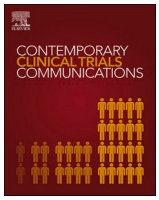
Contemporary Clinical Trials Communications 33 (2023) 101150

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: www.elsevier.com/locate/conctc



Development and feasibility testing of an integrated PTSD and adherence intervention cognitive processing therapy-life steps (CPT-L) to improve HIV outcomes: Trial protocol

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A B S T R A C T

Despite high rates of Post-Traumatic Stress Disorder (PTSD) in persons living with HIV (PLWH) and poor HIV-related health outcomes associated with PTSD, an effective evidence-based treatment for PTSD symptoms in PLWH does not exist. Negative reinforcement conceptual models posit that avoidant behavior (hallmark symptom of PTSD) demonstrated by PLWH with co-occurring PTSD can contribute to poor antiretroviral therapy (ART) adherence. However, research evaluating the impact of evidence-based treatment for PTSD among HIV infected populations on HIV outcomes is scarce. The Cognitive Processing Therapy (CPT) protocol is an evidence-based PTSD treatment that may address internalized stigma with targeted modifications and improve ART adherence and subsequent viral suppression through reduction of avoidant coping. This study will be the first pilot open-label randomized control trial (RCT) to test feasibility of an integrated evidence-based PTSD treatment (CPT) with an adherence intervention (Lifesteps) delivered in a Ryan White clinic to improve PTSD symptoms, adherence to ART, and retention in HIV care. Primary aims are to (1) conduct theater testing of the CPT and Lifesteps research protocol and evaluate acceptability (n = 12) and (2) deliver a modified CPT protocol (CPT-Lifesteps, or CPT-L) in 60 PLWH/PTSD exploring impact of CPT-L on PTSD symptoms and HIV outcomes compared to a Lifesteps + Standard of Care condition. This innovative research extends PTSD treatment approaches as a paradigm to reduce barriers to ART adherence. Findings of this innovative study are significant because they support the Undetectable = Untransmittable (U=U) campaign and can help prevent the transmission of HIV infection through increased viral suppression.

1. Introduction

People living with HIV (PLWH) report higher levels of trauma (e.g., child maltreatment, sexual assault, physical assault) than the general population, with rates from 40 to 90% [1,2]. Higher rates of traumatic events/exposure correspond with higher rates of Posttraumatic Stress Disorder (PTSD) in this population, with rates of PTSD in PLWH estimated to be between 30 and 74% [3,4]. Up to 64% of PLWH endorse PTSD symptoms directly related to their HIV diagnosis or from other issues related to the disease [3,5]. 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 [6,7], and comorbid PTSD and SUD display a worse course of illness, poorer physical health and overall functioning, and increased suicide risk than individuals with only PTSD or SUD [8,9]. Addressing PTSD symptoms can significantly reduce SUD among various populations [10], although this has not been examined among PLWH. PLWH with PTSD have been shown to have faster HIV progression [2,11] twice the rate of death [12], lower ART adherence [13–18], poorer retention in HIV care [19], and increased viral load [20,21] compared to PLWH without co-occurring PTSD.

Additionally, HIV-related stigma (community, anticipated, and internalized) is prevalent among PLWH [22] and associated with problematic HIV outcomes (e.g., poor medication and visit adherence

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https://doi.org/10.1016/j.conctc.2023.101150
Received 22 August 2022; Received in revised form 24 April 2023; Accepted 13 May 2023
Available online 20 May 2023

[23,24]). HIV-related stigma is shame or disgrace affiliated with HIV and associated with negative health outcomes for PLWH [25]. Fear of being judged by others predicted decreased ART adherence among PLWH [26,27] and internalized HIV-stigma predicted poor ART adherence [28]. 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 [29]. More specifically, trauma-focused treatment provides patients an opportunity to challenge negative and maladaptive thoughts [30], including thoughts that are related to direct and/or indirect experiences of stigmatization and discrimination. While trauma treatment cannot change the stigmatization they may experience, it can assist them in processing and challenging thoughts associated with the experience. Thus, trauma-focused treatment can be enhanced further to address discrimination by assisting patients in identifying their own stigmatized identities, how these identities shape their experiences living with HIV and PTSD, and help challenge negative cognitions associated with intersecting stigmas (e.g., HIV-related intersectional stigma and discrimination). Given the association of HIV internalized stigma with poorer PTSD [31] and ART adherence [32], addressing stigmatization through trauma treatment may help address HIV care outcomes.

Despite high rates of PTSD among PLWH and the link to HIV health related outcomes, 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) [33], have strong evidence for reducing avoidance, as well as traumatic stress, substance use, and depression among adults with complex trauma [34,35]. CPT has also been shown to reduce trauma-related self-blame and guilt [36,37], two factors intimately tied to avoidant coping [38]. 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 [39].

Although CPT has been enhanced to target alcohol use and high risk sexual behavior to prevent HIV among American Indian women [40], CPT, nor other gold-standard, empirically supported individual treatments (e.g., Prolonged Exposure/PE) [41,42], have been adapted for PLWH, nor have they been evaluated to reduce problematic HIV outcomes. There is critical need to examine the utility of evidence-based treatments for PTSD among PLWH and co-occurring PTSD to improve HIV outcomes. To address this tremendous void, this study adapts and examines 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, to improve HIV outcomes among PLWH. We propose to do so in South Carolina, which is ranked 8th state in the country in 2019 for HIV/AIDS incidence and 11th for prevalence. As a state of the Deep South, not only is South Carolina disproportionately affected by HIV, but there are several stigmas related to poorer health, higher poverty rates, historic and systemic racial discrimination, and cultural climates related to gender identity and sexual orientation [43–45]. Globally, PLWH often experience anticipated and internalized stigma related to their HIV diagnosis which creates a fear of disclosing their status to others, poorer mental health outcomes and self-devaluation. PLWH endorsing HIV-related stigma are concerned disclosing will lead to implications of infidelity, violence, and rejection in both their personal and professional lives [46,47]. PLWH that will be enrolled in this study are from the Deep South, and thus likely possess many intersecting stigmatized identities. Therefore, it is expected that individuals who participate in the study may encounter and experience increased levels of stigma (HIV-related and other), itself linked to more avoidant coping and ART non-adherence [48]. The study will tailor CPT for this population by also integrating strategies from evidence-based Lifesteps [49], a one session intervention using cognitive behavioral strategies, problem-solving, and motivational interviewing techniques to promote adherence. Lifesteps briefly identifies maladaptive thoughts that participants may have regarding taking their medication and assists them in overcoming this barrier by identifying positive reasons for taking their medication. Lifesteps was chosen as part of the study protocol since it has shown to be effective in improving adherence to taking ART medication and maintaining this improvement over time [50]. As an evidence-based PTSD treatment, CPT will be integrated with Lifesteps since CPT provides a longer period of time and more tools for participants to focus on unhelpful thoughts that primarily drive avoidance and adherence issues, as well as stuck points related to stigmatization and the traumatic event. Inclusion of an adherence intervention in the control group serves as a strong comparator for highlighting the incremental benefits of PTSD treatment to HIV care outcomes.

2. Methods and study design

2.1. Study aims

Specific Aims of the proposal are to conduct: (1) Theater testing of the CPT and Lifesteps research protocol (see section 2.6) and evaluate acceptability. Theater testing is a pretesting methodology to assess consumer response to a product and has been successfully implemented to assess participants' reactions to HIV-related interventions [51–53]. Using such an empirically-supported approach for adaptation, members of the target population participate in original versions of the evidence-based interventions (e.g., unadapted CPT) and provide session by session feedback to guide intervention refinement, to enhance its relevance and efficacy for the new target population (i.e., PLWH with PTSD). The team will train the trauma-specialized therapist in Lifesteps and deliver the full protocol and delivery of CPT and Lifesteps with 12 clinic patients with comorbid PTSD and HIV. Exit interviews and topical expert feedback on protocol enhancement and satisfaction will be systematically collected and analyzed (2) A pilot RCT of CPT-L vs. Lifesteps + Standard of Care (i.e. SOC group). to assess feasibility of fully-powered Stage III clinical trial. Feasibility of the two-armed RCT in treating PTSD and increasing ART adherence will be measured via recruitment metrics, randomization processes, assessment burden, electronic medical record collection (e.g., attendance, CD4 count, viral load), treatment attrition, rates of missing data at each time point, and participant satisfaction. These feasibility measures will be assessed using a randomized controlled design assigning 30 participants to CPT-L and 30 to SOC control group, with measures collected at baseline, post-intervention (6 weeks), and a 3-month follow-up.

2.2. Overview

This three year feasibility study will proceed in two phases. In phase 1, we will beta test the research protocol, including recruitment of participants through clinic PTSD screener and delivery of the CPT and Lifesteps interventions, with feedback from participants and topical experts. We will utilize feedback through exit interviews collected from participants and experts to shape protocol refinements. Suggestions for improving the treatment and/or research protocol will be integrated. In Phase 2, the small scale RCT feasibility trial follows a 2 (treatment) x 3 (time points) design. We will recruit 60 patients from local Ryan White HIV care clinics (i.e., individuals living with HIV) aged 18 and older, that have experienced a traumatic event, and report current PTSD symptoms. Ryan White clinics are found nationally, and are part of a federally funded program that helps coordinate comprehensive medical care for people living with HIV/AIDS. Participants will be randomized to the treatment condition (CPT-L for PTSD; n = 30) or to the control condition (SOC; n = 30).

2.3. Recruitment/inclusion/exclusion criteria

Recruitment will occur through multiple avenues: (1) a main referral

stream will be identified through the trauma screening questions (Primary Care PTSD Screener for DSM-5 [52]) included in case manager clinic intake procedures; (2) clinicians and staff in the HIV care clinic will refer patients that have disclosed trauma to the research team to discuss interest after sharing a study flyer; and (3) researchers will include trauma and PTSD screening [54] in the clinical database completed with patients before appointments at the ID clinic. Clinicians and case managers will inform potential patients with a project pamphlet and ask if they would like to speak with a research team member to learn about the study. Referred patients will be approached by a research team member after their appointment or called after referral from case manager. If the patient is interested, they will complete the informed consent process, sign a release of information (for chart reviews) and answer additional questions of eligibility (e.g., Montreal Cognitive Assessment), as well as complete a structured diagnostic clinical interview to assess clinical threshold of a DSM-V PTSD diagnosis (Clinician Administered PTSD Scale-5, CAPS-5 [55]). Baseline study visit (i.e., self-report assessments) will be conducted during the appointment for patient convenience. However, if the participant would like more time to complete the appointment, they will be provided alternative times. Research study personnel and the participant will exchange contact numbers to arrange a time to meet participant in the community for data collection completion.

Eligible participants for the study will be PLWH with PTSD meeting inclusion criteria: 1) age 18 or older; 2) any ethnicity, sex and/or gender; 3) enrolled in the MUSC Ryan White clinic; 4) report at least one traumatic event experience (defined as Criterion A of the CAPS-5 interview) in their lifetime and report at least three PTSD symptoms on the Primary Care PTSD Screener; 5) meet full PTSD diagnostic criteria on the CAPS-5 clinical interview; 6) no changes in psychotropic medication within 4 weeks of study enrollment; 7) able to speak, read, and write English; 8) 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 appointment 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; 9) A score of at least 10 (i.e., including scores indicative of mild [scores 18–25] to moderate [scores 10–17] cognitive impairment) on the adapted Montreal Cognitive Assessment (MoCA) test without visual elements [56] to ensure patient can effectively engage in CPT exercises. Exclusion criteria: 1) significant cognitive disability, developmental delays, pervasive developmental disorder, or active suicidal or homicidal ideations (assessed in the pre-eligibility screening and confirmed in electronic medical record review); 2) psychotic symptoms (e.g., active hallucinations, delusions, impaired thought processes). A wide range of adverse childhood experiences (ACEs) will be assessed during the eligibility process to include interpersonal violence, victims of natural disasters, combat, immigration-related trauma, HIV-related trauma, and other events endorsed as inducing fear of serious harm to self or loved one.

2.4. Randomization

Upon completion of study intake procedures, participants will be randomized to receive 3 months of CPT-L (from a therapist, part of research staff)or SOC (from a trained Ryan White peer advocate, part of clinic staff) using a stratified randomized blocks procedure to assign participants in a 1:1 allocation while stratifying on potentially confounding variables [57]. These stratification factors are detectible viral load (yes/no) at study entry and self-identified gender (as recommended by the Fenway Institute for SOGI [Sexual Orientation and Gender Identity] data collection [58]. Baseline viral load stratification was chosen to assure balance as viral load is an acceptable surrogate for several of the proposed outcomes (viral load, ART adherence, visit attendance). Gender was chosen since women are twice as likely to develop PTSD than men [59]. While we anticipate that PTSD severity will be similar across groups due to nature of randomization, preliminary analyses will examine for differences in PTSD severity across the intervention and control group and incorporate appropriate statistical methods to control for any potential effects.

2.5. Study outcomes

2.5.1. Primary feasibility and protocol adherence

The primary aim is to assess the feasibility of the modified CPT protocol (CPT-L) compared to SOC over 6 weeks of study treatment (i.e., 2 sessions per week [60,61]) and 3 months of follow up. Primary feasibility will be determined by the ability to adequately randomize and retain study participants throughout the study intervention and follow-up. This will be operationalized as successfully randomize 4+ patient per month for 18 months and retaining 90% of randomized patients throughout study treatment and follow up visits. In addition to retention, a low rate of missing primary outcome data ($\leq$10% missing) will demonstrate the ability to integrate the study intervention with standard clinical care components and medical health records. Study protocol adherence will be monitored weekly and reported as the proportion of weekly self-reported PTSD symptom surveys (i.e., PTSD Checklist for DSM-5, or PCL-5 [62]) completed as well as distribution of the clinician rated treatment engagement and cooperation levels. Acceptable protocol adherence will be determined by completion of $\geq$80% of assigned weekly PCL checklists across randomized participants. See Table 1 for complete list of research instruments. In the event that these feasibility benchmarks are not met, study investigators will continue refining protocol implementation utilizing results from the Client Satisfaction Questionnaire [63], an acceptability questionnaire (rating of satisfaction with treatment, usefulness, perceived barriers and general experience), and exit interviews.

2.5.2. Efficacy and visit adherence

A secondary aim is to determine efficacy and variability estimates to aid in design of future fully powered randomized clinical trials. Efficacy outcome variables (see Table 1) include changes in measures of symptoms and self-management (PTSD, ART adherence, avoidant coping), quality of life (QOL), Substance use, HIV related lab outcomes (CD4 count, viral load), and visit adherence (number of appointments kept). Both the CAPS-5 and PCL will examine PTSD severity. ART adherence will be measured by the proportion of medication doses taken during active treatment and follow-up utilizing measurements suggested by Saberi [64] which uses participant-provided photographs of pill count and prescription refill dates to arrive at a more objective adherence measurement. Substance use/misuse will be collected using the AUDIT [65] and the DAST [66] while quality of life will be measured with the HIV Quality of life scale (WHOQOL-BREF) [67]. Clinical HIV outcomes will be determined from electronic medical record data.

2.6. Study intervention

Experimental Condition: (Lifesteps + CPT + SOC): Life-Steps for Medication Adherence. Life-Steps [68] is a one-session intervention using cognitive behavioral, problem-solving, and motivational interviewing techniques to promote adherence [29,69]. Lifesteps includes psychoeducation on the benefits of ART adherence, modification of maladaptive cognitions about taking medications, review of potential barriers to being adherent, and problem-solving techniques for problematic adherence. Cognitive Processing Therapy (CPT) is an evidence-based PTSD treatment with demonstrated efficacy through several RCT designs and comparators, with several vulnerable populations, and for a range of traumatic events (e.g., rape, domestic violence, child sexual abuse, military combat and several ACEs). CPT [70] is based on information processing theory and includes education and cognitive components that challenge and modify unhelpful beliefs related to trauma and/or living with HIV. Thus, the patient creates a

Table 1
Research instruments.

Assessment	Res	BL	Post	3 mon*	weekly	Description
Demographics questionnaire	P	x				Data collected from participant after consent; includes ethnicity, age, sex at birth, gender identity, sexual orientation, pregnancy status, living conditions, partner status, employment status, and highest level of education
BRICS (Biomedical Research Informatics Computing System) NINR (National Institute on Nursing Research) Social Determinants of Health	P	x				18 items assess financial resource strain, physical activity, social connectivity/isolation, safety, and family income [99].
HIV, Trauma, PTSD, and Related Outcomes from Clinical Interview and Self-Report						
ART adherence (self-report)	P	x	x	x		AIDS Clinical Trial Group (ACTG) is a self-report questionnaire that measures adherence of ART medication within the past 30 days (n = 15 items) symptoms experienced in the past 30 days (n- 20 items), self-efficacy and beliefs regarding the effectiveness of ART medication (n = 3 items), psychological distress (n = 17 items), social support (n = 2 items), alcohol and drug use (n = 7 items), and sociodemographic characteristics (n = 9 items) [100].
HIV Quality of Life (World Health Organization 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'sperception of quality of life and assesses changes in quality of life across treatment; good psychometric properties [101].
HIV stigma measure	P	x	x	x		40 item measure developed by Berger et al. [97], revised by Bunn et al. [25]; multiple dimensions of stigma; good reliability and validity
Clinician- Administered PTSD (CAPS-5) 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. Inter- view items focus on symptom presence, onset and duration of symptoms, subjective distress, impact of symptoms on social and occupational functioning and improvement in symptoms; strong inter-rater reliability and re-test reliability [55].
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; psychometric properties for LEC-5 unavailable but deemed to have few psychometric property differences from original LEC, which had adequate convergent validity [102].
PTSD Checklist (PCL-5)	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 [62]
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); good omega and alpha reliabilities [80].
Substance use: Alcohol Use Disorders Identification Test (AUDIT); Drug Abuse Screening Test (DAST)	**P**	**x**	**x**	**x**		Each self-report consists of 10 items; excellent reliability and convergent validity [65,66]
PROMIS (Patient-Reported Outcomes Measurement Information System) 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).; high reliability rates [28].
Patient Health Questionnaire (PHQ-9)	**P**	**x**	**x**	**x**		Validated for use to monitor the severity of depression and response to treatment; 9 items score major depressive episode criteria as "0" (not at all) to "3" (nearly every day); high internal consistency, sound reliability and validity [103].
Participant Treatment Engagement						
Treatment Expectancy Scale	P				X (first wk.)	6-item scale assesses patient expectancy for the intervention to improve their lifestyle/functioning; high internal consistency and good test-retest reliability [104].
Credibility Expectancy Questionnaire	P	x				Assesses how much participant believes that the intervention will reduce their mental health symptoms; high internal consistency and good test-retest reliability [104].
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 [98]; records type and amount of services participants engaged in for PTSD symptoms, including mode (group, in- dividual couples, family, self-help, medication) and number of hours in each service; satisfactory reliability
Support Electronic Survey	PC				x	Captures more ecologically valid data than retrospective recall at three data assessment points (0, post intervention, 3 months follow up), support services will be collected via REDCap survey on a weekly basis from baseline until 3 months 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.
Ryan White appointment adherence**	PC	x		x		Electronic medical record data coding at end of study for clinic appointment attendance with a provider with prescribing privileges. Appointment adherence to the ID clinic will consider cancellations made

(*continued on next page*)

Table 1 (*continued*)

Assessment	Res	BL	Post	3 mon*	weekly	Description
						by the patient, no shows, and care appointments occurring more than 6 months apart.
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 Re- view	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; high concurrent validity, high internal consistency [105].
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 In- ventory-Short Revised (WAI-SR)	P		x		x (wk. 3; mid treat- ment)	10 item survey that aassesses 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; good psychometric properties [106].
Exit Interview	PC		x			Conducted with PC to avoid potential impression management bia. "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 Inter- view	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 Ryan White 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.

new understanding and conceptualization of the trauma and/or HIV status to reduce ongoing negative effects on current life. 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. For the subset of patients with dissociative symptom presentation (identified through the initial CAPS-5 assessment), an additional detailed account of the traumatic event(s) is used to break the pattern of avoiding thoughts and feelings associated with the trauma [71]. For those without dissociative symptoms, this trauma account is omitted (CPT-C) and rather includes ongoing practice of cognitive techniques. The current study refers to both models as CPT for description of the research protocol. The therapist uses Socratic questioning on unhelpful thoughts (e.g., self-blaming thoughts) to modify maladaptive thinking (e.g., "I'm unlovable"). Upon identifying and addressing 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. In CPT-L (the resulting integrated treatment), the team anticipates incorporating brief continuous reminders of the benefits of ART adherence and including quick check-ins to identify potentially maladaptive thoughts about taking medications, thus building on skills implemented in the first session of Lifesteps. Potential adaptations in CPT-L based on PI preliminary case study (López et al., 2019), CAB input, and consultant feedback are demonstrated in Table 2.

The Control Condition: Standard of Care + Lifesteps. Participants assigned to SOC (N = 30) will receive the standard treatment that an individual with a trauma history and co-occurring HIV and PTSD symptoms would receive at a local Ryan White clinic (varying levels of case management services and program referrals) in addition to one session of Lifesteps. SOC interventions 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; and referrals to community agencies.

3. Study phase 1

Therapy sessions and exit interviews will be audio-recorded and analyzed using NVivo12 for improvements to the research protocol (or CPT intervention). Qualitative data analysis is inductive, iterative, and eclectic [72]. Qualitative content analysis, specifically latent and manifest content analysis, informed by grounded theory [73], will identify and describe major themes and sub-themes [74,75]. This is a dynamic type of analysis oriented toward recognizing, coding and categorizing patterns from text data [74,75]. Manifest content analysis involves the visible, obvious components of the transcript; latent content analysis involves interpretation of the underlying meaning of the text. Methods will explore participants' unique perspectives via identification of themes/patterns that naturally emerge from the data and systematic classification of themes [76]. Specifically, a three-step inductive approach will be utilized, in which each participant's interview responses will be examined to develop a comprehensive codebook to capture themes. The codebook will be used by two independent coders to code and analyze

Table 2
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 (e.g.,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 Phase 1 process

each participant's interview responses [77,78], inter-rater reliability will be explored via interclass correlation coefficients (ICCs). Themes will be refined, merged, and/or subdivided into subthemes via collaborative discussion. Principal investigators will review emerging themes with CAB members and Consultants to ensure fidelity to manual for any suggested changes to CPT-L. Data collected in phase 1 will provide the pathway to improve the research protocol and ensure feasibility and acceptability.

4. Study phase 2

4.1. Sample size determination

As the study is designed to demonstrate feasibility, sample size was determined based on pragmatic considerations, rather than through formal power analysis. The study will randomize 60 PLWH to the CPT-L or SOC condition (1:1), which is adequate to assess feasibility outcomes such as enrollment, attrition, retention, adherence to protocol and fidelity. The sample size during our recruitment period (18 months) will allow our team to justify a reasonable sample for a larger RCT in an expanded recruitment period. Further, with a target retention rate of $\geq$90%, an enrolled sample of 60 participants produces a 95% confidence interval of retention from 82% to 98% and an adherence rate of 80% will produce a 95% confidence interval between 70% and 90%. Mean PCL and CAPS-5 scores will be assessed post-intervention and 30 participants in each group will provide adequate power to determine an estimated confidence interval of the group difference of ½ standard deviation (0.5 SD). Although not specifically powered to detect clinically relevant differences in efficacy measures, with 30 participants randomized to each group, we will have 80% power with a type 1 error rate of 5% and an attrition rate of 10% during the 6 week treatment period to detect an effect size of (Cohen's) $d = 0.78$ in continuous variables (PCL, CAPS-5, WHOQOL-BREF, PROMIS, etc).

4.2. Primary analysis

4.2.1. Feasibility

Demographic and clinical variables obtained at baseline will be described via measures of central tendency (mean, median), variability and frequency distributions as appropriate. Specifically, 95% confidence intervals for proportions will estimate dichotomous outcomes and for continuous outcomes, frequency distributions and the median and mean responses with 95% confidence intervals will be obtained. A key feature of the proposed feasibility study is demonstration that recruitment of eligible participants is possible for a future large-scale RCT. Thus, we will report the number of referrals obtained each week from each source of recruitment (e.g., provider, flyer, case manager, clinical database) including the number referred and assessed for eligibility, excluded and reasons for exclusion, randomized, the allocation of randomization, the number randomly allocated who did and did not receive treatment, the number in each allocation who did and did not complete each follow-up assessment, and included/excluded from analyses and reasons for exclusion. Randomization success and failure metrics as well as subsequent remedies will be reported. Finally, we will report the percentage of missing data at the item level, and the rate of assessment completion at each time point to examine if assessment timing is optimal.

4.2.2. Efficacy analysis

Both the CAPS-5 and the PCL-5 will examine PTSD severity at baseline, post-intervention and 3-month follow-up. Additionally, the PCL-5 will be assessed weekly during the intervention and follow-up periods. Outcomes will be estimated with generalized linear mixed effects regression models. Linear slope trends over time and group level differences at each study visit (noted as Cohen's *d*, partial eta [79]) will be calculated for each treatment assignment. As PCL-5 scores are measured weekly, non-linear mixed effects models will be fit to estimate cubic or quadratic trends that occur during treatment and estimates of when treatment efficacy shows changes in effect size will be assessed and reported. For continuous measures (CD4 count), the difference between pre-and post-intervention will be estimated via generalized mixed effects models and 95% confidence intervals. Given that objectives of the project also include lab results from the electronic medical record, the percentage of missing electronic medical record data will be reported as an outcome of this feasibility study; initial correlational data between this biomarker data and key clinical outcomes will also be reported in project outcomes.

4.3. Exploratory analysis

It is hypothesized that changes in avoidant coping (measured by the Emotion Regulations Questionnaire, or ERQ [80]) following the

intervention will mediate the relationship between treatment and HIV-related outcomes. Mediation models will estimate the indirect and direct effects using the PROCESS macro [81]. Bootstrap resamples (1000 resamples) will be used to provide both 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.

Exploratory investigations of substance use/misuse will also be collected using the AUDIT and DAST. Changes in the proportion of participants reporting alcohol and drug use between groups following study treatment and at study follow-up will be compared using modified Poisson regression models adjusted for baseline use and study treatment visit. Continuous AUDIT and DAST scores will be assessed in those who report use and compared between groups using generalized linear mixed effects models. Similarly, depression will be assessed at the same time points using the PROMIS Emotional Distress – Depression short form.

5. Discussion

PLWH experience higher rates of PTSD due to increased exposure to trauma. PTSD has harmful outcomes for PLWH, with faster HIV progression, poorer ART adherence, increased viral load, and twice the death rate when compared to PLWH without co-occurring PTSD. Furthermore, exposure to trauma and PTSD among PLWH has been associated with ART adherence [16–18,82] with people exposed to traumatic events being over 4 times more likely to experience ART failure compared to those who are not exposed [12]. Poor ART adherence and difficulties with medication adherence have been associated with many other factors related to PTSD among [83–85] PLWH. Moreover, negative reinforcement conceptual models posit that avoidant behavior among PLWH with PTSD can contribute to poor ART adherence. The individual may avoid aspects of HIV status and/or treatment that serve as a direct cue or reminder of the trauma and are thus avoided; this avoidant behavior can be negatively reinforced when it "successfully" and temporarily reduces distress about HIV status, hence resulting in disengagement with HIV treatment and decreased likelihood of achieving viral suppression [86]. Thus, the negative reinforcement conceptual model (e.g., avoidant coping) provides a theoretical framework for the link between PTSD and poor HIV outcomes.

Understanding the context of PTSD within people living with HIV warrants further attention given potential interactive pathways between the two diagnoses. In addition to the combined effect described in the reinforcement conceptual model, PTSD and HIV comorbidity may interact to produce unique biological and psychological outcomes compared to outcomes associated with each condition in isolation [87]. For instance, the glucocorticoid pathway of the HPA axis and neuronal inflammation are associated with increased vulnerability [88] and development of PTSD [89]. Both become dysregulated due to HIV infection [90], resulting in neurobiological vulnerabilities of PLWH to stress/PTSD [87]. In other words, vulnerabilities related to HIV may already increase the likelihood of individuals with HIV who experience a traumatic event to develop PTSD. These interactions are particularly detrimental given the increased rate of exposure to traumatic events experienced by PLWH [91]. Due to the possible cyclical relationship between PTSD with HIV through biological underpinnings as well as theoretical models, addressing PTSD with psychosocial interventions may have an indirect improvement on HIV-related health outcomes [87].

CPT has been identified as an evidence-based psychosocial intervention with the potential to help address the factors contributing to the relationship between PTSD and HIV [92]. The flexibility of CPT to focus on unhelpful thoughts and thinking patterns would allow patients to address both trauma- and HIV-related stigma cognitions in treatment. In line with the goal of the Undetectable = Untransmittable (U=U) initiative to end HIV- related stigma, this proposal can have broad public health implications, but also implications for the self-esteem of individuals by reducing stigma associated with HIV. Further, the 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 the unique issues related to disclosing HIV status, and with managing and coping with HIV in interpersonal and intrapersonal domains. CPT dismantling studies have demonstrated improved engagement and PTSD outcomes among complex and traditionally hard-to-reach populations [93–95], and can potentially decrease substance use in addition to reductions in PTSD symptoms [96], further supporting the fit of the intervention for the 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.

An additional strength of the study protocol includes the active control condition of the Lifesteps adherence intervention. This control condition was purposely chosen to show the incremental value of adding a trauma-focused cognitive intervention for improved outcomes in HIV care behaviors. The team anticipates that there will be improvement in HIV care behaviors in the control condition, but we also hypothesize that the intervention group will have even greater gains in both HIV care behaviors and PTSD symptom recovery than the control group. Selecting a control condition that was both scientifically justified and helped address community concerns about participating in research was of utmost importance to the team. Thus, using a design that allowed for all participants to potentially draw benefit through an active control group was chosen.

5.1. Limitations

There are several noteworthy study strengths discussed above, including an innovative paradigm for approaching HIV care outcomes through PTSD treatment, an integrated approach to best address unique features of PLWH with co-occurring PTSD (e.g., capacity of CPT-L to address PTSD and HIV-related stigma), implementation of trauma screening within the Ryan White clinic, strong comparator condition, and several measures of HIV care outcomes to assess effects. Some study limitations also warrant mention. Electronic medication devices are popular measures of medication adherence and could add another objective assessment of ART adherence. However, given that electronic medication bottles/devices are expensive and have been reported to activate HIV-related stigma, we believe the inclusion of the Saberi method of measurement is a reasonable and responsive approach to strengthening the objectivity of ART adherence. The Saberi methods show evidence of validity and we are confident based on previous work in this community that our participants will have access to smart phone and texting services to send text-messaged photographs of pharmacy refills for refill-based adherence and text-messaged photographs of antiretroviral medications to estimate pill-based adherence as described in the Saberi protocol. Finally, because recruitment occurs within the Ryan White clinic, participants will not include PLWH for whom avoidance of PTSD and HIV-related stigma are the most prominent: those who do not initiate care at the Ryan White clinic to begin with.

5.2. Conclusions

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 (e.g., viral suppression in PLWH) and health promotion efforts. No research to date has examined whether HIV outcomes can be improved among the large number of PLWH with comorbid PTSD and related consequences (*e.g.*, substance misuse) by treating PTSD symptoms. 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. If aims of this feasibility trial are supported, the next step will be a Stage II fully powered RCT. If proven efficacious through the RCT, subsequent

collaborations can build upon strengths of the team to partner with affiliated Ryan White agencies to disseminate this model and increase uptake to improve ART adherence nationwide. This line of research extends PTSD treatment approaches to be conceptualized as a paradigm to reduce barriers to ART adherence, which is an innovative use of established behavioral interventions and significant because results support the U=U campaign and can help prevent the transmission of HIV infection through increased viral suppression.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Patricia Resick receives royalties from Guilford Publications and conducting workshops on cognitive processing therapy. Dr. Steven Safren receives royalties from Oxford University Press, Guildford Publications, and Springer/Humana Press as an author of books related to cognitive behavioral therapy, health psychology, and LGBT-affirmative psychotherapy. The authors declare that they have no other known competing financial interest.

Acknowledgements

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