Research Protocol

Testing the effectiveness of an evidence-based transdiagnostic cognitive behavioral therapy approach for improving HIV treatment outcomes among violence-affected and virally unsuppressed women in South Africa

June 30, 2025

Version 1.8

NCT04242992

Statistical Analysis Plan- ***pages 30-33***

Wits Protocol No. : M200353
BU Protocol No: H-39746
Hopkins Protocol No: 12546
Columbia Protocol No: IRB-AAAS9661

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SUMMARY

There are just under one million people with HIV in South Africa who have initiated antiretroviral therapy (ART) but remain unsuppressed. South Africa has been making progress towards UNAIDS 90-90-90 targets but currently only 47% of those infected are suppressed. In South Africa, one major barrier to consistent treatment is intimate partner violence (IPV); nearly 50% of women have experienced IPV. The Common Elements Treatment Approach (CETA) is an evidence-based intervention intended to provide coping skills to women who have experienced IPV, and is comprised of cognitive-behavioral therapy elements. It is a transdiagnostic tool that can flexibly address a range of mental health problems (e.g. depression, anxiety) and represents the current best practice in global mental health as a more cost-effective, scalable and sustainable model. CETA is one of the most promising interventions to impact HIV outcomes through addressing the indirect effects of IPV on adherence and continuity of care.

We will conduct a randomized controlled trial of HIV-infected women, with or without their partners, who have experienced IPV and have an unsuppressed viral load or have defaulted on treatment to test the effect of CETA, in increasing retention and viral suppression, and reducing violence. The study has four aims:

- Aim 1: Among HIV-infected women on ART who have experienced IPV and have an unsuppressed viral load, have missed or late visits or who have defaulted on treatment, we will assess the effectiveness of CETA vs. active control at increasing the proportion retained and virally suppressed by 12 months and at decreasing the severity and incidence of IPV and other mental and behavioral health problems using an individually randomized trial;
- Aim 2: To identify mediators and moderators of CETA's effect on the primary outcome (retention and viral suppression);
- Aim 3: To assess the cost and cost-effectiveness of CETA vs. active control at increasing the proportion who are retained and virally suppressed by 12 months. Female patients will be recruited from the Themba Lethu HIV Clinic in Johannesburg, South Africa.
- Aim 4: To explore the experiences and perceptions of receiving CETA from the perspective of CETA participants post-intervention, including knowledge and skills obtained, acceptability, and reporting on and discussing trauma and violence, as well as perceptions and experiences of CETA providers and healthcare providers at CETA sites.

The study team will work with the clinic staff to refer eligible patients for the study. Patients who agree to be referred to a member of our study team will be given a brief screening consent. Study staff will obtain full informed consent from those who meet inclusion criteria. For those that agree to participate, study staff will then randomize patients to CETA or control using computer generated randomization assignment.

All subjects will be followed for 24 months to ensure data for primary and secondary outcomes is complete. Follow-up HIV data will be passive using routinely collected medical records from the clinics. HIV outcomes will be assessed at 3-, 12- and 24-months post-baseline. Questionnaires on violence, substance use, and mental health will be administered at baseline, and at 3 months (following CETA end) and 12 months post-baseline. These include: Severity of Violence Against Women Scale, Center for Epidemiological Studies-Depression Scale, Harvard Trauma Questionnaire, and Alcohol, Smoking, and Substance Involvement Screening Test. The primary outcome will be retention and viral suppression (<50 copies/mL) by 12 months after randomization. Secondary outcomes will include: 1) Viral

suppression at 3 and 24 months; 2) Attrition at 12 and 24 months; 3) IPV, mental/behavioral health, alcohol and other substance use at 3 and 12 months; and 4) Cost and cost-effectiveness of the intervention.

Our primary aim is to analyze the impact of CETA in the full study population; however, we have calculated our sample size to ensure our ability to detect differences separately among women who include a partner in the CETA intervention and those who do not. We will include a sample of 400 women, which will give us 80% power to detect an absolute 21% difference between arms. Our primary analysis will be a comparison of intervention and control by risk differences with 95% confidence intervals. We will analyze direct effects of CETA on continuous outcomes (e.g., mental health) with linear mixed models. We will evaluate the impact of potential moderators on retention and mental health outcomes using interaction terms. Micro costing methods will be used to cost all resources utilized and the cost effectiveness of CETA achieving the primary outcome will be evaluated.

We will also qualitatively explore participant and health provider perceptions and experiences of CETA. For this qualitative component we will use a sample of up to 50 participants which will consist of 3 focus group discussion and 10 in-depth interviews from CETA participants who completed CETA sessions in 2023, as well as up to 10 in-depth interviews with CETA providers and healthcare providers from implementing sites. The findings from these qualitative interviews and discussions will be thematically analyzed.

INVESTIGATORS

This evaluation will be conducted by investigators from Boston University (School of Public Health), Wits University (Health Economics and Epidemiology Research Office, Wits Health Consortium), Johns Hopkins University (School of Public Health) and Columbia University (School of Public Health) in close collaboration with the Department of Health of South Africa. Individual investigators are:

Boston University (BU)

Boston University Principal investigator
Dr. Matthew Fox
Professor
Departments of Epidemiology and Global Health
Boston University School of Public Health (BUSPH)
United States

Co-investigator
Dr. Donald Thea
Professor
Department of Global Health
Boston University School of Public Health (BUSPH)
United States

Co-investigator
Dr. Lawrence Long
Assistant Professor
Department of Global Health
Boston University School of Public Health (BUSPH)
United States

HE^{2}RO (Wits Health Consortium, Wits University)

HE^{2}RO Principal Investigator
Dr. Sophie Pascoe
Principal Researcher
Health Economics and Epidemiology Research Office (HE^{2}RO)
South Africa

Additional co-investigators from HE^{2}RO may be added prior to starting the evaluation.

Johns Hopkins (JH)

Johns Hopkins Principal investigator
Dr. Laura Murray
Senior Scientist
Department of Mental Health
Johns Hopkins Bloomberg School of Public Health (JHBSPH)
United States

Columbia University (CU)

Columbia University Principal investigator
Dr. Jeremy Kane
Assistant Professor
Department of Epidemiology
Columbia Mailman School of Public Health (CMSPH)
United States

BACKGROUND, RATIONALE, AND OBJECTIVES

a. Background

There are currently just under one million people with HIV in South Africa who have initiated antiretroviral therapy (ART) but remain unsuppressed and globally that number is far greater. South Africa has the largest HIV care and treatment program in the world, yet progress towards the UNAIDS 90-90-90 targets—90% of infected patients knowing their status, 90% of those on ART and 90% of those virally suppressed—has stalled. Recent estimates suggest that just 47%(1) of all infected patients in South Africa are suppressed, significantly lower than the UNAIDS target of 72%. Our work has shown that the third 90 target, which encompasses both long-term retention in HIV care and adherence to treatment, is well below ideal (with nearly 1 million people unsuppressed on ART) and new strategies are needed to address barriers to remaining in care and virally suppressed. Unsuppressed patients can suffer from morbidity and mortality associated with HIV and can pass on the infection to uninfected partners. Therefore, if effective approaches could be found to keep patients on treatment, adhering and virally suppressed, the impact would be significant.

Most interventions that have been tested to support patients who have struggled to remain adherent on ART have shown limited results(2). The majority focus on counselling patients on how to adhere to treatment but don't address the many overt or indirect barriers patients face in consistently taking ART. In South Africa, intimate partner violence (IPV), experienced by up to 50% of women, is one major barrier to adherence(3,4). Addressing IPV is of critical importance by itself and could have large effects in supporting ART adherence.

The Common Elements Treatment Approach (CETA)(5) is an evidence-based intervention comprised of cognitive-behavioral therapy (CBT) elements. It is unique from other CBT models in that it can flexibly address a range of commonly co-occurring mental and behavioral health problems prevalent among people living with HIV, including IPV, depression, traumatic stress, anxiety and substance use. It also deals with the key practicality issues in global mental health as it is a more cost effective, scalable and sustainable model that addresses disease comorbidities and is delivered by lay counselors. The group that has been assembled for this study have completed three clinical trials of CETA in low- and middle-income countries (LMIC) among violence-affected populations. In Iraq and Thailand(5–7), CETA had large statistically significant effects on improving depression, posttraumatic stress, and anxiety (Cohen's *d* range: 0.80 to 2.38 across outcomes). In Zambia among an adult sample in which 33% were HIV-infected, CETA was both statistically and clinically superior to standard of care in reducing IPV (d=0.49) and hazardous alcohol use (d=0.43)(8) with high treatment engagement (>80%). Studies also show the CBT elements within CETA are effective for improving ART adherence(9–16). The group has also tested Telephone CETA (T-CETA) where CETA is delivered by phone or smartphone, with or without video and

shown its success. CETA therefore has strong potential to improve HIV outcomes in violence-affected populations.

b. Rationale

South Africa has the largest HIV epidemic in the world, including one of the highest HIV prevalence estimates and the largest treatment program globally. An estimated 7 million people are living with HIV in South Africa and over 4 million are accessing antiretroviral therapy (ART)(17). The national ART program has made impressive gains in terms of reducing morbidity and increasing life expectancy(18–22) but incidence remains high (0.79% per year among adults)(23) particularly among young women. Some of this is related to those transmitting HIV in the absence of treatment, while in other cases it is related to patients with elevated viral loads currently or previously on treatment.

Poor HIV treatment outcomes reduce the impact of the massive investment in treatment. Poor retention and viral suppression leads to treatment failure, disease progression, transmission and sometimes death(24–33). If patients return to care after defaulting, they often require more expensive second-line drugs(34,35) as we have shown in South Africa(34,36). Successful treatment requires sustained lifetime adherence. Only with high rates of linkage, early initiation, adherence, retention and viral suppression will transmission decrease(24).

Violence negatively affects treatment outcomes including adherence and retention in HIV care and is a major barrier to achieving the 90-90-90 goals. Violence is an endemic problem in South Africa, particularly IPV. A 2016 survey among 3,515 South African young adults found that lifetime reports of physical abuse was 56% with 18% reporting abuse in the past year(37). The link between IPV and negative HIV treatment outcomes has also been established worldwide(3,38) and in South Africa(4). Women with HIV who experience IPV are less likely to adhere to PMTCT regimens(39), PrEP(40) and ART(41). A 2015 review found that among HIV-positive women, IPV was associated with a 50% reduction in ART adherence (OR 0.48; 95% CI: 0.30-0.75) and a 36% reduction in viral suppression (OR 0.64, 95% CI: 0.46-0.90), though most of the data came from the U.S.(42). One recent study from South Africa found that among young adults, IPV was associated with a 5-fold decrease in ART adherence (OR 5.37; 95%CI: 1.37 to 21.1), a 4-fold increase in depression (OR 4.25; 95% CI: 1.64 to 11.0), and a 4-fold increase in substance abuse (OR 4.11; 95% CI: 1.42 to 11.9)(43). These studies suggest that achieving 90-90-90 would be strongly supported by addressing IPV.

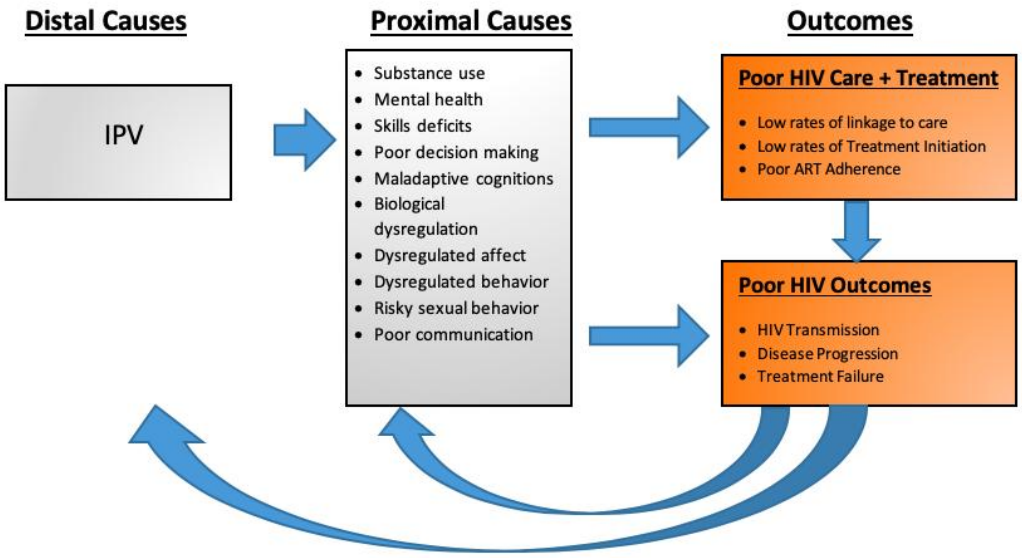


Figure 1 - Conceptual Model

HIV positive women who experience IPV are at high risk for mental health and substance use problems that also negatively impact HIV outcomes (Figure 1 Conceptual Model). IPV occurs at high rates among HIV-positive women(44–47) and has been found to *directly* impact HIV outcomes(48) (CD4 counts and viral loads). IPV may also impact HIV outcomes *indirectly*, mediated through comorbid mental health problems and substance use.(46,49,50). Co-occurrence or comorbidity of IPV, substance use and mental health symptoms is the "norm" and puts individuals at even greater risk for poor HIV outcomes(51,52). We hypothesize that by reducing mental health problems, violence and substance use, we will be able to create more healthy behavior changes including increased adherence.

There is a lack of effective, evidence-based interventions that address multiple, comorbid underlying barriers to HIV care and treatment. Several reviews suggest behavioral interventions directly targeting adherence alone, such as medication reminders, counseling support and contingency management, can improve ART adherence, although the effects are rarely durable(13,16,53–55). Other studies have focused on treating one co-occurring mental health or social problem (e.g., depression, traumatic stress) that correlates with poor ART adherence and retention. Although these approaches have shown promise at both treating mental health problems and initially increasing ART adherence, maintenance of adherence over time shows mixed results(12,56–60). A review of violence and HIV interventions found that treating IPV within an HIV clinic is acceptable and feasible, however, most approaches(61) (e.g. education, safety planning) were not effective in reducing IPV nor improving HIV outcomes. To date, interventions have been siloed (to treat one disorder only), and are prescribed interventions that do not account for the normal comorbid presentation of individuals such as IPV, substance use *and* mental health(48,62,63)., Approaches that address the multitude of comorbid underlying problems unique to each client are urgently needed to combat negative HIV outcomes.

There is currently limited evidence on effective ways to intervene on IPV to improve HIV *treatment* outcomes. The Common Elements Treatment Approach (CETA)(5,64) is a Cognitive Behavioral Therapy (CBT) approach pioneered by our research team (Johns Hopkins PI Murray) and has been shown to be effective at reducing IPV as well as other comorbid problems related to HIV outcomes, including traumatic stress, depression, anxiety and substance use (see preliminary studies(5–8,65)). CETA consists of the same individual CBT elements found to reduce depression and traumatic stress, as well as to

increase adherence in HIV affected populations. Uniquely, CETA is a multi-problem, flexible approach that allows for the elements to be individualized to the client and targets both the distal (violence) and proximal (mental health, substance use) causes of poor HIV treatment outcomes within a single approach. CETA can be delivered by lay providers, and usually consists of 6-12, 1-hour sessions. Based on the problem presentation, CETA providers decide which elements, order and dose (of each element) will best address the reported problems.

Evidence-based cognitive-behavioral therapy for HIV-infected women experiencing IPV addresses key sequelae associated with experiencing IPV, including mental health problems, substance use, and skills deficits. Addressing violence and comorbid underlying problems rather than simply trying to incentivize retention and viral suppression, has stronger potential to impact HIV treatment outcomes.

c. Objectives

We will test CETA's effectiveness at increasing viral suppression and reducing violence in a community-based randomized trial of 400 HIV-infected women who have recently experienced IPV, with CETA delivered to them alone or with their male partners (with at least 75 women with partners). Our aims are:

- **Aim 1:** Among HIV-infected women on ART who have experienced IPV and have an unsuppressed viral load or have missed or late visits, we will assess the effectiveness of CETA vs. active control at increasing the proportion retained and virally suppressed by 12 months and at decreasing the incidence and severity of IPV and other mental and behavioral health problems using an individually randomized trial. *Hypothesis:* CETA will improve retention and viral suppression and reduce IPV, mental, and behavioral health problems vs. active control.

- **Aim 2:** To identify mediators and moderators of CETA's effect on the primary outcome (retention and viral suppression by 12 months). Our primary mediator will be IPV and primary moderator will be partner involvement. *Hypothesis:* Reduction in IPV after CETA will mediate improvement in retention and viral suppression among women who receive CETA; partner involvement in CETA will increase the effect size.

- **Aim 3:** To assess the cost and cost-effectiveness of CETA vs. active control at increasing the proportion of unsuppressed women who have experienced IPV who are retained and virally suppressed by 12 months. *Hypothesis:* CETA will involve additional costs vs. standard of care but with better retention and viral suppression at 12 months, making it cost effective.

- Aim 4: To explore the experience of receiving CETA from the perspective of CETA participants post-intervention, including knowledge and skills obtained, acceptability of reporting on and discussing violence, as well as perceptions of the impact of CETA 24 months or more post-intervention. Hypothesis: The qualitative exploration will provide an in-depth understanding on the real experiences, perceptions and acceptability of CETA and durability of the intervention.

OVERVIEW OF STUDY DESIGN

In order to achieve all three aims, we will conduct an individually randomized trial of the effectiveness of CETA for improving viral suppression and retention in HIV care among virally unsuppressed women experiencing IPV. Recruitment will be from an HIV clinic and we will enroll women who: 1) have experienced IPV within the last 12 months; 2) have initiated HIV treatment; and 3) have a last unsuppressed viral load or who have defaulted on treatment or missed or were late for visits in the last year. Women will be encouraged to invite a partner to be part of the CETA intervention. The woman will be the unit of analysis. The primary outcome is a composite measure of retention in care and viral suppression by 12 months. Because it is critical to know if any effects of CETA on retention and suppression are sustained, we will continue to follow women for a total of 24 months, approximately 21 months after CETA is complete, to identify long term effects. We will also assess whether having a partner involved in CETA is a moderator of CETA's effects and examine possible mediators of CETA's impact on HIV outcomes, including IPV, mental health and substance use. Potential mediators and moderators will be measured with a battery of instruments and administered using a tablet-based questionnaire. This study is an effectiveness trial in that recruitment and care will be conducted within care systems already in place.

To achieve the 4th aim, we will conduct 3 focus group discussions (with 6-10 participants per group) and 10 in-depth interviews with study participants (this may include those who have been part of the FGD) post-intervention who completed the intervention in 2023. We will also conduct 5 in-depth interviews with the clinic healthcare providers (adherence counselors) and 5 in-depth interviews with CETA providers. The maximum total sample size for this objective will be 50 participants. All participants will be purposively selected.

STUDY SITES AND POPULATION

a. Study Sites

The study will be conducted in Johannesburg, South Africa at one or more large HIV public sector sites. One such site will be the Themba Lethu HIV clinic**,** a comprehensive care management and treatment site in Gauteng Province. Themba Lethu is a large HIV testing, care, and treatment site located at the Helen Joseph Hospital. Themba Lethu is one of the largest HIV clinics in South Africa as it has initiated > 30,000 adult patients on ART. If a sufficient number of women are not eligible to enroll in the study at TLC, then other suitable HIV clinics in Gauteng will be identified and included in the study.

b. Inclusion and Exclusion Criteria

Study participants will be adult women who are HIV positive, have initiated HIV treatment, have an unsuppressed viral load or who have defaulted from treatment since their last viral load, and have experienced intimate partner violence (IPV). Participants will be recruited by study staff after a warm hand-off referral from clinic staff. We will also enroll their male partners if the woman chooses to include them. The minimum age of research subjects will be 18. All subjects will be recruited from HIV clinics.

Patient inclusion criteria will be:

- Adult HIV positive women >= 18 years old

- Initiated HIV treatment
- Most recent viral load >50 copies/mL, have defaulted from treatment or had a missed or late (>14 days) visit in the last year
- Has experienced IPV in the past 12 months
- Has their own phone and can receive text messages
- Literate and able to speak and read one of: English, Zulu, SeSotho
- If including a partner, the woman has disclosed HIV status to the partner that will be invited to participate

Exclusion criteria will be:

- Unwilling to complete the informed consent process
- Currently psychotic or on unstable psychiatric regimen
- Suicide attempt/ideation with intent and plan, and/or self-harm in the past month
- Enrolled in any other HIV treatment intervention study

For Men, the inclusion/exclusions criteria will be

Male inclusion criteria will be:

- Adult >= 18 years old
- Invited by partner to be in the study
- Partner has disclosed their HIV status
- Has their own phone and can receive text messages
- Literate and able to speak and read one of: English, Zulu, SeSotho

Exclusion criteria will be:

- Unwilling to complete the informed consent process
- Currently psychotic or on unstable psychiatric regimen
- Suicide attempt/ideation with intent and plan, and/or self-harm in the past month

Note that having one's own phone means not sharing it with anyone else, including their partner. If a couple is participating, each partner would have to have their own phone that is not shared between them to be enrolled in the study.

Inclusion and Exclusion Criteria for Qualitative Study Phase

Inclusion criteria for participants - CETA users
- Has participated in the CETA study in 2023 and was randomized into the treatment arm
- Have received at least 5 completed CETA sessions and completed their CETA sessions in 2023
- Willing to complete the informed consent process

Exclusion criteria for participants - CETA users
- Unwilling to complete the informed consent process
- Currently psychotic or on unstable psychiatric regimen
- Suicide attempt/ideation with intent and plan, and/or self-harm in the past month

Inclusion criteria for healthcare providers

- Healthcare providers (Adherence counselors at Ithembalethu clinic and Zola Clinic) during CETA study (November 2021 – August 2023) and actively participated in the patient referral to CETA study
- Willing to complete the informed consent process

Exclusion criteria for healthcare providers

- Unwilling to complete the informed consent process
- Did not actively participate in CETA study referral during implementation

Inclusion criteria for CETA providers

- Willing to consent to be part of the CETA qualitative phase
- Has been actively providing CETA sessions to study participants since study implementation and in 2023

Exclusion criteria for CETA providers

- Unwilling to complete informed consent process

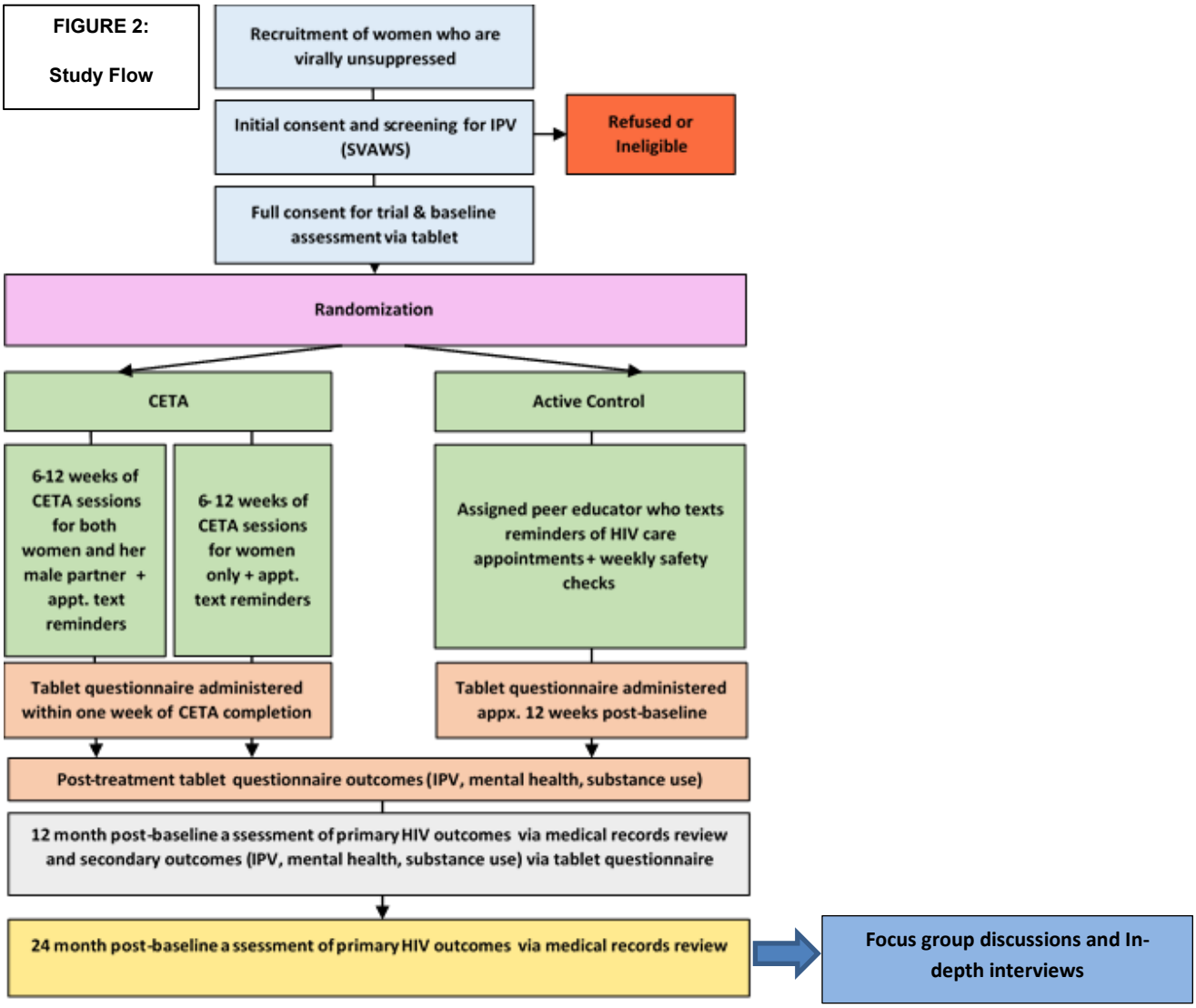
STUDY PROCEDURES

a. Overview

Figure 2 below show the study flow. Below we describe each aspect of the study in detail.

FIGURE 2:

Study Flow



b. Clinic Engagement

Before any data collection begins all local approval processes required by the Department of Health will be followed; meetings with clinic staff will take place in order to explain the procedures of the study, the risk and benefits, the confidentiality of results, to establish distress protocols and the referral processes that should be followed at the clinic, identify space to conduct the study, and to allow for any questions. Study participants will be enrolled from subjects referred from the HIV clinic by clinic staff. Study staff will work with clinic staff to ensure they refer to us patients they believe meet the screening criteria of HIV-positive, on ART and having an unsuppressed viral load or evidence of defaulting from treatment or missed/late visits but not necessarily around experiences of violence.

c. Recruitment

Recruitment will be from HIV clinics. Initial recruitment will be done by clinic staff (nurses and doctors) who will refer women to study staff whom they believe to be eligible by virtue of being on ART and virally unsuppressed, defaulted from treatment or had missed/late visits. They will describe the study as testing an approach to help those struggling with treatment adherence. Specifically, we will ask clinic staff to refer adult women who have initiated ART and are virally unsuppressed (viral load > 50) or have defaulted from treatment or had a missed or late visit in the last year to a member of our study team. This would be typical knowledge clinic staff has on women. Recruitment materials will not be provided as this may result in increased risk if there is a paper laying around the clinic with criteria. Clinic staff will not ask any questions of these women about experiences of violence beyond what they might otherwise do as part of usual clinical care. During our previous research, this has worked well.

Study staff will speak with any woman who expresses a willingness to learn more about the study. Therefore, potential participants will have no initial contact with study staff unless they express an interest in hearing more about the study. Study staff will be highly trained and will receive specific training in human subject's research and good clinical practice. All referrals happen in person and introductions will occur at standard of care visits.

d. **Recruitment process for Focus group discussion and In-depth interviews**

Recruitment of participants for the qualitative phase of the study, will be done in the post intervention period. All those participants who were enrolled into the CETA study and randomized to the CETA treatment arm between 1 January and 31 July 2023 will be contacted via SMS using the contact details they provided, and asked if they are interested in participating in a follow-on discussion to the intervention. Those study participants who can be reached and express an interest in participating will then receive a phone call from the study team member who will explain the additional consent process. The full informed consent process will be completed in person before the FGDs and IDIs.

The recruitment process will adopt a purposive sampling method, as we are only selecting participants from the treatment arm who completed the intervention in 2023, making the sampling population much smaller, so this method will allow us, to maximize on the available population size to gain in-depth insights from the participants. For the recruitment of healthcare providers and CETA providers, they will be contacted and informed about this phase of the study and then asked if they will be interested in participating, informed consent will be conducted before the interview.

e. Screening and Screening Consent

Patients who agree to be referred to a member of our study team will receive a brief consent form only for screening to determine eligibility. This conversation will take place in a private location and include only the study staff and the patient. Potential participants will be counseled that they can refuse to participate in the study and still receive HIV care at the treatment site with no risk to the quality of care they receive. The short consent form will explain what questions participants will be asked, including questions related to IPV, as part of the screening process. All those consenting to be screened will be assigned a unique Screening ID (generated *a priori* by a study team member) and administered a screening questionnaire to confirm the inclusion/exclusion criteria. This will include the Severity of Violence Against Women Scale (SVAWS) physical/sexual violence subscale to assess IPV exposure, which previously been used among women who experienced IPV in South Africa. This is a self-administered tablet-based form. Results of the screening will be documented on a tablet-based screening form

immediately. For those meeting all inclusion criteria, study staff will obtain full informed consent (described next). Consent will cover all remaining study activities (full assessments, randomization, intervention, data collection, etc.). All women who are screened for this study will be given resources for hotline and other local programs/experts in IPV, regardless of the type of abuse they may report (including verbal). Consent documentation will be done either using a paper form or via electronic consent by having the participant sign the document in REDCap. If an electronic signature is used, it will be on a PDF version of the IRB approved and stamped consent form. This will be done via a tablet in person (as would be done for a paper consent) and the participants will have access to the consent form as the consent process is taking place. Even if participants sign the consent electronically, they can also have a paper copy of the information sheet. As such, no electronic version of the e-consent will be made available to the participants.

None of the screening data contains identifiable information. We will store paper files in locked filing cabinets. We will store electronic files in computer systems with password protection and encryption. For those who screen in and choose to participate, screening data will be linked to enrollment data through a study ID. For patients who screen out or who screen in and choose not to participate, only their screening data will be stored in order to allow us to later describe reasons for being excluded from the study. As with all other data, the data will be kept for 7 years post closure and then destroyed. No contact information will be kept for future research. Data access will be limited to the study team.

f. Full Consent

The full consent process, including signed informed consent, will be administered by a trained study staff member. The study staff will emphasize the voluntary nature of the study. The full consent form, for those who are eligible and interested in being in the study, will describe the nature and goals of the study and assure subjects their information will be kept confidential. We will explain to subjects the possible treatment options in the study and that they will not get to decide which group they will be in, but rather that we will decide by chance and they will have a 50-50 chance of being in either group. We will explain that if they are randomized to the intervention arm (CETA) their care will be different from the active control (text+safety) arm and the options they have to not participate. It will also be explained that they will be free to withdraw from the study at any time with no risk to the healthcare they receive at the clinic. The consent process will take place in a private space and women will be given adequate time to decide whether they want to participate and will be allowed to leave the clinic and return at a later time to complete the consent process if they choose to. Consent documentation will be done either using a paper form or via electronic consent by having the participant sign the document in REDCap. If an electronic signature is used, it will be on a PDF version of the IRB approved and stamped consent form. This will be done via a tablet in person (as would be done for a paper consent) and the participants will have access to the consent form as the consent process is taking place. Even if participants sign the consent electronically, they can also have a paper copy of the information sheet. As such, no electronic version of the e-consent will be made available to the participants.

For safety reasons, we will inform women that they do not need to take a copy of the consent form if they do not wish to do so in order to minimize disclosure of information since the woman's consent form includes experience with violence.

The consent form will include permission to access their clinic records. The consent form will also state that the subject agrees to complete a baseline questionnaire for our study and that the questionnaire responses can also be linked to the subject's treatment records. Participants will be assured that data

collected for our study will be kept strictly confidential and will never be reported to clinic staff or anyone outside the study team. We will also make clear to women the potential risks to being in the study, including the potential for increased risk of violence if associated with being part of a study. It will also be explained to the participant that they are also able to include their/a current male partner to participate in the study with them if they are randomized to the intervention arm and why this might be beneficial. Details of partner inclusion in the study are described next. Because inclusion in the study requires being able to send appointment reminders and questions to assess the safety of participants, contact details including a cell phone number that the participant can access safely to receive study messages and reminders will be collected and checked. After explaining the study, the study staff member will allow time for questions. They can take as long as they like and can return at another time to complete the process.

g. Qualitative component consent

For the FGDs and in-depth interviews with both recipients of care and providers, a separate information sheet and consent form will be administered by a study interviewer. We will make it clear to the study participant that this qualitative exploration activity is voluntary and that, if they decide to not participate in the FGDs and/or IDIs, it will not influence anything in the study or their follow up assessments or any aspect of their healthcare, and will not affect their work at the healthcare facilities as healthcare providers.

h. Male Partners

The violence literature encourages intervention with both males and females to effectively address IPV. After a detailed explanation of the intervention, women who consent will be asked if they are willing to include a current male partner in the intervention if they are randomized to the CETA arm. They will be informed that this is **not** a requirement to be in the study and that they can participate whether or not they want to include their current male partner. We will explain that if the woman is randomized to CETA and a male partner is included, both partners will be invited to participate in CETA *separately*; they would not be counselled together. In our team's experience in Zambia, there were many males interested in participation and who enrolled and remained in CETA treatment throughout. Our qualitative findings indicated that women wanted their partners to join them in treatment and were generally invested in trying to improve the relationship (rather than exit it). We will explain to the woman participant that we will not disclose to the male partner that the woman has reported IPV.

Women who wish to include a partner will be given an information sheet to give to their partner describing the study and inviting them to participate. The information sheet will invite the male to participate in a program that can help improve health and interpersonal relationships and will note that there will be tea/biscuits at the visit. This information sheet that will be given to the male partner will not mention IPV. Those men who are willing to know more about the study and potentially participate will be asked to either attend information sessions at the clinic on a specified time and date or to ring a free study number where they will be given more information about the study. Alternatively, they could complete their contact details and sign the form indicating that they give consent for the study team to contact them. They can then either return the form themselves to a secure designated collection point at the clinic or return it with their partner. Appointments will be made with all those men who indicate they are interested in the program to come to the clinic or meet at alternative secure locations to complete the consent process. The consent will focus on our primary outcome of adherence, and CETA work with the males will focus on increasing healthy behaviors and skill building to support their

partner. We feel that in order to help ensure the safety of the women participants, it is important not to state that they were asked to join specifically because of violence.

Included male partners will be consented and participate in CETA, but we will not collect any study outcome data on them; only demographic and intervention data. We are not capturing outcome data on men because no men will be included in the control group to conduct a comparative analysis and our previous trial already established CETA effectiveness for reducing men's hazardous alcohol use and IPV perpetration. In addition, members of the study team previously showed that CETA can reduce women's experience of IPV by reducing men's hazardous alcohol use and aggression. However, we also acknowledge that in real-world HIV care settings, recruitment of couples will not always be possible, that there are many women who experience IPV outside of a long-term relationship, and that impacts of IPV can persist even after the relationship has ended. To enhance generalizability, we will include women who will have a male partner participate *and* women who will participate without a male partner. The consent process for men will take place in a private space and they will be given adequate time to decide whether they want to participate and will be allowed to leave the clinic and return at a later time to complete the consent process if they choose to. Consent documentation will be done either using a paper form or via electronic consent by having the participant sign the document in REDCap. If an electronic signature is used, it will be on a PDF version of the IRB approved and stamped consent form. This will be done via a tablet in person (as would be done for a paper consent) and the participants will have access to the consent form as the consent process is taking place. Even if participants sign the consent electronically, they can also have a paper copy of the information sheet. As such, no electronic version of the e-consent will be made available to the participants.

We will include only one partner per woman and the partner must be a current partner. To help support the safety of women who enroll a partner in the study, we will take two steps. First, after each session that a male partner attends, we will send an additional safety check in text to the female partner to ensure her safety. Second, if a female in the study reports that her male partner's participation in the study has led to increased risk to her, we will terminate participation of the male partner. We will however refer the male partner for support counselling outside of the study.

i. Baseline Assessment

Women who consent to be in the trial will complete a baseline assessment (about 30-45 minutes) using a self-administered tablet-based questionnaire (as with the SVAWS screener). This approach has been shown to be feasible and acceptable in studies conducted with this population as the majority reads written English (though it will be done in English, SeSotho and Zulu, the main languages at the clinic). The system allows responders to navigate and answer sensitive questions privately and discreetly, with the blinded assessor available to respond to questions.

This baseline assessment will be completed immediately after consenting when possible. If not possible due to extended time at the clinic or if a woman wishes to consider consent, an appointment will be made as soon as possible to complete the baseline assessment. It will take place in a private location in the clinic and can be done while participants wait for their medications after they have seen a clinic provider given that typical wait times can be up to two hours. Food will be offered to participants during the assessment, as is customary when completing a research survey particularly in low-resource settings.

j. Randomization

At the clinic, study staff will have a randomization code within the tablet system used for data collection. Following completion of the baseline assessment, the computer will generate the next randomization group. Randomization will be blocked to ensure that roughly equal numbers end up in each arm. The computer will also generate the randomization assignment for the Randomization ID assigned to the patient (and subsequently linked with their Screening ID). Randomization IDs and assignments will be generated *a priori* by a U.S.-based study team member and linked into the computer system. We will inform the participant of their assignment immediately after the baseline assessment. Those participants who are assigned to CETA will then be asked whether they want to invite a partner and if so, will be given the information sheet and forms to be completed and returned by their partner. Because randomization will occur only after the baseline assessment, some subjects may drop out before randomization, which will be tracked.

k. Study Arms: Common Elements Treatment Approach (CETA)

CETA, developed by Dr. Murray (Johns Hopkins PI), is a modular, multi-problem, flexible psychotherapy approach that trains a lay provider in nine evidence-based CBT elements so they can treat a variety of common problems, including violence, substance use, depression, anxiety, risky behaviors (sexual, non-adherence), and other trauma-related symptoms. It is well known that individuals often present with comorbid problems – yet treatments are often focal or single-problem focused – for example an intervention that only addresses depression. CETA follows the past decade of the mental/behavioral health research in both high and low-income settings suggesting that focal treatments, while useful in some contexts, are wrought with challenges of scalability, sustainability, cost, and minimal ability to address the multi-faceted needs of most populations. CETA is not a new treatment, but a more cost-effective, scalable, and sustainable approach to delivering evidence-based CBT principles (Table 2) in low-resource settings. As it is comprised of evidence-based, widely used CBT elements, CETA teaches decision rules on which elements to provide based on research evidence generated worldwide, including South Africa, but permits flexibility, allowing for the ability to address comorbidity and individualized treatment(48). CETA is unique in that: a) it is built specifically for lower-income settings and use by lay providers, b) it addresses multiple problems linked to poor HIV outcomes, c) it has been well-studied through rigorous trials in LMIC (6,7), d) it is the only common elements treatment showing strong effectiveness for violence in a sub-Saharan African trial, and e) it is comprised of the same CBT elements that positively impact adherence and retention in both HIC and LMIC(56–58,66–69). In summary, unlike other single-problem-focused HIV CBT interventions, CETA targets multiple proximal causes (e.g. depression, trauma, anxiety, AND substance use) of non-adherence and attrition as well as the distal causes (i.e. IPV) (Figure 1)

Table 2: Common Elements Treatment Approach (CETA)		
Component	**Content**	**Target**
Engagement	Discuss how program helps, identify obstacles to engagement	Promote client buy in
Safety	Assess client risk or harm to self/others, IPV, abuse; initiate safety planning as needed.	Assess/address client safety
Empirically-supported cognitive behavioral elements		
Psychoeducation/Introduction	Program information, normalize symptoms and problems	Psychoeducation; Reduce stigma
Substance Use Reduction	CBT and MI merged to set goals and reduce substance use; identification and strategies for "drivers" of substance use	Reduce substance use, increase social support
Behavioral Activation	Identify and Engage in pleasurable activities	Reduce depressive symptoms; Activate action to engage in helpful programs (e.g., HIV care)
Cognitive coping/restructuring	Identify and connect thoughts, feelings and behaviors; replace unhelpful thoughts with helpful ones in order to feel better and behavior in a more healthy, productive way	Reduce depressive, anxious and trauma-related symptoms, reduce self-blame and stigma, reduce negative thoughts on HIV care; reduce aggressive/violent behavior, reduce risk-taking, improve retention and adherence
Relaxation	e.g., breathing, imagery,	Reduce anxiety and stress-related symptoms
Exposure	Talk about trauma memories or face fears using gradual desensitization	Reduce trauma and anxiety symptoms
Problem Solving	Teach a process of steps to solve problems and make healthy decisions.	Promote health decision making, Skills training for problem solving; improve relationships and communication

* MI = motivational interviewing

CETA is a multi-problem, flexible approach that allows for the elements to be individualized to the client. CETA treatment is typically between 6 to 12 sessions. Sessions are on a weekly basis for approximately 60 minutes and may consist of the following elements: Encouraging Participation/Introduction (i.e. learning about the symptoms and program), Cognitive Coping/Restructuring, Gradual Exposure for trauma, Behavioral Activation, Substance Use Reduction, Problem Solving, Relaxation and Safety. The elements implemented as well as their dosing is dependent on the client's clinical presentation. CETA is flexible in what elements are used, their order, and the dose (the number of sessions an element is done).

CETA has been shown to be effective in reducing mental health symptoms in three different randomized trials in LMIC. A recent study by us utilizing CETA in Zambia showed its effectiveness in reducing reports of IPV from both males (with respect to IPV perpetration) and females (with respect to experiencing IPV) in a relationship. Because CETA addresses multiple problems depending on individual presentation, it has the ability to target several correlates of IPV including traumatic stress responses, communication patterns, behavioral problems like aggression, safety planning, and substance use – all from either a perpetrator or survivor angle. IPV will be addressed in multiple additional ways including: 1) Clients will

participate in safety planning, which includes assessing the severity of the safety concern and developing a plan to prevent IPV when possible as well as a plan to implement when a partner becomes violent. These plans will be created in the first session and updated as needed throughout treatment. 2) Individuals and their partners will be receiving treatment that may address underlying problems related to their perpetration of violence (e.g. substance misuse, unhelpful thinking, trauma symptoms, etc.). We will include women who choose to have a male partner participate *and* women who choose to participate without a male partner.

To address HIV adherence and retention, the content of some of the skills is adjusted. For example, an unhelpful thought we would work on might be "I will never be able to be consistent with taking my medication." With the problem-solving element, we may specifically work on how to better manage consistently taking medication.

At the beginning of each individual session (for both females and males), the Client Monitoring Form (CMF) will be administered. The CMF is administered at the beginning of every CETA session to track symptomology and make clinical decisions. This is a short list of questions that ask about current symptoms and problems, and help an approach like CETA tailor its element choice to the participants' needs, while also tracking progress. This is a clinical tool to help providers and supervisors deliver CETA. Following the end of the study we may also conduct de-identified analysis with the CMF data to explore trajectories of symptom change over the course of CETA treatment.

CETA can (and in this study will) also be delivered by telephone or smartphone, with or without video and is referred to as Telephone CETA or T-CETA. A T-CETA manual has been developed that includes key ideas and techniques specific to virtual administration of CETA elements, including confidentiality, privacy, and ensuring proper connection. This manual has been utilized with success across many project locations, including Zambia, Ukraine, Moldova, Myanmar, Lebanon, Syria, and Mexico. T-CETA reduces the burden of travel for the patient making it easier to engage with the full CETA program. T-CETA requires ensuring that participants have a safe and private space to engage in CETA over the telephone and then following all the procedures of in person CETA but adapted to the telephone modality.

d. CETA training and supervision

CETA leverages lay providers and/or community health workers, usually without any formal mental health or counseling training. In South Africa's National Adherence Guidelines, lay counsellors and CHWs are responsible for mental health screening. In the field of global mental health, this is a widely accepted practice (i.e., task shifting) which is supported by the WHO as well as numerous rigorous trials and a Cochrane review proving they can deliver cognitive behavioral and similar psychotherapeutic treatments with fidelity and effectiveness.

Training will follow the widely accepted apprenticeship model utilized in global mental health of 10 days of in person training, followed by local supervision groups, led by a local supervisor. This model notes

the literature showing that one-off trainings are ineffective, and providers require on-the-job training with supervision and feedback. First, providers (study staff members) are taught to use the evidence-based CBT elements in varying combinations of elements, order and dose to address multiple areas such as violence, substance use, mental or behavioral health problems, and skills deficits that affect HIV care (e.g., healthy decision making, adherence). Within the providers, 2-4 are chosen as local supervisors and receive additional training on how to supervise. Following the 10 day in–person training, groups of 5-6 providers meet each week with one of the local CETA supervisors for approximately 2 hours to review cases, present problems, and decide which treatment elements should be used for each individual. Each local supervisor has weekly calls with CETA trainers for supervision, trouble shooting and further capacity building.

Counselors will also receive an additional 2-day training by a Master CETA Trainer on administering CETA elements via telephone (i.e., T-CETA). This training includes a review of the adaptations as well as live practice of the element adaptations.

e. CETA Delivery

Patients randomized to CETA will meet weekly with a lay provider or community health worker member of the study staff for about an hour once each week, approximately 6-12 times depending on presentation and symptom level. This can be done at a location of the person's choosing or by telephone if they choose, including the clinic but can also be a private space in the community to make it more convenient and comfortable for the participant. This treatment arm will include SMS reminders of their HIV care appointments, similar to the active control group (described below).

f. CETA for male partners

The rationale for including male partners is two-fold: a) extensive violence literature suggests interventions should focus on both the female and male counterparts to effectively combat IPV, and b) our previous trial showed that CETA can reduce women's experience of IPV by reducing men's hazardous alcohol use and aggression.

Female participants will be asked if they would like their male partner included or not. If they would like their male partner included, the female participant will be given an information sheet to bring home to their partner that invites the male to participate in a program to improve health and interpersonal relationships/family life. There will be no mention that any IPV was disclosed by their partner in order to protect the female partner. The letter will indicate that someone will call the male within a week to see if he is interested in the program, and if so, will set up a time for him to come to the clinic or meet at an agreed upon place.

Male partners who consent to receive CETA will complete some short assessments designed to help individualize the CETA treatment. Male partners only involvement is to attend **individual CETA sessions** CETA is provided to each male separately and will be tailored towards general skill building to support their partner. We will not collect outcome data from the men, however, we will track whether or not the men successfully complete CETA treatment. The providers of CETA for men will be the same providers as for the women, and proceed through the same Apprenticeship model of training and ongoing supervision. There will be no disclosure about reports of IPV from their partners and CETA will be tailored to meet the needs of the male. We are not capturing outcome data on men because no men will be included in the control group to conduct a comparative analysis and our previous trial already

established CETA effectiveness for reducing men's hazardous alcohol use and IPV perpetration. Male participants also may not have HIV so they wouldn't be eligible for our primary outcome anyway.

For this study, the female participant will be given an information sheet to bring home to their partner that invites the male to participate in a program to improve health and interpersonal relationships/family life. The letter will invite these men to either attend information sessions at the clinic on a specified time and date or to ring a free study number where they will be given more information about the study. Alternatively, they can complete their contact details and return the form themselves to a secure designated collection point at the clinic or with their partner. Appointments will be made with all those men who indicate they are interested in the program to come to the clinic or meet at alternative secure locations to complete the consent process.

To help support the safety of women who enroll a partner in the study, we will take two steps. First, after each session that a male partner attends, we will send an additional safety check in text to the female partner to ensure her safety. Second, if a female in the study reports that her male partner's participation in the study has led to increased risk to her, we will terminate participation of the male partner. We will however refer the male partner for support counselling outside of the study.

CETA fidelity and competency

A fidelity monitoring system for CETA has been well established through the Hopkins teams' clinical trials, where session information is documented by the CETA provider, the local CETA supervisor, and the CETA trainer (all members of the study team). Since audio-taping is not a feasible long-term monitoring technique in LMICs, we developed a process of triangulation across the counselor, supervisor and trainer to document and monitor fidelity, allowing for flexibility in "fit" and cultural modifications. Counselors and supervisors are trained to objectively document what they did in each session relating to specific steps outlined in each CETA element. Counselors document and report this to local supervisors, who document the case details in a database. This database is reviewed weekly by the trainer who gives feedback and coaching on each case until competency is reached. Each element in the CETA manual is executed through detailed "steps" – many of which are direct quotes. This design was deliberate and lends CETA to have fidelity tracked easier than many psychotherapeutic manuals. If counselors miss steps (i.e. low fidelity), they are expected to complete or re-do the element steps to prevent significant severe "drift" from the outlined intervention. Our fidelity includes what CETA elements are chosen, when they are delivered, completion of steps within each element, and the frequency in which each element is delivered.

g. Study Arms: Active control (Texting + Safety)

Reviews of mHealth have concluded there have been few efficacy studies for retention and viral suppression and results have been mixed (some showing positive effects on adherence, some no effects). Despite this, mHealth interventions have been recommended as a cost-effective improvement upon standard of care for HIV retention in sub-Saharan Africa and therefore make an appropriate active attention control.

Our comparison arm will be an active control receiving usual care for IPV, which, in South Africa means no formal intervention. However, we will send text messages monthly to our control group participants to remind them of HIV care appointments(70). The widespread use of mobile phones in LMICs has led to numerous studies investigating how text-messaging can promote adherence and retention(71–76).

Despite mixed results, it remains a suggested, low-cost method that may help improve retention and adherence, and thus viral suppression. Nearly everyone in our clinic population has a phone. Sometimes a phone is shared within a family or friends. This text messaging activity will also be provided in the CETA arm.

In previous CETA studies, the team has utilized text messaging with HIV women experiencing IPV. Text messages will be discussed with the individual and can be "in code" and will not include HIV or IPV specific information. This allows for women to have check-ins as needed without the increased risk. Study staff will receive training on simple example messages (e.g. "Please remember to come to the clinic this Wednesday for your appointment. We will be happy to see you as this is important."), but actual texts can be personalized. Texts may be anonymized to avoid stigma by leaving out references to the clinic (e.g. "We are looking forward to seeing you Wednesday."). Messages can also be more covert such as "Remember to walk Wednesday". If participants are sharing a phone, we will always be talking to participants about phrasing texts in certain ways to assure safety and confidentiality. Study staff will SMS patients in both arms for appointment reminders. Text message appointment reminders will not be interactive. These follow typical procedures at the clinic around HIV care and treatment and are just a reminder message of the appointment day and time.

h. Training and Tracking

Study staff will receive training on simple example messages (e.g. "Please remember to come to the clinic this Wednesday for your appointment. We will be happy to see you as this is important."), but actual texts can be personalized. Texts may be anonymized to avoid stigma by leaving out references to the clinic (e.g. "We are looking forward to seeing you Wednesday."). Messages can also be more covert such as "Remember to walk Wednesday". Personalization and anonymization of messages will be discussed and agreed with the participant at the recruitment/baseline visit. Study staff will SMS patients in both arms for appointment reminders.

i. Safety for both arms

Ethically, due to the population being violence affected, we will need to maintain a safety net for everyone in the study. We will individually meet with each woman to assess the IPV situation and severity, and give community resources to those in the active control arm. At this "zero" session, we will explain that we are going to check in weekly on their safety – including suicide and violence and we will ask how best to do this to assure safety and confidentiality. For example, women may suggest a number of a neighbor or family member, or we will agree on a "code" text that they could explain to others should their phone be shared or lost. We will request multiple ways to contact the women, including ability to message others in case we do not hear from them. Research on suicide and violence indicate that it is much more dangerous NOT to ask someone, than to ask. This in no way has been translated to increased risk, but instead is received as someone looking after them or caring for them. A text does not "force" an individual to do anything that would increase risk.

Before participation in the study begins, we will be meeting with each individual woman to assess her IPV situation and severity and develop a safety plan for identified concerns. Therefore, all women would have a plan that they could put into action. Those in the active control arm will be given community resources including a 24/7 hotline they could call. Those in the CETA condition will be asked weekly about the IPV situation and will continue to receive modifications to a detailed safety plan as needed, as

well as have access to the CETA provider via SMS and the 24/7 hotline. South Africa has numerous such hotlines and programs to support victims of rape and violence. These include:

1. The Tears Foundation which have a 24/7 hotline for anyone experiencing Gender-Based Violence or Domestic Abuse, which is accessible 24/7 and in all 9 provinces in South Africa (https://www.tears.co.za/gbv-domestic-abuse/)
2. People Opposing Women Abuse (POWA) offer counselling (face to face) and legal support as well as some short-term sheltering (https://www.powa.co.za/POWA/get-help/)
3. Child Line offer counselling support to abused and abandoned children and their families – for any woman who has concerns for their children. They offer a 24/7 line (https://childlinegauteng.co.za/)
4. LifeLine South Africa have a dedicated 24/7 counselling line for victims of IPV/domestic violence/gender abuse (http://lifelinesa.co.za/)
5. SheConquers SA also has support hotlines for women experiencing violence (http://sheconquerssa.co.za/emergency-connect/)

To maintain a safety net during the study, we will send three suicide questions and one IPV safety question via SMS weekly during the intervention period (3 months). These questions are:

1) "Are you thinking of killing yourself?"
2) "Do you have a plan to kill yourself?"
3) "Do you have the means to kill yourself?"
4) "Are you at risk of serious injury or death from interpersonal violence?"

We note that the last question will not be sent to male partners, only to women. We can also provide cell phones to those enrolled (regardless of arm) if they do not have their own, though as this is an inclusion criteria, this would only likely happen if a woman lost her phone during the course of the study. Questions can also be modified, working with the study participant to ensure that the question is disguised.

Texts on IPV may be altered to avoid risk if there is concern that a partner or other perpetrator of violence might pick up this message (for example we may say "Please type Yes if there is any issues you need help with"). These same questions are asked weekly for all study participants (not just those receiving CETA). If all the responses are no, the study staff will do nothing. If any of the responses are yes, the study staff, who will be trained in safety planning, will telephone the participant to ask additional safety questions to assess risk. If the study staff member determines there is minimal risk, a telephone safety contract will be completed. This involves asking the participant to "promise" to keep themselves safe and alive for the next 7 days. If the study staff member decides the participant needs further evaluation or requires assistance, they will phone a CETA supervisor who will call the participant and complete safety planning. CETA supervisors are more trained in safety assessment and planning and will assess, and if needed, plan to meet the participant to assure safety. A supervisor will either speak directly with the client or even travel to their home should there be imminent danger. Johns Hopkins PI, Dr. Murray, wrote a seminal paper on integrating safety planning within LMIC programs regardless of location or availability of professionals – and has successfully delivered this in multiple programs and trials(77). If there is no response we would text again and if still no response we could call. If a patient has previously shown signs of distress, we would attempt a home visit where safe and possible, otherwise the patient will be considered lost to follow up. As the clinic already has protocols for supporting admission to the hospital or referral for services for distressed patients and they already

have strong links to the hospital providers, we will work with the clinic staff to ensure distressed participants get the care they need.

We will be ensuring that study participants have their own phones to enhance safety. The sharing of phones and potential for others to read messages will be discussed when we agree how to send messages to participants. Male participants will require a phone that receive texts as they will follow the same protocol as the women participants for safety concerns (i.e. suicidal thoughts, homicidal thoughts and victimization of IPV).

For women who choose T-CETA we will work with them during the initial in person session to determine ways to keep them safe. We will discuss the risks associated with T-CETA to ensure they have a clear understanding of the potential for their conversations to be overheard and the risk for violence should an abusive partner hear the conversation. This session will include planning to ensure they have a safe and private place to be when in T-CETA sessions, having the option for the participant to contact the team using a free “call me” text message to inform the counsellor they are ready and in a safe place if they choose and ways that any communications between the counselor and the participant can be coded to ensure privacy. For example, rather than asking, "are you in a safe and private space for today's session?" the counselor might use an initial coded question tailored to that participant associated with several possible benign responses, determined in advance, to indicate "YES" I am alone, it's ok to continue, or "NO" I can't talk, with an exit strategy planned as well. The safety plan will also include a pre-determined plan to decide what will happen if the counsellor hears voices in the background, or the participant’s tone of voice changes, etc. These can include changing the topic of conversation or ending the conversation completely and then later rescheduling the session.

We will end each T-CETA session with a plan for determining the success of the T-CETA approach and any plans to change to in person CETA. This can be done in coded form if the participant wants.

j. Follow-up and Retention

There will be four data collection points: baseline, and 3, 12, and 24 months post baseline. For a purposively selected sample of those participants (n=40) who completed the intervention in 2023 there will also be a qualitative data collection point around 24 months (+/- 3 months) post intervention. Electronic medical records will be obtained to assess our primary outcome. This data collection will be completed in-person. We will assess, violence, mental health and substance use at 3 data collection points: baseline, 3 months post-baseline (the approximate length of CETA treatment and again at 12 months (Figure 2). Because our primary outcomes are retention based (retention and viral suppression) we have no plan to retain patients in the study beyond outreach to complete the CETA intervention. Any effort to do so would undermine the results of the trial.

At 3 months post-baseline (end of the CETA intervention) and 12 months post-baseline, participants will again complete the following tablet-based instruments: SVAWS, CES-D, HTQ, and ASSIST. Although the 3-month time-point could impact the primary retention-based outcome, we feel it is important given the dynamic nature of mental/behavioral problems, and any impact should be equal across arms. **With the exception of contacting participants for post-baseline assessments , qualitative data collection and safety checks, research staff <u>will not contact participants for the reasons stated above</u>**. This is essential for the trial given the intervention is designed to improve retention and viral suppression as well as reduce violence. Questionnaire data will also provide key patient-level data for evaluating costs and we will also collect resource utilization data (drugs, lab tests, supplies, staff cadre consulted etc.)

DATA SOURCES AND MANAGEMENT

a. Baseline and follow up data

At the baseline visit we will collect the following information:

- **Enrollment Information** (e.g., clinic ID, enrollment date, etc.)
- **Contact information** (e.g. phone number, address where they stay, who they share their household with)
- **Demographic information** (e.g., date of birth, sex, socioeconomic data, etc.)
- **HIV-related information** (only for women): (e.g., initiation date, ART regimen, pharmacy data, lab results, etc.)

At the baseline and at 3 and 12 months, participants will complete the following tablet-based instruments:

- **Severity of Violence Against Women Scale** (SVAWS): 46 items assessing frequency of recent IPV. Subscales include: a) threats of violence (19 items); b) physical violence (21 items); and c) sexual violence (6 items). It was previously used in a study of IPV among women with partners who have alcohol abuse in South Africa(78).
- **Center for Epidemiological Studies-Depression Scale** (CES-D): 20 items assessing frequency of depression symptoms over the past week (never, 1-2 days, 3-4 days, 5-7 days)(79).
- **Harvard Trauma Questionnaire** (HTQ): 17 items assessing lifetime traumatic events. 39 items assessing post-traumatic stress symptoms in past week (not at all, a little, quite a bit, extremely)(80).
- **Alcohol, Smoking, and Substance Involvement Screening** Test (ASSIST): A comprehensive assessment of substance use for a range of substance types(81) .

b. Primary outcome data

Follow-up data for the *primary outcome* for both arms will be passively gathered using routinely collected medical records from the clinics. This is important as any attempts at active follow up would impact our primary outcome, which is viral suppression and retention. As noted, we have successfully used this process at Themba Lethu in the past as data collection is strong and mostly electronic at this site. Themba Lethu has a direct data link with the National Health Laboratory Service which completes all the lab work. Thus, if a viral load is done, no data entry is required for the result to be in the electronic data record at the site. We will not implement any other data collection or follow-up procedures during the study. We will extract the data on all clinic visits and viral loads at 3-, 12- and 24-months post baseline.

c. Secondary outcome data

The tablet-based questionnaire assessments (described above) will be repeated at 3 months post-baseline (end of the CETA intervention) and at 12 months post-baseline for both arms. Although the 3 month time-point could impact the primary retention-based outcome, we feel it is important given the dynamic nature of mental/behavioral problems, and any impact should be equal across arms. With the exception of contacting participants for post-baseline assessments and safety checks, study staff will not

contact participants. Questionnaire data will also provide key patient-level data for evaluating costs and we will also collect resource utilization data (drugs, lab tests, supplies, staff cadre consulted etc.). For patients in the control arm for whom we identify significant mental health issues, we will refer for care.

For the qualitative component, focus group discussions and in-depth interviews will provide an in-depth understanding and insight on perceptions, experiences, feasibility, acceptance and durability of the CETA intervention.

d. Data Sources

The study will require individual research material from several different sources: 1) routinely collected clinic records stored in electronic format (with paper files as backup only if necessary), 2) study questionnaire and resource utilization data, and 3) intervention data and 4) qualitative data from FGDs and IDIs. All data collected by the study will be identified using a Study ID number only. A password protected linking file that links Study ID numbers to patient identifiers (client names, clinic ID numbers, etc.) will be held separately in a secure location. This linking file will be used to 1) allow follow-up clinic record data to be matched to baseline data, and 2) allow the research team members assigned to the case to engage participants in the intervention.

i. Clinic records

No clinic record data will be needed beyond what is routinely collected for patient management. The clinics have agreed to make available for analysis its clinic records in an electronic format that we have been working with for over a decade. We will obtain permission from participants to access these records during informed consent. We will use the following data from medical records at baseline and up to 24 months post-baseline to assess primary and secondary outcomes:

- All visit dates and scheduled visit dates, reasons
- All confirmation HIV tests, CD4, viral load results and dates
- Date of ART initiation and ART regimen
- Pharmacy refill records
- Resource utilization: drugs, lab tests, supplies, etc.

ii. Study questionnaires

After subjects' consent for the study they will be screened for eligibility. The screening questionnaire will contain questions related to mental health, experiences with intimate partner violence and experiences with HIV care and ART initiation. If eligible, and the participant agrees to the second informed consent, participants will be administered a baseline questionnaire. The study instrument, called the Client Monitoring Form (CMF), will be administered to clients using a tablet which allows the responder control to navigate and ability to answer sensitive questions privately and discreetly. The assessment asks questions about symptoms related to common mental and behavioral health problems. It will be kept in a password protected database with identifiers removed. Data collected will be electronically transferred from the field devices into the study database at HE^2RO offices daily. Data on the devices will then be permanently deleted. Data will be securely transferred to BU and JHU weekly.

iii. Intervention records

Intervention data will be maintained for all participants in password protected databases. The data will include no identifying information about the client, only his/her study ID number. These data will include:

- Dates, times and SMS messages sent for both arms
- Attendance at CETA sessions (both in person and T-CETA)
- Weekly checks of symptom severity (e.g., substance use, mental health)
- Clinical notes recorded after each session by the peer educator
- Responses to the weekly safety questions and any additional notes on safety

iv. Focus Group Discussion and In-depth Interviews

For the CETA user insights, FGD's and IDI's will include CETA treatment arm study participants from Zola CHC, who completed the intervention in 2023. Participants need to have participated in at least 5 CETA sessions.

For insights from CETA providers and facility healthcare providers from both study sites (Themba Lethu clinic and Zola CHC). We will also conduct IDI's, with CETA providers, who need to have conducted CETA sessions for the duration of the study, and with healthcare providers who were part of the CETA study's referral of participants and know about the CETA study.

The FGD's and in-depth interviews with the CETA participants, will include questions around experiences with CETA, their perceptions on the varying dynamics of reporting violence and trauma as well as any cultural nuances associated dealing with and reporting of violence and mental health. The in-depth interviews with the CETA providers, will include questions around their experiences in delivering CETA, as well as their perceptions on the feasibility and acceptability of CETA.

Before starting the FGDs and the IDIs, the study team will go through the appropriate information sheet, the participant will then be taken through the consenting process in which permission to record the discussions and take notes will also be solicited. Written participants' consent will be requested first prior to recording any interviews and discussions. The recorded transcripts from these discussions will be saved electronically in a password protected database without any identifiers, including names and or/contact numbers.

All the IDIs and FGDs will take place in-person, at the spaces provided by the community health facilities that we previously used for the trial, as this is much more convenient for the participants to travel to. The informed consent process will be done individually with each participant before starting the FGDs, so when the individuals are gathered in a group for the FGD, they will have all completed the consent process individually in-person. Similarly, for IDIs, the informed consent process will be completed and determined with the individual participant before the IDI discussion starts.

e. Data Entry and Storage

We anticipate entering all clinical and questionnaire data into electronic databases on site, so that paper forms do not need to be removed from the study clinics. In some cases (e.g. if there are power failures or other difficulties with using computers on site), it may be necessary to enter data onto paper study forms and then enter them into a database at the local office. These forms will be stored in a locked cabinet at the study sites, with access limited to the study team. Electronic data files will be stored on

secure, protected drives at the Health Economics and Epidemiology Research Office (HE^2RO) in Johannesburg, with access limited to relevant study staff. In order to support data safety and compliance with South African privacy laws, only de-identified data (with the exception of the signed consent forms) will be sent to and stored at the three US sites.

All subjects will be assigned a seven-digit, sequential identification number. The study ID number will be used to identify individual subjects in the study databases and for all data analysis. For each subject in the study, electronic clinic record number, date of birth, contact information and name will be collected to allow linking of fields extracted from multiple data sources (questionnaires, registers, records, lab reports, etc.) and for longitudinal follow up. Data will be collected using an electronic data entry system (described below). The data will only be collected in an electronic database (i.e. no paper forms will be used) and the form collecting identifying information is separate to and will be stored in a separate database from the remaining questions. An electronic linking file will be created to link this information to a patient ID number. The linking file (i.e. the database containing the study ID and identifying information) will be stored separately from all other data. It will be kept on a secure server at the study office and stored securely, separately from the study data sets, with access limited to the South African study team. The linking file will be kept until all data collection is complete and the final analytic dataset has been created. We will also link data from women with any data from their participating male partner through their study IDs. We will keep a linking file in South Africa that allows us to connect the two and therefore link information on completion of CETA by the male partner and study data for the female partner. All data including the linking files will be stored securely for 7 years post closure and then destroyed. All data collection files will be coded using study ID numbers and not contain subject identifiers. All data will be stored and transferred securely in accordance with HE^2RO and BU policy on data classification and storage.

REDCap or a similar software program requiring secure log-in and access by invitation will be used to create an electronic database to manage any quantitative study data not entered directly into tablets. The database will be used by field staff to double enter data where necessary. Data files will be reviewed by the study team on a monthly basis and queries returned to the site-level staff for response. On a regular basis, the data will be converted to SAS, STATA or SPSS for final cleaning and data analysis. All analytic databases will be password protected with access restricted to the members of the study team.

DATA ANALYSIS

a. Primary Outcome

Our primary outcome is the proportion of participants who are retained and suppressed by 12 months post randomization(34,82). Viral load testing is routinely done at the clinic at 6- and 12-months post ART initiation and every 12 months thereafter. Due to the variability in when viral load testing is done, we will define the primary outcome to be suppression (i.e. a viral load <50 copies/mL) any time up to 18 months. As our primary outcome includes retention, we are not able to contact patients who miss routine viral loads as this would affect attrition. Instead we will use routine clinic data collection (as we have done in the past (83–86)) to determine outcomes. Missing viral loads will be a negative outcome.

b. Secondary Outcomes

- Viral suppression at 3 and 24 months: CETA may have some effects on suppression and retention over the first year on treatment mediated through the increased contact with patients that CETA

entails. It is not clear for how long after the CETA intervention effects will be sustained. Thus, we will look at suppression at 24 months, long after CETA is complete. As our population should be monitored for suppression more frequently than every 12 months, we will also examine suppression within 3 months.

- Attrition at 12 and 24 months - Attrition (the opposite of retention) will be defined as being more than 90 days late for a study visit.
- IPV, mental/behavioral health, alcohol and other substance use: We will measure the effectiveness of CETA in reducing IPV and stress-related problems commonly associated with IPV and HIV, mental health (trauma, depression, anxiety), and alcohol and substance use. We will also assess whether a change in these factors mediates the effectiveness of CETA on the primary outcome.
- Cost and cost-effectiveness: We will estimate the incremental cost-effectiveness of CETA versus active control in achieving the primary study outcome, retained in care and virally suppressed by 12 months, from the provider perspective. If found to be effective, a budget impact analysis will be conducted to estimate the affordability of routine implementation of the intervention at scale.
- Perceptions and acceptability of CETA: Using qualitative focus group discussions and in-depth interviews with both study participants in the treatment arm, CETA providers and healthcare providers. we will also explore the perceptions, acceptability and durability of the intervention, both as a recipient of care and provider and also the feasibility of delivering this intervention which will help inform recommendations for further implementation and scale up of the intervention, which will help inform recommendations for further implementation and scale up of the intervention.

c. Sample Size

Based on the ENHANCE study(85), we estimate that only 40% of those who are unsuppressed will be retained in care and virally suppressed 12 months post-baseline in the control arm. We believe a 20% increase in the percent suppressed and retained between the CETA and control arms would be clinically meaningful. Our primary aim is to analyze the impact of CETA in the full population; however, we have calculated our sample size to ensure our ability to detect differences separately among women who include a partner. With 80% power and 2-sided α=0.05, using a chi-squared test for independent proportions our sample size required is 91 per arm (182 total). To have power to detect mediators and moderators (Aim 2), we will increase the sample size to **400 total** with a minimum of 75 women in the CETA arm who include partners (max of 100), which will give us 80% power to detect an absolute 21% difference between arms in women with partners. To get 75 women who include partners in the CETA arm we will have to randomize about 150 women willing to include a partner if randomized to CETA. We will also include at least 75 partners of women, up to 100.

Themba Lethu clinic alone has about 4000 female patients, while other clinics have similar numbers of patients. Of these, about 1000 had an unsuppressed viral load in the past year. We anticipate that 50% of those we screen will be eligible for the study and of those 50% will enroll. We therefore estimate we will need to **screen approximately 1600 patients** over 18 months, requiring us to screen about 20 patients and enroll approximately 5 patients per week over the enrollment period.

Given we are randomizing 400 women and including up to 100 men, the total sample size for the IRB will be 500.

The IPV literature strongly suggests that more needs to be done with perpetrators of violence (not just survivors), and we know from studies like ours in Zambia that helping male partners led to many positive changes on outcomes, and from the perspective of the women. However, for this study, we wanted the choice to be the womans' – for ethical and safety reasons. Therefore, we could not confirm the ultimate number of male participants we would have.

Sample Size – Qualitative Study Component

For the FGDs and IDIs we will purposively select participants from the main study. We will recruit a total of 40 participants from the treatment arm who completed the trial in 2023. There will be 3 FGDs, with 6-10 participants in each FGD, and 10 IDIs with study participants. We will also recruit 5 CETA providers and 5 healthcare providers who supported referral to CETA from Themba Lethu Clinic and Zola clinic (adherence counselors), for in-depth interviews.

d. Primary Analysis

All primary analyses will be by intention-to-treat. The unit of analysis will be the woman. Our primary analysis will be a comparison of risk differences with 95% confidence intervals. If we identify differences (RD) in baseline covariates we will conduct an adjusted linear regression to get an adjusted RD.

We will analyze direct effects of CETA on continuous secondary outcomes (e.g., IPV [via SVAWS], mental health [via CES-D and HTQ], and substance use [via ASSIST score]) using linear mixed models. Fixed effects will include treatment arm, time, and arm X time interactions. Random effects will include participant ID to account for repeat measures. We will calculate robust standard errors. The models will estimate the difference in mean symptom change from baseline to each post-assessment between the treatment groups. The difference in mean change will be standardized to calculate Cohen's d effect size.

e. Moderator Analysis

In addition to main effects for the primary and secondary outcomes, we will evaluate the impact of potential moderators (e.g., lack of viral suppression, partner involvement, age, ethnicity, HIV knowledge and attitudes, education, physical health, duration on treatment, presence of side effects, regimen) on suppression and retention and mental health outcomes. An interaction between the moderator and treatment arm will be included in models described above. The interaction term will serve as the coefficient of interest in assessing whether treatment effects varied by levels of the moderator. For the effect of CETA by inclusion of partners we will compare women who included a partner in the CETA arm to those who said they would have included a partner in the control arm. Risk differences will be used to assess effect sizes within moderator levels.

f. Mediator Analysis

We will assess the role of potential mediating variables (IPV, mental health, substance use) on the impact of treatment on our primary outcome to tease out the direct and indirect effects of CETA. Several of the proposed mediators (e.g., interpersonal violence) may reasonably be expected to interact with the treatment arm to impact our primary outcomes. Invalid estimates may occur if this interaction is not considered in the mediator analysis. To allow for the possibility of exposure-mediator interactions, we will use a counterfactual approach and follow methods described by VanderWeele and Vansteelandt(87,88) and Valeri and VanderWeele(89). These methods are appropriate for both

continuous and binary mediators and outcomes and allow for estimating valid controlled direct effects as well as natural direct and indirect effects.

g. Cost Effectiveness Analysis and Budget Impact Analysis

Costs will be estimated from the provider perspective over the 12-month study period. Micro costing methods will be used to cost all resources utilized for the care and treatment of the patient during this period, including drugs dispensed, laboratory tests performed, and consultations with clinical staff. This resource utilization will be estimated based on routine patient medical records in addition to study specific patient records. The cost will then be estimated by multiplying the resource usage with the relevant unit costs. In addition to the resources utilized directly by the patient we will estimate costs of infrastructure and shared services including equipment, space, utilities, general supplies and non-clinical staff. These costs will be allocated to the patient using an appropriate allocation factor. Trial specific costs which would not be incurred in routine implementation will be excluded (i.e. screening, informed consent). Unit costs and shared indirect costs will be collected from various sources including national drug tender price lists, state price lists for laboratory and diagnostic tests, national public sector salary banding, site level financial and management reports and our prior HIV costing studies.

Based on the primary outcome, the difference in the cost of producing a patient retained and suppressed by 12 months between arms (total costs of all patients in an arm divided by number achieving primary outcome) as well as the incremental cost effectiveness ratio (ICER) between the study arms (difference in costs divided by difference in effectiveness) will be evaluated. Because cost data are often skewed, and the costs per successful outcome and ICER are ratios of random variables, bootstrapping methods will be used to produce confidence intervals around the cost differences.

If the intervention is found to be effective, we will conduct a budget impact analysis (BIA) to understand the affordability of the intervention based on various possible scale up strategies. This will consider how the intervention may replace (or not) any existing interventions, whether it is likely to change health care utilization and likely intervention uptake. The BIA will take the payer's perspective using a short-term time horizon.

h. **Qualitative Data Analysis**

We will conduct a thematic analysis using NVivo, or similar software such as MAXQDA 2022 (which has artificial intelligence features) to code and analyze findings from the focus group discussions and in-depth interviews. We will develop a codebook, which will be based on key themes coming from the data and the key concepts of the research questions. The codebook and themes will be reviewed and discussed by the coders, ranked in order of relevance and importance to the main objectives before finalizing. Qualitative data will also be triangulated with data from questions related to implementation completed by participants at the 3-month and 12-month follow-up. Qualitative data will be reported based on the key themes and concepts that are identified including any recommendations for adaptation of the intervention that arise from this work.

i. Dissemination of Findings

We seek to disseminate our results as widely as possible including through presentation to key stakeholders, presentation at national and international conferences and through publication in peer reviewed journals. We will also ensure that the study is registered in clinicaltrials.gov before the study begins and then we will ensure that the study results are updated in clinicaltrials.gov as required by NIH

policy. Further, Boston University has an internal policy in place to ensure that clinicaltrials.gov registration and updating is completed which includes a dedicated person who monitors all submissions to the system to ensure that timely updating is completed. Finally, we will ensure that informed consent documents for the trial include a specific statement noting that results will be posted to clinicaltrials.gov.

h. Costs and Payments

Study subjects will not incur any costs from study participation in the study though they may incur transportation costs for CETA study visits. Participants will not incur costs for text messaging or airtime as the program will pay for all messages that are sent to the participant, for messages that are responses to the safety questions and for talk time for CETA sessions done by telephone/video. Participants will be reimbursed 150 rand per study visit. For CETA visits, because adherence to the protocol and retention in care are our outcomes, payment for study visits would have an influence on the outcome and make it impossible for the intervention to be used in practice. Instead for CETA visits we will be reimbursed 50 rand per visit for the cost of transportation if the sessions are completed by telephone, sufficient talk time will be provided for the T-CETA sessions.

i. k. Qualitative Participants – Costs and Payments

Participants, CETA users and CETA providers will be reimbursed R350 rand per study visit, for an FGD and IDI to reimburse them for their time and travel costs.

DATA SAFETY AND MONITORING PLAN

a. Roles and Responsibilities

The PIs, with the assistance of co-investigators, will assume principal responsibilities for monitoring the consent, data collection, data security and safety of the participating staff from the service institutions. As databases are completed, they will be checked for completeness by a member of the study team to ensure missing or illogical data are corrected when possible. Bi-monthly updates on study enrollment numbers and randomization allocation will be sent by the site study team to the MPIs for monitoring progress. Data completeness and quality will also be reviewed on a monthly basis by Drs. Kane and Fox. Calls with the local study team (at least every two weeks, often weekly) will be conducted by Dr. Fox and Dr. Murray, and the CETA intervention will include weekly supervision by the local PI.

We will convene a 3 member DSMB including a violence in LMIC specialist, a statistician, a HIV expert, and ethical specialist. They will assist the study in monitoring adverse events and the random allocation of participants to study arms. The DSMB will meet at least once yearly via phone conference calls for the enrollment phase of the project and through the completion of all active passive follow up, which includes the first three months of the intervention period. Once the enrollment and active intervention period is completed (3 months after the last enrolled client), the DSMB will continue to receive quarterly updates until all one year follow ups are completed but will not meet. Rather, at that point they will discuss the quarterly reports by email and sign off on a yearly report. The DSMB will cease to meet once all one year follow ups are completed for all participants in the study. The DSMB met this milestone and signed off on the last report March 2025 with the completion of all one-year follow-ups for participants. The addition of this qualitative component will not involve any review by the DSMB or body outside of the PI and study team.

At the initial meeting the DSMB will review and approve all study protocols before study initiation to ensure participant safety. Protocols will include formal procedures for reporting and tracking all adverse events; tracking progress in the study; and identifying any need for premature termination of the protocol. Also, during this initial meeting, the DSMB will provide feedback to the PIs concerning enrollment, attrition, and adverse events. At subsequent meetings the DSMB will be provided with summary study progress reports and adverse events. We will not require the DSMB to conduct interim analyses of data prior to end of study because the intervention is not considered harmful, and to avoid erroneous conclusions by doing multiple analyses during the study. The RCT will be registered in clinicaltrials.gov prior to data collection.

b. Trial Safety

Some risk is due to the assessment measures inherent in any mental health care with questions asking about thoughts, feelings, and personal difficulties that may be private (e.g., alcohol, substance use, trauma-related or depressive symptoms). Risks also include possible embarrassment, distress, or inconvenience related to questions regarding personal information and mental health problems. Assessment measures of mental health symptoms include items regarding suicidal or homicidal ideation, and disclosure of traumatic events inclusive of abuse. By US and local ethics standards, reports of suicidal and/or homicidal ideation also ethically require follow-up by the counselors and investigators, and could potentially result in the need to violate confidentiality in order to protect the participants and their families. Thus, this represents a potential limit to confidentiality. For this and other reasons, possible breaches of confidentiality also pose a potential risk in the proposed study. Our team has published specifically on developing safety protocols in low-resource settings and has implemented these in previous work. Still, each of these risks is carefully considered below.

c. Assessment of Safety and Data Safety Monitoring Plan (DSMP)

Adverse Events. The PIs will be responsible for oversight of potential adverse events. An adverse event (AE) is any untoward medical occurrence in a subject during participation in the study. We anticipate two potential types of AEs that could be directly related to study participation. These include distress experienced with regard to research participation and breach of confidentiality and privacy. With regard to both matters, we have protocols in place that include conferring with the PIs or a project mental health provider and appropriate safeguards to reduce risk of breach of confidentiality and privacy (see Human Subjects plan). We anticipate that AEs related to suicidal ideation and/or intent, homicidal ideation and/or intent, clinical worsening necessitating a higher level of care, and neglect/abuse may come to the attention of study staff during the consenting and during provision of care. We note that given the study population, it is anticipated that some women will continue to experience violence and suicidal ideation. Further given the population includes women who are not virally suppressed on the HIV treatment, some deaths may occur due to HIV.

Participants will be asked if they believe there has been any increase in partner violence due to the study. If a participant believes an increase in IPV is a direct result of study participation, we would report this to the DSMB, and immediately move into the safety protocol regardless of condition. If there is an increase in the level of severity of IPV against a participant such as a rise to severe physical harm or severe danger (hospitalized, broken bones…etc.), we would report these to the DSMB. We will report increases in severity of physical harm to the DSMB even if they are not considered to be related to study participation. During the intervention period, the DSMB examined all events at least quarterly during enrollment and completion of one year of follow up for all participants. If there was concern, they examined the violence data from all participants in the study on a weekly basis. All DSMB activities for

the main portion of the study were completed and signed off by March 2025. The addition of the qualitative component will not involve any further DSMB monitoring. Rather, the PI and study team will monitor this portion for adverse events and other reportable information.

Definitions

Serious Adverse Event (SAE) is any adverse event that:

(1) results in death;
(2) is life-threatening;
(3) results in inpatient hospitalization or prolongation of existing hospitalization;
(4) results in a persistent or significant disability/incapacity;
(5) results in a congenital anomaly/birth defect; or
(6) based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Life-threatening means that the event places the subject at immediate risk of death from the event as it occurred.

Unanticipated Problem is defined as an event, experience or outcome that meets **all three** of the following criteria:

- is unexpected; AND
- is related or possibly related to participation in the research; AND
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research

Unexpected means the nature, severity, or frequency of the event is not consistent with either:

- the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol–related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
- the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

AEs will be classified by severity (mild, moderate, or severe) depending on the intensity of the event on the patient. An AE will be "mild" if it does not have a major impact on the patient, "moderate" if it causes some inconvenience, and "severe" if it causes a substantial disruption to the patient's well-being. A severe AE is distinct from a serious adverse event (SAE), which is any AE that is medical and results in death, a life-threatening event, inpatient hospitalization, disability, congenital anomaly or birth defect,

and/or an important medical event based upon appropriate medical judgment. AE's and SAE's will also be classified according to the likelihood that they are related to the study intervention (CETA or Control).

Safety Review

Both the risks listed below and unknown risks will be monitored as follows:

1. The risks that will be monitored in this study are 1) intimate partner violence episodes; and 2) new onset suicidal or homicidal ideation.
2. These will be assessed by study staff and elevated to study supervisors who will have been trained in clinical matters such as identifying levels of distress, local referral options and processes, and clinical interviewing on sensitive topics and when detected. Should they detect a level of urgency and immediacy, the event will be elevated to the local clinical psychologist and, if required, will do an evaluation of the severity, seriousness, relatedness and expectedness of the event. The clinical psychologist's assessment will determine the immediate need for intervention and referral to a higher level of care.
3. If the event is considered to be serious, related and unexpected, the clinical psychologist will inform the MPIs of the event within 48 hours.
4. The aggregate SAEs will be reviewed by the MPI's in real time and passed on to the DSMB quarterly. The DSMB will assess the frequency (by study arm), severity and relatedness of the SAEs on a quarterly basis to determine if the study intervention is posing an increased risk. If there is concern, they will examine the violence data from all participants in the study on a weekly basis.
5. As this is not a blinded study, there will be no need to provide guidance to the DSMB for when/if to unblind the study.
6. The qualitative portion of the study will be monitored by the PI and study team, not the DSMB.

Reporting Plans

The Principal Investigator at BMC/BU Medical Campus will report Unanticipated Problems, safety monitors' reports, and Adverse Events to the BMC/BU Medical Center IRB in accordance with IRB policies. The local PI will report all such events to the Wits HREC in accordance with their policies and on request:

- Unanticipated Problems occurring involving a fatal or life-threatening event will be reported to the IRB within 2 days of the investigator learning of the event.
- Unanticipated Problems occurring not involving a fatal or life-threatening event will be reported to the IRB within 7 days of the investigator learning of the event.
- Reports from safety monitors with recommended changes will be reported to the IRB within 7 days of the investigator receiving the report.
- Adverse Events (including Serious Adverse Events) will be reported in summary at the time of continuing review, along with a statement that the pattern of adverse events, in total, does not suggest that the research places subjects or others at a greater risk of harm than was previously known.
- Reports from safety monitors with no recommended changes will be reported to the IRB at the time of continuing review.

The PIs will submit a report to the DSMB within 10 working days of events that meet the definition of an unanticipated problem involving risks to subjects or others. One exception may be if the SAE involved death and indicates that participants or others are at increased risk of harm, the PIs will be required to submit a report to the DSMB within 3 days. We will report to the DSMB any events that represent increased severity of violence whether or not the event is considered to be related to the study or not. Another exception will be if the details of the death are delayed as often happens in low-resource countries. However, all attempts will be made to report as soon as possible. Reports will be submitted electronically to the DSMB chair. The DSMB representative, when necessary in conjunction with the full DSMB, will review reports and decide whether the event meets the definition of an unanticipated problem increasing risks to subjects or others. Events that meet these criteria will be considered unanticipated problems involving risks to participants or others, will be reviewed by the convened DSMB. We will also notify all IRBs of any deaths. The Principal Investigator will report Severe Adverse Events not related to study participation and all Adverse Events to the DSMB on a yearly basis.

In addition, participants will be asked if they believe there has been any increase in partner violence due to the study. If a participant believes an increase in IPV is a direct result of study participation, we would report this to the DSMB, and immediately move into the safety protocol regardless of condition. If there is an increase in the level of severity of IPV against a participant such as a rise to severe physical harm or severe danger (hospitalized, broken bones…etc.), we would report these to the DSMB. We will report increases in severity of physical harm to the DSMB even if they are not considered to be related to study participation. The DSMB will examine all events at least quarterly and if there is concern, they will examine the violence data from all participants in the study on a weekly basis.

We note that given the study population, we do expect experiences of violence (given the inclusion criteria) and some hospitalizations and deaths to occur related to HIV treatment.

A Data Safety Monitoring Board charter document has been attached as an appendix describing the purposes and specific functions and processes of the DSMB.

The qualitative portion of the study will be monitored by the PI. The DSMB will not be involved in this portion of the study.

Stopping Rules

The study has no stopping rules.

ETHICAL CONSIDERATIONS

a. Human Subjects Involvement, Characteristics, and Design

The proposed research is a randomized controlled trial of a cognitive behavioral therapy approach (CETA) compared to an active control (mHealth) for women with unsuppressed viral loads or who have defaulted from HIV treatment in South Africa and for some of them, inclusion of their male partners in the intervention process. The study will involve enrolling and randomizing women at an HIV treatment clinic who are HIV positive women with an unsuppressed viral load, had missed or late visits in the last year or who have defaulted from treatment and who experienced IPV. They will be randomized into two groups, an intervention arm and a control arm. The study team will interact with these populations for the duration of the intervention and collect medical data through routine clinic records. Our plan to protect human subjects is detailed below.

The proposed study will fall under the purview of the local South African Institutional Review Board (The University of the Witwatersrand Human Research Ethics Committee), Boston University, Columbia University and Johns Hopkins University Institutional Review Boards. Every effort will be made to assure that the principles of ethical research—beneficence, justice, and respect for persons—are maintained. All study staff have obtained (or will obtain prior to the study in the case of new hires) their institution's required certification to conduct ethical research.

The University of the Witwatersrand Human Research Ethics Committee is a leader in evaluating and supervising the ethical conduct of research. They have worked with BU and HE^{2}RO in previous research with similar populations and are familiar with the particular ethical considerations that arise when working with this population.

b. Characteristics of the subject population

Study participants will be adult women who are HIV positive, have initiated HIV treatment, have an unsuppressed viral load or have defaulted from treatment since their last viral load, and have experienced intimate partner violence (IPV). Participants will be recruited by study staff after referral from clinic staff. We will also enroll their male partners of women randomized to the intervention if they choose to include them. The minimum age of research subjects will be 18. All subjects will be recruited from HIV clinics.

Patient (women) inclusion criteria will be:

- Adult HIV positive women >= 18 years old
- Initiated HIV treatment
- Most recent viral load >50 copies/mL, they have defaulted from treatment or had a missed or late (>14 days) visit in the past year
- Has experienced IPV in the past 12 months
- Has their own phone and can receive text messages
- Literate and able to speak and read one of: English, Zulu, SeSotho
- If including a partner, the woman has disclosed HIV status to the partner that will be invited to participate

Exclusion criteria will be:

- Unwilling to complete the informed consent process
- Currently psychotic or on unstable psychiatric regimen
- Suicide attempt/ideation with intent and plan, and/or self-harm in the past month
- Enrolled in any other HIV treatment intervention study

Males partners will also be included, though we will not collect data from them for research purposes. The partners will be one per woman and will be a current partner as she defines it.

For Men, the inclusion/exclusions criteria will be

Male (partner) inclusion criteria will be:

- Adult >= 18 years old
- Invited by partner to be in the study

- Partner has disclosed HIV
- Has their own phone and can receive text messages
- Literate and able to speak and read one of: English, Zulu, Sesotho

Exclusion criteria will be:

- Unwilling to complete the informed consent process
- Currently psychotic or on unstable psychiatric regimen
- Suicide attempt/ideation with intent and plan, and/or self-harm in the past month

c. Referral of individuals with exclusion criteria

If serious mental illness or active suicidal intent is found, there are several options our team has utilized over the past 20 years in our work. HE^{2}RO has a wealth of connections to medical doctors that are well versed in psychiatric symptoms, particularly in conjunction with HIV, and are available for consultation to better assess and determine a treatment plan. The hospital where the clinic we will recruit from is located, the Helen Joseph Hospital in Johannesburg, also has a psychiatric department which specializes in serious mental health problems and is available for individuals either outpatient or inpatient. As other study sites are added to the study, the referral process for psychiatric emergencies at each site will be established and followed. As part of the study we will also have a clinical psychologist based at the clinic to consult and oversee appropriate referral of such cases. In addition, Dr. Marnie Vujovic is a clinical psychologist with over ten years' experience working as a consultant psychologist and as a Programme Manager on psychosocial-related research programs in South Africa. She is available to help out with referrals as needed (see letter of support).

d. Vulnerable populations

This study will be conducted among women who have experienced recent IPV. No children will be included in this study. While data from vulnerable populations such as pregnant women will be included in the study, we may not be aware of their pregnancy status. We do not anticipate the research will have any additional negative consequences for pregnant women, and in fact is likely to help. We believe it would be unethical to purposefully exclude them.

e. Collaborating sites and data

The research team will be from Departments of Global Health at Boston University, the Health Economics and Epidemiology Research Office (HE^{2}RO) in Johannesburg, South Africa, Columbia and Johns Hopkins University. Participants will be recruited from HIV clinics identified in Gauteng province in South Africa. A wide range of study instruments will be administered using a tablet-based questionnaire. This tablet-based approach, which we have used in previous studies in South Africa, gives the responder the ability to answer sensitive questions privately and discreetly and data is immediately exported with only the study ID numbers. Data will also consist of detailed session notes on the interventions so that fidelity to the interventions can be monitored. Finally, we will also collect HIV care and treatment data, including data on viral suppression and retention in HIV care, all from normal clinic practice databases. All data files will be password-protected, with access limited to authorized study staff. Study subjects will be assigned a random study ID number upon enrollment, and data files will contain study ID

numbers only, without any other individual identifiers. Identifiers will be kept in a separate, password protected linking file (with access limited to study staff) that will be used to link the intervention data to clinical data with any paper versions needed for contacting study subjects kept in a locked cabinet. Only deidentified data will be sent to the US sites, with the exception of the signed consent forms. Routinely collected clinical data will be obtained in electronic format (with paper back up if needed) by study staff and linked to the Study ID numbers in order to link to other study documents, then all identifiers will be removed after the final analytic dataset is created. The electronic database will be password protected and will not include identifying information.

f. Potential Risks

We will not collect any biomedical samples for this study that would not be collected as part of routine care. All biomedical data for the study will be drawn from routinely collected medical records. The only other new data generated for the study will be responses to questionnaires.

Psychological risks for participants posed by the research may be related to the sensitivity of some of the measures. Items include thoughts, feelings, and personal difficulties that may be private, such as acts of violence and/or symptomatology related to common mental health problems and/or substance use. Risks also include possible embarrassment, distress, or inconvenience related to questions regarding personal information and mental health problems. Assessment measures of mental health symptoms include items regarding suicidal or homicidal ideation, and disclosure of traumatic events inclusive of sexual and physical abuse commonly experienced by violence-affective populations. By US and local ethics standards, reports of suicidal and/or homicidal ideation also ethically require follow-up by the counselors and investigators, and could potentially result in the need to violate confidentiality in order to protect the participants. Thus, this represents a potential limit to confidentiality. For this and other reasons, possible breaches of confidentiality also pose a potential risk in the proposed study. There is a risk that the interventions (CETA; mHealth + safety) will not be efficacious for some individuals or that the interventions could lead to a worsening of symptoms. The Johns Hopkins PI (Dr. Murray) has published specifically on developing safety protocols in low-resource settings and has implemented these in her 15+ years of work in multiple low resource settings. Still, each of these risks is carefully considered below.

g. Emotional distress protocol

Some participants may experience emotional distress as a result of responding to the assessments or receiving feedback. We will take multiple measures to minimize this occurrence. First, study staff and counselors will be trained in responding to distress. Second, multiple levels of back-up support will be developed for our study staff. Dr. Murray will train supervisors as part of the CETA training who will receive thorough training in clinical matters such as identifying levels of distress, local referral options and processes, and clinical interviewing on sensitive topics. Our team will also be able to contact Dr. Vujovic (a clinical psychologist) who has worked closely with the clinical psychologists at the hospital where the clinic is based if required. Finally, in the event that an individual is experiencing significant distress, the local research team can consult with Dr. Murray. The instruments in this study have been used by the JHU team in several projects in LMIC, without undue distress occurring. All participants will also be told that they can refuse to answer any questions and still participate in the project.

It is also possible that the participants could become distressed by participation in the interventions, CETA or mHealth + safety checks. Many therapeutic interventions like CETA deal with small degrees of stress within a session as part of the treatment. Based on research and experience, the expected degree

of distress will be minimal and therapeutic rather than harmful. In cases where distress does occur, the participant would be with a trained counselor who is skilled at handling such situations. In addition, these counselors will have local supervisors, Dr. Vujovic, and supervision from Dr. Murray (MPI; Clinical Psychologist) as needed. In addressing safety, there can be some distress in planning for preventing suicide. Again, the research is strong that this is life-saving and therapeutic rather than harmful.

For those participants selected to participate and enrolled in the qualitative phase of study who may become distressed during the FGDs and IDIs when they are asked to recall their experiences with CETA, we will follow the same distress protocol that is described above. Data collection for those sessions will pause or stop as needed and support provided. Dr. Vujovic will again be on hand to provide clinical support and guidance and clinic referral processes will be followed as needed.

h. Disclosure of HIV status, violence/abuse, or other confidential information

A potential risk of the study concerns the confidentiality of data about experiences of violence, mental health, HIV status and HIV treatment program enrollment. A high level of stigmatization continues to inhibit the disclosure of HIV status in the study population. Given that we are pulling from a clinic, participants will already be interacting with staff around their HIV status. IPV, mental health problems, and substance use may also be stigmatizing. When doing psychotherapy, disclosure of significant social problems such as violence, substance use, abuse and/or other related problems, may result in negative stigma being associated with the individual and/or family, and other such problems. It has been established that these social problems are common and exist in South Africa and attempts are currently underway to reduce the problems attached to admittance and discussion of such social/interpersonal/behavioral problems. Research shows that admitting and disclosing is the first step to healing, so even in assessment we will attempt to make participants comfortable with disclosing if they are experiencing IPV or other social or behavioral problems. We recognize that stigma may occur despite efforts and we will therefore do everything possible to maintain privacy for our participants. The counselors and study staff consenting will all be specifically trained in how to handle disclosures ethically, legally and sensitively. If there are questions, the counselor and supervisor may also work with the local supervisors, the clinical psychologist and Dr Vujovic, and/or Dr. Murray (who has extensive experience with sensitive disclosures). We also note that given some participants may choose T-CETA, the risk of disclosure of being in the study may increase if the participant chooses not to take the call in a private space.

The local teams will also be trained in how to handle disclosures, what resources are available in the community, and the JHU safety protocol. This protocol teaches specific steps if there is concern, including immediately calling a local supervisor, asking additional questions, and consulting with the supervisors and either Dr. Vujovic or Dr. Murray to make a plan.

To ensure confidentiality and minimize the risk of accidental disclosure of sensitive information during the qualitative phase of this study, all individual interviews with participants will be conducted in a private area or room designated for this purpose at location that is convenient for the participant. For the focus group discussions, we will explain the importance of confidentiality and request that the

participants use a nickname or made-up name that is not their own and that they do not share what they have heard in the group session with anyone outside of the group. However, we cannot guarantee that they will not share the information and this will be made clear during the consent process.

i. Violations of Confidentiality

There is always the possibility of an accidental breach of confidentiality when conducting research. Further because data will be linked between women and any included partner, breach of confidentiality of one partner could reveal inclusion of the other partner. While this is acknowledged, we feel there is a very low likelihood of this occurring because of the precautions that will be taken to protect confidentiality and based on our experience conducting trials among HIV- and IPV-affected families. Disclosure of significant social problems such as intimate partner violence, may result in negative stigma being associated with the individual and/or family, fear of imprisonment of a family bread-winner who is a perpetrator, and other such problems. Domestic violence disclosure may result in unwanted intervention and consequences for the individual responsible. Our team has over a decade of experience specifically working with youth and families that experience abuse and violence and believe that the benefits of these issues coming out far outweighs the risks inherent in violence and abuse situations. We also believe we have established an effective method to reduce this risk.

j. Violence Reports

Previously undisclosed interpersonal violence (IPV) incidents may be revealed. In South Africa, violence is usually not reported to any officials. However, if there is physical harm being caused (i.e., not just verbal abuse), the victim will be given information about their rights, the South African laws and how and where to report if they are interested in this. This report may result in unwanted intervention and consequences for the individual responsible. We also recognize that given the gender-based hierarchies present in South African culture, this may have a detrimental effect on the participant. To address this potential risk, we will not report any disclosures – this will be the participant's choice as is allowed under South African law. With disclosures, the potential benefit to the safety of the woman (and her family) is deemed as outweighing these potential negative consequences. Individuals who disclose experiences of violence will be randomized, and also be given a list of services that may be available. In addition, all active study participants will receive safety planning.

k. Suicidal intent

Participants may reveal severe depression and/or suicidal intent during the course of the study. Although this is not a direct risk with participation of this study, and thus a low likelihood, it is important to have a plan in place, particularly in a low-resource setting. All counselors will be trained specifically in how to assess for suicide risk, and the procedure to follow if there is intent. The protocol includes an immediate evaluation by a trained CETA supervisor to understand the seriousness of the suicidal ideation/intent and activation of a safety plan for the individual. The procedure to follow for study staff and CETA providers includes: a) immediately contacting a local supervisor, b) the supervisor will guide them through additional questions and help make a decision if the individual needs to be brought to see someone, or if a safety contract or safety "watch" may be completed, c) The clinical psychologist on hire (Dr. Vujovic) and the local PI Dr. Sophie Pascoe will be contacted immediately by the supervisor to help confirm if further assessment is needed and/or give recommendations, and d) Dr. Murray and Dr. Fox will be contacted within 24 hours and notified of the situation. Given our decades of work in LMIC (many

in sub-Saharan Africa), we have multiple medical contacts through HE^{2}RO and could also refer to a psychiatrist at the Helen Joseph Hospital where the Themba Lethu clinic is located.

l. Violence associated with being in the study

In our experience to date, we have not observed an increase in violence or severity of violence towards women because of being in studies of CETA or other cognitive behavioral therapies, however, we do acknowledge that it is possible that such a situation could arise. This could occur if a partner who was abusive increased their level of abusiveness because the women chose to be in the study or if being in the study without telling the violent partner was unintentionally discovered. Accordingly, we have a plan for dealing with this should it arise. We will mitigate this risk (as described below) through a series of steps designed to minimize accidental disclosure of being in the study for women who do not want their participation revealed and through training of study staff to support women in employing CETA techniques as they are comfortable.

ADEQUACY OF PROTECTION AGAINST RISKS

a. Protection Against Risk

Study staff and peer educators will be trained in responding to distress and multiple levels of back-up support have been developed. If any issue arises, study staff are encouraged to contact the clinical supervisor who will have received additional training in clinical matters such as identifying levels of distress, local referral options and processes, and clinical interviewing on sensitive topics. The clinical supervisors have regular 24-hour access to CETA trainers and will alert them to any case with an issue. Dr. Vujovic is a local clinical psychologist that will also help with any issues. Counselors and study staff will also have a safety protocol that will be developed in collaboration with our local partner which lays out the plan: a) immediately contacting their supervisor, b) the supervisor will guide them through additional questions and help make a decision if the woman needs to be referred somewhere, or if a safety contract may be completed, c) a CETA trainer will be contacted immediately by the supervisor to further assess and give recommendations, d) Dr. Vujovic will be called if needed, and d) MPIs Fox and Murray will be contacted within 24 hours and notified of the situation. This safety protocol has been used successfully by MPI Murray and her team in multiple LMIC for over 15 years.

b. Safety

Assessments and Intervention: All participants will be directly asked a set of questions each week during the active treatment phase (first 3 months after baseline) to assess suicide and homicide risk, and IPV. For CETA participants, this will be done during CETA sessions. For control participants, this will be via a mobile safety survey. The primary outcome of the proposed study is retention in HIV care and suppression by 12 months. Therefore, we want to minimize research contacts with participants as much as possible. We must balance that research aim, however, with the need to clinically monitor our study participants for safety. If a participant indicates any level of risk of harm to themselves, others or are being hurt by someone else, the study staff will immediately follow the locally developed safety protocol described above. In the active control, if the participant does not respond within 24 hours to the mobile safety survey, a staff member will call them and/or do a home visit when possible (though this has to be balanced against safety of staff) to assure response to safety questions. Study staff will be trained in how to recognize and respond to distress that may occur during the intervention and will call their supervisor if they are unsure of how to handle the situation.

Texts on IPV and/or safety may be altered to avoid risk if a partner is not involved or has not discussed IPV (for example we may say "Please type Yes if there are any issues you need help with"). We will individually meet with each woman to assess the IPV situation and severity, and give community resources to those in the control condition. At this "zero" session, we will explain that we are going to check in weekly on their safety – including suicide and violence and asked how best to do this to assure safety and confidentiality. For example, women may suggest a number of a neighbor or family member, or we will agree on a "code" text that they could explain to others should their phone be shared or lost. In the event that a response via text or phone, or home visit, indicates that someone is thinking of killing themselves, or someone in the house was in danger from the violence, the safety protocol of CETA will be utilized with an experienced Supervisor. This is a protocol used in multiple trials by the JHU team effectively. In this protocol, a supervisor would be called immediately by the researcher, ask a number of questions, and either speak directly with the client or even travel to their home should there be imminent danger.

The study team will review data collected to assure that no study findings warrant immediate intervention. Additionally, weekly research meetings and team calls will serve as another mechanism through which to monitor treatment of random treatment cases. Clinical interventions will be provided as clinically warranted on an ongoing basis.

We will track and report any severe increases in IPV, or any increase that participants feel is directly related to the study. If a participant believes an increase in IPV is a result of study participation, we would report this to the DSMB, and immediately move into the safety protocol regardless of condition. If there is an increase in the level of severity of IPV against a participant, such as physical harm or severe danger (hospitalized, broken bones…etc.), we would report these to the DSMB. We will report increases in severity of physical harm to the DSMB even if they are not considered to be related to study participation. During the intervention period, the DSMB examined all events at least quarterly during enrollment and completion of one year of follow up for all participants. If there was concern, they examined the violence data from all participants in the study on a weekly basis. All DSMB activities for the main portion of the study were completed in March 2025. The addition of the qualitative component will not involve any further DSMB monitoring. Rather, the PI will monitor this portion for adverse events and other reportable information.

c. Disclosure of HIV, violence/abuse, or other confidential information

Subjects will be protected against the risk and repercussions of accidental disclosure of HIV status and other confidential information, in several ways. First, all study data will be de-identified. That is, it will contain only a unique study ID number. The link between the ID and the participant's identifying information will be kept in a password protected database in a locked office in South Africa. We also note that given some participants may choose T-CETA, the risk of disclosure of being in the study may increase if they were overheard and as such we will work with participants to ensure they are in a safe and private location for any T-CETA sessions. To protect against other violations of confidentiality, study staff will be trained in expectations that they are not to disclose any information collected in the study to anyone outside the study team. All study staff will be trained in human subjects' research and required to pass an ethics certification course and receive training in Good Clinical Practices. All participants will be encouraged to contact the local study coordinator, local investigators, or other staff to report any undesirable conduct associated with the study. These reports will be brought to the attention of the study coordinator, local PI and co-Is and the MPIs, and appropriate steps will be taken to solve the problems, including reporting to the ethical review boards.

d. Interpersonal Violence Disclosures

Previously undisclosed IPV incidents may be revealed. As is true for most countries, in South Africa, IPV is usually not required to be reported to any officials. Providers serving these populations are not mandated to report IPV unless requested by the client directly. All participants in the study will have reported varying levels of violence in the past year. As such study staff will follow the same safety protocol listed above and will support clients by providing assistance and access to referral sources that can help with reporting at the client's request. All participants at the screening visit will receive a comprehensive list of available services for victims of violence and alcohol abuse problems. They will also be informed of their rights according to South African law. We will also explicitly ask at all of these check-ins if she would like us to help her report any current or past violence to the police, seek any other services, or receive help in having her and her children leave the home. In the event of severe psychiatric difficulties, the study team will aid in appropriate referral for services.

e. Suicidal intent

Although this is not a direct risk with participation of this study, it is important to have a plan in place, particularly in a low-resource setting. All study staff with patient contact will be trained specifically in how to assess for suicide risk, and the procedure to follow if there is intent. In the event that a participant indicates a positive response to a suicide question, the above safety plan will be followed. The protocol will include an immediate evaluation of risk by the study staff with consultation from the clinical supervisor and/or clinical psychologist and as needed direct evaluation by a CETA clinician, supervisor or the clinical psychologist depending on the seriousness of the suicidal ideation/intent. In all cases study staff will work to develop and activate a safety plan for the individual. This includes a range of activities from setting up a suicide contract that includes 24-hour supervision of the individual by a community member(s) until the crisis subsides to a full evaluation by a psychiatrist.

f. Violence associated with being in the study

As noted, we consider this risk to be small given our previous experience working with CETA in low-income countries, however it is a possibility. Accordingly, we have a plan for dealing with this should it arise. First, we will attempt to minimize the risk through fully informing all participants at enrollment and consent that this is a possibility and that we will work with them to anticipate ways that accidental disclosure could occur and plan to prevent this. Second, we will work with participants to ensure that the text messages that the team sends are acceptable to the participant, even if they do not in any way mention safety or violence. Third, all counselors will be trained specifically to be sensitive to this issue and to take steps to ensure they do not accidentally disclose information about study participation. Fourth, should an increase in violence occur, such as physical harm or severe danger (hospitalized, broken bones…etc.), we will consider this an expected risk to participation in the study and will follow all procedures for reporting expected adverse events to the DSMB as described in our Data and Safety and Monitoring Plan.

POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO HUMAN SUBJECTS AND OTHERS

a. Clients

There may be no direct benefit to patients participating in the study. However, through participation in the research, client participants will receive assessments that may benefit them by providing information about some of their problems. Further, some will be provided treatment (CETA) that is likely

to be of benefit in addressing their violence and related mental/behavioral health problems that may be negatively affecting their HIV care and treatment. Risks to the client participants are not great in that they will receive CETA, which has been proven to be efficacious in addressing violence and related symptoms, as well as helping with maintenance and adherence. In addition, some individuals may choose to take advantage of a referral to someone they can talk with, and therefore benefit.

b. Policy

A core principle of this research is that key stakeholders, including policymakers such as the South African Department of Health and implementing partner organizations (e.g. Right to Care), will be involved in the study. Relevant members of these organizations will be invited to the workshops and relevant meetings, and included on relevant communications, to share the research data for scaling up and sustaining violence-related services. Their involvement will serve as a compass for the work of this study and allow real-time policy influence. If CETA proves effective in improving retention and viral suppression, the design of this project is such that South Africa will be positioned to scale-up and ideally sustain the intervention in country. In addition, if effective, this use of CETA to improve HIV care and treatment could be replicated and used in other areas of South Africa and in other countries globally.

IMPORTANCE OF THE KNOWELDGE TO BE GAINED

The knowledge to be generated by this study will allow HIV treatment programs to identify what strategies may improve HIV treatment outcomes and reduce experiences of violence for women with elevated viral loads. Research on this area is desperately needed given the strong connection between violence and poor HIV outcomes. This study will produce evidence on the effectiveness of an intervention to improve the HIV care cascade. Given the extensive evidence on cognitive behavioral therapy as a skill-based resiliency treatment for multiple problems, and the evidence that a common elements approach is feasible and more scalable, it is likely that CETA will prove to be an effective intervention for violence and mental health for this high-stress population even if it does not improve HIV treatment outcomes. The knowledge to be gained in understanding the effectiveness of this important approach outweighs the risks and could have a major impact on HIV services and policy.

Contingency plan for qualitative phase in the case of termination of the NIH no-cost extension

As of January 2025, this study had received approval and a notice of award of a no-cost extension (NCE) from the NIH with permission to complete additional work and analyses up to January 2026. Should further notice be received at any point before that date that work cannot continue under the NCE and that the project needs to be close out then the final qualitative phase of this study would be discontinued and we may potentially seek to secure funding from this phase elsewhere. Even if this phase is partially completed because the intervention period has already been completed no participants will be at risk of loss of treatment or abandonment.

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