Grant Title: Development and Feasibility Testing of an Integrated PTSD and Adherence Intervention Cognitive Processing Therapy-Lifesteps (CPT-L) to Improve HIV Outcomes

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PROTOCOL TITLE:

Development and Feasibility Testing of an Integrated PTSD and Adherence Intervention Cognitive Processing Therapy-Lifesteps (CPT-L) to Improve HIV Outcomes

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1.0 Objectives / Specific Aims

The specific aims of this protocol are to:

Aim 1. (Months 03-12). To theater test and deliver the un-adapted CPT protocol and one session adherence intervention (Lifesteps) with 12 trauma-exposed PLWH presenting for HIV treatment at the MUSC Ryan White Clinic and collect qualitative feedback for modifications to ensure feasible administration and relevant incorporation of HIV-related messages and/or content specific to HIV-related PTSD. Specific activities are to:

A. Test methods and measurement protocol of the beta version of the research protocol.
B. Utilize feedback provided through exit interviews, topical experts, and advisory panel discussion to shape any refinement of the integrated CPT and one session adherence protocol.
C. Incorporate qualitative feedback into the CPT-L manual.

Aim 2. (Months 13-30). To assess feasibility of the modified CPT protocol (CPT-L) compared to Lifesteps in 60 PLWH with comorbid PTSD over 3 months (baseline, post intervention, 3 month follow-up) in a pilot RCT to assess key variables for subsequent efficacy testing (attendance, ART adherence, HIV symptom distress, CD4 count, viral load, PTSD symptoms, avoidant coping). Specific feasibility benchmarks are:

A. Achieve a recruitment rate of 4+ patients per month and retention rate of 80% or higher.
B. Obtain variability estimates of outcomes (less than 10% missing data) and initial indicators of treatment effects for the following hypotheses in the subsequent efficacy trial:
    a. Participants who receive the CPT-L protocol will have improved HIV symptom distress, ART adherence, clinic attendance, and viral load at post intervention and 3-month follow up vs. control.
    b. Participants who receive the CPT-L protocol will report lower PTSD at post intervention and 3-month follow up versus those in the Lifesteps Control.
C. Assess qualitative feedback from exit interviews for high satisfaction, successful saturation of themes, and action plan development, in conjunction with Advisory Board, to refine the intervention for an R01.

Exploratory Aims. 1) We will assess between-group differences in other problems that commonly occur among PLWH and PTSD (substance misuse, depression). 2) Avoidant coping will be examined as a potential mechanism of action for the relationship between CPT-L and improved adherence.

2.0 Background

The prevalence of trauma exposure, and post-traumatic stress disorder (PTSD) in particular, among individuals living with HIV (30-74%)[6,7] is higher than the general population (7-10%).[8] Individuals with co-occurring PTSD and HIV are at high-risk for negative HIV-related outcomes, including low adherence to antiretroviral therapy (ART)[9,10], faster disease progression[11,12], more hospitalizations[13,14], and almost twice the rate of death[15], as well as increased mental health problems.[16] In addition to PTSD resulting from traumatic events, such as sexual and physical assault/abuse, negative reinforcement conceptual models suggest that the avoidant behavior (a hallmark symptom of PTSD) tied to HIV status-related PTSD can also contribute to poor ART adherence and to less success of viral suppression (e.g., by avoiding cues, such as ART medications, that serve as reminders of the HIV status). Despite the high rates of persons living with HIV/AIDS (PLWH) who report PTSD – and the poorer HIV patient outcomes among this population versus those without co-occurring PTSD– evaluation of the impact of evidence-based treatment for PTSD among populations living with HIV <u>on HIV outcomes</u> has been highly neglected in clinical research. In other words, <u>no research to date has examined the critical question of whether HIV outcomes can be improved among the large number of PLWH with co-morbid PTSD and related consequences (e.g., substance misuse) by treating PTSD symptoms.</u> To address this tremendous void in the field, we propose to adapt and examine the acceptability and feasibility of an evidence-based PTSD treatment that has reduced other HIV transmission behavior (e.g., sexual risk), Cognitive Processing Therapy (CPT), at an HIV clinic as a strategy to improve HIV outcomes in this population. We propose to do so in South Carolina (ranked 8th state in the country in 2019 for HIV/AIDS incidence; 11th for prevalence), where PLWH may also encounter additional HIV-related intersectional stigma, itself linked to increased avoidant coping and ART non-adherence.

The multi-disciplinary investigative team housed at the Medical University of South Carolina (MUSC) has leveraged: a) its long-standing relationship with the MUSC Ryan White clinic; b) pilot data collected by PI Dr. Cristina López; c) consultant expertise in the HIV-PTSD link (Dr. S. Safren) and CPT (Dr. P. Resick); and d) an advisory panel made up of stakeholders and consumers (PLWH) to develop the proposed study, which aims to tailor CPT for PLWH with PTSD through integration of an adherence intervention, to demonstrate the acceptability and engagement of PLWH in CPT-L (CPT-Lifesteps), and to assess preliminary efficacy of CPT-L in improved adherence to ART, decreased viral loads, and retention in HIV care.

PREMISE: Although research has demonstrated a clear connection between PTSD and problematic HIV outcomes, the applicability, feasibility, and efficacy of evidence-based treatment for PTSD on HIV outcomes among people living with HIV (PLWH) has not been examined. Cognitive Processing Therapy (CPT) is an evidence-based PTSD treatment that effectively reduces avoidant coping, which similarly has been linked with ART non-adherence among PLWH. Thus, we will demonstrate how the proposed framework of an adapted CPT protocol (CPT-Lifesteps or CPT-L) offers great promise as an intervention to improve HIV outcomes related to quality of life, adherence, and subsequent viral suppression in PLWH by targeting PTSD and avoidant coping.

The proposed research plan is directly in line with several recently emphasized priorities of NIMH (*NOT-MH-20-013, Notice of Special Interest: Mental Health Comorbidities in HIV Prevention and Treatment*; and PA-20-141: *Formative and Pilot Intervention Research for Prevention and Treatment of HIV/AIDS*), the U=U campaign, and the national initiative Ending the HIV Epidemic (EHE) through targeting comorbid conditions.

PTSD is prevalent among PLWH and negatively impacts HIV outcomes. PLWH report higher levels of traumatic events (e.g., child maltreatment, sexual assault, physical assault) than the general population, with trauma exposure ranging from 40-90%.[17,18] Higher rates of traumatic events/exposure correspond with higher rates of Posttraumatic Stress Disorder (PTSD) in this population, ranging between 30-74%.[19,20] Beyond PTSD resulting from more conventional definitions of traumatic events (e.g., victimization, disasters), up to 64% of PLWH endorse PTSD symptoms directly related to HIV diagnosis or other issues related to the disease.[19,21] PTSD is associated with other negative consequences, particularly substance use disorders (SUD) and depression. Lifetime prevalence of PTSD among people with SUDs is 50% compared to 7% in the general population[22,23], and comorbid PTSD and SUD display a worse course of illness, physical health and overall functioning, and increased risk of suicide than individuals with only PTSD or SUD.[24,25] Addressing PTSD can significantly reduce SUD among various populations[26], although this has not been examined among PLWH.

The connection of PTSD (HIV- and non-HIV-related traumas) with problematic HIV outcomes has been well-documented. PLWH with PTSD have been shown to have faster HIV progression[18,27] twice the rate of death,[28] lower ART adherence[29-34], poorer retention in HIV care[35], and increased viral load[36,37] compared to PLWH without co-occurring PTSD. Additionally, HIV-related stigma (community, anticipated, and internalized) is prevalent among PLWH[38] and associated with problematic HIV outcomes (e.g., poor medication and visit adherence[39,40]).

Trauma-focused treatment can be enhanced to address discrimination related to stigmatized identities (e.g., HIV-related intersectional stigma) associated with poorer outcomes in PTSD and ART adherence. HIV-related stigma is shame or disgrace affiliated with HIV and associated with negative health outcomes for PLWH.[55] Fear of being judged by others predicted decreased ART adherence among PLWH[56,57] and internalized HIV-stigma predicted poor ART adherence.[58] Although individual treatment may not decrease society's harmful tendency to stigmatize PLWH **[[**and minoritized subgroups**]]**, trauma-focused treatment may combat internalized stigma and misperceptions or over-anticipation of perceived stigma, thus preventing additional psychological distress and non-adherence linked with stigma.[63]

Despite high rates of PLWH with co-occurring PTSD, the link between PTSD on HIV health related outcomes, and the negative reinforcement conceptual model (e.g., avoidant coping) that provides a theoretical framework for this link, research evaluating evidence-based PTSD treatment among seropositive populations on HIV outcomes is scarce. Gold standard, evidence-based treatments for PTSD, including Cognitive Processing Therapy (CPT)[64], have strong evidence for reducing avoidance

symptoms, as well as traumatic stress, substance use, and depression among civilian and military adults with complex trauma histories.[65,66] CPT reduces trauma-related self-blame and guilt[67,68], two factors intimately tied to avoidant coping. Most importantly, reductions in avoidance symptoms (in the context of traumatic stress symptoms) have been linked to increases in (non-HIV) medical regimen engagement, including medication adherence.[69] Mental health treatment studies in adults with Type 2 diabetes (another chronic disease with self-management and adherence barriers) have demonstrated that interventions leading to mental health symptom reduction showed simultaneous improvements in medication adherence, HbA1C scores, and self-care behaviors.[70,71] Although CPT has been enhanced to target alcohol use and high risk sexual behavior to prevent HIV among American Indian women[72], CPT, nor other gold-standard, empirically supported individual treatments (e.g., Prolonged Exposure/PE)[73,74], have been adapted for PLWH or evaluated as an efficacious approach to reduce problematic HIV outcomes. Thus, there is critical need to examine evidence-based treatments for PTSD among PLWH and co-occurring PTSD to improve HIV outcomes. CPT may be particularly beneficial for PLWH due to the focus on unhelpful cognitions, or "stuck points," in the form of assimilation (beliefs related to self-blame) and overaccommodation (extreme beliefs related to self and world).[64] The flexibility of CPT to focus on unhelpful thoughts and thinking patterns would allow patients to address trauma- and HIV-related intersectional stigma cognitions in treatment. In line with the Undetectable=Untransmittable (U=U) initiative to end HIV-related stigma, this proposal has broad implications not only from a public health standpoint, but also for the self esteem of individuals by reducing HIV-related stigma **[[***and other intersecting stigmatized identities***]]**. Themes addressed in CPT (i.e., safety, intimacy, trust, esteem, power, and control), although originally created from theory on sexual assault, may have relevant overlap to unique issues in disclosing HIV status, and with managing and coping with HIV in interpersonal and intrapersonal domains. **[[***Given that 28-52% of PLWH are estimated to experience cognitive impairment (CI)[75,76], CPT is particularly well-matched for application with this population, as CPT has been delivered successfully with veterans who have experienced traumatic brain injury (TBI), resulting in cognitive and affective symptoms similar to PLWH with CI[77,78]***]]**. CPT dismantling studies have also demonstrated improved engagement and PTSD outcomes among complex and traditionally hard-to-reach populations,[79-81] and can potentially decrease substance use in addition to PTSD symptoms,[82] further supporting the intervention for complex mental health treatment needs of PLWH. Taken together, an empirically supported adaptation of CPT for PLWH (i.e., CPT-L) may improve HIV treatment outcomes for PLWH with comorbid PTSD. This study will address vital gaps by conducting the first pilot RCT to use an adapted evidence-based PTSD treatment, integrated with an evidence-based adherence session, (Lifesteps)[83], to improve HIV outcomes among PLWH with co-occurring PTSD in a geographic jurisdiction identified in Phase 1 of the national End the Epidemic plan. To accomplish this goal, across 3 time-points, we will rigorously measure: trauma history, PTSD symptoms and diagnosis, viral load, CD4 count, stigma, ART adherence, clinic attendance, substance misuse, depression, and avoidant coping.

3.0 Intervention to be studied

Overview of Methods using the ADAPT-ITT framework. The proposed adaptation and pilot RCT follows a 2 (treatment type) × 3 (time points) at the MUSC Ryan White Clinic, ideally situated in the Southeast (i.e., a geographic jurisdiction identified in Phase 1 of EHE; where new HIV contraction rates remain in the top 10 in the US). The ADAPT-ITT model provides a framework for adapting HIV-related evidence-based interventions[111] that is widely used in treatment studies with diverse populations.[112-114] ADAPT-ITT consists of eight phases: (1) Assessment of needs of the target population, (2) Decisions around which empirically supported intervention to use or adapt, (3) Administration of novel methods (e.g., theater testing) to adapt the chosen intervention, (4) Production of a first draft of the adapted intervention, (5) Identification of topical experts, (6) Integration of content provided by topical experts for the second draft of the adapted intervention (7) Training staff to implement the adapted intervention, and (8) Testing the adapted intervention. This model has been successfully applied to the cultural adaptation of several HIV programs[112], including the PI's adaptation of an HIV prevention program for Latina adolescents[103] (Davidson et al, 2014), and provides an empirically supported framework to understand the needs of individuals with comorbid PTSD and HIV and identify the "cultural" components (e.g., **[[***HIV-related intersectional stigma***]]**, chronic disease coping, medication adherence, disclosure stress) that may not be addressed by evidence-based PTSD models. This team has begun initial steps of the ADAPT-ITT framework to determine whether adoption of or adaptation to evidence-based treatment was necessary to address this critical gap in comorbid PTSD and PLWH. PI López and colleagues[100] highlight the need to modify CPT to fully encompass unique needs in the intersectionality of trauma and HIV status.

Research informs Assessment of the problem (i.e., Step 1 of ADAPT-ITT) and indicates that exposure to traumatic events and PTSD are high among PLWH and associated with ART nonadherence.[17,115,116] The Decision (Step 2) to use CPT versus other evidence-based treatments for PTSD was based on the potential for CPT to target reductions in symptoms linked to ART adherence including avoidance, hyperarousal, reexperiencing, and depression.[65-68,117] CPT is not an exposure-based intervention, which may often include a stabilization phase to develop skills for distress tolerance before entering exposure faces of treatment. CPT was chosen because of the cognitive, rather than exposure-based, focus. Specifically, CPT addresses problematic cognitions allowing flexibility to target HIV-related stuck points in addition to trauma-specific stuck points, which is central because stigma may increase risk for PTSD and ART nonadherence. Aims will continue to Execute Step 3 of ADAPT-ITT (administration of unadapted CPT and unadapted Life-Steps adherence) in which theater testing is used to deliver the unadapted interventions sequentially to the new target population (i.e., PLWH with PTSD) and obtaining qualitative data from patients and project therapist on integrating adherence principles throughout the modified protocol. The proposal will include steps 3-8 to Adapt CPT and LifeSteps and Test the integrated version (CPT-Life Steps, or CPT-L) in a pilot RCT delivered 2x/week for 6 weeks (i.e., 12 individuals, 90 minute sessions, with homework assigned).

Interventions

Experimental Condition (Lifesteps + CPT + SOC): Life-Steps for Medication Adherence[83] is a one-session intervention using cognitive behavioral strategies, problem-solving, and motivational interviewing to promote adherence. The evidence-based session has been used as an adjunct in other integrated mental health treatments (5R01MH078571-05).[69,128] Lifesteps content includes psychoeducation on benefits of ART adherence, modification of maladaptive cognitions about taking medications, review of barriers to being adherent, and problem-solving techniques for problematic areas with adherence. Adherence monitoring will be included in weekly check-ins during CPT sessions. Cognitive Processing Therapy (CPT) is an evidence-based PTSD treatment with demonstrated efficacy through several RCT designs and comparators, with vulnerable populations, and for a range of traumatic events (e.g., rape, domestic violence, child sexual abuse, military combat and ACEs). CPT[129] is based on information processing theory and includes education and cognitive components to help patients challenge and modify unhelpful beliefs related to trauma and/or living with HIV. The patient creates a new understanding and conceptualization of the trauma and/or HIV status to reduce ongoing negative effects on current life. CPT begins with PTSD psychoeducation, thoughts, and emotions. The patient becomes more aware of the relationship between thoughts and emotions and begins to identify “automatic thoughts” that may maintain the PTSD and intersectional stigma. In CPT-L, the team anticipates incorporating continuous reminders of the benefits of being ART adherent and identifying potentially maladaptive thoughts about taking medication, thus building on skills implemented in the first session of Lifesteps. In CPT, the patient details in an impact statement how the traumatic event and/or HIV diagnosis has impacted beliefs about self, others, and the world. Next, the patient begins more formal processing of the trauma(s). A detailed account of the traumatic event(s) is used to break the pattern of avoiding thoughts and feelings associated with the trauma. The therapist uses Socratic questioning to question unhelpful thoughts (e.g., self-blaming thoughts) to modify maladaptive thinking (e.g., “I’m unlovable”). Upon developing skills to identify and address unhelpful thinking and internalized stigma, the patient modifies beliefs related to trauma and uses adaptive strategies to improve overall functioning and quality of life. CPT focuses on safety, trust, power, control, esteem, and intimacy, as these are domains affected by trauma, but also with HIV-related intersectional stigma. Currently, potential adaptations in CPT-L based on PI preliminary case study (López et al., 2019), CAB input, and consultant feedback are demonstrated in Table 1. Additional modifications are expected after Aim 1 (steps 3-6 of ADAPT-ITT).

Table 1. Initial Modifications Identified for CPT-L

Session(s)	Intervention component	Proposed revisions for CPT-L from Case studies
Adherence – Life-Steps		
1	Psychoeducational information	Benefits of adherence to ART and evidence-based PTSD therapy
1	Consequences of a missing a dose	No changes
1	Enhance motivation with motivational interviewing	For ART adherence, CPT session adherence, and homework compliance
1	Rehearse Adherence-related Behaviors	Modify non-adaptive cognitions for PTSD therapy session adherence also
1	Solve problems interfering with adherence to HAART	Review potential barriers to session adherence as well

1	Accessibility to providers and obtaining medication	No changes
PTSD Treatment – Cognitive Processing Therapy		
1	Overview of PTSD and CPT	Psychoeducation related to HIV and impact of HIV-related intersectional stigma
2-3	Finding Stuck Points	Identifying stuck points related to HIV-related intersectional stigma
4-5	Processing the Index Event	Distinguish trauma event processing from receiving news about HIV status (potentially additional session if two separate events); Processing stigma from learning of HIV status; Explore trauma related to intersecting identities, e.g., racism-related trauma, gender and sexual identity discrimination
6-7	Learning to Self-Challenge	Examples for in session discussion (disclose problem solving with co-worker, challenging intersectional stigma, handling microaggressions related to intersecting identities)
8-10	Trauma Themes – Safety, Trust, and Power/Control	Checklist related to Disclosure Safety; Regain 'control' of health by challenging intersectional stigma stuck points (e.g. impact of intersectional stigma on trauma themes).
11-12 12+	Esteem, Intimacy, and Facing the Future	Challenging intersectional stigma-related non-adaptive cognitions, Duty to warn review for clinician
Alternatives in Delivery		
Format change	Variable Length	Use "stressor sessions" to discuss stigma-related stuck points, including those related to intersecting identities and discrimination[130] in CPT variable length format
All	Adherence self-monitoring	In addition to risk assessment in CPT, CPT-L could include ART adherence monitoring
XXXX	XXXXX	New component(s) from proposed theater testing and ADAPT-ITT process

The Control Condition: Lifesteps + SOC. Participants assigned to Lifesteps (N=30) will receive the one session Lifesteps intervention in addition to the standard treatment that an individual with a trauma history and co-occurring HIV and PTSD symptoms would receive at a local HIV care clinic (varying levels of case management services and program referrals). **[[***Lifesteps developer and consultant Dr. Safren has successfully trained master's level social work clinicians in the intervention. To protect from contamination, two HIV care case managers with master's level social work degrees will be trained by Safren to deliver Lifesteps to participants in the control condition. Independent raters (as described above) will rate 20% of randomly selected recorded Lifesteps sessions to determine appropriate fidelity.***]]** Interventions delivered as SOC are comprehensive and can include (but not limited to) motivational interviewing, supportive counseling, general mental health interventions, crisis counseling, pharmacist consultation, and case management support. This may include referrals to other community agencies. As with Co-I Danielson's previous SOC protocols, close monitoring of the treatment provided has been incorporated into the study design, and the services/techniques administered in each condition will be closely measured to ensure appropriate evaluation comparisons, including: a) audio-taping and random selection of sessions tapes for audit by 2 independent coders[136] b) participants will complete the Services Assessment[137] at each assessment point; c) Chart review across both conditions and; d) weekly service utilization text message/electronic assessment (see Measurement section).

4.0 Study Endpoints

Study end points for both Aims I and II include: successful study completion, participant consent withdrawal, and PI termination due to failure to adhere to the protocol, loss of contact with the participant, and/or unexpected adverse events.

5.0 Inclusion and Exclusion Criteria/ Study Population

AIMS 1 and II Participant Eligibility Screening

A total of seventy-two,18 years old and older HIV-infected adults currently enrolled at a local HIV care clinic (i.e., MUSC or Roper) and prescribed antiretroviral treatment will be recruited into this pilot study. Potentially eligible participants will be screened through:

- Confirmation of participant's HIV diagnosis, medication retroviral treatment, and attendance an MUSC Infectious Disease Clinic (e.g., Ryan White Clinic, ID Outreach, ID Reproductive clinic), Roper Ryan White Clinic or other SC HIV care clinic through query the clinic's EHR.

- Confirmation that the participant meets clinically significant threshold of DSM-V PTSD criteria as determined by a Clinician Administered PTSD Scale for DSM-5 (CAPS-5) through clinical interview.
- Confirmation that the participant exhibits no significant cognitive impairment as assessed by the adapted virtual Montreal Cognitive Assessment Test (MoCA- Blind [MoCA without the visual element]; in the severe range) and/or through EHR clinic chart review
- Confirmation of that the participant is medically stabilized and/or is not exhibiting active psychosis through EHR clinic chart review.

AIMS I and II: Inclusion criteria

The primary selection criteria for participants in both Aims of the study will be that the participants meet ALL of the following criteria:

1. Individuals that are 18 years and older
2. Linked with and/or eligible for treatment at MUSC, Roper Ryan White Clinic or other SC HIV care clinic.
3. Participant meets clinically significant threshold of DSM-V PTSD criteria as determined by a Clinician Administered PTSD Scale for DSM-5 (CAPS-5) clinical interview.
4. No changes in psychotropic medication within 4 weeks of study enrollment.
5. Able to speak, read, and write English.
6. Meet at least one of the following HIV care criteria:
    a. Diagnosed with HIV in the last 3 months;
    b. Detectable viral load in the last 12 months;
    c. Failed to show up for or missed 1 or more HIV care appointments in the past 12 months;
    d. Last HIV care visit was more than 6 months ago;
    e. Self-reporting less than 90% ART adherence in the past 4 weeks.
7. A score of at least 10 on the adapted Montreal Cognitive Assessment test without visual elements (MoCA-Blind)

AIMS I and II: Exclusion Criteria:

Specific study exclusion criteria include the following:

1. Evidence of significant cognitive impairment as assessed by the adapted Montreal Cognitive Assessment Test (MoCA-Blind; in the severe range).
2. Evidence of developmental delays, or pervasive developmental disorder, or active suicidal or homicidal ideations.
3. Evidence of psychotic symptoms (e.g., active hallucinations, delusions, impaired thought processes).

Rationale for Exclusion Criteria: The proposed intervention(s) would likely not be sufficient for these individuals, who may either have a diminished capacity to benefit from cognitive-behavioral therapy.

Statement on the Inclusion of Women: Participants in the proposed project will be recruited from a local HIV Care Clinic in South Carolina. We anticipate 72 participants for enrollment in the study. Based on the demographic composition of patients engaged in services at the Ryan White Wellness Center, we expect to recruit a sample that is 25% female, 74% male, and 1% transgender.

Statement on the Inclusion of Minorities: The proposed research will include minority and non-minority participants, with no restrictions with regard to ethnic or racial background. Analysis of referral patterns for MUSC Ryan White clinic for the proposed study indicates that 64% of the population study will identify as African American, 4% as Hispanic, and 6% as Other and 50% will include men who have sex with men. Based on these referral rates, we expect that approximately 65% of participants included in the proposed study will be minorities. Study recruitment materials will encourage participants from all racial and ethnic backgrounds to volunteer.

Participant Compensation

Aim 1: Upon enrollment, participants will be reimbursed with a $50 gift card for completing baseline assessments via REDCap and master's level administered PTSD Diagnostic Interview (see Table 2). Participants will receive $50 for completion of post-intervention assessments and $25 for completion of a 20-minute exit interview after completion of CPT sessions. Participants will also receive $5 per photo they submit of their prescription bottle and refill (i.e., self-reported adherence; totaling $15 per participant). Participants will be paid up to $140 for participation in Aim I of the study.

Aim 2: Upon enrollment, all participants will be reimbursed with a $50 gift card for completing baseline assessments at the PTSD Diagnostic Interview. Participants assigned to the intervention group will receive $40 for attending the first session, then $60 for post-intervention assessments and 20-minute exit interview after completion of CPT-L sessions (i.e., post intervention ~6 weeks after study enrollment); and a $75 gift card for 3 month follow up surveys collected online or in person (CAPS can be conducted via telehealth by project coordinator). Participants enrolled in the control group will receive $50 for completing the first set of assessments, PTSD Diagnostic Interview, and for enrolling in the study, and then $40 for completing the Lifesteps session. Then, they will receive $60 for post-intervention assessments and 20-minute exit interview after completion of CPT-L sessions (i.e., post intervention ~6 weeks after study enrollment); and a $75 gift card for 3 month follow up surveys. Participants will also receive up to $15 for self-reported adherence photos. Thus, participants can be paid up to $240 for participation in Aim 2.

6.0 Number of Subjects

In total, seventy-two (72) HIV-infected adults will participate in this study. 12 individuals will participate in study Aim I and 60 individuals in study Aim II.

7.0 Setting

All research activities will take place in-person on-campus at MUSC (College of Nursing (CON), MUSC Ryan White Clinic and the National Crime Victims Center (NCVC) and/or remotely with the use of MUSC secure and HIPAA compliant Information technologies (REDCap for data collection and management, and e-Consent).

8.0 Recruitment Methods

AIMS I and II

Participants under each study aims will be recruited through an MUSC Ryan White/Infectious Disease clinic and across the MUSC Enterprise as well as through the Roper Ryan White Wellness Center and other HIV care clinics in South Carolina. Recruitment will occur through several avenues:

- Infectious Disease (ID) clinicians and staff in the HIV care clinic at MUSC will share an IRB study approved flyer with their patients with trauma backgrounds. The flyer will direct interested and potential eligible participants to contact the study team for more information. Staff at Roper Ryan White Wellness Center will provide minimal information about the project (ex. Title, exclusion/inclusion criteria) and relay interested contact information to the research team.
- Study Staff and investigators will work together to pre-screen potential participants and investigators will determine eligibility. The study team will review existing Infectious Disease Division patient databases or EHR to identify patients who meet inclusion criteria. EMR review will be used for pre-screening purposes, but data will not be extracted/recorded from the medical record unless the subject signs an informed consent form.
- Patients that are identified through the trauma screening questions (Primary Care PTSD Screener for DSM-5 [2]) included in the Ryan White clinic intake procedures will be handed a study flyer directing interested and potential eligible participants to contact the study team for more information. Patients can fill out an electronic version of the trauma screener though RedCap.
- Study Flyers will be posted in the general patient waiting room areas of HIV care clinics directing interested and potential eligible participants to contact the study team for more information.

Advertisements will be used throughout the South Carolina area providers that take care of the HIV population as well as social media advertisements with community partners.

- Infectious Disease providers and staff will distribute eligibility survey to potential participants via e-mail as a way to identify potential eligible participants
- We will be utilizing a cold-call method as part of our recruitment plan. We will be submitting a Research Data Request to obtain a recruitment report of MUSC patients who potentially meet eligibility criteria. The study team will not cold-contact any patients who have opt-ed out of receiving contact about research or who have met the maximum number of contact attempts at the time of recruitment. The study team will reach out to potentially eligible participants via e-mail, text, or mailed letter.

Interested patients will be contacted by the Study Coordinator or PI and provided with more information about the study. If interested, participants will then complete informed e-consent. After consent, participants will have their EHR chart reviewed and complete a structured diagnostic clinical interview to assess clinical threshold of DSM-V PTSD (CAPS) to confirm eligibility prior to enrollment.

9.0 Consent Process

Prior to consent, the adapted MoCA-Blind (without visual elements) will be administered to the potential participant as part of the pre-eligibility process; and no PHI will be gathered during it's administration. Research activities will not be conducted without documentation of the adult participant's written informed consent. The informed consent process with take place either in-person at an MUSC Ryan White/Infectious Disease facility in the privacy of a clinic room or remotely via MUSC IRB approved REDCap e-Consent with the participant at a location of their choosing. As this study uses e-CRFs, all study participants will have their consented documented using MUSC IRB approved REDCap e-consent.

Informed consent will be conducted by members of the study team that:

1. are independent of the participant's clinical treatment team;
2. have received UM CITI training in both the Conduct of Human Subject Research and Good Clinical Practice;
3. are designated to perform this process on the PI Delegation of Responsibility log; and,
4. are IRB approved study personnel.

Additionally, these individuals will attend a 1-day training given by the PI on how to provide information about the study and on how to obtain consent for participation in the study (i.e., informed consent), and will role play with the PI until competency is demonstrated in this area. This is so that each person collecting informed consent is familiar with all study aspects and potential questions and issues that may arise among this target population. Training for the assessor (i.e., master's level project coordinator) on the clinical diagnostic interview (CAPS) will include fidelity monitoring until reliability is achieved [4].

During the consent meeting (both in-person and remotely), potential and pre-screened eligible participants will already have spoken with the researchers and been introduced to the opportunity to participate in the study. Additionally, they will have had as much time as requested to read the consent document prior to scheduling the meeting per their individual preference. During the meeting or call, the researcher will review the consent document in its entirety and be available to further answer any and all questions that the participant may have prior to the individual adding their respective signature to the form and submitting the e-consent. Participants will be asked to demonstrate an understanding of the demands of the study by being asked to provide a summary of the main study procedures. The informed consent document will be reviewed with individuals that initially exhibit less than full comprehension until an understanding is gained. Individuals that do not gain an understanding or demonstrate cognitive impairment will be excluded from study participation.

Upon submitting the e-consent, a REDCap trigger will immediately notify the researcher, who will then provide their countersignature to the eCRF while they are physically present with the participant or remotely available on the phone to the participant during this entire process. All e-consents will be maintained in the REDCap study e-consent database for regulatory purposes and compliance

monitoring. All participants will be electronically sent a copy of the fully executed e-consent form to their email address. Hard copies will be printed out and/or mailed to participants upon request. In the case of in-person consenting, research staff will set-up a meeting with the participant at a time per their preference at a community yet private location and follow the same consenting procedures.

10.0 Study Design / Methods

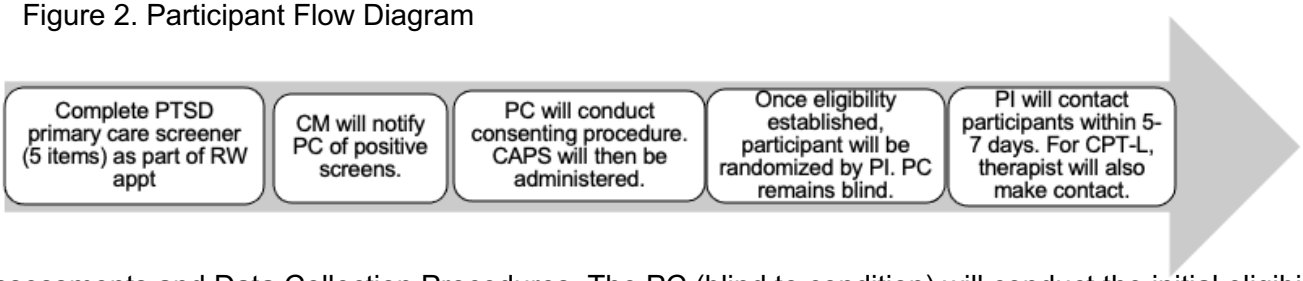
Theater testing (Aim 1) is a pretesting methodology to assess consumer response to a product[118] and has been successfully implemented to assess participants' reactions to HIV-related interventions.[111-113] Using this approach, members of the target population participate in original versions of the evidence-based intervention (e.g., unadapted CPT) and provide feedback to guide intervention refinement, to enhance relevance and efficacy for the new target population.[111] As part of theater-testing, participants will each complete a brief qualitative interview of open-ended questions with follow-up probes at the end of every session to elicit (1) impressions about the un-adapted content (e.g., helpfulness, relevance, language and word choice, homework content), (2) perceptions about the need to adapt content and (3) potential adaptations participants would like incorporated (e.g., different role plays, modified examples). Interview responses will be recorded and coded by two independent coders. Following theater testing with **12** cases (≥18 yrs. old, PLWH with PTSD; step 3 of ADAPT-ITT), which was determined based upon saturation rates from previous similar studies, the team will analyze and integrate qualitative findings using content analyses, where a three-step inductive approach will identify and describe major themes that emerge from the interviews to derive categories from the data.[119] Recommendations from the CAB will be incorporated and brought to the study team, to discuss and finalize what recommendations will be applied and incorporated to develop an adapted protocol (CPT-L; Step 4, Produce a manual). In Step 5, Topical experts (e.g., HIV stigma researchers, Adherence interventionists/experts) and CAB members will review the adapted protocol, providing feedback through individual qualitative interviews to determine if content is relevant and if data from theater testing has been adequately incorporated. The research team will Integrate expert feedback into refinement of the protocol (Step 6 of ADAPT-ITT). Consultants Safren (Life-Steps developer) and Resick (CPT developer) will review CPT-L to ensure adherence-based interventions have been incorporated and stigma-related examples adhere to CPT.

In Aim 2, steps 7-8 of ADAPT-ITT will be completed. The project therapist is trained in evidence-based PTSD treatment, including CPT, thus Training in the integrated CPT-L protocol (step 7) will be relevant for adherence and stigma adaptations. For Testing the adapted intervention (step 8), we will randomize **60 adults** aged 18+ who meet DSM 5 criteria for PTSD and present for treatment at MUSC, Roper Ryan White Clinic, or other HIV care clinic, to either CPT-L + standard of care (SOC) or Lifesteps only + SOC. Participants must have experienced at least one traumatic event and report current clinically significant PTSD symptoms (via CAPS clinical interview[89]). Participants randomized to experimental condition (CPT-L; N=30) will be assigned to the project therapist (trained and supervised in CPT-L). Participants randomized to control condition will receive the unadapted Lifesteps session as well as SOC (measured via chart review), which includes supportive services typically received by PLWH identified as suffering from PTSD. Assessments will be conducted at pre- and post-treatment, and 3-month post study-entry. Outcomes for efficacy testing in the subsequent R01 will be collected, including viral load, ART adherence, clinic attendance, PTSD diagnosis and symptoms, avoidant coping, substance use, and depression.

Randomization Procedures. For Aim 2, we will use an adaptive randomization procedure (urn randomization) to balance confounding variables among participants in each condition.[127] Factors on which the adaptive randomization procedure will operate are viral load and self-identified gender. Computerized urn randomization will use an adaptation of Microsoft Access application gRand (used by Co-I Danielson). Efforts will be made to keep the project coordinator (PC) blind to condition, therefore, PI López will randomize participants. Participants will be randomized following consent and baseline assessment (to determine severity of symptoms for the urn) to one of two conditions: (1) CPT-L + Standard of Care (SOC) or (2) Lifesteps + SOC. Within 7 days of interview and PI's randomization, the PI will contact the participant to inform him/her of condition. Case managers will do phone check-ins between sessions to encourage attendance and provide referrals and information to individuals in both CPT-L and Lifesteps groups. Individuals in the Lifesteps condition will receive the one-session adherence intervention in addition to any other standard treatment that a PLWH with PTSD symptoms would typically receive at a HIV care clinic. SOC treatment will vary in type, duration, and frequency (e.g.,

spiritual counseling, crisis hotline phone call, resource help for case manager,), but will be measured carefully across both conditions through coding of chart review and weekly electronic dairy assessment of service utilization (methods used successfully by Co-I Danielson in prior RCTs[85]) to account for Treatment dosage. Baseline, post-intervention and follow-up assessments will be collected by the PC. In the CPT-L condition, the PI, assigned case manager, and project therapist will make contact within 7 days of randomization. Participants in the control condition will be contacted by one of the Lifesteps-trained HIV care case managers.

Figure 2. Participant Flow Diagram



Assessments and Data Collection Procedures. The PC (blind to condition) will conduct the initial eligibility (baseline) diagnostic assessments and all study assessments. The CAPS will be audio-taped and study personnel will listen to a randomly selected 20% to ensure reliability of CAPS diagnosis over the course of the study. The PC will administer the battery in the HIV care clinic or remotely by phone to the participant, based on participant preference. All timepoints will be collected on all participants, even if they drop out of treatment. Pilot trials indicate that major assessments take between 1.5 – 2 hours to complete. Individuals will be given $50 for completing the baseline interview, $40 for attending the first session, then $60 for post-intervention assessments and 20-minute exit interview after completion of CPT-L sessions (i.e., post intervention ~6 weeks after study enrollment); and a $75 gift card for 3 month follow up surveys. Several questionnaires were drawn from the PROMIS common data elements and NIH sponsored repositories to promote data sharing (e.g., PROMIS depression and BRICS Social Determinants of Health). Participants will complete a brief electronic diary on a weekly basis to assess use of resources/additional supports. Research has demonstrated the validity of this approach, including capturing “real-time” data beyond what can be captured with retrospective reports.[139] Surveys (≤1 minute each) will be electronically collected once a week for the 6 weeks of the intervention period starting one week after randomization (i.e., 6 electronic survey entries), leading up to the 3-month follow up. With input from the CAB, we have established procedures to auto-send an email or SMS text (participant choice) on a set schedule. SMS text messaging is possible via Twilio, embedded within our REDCap system, which allows participants to complete a survey directly from their phone, without having to access a webpage.[139] Participants will be asked permission for the study team to access electronic medical records to collect CD4 count and viral load at the time of enrollment. As an attending physician in the clinic, Co-I Eckard is familiar with these electronic records and will oversee the data pull. CD4 T-cell counts and HIV viral load will be measured as standard clinical practice using standard clinical assays (HIV viral load less than 200 considered virologic suppression. Relevant data from the clinic’s electronic medical record (e.g., CD4 count, no-shows) will be collected at intervals and study completion (i.e., 6 months after participation) to document retention in HIV clinical care using the industry standard[140] of 2 appointments with a provider with prescribing privileges per year, no longer than 6 months apart. PI López has planned for adequate staff training and coverage based on experience. The PI will assist in training research staff on consent, diagnostic interview, assessment measures, and medical chart data retrieval (with Co-I Eckard and Co-I Danielson for service utilization data) and will conduct weekly meetings, quarterly reviews, and booster trainings to ensure standardized procedures. See Table 2 for research instruments.

Table 2. Research Instruments

Assessment	Res.	BL	Post	3 mon*	weekly	Description
Demographics questionnaire	P	x				Data collected from participant after consent
BRICS NINR Social Determinants of Health	P	x				18-items assess financial resource strain, physical activity, social connectivity/isolation, safety, family income.
MOS Social Support Survey	P	x				19-items assessing different types of support (emotional/informational, tangible, affectionate, and positive social interaction

[[*Montreal Cognitive Assessment Test (MoCA)***]]**	P					**[[***A brief 10-item screening tool developed to detect cognitive impairment that measures 8 cognitive domains, takes 5-10 minutes to administer (Nesdarrine et al., 2005), and has been tested in PLWH (e.g., Janssen et al., 2015; Koski et al., 2011).***]]** MoCA-Blind (without requiring visual elements) will be conducted prior to consent as part of the pre-eligibility process.
HIV, Trauma, PTSD, and Related Outcomes from Clinical Interview and Self-Report						
ART adherence (self-report)	P	x	x	x		ACTG trial adherence measure self-report of medication within the last 4 days and self-efficacy.
Saberi Method Adherence	P	x			X (week 4 and week 8)	Another method for ART adherence through collecting self-rated adherence (SRA), Pill count based adherence (PCA), and Proportion of days covered (PDC). PCA and PDC will be collected by the participant sending a text photograph of pharmacy refill and remainder of pills to a MUSC approved study cell phone. SRA, PCA, and PDC will be collected at Baseline, Week 4, and Week 8.
HIV Quality of Life (WHOQOL-BREF)	P	x	x	x		A 26-item measure categorized into four domains (i.e., physical health, psychological well-being, social relationships, and environment); measures effects of disease and health interventions on an individual's perception of quality of life and assesses changes in quality of life across treatment.
HIV stigma measure	P	x	x	x		Developed by Berger et al. (2001)[141], revised by Bunn et al. (2007)[142]; multiple dimensions of stigma
[[*Everyday Discrimination Scale***]]**	P	x	x	x		**[[***Developed by Williams et al (1997), 10-item self report measure is a common approach to measuring intersectional stigma (Turan et al. 2019) by asking parallel questions related to different identities.***]]**
CAPS PTSD Diagnostic Interview	PC	x	x	x		A 30-item structured clinical interview to derive PTSD diagnoses, but also provides PTSD intensity scores. Considered the gold standard in PTSD assessment and corresponds to DSM-5 criteria for PTSD. Interview items focus on symptom presence, onset and duration of symptoms, subjective distress, impact of symptoms on social and occupational functioning and improvement in symptoms
Life Events Checklist (LEC-5)	P	x		x		Assesses exposure to 16 events known to potentially result in PTSD and includes one additional item assessing any other extraordinarily stressful event not captured in the first 16 items.
PTSD Checklist (PCL)	P	x	x	x	x	Corresponds to current DSM-5 PTSD criteria; 20-items scored on a 0-4 Likert scale for each symptom corresponding to "Not at all" to "Extremely". Psychometric data demonstrates good internal consistency (α =.96) and test-retest reliability (r = .84).
Emotion Regulation Questionnaire (ERQ)	P	x	x	x		Consists of 10 items capturing two emotion regulation strategies, cognitive reappraisal and emotion suppression on a 7-point Likert scale ("1" strongly disagree, "4" neutral, and "7" strongly agree).
Substance use: AUDIT; DAST	P	x	x	x		Each self report consists of 10 items; excellent reliability and convergent validity.
PROMIS Depression A-6 items	P	x	x	x		Assesses negative mood (e.g., sadness, guilt), views of self (self-criticism), social cognition (loneliness), decreased positive affect and decreased engagement (loss of interest, meaning).
Patient Health Questionnaire (PHQ-9)	P	x	x	x		Validated for use to monitor the severity of depression and response to treatment; scores major depressive episode criteria as "0" (not at all) to "3" (nearly every day).
Participant Treatment Engagement						
Treatment Expectancy Scale	P				x (first wk.)	6-item scale assesses patient expectancy for the intervention to improve their lifestyle/functioning.
Credibility Expectancy Quest.	P	x				Assesses how much participant believes that the intervention will reduce their mental health symptoms.
Engagement in Session	CM				x	Research clinician rates on a 1 to 5 scale on total patient engagement, cooperation.
Services Tracking Form	P	x	x	x	x	6 items (McLellan et al., 1992)[137]; records type and amount of services engaged in for PTSD symptoms, including mode (group, individual couples, family, self-help, medication) and # of hours in each service.
Support Electronic Survey	P	x	x	x		Captures more ecologically valid data than retrospective recall at three data assessment points (0, post intervention, 3 month follow up), support services will be collected via REDCap survey from baseline until 3 month follow up across both conditions.
Electronic Medical Record Data						
CD4 count	PC	x	x	x		We will use clinic lab test (standard clinical assays) results for our data.
HIV care appointment adherence[†]	PC	x		x		Electronic medical record data coding at end of study for clinic appointment attendance with a provider with prescribing privileges
Viral load	PC	x	x	x		We will use standard clinical assays (collected for clinical purposes). An HIV viral load less than 200 will be considered consistent with virologic suppression.

Services Chart Review	PC	x	x	x		PC will use the same Services Tracking Form to capture data on service utilization entered by case managers of SOC and CPT-L participants in the electronic medical record.
Treatment Assessment						
Clinician Survey on PTSD	PC	x	x	x		Assesses therapist experience and attitudes (completed by the project therapist before training, after training, and at 3-month intervals throughout the trial)
Therapist Fidelity Checklist	CM				x	Checklist used by Drs. Resick and Safren in CPT and Lifesteps protocol studies.
Reactions to Treatment						
Client Satisfaction Questionnaire-8	P		x			Likert scale with 8 items that has been standardized to investigate client satisfaction.
Acceptability	P		x			At the first assessment following treatment graduation or discontinuation, participants will complete a survey (1 = strongly disagree to 4 = strongly agree) on their satisfaction (with intervention, therapist, frequency, length of sessions, with amount of confidentiality and respect received); ratings of usefulness of each session; perceived barriers, general experience with the study, likelihood of recommending the study to other patients, and suggestions for improving treatment.
Working Alliance Inventory-Short Revised (WAI-SR)	P		x		x (wk 3; mid treatment)	Assesses three key aspects of the therapeutic alliance: (a) agreement on tasks of therapy, (b) agreement on goals of therapy and (c) development of an affective bond.
Exit Interview	PC		x			Conducted with PC to avoid potential impression management bias. "what are advantages/ disadvantages of getting referred to PTSD treatment, do family members support you, barriers to participation, are there steps in place to help with participation, what were previous barriers to PTSD treatment; would you recommend this to others; how can this intervention better fit your needs, etc."
Summative Exit Interview	AP		x			A research team member will guide CAB members to understand their reactions to the training and treatment models, perceived fit and usefulness within HIV care clinic treatment settings, identified implementation barriers/facilitators, and recommendations to improve larger scale trial procedures

Note. Res = Respondent; P = Participant; CM = Case Manager; PC = Project Coordinator; AP = Advisory Panel; BL = Baseline
* Collected in Aim 2 participants
† Adherence will be collected up to 6 months after participant completion

Impact and Future Directions. Evaluating evidence-based trauma treatments to target specific needs of hard-to-engage populations will significantly impact public health by improving patient outcomes, engagement, and medication adherence across pathologies and health promotion efforts. This study will provide valuable data for PLWH by establishing the protocol for increasing ART adherence and retention in care through an adapted PTSD treatment, CPT-L.

12.0 Data Management

Sample size, Statistical Power and Analysis

Sample size justification. As the study is designed to demonstrate feasibility, sample size was determined based on pragmatic considerations, rather than formal power analysis.[143] The study plans to enroll 60 PLWH randomized to CPT-L or Lifesteps.[144] This sample size is adequate to assess feasibility outcomes (enrollment, attrition, retention, adherence to protocol and fidelity). The sample size recruited during our recruitment period (18 months) will allow the team to specifically justify that we can approach a reasonable sample for a larger RCT in an expanded recruitment period. Further, with a target retention rate of ≥90%, an enrolled sample of 60 participants produces a 95% confidence interval from 82% to 98% and an adherence rate of 80% will produce a 95% confidence interval between 70% and 90%. The study will produce both within and between treatment group estimates of visit attendance (yes/no), ART adherence (85% of doses taken), and proportion of detectible viral load (yes/no). Further, if mean HIV Symptom Severity, CD4 cell counts, PCL and CAPS-5 scores will be assessed post-intervention and a sample of 30 participants in each group will provide adequate power to determine estimated a confidence interval with a difference of ½ a standard deviation (0.51 SD) of the between group mean estimate. If the difference in proportion of participants with detectible viral load is 10% in the CPT group and 20% in the SOC Lifesteps group at the close of treatment (10% difference), the sample of 30 participants in each study group will provide an 18% confidence interval on either side of the estimated difference.

Data Analysis Aim 1. All therapy sessions and exit interviews will be audio-recorded and analyzed using NVivo12 software by PI Moreland for unique and essential elements to improve the protocol (or CPT intervention). Qualitative data analysis is inductive, iterative, and eclectic.[145] Qualitative content analysis, specifically latent and manifest content analysis[146], will be used to identify and describe major themes and sub-themes that emerge.[121,147] This is a dynamic type of analysis oriented toward recognizing, coding and categorizing patterns from text data.[121,147] Manifest content analysis involves the visible, obvious components of what the transcript says; latent content analysis involves an interpretation of the underlying meaning of the text. Methods are utilized to explore participants' unique perspectives via identification of themes/patterns that naturally emerge from the data and systematic classification of these themes. [[*In qualitative analyses, independent coders will immerse together with their analyses to confirm themes and resolve any divergent analyses through a reconciliation and refinement process*.]] Co-I Moreland has utilized this qualitative approach in 8 federally funded studies, where she has published[106, 148-152] and presented peer-reviewed findings utilizing qualitative data. PI Moreland will review emerging themes with the study team, CAB members, stakeholder, and topical experts to incorporate data from qualitative interviews into each step of the refinement process.[153] Consultants Resick and Safren will ensure fidelity to manual for any suggested changes to CPT-L. Data collected will provide the pathway to improve the protocol and ensure feasibility and acceptability. Contingency Plan. Completion of Aim 1 will allow refinements of the integrated protocol of CPT-L for Aim 2. PI López has assembled a team with extensive expertise in recruiting high-risk and difficult to engage participants in both PTSD and PLWH (Co-Is Danielson, Moreland, Eckard; Consultant Safren) and in feasibility testing for clinical interventions (Consultant Safren, Resick, Co-I Danielson). Low acceptability in Aim 1 will prompt meetings with the CAB to make modifications before implementing Aim 2. Any unanticipated challenges to feasibility will be addressed by the qualitative analyses and the approach will be refined. Exit interviews will provide suggestions to improve the protocol. Data will be examined to find whether specific factors explain differential effects among participants.

Data Analysis Aim 2. Descriptive analyses will characterize the entire sample and two conditions as appropriate using measures of central tendency or frequency distributions and proportions. Feasibility will be determined by patient willingness to be screened, proportion of participants meeting PTSD criteria, and flow of participants through the study. Feasibility of assessments will be examined through self-report and medical record abstraction. While CPT has been evaluated in other populations, acceptability within PLWH is important for feasibility data. Intervention feasibility will be monitored through randomization, session attendance and quality assurance data collection on intervention fidelity and supervision. Exit interviews will be analyzed using the same techniques for qualitative analyses described for Aim 1. Study feasibility will be determined by ability to adequately randomize and retain study participants throughout study intervention and follow-up, determined through ability to successfully randomize 4+ patients per month and retain 90% of randomized patients throughout the study. In addition to retention, a low rate of missing primary outcome data (≤10% missing) will demonstrate ability to integrate the intervention with standard clinical care components and medical health records. Protocol adherence will be monitored weekly and reported as the proportion of weekly PCL checklists completed, and distribution of clinician rated treatment engagement and cooperation levels. Acceptable protocol adherence will be determined by completion of ≥80% of assigned weekly PCL checklists across participants.

In addition to feasibility, efficacy and adherence outcomes will aid in development of the subsequent R01. Parameter and variability estimates of efficacy outcomes will be derived from appropriate statistical models. Specifically, HIV symptom distress (physical and mental), CD4 cell counts, viral load, clinic attendance and ART adherence will be measured at pre- and post-intervention and 3-month follow-up. Proportion of participants with Clinic attendance (yes/no), ART adherence (yes/no), and detectible viral load at the end of treatment and follow up will be compared between study groups using a modified Poisson regression approach with a robust sandwich variance estimator.[154] Initial analytic models for binary outcomes will include the primary treatment effect, study visit and interaction of study visit and treatment as well as variables used to balance the randomization procedure. Adjusted models will explore the additional baseline covariates significantly associated with outcomes. The proportion successful in each treatment group at each visit, the relative risk of success and associated 95% confidence interval will be reported. We anticipate that treatment will decrease CD4 cell counts and HIV

symptom severity more so in the CPT-L group compared to Lifesteps at the follow up clinic visit. Treatment group differences will be assessed using generalized linear models adjusted for baseline cell counts/symptom scores. Normality of model residuals will be assessed using Q-Q plots and data transformations will be performed as needed. The CAPS-5 and PCL will examine PTSD severity at baseline, post-intervention and 3-month follow-up. The PCL will be assessed weekly during study intervention and follow-up. Rates of change from baseline to post-intervention and follow up will be estimated with generalized linear mixed effects regression models. Linear slope trends over time and associated standard errors will be calculated for each treatment assignment using a single model for all data. Estimated CAPS, PCL, and HIV symptom severity scores and associated standard error estimates will be calculated for each study group at each study visit and effect size estimates (Cohen's *d*, partial eta^2) will be tabulated and reported. As PCL scores are measured weekly, non-linear mixed effects models will be fit to not any cubic or quadratic trends that occur during study treatment and estimates of when treatment efficacy begins to show changes in effect size will be assessed and reported.

Exploratory investigations of substance use/misuse will be collected using the AUDIT and DAST. Changes in the proportion of participants reporting substance use between groups following study treatment and follow-up will be compared using modified Poisson regression models adjusted for baseline use and study treatment. Continuous AUDIT and DAST scores will be assessed in those who report use and compared between groups using generalized linear mixed effects models. Depression will be assessed at the same time points using the PROMIS Emotional Distress-Depression short form. Both raw and prorated T-scores will be assessed at each timepoint and treatment group comparisons will be made using generalized linear mixed effect models, adjusted for baseline PROMIS scores and study visit. Exploratory models will be adjusted variables used to balance the randomization procedure and those correlated with study outcomes. Secondary analysis of additional measures (QOL, HIV Stigma, Intersectional Stigma, ERQ) will be assessed between study groups using appropriate statistical methods. Analyses will be conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Exploratory Investigation into Moderators and Mediators. Baseline measures of sex and gender identity as well as history of viral suppression will be assessed as treatment moderators of feasibility, HIV and PTSD outcomes. Moderation will be assessed utilizing addition of interactions into models described above. Although not specifically powered to detect statistically significant interactions, interaction and stratified effect sizes will be presented. Effect sizes will inform relevant hypothesis for future R01 study development. We hypothesize that changes in PTSD-related avoidant coping following the intervention will mediate the relationship between treatment and HIV outcomes at follow up (CD4 Cell Counts, HIV Symptom Severity, ART adherence). Mediation models will estimate indirect and direct effects as well as the proportion mediated using the PROCESS macro.[155] Bootstrap resamples (1000 resamples) will provide point estimates and confidence intervals of the mediating effect of changes in avoidant coping on the relationship between treatment with CPT-L and HIV related outcomes. Feasibility for the subsequent R01 is needed to demonstrate that data can be successfully collected to analyze proposed efficacy and mechanism testing hypotheses (see Form F for Proposed RCT analyses).

Data Capture and Management. This study will use Research Electronic Data Capture (REDCap) for data capture and management. REDCap is a software toolset and workflow methodology for the electronic collection and management of research and clinical trials data. REDCap provides secure, web-based, flexible applications, including real-time validation rules with automated data type and range checks at the time of data entry. Exports are made available for several statistical packages including SPSS, SAS, SATA, R and Microsoft Excel. The study-specific REDCap database will be designed and developed by MUSC research team. The provision of REDCap is made available through the South Carolina Clinical & Translational Research (SCTR) Institute at MUSC with NIH Grant awards UL1RR029882 and UL1TR000062. The recruitment report will be stored in REDCap but will be separate from the research database. Only IRB approved study personnel will have access to the recruitment report. The study team will lose access to the recruitment project at the conclusion of enrollment. The recruitment REDcap will contain both identifiers and health information in the same project.

Regulatory Binders. The MUSC PI will prepare and maintain an electronic regulatory file to include the IRB-approved protocol, IRB correspondence, approved study advertising, and other required study-related regulatory documents.

Deidentification of the research record, data sharing, and retention. At the end of all study activities and upon study closure, the electronic study record will be stripped of any and all personal identifiers. Deidentified data will be maintained per MUSC Records Retention Policy for a period of 6 years for Federal studies before destruction.

13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

DATA SAFETY MONITORING PLAN
The Principal Investigator (Dr. López), with support from Co-Investigators, will be responsible for monitoring the safety and efficacy of this trial, executing the Data and Safety Monitoring (DSM) plan, and complying with the reporting requirements. Data are randomly inspected weekly and inspected thoroughly on a quarterly basis. Dr. López will provide a summary of the DSM reports to NIH/NIMH on an annual basis as part of the progress report. All DSM reports will include a brief description of the trial, baseline sociodemographic characteristics, retention rates and disposition of study participants, quality assurance issues, regulatory issues, AEs and SAEs, as well as any actions or changes with respect to the protocol. The DSM report to NIH will also include, when available, the results of any efficacy data analysis conducted.

SECTION A. Monitoring Entity.
Considering the study rationale, population, intervention and control procedures, and the risk: benefit profile as outlined, the overall risk level for participation in this study is viewed to be classified as: **Minimum Risk.**

DSM Plan Administration
A Data Safety and Monitoring Board (DSMB) will be assembled. The DSMB will act in an advisory capacity to the PI to monitor participant safety, to evaluate the progress of the study, and to review procedures for maintaining the confidentiality of data, the quality of data collection, and data management and analyses. Frequency of meetings of the DSMB will be determined by recruitment milestones (e.g., after 25% of participants have been recruited, etc.), and will follow each SAE report, but meetings will occur no less than once per year. The purpose of these meetings will be to review study progress, data quality, and participant safety.

The DSMB will be made up of professionals with appropriate expertise, who are willing to participate, and who do not have any conflicts of interest. The DSMB will include: 1) one expert in the area of PTSD treatment, 2) one expert in the area of adherence intervention, 3) a statistician with expertise in feasibility measurement, and 4) two members with expertise in the area of HIV care. DSMB membership will be reviewed and approved by the MUSC IRB and NIH. Should there be any questions regarding the independence of the DSMB, it will be addressed and corrected, if necessary, at that time.

Conflict of Interest for DSMB
DSMB members will have no direct involvement with the study investigators or intervention (e.g., no portion of their effort will be covered by the study). Each DSMB member will sign a Conflict of Interest statement which includes current affiliations (if any) with pharmaceutical and biotechnology companies (e.g., stockholder, consultant), and any other relationship that could be perceived as a conflict of interest related to the study and/or associated with commercial interests pertinent to study objectives. Data will be presented in a blinded manner during the open sessions of the DSMB. At DSMB meetings, data and discussion are confidential. Participant identities will not be known to the DSMB members.

DSMB Responsibilities
The responsibilities of the DSM for this study are as follows:
- Review the research protocol, informed consent documents, and plans for data safety and monitoring;
- Evaluate the progress of the pilot trial, including periodic assessments of data quality and

timeliness, recruitment, participant risk versus benefit, performance of the trial site, and other factors that can affect study outcome;
- Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study;
- Review study performance, make recommendations and assist in the resolution of problems reported by the Principal Investigator;
- Protect the safety of the study participants;
- Make recommendations to the Principal Investigator concerning continuation, termination, or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
- Review interim analyses (The interim data analyses will only include safety related results; analyses in regards to study outcome will not be performed. The interim AE reports will provide typology, frequency data and outcomes of all reported and documented AE in the electronic study database);
- Ensure the confidentiality of the study data and the results of monitoring;
- Assist the PI by commenting on any problems with study conduct, enrollment, sample size, and/or data collection;
- The DSMB will have the authority to temporarily or permanently discontinue the study if it perceives that harm is occurring due to the intervention. The DSMB statistician will evaluate the confidentiality and integrity of the database and the procedures for recording and storing confidential files. The DSMB will also review the elements of the plan to manage emergencies.

SECTION B. Procedures for Safety, Risk and Confidentiality

1) Monitoring Study Safety

From the initial screening of the participant by inclusion and exclusion criteria to the informed consent process to the provision of participant study instruction to staff training in Good Clinical Practices (GCP) and regulations pertaining to the Conduct of Human Participant Research to weekly contact with participants to internal monthly quality control audits and protocol fidelity monitoring to the real-time review of AE by the DSM to the oversight of MUSC's IRB, procedures for monitoring study safety are consistently afforded throughout study. Specific procedures include:

- Participants will be screened for inclusion and exclusion per the protocol; the PI or project coordinator (PC) shall verify 100% of participants' eligibility prior to study enrollment through review of inclusion and exclusion criteria with potential participants.
- Participants will be fully informed as to all known risks and the possibility of risk from study participation in the informed consent process. These risks are minimal.
- Participants will be instructed to notify the researchers of any/all suspected or experienced adverse events whether they believe them to be related or not to the intervention.
- The PI or PC will track all reported participant AEs through to resolution. Please see Section C. 1 – 4.
- All investigators and research staff will maintain active CITI training.
- The PI or PC will maintain weekly contact with all participants to elicit information about AE's and to monitor participant study progress, compliance and safety.
- The PI or PC will review participants study logs for fidelity compliance with the CPT-L and Lifesteps Protocols.
- The PI or PC will conduct a monthly internal quality control audit of all participant records to ensure compliance with MUSC IRB regulations; the PI and PC will work together to correct any errors.
- The PI and/or designee will observe and evaluate ten (10%) percent of eligibility screening visits, informed consents and study instructions performed by IRB approved study personnel and provide feedback and/or retraining of study personnel if fidelity to both applicable federal regulations and the protocol is not observed.
- The DSMB Biostatistician shall generate semi-annual AE reports for the PI and DSMB to review.
- Investigator performance and compliance will be provided for through MUSC IRB and ORI study oversight.

2) Minimizing Research-Associated Risk

Diligent study safety monitoring will be conducted by the PI and the study's DSM team throughout the conduct of this study in compliance with the following required elements of MUSC IRB's continuing review process:

1. Tracking and follow-up of participant accrual (inc. withdrawn consents) will minimize risk by identifying, disclosing, and mitigating any potentially unknown risk(s) of harm to study participants. These risks are minimal.
2. Timely and appropriate reporting of informed consent process deficiencies, protocol deviations, privacy breaches, conflicts of interest, and/or changes in personnel.
3. Ongoing soliciting, monitoring and appropriate reporting of adverse event activities.
4. Timely and appropriate IRB submission of safety-related documents such as audit reports, sponsor progress reports, ISM reports, and other materials or communications that might impact the safe conduct of this study.
5. Active cooperation with the IRB, ACO, sponsor, and other applicable entities in the event of a random or for-cause internal or external audit.

Institution-Wide Assurances

This protocol will be conducted fully in keeping with the signed MUSC IRB Principal Investigator Statement of Assurance and Department Chair's Statement of Assurance, when submitted to the IRB as a required component of the MUSC IRB Human Research Review Application. Assurances include the following safety-related agreements.

3) Protecting Confidentiality of Participant data

Participant Screening and Enrollment. All data from participants screened for the study will be entered into a REDCap electronic study database. Screened patients who do not meet study eligibility will have specific screening data entered into this database. The collected data will be helpful in examining the patient population and feasibility of enrollment criteria and will include reason for exclusion. PHI will be immediately stripped from this database for screen failures or for those participants who do not consent or are enrolled into the study. For participant enrolled into the study, dates will be shifted and other Personal Health Information (PHI) will be removed upon completion of the study. All data obtained from this study will be used for research purposes only and will comply with Federal HIPAA regulations. Master Screening and Enrollment Logs will be maintained electronically and will only be accessible to be used by the PIs or PC in preparation of reports on accrual and attrition for the DSMB.

Electronic Case Report Forms. All proposed study specific case report forms (source documents) for data collection will be designed by the PI and transferred by the PI or PC into electronic Case Report Forms (eCRFs) for use in the study's REDCap database. These study specific eCRFs source documents (study logs for correspondence, compensation and other forms such as pre-eligibility screens) will be coded by the participant's unique study ID# for all data collected including study instruments and will be maintained in the participant's unique electronic research record.

Regulatory Binders. The MUSC PI and/or designee will prepare and maintain an electronic regulatory file to include the IRB-approved protocol, IRB correspondence, approved study advertising, and other required study-related regulatory documents.

Data Processing. This study will use Research Electronic Data Capture (REDCap) for data capture and management. REDCap is a software toolset and workflow methodology for the electronic collection and management of research and clinical trials data. REDCap provides secure, web-based, flexible applications, including real-time validation rules with automated data type and range checks at the time of data entry. Exports are made available for several statistical packages including SPSS, SAS, SATA, R and Microsoft Excel. The study-specific REDCap electronic database will be designed and developed by the PI or PC in concert with the biostatistician. The provision of REDCap is made available through the South Carolina Clinical & Translational Research (SCTR) Institute at MUSC with NIH Grant awards UL1RR029882 and UL1TR000062.

Data Security. Ensuring data security, compliance with 45 CFR 46 and maintaining the integrity of PHI is a top priority. MUSC has Standard Operating Procedures (SOP) to ensure a high level of data security while coordinating electronic and paper data management activities for clinical research trials. The REDCap study database will be hosted in the Biomedical Informatics secure data center at MUSC, a secure environment for data systems and servers on campus, and includes firewall, redundancy, failover capability, backups and extensive security checks. The secure data center has strict access control; only authorized core personnel may access the facility un-escorted. Only authorized users are allowed to connect to the network, and the security of the network is actively monitored. Power and environmental controls have several layers of backups, from interruptible power supplies to alternate and redundant feeds to the local utility company. The REDCap system administrator contributes to the maintenance of institutional disaster recovery and business continuity plans. Load balancers and a highly fault tolerant SAN infrastructure contribute to high availability.

The REDCap system itself has several additional layers of protection including password protection. Access to the data and its security is managed institutionally by sponsored login IDs through a Shibboleth login with an MUSC issued NetID and features a user account management filter that controls who can access the data and to what degree. All personnel must pass an employment background check before being issued an ID. Password complexity, history and expiration standards are implemented at the institutional level. Access to individual REDCap projects and their data is managed by the owner of the project. All transactions are securely delivered to the application using Secure Sockets Layer (SSL – SHA-1 with RSA Encryption; 2048-bits). It is then transmitted internally (behind the firewall) to the database server. All transactions are logged at the server layer (httpd logging), application layers (REDCap logs activity to a database table), and the database layer, using both query and binary logging. This feature provides audit trails for all changes, queries, data exports and reports. MUSC Information security policies are available at: https://mainweb-v.musc.edu/security/policy/

Data Entry. Only MUSC IRB approved study personnel that are authorized to have access to the REDCap study database will be granted password access. Study personnel using computers that are connected to the Internet will directly enter data into the remotely housed database. As such, no electronic study data will be stored on hard drives and/or any portable electronic devices. Additionally, all personnel with access to the database will have current University of Miami CITI training in the Conduct of Human Subject Protections, and HIPAA and Information Security trainings that are completed annually. Each participant will be assigned a unique study identifier, all PHIs will be masked, and data exports will be limited to the PIs, the PC, or the project biostatistician for generating reports and the conduct of statistical data analysis.

Data Monitoring. Ongoing quality control procedures will be implemented for data collection, storage and processing. The PI or PC will conduct monthly monitoring of the study database and generate a report for review at team meetings. Standing agenda items for these meetings will include participant recruitment and retention, AE's, protocol deviations, data integrity and overall study conduct. The PI and PC will work to resolve and validate discrepant data. Discrepancies that warrant clarification will be sent to appropriate parties for review and resolution. All data entry and changes made in the study database by authorized study personnel will be automatically logged by REDCap, and provide a transparent visible audit trail for reviewers.

Data Resource Sharing:

1. DATA FORMAT: Data will be delivered in quantitative format using SPSS software.
2. DATA COLLECTION: Data will be collected via print questionnaires entered into redcap data collection portals within 72 hours of collection. The unit of analysis will be the individual respondent.
3. ASSURANCES: Assurances, consent form, etc. will be obtained and be compliant with and reviewed by MUSC IRB.
4. VARIABLE CREATION: All variable creation computation syntax will be in SPSS format and delivered in txt file for reproduction by any interested party. All weighting computations will be

delivered in txt file. All imputation will be outlined and syntax delivered in txt file. A variable definition list / codebook and computational syntax document will be delivered.

PI CONTACT: Information will be included.

SECTION C. Procedures for Identifying, Reviewing and Reporting Adverse Events

1) **Identifying.** Potential minimum risks identified for participants are outlined in the Protection of Human Subjects and will also be outlined in the IRB-approved informed consent document. Additional unknown risks may occur and, if so, will be identified through diligent monitoring by the PIs or PC throughout the conduct of this study. During the informed consent process, participants will be advised of the potential minimum risks of participation as identified in the IRB-approved informed consent document and reminded throughout the study that the researchers should be promptly informed about any concerns regarding potential side effects, adverse events, or clinical deterioration. Participants will also be instructed to notify the PI, PC, and/or designee of any suspected adverse events immediately if possible. Throughout the course of study enrollment, the researchers will maintain weekly telephone and/or face-to-face contact with the study participants to elicit information about experienced AE and to monitor participant progress. The PI or PC will maintain an electronic record of all reported adverse events and notify the DSMB of all reportable events as they occur. The DSM team will have real-time access to the study database to review and monitor all reported serious adverse events (SAE) that were reported as related to the intervention. The PI or PC will generate and provide de-identified monthly administrative human subject safety reports for the DSM team to review participant progress, accrual and attrition rates, and monitor the frequency of all reported side effects and AE. Additionally, the biostatistician will generate and provide de-identified cumulative administrative human participant semi-annual safety reports for the DSMB to review.

2) **Reviewing.** Adverse events will be assessed and graded by the members of the SMC according to the following MUSC's IRB Adverse Event Reporting Policy
http://academicdepartments.musc.edu/research/ori/irb/HRPP/HRPP Guide Section 4.7
   - **Expected/Anticipated**—Identified in nature, severity, or frequency in the current protocol, informed consent, investigator brochure, or with other current risk information.
   - **Unexpected/Unanticipated**—Not identified in nature, severity, or frequency in the current protocol, informed consent, investigator brochure, or with other current risk information.
   - **More Prevalent**—Occurs more frequently than anticipated or at a higher prevalence than expected.
   - **Serious**—Results in death, is life threatening, requires inpatient hospitalization or prolongs existing hospitalization, results in persistent or significant disability/incapacity, cancer, overdose, or causes a congenital anomaly/birth defect. The relationship of adverse events to study participation will be determined by the SMC according to the MUSC IRB Adverse Event Reporting Policy:
   - **Unrelated**—There is not a reasonable possibility that the adverse event may have been caused by the drug, device or intervention.
   - **Possibly Related**—The adverse event may have been caused by the drug, device, or intervention, however there is insufficient information to determine the likelihood of this possibility.
   - **Related**—There is a reasonable possibility that the adverse event may have been caused by the drug, device or intervention.

3) **Reporting**. All reportable AE, SAE and unanticipated problems experienced by participants will be reported to the NIH and MUSC IRB in compliance with their Adverse Event Reporting Policy requirements, using the IRB's password protected on-line secure server adverse event reporting system. Within 24 hours after a reportable AE, SAE or unanticipated problem has been reported by the participant, it will be graded by the PI or PC and submitted by the PI to MUSC IRB. After IRB review and acknowledgement, the PIs or PC will forward a copy of the reportable AE, SAE or unanticipated problem and IRB acknowledgement letter to the NIH Program Officer through MUSC's

OSRP within 24 hours. In addition, all cumulative reportable AE, SAE and unanticipated problems included in the DSMB reports will be submitted to the NIH in the PI's Annual Progress Reports.

4) **Definitions of Potential Reportable Adverse Events.** In accordance with MUSC IRB Adverse Event Reporting Policy, an AE is reportable if it meets all of the following criteria: 1) is unexpected 2) is related and/or possibly related, and 3) is serious and/or suggests that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized. Additionally, per MUSC's policy all participant deaths, protocol deviations, complaints about the research, and breaches of confidentiality are reportable events. In this study we will use the FDA definition of serious adverse events (SAEs). SAEs will be systematically assessed at each clinic visit. Any SAE, whether or not related to study intervention, will be reported to the IRB and NIH. The initial SAE report will be followed by submission of a completed SAE report to both institutions. In the event that a client either withdraws from the study or the investigator decides to discontinue a patient due to SAE, the client will be monitored by the investigators via ongoing status assessment until 1) a resolution is reached i.e., the problem requiring hospitalization has resolved or stabilized with no further changes expected 2) the SAE is determined to be clearly unrelated to the study intervention, or 3) the SAE results in death. Outcome of SAEs will be periodically reported to NIH. A summary of the SAEs that occurred during the previous year will be included in the annual progress report to NIH. During screening, study applicants will undergo a baseline assessment to determine their eligibility and safety of their participation in this study. History of suicidal ideation or suicide attempts, and other suicidal risk factors, including suicidal ideation, intent, and plan will be carefully assessed and monitored through the study. The PI, who is a licensed clinical psychologist, will be contacted immediately regarding clients who are at risk to commit suicide to aid in safety assessment (as described in Human Subjects plan) and will be offered additional treatment (e.g., hospitalization) as needed and appropriate. As noted above, all adverse effects of the interventions, assessment procedures, or any aspect of the study will be documented and reported within 24 hours to the University IRB and the Project Officer(s).

SECTION D. Assessment of External Factors

The PI will conduct a semiannual assessment of external factors through a review of literature related to new developments in the areas of HIV adherence, PTSD symptom management (including avoidant coping and stigma), symptom reporting and other approaches that may have an impact on the safety of participants or on the ethics of the study. To determine whether any changes are necessitated to the study protocol, DSMB will review any identified literature or product safety data that may pose as a potential impact to the risk benefit ratio study and/or safety of study participants.

SECTION E. Interim Analysis

This study aims to test the feasibility and acceptability of an integrated, evidence-based protocol for PTSD and adherence for PLWH within a HIV care clinic. To our knowledge, there are no similar studies specifically designed for this patient population and purpose. As such, the biostatistician will generate semi-annual qualitative interim analysis reports on a) adverse events; and b) data obtained during phone call and returned end-of-study surveys to understand issues related to the uptake, usability, and adoption of this intervention among this population. We will evaluate the screening and enrollment procedures, barriers to participation and retention, including, safety, adherence, acceptability, problems encountered, if any, and feedback from the participants and the case managers. This information gained from this structured process will be used to both guide the refinement of the current protocol and to inform the design of a larger efficacy trial. Interim analysis of outcome variables (e.g., PTSD symptoms, ART adherence, viral load) was not considered to avoid inexact inferences and increased chance of error due to few data points, as well as potential for bias if interim results were known to the investigators. Therefore, there are no planned stopping rules for this study.

14.0 Withdrawal of Subjects

Participants may voluntarily elect to withdraw their consent at any time for any or no given reason while enrolled in the study. The PI may withdraw participants from the study at any time if they decide it is in

the participant's best interest, if they do not follow the investigator's instructions, and/or if they fail to maintain to contact with the researchers or attend study visits. Withdrawals of participants may also occur if there is a protocol violation or early study closure. All data gathered from withdrawn participants will be used in the analysis plan under an Intention-to-Treat (ITT) model.

15.0 Risks to Subjects and Risk Management

We do not anticipate any elevated risk level associated with the comparison of the intervention treatment as compared to the current standard of care. However, there are known inherent risks associated with the conduct of human subject research as well as with the provision of mental health services to this target population. These risks, as well as mitigation strategies, are identified and outlined below, respectively.

Loss of privacy: PHI from participants will be gathered and stored electronically on secure and encrypted servers and there are risks associated for the loss of privacy and confidentiality. We will minimize the potential for loss of confidentiality through the physical separation of participant names from their research record according to the process described below. Clinical interviews will take place in a private setting. Audio recordings of interviews will be uploaded for transcription within 48 hours to an outside agency with which MUSC has established a Business Associates Agreement (BAA). Once uploaded, all audio recordings will be deleted from the portable storage device.

All information obtained from participants will be confidentially maintained. Participants will be reminded on a weekly basis that content of treatment will not be reported to providers and will be anonymous. Research staff will receive training from the Principal Investigator on the importance of privacy and confidentiality and will have a supervision meeting with the Principal Investigator to ensure strict compliance with the Human Subjects Protection plan. With regard to data management, safety, and storage, all data will be collected, managed and maintained through MUSC REDCap survey

Participant will be assigned a unique study ID code. Only participants' study identification codes will be on collected measures and e-CRFs. The REDCap database that links the name of the participant and their study ID will be maintained as a separate REDCap project from the research REDCap database. The secure servers that will house the data files are located at MUSC on SSL (Secure Sockets Layer) 128-bit encrypted servers behind firewalls. Respondent confidentiality will be masked in all data files by the use of uniquely assigned study identification numbers rather than personal information. All other electronic records, including digital audio recordings of sessions, are de-identified in collection and will be maintained in password protected locations also on the secure server. The only document linking participants with identification numbers will be retained in an encrypted file on MUSC REDCap secure server with access limited to the Principal Investigator, Program Coordinator and Nurse Interventionist. Data presented at professional meetings or published in journals or books will not allow identification of individual participants. These procedures are expected to minimize any potential risk of loss of privacy from participating in this study. Audio files of participation in the intervention or exit interviews will be used solely for research purposes. Exit interviews will be conducted either in-person in the privacy of a clinic room at MUSC Ryan White, or remotely via telephone at a time location and setting of the participants choosing. Participants will be informed when the interview recording has begun and ended and will be will receive initial instruction not to use the names of individuals or reveal any personally identifiable information. Audio interview files will be temporarily on a portable recording device, prior to being uploaded within 24hrs to the deidentified research database and later transcribed by a vendor that has executed a BAA with MUSC. Audio files will only be identified by numeric codes of sessions recorded and will be destroyed from the recording device after upload to REDCap. Only the project therapist, raters, and investigators will hear the content of the audio recordings.

The only exceptions to confidentiality include situations involving participant's self-disclosure of potential abuse/neglect or risk of harm to self or others or report of nonconsensual sexual activity. These cases will be contacted by Dr. López, a licensed clinical psychologist (SC # 1227) who has substantial experience successfully handling crises. In addition, the MUSC Institute of Psychiatry clinics have standard protocols

for handling these high-risk situations. If a Research therapist or team member is told that there is any risk of harm to the participant or others, s/he will immediately contact Dr. López. Dr. López will assess safety and provide instructions to the project team member to address any risks (according to the research protocol developed over years of experience at MUSC). Dr. López will conduct a comprehensive risk assessment with the participant. If there is any indication of a potential for harm, Dr. López will take appropriate action (e.g., contacting the police or ensuring the participant is taken to the emergency room). The therapist will have a cell phone number where Dr. López will be available at all times.

If a participant is deemed at risk for suicide and will not contract for safety, or has made a suicidal gesture or attempt, the participant will be assessed by the local emergency department for possible inpatient hospitalization. In circumstances where patients express suicidal ideation and are sincerely willing to contract for safety (i.e., will agree to keep her/himself safe), project therapists will do follow up phone calls to monitor safety until suicidal ideation has decreased. Dr. López will ensure individuals disclosing suicidal ideation are well educated on how to access 24-hour emergency care. A detailed safety plan - detailing what to do and whom to speak with if ideation should escalate - will be discussed, including specifics on how to access 24-hour care for suicidality via dialing 9-1-1 and/or going to the closest emergency department when therapist is not available. Thus, a 24-hour safety plan is in place, including access to medical care 24 hours per day. If a participant is deemed at risk for suicide and the participant will not contract for safety, or has made a suicidal gesture or attempt, assessment and evaluation by a local emergency department for possible inpatient hospitalization will be recommended. Dr. López has the capacity and will coordinate to arrange for direct inpatient admission assessment at the MUSC inpatient units (MUSC Institute of Psychiatry) for individuals requiring such assessment (e.g., concerns about danger to self or others) and who elect to go to MUSC. Routine monitoring of adverse events will also occur through weekly meetings between the Principal Investigator and therapists

Emotional distress: Some of the questions asked may be upsetting to participants or make them feel uncomfortable answering them. Participants will be instructed that if they do not wish to answer a question, they can skip it and go to the next question.

Regarding instances of more significant distress, including suicidality (suicide-related thoughts, intent, plan, and means), participants will undergo a complete battery of psychological tests to determine their eligibility and safety of their participation in this study during the initial assessment. Special attention will be placed on history of suicidal ideation or suicide attempts. Participants who are at high risk of attempting suicide will not be recruited into the study (i.e., have made an attempt in the past 36 hours). They will be offered access to additional treatment (including additional appropriate mental health referrals) if warranted.

For participants enrolled in the study, in any circumstances where an assessor or a therapist is concerned regarding suicidal ideation or attempt, Dr. López or Dr. Danielson will be contacted immediately. All research staff will have a cell phone number where Dr. Lopez will be available 24 hours 7 days a week. In rare instances where Dr. Lopez cannot be reached, Dr. Danielson will serve as a back-up. Dr. Lopez will ensure project therapist is well trained in assessing distress and suicidality (intent, plan, etc). In circumstances where participants in either condition express suicidal ideation and are sincerely willing to contract for safety (i.e., will agree to keep themselves safe), PI Dr. Lopez will form a safety contract with participant and continue to monitor and re-assess risk until risk has been reduced. If a participant is deemed at risk for suicide and will not contract for safety, or has made a suicidal gesture or attempt, the participant will be assessed by local emergency department for possible inpatient hospitalization. Dr. Lopez will help facilitate direct inpatient admission assessment at the inpatient units for individuals requiring such assessment (e.g., concerns about danger to self or others). The project coordinator also will ensure all participating individuals are well educated on how to access 24-hour emergency care (through 9-1-1 or going to the local Emergency Department).

Physical fatigue: Completion of the questionnaire, measures and interviews may be tiring to some participants. Participants will be given ample time to complete the questionnaire and may take breaks as

necessary throughout the process. Participants are also informed in the informed consent process that that may voluntarily stop their participation in the study at any time.

Randomization: Participants are being assigned to the intervention and control group by chance. The intervention under investigation may prove to be less or more effective than currently available standard of care treatment (control).

16.0 Potential Benefits to Subjects or Others

This project will assess the feasibility of providing the CPT-L protocol for PTSD populations with co-occurring HIV infections in an ID clinic. If support for feasibility is found in this project, we plan to conduct a larger-scale evaluation to assess the incremental dissemination, reach, and efficacy of the exercises and tools that will be developed under the current proposal. Taken together, if data from these studies suggest that the integrated intervention enhances engagement and patient outcomes, benefits to participants are potentially very high. The proposed approach is highly sustainable due to low costs of disseminating these resources, and therefore has the ability to reach a large population.

The benefit to be gained to the adults participating in this project is that we are providing evidence-based treatment that they could not previously access. CPT is an evidence-based treatment for PTSD; thus, participants that have not been able to access trauma treatment are expected to experience a reduction in PTSD symptoms, though this cannot be guaranteed. Moreover, it is anticipated that participants will find the co-location of services as a means of better engagement, which may improve their intervention experience. Potential benefits to participants also include improved adaptive functioning (via increased emotional regulation skills/reduced avoidant coping) and increase in ART adherence (with the Lifesteps protocol), though these cannot be guaranteed. Participants will receive comprehensive psychosocial assessments at no charge. Potential benefits may also include personal validation that comes from being told their experiences are important and that the information gathered from the study will be used to learn how to help other people with similar histories. In addition, the successful validation of co-located PTSD treatment programs as an intervention for increasing adherence and viral suppression would be of significant benefit to society.

IMPORTANCE OF KNOWLEDGE TO BE GAINED

Persons who live with HIV experience (PLWH) higher levels of trauma during childhood and continue at increased risk during adulthood (40-90%[5]) relative to the general population. This is particularly unfortunate because trauma experience in this population is associated with increased mental health problems[6], faster disease progression[7], more hospitalizations [8], almost twice the rate of death [9] and, distressingly, and lower adherence to Anti-Retroviral Therapy (ART) [10]. *Effective treatment of posttraumatic stress disorder (PTSD) in PLWH with comorbid PTSD may reduce negative HIV-related outcomes and enhance ART adherence.* Yet, despite the high occurrence and harmful effects of PTSD in HIV-infected individuals, there is relatively little research on the efficacy of treating PTSD in this difficult-to-engage population. Providing *trauma treatment to target the specific needs of PLWH living with comorbid PTSD may reduce avoidant coping in this typically treatment-resistant population and increase ART adherence.*

Despite the exacerbated consequences of trauma exposure related to HIV patient outcomes, improvement of patient access to trauma treatment for populations living with HIV has been neglected. By capitalizing on existing resources (i.e., MUSC Ryan White clinic), the current application proposes to integrate evidence-based trauma treatment (e.g., CPT) with an adherence intervention (Lifesteps) and implement into an ID/HIV care clinic and provide initial test of feasibility and safety for a high risk group with co-occurring PTSD and self-management with HIV care. Data from this pilot RCT are critical to the development of a full-scale appropriately powered trial that would enable us to determine the efficacy of CPT-L intervention on increasing ART adherence and viral suppression, and to identify the best, most cost-effective method for delivering these trauma treatment services with high fidelity to high risk and underserved populations. The tailoring of evidence-based trauma treatments to target specific needs of hard-to-engage populations (e.g., engagement, disclosure distress) can have a significant public health

impact by improving patient outcomes, engagement, and medication adherence across several pathologies and health promotion efforts.

17.0 Sharing of Results with Subjects

As this is a feasibility study, we do not intend to directly share study results with participants. We will however share our findings through Open Access journal publications in alignment with NIH/NIMH policy. These findings will be available to the general public, including previously enrolled study participants.

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