



Efficacy of the Common Elements Treatment Approach (CETA) for Unhealthy Alcohol Use Among Adults with HIV in Zambia: Results from a Pilot Randomized Controlled Trial

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Abstract

This randomized controlled trial tested the efficacy of a multi-session, evidence-based, lay counselor-delivered transdiagnostic therapy, the Common Elements Treatment Approach (CETA), in reducing unhealthy alcohol use and comorbidities among persons living with HIV (PLWH) in Zambia. Adult PLWH with (a) unhealthy alcohol use plus mental health or substance use comorbidities, or (b) severe unhealthy alcohol use were randomized to receive a single-session alcohol brief intervention (BI) alone or BI plus referral to CETA. Outcomes were measured at baseline and a 6-month follow-up and included Alcohol Use Disorders Identification Test (AUDIT) score (primary), depression and trauma symptoms, and other substance use (secondary). We enrolled 160 participants; 78 were randomized to BI alone and 82 to BI plus CETA. Due to COVID-19, the trial ended early before 36 participants completed. Statistically and clinically significant reductions in mean AUDIT score from baseline to 6-month follow-up were observed in both groups, however, participants assigned to BI plus CETA had significantly greater reductions compared to BI alone (-3.2 , 95% CI -6.2 to -0.1 ; Cohen's d : 0.48). The CETA effect size for AUDIT score increased in line with increasing mental health/substance use comorbidity (0 comorbidities $d=0.25$; 1–2 comorbidities $d=0.36$; 3+ comorbidities $d=1.6$). Significant CETA treatment effects were observed for depression, trauma, and several other substances. BI plus referral to CETA was feasible and superior to BI alone for unhealthy alcohol use among adults with HIV, particularly among those with comorbidities. Findings support future effectiveness testing of CETA for HIV outcomes among PLWH with unhealthy alcohol use.

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Keywords Unhealthy alcohol use · Substance use · HIV · Zambia · Randomized controlled trial

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Introduction

Unhealthy alcohol use is a major impediment to achieving the 95–95–95 United Nations targets to ending the HIV epidemic [1–3]. Unhealthy use can contribute to poor HIV outcomes by reducing ART adherence and retention in care [4], and has been linked to inflammatory biomarkers that are associated with increased mortality risk [5]. This is a concern in sub-Saharan Africa (SSA) where prevalence of HIV and unhealthy drinking patterns (e.g., binge drinking, heavy episodic drinking) are among the highest globally [6, 7]. In Zambia, we found that among those who reported any alcohol use, 59% drank at unhealthy levels, that persons living with HIV (PLWH) were 50% more likely to have unhealthy use than persons without HIV, and that unhealthy use was associated with lower odds of both being HIV status aware and being virally suppressed [8].

There is a massive treatment gap for alcohol and substance use problems in Zambia, similar to many low- and middle-income countries (LMIC) [9]. Alcohol-focused interventions within SSA HIV care systems are rare [10, 11] and, when available, have had mixed results. For example, alcohol brief interventions (BIs), which can range from 1 to 4 sessions (but typically are single session), did not significantly reduce unhealthy alcohol use compared to control conditions in Uganda and South Africa [12, 13]. More recently, however, among PLWH in Kenya, a group-based, six-session, para-professional-delivered cognitive behavioral therapy (CBT) proved more effective than healthy lifestyle education [14]. These results suggest that BIs, which are usually not designed or equipped to treat more severe alcohol disorders or comorbid mental health/substance use problems, may not be sufficient as stand-alone treatments. Integrated treatment of alcohol and co-occurring mental health and other substance use problems may be critical in many LMIC populations with high levels of comorbidity, including PLWH [15]. Among HIV-affected Zambians who drank at unhealthy levels, 50% had comorbid mental health (depression or trauma) symptoms or other substance use problems [15, 16].

The Common Elements Treatment Approach (CETA) is a flexible, transdiagnostic, multi-problem treatment approach that was designed specifically to treat comorbid mental and behavioral health problems (www.cetaglobal.org) [17]. CETA elements are based on CBT and can be delivered by lay counselors, which increases its potential to be sustained and scaled-up in LMIC [18]. In four previous randomized trials, CETA reduced a range of mental and behavioral problems in targeted populations with trauma and other mental health symptoms [19–22]. However, none of these trials focused specifically on PLWH

with unhealthy alcohol use nor were delivered within the HIV health system. Given CETA's evidence-base for treating comorbidity, and the high prevalence of unhealthy alcohol use and comorbidities in SSA HIV care settings, we hypothesized that CETA would be more effective than a BI alone at reducing unhealthy alcohol use among PLWH in Zambia. This paper presents the results of a pilot randomized controlled trial testing that hypothesis, the Zambia CETA for Alcohol use Pilot (ZCAP) study. If the hypothesis is confirmed, this would provide rationale for further evaluation of CETA's effectiveness in improving HIV clinical outcomes.

Methods

Design Overview and Setting

Participants in the ZCAP trial were adults (≥ 18 years) living with HIV and reporting unhealthy alcohol use during a regular HIV care visit at two large, urban public-sector Level 1 facilities in Lusaka, Zambia. The clinics are PEPFAR-supported and each serves approximately 8000–10,000 people living with HIV. One hospital serves the lowest income neighborhoods in Lusaka, where the majority of people live on a dollar/day, education levels are low, and most employment is informal. The other hospital serves both low and middle-income communities, where some residents are well-educated and have formal employment.

All participants provided written informed consent. The trial was approved by the Johns Hopkins Bloomberg School of Public Health IRB, the Columbia University Medical Center IRB, the University of Zambia Biomedical Research Ethics Committee, and the National Health Research Authority in Zambia. The trial was monitored by a three-person Data and Safety Monitoring Board (DSMB). Detailed methods were published on ClinicalTrials.gov (NCT03966885) and a previous protocol publication [23].

Participants

Our recruitment strategy replicated anticipated real-world enrollment of patients into alcohol treatment in HIV care. Clinic staff provided information about alcohol and HIV and introduced the ZCAP study during routine health talks conducted in the clinic waiting areas. Interested persons were invited to discuss further with their provider in private. Providers referred interested persons, as well as those who reported alcohol use to a health care worker during the visit, to a research assistant who explained the study in full. Following this discussion, research assistants obtained informed consent from interested persons and proceeded with eligibility screening. Those who were not interested in participating

following this discussion exited and no data were collected from these patients.

Eligible participants were (a) 18+ years of age, (b) living with HIV, (c) receiving care at the clinic, (d) had unhealthy alcohol use in the past three months according to the Alcohol Use Disorders Identification Test (AUDIT; eligibility score thresholds were ≥ 8 among men; ≥ 4 among women) [24, 25], and (e) met criteria for at least one comorbidity: depression, trauma symptoms, or non-alcohol substance use. A participant could also be eligible without having a comorbidity if they met criteria for a more severe alcohol use problem (AUDIT score ≥ 16 among men; ≥ 12 among women) [24, 26]. The screening, which also served as the baseline assessment, was administered via audio computer assisted self-interviewing (ACASI) [16, 27–30], in one of three languages: English, Bemba, or Nyanja. Exclusion criteria were: currently psychotic, actively suicidal and needing immediate hospitalization, or unable to provide informed consent. Participants identified as having safety concerns during screening were immediately seen by a CETA clinical supervisor for assessment with referral, if necessary, to a psychiatrist (author RP) involved in the study.

Randomization and Masking

Participants were randomized 1:1 to either BI alone or BI plus CETA using blocks of $N=20$ stratified by clinic and sex. A statistician not otherwise associated with the study generated four randomization lists: one each for males and females at each of the two clinics. The purpose of having separate lists by clinic and gender was to facilitate approximately equal numbers of BI alone and BI+CETA assignments within each clinic and within both male and female participants. Within each list, the randomization assignments were in random order in blocks of 20 such that 10 were BI alone and 10 were BI+CETA. Randomization assignments were contained within sealed envelopes organized in sequential order in locked cabinets in each of the HIV clinics. Envelopes for males and females were kept separately. Once a participant screened eligible for the study, the RA removed and opened the next available envelope to reveal their assignment. ACASI masked the outcomes assessment and data analysis was also conducted blind. The study counselors, clinical team, study coordinator, and participants were not blinded.

Interventions

CETA is a multi-session transdiagnostic cognitive behavioral therapy approach that was developed to address gaps in mental health and substance use treatment in LMIC [17]. CETA sessions are typically delivered as 1-h weekly sessions for 6–12 sessions depending on clinical complexity

and response. Lay counselors can flexibly deploy nine cognitive-behavioral elements, based on a client's symptom presentation and severity. These elements (described in detail at www.cetaglobal.org and the previously published methods paper [23]) include: Engagement, Introduction/Psychoeducation, Safety, Substance Use Reduction, Cognitive Coping and Restructuring, Problem Solving, Behavioral Activation, Relaxation, and Exposure (Live and Imaginal). CETA was adapted in the for use in HIV clinic settings by study staff and local counselors and supervisors [23]. This included adding HIV and ART-specific content to the manual and creating standard operating procedures for assignment of cases, delivery of sessions, and follow-up within the ART department. CETA sessions were provided in a one-on-one format and at the time and place of client preference. Prior to their first CETA session, participants were asked where they would prefer receiving the intervention—at a private room within the clinic or a convenient location within the community. Community locations could include the participant's own home, a church, or a local market.

In this study, we utilized HIV peer educators ($N=18$) to provide CETA. These are individuals that were already embedded at an HIV clinic close to their residence and provide basic services like adherence counseling, filing, and outreach to patients with suboptimal engagement in care. Study authors (LKM and SS) conducted a 10-day in-person CETA training with the peer educators and local supervisors (experienced CETA counselors) using the apprenticeship model of training and supervision [31]. This entailed teaching the fundamentals of counseling skills, how to deliver each CETA element, and how to implement safety planning. Then, before providing CETA to a study participant, each new counselor completed a supervised pilot CETA case with a clinic patient. Throughout the trial, counselors met weekly with their supervisor to review cases. Supervision sessions were used to assess and promote fidelity to the CETA manual.

The BI consisted of a single 20–30-min session with content adapted specifically for the ZCAP study from the CETA element for Substance Use Reduction by authors (CKD, LKM, SS) with input from local HIV care and mental health partners. The choice of using this novel, evidence-based element as the basis for the BI was to ensure a stronger comparator than the current standard of care BI in Zambia, which was not evidence-based nor consistently delivered [23]. Components of BI are described in the protocol paper [23].

Following screening and randomization, all participants received the BI session on-the-spot, following the principles of a screening, brief intervention, and referral to treatment (SBIRT) program [32]. For those assigned to also receive CETA, supervisors assigned an available counselor at the weekly supervision meeting and then the counselor

contacted the participant by phone to implement the first session, which typically occurred 1–2 weeks following enrollment. We attempted (and succeeded in 84% of CETA cases) to deliberately assign the same counselor for BI and CETA to a participant to enhance treatment continuity and leverage the initial therapeutic relationship built during the BI session.

Measures

The pre-specified primary outcome was change in AUDIT score from baseline to six months post-baseline. The AUDIT is a 10-item measure of unhealthy alcohol use [24, 26]. A total score was calculated across the items with a possible range of 0–40 and higher scores indicating more severe alcohol use problems. In this intervention study, we modified the reference period for the AUDIT, which typically asks about drinking ‘over the past year’, to be ‘in the past three months’ because we were interested in enrolling participants with very recent and/or ongoing unhealthy alcohol use. Secondary outcomes included depression symptoms, trauma symptoms, and non-alcohol substance use. Depression symptoms were measured with the Center for Epidemiological Studies-Depression (CES-D) scale [33]. A total score was calculated with a possible range of 0–60. A cut-off score of ≥ 16 was considered the threshold for clinically significant depression. Trauma symptoms were measured using the Harvard Trauma Questionnaire (HTQ) [34]. An average item score was calculated with possible range of 1–4. An average score of ≥ 2.5 was considered the threshold for clinically significant trauma. Substance use was measured with the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) [35, 36]. A past 3-month specific substance involvement (SSI) score was calculated for seven possible substance types (marijuana, inhalants, cocaine, sedatives, hallucinogens, methamphetamines, and opioids). An SSI score can range from 0 to 39. A cut-off score of ≥ 27 for each substance type was used to indicate problematic substance use.

Outcomes were assessed at baseline and a 6-month post-enrollment follow-up using ACASI. Participants were eligible to complete the 6-month follow-up between 5 and 7 months from enrollment. Follow-ups typically occurred in conjunction with an HIV care visit. After completing the ACASI at the follow-up, participants also provided a 50 ml urine sample for rapid point-of-care ethyl glucuronide (EtG) testing (Confirm Biosciences, San Diego, USA; sensitivity 300 ng/ml), an alcohol metabolite that can be detected in urine for the past few days. In a similar population in Zambia, we found that an EtG dipstick was 98.5% sensitive and 77.4% specific for reported alcohol use in the past 3 days [37].

Although not an explicit outcome in the pilot trial, we also captured and analyzed HIV-related indicators from clinic records after completion of the study using participants’ clinic ID numbers (providing access to these records was part of the informed consent for the study). Among those with available electronic records, we extracted laboratory (HIV viral loads) and pharmacy data (date and amount of medication dispensed at each ART refill) from periods before and after enrollment. We defined late ART refills, an established predictor of loss to follow-up, as > 7 days late and viral suppression as < 40 copies/ml.

Statistical Analysis

We estimated that a sample size of $N = 128$ ($N = 64$ per group) assuming 80% power and $p = 0.05$ would be needed to detect an effect size of $CETA \geq 0.5$, which we believed would be clinically significant. We inflated the sample size by 20% ($N = 160$; 80 per group) to account for possible drop-out/loss-to-follow-up.

Descriptive statistics were used to summarize baseline characteristics of the study sample separately by trial arm. We did not conduct tests of statistical significance for baseline differences between arms.

We estimated linear mixed effects models to estimate the difference in change from baseline to 6-month follow-up between BI plus CETA and BI alone groups for each outcome (AUDIT, CES-D, HTQ, and each ASSIST SSI). Fixed effects included treatment arm (0 = BI; 1 = BI + CETA), time (0 = baseline; 1 = 6-month follow-up) and interaction terms between treatment arm and time. Random effects included client and counselor ID. We report predicted mean difference in change in score between groups and 95% confidence intervals as well as Cohen’s d effect size [38]. A sensitivity analysis was conducted after excluding participants who underreported their alcohol use at follow-up, defined as an AUDIT of 0 points and a positive EtG. An exploratory analysis investigated whether the treatment effects on the primary AUDIT outcome varied by the number of mental health/substance use comorbidities. The purpose of this analysis was to explore whether CETA’s impact was greater among clients with more complex symptom profiles. We re-estimated the AUDIT mixed effects model separately among participants with 0, 1–2, and 3+ comorbidities at baseline. HIV clinic data were analyzed descriptively among those whose records were available; we did not formally investigate the comparative effectiveness of the interventions on HIV outcomes.

Early Termination of the Trial Due to COVID-19 Pandemic

On March 18, 2020, when the 2019 novel coronavirus disease (COVID-19) was first detected in Lusaka, we paused

trial follow-up visits on ethical grounds, and on May 15, 2020, in consultation with the DSMB and IRBs, we stopped the trial early. At that point, all interventions were completed. We did not believe that conducting the remaining follow-ups remotely (e.g., by phone) was appropriate because there were potentially important differences, possibly related to alcohol use, between those who were and were not reachable by phone. Further, our mode of administration for the outcomes assessment via phone would have been much different compared to the rest of the sample that had completed assessments using a validated ACASI instrument. Having never used phone-based assessments before in Zambia, we were not confident that responses to questions on alcohol use, mental health, and substance use would be valid. We therefore present in this paper the results of a modified intention-to-treat analysis, in which we include all participants who had completed their follow-up visit by March 17, 2020. We only included data from participants who had completed their follow-up visit by 17th March because combining the follow-up assessments of pre- and post-COVID-19 participants would very possibly introduce a significant bias into the data given likely meaningful differences in alcohol use and mental health pre- and post-COVID-19.

Results

Participants were recruited and enrolled into the study between June 19 and November 12, 2019. Among 257 persons referred to the research team, 180 (70%) agreed to be screened for eligibility. Eighty-nine percent of screened participants were eligible and enrolled ($N=160$) with 78 participants randomized to BI alone and 82 to BI+CETA. The study sample was 44% female and the average age was 40 years. Most were ART treatment experienced (mean number of years on ART: 6.4; $SD=4.6$ years). At the time of enrollment, pharmacy data were available on 100/160 participants and viral load data on 99/160. Among those with pre-enrollment data available, 38 (38%) had a late ART pickup in the prior 6 months and 68 (69%) had HIV RNA <40 copies/ml at their most recent viral load analysis (within the past year).

There were no meaningful differences in demographics or mental health/substance use variables (AUDIT, CES-D, HTQ, ASSIST) between the treatment groups at baseline (Table 1). Among all participants, 18% had severe unhealthy alcohol use without other mental health or substance use comorbidities, 44% had unhealthy alcohol use plus one mental health/substance use comorbidity, 29% had unhealthy alcohol use plus two mental health/substance use comorbidities, and 9% had three or more comorbidities meaning that they met criteria for unhealthy alcohol use, depression and trauma symptoms, and polysubstance use.

Six-month post-baseline assessments were conducted between November 26, 2019 and March 17, 2020 when the study was stopped due to COVID-19. The average time from baseline to follow-up was 5.5 months (mean of 163.7 days; $SD=13.8$) with no difference between groups. All participants received the BI as intended. All but two participants randomized to BI plus CETA completed CETA. Among participants who were randomized to CETA, 83% ($N=68$) chose to receive CETA sessions in the clinic (as opposed to a community location).

Seventy-two percent ($N=56$) of BI alone participants and 76% ($N=62$) of BI plus CETA participants successfully completed their 6-month follow-up. Other than one participant death (in the BI alone arm), which was unrelated to the interventions or study participation, there were no adverse events and no harmful effects reported related to the interventions. Most missing outcomes ($N=36$) were due to COVID-19. Other reasons for not completing included moving from the study area ($N=2$) and loss to follow-up ($N=3$). There were no significant associations between any baseline characteristic or outcome variables and likelihood of not completing the follow-up assessment. The study flow diagram is presented in Fig. 1.

The modified intent-to-treat analysis included all participants with complete baseline and follow-up data ($N=118$). In the primary outcome analysis (Table 2), the reduction in mean AUDIT score from baseline to 6-months was statistically significantly greater in the BI plus CETA group compared to BI alone (-3.2 points, 95% CI -6.2 to -0.1) with an effect size of $d=0.48$. Results of the primary outcome model stratified by comorbidity number are shown in Fig. 2. Reductions in AUDIT score were greater in the BI plus CETA group than the BI alone group regardless of number of comorbidities, however, the effect size appeared to increase markedly with additional comorbidities (0 comorbidities $d=0.25$; 1–2 comorbidities $d=0.36$; 3+ comorbidities $d=1.6$).

A total of 115 participants (97.5% of all follow-up participants) provided a sample for EtG. Among 105 participants who reported ongoing alcohol use at follow-up, 50 (48%) were EtG-positive. In the 10 who reported alcohol abstinence at follow-up (i.e., AUDIT score = 0), two (20%) were EtG-positive, indicative of underreporting (the overall underreporting rate was therefore 1.7%). In the sensitivity analysis that excluded these two participants, we found a similar treatment effect as the overall analysis for the AUDIT primary outcome (-3.4 points, 95% CI -6.5 to -0.4 , $d=0.50$).

Results from secondary outcome models are presented in Tables 3 and 4. The BI plus CETA group also experienced statistically significantly greater reductions in depression (-4.2 , 95% CI -8.9 to -0.5 , $d=0.5$) and trauma symptoms (-0.2 , 95% CI -0.5 to -0.1 , $d=0.38$)

Table 1 Baseline characteristics

	Total (n = 160)	BI (n = 78)	BI + CETA (n = 82)
Female	70 (44%)	34 (44%)	36 (44%)
Age, mean (SD)	40.2 (9.3)	41.8 (9.0)	38.6 (9.4)
Education			
Never attended school	18 (11%)	8 (10%)	10 (12%)
Attended primary school	39 (24%)	25 (32%)	14 (17%)
Completed primary school	36 (23%)	17 (22%)	19 (23%)
Completed secondary school	40 (25%)	17 (22%)	23 (28%)
Completed higher than secondary school	5 (3%)	1 (1%)	4 (5%)
Other	22 (14%)	10 (13%)	12 (15%)
Employment			
Formally employed	8 (5%)	3 (4%)	5 (6%)
Informally employed	31 (19%)	15 (19%)	16 (20%)
Part-time employed	46 (29%)	25 (32%)	21 (26%)
Unemployed and looking for work	66 (41%)	33 (42%)	33 (40%)
Unemployed and not looking for work	9 (6%)	2 (3%)	7 (8%)
Housing			
Homeowner	32 (20%)	19 (24%)	13 (16%)
Rent	109 (68%)	51 (65%)	58 (71%)
Stay with family member or friends	14 (9%)	5 (6%)	9 (11%)
Other	5 (3%)	3 (4%)	2 (2%)
Marital status			
Never married	16 (10%)	8 (10%)	8 (10%)
Currently married	99 (62%)	50 (64%)	49 (60%)
Separated	15 (9%)	6 (8%)	9 (11%)
Divorced	12 (8%)	6 (8%)	6 (7%)
Widowed	18 (11%)	8 (10%)	10 (12%)
Years on ART, mean (SD)	6.4 (4.6)	7.0 (4.6)	5.8 (4.6)
AUDIT score, mean (SD) [range]	21.5 (6.9) [8–37]	21.2 (7.3) [9–36]	21.8 (6.5) [8–37]
CES-D score, mean (SD)	23.6 (9.3) [6–50]	22.8 (8.9) [6–43]	24.4 (9.7) [7–50]
HTQ score, mean (SD)	2.2 (0.7) [1–4]	2.2 (0.7) [1.1–4]	2.3 (0.6) [1–3.8]
Any past three-month substance use [‡]	68 (43%)	35 (45%)	33 (41%)
Late ART refills, past 6 months*	38 (38%)	17 (35%)	21 (40%)
HIV RNA < 40 copies/ml*	68 (69%)	33 (67%)	35 (70%)
Number of CETA sessions, mean (SD)	–	–	8.0 (1.8)
Number of days between final CETA session and follow-up, mean (SD)	–	–	69.9 (31.5)
Number of days between baseline and follow-up, mean (SD)	163.7 (13.8)	163.9 (13.3)	163.5 (14.4)

BI brief intervention, CETA Common Elements Treatment Approach, AUDIT Alcohol Use Disorders Identification Test, CES-D Center for Epidemiological Studies Depression, HTQ Harvard Trauma Questionnaire, ART antiretroviral therapy

Statistics are N (%) unless otherwise noted

[‡]Includes self-reported use of one or more of the following substance types: marijuana, inhalants, cocaine, amphetamines, sedatives, hallucinogens, opioids, or other (non-alcohol/tobacco) substance type

*HIV clinical records were incomplete; n = 100 had pharmacy data and n = 99 had HIV viral load data at baseline

compared to the BI alone group. Mean reductions in specific substance involvement (SSI) scores were statistically significantly greater in the BI plus CETA group vs. the BI

alone group for cocaine (-6.6 , 95% CI -12.8 to -0.5 , $d=0.86$) and methamphetamines (-6.2 , 95% CI -11.9 to -0.5 , $d=0.81$). Reductions were also greater in the BI

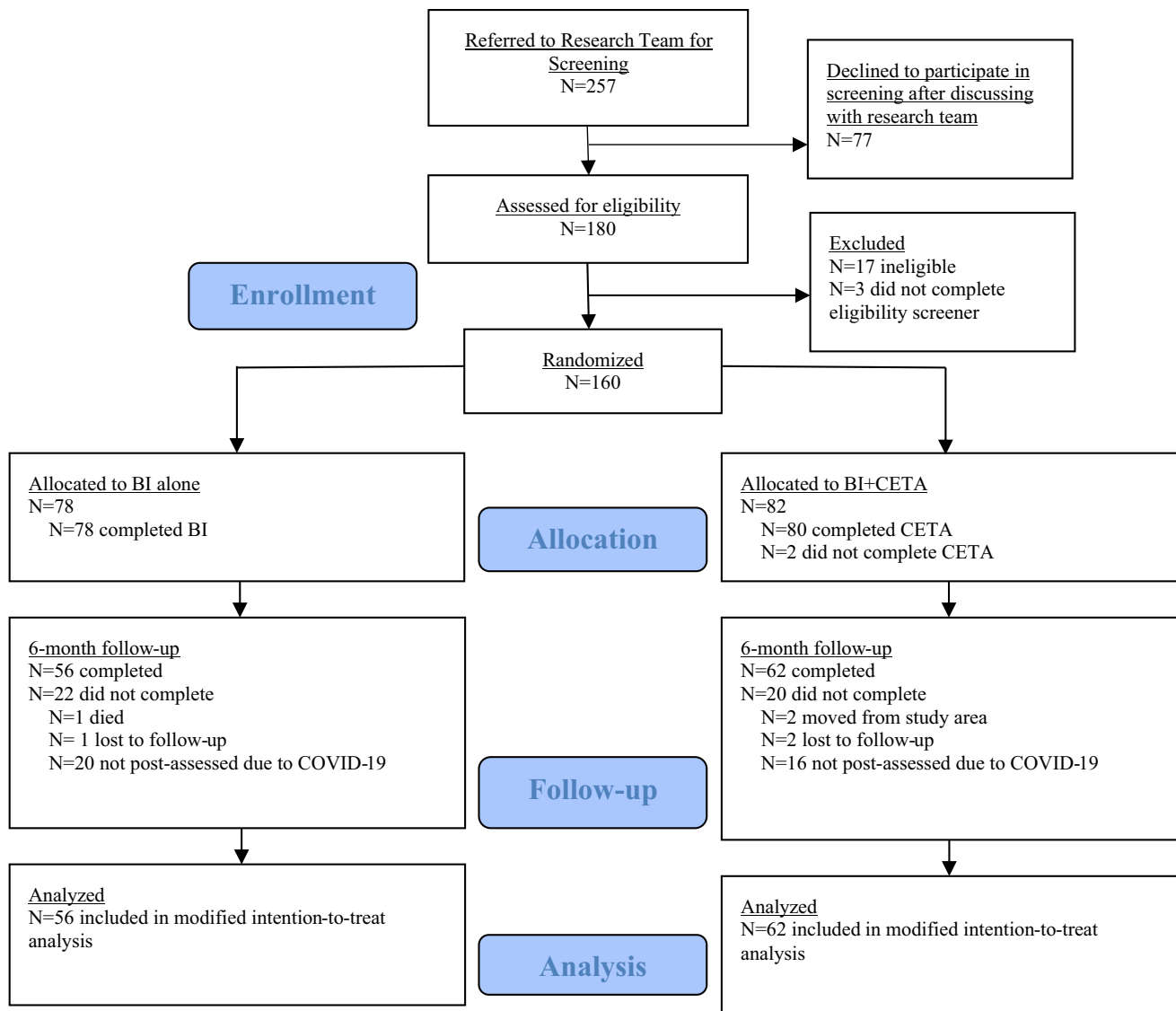


Fig. 1 Study flow diagram

plus CETA group for marijuana, sedatives, hallucinogens, and opioids but the treatment effect was not statistically significant. There was no difference between the groups in change in inhalants SSI.

ART pharmacy records were extracted for 91/160 participants post-enrollment and HIV viral loads were available for 61/160. Among those with available data, the number with late ART pickups during the 6-month post-enrollment period was 28 (31%), including 17 (36%) in the BI alone group and 11 (25%) in the BI plus CETA group. Among those with available post-enrollment viral load data, 54 (89%) had HIV RNA < 40 copies/ml including 28 in the BI alone group (93%) and 26 (84%) in the BI plus CETA group.

Discussion

In a pilot trial at HIV clinics in Zambia, we demonstrated the feasibility and efficacy of an alcohol BI plus referral to CETA, a multi-session transdiagnostic cognitive behavioral therapy approach, for people with HIV, unhealthy alcohol use, and comorbidities. Compared to BI alone, participants also receiving CETA had significantly larger reductions in alcohol use, depression and trauma symptoms, and other substance use (cocaine and methamphetamines). These data represent the first evidence on CETA's integrated delivery at HIV care settings in sub-Saharan Africa and provide further evidence on CETA's

Table 2 Intervention effect of CETA on unhealthy alcohol use

AUDIT ($\alpha=0.63$)	BI (N = 56)		BI + CETA (N = 62)		Between group treatment effect	
	Mean (95% CI)	Mean change from baseline (95% CI)	Mean (95% CI)	Mean change from baseline (95% CI)	Difference in mean change (95% CI)	Cohen's d
Baseline	21.5 (19.7 to 23.3)	–	21.7 (20.0 to 23.5)	–	–	–
6-month follow-up	11.0 (9.2 to 12.8)	– 10.5*** (– 12.8 to – 8.3)	8.0 (6.3 to 9.7)	– 13.7*** (– 15.8 to – 11.6)	– 3.2* (– 6.2 to – 0.1)	0.48

AUDIT Alcohol Use Disorders Identification Test

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

α = Cronbach's Alpha for internal reliability

Estimates for means, 95% CIs, mean change from baseline, difference in mean change are based on predicted values from mixed effects model. Cohen's d effect size is calculated by dividing the predicted difference in mean change from the mixed effects model by the pooled baseline SD. Model included fixed effects of treatment arm, time, and interaction terms of treatment X time as well as random effects of participant ID and counselor ID.

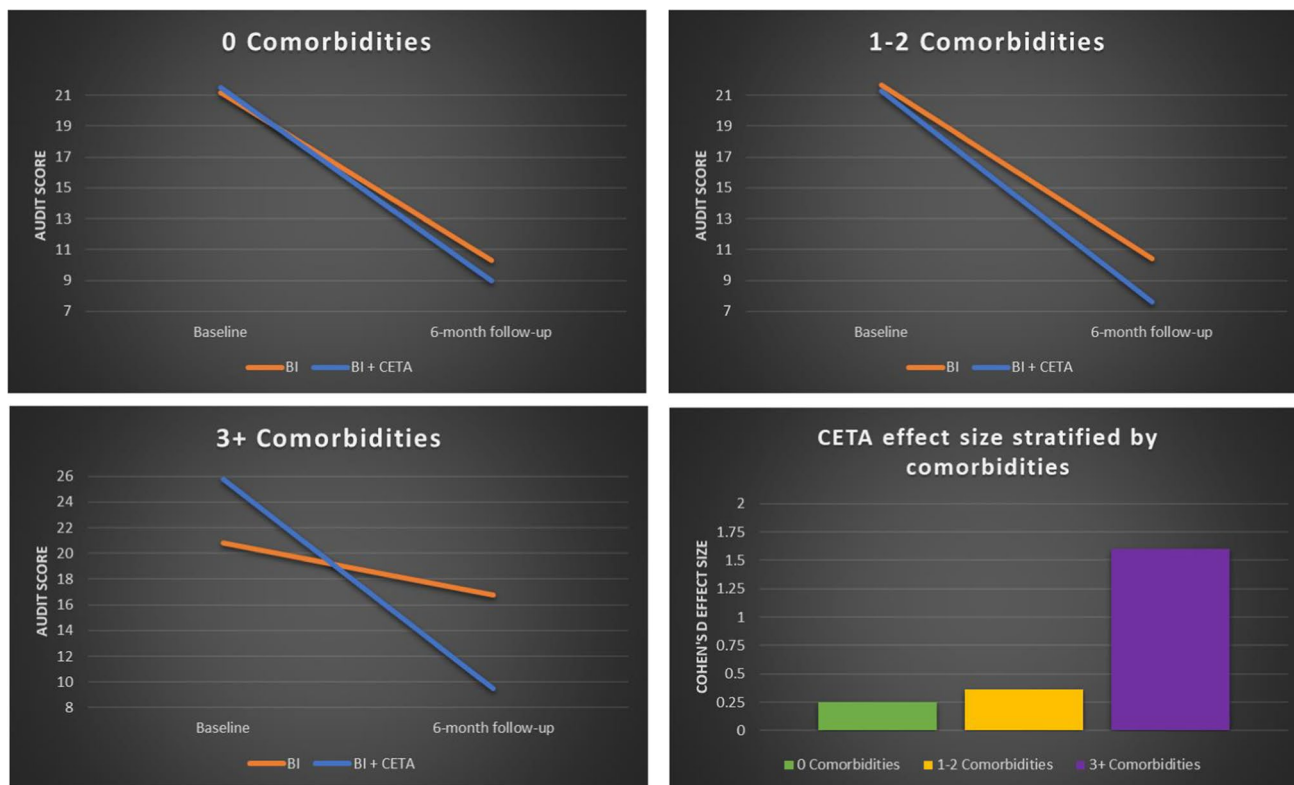


Fig. 2 CETA treatment effects on unhealthy alcohol use (AUDIT score) stratified by number of comorbidities

effectiveness for mental and behavioral health problems in low-resource settings [19–22].

Our main finding was that a multi-session CBT-based intervention lowered alcohol use in people with HIV

compared to a single session BI alone, which is often the only treatment available in SSA HIV clinics. In a trial of a one-session BI in Uganda, Wandera and colleagues found that the BI did not perform better than a control condition in

Table 3 Intervention effect of CETA on depression and trauma symptoms

	BI (N = 56)		BI + CETA (N = 62)		Between group treatment effect	
<i>Depression</i>						
CES-D ($\alpha = 0.86$)	Mean	Mean change from baseline	Mean	Mean change from baseline	Difference in mean change	Cohen's d
	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	
Baseline	22.6	–	25.1	–	–	–
	(20.3 to 25.0)		(22.9 to 27.4)			
6-month follow-up	18.5	– 4.2**	16.3	– 8.9***	– 4.2*	0.5
	(16.1 to 20.8)	(– 7.2 to – 1.1)	(14.0 to 18.5)	(– 11.8 to – 6.0)	(– 8.9 to – 0.5)	
<i>Trauma symptoms</i>						
HTQ ($\alpha = 0.95$)	Mean	Mean change from baseline	Mean	Mean change from baseline	Difference in mean change	Cohen's d
	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	
Baseline	2.2	–	2.3	–	–	–
	(2.1 to 2.4)		(2.2 to 2.5)			
6-month follow-up	1.9	– 0.3**	1.8	– 0.5***	– 0.2*	0.38
	(1.8 to 2.1)	(– 0.5 to – 0.1)	(1.6 to 1.9)	(– 0.7 to – 0.4)	(– 0.5 to – 0.1)	

* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$

CES-D Center for Epidemiological Studies-Depression Scale, HTQ Harvard Trauma Questionnaire, α = Cronbach's Alpha for internal reliability Estimates for means, 95% CIs, mean change from baseline, difference in mean change are based on predicted values from mixed effects model Cohen's *d* effect size is calculated by dividing the predicted difference in mean change from the mixed effects model by the pooled baseline SD Model included fixed effects of treatment arm, time, and interaction terms of treatment X time as well as random effects of participant ID and counselor ID

reducing unhealthy alcohol use among a sample of PLWH and suggested that a greater treatment dosage (i.e., more than one session) might be needed [13]. Our results suggest that a multi-session approach may be more effective than a one-session BI, particularly among PLWH with unhealthy alcohol use and other mental and behavioral health comorbidities. Papas and colleagues similarly reported that a multi-session group-based, paraprofessional-delivered CBT approach reduced unhealthy alcohol use compared to control among PLWH in Kenya [14], but the present trial extends the findings of Papas et al. in several ways. First, our CBT-based intervention (i.e., CETA) was delivered at public health facilities in Lusaka by existing 10–12 grade educated HIV peer counselors who had previously received basic training in HIV adherence counseling but who had no experience or formal education in mental health or substance use therapy (compared to paraprofessionals with a 2-year diploma in counseling who delivered CBT in Papas et al. [14]. The delivery of CETA by lay providers using an apprenticeship model thus has potential to circumvent shortages of professional and even paraprofessional providers in LMIC. Second, the intervention was delivered in one-on-one format, suggesting that the mode of delivery (group vs. individual) may not be critical for intervention efficacy. This is

important as a previous investigation of group-based CETA in Lusaka was found to be infeasible [21]. Third, our trial screened for and specifically recruited PLWH with mental health and substance use comorbidities. In populations with comorbid mental health and substance use problems, such as PLWH [39], transdiagnostic therapies are an efficient and flexible approach, reducing the need to train providers in multiple interventions.

Using EtG testing, we also observed that two out of ten participants who reported achieving abstinence were EtG-positive, indicating recent alcohol use. Unreported alcohol use was also documented in an alcohol treatment trial in Kenya based on Phosphatidylethanol testing [40] and presents a barrier to evaluating treatment interventions. Although our sensitivity analysis excluding under-reporters did not change the inference of the study results, we recommend the continued use of biomarkers as an objective measure of alcohol use to complement self-report in clinical trials.

Our preliminary results support the use of a screening, brief intervention, and referral to treatment (SBIRT) system within HIV care in SSA. Within the BI alone group, significant reductions in unhealthy alcohol use were observed, suggesting that some participants, possibly those without or

Table 4 Intervention effect of CETA on substance use outcomes among participants with any baseline substance use

Marijuana	BI (N = 23)		BI + CETA (N = 18)		Between group treatment effect	
	Mean (95% CI)	Mean change from baseline (95% CI)	Mean (95% CI)	Mean change from baseline (95% CI)	Difference in mean change (95% CI)	Cohen's d
Baseline	12.7 (9.0 to 16.5)	–	15.7 (11.4 to 19.9)	–	–	–
6-month follow-up	9.0 (5.3 to 12.8)	– 3.7 (– 7.6 to 0.2)	6.7 (2.4 to 11.0)	– 8.9*** (– 13.4 to – 4.5)	– 5.2 (– 11.2 to 0.7)	0.55
Inhalants	BI (N = 16)		BI + CETA (N = 21)		Between group treatment effect	
	Mean (95% CI)	Mean change from baseline (95% CI)	Mean (95% CI)	Mean change from baseline (95% CI)	Difference in mean change (95% CI)	Cohen's d
Baseline	13.8 (9.3 to 18.3)	–	10.9 (7.0 to 14.8)	–	–	–
6-month follow-up	6.8 (2.3 to 11.3)	– 7.0* (– 12.9 to – 1.1)	4.3 (0.44 to 8.3)	– 6.5* (– 11.7 to – 1.3)	0.5 (– 7.4 to 8.4)	–
Cocaine	BI (N = 18)		BI + CETA (N = 16)		Between group treatment effect	
	Mean (95% CI)	Mean change from baseline (95% CI)	Mean (95% CI)	Mean change from baseline (95% CI)	Difference in mean change (95% CI)	Cohen's d
Baseline	5.3 (2.0 to 8.7)	–	12.5 (9.0 to 16.0)	–	–	–
6-month follow-up	3.7 (0.3 to 7.0)	– 1.7 (– 5.9 to 2.6)	4.2 (0.7 to 7.7)	– 8.3*** (– 12.8 to – 3.8)	– 6.6* (– 12.8 to – 0.5)	0.86
Sedatives	BI (N = 10)		BI + CETA (N = 15)		Between group treatment effect	
	Mean (95% CI)	Mean change from baseline (95% CI)	Mean (95% CI)	Mean change from baseline (95% CI)	Difference in mean change (95% CI)	Cohen's d
Baseline	6.3 (3.1 to 9.5)	–	8.5 (5.8 to 11.1)	–	–	–
6-month follow-up	2.6 (0 to 5.8)	– 3.7 (– 8.3 to 0.9)	2.0 (0 to 4.6)	– 6.5** (– 10.2 to – 2.8)	– 2.8 (– 8.6 to 3.1)	0.45
Hallucinogens	BI (N = 13)		BI + CETA (N = 20)		Between group treatment effect	
	Mean (95% CI)	Mean change from baseline (95% CI)	Mean (95% CI)	Mean change from baseline (95% CI)	Difference in mean change (95% CI)	Cohen's d
Baseline	10.4 (6.3 to 14.4)	–	11.2 (7.9 to 14.4)	–	–	–
6-month follow-up	4.0 (0 to 8.0)	– 6.4** (– 10.7 to – 2.1)	2.0 (0 to 5.2)	– 9.2*** (– 12.6 to – 5.8)	– 2.8 (– 8.3 to 2.7)	0.31
Methamphetamines	BI (N = 19)		BI + CETA (N = 18)		Between group treatment effect	
	Mean (95% CI)	Mean change from baseline (95% CI)	Mean (95% CI)	Mean change from baseline (95% CI)	Difference in mean change (95% CI)	Cohen's d
Baseline	6.7 (3.5 to 9.9)	–	10.7 (7.4 to 14.0)	–	–	–

Table 4 (continued)

Methamphetamines SSI	BI (N = 19)		BI + CETA (N = 18)		Between group treatment effect	
	Mean (95% CI)	Mean change from baseline (95% CI)	Mean (95% CI)	Mean change from baseline (95% CI)	Difference in mean change (95% CI)	Cohen's <i>d</i>
6-month follow-up	4.8 (1.6 to 8.0)	− 1.8 (− 5.8 to 2.1)	2.7 (0 to 6.0)	− 8.0*** (− 12.1 to − 3.9)	− 6.2* (− 11.9 to − 0.5)	0.81
Opioids SSI	BI (N = 10)		BI + CETA (N = 18)		Between group treatment effect	
	Mean (95% CI)	Mean change from baseline (95% CI)	Mean (95% CI)	Mean change from baseline (95% CI)	Difference in mean change (95% CI)	Cohen's <i>d</i>
Baseline	5.1 (1.1 to 9.1)	−	7.7 (4.7 to 10.7)	−	−	−
6-month follow-up	5.4 (1.4 to 9.4)	0.3 (− 5.4 to 6.0)	2.7 (0 to 5.7)	− 5.0* (− 9.3 to − 0.7)	− 5.3 (− 12.4 to 1.8)	1.0

SSI Specific Substance Involvement score (via the Alcohol, Smoking, and Substance Involvement Screening Test)

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

α = Cronbach's Alpha for internal reliability

Estimates for means, 95% CIs, mean change from baseline, difference in mean change are based on predicted values from mixed effects model

Cohen's *d* effect size is calculated by dividing the predicted difference in mean change from the mixed effects model by the pooled baseline SD

Model included fixed effects of treatment arm, time, and interaction terms of treatment X time as well as random effects of participant ID and counselor ID

Sample includes all participants with baseline SSI scores > 0

with few comorbidities, may not require referral to CETA in a real-world program. This notion is supported by our exploratory efficacy analysis stratified by number of comorbidities, which showed that CETA's effect on alcohol use was larger in PLWH with more comorbidity. A stepped care approach could be implemented, where less complex patients receive the BI alone followed by reassessment to see if referral to CETA is needed. If confirmed in subsequent trials, this would support the availability of both the BI and CETA in a stepped care approach within HIV clinics, in which patients are routinely screened for alcohol use, provided with the BI (if needed) and then referred to CETA (if needed). Patients with more severe symptom presentation (such as those with 3+ comorbidities) may also proceed directly to CETA following screening. An adaptive trial design [41] could be helpful in further delineating for which clients a BI alone, CETA alone, or BI + CETA are most appropriate. Future trials in this area should evaluate effects on HIV outcomes, which are critical to individual outcomes (i.e., HIV mortality) and public health (i.e., ART treatment as prevention). In this trial, both late ART pickups (38% to 31%) and HIV RNA non-suppression (31% to 11%) appeared to reduce from pre- to post-enrollment; however,

the study was not designed to evaluate whether any changes resulted from the interventions.

The high treatment completion of both the BI (100%) and CETA (98%) suggests that this SBIRT approach could possibly represent an intervention package that is feasible and acceptable within this specific HIV clinic context. This may be due to a number of reasons such as: (a) we recruited a very ART-experienced, clinic-based patient population, (b) that alternative treatments were sorely lacking and thus clients were motivated, (c) that participants received transportation reimbursements for participation, (d) that counselors who were recently trained were very motivated to complete their cases and obtain CETA certification, and/or e) that the BI session immediately after screening served as an engagement mechanism that increased the client's comfort with their counselor and therapy, which increased the likelihood that they returned for CETA sessions. Because this was the first study of CETA within an HIV clinic context, a more in-depth understanding of real-world delivery of both the BI and CETA, including rigorous study of implementation factors, is important to include in future investigations.

This study had several limitations. Our main limitation was that COVID-19 caused early trial closure and around

26% of participants did not complete a post-assessment. However, due to the randomized nature of the trial and that COVID-related missing data was similar in both arms, we do not believe this resulted in a biased analytic sample. We also acknowledge that a large amount of missing HIV data prevented us from drawing conclusions around the effects of alcohol reduction, or improvements in mental health comorbidity due to CETA, on engagement in care or viral suppression. HIV indicators will be primary outcomes in a planned larger follow-up trial. Another limitation was our reliance on self-report to assess alcohol outcomes. Although we used ACASI and included an alcohol biomarker, it is possible that participants assigned to BI plus CETA were more prone to social desirability bias and reported lower AUDIT scores than those in BI alone. Recruitment of an urban clinic-based population with a long history of longitudinal HIV care was another possible limitation, although many patients had imperfect engagement in HIV care based on recent late ART drug collections or incomplete HIV RNA suppression. Data from this study may not be generalizable to rural settings and certain subpopulations of PLWH, such as recently HIV-diagnosed individuals or stigmatized key populations, who may require tailored approaches to take up and complete CETA. Of note, we previously evaluated community delivery of CETA in Zambia in a mostly HIV-uninfected population, and similar rates of treatment initiation and completion were seen [21]. We also acknowledge as a limitation that the BI plus CETA arm involved many more sessions than BI alone; therefore, it is possible that some of CETA's effects on alcohol use may be due to non-specific assessment or treatment dosage effects. Having a time and attention-matched control (such as repeated AUDIT screening alone) was not deemed practical or acceptable by the local staff and in a real-world program may have similar costs to assessment alone. The independent effects of the BI alone, our active control condition, were not measured in this trial (i.e., there was no placebo or wait-list control) and compared to standard of care, BI plus CETA's effects may potentially be larger. Finally, this study was designed as efficacy trial and future studies featuring implementation designs will be needed to evaluate treatment effectiveness in less controlled settings.

Conclusions

In summary, BI plus referral to CETA led to a clinically and statistically significantly greater reduction in unhealthy alcohol use, depression and trauma symptoms, and substance use at 6 months compared to BI alone among PLWH in Lusaka, Zambia. CETA was particularly effective for PLWH with the greatest number of comorbidities. CETA was feasible for delivery by lay HIV peer educators at public HIV clinics.

CETA may be a promising intervention for management of complex and co-occurring substance use and mental health problems among PLWH. Future research should focus on whether and to what degree treatment of unhealthy alcohol use and its comorbidities, with an alcohol BI plus or minus CETA, can improve critical ART outcomes including engagement in care and sustained viral suppression.

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Author Contributions MJV and JCK designed the study. AS, TK, SS, CC, MEL, JCK, and MJV oversaw the implementation of the study. LKM is an original developer of CETA and LKM, SS, and CKD developed the BI intervention. LKM and SS conducted the CETA training; SS conducted the BI training and provided clinical supervision. JCK conducted the analysis and wrote the first draft of the manuscript. All authors contributed substantially to the conduct of the study, interpretation of the findings, and the drafting of the manuscript. All authors read and approved the final version.

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Data Availability Data and code are available upon request to corresponding author.

Declarations

Conflict of interest The authors declare no conflicts of interest.

Ethical Approval The trial was approved by the Johns Hopkins Bloomberg School of Public Health IRB, the Columbia University Medical Center IRB, the University of Zambia Biomedical Research Ethics Committee, and the National Health Research Authority in Zambia. The trial was monitored by a three-person Data and Safety Monitoring Board (DSMB). Detailed methods were published on ClinicalTrials.gov (NCT03966885).

Consent to Participate Informed consent was obtained from all individual participants included in the study.

Consent for Publication Not applicable.

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