempt to minimize contamination.

Booster session: A booster group session will be conducted following the six-month evaluation on the same day or within one month. This session will consist of one 2-hour open discussion of a topic selected by caregivers.

5.2 Recruitment and Training of Indigenous Youth Leaders and Adult Study Staff

5.2.1 Recruitment

Indigenous Youth Leaders (youth group sessions)

Consistent with ILOM guidelines (34), protocol team members will work with site study staff and site PIs to identify and recruit 21-30 year-old IYL from local HIV clinics. This age range ensures IYL are older than youth participants, but still close enough in age to be perceived as older peers. A target of six youth per site will be recruited and hired to be trained as IYL to lead the TI-CBT Intervention Arm and Discussion Control Arm youth group sessions.

IYL will be selected for training based on staff ratings of: a) showing responsibility in clinic activities (near to perfect attendance and excellent ART adherence); b) demonstrating dedication, empathy, and good communication skills; c) being adaptable and willing to work; d) being available for training and intervention delivery; and e) no known active substance/alcohol use that would impair ability to lead group sessions. These same criteria will apply to IYL who lead the TI-CBT and Discussion Control group sessions. Refer to the study-specific MOP for further guidance on selection criteria and guidance. Selected IYL will be randomly designated to lead the TI-CBT or Discussion Control group sessions and receive the appropriate training for those group sessions as indicated in Section 5.2.2

Adult Study Staff (caregiver group sessions)

A target of six adult study staff will be identified by site staff to be recruited and trained to lead the Intervention and Discussion Control Arm caregiver group sessions. The adult study staff will ideally have some background in mental health. Identified site staff will be randomly designated to lead the Intervention or Discussion Control group sessions and receive appropriate training for those group sessions as indicated in Section 5.2.2.

5.2.2 Training

Designated expert trainers and the protocol chairs will provide training to all IYL and adult study staff to manage safety concerns among participants.

IYL and adult study staff designated to lead the Discussion Control group sessions will be trained separate from IYL and adults study staff designated to lead TI-CBT group sessions. Separate trainings will minimize the risk of contamination across treatment arms. IYL and adult study staff designated to lead the TI-CBT group sessions will practice delivering the sessions during the training.

Indigenous Youth Leaders (youth group sessions)

TI-CBT Intervention and Discussion Control Arms:

Upon successful completion of training, IYL will be certified to deliver TI-CBT or the Discussion Control group sessions by designated expert trainers following direct observations.

Based on each of the youth's demonstrated ability to lead, a minimum of two certified IYL will be selected to specifically lead the group sessions and one certified IYL will be selected to specifically observe group sessions. Should an IYL be unavailable to deliver a TI-CBT or Discussion Control group session, the observer assigned to that study arm will take his/her place as a facilitator.

TI-CBT Intervention Arm only:

Among the certified IYL, IYL selected to deliver the TI-CBT will be based on their ability to deliver the TI-CBT with fidelity, answer mock questions appropriately, and stand out as excellent role models for youth enrolled in the intervention. Of the IYL selected to deliver TI-CBT, the IYL selected to observe will also complete the fidelity ratings.

IYL designated to lead the TI-CBT group sessions during the Pilot Test and Randomized Trial will receive additional training to implement the TI-CBT using the TI-CBT Training Manual

(refer to Section 5.1.1.1). Initial training will include IYL and the local staff who will supervise IYL over the course of the study.

In addition to the TI-CBT Training Manual, IYL will be trained on using a TI-CBT Youth Intervention Manual (refer to Section 5.1.1.1) to ensure systematic learning of the curriculum and how to lead groups. The TI-CBT Youth Intervention Manual guides the training process for IYL and will provide additional information to assist IYL as they facilitate the intervention.

Refer to the study-specific MOP for additional guidance.

Adult Study Staff (caregiver group sessions)

TI-CBT Intervention and Discussion Control Arms:

Adult study staff will follow similar procedures to training as IYL. Upon successful completion of training, adult study staff will be certified to deliver the sessions by designated outside expert trainers and local site PIs following direct observations.

Based on each of the adult study staff's demonstrated ability to lead, a minimum of two certified adult study staff will be selected to specifically lead the group sessions and one certified adult study staff will be selected to specifically observe group sessions. Should an adult study staff be unavailable to deliver a TI-CBT or Discussion Control group session, the observer assigned to that study arm will take his/her place as a facilitator.

TI-CBT Intervention Arm only:

Adult study staff designated to deliver the two caregiver sessions that accompany the youth TI-CBT will receive additional training specific to HIV knowledge and youth adherence to ARVs. In addition, adult study staff will be trained on using a TI-CBT Caregiver Intervention Manual (refer to Section 5.1.1.1) to ensure systematic learning of the curriculum and how to lead groups. The adult study staff selected to observe will also complete the fidelity ratings.

Refer to the study-specific MOP for additional guidance.

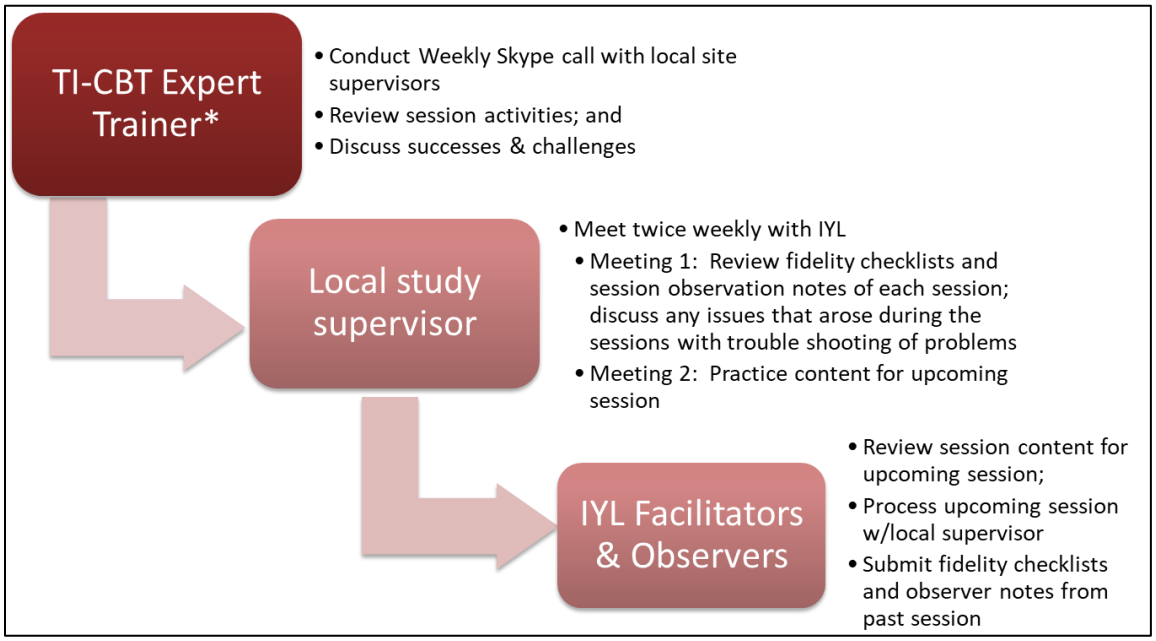
5.3 Supervision of Indigenous Youth Leaders and Adult Study Staff

5.3.1 Indigenous Youth Leaders Supervision

The protocol team will train local study staff to serve as weekly supervisors of IYL. Using a cascading supervision model (refer to Figure 3), an expert trainer will conduct the supervision with the local site PI and supervisors who will then provide supervision to the IYL. This approach will further enhance the in-country capacity to deliver the intervention and increase sustainability of the TI-CBT intervention.

The local supervisor will always be on site during group sessions to assist in the event that an issue arises during group sessions that requires more professional attention. The IYL for both the TI-CBT and Discussion Control arms will be trained to seek out the supervisor for assistance.

Figure 3. Cascading Supervised Training Model



*Note, ad hoc calls between the expert trainer, local study supervisor, and IYL may occur as needed

5.3.2 Adult Study Staff Supervision

The adult study staff will receive ongoing supervision from the expert trainer during supervision sessions. The expert trainer will also provide supervision to the adult study staff who deliver the caregiver sessions. The expert trainer will conduct Skype calls to review any concerns that arise during the caregiver sessions and problem solve best practices.

5.4 Intervention Fidelity

Assessment of the TI-CBT intervention fidelity will be ongoing during the Pilot Test and Randomized Trial in both the youth and caregiver sessions. The recommendations of the Intervention Fidelity Workgroup of the NIH Behavior Change Consortium (134) will be adhered to: a) clear, detailed manuals and facilitator guides; b) standardized training protocols; c) training

to competency; d) session observations; and e) frequent communication between facilitators, investigators, observers, and supervisors. Intervention fidelity will be assessed by IYL and adult study staff self-report and observer ratings of a) adherence to the TI-CBT and caregiver manuals, and b) competence to deliver the intervention. Adherence measures will determine whether the intervention was delivered as planned, and competence ratings will indicate the quality of intervention delivery.

IYL and adult study staff self-report and observer ratings will be collected and source documented at the end of each session (Pilot Test and Randomized Trial) using a fidelity checklist. The fidelity checklist will be used by the expert trainer to provide feedback to IYL and adult study staff to address areas of concerns during supervision. On the checklist, IYL and adult study staff will rate whether they delivered each activity (yes/no), and on a Likert scale from 1 to 5, how smoothly the session went, how well they knew and delivered the material, and their comfort with participants. Open-ended questions will offer opportunities to report challenges, barriers, and successes. Separately, a trained youth leader will observe the IYL sessions and a trained adults study staff member will observe the caregiver sessions. Both observers will use an adapted version of Lane et al.'s (135) Intervention Fidelity Questionnaire. The observers will rate whether each task was completed (yes/no), and indicate on a Likert scale from 0=not very well to 4=excellent: 1) facilitator leadership skills (e.g., explained activity correctly, was non-judgmental); and 2) facilitator adherence and competence on delivery of session-specific activities: a) how smoothly the session went; b) how well facilitators knew and delivered the material; and c) facilitator comfort.

5.5 Study Evaluations and Measures

Youth Participants

Measures collected during the Randomized Trial only (not Pilot Test) form the basis for study evaluation.

Outcome measures include self-reported mental health symptoms [PHQ-9 (136); UCLA PTSD-RI (64); GAD-7 (137)]; self-reported ART adherence (138); barriers to adherence; report of caregiver behavior; AIDS-related stigma scale (139); gender-based violence (140, 141); gender roles; sexual risk behavior and drug/alcohol use (142); demographics; and HIV status disclosure. Measures will be translated and back translated in the local language prior to study use as needed. Measures will be collected at baseline, immediately post-last group session, and at 6- and 12-months post-first group session, with demographics collected once at baseline. Youth will complete self-report measures via Computer-Assisted Self-Interview (CASI), but trained research staff will remain in the room to answer participants' questions or read questionnaire items to participants as needed. In the event CASI is inaccessible due to environmental interference (e.g., power outages) or other unforeseen cause, paper versions of the questionnaires will be administered to participants, and data will be entered into CASI by study staff when CASI is next accessible.

Laboratory based evaluations include quantitative drug concentration levels from hair samples as a biologic measure of adherence; HIV-1 RNA (viral load); and biomarkers of inflammation (e.g., hsCRP, sCD14, IL1β, IL6, D-dimer, and TNFα). Measures are further described throughout Section 5.5 below.

Caregiver Participants

Measures collected during the Randomized Trial only (not Pilot Test) form the basis for study evaluation.

Outcome measures include caregiver-reported HIV attitudes, knowledge, and beliefs, and AIDS-related stigma (139), caregiver involvement in youth adherence using a measure developed for the KIP study in Rwanda, and caregiver report of youth behavior (CBCL) and demographics. Measures will be translated and back translated in the local language prior to study use as needed. Measures will be collected at baseline, immediately post-last group session, and at 6- and 12-months following the first youth group session of the caregiver's youth, with demographics collected once at baseline. Caregivers will complete measures via CASI, but trained research staff will remain in the room to answer participants' questions or read questionnaire items to participants as needed. In the event CASI is inaccessible due to environmental interference (e.g., power outages) or other unforeseen causes, paper versions of the questionnaires will be administered to participants, and data will be entered into CASI by study staff when CASI is next accessible. Measures are further described throughout Section 5.5 below.

5.5.1 General Measures

Demographics (Completed by Youth and Caregiver Participant)

Youth demographic information collected via CASI will include education (e.g., school enrollment status, highest level of education), living arrangements (e.g., housemates, home infrastructure and resources such as electricity, water source and number of rooms), orphan status, and family resources (e.g., youth household income, job, cell phone access).

Caregiver demographic information collected via CASI will include education (e.g., highest level of education) and family resources (e.g., caregiver household income, job).

Disclosure Measures (Completed by Youth Participant)

Youth will report how and when they learned their HIV status (primary HIV disclosure) and, if purposefully told, who told them. Youth will also report if they ever disclosed their HIV status to another person (secondary disclosure) and, if so, who they told. Youth will report their HIV disclosure to sexual partners.

5.5.2 Mental Health Measures

Patient Health Questionnaire – 9 (PHQ-9) (Completed by Youth Participant)

The Patient Health Questionnaire (PHQ-9) includes 9-items assessing the frequency of depression symptoms on a scale from 0=not at all to 3=nearly every day, over a 2-week period. The PHQ-9 has demonstrated reliability for screening depression in adults in Kenya (143), Ethiopia (144), South Africa (145), and HIV-positive patients in Uganda (146). The PHQ-9 is also recommended for screening adolescent depression (147). A threshold score of 10 or greater (range 0–27) has been demonstrated to reflect clinical levels of depression in validation studies (144, 145) with good test–retest reliability and Cronbach's alpha of 0.85 in Ethiopia (144) and similarly Cronbach's alpha of 0.78 in Kenya (143).

General Anxiety Disorder – (GAD-7) (Completed by Youth Participant)

The GAD-7 is a widely used well-validated instrument developed to be consistent with the PHQ-9. The GAD-7 includes 7-items assessing frequency of anxiety symptoms on a scale from 0=not at all to 3=nearly every day, over a 2-week period. Using the range of total scores from 0 to 21, a score of 10 or higher is considered a cutoff for anxiety. The GAD-7 demonstrates strong construct validity, internal consistency, and test-retest reliability (148). The GAD-7 has shown high sensitivity (89%) and specificity (82%) of an anxiety diagnosis for generalised anxiety disorder and panic disorder, social anxiety and post-traumatic stress disorder (149). The cross-cultural construct validity of GAD-7 has been demonstrated in multiple international settings, including a recent study conducted in Côte d'Ivoire and Ghana (150).

UCLA PTSD-Reaction Index (RI) (Completed by Youth Participant)

The UCLA PTSD Reaction Index (RI) is a well-established, widely used scale with demonstrated reliability and validity for assessing DSM-IV criteria for PTSD in youth populations (151). Youth will report on their life experiences and feelings. The measure has five response options from 0=none to 4=most of the time; with a range of total scores from 0 to 51, a score of 35 is considered a cutoff for post-traumatic stress symptoms. This measure has demonstrated strong convergent validity with clinician diagnoses of PTSD using DSM-V criteria and structured diagnostic interviews, such as the PTSD module of the Schedule for Affective Disorders and Schizophrenia for School-Age Children, as well as strong internal consistency and test-retest reliability. The tool has been widely used in low resource countries and has been translated and validated for use in Zambia with good reliability (Cronbach's alpha ≥0.90) among children who experienced sexual abuse (152) and in youth from neighboring Kenya after the 2007 election riots (153).

5.5.3 Adherence Measures

Self-reported ART Adherence (Completed by Youth Participant)

Youth will report on their ART adherence using a well-validated 3-item scale (154). Evidence supports the scale's psychometric characteristics and construct validity when compared to standard electronic drug monitoring. Each of the three self-report items have different response options. To create a summary score, the items are transferred linearly to a 0-100 scale. A single summary self-report adherence score is then calculated by averaging the three 0-100 scales.

Biologic Measures of Adherence (Completed by Youth Participant)

Hair concentrations of ARVs have been the strongest independent predictor of virologic success in large prospective cohorts (132, 155-157) and are stronger predictors of intervention outcomes than self-reported adherence (132, 156) or single plasma ARV concentrations (157). Several published studies have verified the association between ART drug concentration in hair samples and virologic outcomes among children and adolescents (127, 130, 131, 158) as well as adult studies (128, 129, 132). Unlike phlebotomy, hair collection is noninvasive; does not require specific skills, sterile equipment, or specialized storage conditions; provides an ease of obtaining sample (simple cut at the root with scissors, non-invasive); provides easy storage (is not temperature sensitive); and is shipped without precautions for biohazardous materials. Hair samples offer a more long-term window adherence over the last month (similar to a hemoglobin

A1C to evaluate sugar control in diabetes) as opposed to recent within the last day (similar to a random blood glucose).

Barriers to Adherence (Completed by Youth and Caregiver Participant)

Barriers to adherence will be evaluated using an adaptation of a well-established questionnaire used by Buchanan et al (159). Items list potential reasons why youth may skip or miss taking their medications, including but not limited to interference by daily routine, sleep pattern, illness, drug or alcohol consumption, or feelings of depression; medication supply depleted; quantity of pills to be taken; concerns of side effects; or belief of being cured or no longer needing medication.

5.5.4 Behavioral Measures

Gender Roles and Gender-based Violence (Completed by Youth Participant)

Gender-based physical, sexual, emotional, and economic abuse will be evaluated using items from the WHO Multi-Country Study on Women's Health and Life Experiences, Final Core Questionnaire, version 10 © World Health Organization, 2003. This measure was used in the Rwanda study and has found important relationships between abuse and adolescent adherence. The original measure has been modified with authorization of the WHO to adapt terms to the target population; the WHO is not responsible for the adaptation.

Gender roles will be evaluated using an adaptation of the Youth Gender Relations/Roles Scale developed by Rachel Jewkes to capture different dynamics for different types of relationships.

Sexual Behavior and Drug/Alcohol Use (Completed by Youth Participant)

The AIDS Risk Behavior Assessment (ARBA) (142) is a widely used measure of adolescent self-reported sexual behavior and drug/alcohol use. Modified versions of the ARBA have been used with adolescents and young adults in South Africa and Rwanda. Sexual risk questions ask about lifetime and recent sexual activity, condom use, number of partners, and high-risk partners. Drug and alcohol questions ask about lifetime and recent use, frequency of use, and number of times used.

Child Report of Caregiver Behavior (Completed by Youth Participant)

This study will use a shortened version of The Child Report of Parenting Behavior (160), a measure of adolescent reported parental acceptance, rejection, positive involvement, and hostile detachment, to evaluate the youth perceptions of caregiver warmth, acceptance and rejection. Items are rated on a 3-point scale (1=not like my caregiver, 2=somewhat like my caregiver, 3=a lot like my caregiver). The validity of the measure has been widely documented in both European-American and African-American populations (161), and the internal reliability within the current sample was acceptable ($\alpha = .87$). The measure was used in the KIP study, and internal consistency of the scales was high to acceptable at baseline and across three time points: Acceptance (.89 at T1; Range across 3 time points.89-.91), Rejection (.75 at T1; .75-.83), Positive Involvement (.85 at T1;.85-.88), and Hostile Detachment (.67 at T1; .67-76).

The AIDS-Related Stigma Scale (Completed by Youth and Caregiver Participant)

Youth and caregiver stigma will be evaluated using an adaptation of the 9-item AIDS-Related Stigma Scale which has robust evidence of reliability and validity (139). The scale was developed and validated in five South African communities (N=2306) and demonstrated strong internal consistency (alpha=0.75) and test-retest reliability (alpha=0.67). Two-option responses to each item - "agree" or "disagree" - were used to reduce confusion (139).

Caregiver Attitudes and Support for Youth Adherence (Completed by Caregiver Participant)

Caregivers will report their level of involvement in youth ART adherence on a scale adapted from the KIP study in Rwanda. The items were developed for the KIP study, and responses were along 4-point scale from 0=not at all to 3=all the time.

Caregiver HIV knowledge

Caregiver HIV knowledge will be assessed using an adaptation of the scale developed by Kalichman and Simbayi (162) and subsequently validated by Bowen, Govender, & Edwards (163). The validated 10-item measure based on Carey and Schroder's (164) 18-item scale, was adapted for use in South Africa and has been translated into isiXhosa and Afrikaans. Item responses allow for "Yes", "No", or "Don't Know." The number of correct answers converting "Don't Know" to incorrect will be summed. Higher scores indicate more HIV/AIDS knowledge. Evidence for the scale's reliability and validity are strong (163).

Caregiver Report of Youth Behavior (Completed by Caregiver Participant)

Caregivers will report on their youth's behavior problems using the Child Behavior Checklist (165). The CBCL is a widely-used measure of caregiver-reported child behavior over the past six months. The measure produces a score for externalizing problems that include symptoms of aggression, delinquency, disruptive behavior, and oppositional defiant behavior (e.g. "Breaks rules at home, school, or elsewhere"). Items are rated using a 3-point Likert scale as 0=*Not true*, 1=*Somewhat or sometimes true*, or 2=*Very true or often true.* The CBCL has been widely used in South Africa in HIV-infected populations and to compare HIV-infected, HIV-exposed and HIV-uninfected children (166, 167).

5.5.5 TI-CBT Adaptation

At each group session during the Pilot Test and Randomized Trial, logistics data (attendance, punctuality) will be collected as one indicator of acceptability. Youth and caregivers will report on paper 1) how much they enjoyed the intervention, and 2) how much they learned, both on a scale from 1-10 to be collated at the end of each group session.

At the end of the last group session during the Pilot Test and Randomized Trial, the feasibility and acceptability will be assessed using a participant intervention evaluation questionnaire administered via pen and paper in the Pilot Test and CASI in the Randomized Trial. Questions will assess youth and caregiver's satisfaction with the intervention and facilitators (e.g., IYL, adult study staff), comfort interacting with facilitators, facilitator and peer openness, and suggestions to improve the intervention. Interviews with local clinic staff will inquire about the intervention's impact on clinic operations.

5.6 Concomitant Medications

No medications are provided in this study.

All medications received by youth in the Pilot Test and Randomized Trial are considered concomitant medications. As part of the targeted medical histories described in Section 6.5, all ARVs received by these youth, starting at Pre-Entry and continuing throughout follow-up will be source documented and entered into eCRFs.

In addition, all psychiatric medications will be source documented and entered into eCRFs. Receipt of psychiatric medications will have no impact on other aspects of youth participation in the study.

5.7 Other Considerations

5.7.1 Risk of Contamination for the TI-CBT and Control Arm

There is unavoidable risk of contamination in this study but multiple steps to minimize contamination will be taken. Youth and caregivers in both the TI-CBT and Discussion Control groups may be recruited from the same HIV clinics, and it is possible that they will discuss their experiences in the study. However, the TI-CBT and Discussion Control groups will occur at different times to minimize the risk of contact between members of study arms. IYL and adult study staff leading the TI-CBT Arm group sessions will not have study related contact with the IYL and adult study staff leading the Discussion Control groups.

A questionnaire assessing contamination will be administered using CASI at the 6-month Follow-up Study Visit to youth and caregiver in both the TI-CBT and Discussion Control groups. Youth and caregivers will be asked about any discussion of concepts or tools they learned in their assigned group with study participants randomized to the other group. Youth and caregivers will be asked to indicate specific topics discussed with participants in the other group.

6 STUDY VISITS AND PROCEDURES (Pilot Test/Randomized Trial)

Refer to Section 4.6 for a description of the study recruitment, screening, and enrollment process. An overview of the study visits and evaluation schedules for youth are provided in Appendix I-A and Appendix II-A. An overview of the study visits and evaluation schedules for caregivers are provided in Appendix I-B and Appendix II-B. Presented in this section is additional information on visit-specific study procedures.

All study visits should be conducted as close as possible to the specified target visit dates and within the specified targeted windows. Every effort should be made to conduct the visits within the targeted windows; however, the visits are permitted to be conducted within the allowable windows.

Study visits and procedures will generally be performed at the clinical research site. However, if allowed per local law and regulations and/or institutional policies, participants may have study visits conducted in their home or in other off-site locations. At sites where off-site visits are permitted, study staff will discuss this option with participants in advance and agree on where and when such visits may take place, with adequate protections for participant privacy and

confidentiality. Prior to each off-site visit, study staff will confirm the date, location, and time of each visit with the participant. At off-site visits when specimen collection is required, the procedures specified in Section 6.8 must be followed. Off-site visits may only be conducted by designated study staff who are qualified to perform all protocol-specified procedures and have undergone study-specific and all other applicable training relevant to the procedures they will perform off site. These staff should also be adequately trained and qualified to immediately manage any adverse events and/or social harms that may occur during off-site visits (e.g., fainting during blood drawing).

All visits and procedures must be documented in accordance with the NIAID DAIDS policies for source documentation; refer to Section 10 for more information on documentation requirements and entry of eCRFs. Refer to Section 7 for information on expedited adverse event (EAE) reporting, which may be required at any time during follow-up.

In addition to the protocol-specified procedures listed in this section, study staff may complete other tasks consistent with site SOPs, including but not limited to recruiting potential participants; collecting, reviewing, and updating demographic and locator information; reviewing elements of informed consent and assent; scheduling group sessions and individual visits; providing instructions for contacting study staff between visits; providing visit reminders; and following up on missed visits. All such tasks must be documented consistent with site SOPs.

Study staff should also provide participants and their parents or guardians (if applicable) with clinically meaningful findings and test results, and provide referrals to non-study sources of care and treatment when indicated. Clinically meaningful test results will include HIV-1 RNA (viral load) results, which will be monitored routinely in youth participating in the Randomized Trial. Site investigators should review the results of each test as well as trends over time and share these with participants, their parents or guardians (if applicable), and their non-study health care providers, with the expectation that non-study health providers will use these results as part of routine monitoring and management of the participant.

6.1 Youth Pilot Test

6.1.1 Youth Pilot Test: Screening Visit

Screening procedures may be initiated after written informed consent/assent is obtained. Screening procedures for the Pilot Test are targeted to be performed within a target window of up to 30 days prior to the enrollment and an allowable window of up to 60 days prior to enrollment. Multiple visits may be conducted to complete all required screening procedures if necessary. For youth who do not meet the eligibility criteria, screening should be discontinued once ineligibility is determined.

Youth Screening Visit Procedures for Pilot Test (up to 60 days prior to enrollment)		
Administrative and Regulatory		• Obtain written informed consent with written assent as applicable per inclusion criterion 4.1.2 and documentation of youth permission for caregiver participation in the study • Assign participant identification number (PID) • Obtain screening number from study-specific screening log in SES • Assess eligibility
Clinical		• Review medical records to assess study requirements related to HIV infection per inclusion criterion 4.1.3 and ARV history per inclusion criterion 4.1.5, and collect limited demographic screening data
Behavioral and Counseling		• Administer questionnaires via CASI - pen and paper may be substituted per Section 5.5: *Eligibility and baseline measures:* ○ PHQ-9 ○ GAD-7 ○ UCLA PTSD-RI *Baseline measures only:* ○ Demographics ○ Self-reported ART Adherence
Laboratory	**Blood**	• Collect blood only if needed per inclusion criterion 4.1.3 for: ○ Confirmatory HIV testing

6.1.2 Youth Pilot Test: Pre-Entry Visit

Pre-Entry procedures for the Pilot Test are targeted to be conducted on the same day as the Entry Visit with an allowable window of up to 14 days prior to the Entry Visit (refer to Sections 6.1.3 and 6.1.4).

During the Pre-Entry Visit, participants will perform mock procedures for hair and blood collections and complete the questionnaires to assess the logistical feasibility and duration to complete all procedures on the same day or up to 14 days prior to the Group Session 1. No hair or blood will be collected, and no data from the questionnaires will be analyzed. Refer to study-specific MOP for guidance on the mock procedures.

Youth Pre-Entry Visit Procedures for Pilot Test (up to 14 days prior to enrollment)		
Clinical		• Obtain targeted medical/medications history per Section 6.5
Behavioral and Counseling		• Administer questionnaires via CASI - pen and paper may be substituted per Section 5.5: *Following questionnaires completed but data not analyzed*: ○ Disclosure ○ Self-reported ART Adherence ○ Barriers to adherence ○ Gender-based Violence (WHO – Victim/Perpetrator) ○ Gender Roles (Rachel Jewkes) ○ AIDS-Related Stigma Scale ○ AIDS Risk Behavior Assessment (Sexual behavior/Drug and alcohol use) ○ Children's Report of Parenting Behavior Inventory
Laboratory (mock)	**Blood**	• Mock blood collection (*do not draw blood*) for: ○ HIV RNA (viral load) ○ Plasma for inflammatory biomarkers
	Hair	• Mock hair collection for ART concentration (*do not cut hair*)

6.1.3 Youth Pilot Test: Entry Visit

The pool of 12-20 eligible youth who completed Pre-Entry Visit procedures will complete their Entry Visit on the same day as the first group session. Eligible youth will be enrolled during the Entry Visit. No randomization will occur for the Pilot Test; all youth will participate in the TI-CBT Intervention.

Youth Entry Visit Procedures for Pilot Test (same day as Group Session 1)	
Administrative and Regulatory	• Confirm final eligibility determination • Complete paper-based eligibility checklist for Step 1, enter checklist data into SES to enroll the youth, print and file a copy of the confirmation file

6.1.4 Youth Pilot Test: Group Sessions 1-6 Study Visits

Group Session 1 is targeted to occur on the day when group members complete their study Entry Visits. All six group sessions should be completed within eight weeks of the date of Group Session 1. Group sessions may be conducted on separate days or multiple sessions may be conducted on the same day.

Youth Group Sessions 1-6 Procedures for Pilot Test (within 8 weeks of Group Session 1)	
Behavioral and Counseling	• IYL-delivered TI-CBT group session [refer to Section 5.1.1] • Administer the following **after** the group session: o After each group session: Two questions on "Amount of fun had" and "Amount learned" [refer to Section 5.5.5] o After the final group session: Pen/paper-administered Participant Intervention Evaluation [refer to Section 5.5.5]

6.2 Caregiver Pilot Test

6.2.1 Caregiver Pilot Test: Screening Visit / Entry Visit

Screening and entry procedures may be initiated after written informed consent/assent is obtained. Screening and Entry Visit procedures may be combined into one study visit or split across multiple study visits. Procedures may be conducted on a separate day or on the same day as the caregiver's first group session prior to initiation of the group session. Screening Visit will take place up to 60 days prior to enrollment. No randomization will occur for the Pilot Test; all caregivers will participate in the TI-CBT Intervention.

During the Entry Visit participants will complete the questionnaires to assess the logistical feasibility and duration to complete of all procedures, however no data from the questionnaires will be analyzed.

Caregiver Screening Visit / Entry Visit Procedures for Pilot Test (up to 60 days prior to enrollment)	
Administrative and Regulatory	• Obtain youth agreement of caregiver participation • Obtain written informed consent per inclusion criterion 4.3.2 • Assign participant identification number (PID) • Complete eligibility determination and confirmation • Complete paper-based eligibility checklist, enter eligibility checklist data for Step 1 into SES to enroll the caregiver through the same study eligibility checklist linking the PID numbers of the youth and caregiver, print and file a copy of the confirmation file
Behavioral and Counseling	• Administration questionnaires via CASI - pen and paper may be substituted per Section 5.5: *Following questionnaires completed but data not analyzed:* o Demographics o AIDS-Related Stigma Scale o HIV attitudes and support o Barriers to adherence o HIV knowledge o CBCL caregiver report of youth behavior

6.2.2 Caregiver Pilot Test: Group Sessions A and B Study Visits

Caregiver Group Session A and B should be completed within eight weeks of the start of their youth's first group session and will be conducted separately from the youth group sessions. The caregiver Group Sessions A and B will be conducted on separate days, and Group Session B is defined as the Exit Visit for caregivers.

Caregiver Group Sessions A and B Procedures for Pilot Test (within 8 weeks of caregiver's youth Group Session 1)	
Behavioral and Counseling	• Adult study staff delivered caregiver TI-CBT group session [refer to Sections 5.1.1] • Administer the following **after** the group session: ○ After each group session: Two questions on "Amount of fun had" and "Amount learned" [refer to Section 5.5.5] ○ After the final group session: Pen/paper-administered Participant Intervention Evaluation [refer to Section 5.5.5]

6.3 Youth Randomized Trial of TI-CBT

6.3.1 Youth Randomized Trial: Screening Visit

Screening procedures may be initiated after written informed consent/assent is obtained. Screening procedures for the Randomized Trial are targeted to be performed within a target window of up to 30 days prior to the enrollment and an allowable window of up to 60 days prior to enrollment. Multiple visits may be conducted to complete all required screening procedures if necessary. For youth who do not meet the eligibility criteria, screening may be discontinued once ineligibility is determined.

Youth Screening Visit Procedures for Randomized Trial (up to 60 days prior to enrollment)		
Administrative and Regulatory		• Obtain written informed consent with written assent as applicable per inclusion criterion 4.1.2 and documentation of youth permission for caregiver participation in the study • Assign participant identification number (PID) • Obtain screening number from study-specific screening log in SES • Assess eligibility
Clinical		• Review medical records to assess study requirements related to HIV infection per inclusion criterion 4.1.3 and ARV history per inclusion criterion 4.1.5, and collect limited demographic screening data
Behavioral and Counseling		• Administer questionnaires via CASI - pen and paper may be substituted per Section 5.5: *Eligibility and baseline measures:* ○ PHQ-9 ○ GAD-7 ○ UCLA PTSD-RI *Baseline measures only:* ○ Demographics ○ Self-reported ART Adherence
Laboratory	**Blood**	• Collect blood only if needed per inclusion criterion 4.1.3 for: ○ Confirmatory HIV testing

6.3.2 Youth Randomized Trial: Pre-Entry Visit

Pre-Entry procedures for the Randomized Trial are targeted to be conducted on the same day of the Entry Visit with an allowable window of up to 14 days prior to the Entry Visit (refer to Sections 6.3.3 and 6.3.4).

Youth Pre-Entry Visit Procedures for Randomized Trial (up to 14 days prior to enrollment)		
Clinical		• Obtain targeted medical/medications history per Section 6.5
Behavioral and Counseling		• Administer questionnaires via CASI - pen and paper may be substituted per Section 5.5: *Baseline measures*: ○ Disclosure ○ Self-report ART Adherence ○ Barriers to adherence ○ Gender-based Violence (WHO – Victim/Perpetrator) ○ Gender Roles (Rachel Jewkes) ○ AIDS-Related Stigma Scale ○ AIDS Risk Behavior Assessment (Sexual behavior/Drug and alcohol use) ○ Children's Report of Parenting Behavior Inventory
Laboratory	**Blood**	• Collect blood for (*baseline measures*): ○ HIV-1 RNA (viral load test) ○ Plasma for Inflammatory biomarkers
	Hair	• Hair sample (50-60 strands) for ART concentration (*baseline measure*) – *to be collected from the head (scalp) only; not required if participant is bald*

6.3.3 Youth Randomized Trial: Entry Visit

The pool of 12-20 eligible youth who completed Pre-Entry Visit procedures will complete their Entry Visit on the same day as the first group session. Eligible youth will be enrolled and randomized during the Entry Visit.

Youth Entry Visit Procedures for Randomized Trial (same day as Group Session 1)	
Administrative and Regulatory	• Confirm final eligibility determination • Complete paper-based eligibility checklist for Step 2, enter checklist data into SES to enroll/randomize the youth, print and file a copy of the confirmation file

6.3.4 Youth Randomized: Group Sessions 1-6 Study Visits

Group Session 1 for the TI-CBT and Discussion Control arms are targeted to occur on the day when group members complete their study Entry Visits and are randomized to either the TI-CBT Intervention Arm or the Discussion Control Arm. Every effort will be made to keep the TI-CBT and Discussion Control groups separated once youth are randomized to an arm (e.g., group sessions occur in separate buildings, group sessions' start times staggered so one group leaves before the other finishes, etc.)

All six group sessions within an arm should be completed within eight weeks of the date of Group Session 1. Group sessions may be conducted on separate days or multiple sessions may be conducted on the same day.

Youth Group Sessions 1-6 Procedures for Randomized Trial (within 8 weeks of Group Session 1)	
Behavioral and Counseling	• IYL-delivered youth TI-CBT or Discussion Control group session [refer to Section 5.1] • Administer **after** each group session: Two questions on "Amount of fun had" and "Amount learned" [refer to Section 5.5.5]

6.3.5 Youth Randomized Trial: Immediately Post-Last group session Follow-up Study Visit

The Immediately Post-Last group session (IPL) Follow-up Study Visit is targeted to take place immediately following the last group session, either on the same day or within a targeted window of up to 14 days and an allowable window of up to 30 days following the last group session.

Youth Immediate Post-Last group session (IPL) Follow-up Study Visit Procedures for Randomized Trial (up to 30 days following the last group session)		
Clinical		• Obtain targeted medical/medications history per, Section 6.5
Behavioral and Counseling		• Administer questionnaires via CASI - pen and paper may be substituted per Section 5.5: ○ Participant Intervention Evaluation [refer to Section 5.5.5] ○ PHQ-9 ○ GAD-7 ○ UCLA PTSD-RI ○ Self-reported ART Adherence ○ Barriers to adherence ○ Gender-based Violence (WHO – Victim/Perpetrator) ○ Gender Roles (Rachel Jewkes) ○ AIDS-Related Stigma Scale ○ AIDS Risk Behavior Assessment (Sexual behavior/Drug and alcohol use) ○ Children's Report of Parenting Behavior Inventory
Laboratory	**Blood**	• Collect blood for: ○ HIV-1 RNA (viral load test)
	Hair	• Hair sample (50-60 strands) for ART concentration – *to be collected from the head (scalp) only; not required if participant is bald*

6.3.6 Youth Randomized Trial: 6 Month Follow-up Study Visit

The 6 Month Follow-up Study Visit is targeted to take place on Day 182, counted from the day of the first group session as Day 0, with a targeted window of ± 14 days and an allowable window of ± 30 days.

Youth 6 Month Follow-up Study Visit Procedures for Randomized Trial (± 30 days)		
Clinical		• Obtain targeted medical/medications history per Section 6.5
Behavioral and Counseling		• Administer questionnaires via CASI - pen and paper may be substituted per Section 5.5: ○ PHQ-9 ○ GAD-7 ○ UCLA PTSD exposure screener and reaction index ○ Self-report ART Adherence ○ Barriers to adherence ○ Gender-based Violence (WHO – Victim/Perpetrator) ○ Gender Roles (Rachel Jewkes) ○ AIDS-Related Stigma Scale ○ AIDS Risk Behavior Assessment (Sexual behavior/Drug and alcohol use) ○ Children's Report of Parenting Behavior Inventory ○ Risk for Contamination
Laboratory	**Blood**	• Collect blood for: ○ HIV-1 RNA (viral load test) ○ Plasma for Inflammatory biomarkers • Hair sample (50-60 strands) for ART concentration – *to be collected from the head (scalp) only; not required if participant is bald*

6.3.7 Youth Randomized Trial: 6 Month Booster Group Session Study Visit

The 6 Month Booster Group Session should take place after completion of the 6 Month Follow-up Study Visit evaluations. For each participant in a group, the booster group session is targeted to take place on the same day (Day 182) as the 6 Month Follow-up Visit with a targeted window of up to 14 days and an allowable window of up to 30 days following the 6 Month Follow-up Study Visit.

Youth 6 Month Booster Group Session Procedures for Randomized Trial (up to 30 days following the 6 Month Follow-up Study Visit)	
Behavioral and Counseling	• Booster Group Session: IYL-delivered youth TI-CBT or Discussion Control 6-month Booster Group Session • Administer **after** the Booster Group Session: Two questions on "Amount of fun had" and "Amount learned" [refer to Section 5.5.5]

6.3.8 Youth Randomized Trial: 12 Month Follow-up Study Visits / Exit Visit

The 12 Month Follow-up Study Visit is targeted to take place on Day 365, counted from the day of the first group session as Day 0, with a targeted window of ± 14 days and an allowable window of ± 30 days. This visit is each youth participant's Exit Visit.

Youth 12 Month Follow-up Study Visit Procedures / Exit Visit for Randomized Trial (± 30 days)		
Clinical		• Obtain targeted medical/medications history per, Section 6.5
Behavioral and Counseling		• Administer questionnaires via CASI - pen and paper may be substituted per Section 5.5: ○ PHQ-9 ○ GAD-7 ○ UCLA PTSD exposure screener and reaction index ○ Self-report ART Adherence ○ Barriers to adherence ○ Gender-based Violence (WHO – Victim/Perpetrator) ○ Gender Roles (Rachel Jewkes) ○ AIDS-Related Stigma Scale ○ AIDS Risk Behavior Assessment (Sexual behavior/drug and alcohol use) ○ Children's Report of Parenting Behavior Inventory
Laboratory	**Blood**	• Collect blood for: ○ HIV-1 RNA (viral load test) ○ Plasma for Inflammatory biomarkers • Hair sample (50-60 strands) for ART concentration – *to be collected from the head (scalp) only; not required if participant is bald*

6.4 Caregiver Randomized Trial of Youth TI-CBT

6.4.1 Caregiver Randomized Trial: Screening Visit / Entry Visit

Screening and entry procedures may be initiated after written informed consent/assent is obtained. Screening and Entry Visit procedures may be combined into one study visit or split across multiple study visits. Procedures may be conducted on a separate day or on the same day as the caregiver's first group session prior to initiation of the group session. Screening Visit will take place up to 60 days prior to enrollment.

Caregiver Screening Visit / Entry Visit Procedures for Randomized Trial (up to 60 days prior to enrollment)	
Administrative and Regulatory	• Obtain youth agreement of caregiver participation • Obtain written informed consent per Section 12.3 and inclusion criterion 4.3.2 • Assign participant identification number (PID) • Complete eligibility determination and confirmation • Complete paper-based eligibility checklist, enter checklist data for Step 2 into SES to enroll the caregiver through the same study eligibility checklist linking the PID numbers of the youth and caregiver (randomization based on their youth's randomization), print and file a copy of the confirmation file
Behavioral and Counseling	• Administer questionnaires via CASI - pen and paper may be substituted per Section 5.5: *Baseline measures:* ○ Demographics ○ AIDS-Related Stigma Scale ○ HIV attitudes and support ○ Barriers to adherence ○ HIV knowledge ○ CBCL caregiver report of youth behavior

6.4.2 Caregiver Randomized Trial: Group Session A and B Study Visits

Group Session A and B should be completed within eight weeks of the start of their youth's first group session and will be conducted separately from the youth group sessions. The caregiver Group Sessions A and B will be conducted on separate days.

Caregiver Group Sessions A and B Procedures for Randomized Trial (within 8 weeks of caregiver's youth Group Session 1)	
Behavioral and Counseling	• Adult study staff delivered caregiver TI-CBT or Discussion Control group session [refer to Section 5.1] • Administer **after** the group session: Two questions on "Amount of fun had" and "Amount learned" [refer to Section 5.5.5]

6.4.3 Caregiver Randomized Trial: Immediately Post-Last group session Follow-up Study Visit

The Immediate Post-Last group session (IPL) Follow-up Study Visit is targeted to take place immediately following the caregiver Group Session B, either on same day or within a targeted window of up to 14 days and an allowable window of up to 30 days following Group Session B, and in parallel with their respective Youth Follow-up Study Visit.

Caregiver Immediate Post-Last group session (IPL) Follow-up Study Visit Procedures for Randomized Trial (up to 30 days following the Group Session B)	
Behavioral and Counseling	• Administer questionnaires via CASI - pen and paper may be substituted per Section 5.5: ○ Participant Intervention Evaluation [refer to Section 5.5.5] ○ AIDS-Related Stigma Scale ○ HIV attitudes and support ○ Barriers to adherence ○ HIV knowledge ○ CBCL caregiver report of youth behavior

6.4.4 Caregiver Randomized Trial: 6 Month Follow-up Study Visits

The 6 Month Follow-up Study Visit is targeted to take place on Day 182, counted from the day of the caregiver's youth first group session as Day 0, with a targeted window of ± 14 days and an allowable window of ± 30 days, and in parallel with their respective Youth Follow-up 6 Month Study Visit.

Caregiver 6 Month Follow-up Study Visit Procedures for Randomized Trial (± 30 days)	
Behavioral and Counseling	• Administer questionnaires via CASI - pen and paper may be substituted per Section 5.5: ○ AIDS-Related Stigma Scale ○ HIV attitudes and support ○ Barriers to adherence ○ HIV knowledge ○ CBCL caregiver report of youth behavior ○ Risk for Contamination

6.4.5 Caregiver Randomized Trial: 6 Month Booster Group Session Study Visit

The 6 Month Booster Group Session should take place after completion of the 6 Month Follow-up Study Visit evaluations. For each participant in a group, the booster group session is targeted to take place on the same day (Day 182) as the 6 Month Follow-up Study Visit with a targeted window of up to 14 days and an allowable window of up to 30 days following the 6 Month Follow-up Study Visit.

Caregiver 6 Month Booster Group Session Procedures for Randomized Trial (up to 30 days following the 6 Month Follow-up Study Visit)	
Behavioral and Counseling	• Booster Group Session: Adult study staff delivered caregiver TI-CBT or Discussion Control 6-month Booster group session • Administer **after** the Booster Group Session: Two questions on "Amount of fun had" and "Amount learned" [refer to Section 5.5.5]

6.4.6 Caregiver Randomized Trial: 12 Month Follow-up Study Visits / Exit Visit

The 12 Month Follow-up Study Visit is targeted to take place on Day 365, counted from the day of the caregiver's youth first group session as Day 0, with a targeted window of ± 14 days and an allowable window of ± 30 days, and in parallel with their respective Youth 12 Month Follow-up Study Visit. This visit is each caregiver participant's Exit Visit.

Caregiver 12 Month Follow-up Study Visit Procedures for Randomized Trial / Exit Visit for the Randomized Trial (± 30 days)	
Behavioral and Counseling	• Administer questionnaires via CASI - pen and paper may be substituted per Section 5.5: ○ AIDS-Related Stigma Scale ○ HIV attitudes and support ○ Barriers to adherence ○ HIV knowledge ○ CBCL report of youth behavior

6.5 Targeted Medical and Medication History

Targeted medical and medication history information, focused on psychiatric history and medication, will be collected per the schedule of evaluations. At each scheduled time point, available medical records will be reviewed and youth and/or their caregivers will be queried on an individual basis in a private setting separate from other participants to ascertain whether the youth has:

- Been diagnosed with a mental illness (if yes, diagnosis and dates of diagnosis)
- Attempted suicide (if yes, number of times; dates of all attempts)
- Received non-study mental health services (if yes, what kind of services; dates provided)
- Received referral from study staff to non-study mental health services (if yes, date and outcome of referral)
- Received psychiatric medications (if yes, medications received and dates of use)

In addition to the above, information on the youth's ART regimen, starting at screening and continuing throughout follow-up, will be ascertained.

All of the above must be source documented in participant study charts and will be entered into eCRFs and/or self-reported questionnaire administered via CASI. Consistent with Section 7.2, occurrences of insomnia, psychiatric disorders, and suicidal ideation or attempt must be adequately source documented and entered into adverse event eCRFs when applicable.

6.6 Potential Social Harms

Youth and/or caregiver participants' may experience social harms — non-medical adverse consequences — of their study participation. For example, their involvement in the study could become known to others and they could be perceived as being HIV-infected or their HIV-status may be unintentionally disclosed to others. As a result, participants could be treated unfairly, or could have problems being accepted by their families and/or communities.

Unsolicited youth reported social harms will be source documented and entered into eCRFs. As part of routine study monitoring, social harms will be tabulated and reviewed as described in Section 7.2. Study staff and IYL will make every effort to follow-up with the youth reporting a social harm to determine whether or not the social harm is considered a product of study participation Section 8. Descriptive analyses will be performed as needed to provide information to assist the Protocol Team and study staff with minimizing the occurrence of these events and mitigating their impacts should they occur.

In the event that a participant reports a social harm, every effort will be made by study staff to provide appropriate follow-up support and counseling to the participant as necessary; referrals to appropriate non-study resources may also be provided. Each site will provide such support in accordance with local standards of care and site SOP's. While maintaining participant confidentiality, study sites may engage their CAB members in exploring the social context surrounding instances of social harms, to minimize occurrence and to identify appropriate follow-up actions be taken.

6.7 Additional Procedures for Participants Who Express Suicidal Ideations

Youth participants who express suicidal ideation during the Pilot Test or Randomized Trial will need to be evaluated for the severity of their risk for suicide. During each session, the IYL taking notes will also note any talk of suicidal or homicidal thoughts or other safety concerns, including social harms. If any of these are mentioned, the IYL will be trained to immediately notify a study staff member. If any response to a CASI-administered question expresses suicidal or homicidal thoughts or other safety concerns, such as social harms, designated study staff will be notified by email. If the youth poses a risk to self or others, he or she will need to be immediately addressed and treated in accordance with local guidelines and the local standard of care. Such youth may remain on study. Please refer to Sections 7 and 8.1.

6.8 Additional Considerations for Laboratory Procedures

Each study site and laboratory involved in this study will comply with the DAIDS policy on Requirements for DAIDS Funded and/or Sponsored Laboratories in Clinical Trials Policy, which is available at:
https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures

6.8.1 Specimen Collection

Specimens will be collected for this study as indicated in the Schedule of Evaluations and per detailed guidance provided in the Laboratory Processing Chart (LPC), which will be available on the IMPAACT web site: www.impaactnetwork.org.

In accordance with US National Institutes of Health (NIH) recommendations:

- Blood collection for pediatric participants (less than 18 years of age) will not exceed 5 mL/kg in a single day or 9.5 mL/kg in any eight-week period.
- Blood collection for adult participants (18 years of age and older) will not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight-week period.

In the event that the targeted blood collection volumes cannot be collected, available specimens should be prioritized for HIV-1 RNA first, followed by inflammatory biomarkers.

6.8.2 Specimen Preparation, Testing, Storage, and Shipping

All specimens collected for this study will be labeled, transported, processed, tested, stored and/or shipped in accordance with the DAIDS policy referenced in Section 6.8, site and local laboratory SOPs, and the LPC. The frequency of specimen collection and testing will be directed by the Schedule of Evaluations in Appendix I-A, Appendix II-A, Appendix I-B, and Appendix II-B, and specifications for clinical management provided in Section 8. The Laboratory Data Management System (LDMS) will be used to document specimen collection, testing, storage, and shipping as specified in LPC.

HIV-1 RNA (viral load) testing will be performed locally in a VQA-approved laboratory. Hair samples will be collected and stored locally, and are expected to be batched shipped three times to designated testing laboratories for ARV concentration testing after all participant baseline, 6-month and 12-month at a site has been completed.

Plasma will be collected and stored locally until requested for shipment to designated testing laboratories. Testing (of plasma) for inflammatory biomarkers is expected to be performed after all participant follow-up has been completed. Inflammatory biomarkers will include hsCRP, d-dimer, IL1 β, IL6, IL10, sCD14, and TNFα.

After all protocol-specified laboratory testing has been performed, residual specimens may be of interest for future research use. Participants (or their parents/guardians) will be asked to provide written informed consent for future research use of these specimens, if permitted by site IRBs/ECs and other applicable review bodies. Participants (or their parents/guardians) may choose to provide or to decline informed consent for future research use of residual specimens with no impact on other aspects of study participation.

6.8.3 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study as currently recommended by the US Centers for Disease Control and Prevention, NIH, and other applicable agencies. All specimens will be shipped using packaging that meets requirements specified by the International Air Transport Association Dangerous

Goods Regulations for UN 3373, Biological Substance, Category B, and Packing Instruction 650. Culture isolates, if obtained in this study, are to be shipped as specified for UN 2814 Category A Infectious Substances.

7 SAFETY ASSESSMENT, MONITORING, AND REPORTING

Youth safety in the Pilot Test and Randomized Trial will be carefully assessed, monitored, and reported at multiple levels throughout this study. Sections 7.1, 7.2, and 7.3 describe safety-related roles, responsibilities, and procedures. The safety monitoring roles of the Core Protocol Team and the IMPAACT Study Monitoring Committee (SMC) are briefly referenced in Section 7.1 and described in greater detail in Sections 9.5.1 and 9.5.2.

The specifications of this section apply to youth participants in both study arms. Refer to Section 6.6 for additional information on potential social harms.

7.1 Safety-Related Roles and Responsibilities

7.1.1 Site Investigators

Site investigators are responsible for continuous monitoring of youth participants in the Pilot Test and the Randomized Trial and for alerting the Core Protocol Team if unexpected concerns arise. Importantly, site investigators must inform the Core Protocol Team of any of the following:

- Psychiatric adverse events resulting in hospitalizations
- Adverse events involving suicide attempts
- Any other occurrence that, in the opinion of the site investigator, could cause harm to a participant or others

For each of the above-listed types of events, the Core Protocol Team should be informed as soon as possible and within three days of site awareness of the event.

Site investigators will enter safety-related data into electronic case report forms (eCRFs) as indicated in Section 7.2 and complete expedited adverse event (EAE) reporting as indicated in Section 7.3. Site investigators are also responsible for prompt reporting to their IRBs/ECs and other applicable review bodies of any unanticipated problems involving risks to participants or others.

7.1.2 Core Protocol Team

The following Protocol Team members comprise the Core Protocol Team: Co-Chairs, Medical Officers, Statisticians, Data Managers, Clinical Trial Specialists, and at least one Protocol Investigator (impaact.core2016@fstrf.org). The Core Protocol Team will provide guidance as needed to site investigators regarding all aspects of participant management, including but not limited to questions related to participant eligibility and management of adverse events, and study intervention administration. Refer to Section 8 for more information on participant management.

On behalf of the full Protocol Team, the Core Protocol Team will monitor participant safety through routine review of study data reports as described in Section 9.5.

7.1.3 Study Monitoring Committee (SMC)

An independent IMPAACT Study Monitoring Committee (SMC) will monitor participant safety through routine and as needed reviews of study data. Refer to Section 9.5.2 for more information on the composition and role of the SMC in monitoring of this study.

7.2 Safety-Related Data Collection

Note: This section applies only to youth in the Pilot Test and Randomized Trial.

Note: This section describes eCRF data collection for pre-existing conditions and adverse events. As part of this description, reference is made to severity grading and criteria for EAE reporting; refer to Sections 7.3.3 and 7.3.2, respectively, for detailed information on these topics.

The definition of the term adverse event provided in Version 2.0 (January 2010) of the Manual for Expedited Reporting of Adverse Events to DAIDS (DAIDS EAE Manual) will be used in this study. This definition will be applied to youth participants, beginning at the time of enrollment/randomization in the Pilot Test or the Randomized Trial.

Pre-existing conditions and adverse events will be entered into eCRFs as specified below.

Pre-Existing Conditions

All psychiatric diagnoses identified prior to enrollment (including those ongoing at enrollment) will be entered into medical history eCRFs.

Adverse Events

The following adverse events will be entered into adverse event eCRFs.

- Grade 2 or higher suicidal ideation or attempt
- Grade 3 or higher psychiatric disorders
- Grade 3 or higher insomnia
- All adverse events meeting criteria for expedited adverse event reporting per Section 7.3.2

7.3 Expedited Adverse Event (EAE) Reporting

Note: This section applies only to youth participants in the Pilot Test and the Randomized Trial.

7.3.1 EAE Reporting to DAIDS

Requirements, definitions, and methods for expedited reporting of adverse events are outlined in Version 2.0 (January 2010) of the Manual for Expedited Reporting of Adverse Events to DAIDS (DAIDS EAE Manual), which is available on the DAIDS RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted using the DAIDS EAE Form. This form is available on the

DAIDS RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids/paper-eae-reporting.

For questions about DAERS, please contact NIAID CRMS Support at CRMSSupport@niaid.nih.gov. Queries may also be sent from within the DAERS application itself.

For questions about expedited reporting, please contact the DAIDS RSC Safety Office at DAIDSRSCSafetyOffice@tech-res.com.

7.3.2 EAE Reporting Requirements for this Study

The Serious Adverse Events (SAE) Reporting Category, as defined in Version 2.0 the DAIDS EAE Manual, will be used for this study. All serious (as defined in the DAIDS EAE Manual) psychiatric adverse events (e.g., insomnia, psychiatric disorders (including anxiety, depression, mania, and psychosis) and suicidal ideation or attempt) occurring among youth participants in the Pilot Test or the Randomized Trial will be reported as EAEs in this study.

The study interventions for which expedited reporting is required are the TI-CBT Intervention and the Discussion Control provided in the Pilot Test or Randomized Trial.

7.3.3 Grading Severity of Events (applies to EAEs and all other adverse events)

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Corrected Version 2.1, dated July 2017, will be used in this study. This table is available on the RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables.

7.3.4 EAE Reporting Period

The EAE reporting period for this study is the protocol-specified period of follow-up in the Pilot Test or Randomized Trial beginning at the time of enrollment/randomization and ending at the final follow-up visit.

After the protocol-defined EAE reporting period, unless otherwise noted, only Suspected, Unexpected Serious Adverse Reactions (SUSARs) as defined in Version 2.0 of the DAIDS EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

8 PARTICIPANT MANAGEMENT

Note: This section applies only to youth participants in the Pilot Test and the Randomized Trial.

All psychiatric adverse events identified in this study will be source documented in youth research records, consistent with the policies and procedures referenced in Section 10. Among other details, source documentation will include the severity of each event (graded as described in Section 7.3.3) and its relationship to the study intervention (TI-CBT or Discussion Control), assessed by the site clinician according to the following categories and definitions:

Related There is a reasonable possibility that the adverse event may be related to the intervention

Not related There is not a reasonable possibility that the adverse event may be related to the intervention

Further standardized guidance on determining whether there is a reasonable possibility of a relationship is available in the DAIDS EAE Manual, referenced in Section 7.3.1 above.

Psychiatric adverse events will be managed based on their severity and assessed relationship to the study interventions. Management will be according to best available clinical practice standards and the best medical judgment of the site investigator in consultation with the participant's care provider. As stated in Section 7.1.1, site investigators must consult with the Core Protocol Team regarding the management of psychiatric adverse events resulting in hospitalization and/or involving suicide attempts. Management may include premature discontinuation of the study intervention if this is assessed as in the best interest of the participant; site investigators should consult with the Core Protocol Team regarding any such discontinuation.

All psychiatric adverse events must be followed to resolution (return to baseline) or stabilization, with the frequency of repeat evaluations determined by the clinical significance of each event.

8.1 Monitoring of Youth Mental Health Risk by Study Staff and Indigenous Youth Leaders

All study staff members, including but not limited to IYL, will be trained to identify and respond appropriately to participants who may experience psychiatric adverse events, social harms, or other issues that require attention.

Staff identifying safety concerns (e.g., youth exhibiting risk of harming themselves or others, youth exhibiting a mental health risk, events resulting in hospitalization or involving suicide attempt) will consult with a designated on-site study clinician who will address the safety concern and intervene as needed to maintain safety of youth and staff. This intervention may include removing the youth from the group for the rest of the session as needed for safety or to minimize disruptive behavior. Staff who learn of safety concerns at a time outside of a session (e.g., youth contacts staff of a safety concern) will have access to standard of care guidelines and lines of communication to consult with designated professionals.

Staff will provide reports from each study arm group session to their supervisors and will refer participants to study clinicians and/or counselors as appropriate in response to potential issues or problems identified during or outside of these sessions. Study clinicians and/or counselors will further evaluate participants to provide appropriate care, treatment, and support that is consistent with their study-specific roles and responsibilities, and according to standard of care.

In addition, all sites must establish adverse event reporting and emergency response SOPs for this study, which will outline procedures, lines of communication, roles, and responsibilities for responding to participants in crisis. All study staff will be trained on these SOPs prior to study initiation and at least annually thereafter throughout the period of study implementation.

Standard of care

Youth and caregivers who exhibit or report severe mental health symptoms at any point during the study (e.g., suicidal ideation) will be referred for further evaluation and services as described above and according to the local standard of care. Prior to the Pilot Test, site personnel will create a "standard-of-care resource list" describing the mental health resources and lines of communication available to youth and caregivers at each site to ensure youths' needs are adequately addressed. This will be true regardless of randomization arm. All referrals to mental health services and outcomes during the 12-month study period will be recorded on eCRFs (refer to Section 6.5).

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

IMPAACT 2016 is a study of TI-CBT by IYL as an intervention to reduce mental health symptoms in youth living with HIV. Focus Group and Pilot Tests of TI-CBT by IYL will assess feasibility and acceptability at each site to provide information to help adapt the TI-CBT intervention to local culture and conditions. The Randomized Trial is a multi-site, two-arm randomized controlled trial of TI-CBT compared to Discussion Control groups. Participants for both the Pilot Test and Randomized Trial will be youth 15-19 years of age living with HIV who are receiving ART and experiencing mental health distress, as well as their caregivers (when available). Focus Group participants will not be required to be experiencing mental health distress.

Sites will be located in four sub-Saharan countries, with an average of two sites per country. Both TI-CBT and Discussion Control groups will consist of six 2-hour group sessions, with up to 10 youth per group. To avoid the risk of participants in the Discussion Control group experiencing "contamination" by TI-CBT methods, sessions for the two arms will be held at different times and the Discussion Control groups will be led by IYL with no training in TI-CBT. To avoid the risk of differential drop-out before the first group session, study entry and randomization will occur on the day of the first group session when possible.

Groups at each site will be mixed-gender unless it is determined per the local cultural context during the Focus Groups and Pilot Tests (during the ADAPT-ITT process) that it is necessary to have single-gender groups. The ability to draw conclusions about gender differences in response to the study intervention may be limited, because sites may vary in whether groups are mixed or single-gender. Randomization will be stratified by gender to assure approximate balance between study arms. Randomization will not be stratified by route of HIV infection, because the number of youth with behavioral transmission is expected to be too small for it to be feasible; however, it will be examined as a possible factor in the statistical analyses if numbers permit.

9.2 Outcome Measures

The primary and secondary outcome measures listed in Table 4 below will be addressed in the study's primary statistical analysis plan, which will define the content of the primary analysis report. This report will form the basis for the primary study publication and results reporting to ClinicalTrials.gov. Outcomes of interest for secondary and other objectives intended for

subsequent publications are listed under "Other Outcome Measures" in the table. All outcome measures are for the Randomized Trial.

Note 1: Feasibility and acceptability measures are per site.

Note 2: The numbering of the outcome measures in this section corresponds to the numbering of the objectives in Section 2.

Table 4. Outcome Measures

Primary Outcome Measures	
9.2.1.1	Mental Health at 6-months • Depression – PHQ-9 • Anxiety – GAD – 7 • PTSD – UCLA • Composite mental health measure
Secondary Outcome Measures	
9.2.2.2	Mental Health at immediate post-last group session • Depression – PHQ-9 • Anxiety – GAD-7 • PTSD – UCLA-RI • Composite mental health measure
9.2.2.3	ART Adherence at immediate post-last group session and 6-months • Self-report – Wilson 3-item scale
	Viral Load at immediate post-last group session and 6-months • HIV-1 RNA
Other Outcome Measures	
9.2.2.1	TI-CBT Acceptability • Ratings by and interviews with youth, caregivers, and local staff • Number of sessions attended by youth and caregivers • For each session, proportion of youth who attended that session
	TI-CBT Feasibility • Number and proportion of approached youth who agree to undergo screening at each site • Proportion of screened youth who meet inclusion criteria • Proportion of eligible youth who show up for randomization • Proportion of youth inviting a caregiver • Proportion of invited caregivers agreeing to participate • Proportion of caregivers agreeing to participate who show up for sessions
	TI-CBT Fidelity • IYL, adult staff, and observer ratings of adherence to the curriculum
9.2.2.2, 9.2.3.1	Mental Health at 12-months • Depression – PHQ-9 • Anxiety – GAD – 7 • PTSD – UCLA • Composite mental health measure
9.2.2.3	ART Adherence at immediate post-last group session, 6- and 12-months • ART concentration – Hair samples
	ART Adherence at 12-months • Self-report – Wilson 3-item scale
	Viral Load at 12-months • HIV-1 RNA
9.2.2.4	HIV attitudes (structural factors) at immediate post-last group session, and 6- and 12-months • HIV stigma • Barriers to adherence

	Gender-Based Violence at immediate post-last group session, and 6- and 12-months • WHO – Victim • WHO - Perpetrator
	Gender Roles at immediate post-last group session, and 6- and 12-months • Gender Relations Scale - Rachel Jewkes
9.2.2.5	HIV attitudes (structural factors) at immediate post-last group session, and 6- and 12-months in caregivers • HIV knowledge • HIV stigma • Barriers to adherence • HIV attitude and support (involvement in youth adherence)
9.2.2.6	Youth Behavioral Risk (sexual behavior, alcohol/drug use, caregiver report of youth behavior) at immediate post-last group session, and 6- and 12-months • AIDS Risk Behavior Assessment • Child Behavior Checklist (CBCL)
9.2.2.7	TI-CBT Implementation • Individual, social and structural barriers and facilitators
9.2.2.8	Youth adverse events • Grade 2 or higher suicidal ideation or attempts • Grade 3 or higher psychiatric disorder • Grade 3 or higher insomnia
9.2.4.1, 9.2.4.2	Biomarkers at 6- and 12-months • *hsCRP, d-dimer, IL1 β, IL6, IL10, sCD14, and TNFα*

9.3 Randomization

Youth participants in the Randomized Trial will be individually randomized to the TI-CBT Intervention or Discussion Control Arm. If there are youth of the same household (household members) who are both eligible, they will be randomized to the same study arm to avoid contamination. For the purpose of the study, a household member is defined as a person (e.g. sibling) who currently lives in the same dwelling unit and/or shares the same housekeeping arrangements (e.g. performs activities of daily living together). Caregivers will be assigned to the same arm as their youth's randomization. Randomization will be 1:1, using a dynamic permuted block system with balancing by site. Randomization will be stratified by gender to assure approximate balance between study arms; there will be no accrual limits for the strata.

9.4 Sample Size and Accrual

9.4.1 Sample Size

Focus Groups and Pilot Test: As the intent of the Focus Groups and Pilot Test is to assess the acceptability and feasibility of the intervention and to provide information to help adapt the intervention to local conditions, no formal power calculations are warranted for these stages. For the Focus Group component refer to the study-specific MOP. For the Pilot Test, up to 8 youth participants and up to 8 caregivers will be enrolled per site. If it is decided that single-gender groups are required based on cultural acceptability during the formative Focus Groups, two youth Pilot Test groups, one for each gender, for a total of up to 16 youth participants, will be conducted at that site. As the intent of the Pilot Test is to provide information to check logistics and to help adapt the intervention to local conditions, no formal power calculations are warranted. No objectives or outcome measures will be assessed using participant data during the Pilot Test.

Randomized Trial: From past experience in Rwanda and Tanzania, the attrition from the screening evaluation to the first group session is expected to be approximately 15% overall, due to the wait to constitute groups before commencing intervention. For this reason, it is expected

that 16-20 participants will be needed to pass screening at a site in order reach the desired group sizes. Enrollment and randomization will occur after enough participants have passed screening, preferably on the day of the first group sessions (when possible).

At study entry, youth participants will be allocated in a 1:1 ratio to the TI-CBT Intervention versus Discussion Control group. Each arm will have 12-16 groups with an average of 8 participants per group, for a total of 96-128 participants/arm (192-256 total), allowing for adequate power if there is a 10% loss to follow-up between semi-annual follow-up evaluations.

Both study arms will entail participation in groups. Participant outcomes in a given group are expected to correlate to some extent, due to sharing group leaders and co-participants. The intra-cluster correlation coefficient (ICC) is a measure of this within-group correlation. An ICC of zero indicates that the between-group variation outweighs the within-group (cluster) variation to the extreme, so that essentially there is no within-group correlation. In contrast, an ICC of 1 indicates perfect within-cluster correlation.

This study is an individually randomized group trial (IRGT) – that is, individuals will be randomized to either the TI-CBT Intervention Arm or the Discussion Control Arm. For an IRGT, the statistical power to detect a difference between arms depends on the number of groups per arm (m), the ICC, and the number of participants. In a standard cluster randomized trial, the variance of the difference between the two arms' means will be inflated by a factor of $1 + (m - 1)*ICC$ relative to a trial with independent observations, where m is the number of groups per arm; this is known as the variance inflation factor or design effect. This means that if the required sample size for a study without clusters is N, then the required size for a cluster randomized trial to have the same power will be $N_c=N*(1 + (m - 1)*ICC)$ and the average group size will be $n=N_c/m$. In other words, the statistical power to detect a difference between arms decreases with higher ICCs or more groups, and increases with higher average group size.

In an IRGT trial with 2 group-based study conditions, the variance inflation factor is $1 + (m_1 - 1)*ICC_1$ for the first condition and $1 + (m_2 - 1)*ICC_2$ for the second condition, where m_1 and m_2 respectively are the number of groups in each arm. The following power analysis was made assuming that both arms will have the same number of groups and the same ICC (that is, $m_1=m_2$ and $ICC_1=ICC_2$), in which case the design effect will be the same as for a cluster randomized trial. Due to a lack of ICC estimates for group intervention studies, a range of ICCs was examined. The range was based on ICCs considered likely for IMPAACT 2002 since that is also a psychotherapy study; that study team thought the ICC likely to be in the range of 0.02 to 0.05. Here it is assumed that the ICC may be greater for a study using intervention groups, due to the participants' shared experiences. For this study, then, the ICC is anticipated to be in the range of 0.05 – 0.10; a range of 0.05 – 0.15 was used for sample size calculations, which were performed using the cluster randomization module in PASS 11 software.

The primary efficacy outcome is the score on a composite mental health score created by standardizing participants' scores on the three mental health measures and summing them (refer to Section 9.6.1). These scores will be standardized to all be on the same scale, with mean 0 and standard deviation 1 (168). For this reason, the power analysis uses number of standard deviations (effect size) to measure detectable differences between study arms. The sample size was chosen to provide 80% power to detect a clinically important difference in the primary efficacy measures between study arms. Power increases (allowing the detection of smaller effect sizes) when the number of groups increases, the ICC decreases, or (to a lesser extent) the average group size increases. The team will use two-sided tests to ensure power to detect differences between groups

in both directions, but the hypothesis is that TI-CBT groups will lead to better mental health that the Discussion Control groups.

Table 5 shows the detectable differences between arms with 80% power and two-sided α=0.05 for a range of ICCs, numbers of groups per arm, and average numbers of participants per group. The study is expected to have 12-16 groups per arm with an average of 8 participants per group (allowing 6-10 per group), and thus, it is expected the total sample size will be 192-256 participants. This will provide 80% power to detect an effect size of 0.42-0.62 standard deviations between arms, or 0.47 - 0.65 if there is an average loss of 2 participants per group (an average group size of 6).

Table 5. Detectable difference between arms by ICC, number of groups, and number of participants per group

Power Analysis Two-Sided Test, 80% power, alpha=0.05			
ICC	**Number of Groups per Arm (m)**	**Average Number of Participants per Group (n)**	**Detectable Difference (# of s.d.)**
0.05	12	4	0.64
		6	0.55
		8	0.49
		10	0.46
	14	4	0.59
		6	0.50
		8	0.45
		10	0.42
	16	4	0.55
		6	0.47
		8	0.42
		10	0.39
0.10	12	4	0.68
		6	0.60
		8	0.55
		10	0.52
	14	4	0.63
		6	0.55
		8	0.51
		10	0.48
	16	4	0.58
		6	0.51
		8	0.47
		10	0.45
0.15	12	4	0.72
		6	0.65
		8	0.61
		10	0.58
	14	4	0.66
		6	0.59
		8	0.56
		10	0.53
	16	4	0.62
		6	0.55
		8	0.52
		10	0.50

9.4.2 Accrual

Accrual at each site for the Focus Groups and Pilot Test collectively is expected to be completed within three months of when accrual opens at the site. Accrual for the Randomized Trial is expected to be completed within nine months of when the last Pilot Test is completed.

9.5 Monitoring

The Randomized Trial will be monitored at multiple levels, consistent with standard IMPAACT procedures. A study monitoring plan that details monitoring roles and responsibilities and data to be reviewed at each level will be prepared before the study opens to accrual. The Core Protocol Team (Section 7.1.2) is responsible for closely monitoring study progress, including timely achievement of key milestones, the quality of study conduct, and safety. IMPAACT leadership will also monitor study progress and quality. The IMPAACT Study Monitoring Committee (SMC) will also conduct formal reviews of study conduct and safety. Unless otherwise specified, monitoring reports distributed to the protocol team will be pooled across the TI-CBT and Discussion Control Arms. Monitoring reports distributed to the SMC may be broken out by blinded study arm. In addition, an interim assessment of assumptions made in the power analysis will be performed as noted in Sections 9.5.1 and 9.5.2.

Section 7 provides more information on safety assessment and reporting. Sections 10 and 11 provide more information on on-site monitoring and quality management at the site level. Further information on monitoring of study progress, quality of study conduct, and participant safety across sites is provided below.

9.5.1 Monitoring by the Protocol Team

ADAPT-ITT Progress

The Core Protocol Team will monitor the outcomes of the ADAPT-ITT process. If the TI-CBT Intervention is not acceptable or feasible at one of the sites, the team will discuss either adding a site or increasing the number of TI-CBT and Discussion Control groups at other sites.

Randomized Trial Progress and Quality of Study Conduct

The Core Protocol Team is responsible for continuous monitoring of study progress, including timely achievement of key milestones, and quality of study conduct. They will closely monitor participant screening and accrual based on reports that will be generated at least monthly by the DMC during accrual and quarterly once accrual is complete. The protocol team may decide to revise this schedule as needed. The protocol team has developed a study accrual plan that includes site-specific and total enrollment projections over the course of the accrual period, and actual accrual will be monitored relative to these projections. Accrual performance will be reported by the DMC, by site and across sites, and the protocol team will review and discuss study progress at least monthly. For any site that falls short of its accrual projections, the protocol team will communicate with the site to identify the barriers the site has encountered and the operational strategies and action plans to address these.

Participant Retention

The Core Protocol Team will similarly review participant accrual, and other key indicators of the quality of study conduct (e.g., data and specimen completeness) based on reports with pooled data generated at least monthly by the DMC and take action with study sites as needed to ensure high quality study conduct throughout the period of study implementation.

Participant Safety

Participant safety will be closely monitored by the Core Protocol Team through periodic reviews of adverse event reports (pooled across the TI-CBT and the Discussion Control Arms) generated by the DMC. These reports will provide summaries of ≥ Grade 2 psychiatric adverse events, suicide attempts, and social harms (refer to Sections 7.2 and 6.6). At each review, the DAIDS Medical Officer will also review any EAEs (refer to Section 7.3) reported to the DAIDS Safety Office that are not yet reflected in the data reports. Core team members will continually evaluate the pattern and frequency of reported adverse events and assess for any individual occurrences or trends of concern. Relationship status of adverse events to the TI-CBT or Discussion Control Arm participation will also be summarized.

9.5.2 Monitoring by the SMC

An independent IMPAACT Study Monitoring Committee (SMC) will review this study regularly, following policies described in the IMPAACT Manual of Procedures. The composition of the SMC will include the SMC Chair; IMPAACT Co-Chairs; IMPAACT Complications Scientific Committee Chair or Vice Chair; representatives of the IMPAACT Operations Center, Statistical and Data Management Center, and representatives of NIAID, NICHD, and NIMH.

SMC reviews will occur at least annually and on a more frequent or *ad hoc* basis if any safety issues or concerns arise. There will be an SMC review to monitor enrollment 6 months after the first participant is enrolled, and then every six months or as needed during the enrollment period. *Ad hoc* reviews may also be triggered per protocol team request. No interim efficacy analyses are planned for the primary outcome measures at the 6-month timepoint because the entire sample size will be required to assess the efficacy of the intervention. Based on any of its reviews, the SMC may recommend that the study proceed as currently designed, proceed with design modifications, or be discontinued. The SMC may also provide operational recommendations to help address any study implementation challenges that may be identified during their reviews.

Study Progress, Quality of Study Conduct and Participant Safety

The SMC will monitor study accrual, progress, quality of study conduct, retention, and participant safety. The SMC will review indicators of study feasibility, including whether study implementation and accrual targets are being met. The SMC will generally review the same types of monitoring reports as the Protocol Team; however, monitoring data will be made available to the SMC by masked study group.

Two months after the first four sites have all finished their Pilot Tests and opened to enrollment for the Randomized Trial, the SMC will examine accrual status. If the sites are having trouble accruing enough participants to start the treatment groups, the team will contact them to determine what the barriers to accrual are and whether there are adaptations that could alleviate them.

Sample Size Evaluation

The SMC will review the interim analysis report on the validity of the assumptions used for sample size calculations and the recommendation to maintain or increase the sample size. The interim analysis report and data will be made available to the SMC by the statistician. The SMC will make the final determination on whether it is necessary to increase the number of participants to be enrolled to ensure adequate statistical power for the primary study objective.

To check the validity of the assumptions used for sample size calculations, an interim analysis will use the scores on the primary mental health outcome measures and the composite measure to estimate ICCs pooled across study arms. This will happen once five groups in each study arm have completed their six sessions. If the estimated ICC is greater than 0.15 (the largest value for which the selected sample size provides 80% power to detect acceptable minimum differences). When the five groups/arm have reached the end of the window for their 6-month follow-ups, the proportion of enrolled participants in the Randomized Trial who do not have six-month follow-up assessments will be assessed to see if it exceeds 10%. At each of these milestones, the protocol statistician will provide an interim analysis report including relevant data and assessment outcome, with a recommendation to maintain or increase the sample size for the SMC to review and make a final determination. If the SMC determines that the ICC or loss to follow-up rate require a sample size recalculation, the team will work with a blinded non-protocol statistician.

9.6 Analyses

This section provides a brief overview of the data analyses to address the objectives of the study. Analyses of participant outcome measures will be intent-to-treat. All randomized participants will be included regardless of the number of sessions attended. Baseline characteristics (gender, age, mode of transmission, severity of mental health scores, and viral load suppression status) will be compared between evaluable versus non-evaluable participants both overall and within the TI-CBT Intervention and Discussion Control Arms. Loss to follow-up rates will be compared between study arms.

9.6.1 Primary Outcome Measures

The primary analysis for IMPAACT 2016 will focus on outcome measures at six months, because the protocol team believes that in order to see the full effect of the intervention, participants must have time post-intervention to incorporate and use the skills they learned from TI-CBT. It is expected that the three mental health measures (PHQ-9, GAD-7, UCLA PTSD-RI) will be correlated; they will therefore be analyzed as a composite measure for the primary analysis, which will be constructed by standardizing participants' scores on the three mental health measures and summing them. These scores will be standardized to all be on the same scale, with mean 0 and standard deviation 1 (168). The internal consistency of this composite will be checked by examining Cronbach's alpha for the three standardized mental-health measure scores to see if they form a coherent measure.

The primary analysis for comparisons of the composite score between arms will be a cluster-level analysis. For cluster randomized trials, one valid method for analyzing intervention effects is to compute the mean for each site and then do a two-sample t-test on the site-specific measures (169). Hoover (170) recommends using the Satterthwaite t-test for unequal variances for individually randomized group trials, to take into account the possibility of intervention and control arms having different variances. The same procedure will be done to analyze each individual mental health measure.

Supplementary analyses using individual data will also be conducted to incorporate both individual and group characteristics as covariates and allow a multivariate outcome. Potential covariates include gender, caregiver participation, route of infection, and reported contamination between groups. The three primary outcome measures will be standardized as above and used as a multivariate outcome measure in a mixed model, with individual group as a random effect and individual participants nested within groups (to account for group effects). If there are significant differences between groups, site and group characteristics (such as number of visits) will be examined for incorporation into the mixed models.

In mental health research, there is concern about biased results due to loss to follow-up. For that reason, if more than 10% of participants are lost to follow-up before six months, or if a larger proportion of participants are lost to follow-up in one arm (especially if the loss is due to serious adverse events, or suicide attempts), analyses will be undertaken to explore the potential effects of missing data on the conclusions of the study. The characteristics at study entry (gender, age, mode of transmission, severity of mental health distress and viral load suppression status) for participants who discontinued from the study before six months will be compared between the TI-CBT and Discussion Control arms. Characteristics of participants discontinuing vs. not discontinuing will be compared overall and within intervention and control arms. In addition, the reasons for losses to follow-up will be assessed and compared between intervention and control arms. The probability and timing of loss to follow-up will be summarized and compared between arms using Kaplan-Meier plots and the log-rank test.

9.6.2 Secondary and Other Outcome Measures

The analyses for the secondary outcome measures will be the same as those for the primary outcome measures. For dichotomous measures (e.g., viral suppression), the first stage of the cluster-level analyses will involve calculating the proportion with that outcome at each site, and then proceeding as above using t-tests. Similar analyses will be used for the other outcome measures.

10 DATA HANDLING AND RECORD KEEPING

10.1 Data Management Responsibilities

As described in Section 4.6, data on screening and enrollment in this study will be collected using the DMC SES.

Study sites must maintain adequate and accurate research records containing all information pertinent to the study for all screened and enrolled participants, including paper-based CRFs (if used), eCRFs, and supporting source data. In maintaining these records, sites must comply with the standards of source documentation specified in the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (available on the website referenced in Section 10.2).

eCRFs and an eCRF completion guide will be made available to study sites by the DMC. Study site staff will enter required data into eCRFs using Medidata Rave (refer to Table 6, Table 7, Table 8, and Table 9 below) with system checks applied and data queries generated immediately upon saving the entered data. Data must be entered within timeframes specified by the DMC; queries must also be resolved in a timely manner. Selected laboratory data will be transferred

electronically to the DMC through the LDMS. Further information on eCRFs and IMPAACT data management procedures will be provided by the DMC. A User Manual for the Subject Enrollment System is available on the DMC portal at: https://www.frontierscience.org

Data collected on questionnaires administered to participant via CASI will be stored in the central database at the DMC and transferred through standardized mechanisms to the protocol statistician for analysis. The data will not be entered into eCRFs (refer to Table 6, Table 7, Table 8, and Table 9 below). In the event CASI is not accessible due to environmental interference (e.g. power outage, off-site visit) at the time of administering to participants, paper versions of the questionnaires will be administered to participants, and data will be entered into CASI by study staff when CASI is next accessible.

Table 6. Documentation Requirements for Youth in Pilot Test

Assess for and Source Document	Enter into eCRFs, CASI, or other
Baseline	
Screening data (date of birth, sex at birth, ethnicity, and race)	Subject Enrollment System or eCRF
Youths decision on caregiver participation	Subject Enrollment System
Past and current psychiatric conditions	eCRF, per Section 6.5
Current ARVs and psychiatric medications	eCRF, per Section 5.6
Demographics, mental health, HIV disclosure, self-reported ART adherence, HIV stigma, barriers to adherence, behavioral risks, gender roles, gender violence, and perception of caregiver behavior	CASI
Group Sessions	
Questionnaires "fun had" and learned	eCRF (individual participant responses collated and entered into eCRF with logistical data)
Logistical data (attendance, punctuality)	eCRF
Participant Intervention Evaluation	eCRF (collected via pen/paper after last group session and entered into eCRF)

Table 7. Documentation Requirements for Youth in Randomized Trial

Assess for and Source Document	Enter into eCRFs, CASI, or other
Baseline	
Screening data (date of birth, sex at birth, ethnicity, and race)	Subject Enrollment System or eCRF
Youths decision on caregiver participation	Subject Enrollment System
Past and current psychiatric conditions	eCRF, per Section 6.5
Current ARVs and psychiatric medications	eCRF, per Section 5.6
Demographics, mental health, HIV disclosure, self-reported ART adherence, HIV stigma, barriers to adherence, behavioral risks, gender roles, gender violence, and perception of caregiver behavior	CASI
Group Sessions	
Questionnaires "fun had" and learned	eCRF (individual participant responses collated and entered into eCRF with logistical data)
Logistical data (attendance, punctuality)	eCRF
Follow-up	
Referrals to non-study mental health services	eCRF, CASI
Reports of social harms since the last visit.	eCRF
Current status of psychiatric conditions that were ongoing at the previous visit	eCRF (Any updates of previous entries, e.g., resolution dates)
Occurrence of any new psychiatric conditions since the last visit	eCRF, per Section 7.2
Current status of ARV and psychiatric medications that were ongoing at the previous visit	eCRF (Any updates of previous entries, e.g., stop dates)
Use of any new ARVs and psychiatric medications since the last visit	eCRF, per Section 5.6
Mental health, self-reported ART adherence, HIV stigma, barriers to adherence, behavioral risks, gender roles, gender violence, and perception of caregiver behavior	CASI
Participant Intervention Evaluation	CASI
Risk for contamination	CASI

Table 8. Documentation Requirements for Caregiver in the Pilot Test

Assess for and Source Document	Enter into eCRFs, CASI, or other
Screening and Pre-entry	
Demographics, HIV stigma, HIV attitudes, HIV knowledge, barriers to adherence, and perception of youth behavior	CASI
Group Sessions	
Questionnaires "fun had" and learned	eCRF (individual participant responses collated and entered into eCRF with logistical data)
Logistical data (attendance, punctuality)	eCRF
Participant Intervention Evaluation	eCRF (collected via pen/paper after last group session and entered into eCRF)

Table 9. Documentation Requirements for Caregiver in the Randomized Trial

Assess for and Source Document	Enter into eCRFs, CASI, or other
Screening and Pre-entry	
Demographics, HIV stigma, HIV attitudes, HIV knowledge, barriers to adherence, and perception of youth behavior	CASI
Group Sessions	
Questionnaires "fun had" and learned	eCRF (individual participant responses collated and entered into eCRF with logistical data)
Logistical data (attendance, punctuality)	eCRF
Follow-up	
HIV stigma, HIV attitudes, HIV knowledge, barriers to adherence, and perception of youth behavior	CASI
Participant Intervention Evaluation	CASI
Risk for contamination	CASI

10.2 Essential and Source Documents and Access to Source Data

All DAIDS policies referenced in this section are available at:
https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures

Study sites must comply with DAIDS policies on Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials and Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. In its policy on Requirements for Manual of Operational Procedures, DAIDS requires sites to establish SOPs for maintaining essential and source documents in compliance with these policies. Site SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study, and site SOPs should be followed throughout the study.

Per the DAIDS policy on Storage and Retention of Clinical Research Records, study records must be stored in a manner that ensures privacy, confidentiality, security, and accessibility during the conduct of the study and after the study is completed. Records must be retained for a minimum of three years after the completion of the study.

All study records must be accessible for inspection, monitoring, and/or auditing during and after the conduct of the study by authorized representatives of the study sponsors and their contracted monitors, IMPAACT, site regulatory authorities, site IRBs/ECs, OHRP, and other US, local, and international applicable entities. Records must be kept on-site throughout the period of study implementation; thereafter, instructions for off-site storage may be provided by NIAID. No study records may be removed to an off-site location or destroyed prior to receiving approval from NIAID.

10.3 Quality Control and Quality Assurance

Study sites must ensure that essential documents and participant research records are subject to continuous quality control and quality assurance procedures consistent with the DAIDS policy on Requirements for Clinical Quality Management Plans, which is available at:
https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures

11 CLINICAL SITE MONITORING

Site monitors under contract to NIAID will visit study sites to inspect study facilities and review participant study records including consent forms, paper-based CRFs (if used), eCRFs, medical records, laboratory records, and pharmacy records, to ensure protection of study participants, compliance with the IRB/EC approved protocol, and accuracy and completeness of records. The monitors also will review essential document files to ensure compliance with all applicable regulatory requirements. Site investigators will make study facilities and documents available for inspection by the monitors.

12 HUMAN SUBJECTS PROTECTIONS

12.1 Institutional Review Board/Ethics Committee Review and Approval

Prior to study initiation, site investigators must obtain IRB/EC review and approval of this protocol and site-specific ICFs in accordance with 45 CRF 46; subsequent to initial review and approval, IRBs/ECs must review the study at least annually. Site investigators must also promptly report to the IRB/EC any changes in the study and any unanticipated problems involving risks to participants or others.

All IRB/EC policies and procedures must be followed and complete documentation of all correspondence to and from the IRBs/ECs must be maintained in site essential document files. Sites must submit documentation of both initial review and approval and continuing review to the DAIDS Protocol Registration Office (PRO) in accordance with the DAIDS Protocol Registration Manual (refer to Section 13.2).

12.2 Vulnerable Participants

Study sites must comply with the requirements of the DAIDS policy on Enrolling Children (including Adolescents) in Clinical Research, which is available at: https://www.niaid.nih.gov/sites/default/files/enrollingchildrenrequirements.pdf.

The children enrolled in this study are considered vulnerable participants per 45 CFR 46 Subpart D. Site IRBs/ECs must consider the potential benefits, risks, and discomforts of the study to children and assess the justification for their inclusion in the study. As part of this assessment, IRBs/ECs must determine the level of risk to children in the categories specified in 45 CFR 46.404-407. Documentation of this determination is required to complete the DAIDS protocol registration process described in Section 13.2. IRBs/ECs may assign a different level of risk to the Focus Groups, Pilot Test, and Randomized Trial.

The risk category assigned by the IRB/EC determines whether parental/guardian permission is required, and if so, the informed consent requirements for the study at each site. Per 45 CFR 46.408 (b), the IRB/EC may find that the permission of one parent is sufficient for research to be conducted under 46.404 or 46.405. Where research is covered by 46.406 or 46.407, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child (as determined locally). Alternatively, IRBs/ECs may allow sites to obtain a waiver for parental permission per 45 CFR 46.408 (c), given the perceived minimal risk and potential benefit to participants. IRBs/ECs must document their risk determination and study sites should adapt the signature pages of their site-specific informed consent forms as needed to accommodate the parental consent requirements, if needed, associated with the IRB/EC determination.

12.3 Informed Consent

Refer to Section 4.6 and the study-specific MOP for further information on informed consent procedures for this study.

Written informed consent, and youth assent when applicable, for participation in the Focus Groups, Pilot Test, and Randomized Trial will be obtained before study-specific procedures are performed. Informed consent and assent processes will include information exchange, discussion,

and assessment of understanding of required elements of informed consent, including the potential risks, benefits, and alternatives to study participation.

Study sites must establish SOPs that describe procedures, roles, and responsibilities for obtaining informed consent and informed assent for youth and caregiver participation consistent with applicable IRB/EC policies and procedures. Study staff involved in obtaining informed consent must have documented training on these SOPs prior to study initiation.

Youth Participants

Study staff will be required to determine participant age and ability to provide independent informed consent for study participation, consistent with the SOPs referenced above. Based on this determination, written informed consent and written assent will be obtained for youth participants in the Focus Groups, Pilot Test, and Randomized Trial as follows:

- If the potential youth participant is not of legal age to provide independent informed consent: Parent or legal guardian must provide written informed consent and the potential participant must provide written assent.

  Note: Refer to Section 12.2 for considerations related to parental consenting requirements; IRB/EC risk determinations will guide whether the consent of one or both parents may be required for this study. All IRB/EC requirements must be followed.

- If the potential participant is of legal age to provide independent informed consent, the potential participant must provide written informed consent.

Each potential youth participant who is not of legal age to provide independent informed consent is generally expected to take part in the informed consent process with his or her parent or legal guardian and both the assent of the participant and the consent of the parent or legal guardian will be required. For example, if the participant does not provide assent, or the parent or legal guardian does not provide consent, the participant will not be enrolled in the study.

For youth who are not of legal age to provide independent consent at study entry, written informed consent must later be obtained if the legal age of consent is reached any time following entry. At the next scheduled visit after the legal age is reached, an informed consent process must be conducted with the participant. If written informed consent is obtained, the participant will continue in the study as originally planned; if written informed consent is not obtained, the participant will be discontinued from the study.

One sample consent form is provided to use for youth independent informed consent, youth assent, and parent (or legal guardian) informed consent in Appendix III for the Focus Group, Appendix IV for the Pilot Test and Appendix VI for the Randomized Trial. A separate signature page is included in each form for the youth independent consent, youth assent, and parent (or legal guardian) consent. Study sites are also permitted to develop separate assent and consent forms for this study, if required by site or IRB/EC policies and procedures.

Should the consenting parent or guardian of a youth participant die or no longer be available for any reason, all applicable IRB/EC policies and procedures should be followed. In general, it is expected that conduct of study visits and procedures will be discontinued until informed consent for continued study participation is obtained from the youth's authorized guardian, as defined locally. If an authorized guardian cannot be identified, or if the authorized guardian does not consent to continued study participation, the youth must be withdrawn from the study. In accordance with the DAIDS policy on Enrolling Children (including Adolescents) in Clinical Research (available at the website referenced in Section 12.2), all study sites must establish and maintain written procedures describing the standards that will be followed to identify who may serve as guardian for an enrolled youth, reflective of applicable IRB/EC guidance for conduct of human subjects research within the context of available local law, regulation, or government policy.

As part of the informed consent process, consenters will be asked whether they agree to storage and future research testing of biological specimens remaining after all protocol-specified testing has been performed (Appendix VIII). This storage and future use is optional and may be declined with no impact on other aspects of study participation. Likewise, genetic testing of residual specimens is optional and may be declined.

Caregivers

As indicated in Section 4.3, caregivers must be of legal age and able to provide independent informed consent. Written informed consent is required for caregiver participation in the Focus Group, Pilot Test and Randomized Trial. A sample consent form for caregivers is provided in Appendix III for the Focus Group, Appendix V for the Pilot Test and Appendix VII for the Randomized trial.

12.4 Potential Benefits

All participants in this study may experience no direct benefit. The study may help youth participants gain skills to assess and monitor their mental health symptoms and improve their levels of functioning through participation in group TI-CBT. This study may help caregivers gain skills to assess and monitor their youth's mental health symptoms and improve their level of support for their youth. All participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may lead to the development of TI-CBT manuals and sessions for youth living with HIV at participating sites and additional sites in in sub-Saharan. Participants also may appreciate the opportunity to contribute to the field of HIV and mental health research. Youth participants will receive laboratory testing and treatment counseling. For other medical conditions identified as part of the study screening and/or follow-up procedures, participants will be referred to other sources of care available in their community. Some youth participants may have the opportunity to access expedient treatment and decreased morbidity due to early diagnosis and treatment of abnormalities identified during tests, examinations, and referrals.

12.5 Potential Risks

12.5.1 General

It is not expected that this trial will expose participants to unreasonable risk. For youth participants in the Randomized Trial, phlebotomy may lead to discomfort, feelings of dizziness or faintness, and/or bruising, swelling and/or infection. Youth participants may experience discomfort when answering questions of a personal nature, such as questions dealing with sexual behaviors.

Risk of involvement in this study will be minimized by ensuring that all study staff members are trained to understand confidentiality. This intervention is designed to be supportive, non-confrontational and to minimize the discomfort of the participants. If a participant becomes uncomfortable during an interventional session, they will be reminded that they can terminate or withdraw at any time. Participants will be provided access to referral services if needed.

Although study sites make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result, refer to Section 6.6. For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities.

12.5.2 Unimproved Mental Health or Clinical Deterioration

Continued or worsening of mental health symptoms is always a risk regardless of use of counseling. In addition, as suicidal ideation is a symptom of depression, suicide or suicide attempt is a risk. Clinical deterioration due to the underlying psychiatric condition(s), or the study intervention (TI-CBT), is also a risk.

12.6 Reimbursement/Compensation

Pending IRB/EC approval, participants will be reimbursed for costs associated with completing study visits (e.g., transport costs). Reimbursement amounts will be specified in site-specific ICFs or other materials if applicable per IRC/EC policies and procedures.

12.7 Privacy and Confidentiality

All study procedures will be conducted in private and every effort will be made to protect participant privacy and confidentiality to the extent possible. Participant information will not be released without written permission to do so except as necessary for review, monitoring, and/or auditing as described in Section 10.2. Sites will inform potential youth and caregiver participants (or other authorized guardians if applicable) about any limits to confidentiality, including local laws that require reporting of abuse or harm to the participant or others.

All study-related information will be stored securely. Participant research records will be stored in locked areas with access limited to study staff. All laboratory specimens, eCRFs, and other documents that may be transmitted off-site (e.g., EAE report forms, photographs of observed reactions) will be identified by PID only. Likewise, communications between study staff and protocol team members regarding individual participants will identify participants by PID only.

Study sites are encouraged but not required by DAIDS policies to store study records that bear participant names or other personal identifiers separately from records identified by PID. All local databases must be secured with password protected access systems. Lists, logbooks, appointment books, and any other documents that link PID numbers to personal identifying information should be stored in a separate, locked location in an area with limited access.

12.8 Communicable Disease Reporting

Study staff will comply with local requirements to report communicable diseases including HIV infection identified among study participants to health authorities. Participants will be made aware of all applicable reporting requirements as part of the study informed consent process.

12.9 Management of Incidental Findings

Site clinicians will inform youth and caregiver participants (or other authorized guardians if applicable) of all clinically meaningful safety concerns identified and laboratory test results, including results of HIV tests and HIV viral load for youth participants as part of screening, pre-entry, and throughout the study intervention and follow-up. When applicable, site clinicians will provide referrals to non-study sources of medical care for further evaluation and/or treatment of these findings.

12.10 Management of New Information Pertinent to Study Participation

Participants enrolled in the study (or other authorized guardians if applicable) will be provided any new information learned over the course of the study that may affect their willingness to remain in the study.

12.11 Post-Trial Access to Study Intervention

After youth and caregiver participants complete their participation, the study intervention will not be provided. However, each site may choose to continue to deliver the program if determined to be effective, and participants may be referred to any available standard of care clinical and/or mental health services (outside of the study) that may be of benefit to them.

13 ADMINISTRATIVE PROCEDURES

13.1 Regulatory Oversight

This study is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and National Institute of Mental Health (NIMH), which are part of the United States National Institutes of Health (NIH).

The Division of AIDS (DAIDS) within the NIAID is responsible for regulatory oversight of this study. DAIDS will distribute safety-related information pertaining to the study products prior to and during the conduct of the study, in accordance with its sponsor obligations.

NIAID provides funding to the clinical research sites at which this study will be conducted. Each institute contracts with independent clinical site monitors who will perform monitoring visits as described in Section 11. As part of these visits, monitors will inspect study-related documentation to ensure compliance with all applicable US and local regulatory requirements.

13.2 Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol ICFs approved, as appropriate, by their local IRB/EC, local IBC, and any other applicable regulatory entity. Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific ICFs will be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

For any future protocol amendments, upon receiving final IRB/EC and any other applicable regulatory entity approvals, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) will not be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual, which is available on the RSC website:
http://rsc.tech-res.com/protocolregistration/

13.3 Study Implementation

This study will be conducted in accordance with the protocol, international good clinical practice guidelines, and all applicable US and local regulations. Study implementation will also be guided by the IMPAACT MOP, study-specific MOP, LPC, and other study implementation materials, which will be available on the IMPAACT web site: www.impaactnetwork.org.

Study implementation at each site will also be guided site-specific SOPs. The DAIDS policy on Requirements for Manual of Operational specifies the minimum set of SOPs that must be established at sites conducting DAIDS funded and/or sponsored clinical trials (available on the website referenced in Section 10.2. These SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study.

13.4 Protocol Deviation Reporting

Per the policy for Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (available at the website referenced in Section 10.2), all protocol deviations must be documented in participant research records. Reasons for the deviations and corrective and preventive actions taken in response to the deviations should also be documented.

Deviations should be reported to site IRBs/ECs and other applicable review bodies in accordance with the policies and procedures of these review bodies. Serious deviations that are associated with increased risk to one or more study participants and/or significant impacts on the integrity of study data must also be reported within IMPAACT, following procedures specified in the IMPAACT Manual of Procedures.

13.5 Critical Event Reporting

Per the DAIDS policy on Identification and Classification of Critical Events, a critical event is defined as an unanticipated study-related incident that is likely to cause harm or increase the risk of harm to participants or others or has a significant adverse impact on study outcomes or integrity. All such events must be reported following procedures specified in the DAIDS Critical Events Manual, which is available at: https://www.niaid.nih.gov/research/daids-clinical-research-event-reporting-safety-monitoring.

13.6 ClinicalTrials.gov

This protocol is not subject to the Food and Drug Administration Amendments Act of 2007 (FDAAA). However, it will be registered in ClinicalTrials.gov to meet International Committee of Medical Journal Editors requirements.

14 PUBLICATIONS

All presentations and publications of data collected in this study are governed by IMPAACT policies, which are available in the IMPAACT Manual of Procedures.

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APPENDICES

Appendix I-A: Schedules of Evaluations for Youth – Pilot Test

Study Visit/Session	Screen	Pre-Entry[1]	Youth Group Sessions (within 8 weeks of session 1)					
			Entry/ Session 1[3]	Session 2	Session 3	Session 4	Session 5	Session 6/ Exit Visit
Clinical								
Informed Consent/Assent	X							
Review medical records (eligibility)/collect screen data	X							
Medical/medications history		X						
Youth decision on caregiver participation	X							
Mock hair sample (ART concentration)		X[2]						
Behavioral and Counseling								
TI-CBT Intervention			X	X	X	X	X	X
Administer questions on "fun had" and "learned"			X[4]	X[4]	X[4]	X[4]	X[4]	X [4]
Participant Intervention Evaluation Questionnaire								X [4]
CASI administered questionnaires (pen and paper may be substituted per Section 5.5)								
Patient Health Questionnaire – 9	X							
General Anxiety Disorder – 7	X							
UCLA PTSD-RI	X							
Demographics	X							
Disclosure		X[2]						
Self-reported ART adherence	X	X[2]						
Barriers to adherence		X[2]						
Gender-based Violence (WHO – Victim/Perpetrator)		X[2]						
Gender Roles (Rachel Jewkes)		X[2]						
AIDS-Related Stigma Scale		X[2]						
AIDS Risk Behavior Assessment		X[2]						
Children's Report of Parenting Behavior Inventory		X[2]						
Laboratory								
HIV-1 test (confirmatory tests as needed)	5 mL							
Mock HIV-1 RNA (viral load) – no blood collected		X[2]						
Mock plasma for inflammatory biomarkers – no blood collected		X[2]						
Total maximum blood volumes	5 mL	--						

1: Pre-Entry Visit procedures should be conducted on the same day or up to 14 days prior to enrollment.
2: No data in the questionnaires are analyzed. Mock blood and hair collection: no specimens are collected.
3. Entry (enrollment) must occur within 60 days of screening and will be on the same day of Group Session 1. The day of Group Session 1 is considered Day 0 for youth.
4: Administer following completion of the group sessions.

Appendix I-B: Schedules of Evaluations for Caregivers – Pilot Test of TI-CBT Intervention

Study Visit/Session	Screen/Entry[1]	Caregiver Group Sessions (within 8 weeks of caregiver's youth session 1)	
		Session A[3]	Session B[3]/ Exit Visit
Clinical			
Informed Consent	X		
Youth agreement for caregiver participation	X		
Behavioral and Counseling			
TI-CBT Intervention		X	X
Administer questions on "fun had" and "learned"		X [4]	X [4]
Participant Intervention Evaluation Questionnaire			X [4]
CASI administered questionnaires (pen and paper may be substituted per Section 5.5)			
Demographics	X[2]		
AIDS-Related Stigma Scale	X[2]		
HIV attitudes and support	X[2]		
Barriers to adherence	X[2]		
HIV knowledge	X[2]		
CBCL caregiver report of youth behavior	X[2]		

1: Screening and Entry Visit procedures may be combined into one study visit or split across multiple study visits; may be conducted during the caregiver's first Group Session prior to initiation of the group session; and may take place in parallel with their respective Youth Screening, Entry Visit, or Group Session. Procedures may take place up to 60 days prior to enrollment.

2. No data in the questionnaires is analyzed.

3: Caregiver Group Session A and B should be completed within eight weeks of the start of their youth's first group session and conducted separately from the youth group sessions. Group Session A and B will not be combined into one study visit.

4: Administer following completion of the group sessions.

Appendix II-A: Schedules of Evaluations for Youth – Randomized Trial of TI-CBT Intervention

Study Visit/Session	Screen	Pre-Entry[1]	Youth Group Sessions (within 8 weeks of youth's session 1)						Youth Follow-up[7]		
			Entry/ Session 1[2]	Session 2	Session 3	Session 4	Session 5	Session 6	IPL [5]	6-mo	12-mo/ Exit
Clinical											
Informed Consent/Assent	X										
Review medical records (eligibility)/collect screen data	X										
Medical/medications history		X[3]							X	X	X
Youth decision on caregiver participation	X										
Hair sample (ART concentration)		X[3]							X	X	X
Behavioral and Counseling											
TI-CBT Intervention or Control			X	X	X	X	X	X			
Booster (Intervention or Control)										X	
Administer questions on "fun had" and "learned"			X[4]	X[4]	X[4]	X[4]	X[4]	X[4]		X[4]	
CASI administered questionnaires (pen and paper may be substituted per Section 5.5)											
Patient Health Questionnaire – 9	X[3]								X[6]	X[6]	X
General Anxiety Disorder – 7	X[3]								X[6]	X[6]	X
UCLA PTSD-RI	X[3]								X[6]	X[6]	X
Demographics	X[3]										
Disclosure		X[3]									
Self-reported ART adherence	X	X[3]							X[6]	X[6]	X
Barriers to adherence		X[3]							X[6]	X[6]	X
Gender-based Violence (WHO)		X[3]							X[6]	X[6]	X
Gender Roles (Rachel Jewkes)		X[3]							X[6]	X[6]	X
AIDS-Related Stigma Scale		X[3]							X[6]	X[6]	X
AIDS Risk Behavior Assessment		X[3]							X[6]	X[6]	X
Children's Report of Parenting Behavior Inventory		X[3]							X[6]	X[6]	X
Risk for Contamination										X[6]	
Participant Intervention Evaluation									X[6]		
Laboratory											
HIV-1 test (confirmatory tests as needed)	5 mL										
HIV-1 RNA (viral load)		10mL[3]							10mL	10mL	10mL
Plasma for inflammatory biomarkers		5mL[3]								5mL	5mL
Total maximum blood volumes	**5 mL**	**15mL**							**10mL**	**15mL**	**15mL**

1: Pre-Entry Visit procedures should be conducted on the same day or up to 14 days prior to enrollment.
2: Entry (enrollment and randomization) must occur within 60 days of screening and will be on the day of Group Session 1.
3: Baseline measures.
4: Administer following completion of the group sessions.
5: Immediately post-last group session (IPL) follow-up evaluations are targeted to be conducted immediately following Group Session 6 on the same day or within 30 days.
6: If IPL conducted at Group Session 6, administer following delivery of intervention. At 6-month Follow-up Study Visit, administer prior to delivery of booster.
7: 6 and 12-month Follow-up evaluations are targeted to be conducted with associated allowable windows on Day 182 ± 30 days and Day 365 ± 30 days. The day of Group Session 1 is considered Day 0 for youth. The 6-month Booster must occur within 30 days following the 6-month Follow-up Study Visit.

Appendix II-B: Schedules of Evaluations for Caregivers – Randomized Trial of TI-CBT Intervention

Study Visit/Session	Screen / Entry[1]	Caregiver Group Sessions (within 8 weeks of caregiver's youth session 1)		Caregiver Follow-up[7]		
		Session A[2]	Session B[2]	IPL [3]	6-mo	12-mo/Exit
Clinical						
Informed Consent	X					
Youth agreement for caregiver participation	X					
Behavioral and Counseling						
TI-CBT Intervention or Control		X	X			
Booster (Intervention or Control)					X	
Administer questions on "fun had" and "learned"		X[5]	X[5]		X[5]	
CASI administered questionnaires (pen and paper may be substituted per Section 5.5)						
Demographics	X[4]					
AIDS-Related Stigma Scale	X[4]			X[6]	X[6]	X
HIV attitudes and support	X[4]			X[6]	X[6]	X
Barriers to adherence	X[4]			X[6]	X[6]	X
HIV knowledge	X[4]			X[6]	X[6]	X
CBCL caregiver report of youth behavior	X[4]			X[6]	X[6]	X
Risk for Contamination					X[6]	
Participant Intervention Evaluation				X[6]		

1: Screening and Entry Visit procedures may be combined into one study visit or split across multiple study visits; may be conducted during the caregiver's first Group Session Study Visit prior to initiation of the group session; and may take place in parallel with their respective Youth Screening, Entry Visit or Group Session Study Visits. Procedures may take place up to 60 days prior to enrollment.

2: Caregiver Group Session A and B should be completed within eight weeks of the start of their youth's first group session and conducted separately from the youth group sessions. Group Session A and B will not be combined into one study visit.

3: Immediately post-last group session (IPL) follow-up evaluations should be conducted immediately following Group Session 6 on the same day or within 30 days.

4: Baseline measures.

5: Administer following completion of the group sessions.

6: If IPL conducted at Group Session B, administer following delivery of intervention. At 6-month Follow-up Study Visit administer prior to delivery of booster.

7: 6 and 12-month Follow-up evaluations are targeted to be conducted with associated allowable windows on Day 182 ± 30 days and Day 365 ± 30 days. The day of Group Session 1 for a caregiver's youth is considered Day 0 for caregiver. The 6-month Booster must occur within 30 days following the 6-month Follow-up Study Visit.

Appendix III
Sample Informed Consent Form for Youth and Caregivers in the Focus Group

IMPAACT 2016
Evaluating a Group-Based Intervention to Improve Mental Health and ART Adherence Among Youth Living with HIV in Low Resource Settings

Version 1.0, 29 August 2018

Introduction

[You are/Your youth is] being asked to take part in a Focus Group for the research study named above.

The study named above is being done by the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) and *[insert site name]* is doing this Focus Group. The person in charge of the study at *[insert site name]* is *[insert name of IoR]*. The United States National Institutes of Health is paying for the study.

This form gives information about the Focus Group. Please read it, or have it read to you, and ask any questions. You can take as much time as you need to understand the Focus Group. We will ask you questions to make sure you understand the Focus Group clearly.

After you understand, if [you/your youth] decide to take part, we will ask you to sign or make your mark on this form. You will be offered a copy to keep.

About the Focus Group

1. It is your decision whether or not [you join/your youth joins] the Focus Group.

Deciding to join the Focus Group is voluntary (your choice). You are free [to allow your youth] to take part or not. Your decisions will have no effect on the services that [you/your youth] would normally receive. [Your/Your youth's] access to services, and the benefits and rights [you normally have/your youth normally has], will not be affected.

If [you take/your youth takes] part in the Focus Group, [you/your youth] cannot participate in the main study.

2. What happens in the Focus Group?

There will be two focus groups, one for youth who have HIV and one for caregivers of youth who have HIV. About 5 people will take part in each Focus Group and each group will meet for about 2 hours.

In the Focus Group, participants will be told about the study and asked to give opinions about how some parts of the study are planned to be done. The discussion in the Focus Group will be on topics such as the mental health of youth who have HIV, how youth cope with having HIV, and how youth take medications for HIV.

The people leading the Focus Group will take notes during the discussion. They will write down the opinions that are given during the discussions, but they will not write down the names of people who gave the opinions. Names will not be recorded on any papers other than this form. All forms and notes from the Focus Group will be kept in secure locations. Discussions will also be audio recorded for future reference.

Risks of the Focus Group

3. There is little risk from the Focus Group procedures.

Some issues discussed in the Focus Group could make [you/your youth] feel uncomfortable, embarrassed, or upset. [You/Your youth] or other people may talk about experiences that are upsetting or stressful. [You/Your youth] may give opinions that other people in the Focus Group do not agree with. The people leading the Focus Groups are trained to help participants feel comfortable in the discussion. However, [you/your youth] do not have to answer any questions or discuss any issues that [you do/your youth does] not want to.

All people who take part in the Focus Groups are asked to respect the privacy of others in the Focus Group. However, it is possible that people in the Focus Group could talk about the content with others. If this happens, others could find out that [you/your youth] took part in a Focus Group. [You/Your youth] could be treated badly or unfairly. [You/Your youth] could feel stress or embarrassment.

Although there may be no direct benefit to [you/your youth] from taking part in this Focus Group; [you/your youth] will be contributing to research for youth who have HIV.

4. There is no cost for being in the Focus Group.

*[Insert additional information about compensation/reimbursement here, e.g., [*You/Your youth] will be provided a snack and reimbursed for the cost of transport to visits. For each visit, [you/your youth] will be given (specify amount).*]*

5. Study records may be reviewed by study staff and groups that oversee the study.

Groups that oversee the study include:

- *[insert name of site IRB/EC]*
- *[insert name of other site regulatory entities]*
- The United States National Institutes of Health and its study monitors
- The United States Office for Human Research Protections
- The IMPAACT Network that is coordinating the study
- Other US, local, and international regulatory groups

The study staff and these groups are required to keep records from the groups private and confidential. *[Site to insert applicable requirements per local regulations, e.g.* If the study staff learns of possible abuse and/or a risk of harm to [you/your youth] or others, they will be required to tell the proper authorities].

Information from the Focus Group may be presented publicly or published. However, no presentation or publication will use your name or identify you personally.

A description of the study will be available on ClinicalTrials.gov. This website will not include information that can identify you. At most, the website will include a summary of the results of the study. You can search this website at any time.

6. If you have questions, concerns, or problems, use these contacts.

- If you have questions about the Focus Group:
  [insert name and telephone number of investigator or other study staff]

- If you have questions about your [youth's] rights or concerns about how [you are/your youth is] treated in a Focus Group:
  [insert name and telephone number of IRB/EC contact person or other appropriate person/organization]

- If [you have/your youth has] any other problem that may be related to participation in a Focus Group:
  [insert name and telephone number of investigator or other study staff]

Signatures

If you decide to [let your youth] take part in a group, sign or make your mark below.

Before deciding whether to [let your youth] take part in this Focus Group, make sure you have read this form, or had it read to you, and all your questions have been answered. You should feel that you understand the Focus Group, the risks and benefits, and what is expected of you [and your youth] if you decide [to allow your youth] to take part.

You do not give up any rights by signing this form.

[Youth Participants Only]

For the optional caregiver participation, write a 'X' to indicate your decision.

_____ *Yes, I agree to have my caregiver take part in a focus group*

_____ *No, I don't want to have my caregiver take part in a focus group*

[Insert initial and signature blocks as required by site IRB/EC policies and the IRB/EC determination of the level of risk to children in the categories specified in 45 CFR 46.404-407.]

Signature blocks for youth participants <u>below</u> legal age to provide independent informed consent for the Focus Group

Participant Assent

Name of Participant (print)	Signature of Participant	Date

Parent or Guardian Consent

Name of Parent or Guardian (print)	Signature of Parent or Guardian	Date

Parent or Guardian Relationship to youth participant

Name of Study Staff Conducting Consent Process (print)	Signature of Study Staff	Date
Name of Witness (as appropriate; print)	Signature of Witness	Date

Signature blocks for youth participants of legal age to provide informed consent for the Focus Group

Name of Participant (print)	Signature of Participant	Date
Name of Study Staff Conducting Consent Process Name (print)	Signature of Study Staff	Date
Name of Witness (as appropriate; print)	Signature of Witness	Date

Signature blocks for caregiver participants for the Focus Group

Name of Participant (print)	Signature of Participant	Date
Name of Study Staff Conducting Consent Process Name (print)	Signature of Study Staff	Date
Name of Witness (as appropriate; print)	Signature of Witness	Date

Appendix IV
Sample Informed Consent Form for Youth in Pilot Test

IMPAACT 2016
Evaluating a Group-Based Intervention to Improve Mental Health and ART Adherence Among Youth Living with HIV in Low Resource Settings

Version 1.0, 29 August 2018

Introduction

[You are/Your youth is] being asked to take part in a Pilot Test for the research study named above.

This form gives information about the Pilot Test. Please read it, or have it read to you, and ask any questions. You can take as much time as you need to fully understand the Pilot Test. We will ask you questions to see if we have explained the Pilot Test clearly.

After you understand the Pilot Test, if you decide that [you/your youth] will participate, you will be asked to sign or make your mark on this form. You will be offered a copy to keep.

About the Study

The study named above is being done by the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) and *[insert site name]* is doing this Pilot Test. The person in charge of the study at *[insert site name]* is *[insert name of IoR]*. The United States National Institutes of Health is paying for the study.

The study is being done to find out if group sessions led by older peers can help youth living with HIV. The study will look at the effects of the group session on mental health and how well youth are able to take their medicines for HIV (ARVs). The study will include about 200 youth from Botswana, Malawi, South Africa, and Zimbabwe. The study will also include caregivers of these youth.

About the Pilot Test

1. The Pilot Test is being done to prepare for the study.

In the Pilot Test, we will practice the procedures planned to be done in the study. This will help us learn the best way to conduct the study. For example, we will learn how long the procedures take and the best way to talk about HIV and other issues in the group sessions. We will also discuss the stresses of living with HIV and helpful tips on how to cope with this.

The Pilot Test will include about 8 youth and about 8 caregivers here at *[insert site name]*. Each youth will be in the Pilot Test for about 6 to 8 weeks. During this time, youth will take part in individual visits and group sessions with other youth living with HIV. The rest of this form gives more information about the visits and group sessions that will be done in the Pilot Test.

2. It is your decision whether or not [you join/your youth joins] the Pilot Test.

Deciding to join the Pilot Test is voluntary (your choice). You are free to [allow your youth to] take part or not. If you decide to [allow your youth] take part, you can change your mind and [leave the Pilot Test/take your youth out of the Pilot Test]. Your decisions will have no effect on the services that

[you/your youth] would normally receive. [Your/Your youth's] access to services, and the benefits and rights [you normally have/your youth normally has], will not be affected.

Take your time and consider your decision carefully. If you wish, you can talk to other people about the Pilot Test. You can also bring other people here to learn about the Pilot Test with you.

If [you take/your youth takes] part in the Pilot Test, [you/your youth] cannot participate in the study.

Finding out if you qualify

3. We will ask questions, perform tests, and discuss the Pilot Test requirements with you.

To find out if [you qualify/your youth qualifies] for the Pilot Test, we will:

- Review medical records to confirm [you are/your youth is] living with HIV and prescribed ART, and collect information about [your/your youth's] age, gender, ethnicity, and race.
- Talk with you about the study requirements and if [you are/your youth is] able to meet them.
- Ask [you/your youth] to answer questions about [your/(his/her)] mental health using either paper and pen or a computer. This may include questions about feelings, trauma and other mental health symptoms. We will also ask questions about taking ART and some questions about [yourself/your youth], [your/your youth's] family, and the household.
- Draw blood (5 mL or about 1 teaspoon) to confirm [you have/your youth has] HIV. There are certain HIV tests that are required for the Pilot Test. If the required tests are not in the medical records, we will draw blood and do the tests that are needed. If the required tests are in the medical records, we will not draw blood.

These procedures will take about 2 hours *[here and throughout this form, sites may modify the expected visit duration as needed]*.

4. We will tell you if [you/your youth] qualifies for the Pilot Test.

We will give you the results of all procedures and explain the results to you.

If [you do not/your youth does not] qualify for the Pilot Test, we will tell you this. [You/Your youth] will not be entered into the Pilot Test. We will tell you about other places where you can go for services that may be needed.

If [you do/your youth does] qualify, [you/your youth] will be asked to return to the clinic to complete additional procedures before starting the first group session. [You/Your youth] may complete these procedures on the same day or on a different day as the first group session.

If [you do not/your youth does not] enter the study

If [you do not/your youth does not] enter the study, we will still use some information collected about [you/your child]. This will include age, gender, ethnicity, and race, as well as information on education, household, job, ART adherence, and mental health. We will use this information to look at patterns or common reasons for not entering the study. The information may also help researchers understand more about ART adherence and mental health.

Being in the Pilot Test

5. We will ask [you/your youth] more questions and complete the procedures.

[You/Your youth] will answer questions about taking ART, violence in relationships, roles of men and women, stigma, alcohol and drug use, sexual activity, and [your/their] caregiver behaviors. These questions will be answered on a computer. We will review medical records to confirm changes in [your/your youth's] health and/or medications. We will also pretend to collect [your/your youths] hair and blood, but we will not cut any hair or draw blood.

6. [You/Your youth] will take part in group sessions at the clinic with other youth.

[You/Your youth] will return to the clinic for up to 6 visits over approximately 6 to 8 weeks to participate in group sessions with other youth. The group sessions will be led by older peers who are living with HIV. The first group session may be done on the same day as the procedures in #5 or on a different day. The number of visits to the clinic [you/your youth] will have will depend on when all youth in the group agree to meet. It is possible that the group may choose to combine multiple visits into one. This will decrease the total number of visits to the clinic.

[You/your youth] will receive information and participate in activities during each session. The information [you/your youth] receive and activities during the sessions will be different at each visit. Some of the content covered in the sessions will include stresses of living with HIV and helpful tips on how to cope with this, discussing differences between thoughts, feelings, and behaviors; discussing relationships, problem solving skills, and more.

Each visit will take about 2-4 hours. *[here and throughout this form, sites may modify the expected visit duration as needed]*. At the end of each session during the visit we will ask [you/your youth] how much fun [you/they] had and what [you/they] learned.

7. [You/Your youth] can invite [your/their] caregiver to take part in the Pilot Test.

[You/Your youth] will have the choice to invite a family member or other person who helps [you/your youth] or takes care of [you/your youth] to participate in the Pilot Test. This person is called a "caregiver." This choice is up to [you/your youth]. [You/Your youth] can still take part in the Pilot Test if [you do/your youth does] not want to invite a caregiver.

If [you choose/your youth chooses] to invite a caregiver, we will contact the caregiver to find out if he/she would like to participate in the Pilot Test. The caregiver will be free to say yes or no. Even if the caregiver says no, [you/your youth] can still be in the Pilot Test.

If the caregiver takes part in the Pilot Test, he or she will have 2 group sessions with other caregivers over about 6 weeks. The group sessions for caregivers are separate from group sessions for youth, so the caregiver will not be in the same group session as [you/your youth].

If [you do/your youth does] not provide permission for a caregiver to participate, the caregiver will not be contacted and will not be invited to join.

8. We may take [you/your youth] off the Pilot Test early.

[You/Your youth] will stay in the Pilot Test until all the sessions have been completed. However, we may take [you/your youth] off early if:

- The Pilot Test is stopped for any reason.
- We determine that [you/your youth] cannot meet the pilot test requirements
- We determine that staying in the Pilot Test might harm [you/your youth].

If [you are/your youth is] taken off the study early, [your/your youth's] caregiver may continue to participate in the study. If [your/your youth's] caregiver is taken off the study early, [you/your youth] may continue to participate in the study.

9. Please tell us if [you want/your youth wants] to leave the Pilot Test.

If you decide to [take part/let your youth take part] in the Pilot Test, we hope [you/your youth] will complete all visits and group sessions. However, [you are/your youth is] free to leave the Pilot Test at any time for any reason – you just need to tell us. The care that [you/your youth] would normally receive will not be affected, but it is important that we know your decision.

Risks of the Pilot Test

10. There is little risk from the Pilot Test procedures.

Most procedures done are routine clinical procedures, with little risk.

Some issues discussed in the group could make [you/your youth] feel uncomfortable, embarrassed, or upset. [You/Your youth] or other people may talk about experiences that are upsetting or stressful. [You/Your youth] may give opinions that other people in the group do not agree with; other people may not agree with [you/your youth]. The people leading the groups are trained to help participants feel comfortable taking part in the discussion. However, [you do/your youth does] not have to answer any questions or discuss any issues that [you/they] do not want to.

All people who take part in the group session are asked respect the privacy of others in the group. However, it is possible that people in the group could talk about the group with others. If this happens, others could find out that [you/your youth] took part in a group. [You/your youth] could be treated badly or unfairly. [You/Your youth] could feel stress or embarrassment.

Other Risks

Continued or unimproved depression, anxiety, and/or post-traumatic stress or worsening of symptoms is always a risk of depression, anxiety, and post-traumatic stress regardless of participating in the Pilot Test. In addition, suicide or suicide attempt is a risk of depression. These risks will be monitored during clinic visits.

11. There could be risks of disclosure of your information.

We will make every effort to keep [your/your youths] information private and confidential. Study records will be kept in secure locations. Almost all records will be labeled only with a code. All information entered into a computer is secured and will only be labelled with a code. Once you have finished all the questions, the whole interview will be locked and will be kept confidential, except when there is a risk of harm.

However, [your/your youths] name will be written on some records that are kept in the clinic. Despite our best efforts to keep this information private, it is possible that the information could be obtained by someone who should not have it. If this were to happen, [you/your youth] could be treated badly or unfairly. [You/Your youth] could feel stress or embarrassment.

In addition, [you/your youth] will be in a group where private, personal information may be shared. Although everyone will be told to keep everything that is said in the program private, it is possible that a group member may tell others what was said in the group. We cannot guarantee that other participants will not accidentally or on purpose repeat what has been said in the group discussions and sessions.

Benefits of the Pilot Test

12. There may be no benefit from being in the Pilot Test.

Participating in this Pilot Test may give [you/your youth] knowledge and skills that may help improve [your/their] mental health and adherence to ART and/or help [you/your youth] help others improve their mental health and adherence to ART. If the caregiver participates, the study may improve his/her ability to help [you/your youth] feel better and take your medicine on time. What we learn about counseling in youth may help youth in the future manage, cope and improve their mental health and adherence to ART.

Other information about the Pilot Test

13. There is no cost to you for being in the Pilot Test.

[Insert additional information about compensation/reimbursement here, e.g., You will be provided a snack and reimbursed for the cost of transport to visits. For each visit, you will be given (specify amount)*.]*

14. Study records may be reviewed by study staff and groups that oversee the study

Groups that oversee the study include:

- *[insert name of site IRB/EC]*
- *[insert name of other site regulatory entities]*
- The United States National Institutes of Health and its study monitors
- The Office for Human Research Protections (OHRP)
- The IMPAACT Network that is coordinating the study
- Other US, local, and international regulatory groups

The study staff and these groups are required to make every effort to keep study records private and confidential. *[Site to insert applicable requirements per local regulations, e.g.* If the study staff learns of possible abuse and/or a risk of harm to you or others, they will be required to tell the proper authorities].

The results of the study may be presented publicly or published. However, no presentation or publication will use your name or identify you personally.

A description of this study will be available on ClinicalTrials.gov. This website will not include information that can identify you. At most, the website will include a summary of the results of the study. You can search this website at any time.

15. If [you get/your youth gets] sick or injured, contact us immediately.

[Your/Your youth's] health is important to us. We will make every effort to protect [your/your youths] well-being and minimize risks. It is possible, however, that [you/your youth] could have an illness or injury or other negative reaction (e.g., stigma) that is study-related. This means the illness or injury or negative reaction occurred as a direct result of being in the study.

[Sites may modify this paragraph to reflect local institutional policies; information regarding coverage available through clinical trial insurance obtained by the site should be included if applicable; the statement regarding no program for compensation through the NIH may not be removed.] If a study-related negative reaction occurs, we will treat [you/your youth] or tell you where you can get the treatment. The cost for this treatment may be charged to you or your health insurance. There is no program to pay money or give other forms of compensation for study-related negative reaction through *[site name or]* the United States National Institutes of Health.

Who to Contact

Please contact us if [you have/your youth has] questions about anything we have said or if [you experience/your youth experiences] any health symptoms such as depression or suicidal ideation at any time; we are here to help. We can refer you to the appropriate place for care; alternatively, you can contact your health care provider.

- If you have questions about the study:
  [insert name and telephone number of investigator or other study staff]

- If you have questions about your rights as research participants or concerns about how you are being treated in the study:
  [insert name and telephone number of IRB/EC contact person or other appropriate person/organization]

Signatures

If you decide to [let your youth] join the Pilot Test, sign or make your mark below.

Before deciding whether to [let your youth] join this Pilot Test, make sure you have read this form, or had it read to you, and that all of your questions have been answered. You should feel that you understand the study, its risks and benefits, and what is expected of [you/your youth] if you decide to [allow your youth] join.

We will tell [you/your youth] any new information from this study or other studies that may affect [your/your youth's] willingness to stay in the Pilot Test. You can ask questions or request more information at any time.

You do not give up any rights by signing this form.

[Youth Participants Only]

For the optional caregiver participation, write a 'X' to indicate your decision.

_____ Yes, I agree to have my caregiver join the study

_____ No, I don't want to have my caregiver join the study

[Insert initial and signature blocks as required by site IRB/EC policies and the IRB/EC determination of the level of risk to children in the categories specified in 45 CFR 46.404-407.]

Signature blocks for youth participants <u>below</u> legal age to provide independent informed consent

Participant Assent

Name of Participant (print)	Signature of Participant	Date

Parent or Guardian Consent

Name of Parent or Guardian (print)	Signature of Parent or Guardian	Date

Parent or Guardian Relationship to youth participant

Name of Study Staff Conducting Consent Process (print)	Signature of Study Staff	Date
Name of Witness (as appropriate; print)	Signature of Witness	Date

Signature blocks for youth participants of legal age to provide independent informed consent

Name of Participant (print)	Signature of Participant	Date
Name of Study Staff Conducting Consent Process (print)	Signature of Study Staff	Date
Name of Witness (as appropriate; print)	Signature of Witness	Date

Appendix V
Sample Informed Consent Form for Caregiver in Pilot Test

IMPAACT 2016
Evaluating a Group-Based Intervention to Improve Mental Health and ART Adherence Among Youth Living with HIV in Low Resource Settings

Version 1.0, 29 August 2018

Introduction

You are being asked to take part in a Pilot Test for research study named above.

This form gives information about the Pilot Test. Please read it, or have it read to you, and ask any questions. You can take as much time as you need to fully understand the Pilot Test. We will ask you questions to see if we have explained the Pilot Test clearly.

After you understand the Pilot Test, if you decide to participate, you will be asked to sign or make your mark on this form. You will be offered a copy to keep.

About the Study

The study named above is being done by the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) and *[insert site name]* is doing this Pilot Test. The person in charge of the study at *[insert site name]* is *[insert name of IoR]*. The United States National Institutes of Health is paying for the study.

The study is being done to find out if group sessions led by older peers can help youth living with HIV. The study will look at the effects of the group session on mental health and how well youth are able to take their medicines for HIV (ARVs). The study will include about 200 youth from Botswana, Malawi, South Africa, and Zimbabwe. The study will also include caregivers of these youth.

About the Pilot Test

1. The Pilot Test is being done to prepare for the study.

In the Pilot Test, we will practice the procedures planned to be done in the study. This will help us learn the best way to conduct the study. For example, we will learn how long the procedures take and the best way to talk about HIV and other issues in the group sessions.

The Pilot Test will include about 8 youth and about 8 caregivers here at *[insert site name]*. Each caregiver will be in the Pilot Test for about 6 to 8 weeks. During this time, caregivers will take part in individual visits and group sessions with other caregivers of youth participating in the Pilot Test. The rest of this form gives more information about the visits and group sessions that will be done in the Pilot Test.

2. It is your decision whether or not to join the Pilot Test.

Deciding to join the Pilot Test is voluntary (your choice). You are free to take part or not. If you decide to take part, you can change your mind and leave the Pilot Test. Your decisions will have no effect on the services that you or your youth would normally receive. Yours and your youth's access to services, and the benefits and rights you and your youth normally have, will not be affected.

Take your time and consider your decision carefully. If you wish, you can talk to other people about the Pilot Test. You can also bring other people here to learn about the Pilot Test with you.

If you take part in the Pilot Test, you cannot participate in the study.

Finding out if you qualify and being in the Pilot Test

3. We will ask you more questions and practice procedures.

You are being invited to join the Pilot Test because your youth you care for has agreed to join the Pilot Test and is interested in having you join as well. After you have agreed to join the Pilot Test, you will be asked to stay or return to the clinic to answer some questions.

You will answer questions about yourself and your household; your involvement in your youth's adherence to ART; youth's behavior; barriers to adherence; and HIV knowledge and stigma. These questions will be answered on a computer, and no information will be analyzed.

These procedures will take about 1 hour *[here and throughout this form, sites may modify the expected visit duration as needed]*.

4. You will take part in group sessions at the clinic with other caregivers.

You will return to the clinic for 2 visits over approximately 6 to 8 weeks to participate in group sessions with other caregivers. The group sessions will be led by trained study staff. The first session may be done on the same day as the procedures in #3 or on a different day. Your youth will not participate in the group sessions with you, and these sessions will be different from the sessions your youth attend.

You will receive information and participate in activities during each session. The information you receive and activities during the sessions will be different at each visit. Some of the content covered in the sessions will include obstacles to youth ART adherence, methods on how to help youth adhere to ART and how to communicate effectively with youth, and stigma associated with living with HIV.

Each visit will take about 2-4 hours. *[here and throughout this form, sites may modify the expected visit duration as needed]*. At the end of each session during the visit we will ask you how much fun you had and what you learned.

5. We may take you off the Pilot Test early.

You will stay in the Pilot Test until all the session have been completed. However, we may take you off the study early if:

- The Pilot Test is stopped for any reason.
- We determine that you cannot meet the requirements.
- We determine that staying in the Pilot Test might harm you.

If you are taken off the study early, your youth may continue to participate in the study. If your youth is taken off the study early, you may continue to participate in the study.

6. Please tell us if you want to leave the Pilot Test.

If you decide to take part in the Pilot Test, we hope you will complete all visits and group sessions. However, you are free to leave the Pilot Test at any time for any reason – you just need to tell us. The care that you would normally receive will not be affected, but it is important that we know your decision.

Risks of the Pilot Test

7. There is little risk from the Pilot Test procedures.

Some issues discussed in the group could make you feel uncomfortable, embarrassed, or upset. You may give opinions that other people in the group do not agree with; other people may not agree with you. The people leading the groups are trained to help participants feel comfortable taking part in the discussion. However, you do not have to answer any questions or discuss any issues that you do not want to.

All people who take part in the group sessions are asked respect the privacy of others in the group. However, it is possible that people in the group could talk about the group with others. If this happens, others could find out that you took part in a group. You could be treated badly or unfairly. You could feel stress or embarrassment.

8. There could be risks of disclosure of your information.

We will make every effort to keep your information private and confidential. Study records will be kept in secure locations. Almost all records will be labeled only with a code. All information entered into a computer is secured and will only be labelled with a code. Once you have finished all the questions, the whole interview will be locked and will be kept confidential, except when there is a risk of harm.

However, your name will be written on some records that are kept in the clinic. Despite our best efforts to keep this information private, it is possible that the information could be obtained by someone who should not have it. If this were to happen, you could be treated badly or unfairly. You could feel stress or embarrassment.

In addition, you will be in a group where private, personal information may be shared. Although everyone will be told to keep everything that is said in the program private, it is possible that a group member may tell others what was said in the group. We cannot guarantee that other participants will not accidentally or on purpose repeat what has been said in the group discussions and sessions.

Benefits of the Pilot Test

9. There may be no benefit from being in the Pilot Test.

Participating in this study may give you knowledge and skills that may help you improve your youths' mental health and adherence to ART. What we learn about counseling in youth may help youth in the future to manage, cope and improve their mental health and adherence to ART.

Other information about the Pilot Test

10. There is no cost to you for being in the Pilot Test.

[Insert additional information about compensation/reimbursement here, e.g., You will be provided a snack and reimbursed for the cost of transport to visits. For each visit, you will be given (specify amount)*.]*

11. Study records may be reviewed by study staff and groups that oversee the study.

Groups that oversee the study include:

- *[insert name of site IRB/EC]*
- *[insert name of other site regulatory entities]*
- The United States National Institutes of Health and its study monitors
- The Office for Human Research Protections (OHRP)
- The IMPAACT Network that is coordinating the study
- Other US, local, and international regulatory groups

The study staff and these groups are required to make every effort to keep study records private and confidential. *[Site to insert applicable requirements per local regulations, e.g.* If the study staff learns of possible abuse and/or a risk of harm to you or others, they will be required to tell the proper authorities].

The results of the study may be presented publicly or published. However, no presentation or publication will use your name or identify you personally.

A description of this study will be available on ClinicalTrials.gov. This website will not include information that can identify you. At most, the website will include a summary of the results of the study. You can search this website at any time.

12. If you get sick or injured, contact us immediately.

Your health is important to us. We will make every effort to protect your well-being and minimize risks. It is possible, however, that you could have an illness or injury or other negative reaction (e.g., stigma) that is study-related. This means the illness or injury or negative reaction occurred as a direct result of being in the study.

[Sites may modify this paragraph to reflect local institutional policies; information regarding coverage available through clinical trial insurance obtained by the site should be included if applicable; the statement regarding no program for compensation through the NIH may not be removed.] If a study-related illness, injury or negative reaction occurs, we will treat you or tell you where you can get the treatment. The cost for this treatment may be charged to you or your health insurance. There is no program to pay money or give other forms of compensation for study-related illness, injury or negative reaction through *[site name or]* the United States National Institutes of Health.

Who to Contact

Please contact us if you have questions about anything we have said or if you or your youth experience any health symptoms such as depression or suicidal ideation at any time; we are here to help. If you contact the study team we can refer you to the appropriate place for care; alternatively, you can contact your health care provider.

- If you have questions about the study:
  [insert name and telephone number of investigator or other study staff]

- If you have questions about your rights as research participants or concerns about how you are being treated in the study:
  [insert name and telephone number of IRB/EC contact person or other appropriate person/organization]

Signatures

If you decide to join the Pilot Test, sign or make your mark below.

Before deciding whether to join this study, make sure you have read this form, or had it read to you, and that all of your questions have been answered. You should feel that you understand the study, its risks and benefits, and what is expected of you if you decide to join.

We will tell you any new information from this study or other studies that may affect your willingness for you to stay in the study. You can ask questions or request more information at any time.

You do not give up any rights by signing this form.

[Insert signature blocks as required by site IRB/EC policies.]

Name of Participant (print)	Signature of Participant	Date
Name of Study Staff Conducting Consent Process (print)	Signature of Study Staff	Date
Name of Witness (as appropriate; print)	Signature of Witness	Date

Appendix VI
Sample Informed Consent Form for Youth in Randomized Trial

IMPAACT 2016
Evaluating a Group-Based Intervention to Improve Mental Health and ART Adherence Among Youth Living with HIV in Low Resource Settings

Version 1.0, 29 August 2018

Introduction

[You are/Your youth is] being asked to take part in the research study named above.

This form gives information about the study. Please read it, or have it read to you, and ask any questions. You can take as much time as you need to fully understand the study. We will ask you questions to see if we have explained the study clearly.

After you understand the study, if you decide that [you/your youth] will participate, you will be asked to sign or make your mark on this form. You will be offered a copy to keep.

About the Study

The study named above is being done by the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) and *[insert site name]* is doing this study. The person in charge of the study at [insert site name] is [insert name of IoR]. The United States National Institutes of Health is paying for the study.

The study is being done to find out if group sessions led by older peers can help youth living with HIV. The study will look at the effects of the group session on mental health and how well youth are able to take their medicines for HIV (ARVs). The study will include about 200 youth from Botswana, Malawi, South Africa, and Zimbabwe. The study will also include caregivers of these youth.

1. The study will see if counseling group sessions help youth living with HIV.

Youth who are living with HIV and taking ART may experience mental health distress such as depression, anxiety, or post-traumatic stress and have questions on how to improve distress and better adhere to ART. Studies have shown TI-CBT, which stands for Trauma-Informed Cognitive Behavioral Therapy helps provide resources to improve distress and adherence. Additionally, having family and friends learn about what their youth are experiencing may help them provide support and care. The study will see if group sessions lead by older peers with similar experience and involvement of caregivers will help improve mental health and adherence to ART regimens. For the remainder of the form, the term TI-CBT will be replaced with counseling.

2. It is your decision whether or not [you join/your youth joins] the study.

Deciding to join the study is voluntary (your choice). You are free to [allow your youth to] take part or not. If you decide to [allow your youth] take part to take part, you can change your mind and leave the study. Your decisions will have no effect on the services that you would normally receive. Your access to services, and the benefits and rights [you normally have/your youth normally has], will not be affected.

Take your time and consider your decision carefully. If you wish, you can talk to other people about the study. You can also bring other people here to learn about the study with you.

Finding out if you qualify

3. We will ask questions, perform tests, and discuss the study requirements with you.

To find out if [you qualify/your youth qualifies] for the study, we will:

- Review medical records to confirm [you are/your youth is] living with HIV and prescribed ART, and collect information about [your/your youth's] age, gender, ethnicity, and race.
- Talk with you about the study requirements and if [you are/your youth is] able to meet them.
- Ask [you/your youth] to answer questions about [your/(his/her)] mental health using either paper and pen or a computer. This includes questions about feelings, trauma and other mental health symptoms. We will also ask questions about taking ART and some questions about yourself, [your/your youths] family, and the household.
- Draw blood (5 mL or about 1 teaspoon) to confirm [you have/your youth has] HIV. There are certain HIV tests that are required for the Pilot Test. If the required tests are not in the medical records, we will draw blood and do the tests that are needed. If the required tests are in the medical records, we will not draw blood.

These procedures will take about 2 hours *[here and throughout this form, sites may modify the expected visit duration as needed]*.

4. We will tell you if [you/your youth] qualifies for the study.

We will give you the results of all procedures and explain the results to you.

If [you do not/your youth does not] qualify for the study, we will tell you this. [You/Your youth] will not be entered into the study. We will tell you about other places where you can go for services you may need.

If [you do/your youth does] qualify, [you/your youth] will be asked to return to the clinic to complete additional procedures before starting the first group session. [You/Your youth] may complete these procedures on the same day or on a different day as the first group session.

This visit will take about 2 hours. *[here and throughout this form, sites may modify the expected visit duration as needed]*.

We will:

- Ask [you/your youth] to answer questions using a computer. This includes questions about taking ART; violence in relationships; roles of men and women; stigma; alcohol and drug use; sexual activity; and [your/their] caregiver's behavior.
- Draw blood (15 mL or about 3 teaspoons) to check the amount of HIV that is in [your/your youth's] blood. This is called HIV viral load. Some blood will be saved for later testing. The later test will look at factors in the blood to look for signs of other health considerations.
- Cut about 50-60 strands of hair to check the amount of ARVs in [your/your youth's] body.
- Review medical records to confirm changes in [your/your youth's] health and/or medications.

If [you do not/your youth does not] enter the study

If [you do not/your youth does not] enter the study, we will still use some information collected about [you/your child]. This will include age, gender, ethnicity, and race, as well as information on education, household, job, ART adherence, and mental health. We will use this information to look at patterns or common reasons for not entering the study. The information may also help researchers understand more about ART adherence and mental health.

Being in the study

5. [You/Your youth] will be assigned to receive either counseling group sessions or discussion group sessions.

Which group sessions [you/your youth] receive is decided by chance, like tossing a coin. About half of the participants will be in each group. Participants in both groups will attend 6 group sessions over approximately 6 to 8 weeks. [You/your youth] will attend the group sessions together with [your/their] peers. The group sessions will be led by older peers who are living with HIV.

One group will be called the counseling group, and the other group will be called the discussion group.

6. The information and activities in each group (counseling or discussion) will be different.

— **If [you are/your youth is] assigned to the counseling group:** [You/your youth] will receive information and participate in activities during each session. The information you receive and activities during the sessions will be different at each visit. Some of the content covered in the sessions will include stresses of living with HIV and helpful tips on how to cope with this, discussing differences between thoughts, feelings, and behaviors; discussing relationships, problem solving skills, and more.

— **If [you are/your youth is] assigned to the discussion group**: The information [you/your youth] receive and activities [you/your youth] participate in during the sessions will be chosen by [you/your youth] and the other youth attending the sessions.

7. [You/Your youth] will take part in group sessions at the clinic with other youth.

The first group session may be done on the same day as the procedures in #4 or on a different day. The number of visits to the clinic to attend the sessions will depend on when [you/your youth] and [your/their] peers agree to meet. [You/your youth] may have to come back for up to 5 more visits to complete the other sessions. It is possible that the sessions may be combined and take place on one day. This will decrease the total number of visits to the clinic.

Each visit will take about 2-4 hours *[here and throughout this form, sites may modify the expected visit duration as needed]*. At the end of each session during the visit we will ask [you/your youth] how much fun [you/they] had and what [you/they] learned.

Immediately following the last group session or within 30 days of the last group session, we will also:

- Ask [you/your youth] to answer questions using a computer about your mental health. This may include questions about your feelings, trauma and other mental health symptoms.
- Ask [you/your youth] to answer additional questions using a computer. This may include questions taking ART; violence in relationships; roles of men and women; stigma; alcohol and drug use; sexual activity; [your/their] caregiver's behavior; and [your/their] feedback on all of the visits.
- Collect [your/their] blood to test for HIV viral load (10 mL or about 2 teaspoons).
- Cut about 50-60 strands of hair to check the amount of ARVs in [your/their] body.
- Review medical records to confirm changes in [your/your youth's] health and/or medications.

8. After [you/your youth] take part in the group sessions, [you/they] will have 2 visits.

After the last group session, [you/your youth] will return to the clinic for 2 visits at 6- and 12-months following the day of the first group session. Each visit will take about 2 hours. *[here and throughout this form, sites may modify the expected visit duration as needed]*.

At all of these visits, we will ask [you/your youth] to answer the same questions [you/they] answered when [you/they] first began the study using a computer. The blood test (15 mL or about 3 teaspoons of blood) to check the amount of HIV and biomarkers in [your/your youth's] blood, and the hair sample will be repeated. We will also repeat a review of medical records to confirm changes in [your/your youth's] health and/or medications.

After the 6-month visit, [you/your youth] will also have one additional group session. This group session may be done on the same day as 6-month visit or [you/your youth] may have to come back within 30 days to complete the group session. [You/Your youth] will meet with [your/their] group one final time. If [you are/your youth is] assigned to the **counseling group**, [you/they] will review what [you/they] previously discussed, and if [you are/your youth is] assigned to the **discussion group, [**you/they] and the other youth will choose what to discuss. At the end of the session we will ask [you/your youth] how much fun [you/they] had and what [you/they] learned.

9. [You/Your youth] can invite [your/their] caregiver to take part in the study.

[You/Your youth] will have the choice to invite a family member or other person who helps [you/your youth] or takes care of [you/your youth] to participate in the study. This person is called a "caregiver." This choice is up to [you/your youth]. [You/your youth] can still take part in the study if [you do/your youth does] not want to invite a caregiver.

If [you choose/your youth chooses] to invite a caregiver, we will contact the caregiver to find out if he/she would like to participate in the study. The caregiver will be free to say yes or no. Even if the caregiver says no, [you/your youth] can still be in the study.

If [you do/your youth does] not provide permission to invite a caregiver, the caregiver will not be contacted and will not be invited to join.

If the caregiver takes part in the study, he or she will have 2 group sessions with other caregivers over about 6 weeks. The group sessions for caregivers are separate from group sessions for youth, so the caregiver will not be in the same group session as [you/your youth].

After the last group session, we will also ask the caregiver to answer questions including questions about themselves, their family, and their household; their involvement in you taking ART; barriers to taking your ART; HIV knowledge and stigma; and feedback on all of the visits. We will ask the caregiver to return to the clinic for 2 more visits at 6- and 12-months following the day of your first session to answer the same questions. At the 6-month visit, the caregiver will also have one additional group session.

10. We may take [you/your youth] off the study early.

[You/Your youth] will stay in the study until all the sessions have been completed. However, we may take [you/your youth] off early if:

- The study is stopped for any reason.
- We determine that [you/your youth] cannot meet the study requirements.
- We determine that staying in the study might harm [you/your youth].

If [you are/your youth is] taken off the study early, [your/your youth's] caregiver may continue to participate in the study. If [your/your youth's] caregiver is taken off the study early, [you/your youth] may continue to participate in the study.

11. Please tell us if [you want/your youth wants] to leave the study.

If you decide to [take part/let your youth take part] in the study, we hope [you/your youth] will complete all visits and group sessions. However, [you are/your youth is] free to leave the study at any time for any reason – you just need to tell us. The care that [you/your youth] would normally receive will not be affected, but it is important that we know your decision

Risks of the Study

12. There is little risks from the study procedures.

Most procedures done in this study are routine clinical procedures, with little risk.

Some issues discussed in the group could make [you/your youth] feel uncomfortable, embarrassed, or upset. [You/Your youth] or other people may talk about experiences that are upsetting or stressful. [You/Your youth] may give opinions that other people in the group do not agree with; other people may not agree with [you/your youth]. The people leading the groups are trained to help participants feel comfortable taking part in the discussion. However, [you/your youth] do not have to answer any questions or discuss any issues that [you/they] do not want to.

All people who take part in the group session are asked respect the privacy of others in the group. However, it is possible that people in the group could talk about the group with others. If this happens, others could find out that [you/your youth] took part in a group. [You/Your youth] could be treated badly or unfairly. [You/Your youth] could feel stress or embarrassment.

Blood Drawing
Having blood drawn may cause discomfort, feelings of dizziness or faintness, and/or bruising, swelling and/or infection.

Other Risks
Continued or unimproved depression, anxiety, and/or post-traumatic stress or worsening of symptoms is always a risk of depression, anxiety, and post-traumatic stress regardless of participating in this study. In addition, suicide or suicide attempt is a risk of depression. These risks will be monitored during clinic visits.

13. There could be risks of disclosure of your information.

We will make every effort to keep [your/your youths] information private and confidential. Study records will be kept in secure locations. Almost all records will be labeled only with a code. All information entered into a computer is secured and will only be labelled with a code. Once [you have/your youth has] finished all the questions, the whole interview will be locked and will be kept confidential, except when there is a risk of harm.

However, [your/your youths] name will be written on some records that are kept in the clinic. Despite our best efforts to keep this information private, it is possible that the information could be obtained by someone who should not have it. If this were to happen, [you/your youth] could be treated badly or unfairly. [You/Your youth] could feel stress or embarrassment.

In addition, [you/your youth] will be in a group where private, personal information may be shared. Although everyone will be told to keep everything that is said in the program private, it is possible that a group member may tell others what was said in the group. We cannot guarantee that other participants will not accidentally or on purpose repeat what has been said in the group discussions and sessions.

Benefits of the Study

14. There may be no benefit from being in the study.

Participating in this study may give [you/your youth] knowledge and skills that may help improve [your/their] mental health and adherence to ART and/or help [you/your youth] help others improve their mental health and adherence to ART. If the caregiver participates, the study may improve his/her ability to help [you/your youth] feel better and take your medicine on time. What we learn about counseling in youth may help youth in the future manage, cope and improve their mental health and adherence to ART.

Other information about the study

15. There is no cost to you for being in this study.

[Insert additional information about compensation/reimbursement here, e.g., You will be provided a snack and reimbursed for the cost of transport to study visits. For each visit, you will be given (specify amount)*.]*

16. Study records may be reviewed by study staff and groups that oversee the study.

Groups that oversee the study include:

- *[insert name of site IRB/EC]*
- *[insert name of other site regulatory entities]*
- The United States National Institutes of Health and its study monitors
- The Office for Human Research Protections (OHRP)
- The IMPAACT Network that is coordinating the study
- Other US, local, and international regulatory groups

The study staff and these groups are required to make every effort to keep study records private and confidential. *[Site to insert applicable requirements per local regulations, e.g.* If the study staff learns of possible abuse and/or a risk of harm to you or others, they will be required to tell the proper authorities].

The results of the study may be presented publicly or published. However, no presentation or publication will use your name or identify you personally.

A description of this study will be available on ClinicalTrials.gov. This website will not include information that can identify you. At most, the website will include a summary of the results of the study. You can search this website at any time.

17. If you get sick or injured, contact us immediately.

[Your/Your youth's] health is important to us. We will make every effort to protect [your/your youths] well-being and minimize risks. It is possible, however, that [you/your youth] could have an illness or injury or other negative reaction (e.g., stigma) that is study-related. This means the illness or injury or negative reaction occurred as a direct result of being in the study.

[Sites may modify this paragraph to reflect local institutional policies; information regarding coverage available through clinical trial insurance obtained by the site should be included if applicable; the statement regarding no program for compensation through the NIH may not be removed.] If a study-related illness or injury or negative reaction occurs, we will treat [you/your youth] or tell you where you can get the treatment. The cost for this treatment may be charged to you or your health insurance. There is no program to pay money or give other forms of compensation for study-related illness or injury or negative reaction through *[site name or]* the United States National Institutes of Health.

Who to Contact

Please contact us if [you have/your youth has] questions about anything we have said or if [you experience/your youth experiences] any health symptoms such as depression or suicidal ideation at any time; we are here to help. We can refer you to the appropriate place for care; alternatively, you can contact your health care provider.

- If you have questions about the study:
  [insert name and telephone number of investigator or other study staff]
- If you have questions about your rights as research participants or concerns about how you are being treated in the study:
  [insert name and telephone number of IRB/EC contact person or other appropriate person/organization]

Signatures

If you decide to [let your youth] join this study, sign or make your mark below.

Before deciding whether to [let your youth] join this study, make sure you have read this form, or had it read to you, and that all of your questions have been answered. You should feel that you understand the study, its risks and benefits, and what is expected of [you/your youth] if you decide to [allow your youth] join.

We will tell [you/your youth] any new information from this study or other studies that may affect [your/your youth's] willingness to stay in the study. You can ask questions or request more information at any time.

You do not give up any rights by signing this form.

[Youth Participants Only]

For the optional caregiver participation, write a 'X' to indicate your decision.

_____ Yes, I agree to have my caregiver join the study

_____ No, I don't want to have my caregiver join the study

[Insert initial and signature blocks as required by site IRB/EC policies and the IRB/EC determination of the level of risk to children in the categories specified in 45 CFR 46.404-407.]

Signature blocks for youth participants who cannot provide independent informed consent

Participant Assent

Name of Participant (print)	Signature of Participant	Date

Parent or Guardian Consent

Name of Parent or Guardian (print)	Signature of Parent/Guardian	Date

Parent or Guardian Relationship to youth participant

Name of Study Staff Conducting Consent Process (print)	Signature of Study Staff	Date

Name of Witness (as appropriate; print)	Signature of Witness	Date

Signature page for youth participants of legal age to provide independent informed consent

Name of Participant (print)	Signature of Participant	Date

Name of Study Staff Conducting Consent Process (print)	Signature of Study Staff	Date

Name of Witness (as appropriate; print)	Signature of Witness	Date

Appendix VII
Sample Informed Consent Form for Caregivers in Randomized Trial

IMPAACT 2016
Evaluating a Group-Based Intervention to Improve Mental Health and ART Adherence Among Youth Living with HIV in Low Resource Settings

Version 1.0, 29 August 2018

Introduction

You are being invited to take part in the research study named above.

This form gives information about the study. Please read it, or have it read to you, and ask any questions. You can take as much time as you need to fully understand the study. We will ask you questions to see if we have explained the study clearly.

After you understand the study, if you decide that you will participate, we will ask you to sign or make your mark on this form. You will be offered a copy to keep.

About the Study

The study named above is being done by the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) and *[insert site name]* is doing this study. The person in charge of the study at [insert site name] is [insert name of IoR].

The study is being done to find out if group sessions led by older peers can help youth living with HIV. The study will look at the effects of the group session on mental health and how well youth are able to take their medicines for HIV (ARVs). The study will include about 200 youth from Botswana, Malawi, South Africa, and Zimbabwe. The study will also include caregivers of these youth.

1. The study will see if counseling group sessions and caregiver involvement help youth living with HIV.

Youth who are living with HIV and taking ART may experience mental health distress such as depression, anxiety, or post-traumatic stress and have questions on how to improve distress and better adhere to ART. Studies have shown TI-CBT, which stands for Trauma-Informed Cognitive Behavioral Therapy helps provide resources to improve distress and adherence. Additionally, having family and friends learn about what their youth are experiencing may help them provide support and care. The study will see if group sessions lead by older peers with similar experience and involvement of caregivers will help improve mental health and adherence to ART regimens. For the remainder of the form, the term TI-CBT will be replaced with counseling.

2. It is your decision whether or not to join the study.

Deciding to join the study is voluntary (your choice). You are free to take part or not. If you decide to take part, you can change your mind and leave the study. Your decisions will have no effect on the services that you or your youth would normally receive. Yours and your youth's access to services, and the benefits and rights you and your youth normally have, will not be affected.

Take your time and consider your decision carefully. If you wish, you can talk to other people about the study. You can also bring other people here to learn about the study with you.

Finding out if you qualify and being in the study

3. We will ask you more questions and discuss the study requirements with you.

You are being invited to join the study because your youth you care for has agreed to join the study and is interested in having you join as well. After you agree to join the study, you will be asked to stay or return to the clinic to answer some questions before starting the first group session.

You will answer questions about yourself and your household; your involvement in your youth's adherence to ART; youth's behavior; barriers to adherence; and HIV knowledge and stigma. These questions will be answered on a computer.

These procedures will take about 1 hour *[here and throughout this form, sites may modify the expected visit duration as needed]*.

Being in the study

4. You will be assigned to receive either counseling group sessions or discussion group sessions.

Which group sessions you receive are decided by chance, like tossing a coin. About half of the participants will be in each group. Participants in both groups will attend 2 group sessions over approximately 6 to 8 weeks. You will attend the group sessions together with other caregivers. The group sessions will be led by trained study staff.

One group will be called the counseling group, and the other group will be called the discussion group.

5. The information and activities in each group (counseling or discussion) will be different.

- **If you are assigned to the counseling group:** You will receive information and participate in activities during each session. The information you receive and activities during the sessions will be different at each visit. Some of the content covered in the sessions will include obstacles to youth ART adherence, methods on how to help youth adhere to ART and how to communicate effectively with youth, and stigma associated with living with HIV.

- **If you are assigned to the discussion group**: The information you receive and activities you participate in during the sessions will be chosen by you and the other youth attending the sessions.

6. You will take part in group sessions at the clinic with other caregivers.

You will attend 2 group sessions over approximately 6 to 8 weeks. Your first group session may be done on the same day as the procedures in #3 or on a different day. Your youth will not participate in the group sessions with you, and these sessions will be different from the sessions your youth attend.

Each visit will take about 2 hours. *[here and throughout this form, sites may modify the expected visit duration as needed]*. At the end of each session during the visit we will ask you how much fun you had and what you learned.

Immediately following the last group session or within 30 days of the last group session, we will ask you to answer questions using a computer including questions about your involvement in your youth's adherence to ART; youth's behavior; barriers to adherence; HIV knowledge and stigma; and feedback on all of the visits.

7. After you take part in the group sessions, you will have 3 visits.

After your last group session, you will return to the clinic for 2 visits at 6- and 12-months following the day of your youth's first session.

Each visit will take about 1 hours. *[here and throughout this form, sites may modify the expected visit duration as needed]*.

At all of these visits, we will ask you to answer the same questions you answered when you first began the study using a computer.

After the 6-month visit, you will also have one additional group session. This group session may be done on the same day as 6-month visit or you may have to come back within 30 days to complete the group session. You will meet with your group one final time. If you are assigned to the **counseling group**, you will review what you previously discussed, and if you are assigned to the **discussion group**, you and the other caregivers will choose what to discuss. At the end of the session we will ask you how much fun you had and what you learned.

8. We may take you off the study early.

You will stay in the study until you have completed all the sessions and study visits. However, we may take you off the study early if:

- The study is stopped for any reason.
- We determine that you cannot meet the study requirements.
- We determine that staying in the study might harm you.

If you are taken off the study early, your youth may continue to participate in the study. If your youth is taken off the study early, you may continue to participate in the study.

9. Please tell us if you want to leave the study.

You are free to leave the study at any time for any reason – you just need to tell us. The care that you or your youth would normally receive will not be affected, but it is important that we know your decision. We will answer any questions you may have and tell you how to contact us in the future, if you wish.

Risks of the Study

10. There is little risk from the study procedures.

Some issues discussed in the group could make you feel uncomfortable, embarrassed, or upset. You may give opinions that other people in the group do not agree with; other people may not agree with you. The people leading the groups are trained to help participants feel comfortable taking part in the discussion. However, you do not have to answer any questions or discuss any issues that you do not want to.

All people who take part in the group sessions are asked respect the privacy of others in the group. However, it is possible that people in the group could talk about the group with others. If this happens, others could find out that you took part in a group. You could be treated badly or unfairly. You could feel stress or embarrassment.

11. There could be risks of disclosure of your information.

We will make every effort to keep your information private and confidential. Study records will be kept in secure locations. Almost all records will be labeled only with a code. All information entered into a

computer is secured and will only be labelled with a code. Once you have finished all the questions, the whole interview will be locked and will be kept confidential, except when there is a risk of harm.

However, your name will be written on some records that are kept in the clinic. Despite our best efforts to keep this information private, it is possible that the information could be obtained by someone who should not have it. If this were to happen, you could be treated badly or unfairly. You could feel stress or embarrassment.

In addition, you will be in a group where private, personal information may be shared. Although everyone will be told to keep everything that is said in the program private, it is possible that a group member may tell others what was said in the group. We cannot guarantee that other participants will not accidentally or on purpose repeat what has been said in the group discussions and sessions.

Benefits of the Study

12. There may be no benefit from being in the study.

Participating in this study may give you knowledge and skills that may help you improve your youths' mental health and adherence to ART. What we learn about Counseling in youth may help youth in the future to manage, cope and improve their mental health and adherence to ART.

Other information about the Pilot Test

13. There is no cost to you for being in the study.

[Insert additional information about compensation/reimbursement here, e.g., You will be provided a snack and reimbursed for the cost of transport to study visits. For each visit, you will be given (specify amount)*.]*

14. Study records may be reviewed by study staff and groups that oversee the study.

Groups that oversee the study include:

- *[insert name of site IRB/EC]*
- *[insert name of other site regulatory entities]*
- The United States National Institutes of Health and its study monitors
- The Office for Human Research Protections (OHRP)
- The IMPAACT Network that is coordinating the study
- Other US, local, and international regulatory groups

The study staff and these groups are required to make every effort to keep study records private and confidential. *[Site to insert applicable requirements per local regulations, e.g.* If the study staff learns of possible abuse and/or a risk of harm to you or others, they will be required to tell the proper authorities].

The results of the study may be presented publicly or published. However, no presentation or publication will use your name or identify you personally.

A description of this study will be available on ClinicalTrials.gov. This website will not include information that can identify you. At most, the website will include a summary of the results of the study. You can search this website at any time.

15. If you get sick or injured, contact us immediately.

Your health is important to us. We will make every effort to protect your well-being and minimize risks. It is possible, however, that you could have an illness or injury or other negative reaction (e.g., stigma) that is study-related. This means the illness or injury or negative reaction occurred as a direct result of being in the study.

[Sites may modify this paragraph to reflect local institutional policies; information regarding coverage available through clinical trial insurance obtained by the site should be included if applicable; the statement regarding no program for compensation through the NIH may not be removed.] If a study-related illness, injury or negative reaction occurs, we will treat you or tell you where you can get the treatment. The cost for this treatment may be charged to you or your health insurance. There is no program to pay money or give other forms of compensation for study-related illness, injury or negative reaction through *[site name or]* the United States National Institutes of Health.

Who to Contact

Please contact us if you have questions about anything we have said or if you or your youth experience any health symptoms such as depression or suicidal ideation at any time; we are here to help! If you contact the study team we can refer you to the appropriate place for care; alternatively, you can contact your health care provider.

- If you have questions about the study:
  [insert name and telephone number of investigator or other study staff]

- If you have questions about your rights as research participants or concerns about how you are being treated in the study: *[insert name and telephone number of IRB/EC contact person or other appropriate person/organization]*

Signatures

If you decide to join this study, sign or make your mark below.

Before deciding whether to join this study, make sure you have read this form, or had it read to you, and that all your questions have been answered. You should feel that you understand the study, its risks, benefits, and what is expected of you if you decide to join.

We will tell you any new information from this study or other studies that may affect your willingness for you to stay in the study. You can ask questions or request more information at any time.

You do not give up any rights by signing this form.

[Insert signature blocks as required by site IRB/EC policies.]

Name of Participant (print)	Signature of Participant	Date
Name of Study Staff Conducting Consent Process (print)	Signature of Study Staff	Date
Name of Witness (as appropriate; print)	Signature of Witness	Date

Appendix VIII
Sample Informed Consent Form for Specimen Storage and Future Use for Participants

IMPAACT 2016
Evaluating a Group-Based Intervention to Improve Mental Health and ART Adherence Among Youth Living with HIV in Low Resource Settings

Version 1.0, 29 August 2018

You have decided [to allow your youth] to join the research study named above. As part of the study [your/your youth] will have blood collected. After these samples are tested for the study, some blood may be left over. We call these leftover samples. The IMPAACT Network would like to keep these leftover samples for other research in the future.

This form gives information about use of leftover samples. Please read this form, or have it read to you, and ask any questions you may have. After we discuss the information with you, you will record your decisions on use of leftover samples at the end of the form.

1. It is your decision whether to allow the leftover samples to be used.

You are free to say yes or no, or to change your mind at any time. Your decision will not affect your [your youth's] participation in the study. If you say no, all leftover samples will be destroyed.

2. If you agree, your [youth's] leftover samples will be kept in a repository.

[Sites should insert one of the two options shown below. Choose/adapt the second option if local regulations do not permit storage of samples for future research use in the United States.]

A repository is a secure facility that is used to store samples. The IMPAACT Network repository is in the United States. If you agree to have leftover samples stored, the samples will be kept in this repository. There is no limit on how long the samples will be kept *[sites may insert time limits or additional site-specific requirements here if required by local authorities]*.

A repository is a secure facility that is used to store samples. The IMPAACT Network has a repository in the United States. However, our local regulations require that leftover samples be stored in our country. Therefore, we will keep the samples here at our laboratory. There is no limit on how long the samples will be kept *[sites may insert time limits or additional site-specific requirements here if required by local authorities]*.

3. Leftover samples could be used for different types of research.

Leftover samples may be used for research on HIV, the immune system, and other diseases. The research may be done in the United States or in other locations.

If you agree, leftover samples could be used for research that looks at your [youth's] genes. Genes are passed to children from their birth parents. They affect how people look and how their bodies work. Differences in people's genes can help explain why some people get a disease while others do not. Your [youth's] leftover samples would be used to look at genes related to HIV and the immune system, mental health, inflammation, immune activation, and vascular dysfunction.

Any research done with leftover samples must be reviewed and approved by the IMPAACT Network. The research must also be approved by an ethics committee. The role of an ethics committee is to review the research plan and protect the rights and well-being of the people whose samples will be used.

The research done with your [youth's] leftover samples that is not expected to give any information relevant to your [youth's] health will not be given to study staff, your [youth's] doctor, you, and will not be placed in your [youth's] clinical and study records.

4. There is little risk to [you/your youth].

When leftover samples are used for research, they are labeled with a code number only. To protect your [youth's] privacy, no names are used. However, information such as age, gender, HIV status, and other health information may be linked to the samples.

There may be some risks from tests of your [youth's] genes. If others found out the results of these tests, they could treat [you/your youth] badly or unfairly. However, this is almost impossible because the results of these tests will only be given to study staff or to you [your youth], and placed in your [youth's] study records, if results are relevant to your [youth's] health.

5. There may be no benefit to [you/your youth].

By allowing leftover samples to be used for research, your [youth] will be part of the search for new information that may benefit people with HIV in the future. However, the research done with the samples may not directly benefit [you/your youth] in any way.

6. You will not be paid for use of your [youth's] samples.

There is no cost to you for use of your [youth's] leftover samples. The samples will not be sold and you will not be paid for use of the samples. It is possible that research done with the samples could lead to a new discovery or a new product. If this happens, there is no plan to share any money with [you/your youth].

7. Information from research using leftover samples may be reviewed by groups that oversee the research.

These groups include:

- The IMPAACT Network
- The ethics committees that review and approve the research
- The United States National Institutes of Health and its study monitors
- The United States Office for Human Research Protections
- Other US, local, and international regulatory entities

The people who do research with the samples and the groups listed above are required to make efforts to information private and confidential.

The results of research done with leftover samples may be presented publicly or published. However, no presentation or publication will use your [youth's] name or identify [you/your youth] personally.

8. If you have any questions, concerns, or problems related to your [youth's] leftover samples, use these contacts.

- If you have questions about use of your [youth's] leftover samples:
  [*insert name and telephone number of investigator or other study staff*].

- If you later change your mind about use of your [youth's] leftover samples:
  [*insert name and telephone number of investigator or other study staff*].

- If you have questions about your [youth's] rights as a research participant or concerns about how [you/your youth] is being treated in the study:
  [*insert name and telephone number of IRB contact person or other appropriate person/organization*].

Signatures

Before deciding whether to allow your [youth's] leftover samples to be used for research, make sure you have read this form, or had it read to you, and that all your questions have been answered. You should feel that you understand your options and the possible risks and benefits before making your decision.

You do not give up any rights by signing this form.

[Insert initial and signature blocks as required by site IRB/EC policies and the IRB/EC determination if the level of risk to children in the categories specified in 45 CFR 46.404-407. Separate consent decisions must be documented for genetic testing.]

Please write your initials or make your mark next to your choices:

_____ I allow my [youth's] leftover samples to be used for research on research on HIV, the immune system, and other diseases. I also allow my [youth's] leftover samples to be used for tests of my [youth's] genes.

_____ I allow my [youth's] leftover samples to be used for research on research on HIV, the immune system, and other diseases. I do not allow my [youth's] leftover samples to be used for tests of my [youth's] genes.

_____ I do not allow my [youth's] leftover samples to be used for any research.

Signature blocks for youth participants who cannot provide independent informed consent

Participant Assent

Name of Participant (print)	Signature of Participant	Date

Parent or Guardian Consent

Name of Parent or Guardian (print)	Signature of Parent/Guardian	Date

Parent or Guardian Relationship to youth participant

Name of Study Staff Conducting Consent Process (print)	Signature of Study Staff	Date

Name of Witness (as appropriate; print)	Signature of Witness	Date

Signature blocks for youth participants of legal age to provide independent informed consent

Name of Participant (print)	Signature of Participant	Date

Name of Study Staff Conducting Consent Process (print)	Signature of Study Staff	Date

Name of Witness (as appropriate; print)	Signature of Witness	Date