Trials

STUDY PROTOCOL

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ImpACT+, a coping intervention to improve clinical outcomes for women living with HIV and sexual trauma in South Africa: study protocol for a randomized controlled trial

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Abstract

Background: Addressing sexual trauma in the context of HIV care is essential to improve clinical outcomes and mental health among women in South Africa. Women living with HIV (WLH) report disproportionately high levels of sexual trauma and have higher rates of posttraumatic stress disorder. Adherence to antiretroviral therapy (ART) may be difficult for traumatized women, as sexual trauma compounds the stress associated with managing HIV and is often comorbid with other mental health disorders, further compromising care engagement and adherence. ART initiation represents a unique window of opportunity for intervention to enhance motivation, increase care engagement, and address the negative effects of trauma on avoidant coping behaviors. Mental health interventions delivered by non-specialists in low- and middle-income countries have potential to treat depression, trauma, and effects of intimate partner violence among WLH. This study will examine the effectiveness of Improving AIDS Care after Trauma (ImpACT+), a task-shared, trauma-focused coping intervention, to promote viral suppression among WLH initiating ART in a South African clinic setting.

Methods: This study will be conducted in Khayelitsha, a peri-urban settlement situated near Cape Town, South Africa. Using a hybrid type 1 effectiveness-implementation design, we will randomize 350 WLH initiating ART to the ImpACT+ experimental condition or the control condition (three weekly sessions of adapted problem-solving therapy) to examine the effectiveness of ImpACT+ on viral suppression, ART adherence, and the degree to which mental health outcomes mediate intervention effects. ImpACT+ participants will receive six once-a-week coping intervention sessions and six monthly maintenance sessions over the follow-up period. We will conduct mental health and bio-behavioral assessments at baseline, 4, 8, and 12 months, with care engagement data extracted from medical records. We will explore scalability using the Consolidated Framework for Implementation Research (CFIR).

Discussion: This trial is expected to yield important new information on psychologically informed intervention models that benefit the mental health and clinical outcomes of WLH with histories of sexual trauma. The proposed ImpACT+ intervention, with its focus on building coping skills to address traumatic stress and engagement in HIV

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care and treatment, could have widespread impact on the health and wellbeing of individuals and communities in sub-Saharan Africa.

Trial registration: Clinicaltrials.gov NCT04793217. Retrospectively registered on 11 March 2021.

Keywords: HIV, Adherence, Antiretroviral therapy, Sexual violence, Traumatic stress, South Africa, Randomized controlled trial

Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

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Introduction

Background and rationale {6a}

Addressing sexual trauma in the context of HIV care is essential to improve clinical and mental health outcomes. Women living with HIV (WLH) report disproportionately high levels of sexual trauma and have high rates of posttraumatic stress disorder (PTSD) [1, 2]. Adherence may be difficult for traumatized women, as sexual trauma adds to the stress of managing HIV and increases avoidant behavior [3–7], acting as a barrier to care engagement [4, 8] and resulting in compromised immune functioning and increased infectivity [9–16]. Addressing the synergy of mental health and behavioral factors may be an effective strategy to improve adherence and clinical outcomes from the outset of ART initiation [9, 15, 16]. With increased global access to highly effective antiretroviral treatment (ART) that has resulted in viral suppression as an achievable goal, innovative intervention strategies are needed to address underlying causes of treatment failure and build resilience to maintain adherence [17].

In South Africa, the country with the highest burden of HIV, nearly half of all women experience physical or sexual assault from a male partner in their lifetime [5, 18, 19] and over a third have histories of sexual abuse during childhood [20]. These instances of violence frequently result in high levels of post-traumatic stress among WLH [21–23]. The experience of sexual trauma and HIV may be linked either directly (acquiring HIV through sexual abuse or violence) or indirectly (through behavioral sequelae, disclosing to a violent partner, or internalized stigma) [24]. Traumatic stress is often comorbid with other mental health disorders, such as depression, anxiety disorders, and substance use [25–27], which are also linked to poor care engagement [28, 29]. The high burden of sexual trauma among WLH in South Africa [19, 30, 31] may therefore be a significant contributing factor for the low rates of viral suppression seen among WLH [32].

The intersection of HIV and trauma highlights the importance of integrated mental health treatment and HIV care, particularly in a setting like South Africa where mental health services are limited, and women are both more likely to be living with HIV [33] and face overlapping epidemics of gender-based violence and sexual trauma [34]. Specifically, effective interventions are needed that address the combined stress of trauma and HIV among WLH to improve psychological and clinical outcomes from the outset of ART initiation [35, 36]. There is strong reason to expect that reducing traumatic stress would decrease avoidance [37, 38] and increase care engagement [1], thus increasing viral suppression. Although some interventions aimed at treating sexual trauma among WLH in order to improve care engagement have been developed [1, 37–39], and treatments aimed at addressing IPV in this population have shown promise [40], we are unaware of any full-scale trials that test the effectiveness and examine the underlying mechanisms of change of a trauma-related coping intervention to improve or maintain viral suppression and related clinical outcomes.

ART initiation represents a unique window of opportunity to enhance motivation and address the negative effects of trauma on avoidant coping behaviors [41, 42] to increase care engagement and interrupt losses that occur throughout HIV care cascade [43, 44]. In 2016, we conducted a pilot trial of ImpACT, a task-shared intervention that sought to improve mental health and clinical outcomes among WLH with sexual trauma histories in South Africa by addressing coping with HIV and trauma and therefore increasing adherence to antiretroviral therapy (ART) [45, 46]. The ImpACT intervention was based on *Living in the Face of Trauma* (LIFT), a CDC—and SAMHSA—evidence-based intervention for adults living with HIV with histories of childhood sexual abuse in the United States (US). LIFT significantly reduced incidents of unprotected sex [47], substance use [48], and traumatic stress symptoms [37]. Notably, reductions in traumatic stress were fully explained by reductions in avoidant coping. ImpACT was adapted and refined to become ImpACT + and is the intervention evaluated in this trial. Task-shared for delivery by a non-specialist, ImpACT + shows promise to address the synergistic stress of sexual trauma and HIV and the multifaceted needs of WLH in South Africa. In this trial, we aim to prove the efficacy of this acceptable, feasible, and culturally relevant intervention to improve clinical outcomes.

The paucity of culturally relevant evidence-based mental health treatments is accompanied by two significant barriers to scalability: (1) the shortage of trained mental healthcare providers across low resource settings [49] and (2) uncertainty as to the best setting for delivery [50]. There is increasing evidence that culturally adapted mental health interventions delivered by nonspecialists in LMICs have potential to treat depression, trauma, and effects of intimate partner violence (IPV) among WLH [40, 45, 51]. Care providers in LMICs emphasize the need for mental health interventions that can be integrated into chronic care systems and strengthen the healthcare system [52]. Integrating a targeted, task-shared trauma intervention into HIV care may help address the limited capacity of the mental health care system to identify and treat women with traumatic stress.

The current study will examine the effect of ImpACT +, a task-shared, trauma-focused intervention at promoting viral suppression among WLH initiating ARVs in a South African clinic setting. We will also examine whether the intervention's effects are mediated by improvements in mental health and coping outcomes. The study design will allow us to explore the potential for implementation and scale-up of ImpACT +, thereby accelerating the process of translating research into practice.

Objectives {7}

The primary objective of this trial is to determine the effectiveness of ImpACT + on viral load suppression by reducing avoidant coping and traumatic stress among WLH with sexual trauma in Cape Town, South Africa.

The specific objectives are:

1. To determine the effectiveness of ImpACT +, compared to adapted problem-solving therapy (PST), on clinical outcomes over a 12-month period among WLH with sexual trauma who are initiating ART
2. To examine underlying mechanisms of change by evaluating the degree to which improvements in mental health and coping mediate intervention effects on primary (viral suppression) and secondary outcomes (adherence and care engagement)
3. To explore the scalability of ImpACT +, guided by the Consolidated Framework for Implementation Research (CFIR) [53], to better understand facilitators and barriers to full-scale implementation

Our primary hypothesis is that a greater proportion of ImpACT + participants will be virally suppressed (primary outcome), adherent, and engaged in care (secondary outcomes) at 12 months compared to PST participants. Our secondary hypothesis is that over time, ImpACT + participants, as compared to PST participants, will report greater reductions in (1) traumatic stress and (2) avoidant coping, which, in turn, will lead

to (causally mediated) improvements in ART adherence, care engagement, and viral load (VL) at 12 months.

Trial design {8}

We will employ a hybrid type 1 effectiveness-implementation design [54] to test the effectiveness of ImpACT + and explore its potential for implementation. This trial is a two-arm, randomized controlled trial comparing ImpACT + to adapted PST among WLH with sexual trauma (see Fig. 1 for study flow). Both arms enhance standard clinical care.

Methods: participants, interventions, and outcomes

Study setting {9}

The study will be conducted in four primary healthcare facilities located in the peri-urban suburb of Khayelitsha, situated on the outskirts of Cape Town, South Africa. Khayelitsha is one of the fastest growing informal areas of South Africa, with a conservatively estimated population of 500,000 [55]. Khayelitsha is the region with the highest HIV prevalence in the Western Cape [56] and is characterized by high rates of unemployment and poverty, with almost half of residents living in overcrowded, poor quality housing without electricity, indoor sewage, and/or running water [57]. The healthcare facilities offer comprehensive HIV care, and staff are comprised of nurses, adherence counselors, community care workers, pharmacists, medical officers, and social workers. Each of the four facilities serves between 7500 and 10,000 patients living with HIV, of which two-thirds are female and a majority are Black African and isiXhosa-speaking. Universal test and treat guidelines were introduced in South Africa in 2016, and ART initiation at the clinic follows the standard protocol per government guidelines [58]. The ART initiation clinics serve naive initiators (often newly diagnosed), restarters (absent from care ≤ 3 months), and defaulters (absent from care > 3 months).

Eligibility criteria {10}

The study will enroll women living with HIV engaging with care at one of the four study clinics. Women will be eligible for enrollment in the trial if they meet the following criteria: (1) Living with HIV and between 2 weeks and 4 months since initiation of first-line ART (as new initiators, restarters or defaulters); (2) history of sexual abuse or assault during childhood, adolescence, or adulthood, using four items based on the WHO CIDI [59] and the Childhood Trauma Questionnaire [60]; (3) endorsement of any PTSD symptoms as assessed by the Breslau PTSD screener [61]; (4) 18 years or older; (5) isiXhosa speaking; and (6) receiving HIV care services at a study clinic. Patients will be excluded and referred to psychiatric services if they meet criteria for high risk of suicide. Suicidal ideation and severity will be assessed using items adapted from the suicidality subscale of the Mini International Neuropsychiatric Interview [62]. Pregnant women will be eligible to enroll. Additional exclusion criteria include patients initiated on second- or third-line ART, the inability to provide informed consent, or inability to communicate in isiXhosa or English.

Who will take informed consent? {26a}

Prior to baseline assessment, study staff will provide participants with verbal and written information about the study in their preferred language (English or isiXhosa). Participants will be asked to provide written consent if they agree to be part of the study. Participants will sign two copies of the informed consent form, one for the study records and one to take for their personal documentation.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

We will request consent for review of participants' medical records, and for the collection of blood samples to assess viral load and adherence.

Interventions

Explanation for the choice of comparators {6b}

ImpACT + was developed for a South African clinic setting in the context of limited mental health resources and with national guidelines indicating rapid ART initiation and universal treatment for all HIV-infected persons. Integrating a targeted trauma intervention into HIV care may help address the limited capacity of the mental health care system to identify and treat women with traumatic stress. For the control condition, we decided to provide another mental health treatment (adapted PST) rather than standard of care for mental health treatment (referral to the clinic medical officer). This decision was based primarily on the following: (1) ethical grounds, to provide a reasonable comparison intervention for this vulnerable patient population; PST is being explored in an implementation trial in Cape Town [63, 64], and (2) to utilize a control condition that provides a relatively high level of care and accounts for the potential impact of general stress reduction, thus, setting a high standard for determining the effectiveness of ImpACT +. With the absence of trauma-informed care in this setting, our research process identifies women with sexual trauma that may otherwise go unaddressed. A control condition with minimal interaction, or even treatment as usual,

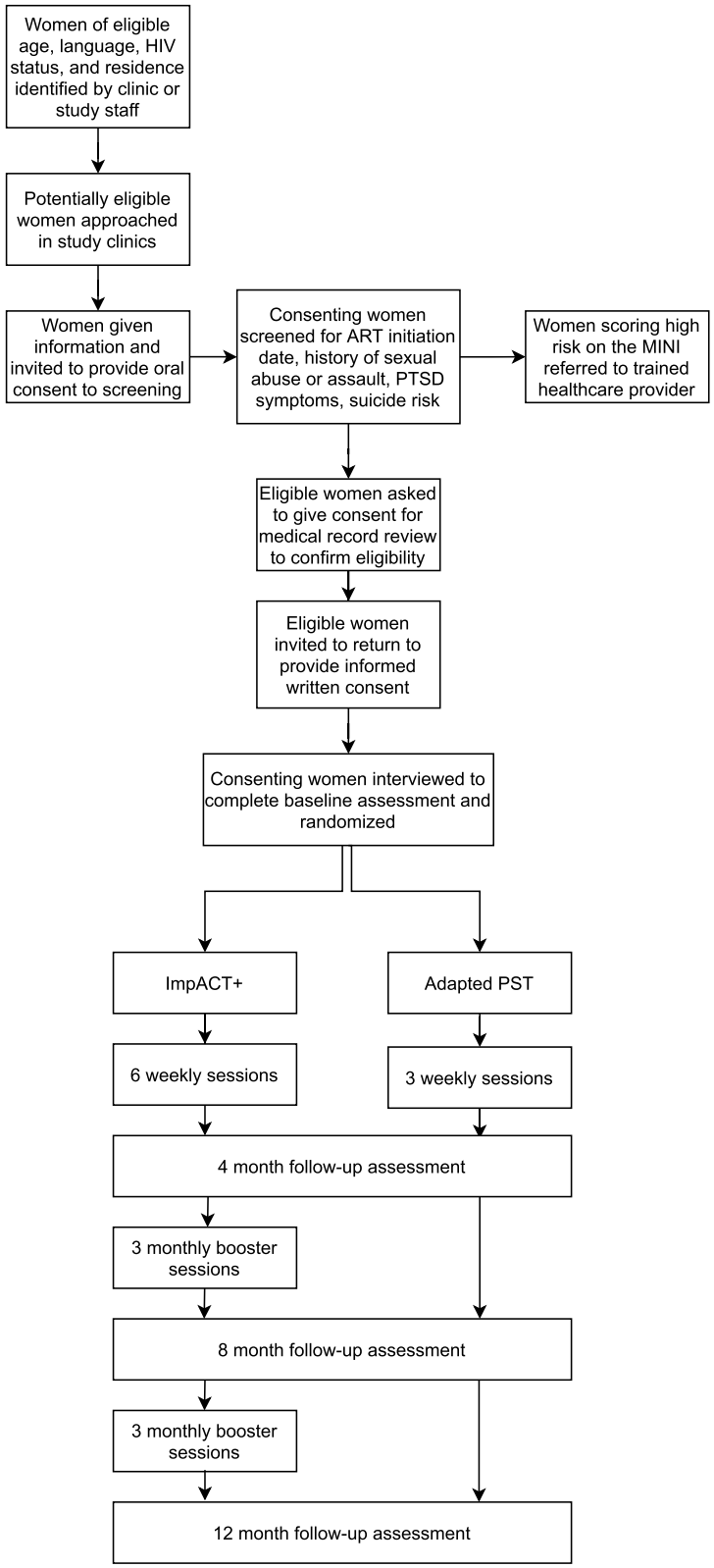

Fig. 1 Study flow

is insufficient. We have chosen this control condition because we believe that the greatest priority is to measure the effectiveness of ImpACT + in comparison to recommended mental health care services, even if they have not yet been brought to scale in the settings.

Intervention description {11a}

Intervention arm

Treatment condition: ImpACT+. ImpACT + integrates skills for coping with trauma and HIV treatment adherence, tailored to the South African context. Culturally adapted and guided by the evidence-based intervention *Living in the Face of Trauma* (LIFT) [37, 47, 48], ImpACT + targets women who are initiating ART, making use of a window of opportunity to maximize the impact on HIV care engagement. ImpACT + draws on LIFT as a conceptual foundation [65] and the pilot trial of ImpACT for cultural adaptation [46, 66]. Areas of focus include exploration of values informing care engagement, recognizing the synergistic stress of sexual trauma and HIV, understanding the contribution of stressors to maladaptive coping, and developing adaptive methods for coping (including disclosure) as alternatives to avoidance. Key intervention components were developed for cultural saliency. For example, a "coping pebbles" activity was used to translate the coping framework [67, 68] into a tangible analogy to represent the burden of a global stressor, with stress appraisal using color-coded pebbles to distinguish changeable and unchangeable stressors. Concepts from LIFT related to safety, trust, power, and self-esteem were symbolized by the locally relevant *Imbiza pot*, with three legs and a lid representing these concepts. Intervention materials developed include a detailed manual, workbook, and flipbook for in-session use. See Table 1 for key conceptual concepts.

ImpACT + will be delivered in private, study offices at each research site and will consist of six weekly (over 2 months) structured individual sessions lasting 60 min, followed by six monthly maintenance check-ins lasting 30 min linked to routine appointments. Sessions will focus on motivational enhancement, coping skills related to HIV and trauma, adherence, and care engagement during a critical period of initiation, while maintenance check-ins will reinforce positive change and support the ongoing implementation of skills as new challenges arise. Evidence supports a six-session format, with interventions of similar length shown to be effective in low-resource settings [64, 69], and maintenance check-ins for longer term effects [68, 70, 71]. Individual sessions will begin within 2 weeks after the baseline survey, and maintenance check-ins will begin following the 4-month assessment.

Personnel: recruitment, training, and supervision. The ImpACT + intervention will be conducted by trained and supervised healthcare providers with a 4-year degree or diploma program, including relevant mental health training or prior experience in providing care or support to women with HIV and/or trauma histories. Although this is a task-shared intervention, the trauma-focused nature of the intervention indicates that some prior experience in mental health care is necessary to ensure the mental wellbeing of the interventionists. Interventionist training will be conducted over 5 weeks; the first 2 weeks of intensive face-to-face training will focus on learning the ImpACT + manual and workbook, followed by 3 weeks of practice administering individual components, mock sessions, and training on ethical conduct of counseling. Training will be ongoing throughout the trial, particularly in the first 3 months of intervention delivery. Additionally, interventionists will engage in weekly group supervision throughout the trial which will include review and feedback on randomly selected session recordings (10%, stratified by interventionist and session number), review of session workbook notes, and quality assurance checklists. Supervisors will use an adapted version of the Enhancing Assessment of Common Therapeutic factors (ENACT) rating scale to rate sessions and determine fidelity [72]. Interventionists will furthermore participate in monthly debriefing sessions with a trained clinical psychologist who specializes in treating traumatized women. Additional debriefing sessions will be available upon request.

Control arm

Control condition: *adapted PST*. Participants randomly assigned to the control condition will receive three, 40-min individual sessions of adapted PST. The version of PST developed for the purposes of this study is based on Problem Management Plus (PM+), a component of the open-access WHO Mental Health Gap Action Programme (mhGAP) [73]. PST is a psychoeducational treatment focused on managing the negative effects of stressful life events. PST has been found to be effective for a range of problems, such as depression, and is recommended for implementation in low-resource settings. The goal of PST in this study is to identify problems that interfere with daily activities and address them through problem-orientation work. We anticipate stressors will include (a) relationship difficulties, including family stress, (b) financial stress and unemployment, (c) general impact of HIV infection, and (d) overall chronic stress. Thus, PST is stress management focused, but will not address the intersection of HIV and trauma specifically. PST interventionists will not prevent participants

Table 1 ImpACT + components and timing

Component	Focus for trauma and adherence	Sessions						
		1	2	3	4	5	6	M1-6
Start Strong, Stay Strong	Value of lifelong ART for achieving goals; touchstone for care engagement	■	▪	■	▪	■	▪	▪
Values Bridge	Personal motivators & values for ART adherence and HIV care engagement	■	▪	■	■	■	▪	▪
3H (Head, Heart, Hands)	Impact of trauma on throughs, feelings, and relationships	■	■	■	■	■	▪	▪
Trauma Symptoms	Relating experiences with trauma to common challenges reported by others		■	■	▪	▪	▪	▪
Emotion Wheel	Understanding emotional impact of trauma on personal goals, care engagement		■	▪	▪	▪	▪	▪
Imbiza Pot	Functioning in the face of trauma; Belief in support, recovery, resilience		■	▪	■	▪	■	▪
Relaxation Breathing	Encouraging a calm mind through a calm body, healthy coping	■	▪	▪	▪	▪	▪	▪
Coping Pebbles	Coping model; Problem-Focus and Emotion-Focused strategies for coping		■	■	■	■	■	▪
Goal-setting: Adherence	Apply coping model to one adherence-related goal; identify barriers & solutions		■	■	▪	▪	▪	▪
Disclosure	Facilitate disclose decision-making and communication skills			■	■	▪	▪	▪
HIV Care Story	Normalize trauma and care challenges; Narrative to reflect and address barriers			■	■	▪	▪	▪
Action Plan: Adherence	Structured goals and timeline using active coping framework for adherence			■	■	■	■	▪
■ Key intervention component ▪ Component used as needed								

from discussing sexual trauma and HIV, but the stress and coping skills training related to the synergy between trauma and ART adherence will not be incorporated into the PST interventionist training. These procedures will maintain the distinction between the ImpACT + intervention and the control condition. Participants randomized to the PST condition will begin sessions within 2 weeks post-baseline.

Personnel: recruitment, training, and supervision. Adapted PST will be conducted by a trained and supervised lay counsellor. The PST counsellor will have at minimum a secondary school education and experience in providing counselling to women living with HIV. Intervention training will be conducted over a 4-week period, with two weeks of intensive face-to-face training using an adapted PST manual and workbook developed by study research staff, followed by 2 weeks of practice administering intervention sessions, conducting mock sessions, and learning basic counselling skills and therapeutic conduct. Supervision is similar to that of the ImpACT + interventionists. The PST counsellor engages in weekly one-on-one supervision for review of a random subset of sessions, session workbooks, and ENACT forms. The PST counsellor participates in monthly debriefing sessions separate from the ImpACT + interventionists to mitigate risk of intervention contamination.

Criteria for discontinuing or modifying allocated interventions {11b}

Intervention sessions will be discontinued if participants request to withdraw from the study. Participants may be withdrawn by the investigator in the event of a serious adverse event that precludes participation in the intervention.

Strategies to improve adherence to interventions {11c}

The ImpACT + intervention manual was designed to allow the interventionists to tailor content to traumatic

experience, stress symptoms, and adherence challenges depending on the personal history and mental health state of participants. As such, the intervention will vary between participants and adherence to the manual will be high. In the event that participants are unable to attend one or several sessions of the intervention, the following sessions will be adapted to include key components missed. Following each session, ImpACT + interventionists and PST counsellors will complete a quality session-specific fidelity checklists and note any issues that arose. ImpACT + and PST providers will engage in separate weekly group supervision, including review and feedback on select audio recordings of sessions, and review of session workbook notes and quality assurance checklists. Each week, supervisors will listen to a random selection of session audio recordings, using the ENhancing Assessment of Common Therapeutic factors (ENACT) rating scale to assess therapeutic competence and intervention fidelity [72].

Relevant concomitant care permitted or prohibited during the trial {11d}

Mental health services outside of protocol will be monitored throughout the trial.

Provisions for post-trial care {30}

There are no plans for post-trial care. Potential participants will be informed of the risks associated with participating in the trial. Referrals will be made if deemed necessary and appropriate.

Outcomes {12}

The primary outcome measure is viral suppression at 12 months, determined by HIV viral copies per milliliter of blood. Viral suppression will be reported as a dichotomous variable with the threshold for viral suppression defined as < 50 copies/mL, as determined by the Abbott Alinity assay (Sensitivity Limit of Detection 20 copies/mL).

The following secondary outcome measures will be assessed at baseline, 4, 8, and 12-month timepoints:

- ART adherence:
  - Dried blood spots measuring levels of tenofovir-diphosphate (TFV-DP) (at 12 months)
    - Medical record abstraction of pharmacy visits and pharmacy refill data
  - Adapted Adult AIDS Clinical Trials Group self-report measure of adherence [74, 75]
- HIV care engagement (medical record abstraction):
  - Missed visits (# of monthly visits missed and binary indicator of any missed monthly visit)
  - Visit adherence (proportion of visits kept)
  - Gaps in care (whether > 90 days have elapsed between visits)
  - Visit constancy (# of 90-day intervals with > 1 completed visit).
    - Mental health mediators will be assessed by the following measures (all timepoints):
- Post-Traumatic Stress (PTSD Checklist-Civilian version for the DSM-5 (PCL-5) [76]
- Coping [45], adapted from [77–81].

Implementation and scalability

In addition to examining the efficacy of ImpACT +, this trial will include a mixed-method process evaluation of intervention feasibility and acceptability. We will explore the scalability of ImpACT + by assessing potential facilitators and barriers to full-scale implementation, guided by the CFIR [53]. The CFIR helps evaluate an intervention's effectiveness in a specific context and identify strategies to optimize intervention benefits. We will draw on these CFIR domains: (1) intervention characteristics, (2) outer setting, (3) inner setting, and (4) process. After recruitment is complete, we will conduct in-depth qualitative interviews with clinic staff ($n = 10$ per clinic, 20 total: nurses, physicians, social workers, adherence counsellors, community health workers) and ImpACT + interventionists to explore intervention factors that would facilitate or impede roll-out and the sustainability of implementation. Interviews with clinic staff and managers at the City of Cape Town Health Department ($n = 10$) will explore patient needs and resources, and external policies and incentives that could impact future implementation and scalability. A random subset of ImpACT + participants (10%; $n = 18$) will be asked to participate in an in-depth interview on acceptability of the intervention and barriers and facilitators to implementation.

Participant timeline (Table 2) {13}

Sample size {14}

Our enrollment target is 350, which will allow detection of intervention effects on viral suppression at 12-month follow-up. Based on data from our preliminary studies [66] and corroborated by national estimates [32], we expect that 57% of women who are newly initiating ART and randomized to the PST condition will be virally suppressed at the 12-month follow-up. With 350 women randomized equally to both conditions, we will have 80% power with a two-tailed alpha level of 0.05 to detect differences between a proportion of 57% in the PST condition and 73% in the ImpACT + condition. This power

Table 2 Schedule of enrollment, interventions, and assessments

	Screen	Enrollment & Baseline	Allocation	Post-allocation	Follow-up		
TIMEPOINT	t-2	t-1	0	t1 (0-4M)	t2 (4 M)	t3 (8M)	t4 (12 M)
ENROLLMENT:							
Eligibility screen	x						
Oral consent	x						
Informed consent		x					
Allocation			x				
INTERVENTIONS:							
ImpACT+				←	← – – – – – – – →		
Adapted PST				←			
ASSESSMENTS:							
Screen variables[a]	x						
Socio-demographic variables		x			x	x	x
Primary outcome: Viral suppression							x
Secondary outcomes[b]		x			x	x	x
Mediating variables[c]		x			x	x	x
Implementation outcomes[d]							x

[a]ARV initiation status, Depression (PHQ-2), Intimate partner violence (CTS2), Sexual abuse history, Traumatic stress, Suicide MINI

[b]HIV care engagement, ARV adherence

[c]Coping strategies, Traumatic stress (PCL-5)

[d]Participant exit interviews, Key informant interviews

calculation assumes we will retain 80% of participants over the study period. In the pilot, we were able to successfully retain 80% of all participants (83.3% of newly initiating participants) for the duration of the study [45].

Recruitment {15}

Clinic staff will refer all women who receive a positive HIV diagnosis or present themselves for care at the ARV initiation clinic to our study offices. In a private office, English and isiXhosa-speaking study staff will greet potential participants and ask if they would like to participate in a screening questionnaire. Prior to screening, study staff will administer oral consent that highlights confidentiality and enumerates the sensitive nature of the screening items. As receipt of an HIV diagnosis and disclosure of traumatic sexual experiences can both be distressing, study staff will judge whether newly diagnosed women should be screened same day or at her next clinic visit. Our window period of 2 weeks to 4 months post ART initiation allows for flexibility in recruitment based on individual participant needs.

Screening consists of three major sections: (1) oral consent for screening; (2) a questionnaire that includes six questions on demographics, three questions on interpersonal violence (IPV), four questions on sexual trauma, two questions on depression, and seven questions on traumatic stress symptoms; and (3) written consent for medical record access in order to confirm eligibility. Eligible participants will be given information about the trial and, if interested, scheduled for a baseline assessment. Participants who indicate high risk of suicide during screening will be assessed by on-site study interventionists to determine need for referral for additional mental health care. The project manager and clinical supervisor will confirm the interventionist's assessment and determine whether the participant should be excluded.

Assignment of interventions: allocation

Sequence generation {16a}

1:1 allocation to either the intervention or control condition will be determined by a random number chart

generated using an independent web-based online system (https://www.sealedenvelope.com). Randomization will be stratified by initiation status (naïve initiator, restarter, defaulter), clinic, and pregnancy status (pregnant, not pregnant) to ensure equal distribution of study conditions.

Concealment mechanism {16b}

Randomized blocks of 4 and 6 will be used within the study sites to ensure that assessment staff are unaware of condition prior to allocation and to ensure balanced assignment to condition over time.

Implementation {16c}

Study staff at Columbia University and Irving Medical Center will create the allocation table and upload it to REDCap. Following completion of the baseline assessment, study staff will use the Research Electronic Data Capture (REDCap) [82] randomization form to assign the participant to either ImpACT + or the PST condition. Participants will be informed that they have been assigned to either a 6-session or 3-session intervention and that they will receive further details at the first treatment session.

Assignment of interventions: blinding

Who will be blinded {17a}

Given differences in content and number of sessions, the experimental (ImpACT +) and control (PST) providers delivering the intervention cannot be masked to participant allocation. To avoid contamination, ImpACT + and PST providers will be trained separately and receive supervision by two distinct psychologists with separate debriefing sessions throughout the trial. Research assistants will inform participants of their intervention allocation post-baseline and are therefore not blinded post randomization. An independent assessor blinded to participant condition will conduct 4-, 8-, and 12-month assessments. The independent assessor will be trained, supervised, and attend debriefing sessions separately throughout the trial. Investigators, data analysts, and outcome assessors will be masked to participant allocation, with condition revealed at the conclusion of analysis.

Procedure for unblinding if needed {17b}

Randomization allocation will be revealed to the statistician after finalization of the main data analysis.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Participants will go through the full trial informed consent process at baseline, after which RAs will verbally administer a battery of psychological assessments and other self-report measures in isiXhosa. Independent assessors will administer the same battery at 4-, 8-, and 12-month follow-up assessments. Assessments will take approximately 60 min and will be conducted in a private room at the clinic. Study staff will clarify any questions and refer participants who indicate high suicide risk during the interviews to the medical officers for further assessment and referral. Blood samples to measure viral load and ARV adherence via DBS will also be collected at all follow-up assessments. Relevant HIV care data will be abstracted from participants' medical records.

Plans to promote participant retention and complete follow-up {18b}

Study staff will emphasize the importance of attending all intervention sessions and assessment appointments. We will collect detailed contact information for participants and close contacts. We will reschedule appointments as needed and follow-up with participants who miss sessions and assessments.

Data management {19}

The PI and UCT PI, CUIMC Project Coordinator, and UCT Project Director will oversee the data management protocol and established Standard Operating Procedures (SOPs) for data collection, quality control, and data extraction and transfer. See the confidentiality section for precautions and quality assurance measures designed to protect the privacy of participants and maintain confidentiality of research data during collection and transfer. To ensure compliance with the monitoring plan, all study staff will be well trained and will receive ongoing supervision in confidentiality and data security procedures, specifically in ethical conduct, confidentiality protection, review of medical records, mandated reporting, data reporting across study sites, and other topics of human participant protection.

Surveys will be administered via password-protected, encrypted tablet computers by individual interview and entered in real time into REDCap projects. Screening, baseline, and follow-up assessments will be conducted in person. Survey data collected on the tablet will be coded with the participants' ID numbers and will not contain participant names or contact information.

Confidentiality {27}

Study staff will be trained and will receive ongoing supervision in confidentiality and data security procedures. As part of the consent procedure, participants will be informed of the limits of confidentiality

(i.e., reporting of imminent harm to self or others) and mandated reporting requirements (i.e., reporting of child abuse). Interviews, discussions, study assessments, and intervention sessions will be conducted in closed and private rooms on password-protected tablets. Participant information will be stored on password-protected computers or locked cabinets and will not be linked to participant names or locator data. Audio files from intervention sessions will be deidentified and audio-translated into English for quality assurance purposes, and the original files will be deleted upon completion of all analyses. Data will be stored for as long as necessary to complete the study and for adherence to IRB regulations. Biospecimens will be de-identified and destroyed 5 years after study completion. The information gathered in this study will be used only for scientific, educational, or instructional purposes.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Trained personnel will take the blood samples, using only new, sterile equipment, and bandage the site to minimize any potential side effects. Staff will have received prior training in phlebotomy and will review best practices recommended by WHO guidelines on drawing blood. Blood samples will be assigned a unique study ID number and will be stored securely in a locked cabinet at the clinic until they can be transported in a batch to the laboratory for testing. Results will be confidential, following the same procedures as other study data. Viral load results are identifiable only by a study number. Laboratory staff will make results available on a password-enabled, HIPAA-compliant website and will communicate by direct e-mail to the study coordinator.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

To assess intervention effects on the primary outcome (viral suppression), we will compare the proportion of participants achieving HIV viral suppression at 12 month follow-up across study conditions by estimating a risk ratio and obtaining confidence intervals using robust error variances with a modified Poisson model and log link [83]. We will similarly obtain risk ratio estimates to assess intervention effects on the secondary outcomes (i.e., measures of ART adherence and care engagement) using the modified Poisson approach appropriate distribution and link function based on the outcome examined.

To examine the underlying mechanisms of the intervention effects on primary and secondary outcomes at 12 months, we will evaluate the effects of ImpACT+, compared to PST, on hypothesized mediators (e.g., levels of traumatic stress and avoidant coping). Our analytic approach will incorporate the appropriate distribution and link function depending on the distribution of these mediators. We will then examine the effect of both mediators on viral load. If the product of these two paths is greater than zero, this will serve as evidence of mediation [84]. The same approach will be utilized to evaluate the degree to which changes in traumatic stress and avoidant coping mediate intervention effects on secondary outcomes (ART adherence and care engagement).

Finally, qualitative data will be analyzed using a thematic analysis approach [85]. Memos will be written for each transcript to synthesize the emerging themes across the CFIR domains. Themes will be identified via consensus discussion after independent review of transcripts and textually coded using NVivo and/or ATLAS.ti software by multiple coders. Data display matrices will be used to examine commonalities and differences across informants [86]. A diagrammatic visual, overlaid on the CFIR framework [53] will highlight the potential barriers and facilitators to full-scale implementation.

Interim analyses {21b}

No additional analyses are planned.

Methods for additional analyses (e.g., subgroup analyses) {20b}

No additional analyses are planned.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

All analyses will be based on the intention-to-treat (ITT) principle such that participants will be analyzed in the arm to which they were randomized, regardless of intervention exposure. We will perform sensitivity analyses to address loss to follow-up (LTFU). We will summarize baseline characteristics by LTFU status separately by study conditions to identify possible predictors of LTFU and whether they differ by condition. Covariates that are predictive of LTFU will be included in regression models to assess any changes to conclusions based on an assumption of missing-at-random dependent on covariates. Pattern mixture approaches will be used to explore possible missing-not-at-random mechanisms [87].

Plans to give access to the full protocol, participant-level data, and statistical code {31c}

The primary investigators, project coordinator at CUIMC, project director at UCT, and statisticians at CUIMC will be given full access to trial data.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

A formal coordinating center is not needed for this single-site study.

Daily support for the trial is provided by:

Principal Investigators: provides scientific oversite and responsibility.

Clinical supervisor: supervises nonspecialists interventionists.

Clinical psychologist: emotionally supports field staff.

Project director: oversees daily trial activity and supervises control.

Senior research assistant: supervises research assistants and field data collection.

Project coordinator: organizes data collection, ensures data quality, trial registration, and annual reports.

Research assistants: take informed consent, administer assessments, and schedule appointments.

The study team meets weekly.

Composition of the data monitoring committee, its role, and reporting structure {21a}

Throughout the course of the trial, all protocol modifications will be reported to the University of Cape Town's Human Resources and Ethics Committee (HREC), Columbia University IRB, and the Data Safety and Monitoring Board (DSMB). The DSMB is comprised of independent, experienced, and highly qualified members who are free of any professional or financial conflict of interest with the study project and investigators. The DSMB reviewed the study protocol and data monitoring procedures prior to trial recruitment and approved the data monitoring plan for the remainder of the study. The DSMB will meet on an annual basis to review study progress, enrollment, randomization, and retention data (including reasons for dropout and retention by study condition); data integrity; and patient safety data, including reported adverse events and protocol deviations.

Adverse event reporting and harms {22}

All adverse events will be recorded. We will follow the reporting guidelines as set out by UCT HREC, CUIMC IRB, NIMH, and our DSMB.

Frequency and plans for auditing trial conduct {23}

CUIMC IRB and UCT HREC will meet annually to review trial progress and conduct throughout the trial period. In addition, all adverse events and protocol deviations will be reported according to IRB And HREC guidelines.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

We will seek approval from CUIMC and UCT HREC prior to implementing any protocol amendments, and to NIMH when required.

Dissemination plans {31a}

In addition to academic manuscripts and presentations, we will collaborate with the City of Cape Town and HIV and policy makers to disseminate lessons learned in our research. If effective, we will work towards full-scale implementation of ImpACT + in the region and be available to adapt the intervention for other global settings.

Discussion

There is a substantial treatment gap for women living with HIV (WLH) who have experienced sexual trauma. The scientific evidence on the coexisting burdens of HIV infection and sexual trauma among women in South Africa, and the well-documented drop-off from linkage to HIV care to viral suppression across the HIV care cascade [32, 43, 88] demonstrate the need for evidence-based, scalable interventions that address HIV care engagement in this context. Specifically, there is an urgent need to address the psychological sequelae of HIV, sexual trauma, and mental health, which can significantly impact HIV treatment adherence.

This trial is unique for several reasons. Firstly, despite robust evidence highlighting the adverse impact of sexual trauma on HIV treatment adherence and care engagement, we have not identified any full-scale randomized controlled trials demonstrating the effectiveness of trauma-focused psychological and behavioral interventions to improve biological outcomes in South Africa, or other low- and middle-income countries (LMIC) [89, 90]. This study aims to determine whether a mental health intervention to reduce avoidant coping and traumatic stress in comparison to a high-quality control intervention condition can improve clinical HIV outcomes, including viral suppression (primary outcome) and ART adherence and HIV care engagement (secondary outcomes). This type of holistic approach is not only key to improve individual outcomes, but also to motivating health departments to increase resources dedicated to integrating mental health services into chronic disease settings. As the revised UNAIDS care cascade goals move towards even higher rates of ART initiation, care retention, and viral load suppression, health systems will need to develop ways to address important behavioral and psychosocial determinants of treatment failure.

The second important innovation is that this study will explore whether increased likelihood of viral suppression is mediated by improvements in mental health. Demonstrating that improvement in psychological symptoms mediates the effectiveness of a behavioral intervention to improve adherence will strengthen the case for mental health services to be integrated in primary health care settings, particularly in the context of large mental health treatment gaps in LMICs [91]. In the absence of adequate numbers of trained psychologists and other mental health specialists, the use of culturally appropriate, manualized, and task-shared approaches becomes even more compelling. Given the sensitivity required to broach topics of sexual trauma and the potential for vicarious trauma, ImpACT + is intended for delivery by trained and supervised interventionists. Nurses and social workers are frequently employed in primary healthcare settings and are therefore the most likely candidates for interventionists. These cadres represent a key resource in the South African primary health care system, as well as in many other LMIC.

The third innovation is that we will report on critical implementation outcomes within the context of primary health care. Qualitative data from interventionists, facility managers, local stakeholders, and WLH with lived experience of trauma will inform potential and plans for implementation. Therefore, this trial will systematically evaluate feasibility and acceptability in addition to primary effectiveness. The implementation outcomes of this study will be presented to key stakeholders for consideration for adoption in health system training and capacitation programs. Our goal is to contribute to future policy and practice in the wider health care system.

Despite the strengths of this trial, implementation challenges may arise. We anticipate some difficulties in recruiting participants experiencing traumatic stress in busy clinic settings. To address this, we will work collaboratively with staff involved in HIV care at our study sites to established routine referral systems. Confidentiality and sensitivity will be paramount to the success of this trial. Participant retention is a second potential challenge. We anticipate that almost all of our participants will live in peri-urban areas and may therefore struggle to attend intervention sessions or scheduled assessments for reasons associated with informal employment, illness, and interprovincial migration. To address this, our study team will endeavor to establish collaborative relationships with participants. Moreover, we aim to enhance retention through maintenance of detailed contact information and using clinic records to align intervention-related visits with scheduled clinic appointments. Lastly, we aim to pre-empt potential vicarious trauma, compassion fatigue, or emotional distress among field staff by holding regular debriefing sessions with a clinical psychologist.

It must be acknowledged that even if this intervention is proven effective and is implemented into care settings in South Africa, it cannot address the systemic roots of sexual trauma and HIV infection. Extreme inequality linked to historic disparities impacts many upstream issues such as education, housing, and poverty. These inequalities must be addressed in order to truly improve national health outcomes [92, 93]. However, women today are living in settings that put them at increased risk for sexual violence and HIV, and they need treatment at a faster pace than is possible on a policy level. As such, we feel obligated to work towards improving current mental health needs and clinical HIV outcomes.

In summary, this trial is expected to yield important new information on psychologically informed intervention models that benefit the mental health and clinical outcomes of WLH with histories of sexual trauma. The proposed ImpACT + intervention, with its focus on building coping skills to address traumatic stress and engagement in HIV care and treatment, could have widespread impact on the health and wellbeing of individuals and communities in sub-Saharan Africa.

Trial status

Enrollment of participants commenced in February 2021 and is expected to run through to November 2023.

Abbreviations

AIDS: Acquired immune deficiency syndrome; ANC: Antenatal care; ART: Antiretroviral therapy; ARV: Antiretroviral; CFIR: Consolidated Framework for Implementation Research; CIDI: Composite International Diagnostic Interview; COVID-19: Coronavirus disease 2019; CUIMC: Columbia University and Irving Medical Center; DBS: Dried blood spot; DSMB: Data Safety and Monitoring Board; ENACT: Enhancing Assessment of Common Therapeutic factors; HIV: Human immunodeficiency virus; HREC: Human Research Ethics Committees; ImpACT: Improving AIDS Care after Trauma; ImpACT +: Improving AIDS Care after Trauma plus; IRB: Institutional Review Board; mhGAP: WHO Mental Health Gap Action Programme; NIMH: National Institutes for Mental Health; NHLS: National Health Laboratory Service; PCL-5: PTSD Checklist-Civilian version of the DSM-5; PMTCT: Prevention of mother-to-child transmission; PST: Problem-solving therapy; PTSD: Post-traumatic stress disorder; RA: Research Assistant; REDCap: Research Electronic Data Capture; UCT: University of Cape Town; WHO: World Health Organization; WLH: Women living with HIV.

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Authors' contributions {31b}

KS, MW, MM, PW, and JJ conceived and designed the study. KS, SR, AK, LA, EN, SM, CO, and JJ are responsible for trial implementation. MM and PW contributed to the statistical analysis plan. SR, SM, AM, and EN are involved in ongoing supervision of field staff. AK and SM are responsible for data management. CO is responsible for

ensuring appropriate biomarker protocols. The manuscript was drafted by KS, SR, AK, and JJ. All authors reviewed and approved the final manuscript.

Authors' information
Not applicable.

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Availability of data and materials {29}
An anonymized (permanently de-identified) dataset will be prepared for public sharing.

Declarations

Ethics approval and consent to participate {24}
The trial was approved by the Human Research Ethics Committee (HREC) of the University of Cape Town (HREC 137/2019), the Institutional Review Board (IRB) of the Columbia University (IRB Study Number: AAAS3667), and the City of Cape Town research office (8274/24822). The trial is additionally registered with ClinicalTrials.gov (REF NCT04793217). Our proposed DSMB was approved by NIMH. All participants will give written informed consent prior to enrollment, which includes information on foreseeable risks, voluntary participation, and confidentiality. Across both conditions, the allocated intervention will be discontinued for participants who withdraw consent. Trial data will be stored in a safe, HIPAA-compliant fashion. All identifiable data will remain at UCT. Adverse events and protocol deviations will be reported according to Columbia University, UCT, and NIMH guidelines.

Consent for publication {32}
No individual participant data is shared in this manuscript. Informed consent materials are available from the corresponding author on request.

Competing interests {28}
The authors declare that they have no competing interests.

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