An evaluation of a combined psychological and parenting intervention for HIV-positive women depressed in the perinatal period, to enhance child development and reduce maternal depression: Study Protocol for the Insika Yomama Cluster Randomised Controlled Trial

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Study protocol

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Abstract

Background: The combination of poverty, HIV and depression in the perinatal period represents a major public health challenge in many Southern African countries. In some areas, up to a third of HIV-positive women experience perinatal depression. Perinatal depression is associated with negative effects on parenting and key domains of child development including cognitive, behavioural and growth, especially in socio-economically disadvantaged communities. Several studies have documented the benefits of psychological interventions for perinatal depression in low- and middle-income countries, but none have evaluated an integrated psychological and parenting intervention for HIV-positive women using task-sharing. This randomised controlled trial aims to evaluate the effect of a home-based intervention, combining a psychological treatment for depression and a parenting programme for perinatally depressed HIV-positive women.

Methods: This study is a cluster-randomised controlled trial, consisting of 48-60 geospatial clusters. A total of 528 pregnant HIV-positive women aged ≥16 years who meet the criteria for depression on the Edinburgh Postnatal Depression Scale (EPDS, score ≥9)) are recruited from antenatal clinics in rural KwaZulu-Natal, South Africa. The geospatial clusters are randomised on an allocation ratio of 1:1 to either the intervention or Enhanced Standard of Care. The intervention group receives 10 home-based counselling sessions by a lay-counsellor (4 antenatal and 6 postnatal sessions) and a booster session at 16 months. The intervention combines Behavioural Activation for depression with a parenting programme, adapted from the UNICEF/WHO Care for Child Development programme. The ESoC group receives two antenatal and two postnatal support and advice telephone calls. The co-primary outcomes are child cognitive development at 24 months assessed on the cognitive sub-scale of the Bayley Scales of Infant Development-Third Edition and maternal depression at 12 months measured by the EPDS.

Analysis: The primary analysis will be a modified Intention-to-Treat analysis. The primary outcomes will be analysed using mixed-effects linear regression.

Discussion: If this treatment is successful, policymakers could use this model of mental health-care delivered by lay-counsellors within HIV treatment programmes to provide more comprehensive services for families affected by HIV.

Introduction

Background and rationale

Perinatal depression in the context of HIV

Perinatal depression is common amongst HIV-positive women globally and a major public health challenge (1,2). A 2015 systematic review of African studies of perinatal depression among HIV-positive women reported rates between 23.4 and 43.5% in the antenatal and 22.5 and 31% in the postnatal periods (3). More recently, a global meta-analysis comparing rates of depression amongst HIV-positive and HIV-negative women in both the antenatal and postnatal periods, found that HIV-positive women had significantly higher odds of depressive symptoms (2); 36% of HIV-positive women experienced antenatal depression compared to 26% of HIV-negative women, whilst 21% of HIV-positive women

experienced postnatal depression compared to 16% of HIV-negative women. Given that up to a third of all women attending antenatal services in Southern Africa are HIV-positive, these differences are clinically important.

Perinatal depression may contribute both directly and indirectly to a wide range of maternal and child health risks (4,5). Studies show that perinatal depression amongst HIV-positive women is associated with increased suicidal ideation, with rates as high as 40% in some studies (3,6). Amongst HIV-positive women, perinatal depression has been associated with lower clinic attendance and poor adherence to antiretroviral treatment (ART) (7,8). A recent systematic review and meta-analysis estimated that, for people living in sub-Saharan Africa, depression approximately doubled the odds of non-adherence (OR 2.54 95% CI[1.7-3.9]) (9). Psychological therapies, especially those using cognitive behavioural approaches have been shown to improve both depression and adherence to ART in the United States (10,11), although more evidence is needed in African countries (12).

The potential impact of perinatal depression on parenting and child development is of major concern. Studies have consistently shown that perinatal depression is associated with negative effects on children's cognitive, language, behavioural and emotional development as well as growth, including risks of stunting (5,13). The persistence of depression appears to be more likely to lead to negative effects on the child (14), highlighting the need for treatment. The quality of caregiving is a key mediator of the negative effects of parental depression on child development. An important reason for this is the effects of rumination, a core characteristic of cognition in depression, on responsiveness to a young child (15). Rumination consists of recurrent negative thoughts that are intrusive and difficult to dismiss, absorb attention, and are associated with reduced problem-solving, speed of response to external stimuli, and disturbances in attention. This is important because focused maternal attention to the infant and contingent responsiveness to infant cues and behaviour is essential to early cognitive and emotional childhood development. Furthermore, depression disrupts the ability to scaffold and support an infant's exploratory behaviour and emotional states, especially infant distress and this can disrupt emotional and behavioural development (5,16).

Finally, maternal depression may affect child growth, gastrointestinal and respiratory infections, and general health through shorter duration of exclusive breastfeeding (EBF) and lower rates of health and hygiene promoting behaviours (17,18). EBF is of particular importance in HIV-positive populations as studies have found that optimal early-life feeding practices ameliorate the effects of being born to an HIV-positive mother (19). Furthermore, EBF has been shown to reduce episodes of diarrhoea in infants born to HIV-positive mothers (20).

Consequently, maternal depression in the context of HIV is associated with several maternal and child health risks. The combination of HIV and depression in the perinatal period is especially important because the negative impact of depression on children is amplified by socio-economic adversity and lack of support (4,5), which are associated with HIV (21). Thus, the clinical implications of perinatal depression amongst HIV-positive women are likely extensive in HIV-endemic regions.

These effects of depression in the context of HIV on child development forms part of a growing body of literature underscoring the importance of early life exposures for long-term health and development (22–24). As a result,

international agencies, including the World Health Organization, are developing evidence-based policies and interventions aiming to improve early child development, encapsulated in the Nurturing Care Framework (25). The Nurturing Care Framework has two guiding implementation features; firstly, to ensure the child receives multiple intervention inputs required to support healthy development, including adequate nutrition and health, early learning opportunities, safety and security, and responsive care. Secondly, the framework attends to the enabling environment of care, including the mental health of caregivers and their support (24). The present study is situated within this new scientific and policy focus.

Interventions for perinatal depression in LMIC

In recent years, task-shifting of mental health care services to trained lay health care workers has been strongly advocated for in an effort to increase treatment coverage for mental health disorders in LMICs (26,27). A range of intervention studies in LMICs has used task-shifting to Community Health Care Workers (CHW) or lay counsellors to support women with perinatal depression. Internationally, such studies report that psychological treatment by peer or lay-counsellors is feasible and generally has positive effects compared to routine standard of care (27). A 2014 review of nine South African psycho-social interventions delivered by CHW or lay counsellors (several of which targeted pregnant women) reported that the majority of studies provided evidence for the effectiveness of task-shifted interventions which include psychological content (28); although one recent RCT in South Africa for perinatal depression, not specifically targeting HIV positive women, did not report significant effects on maternal mood (29). A 2014 review of nine South African psycho-social interventions delivered by CHW or lay counsellors (several of which targeted pregnant women) reported that the majority of studies provided evidence for the effectiveness of task-shifted interventions which include psychological content (28); although one recent randomised controlled trial (RCT) in South Africa for perinatal depression, not specifically targeting HIV positive women, did not report significant effects on maternal mood (29).

There has been one example of a randomised controlled treatment trial (Masihambisane Trial) which tested the effectiveness of a clinic-based peer mentor support intervention addressing health, including mental health, and stigma faced by perinatal HIV-positive women (not necessarily experiencing depression) in rural KwaZulu-Natal, South Africa. This study showed improvements in maternal mental health but also found that centre-based activities presented significant challenges to retention (30). To our knowledge, only one published RCT in Africa has directly tested the effects of an intervention specifically for HIV-positive pregnant women on perinatal depressive symptoms (and prenatal disclosure rates of HIV). The trial compared a six-week psychosocial support group facilitated by nursing staff with the standard of care (SoC) in Dar es Salam, Tanzania. The trial found that marginal non-significant improvements in the intervention arm compared to the SoC arm and there was a high attrition rate (31).

Interventions for Parenting in LMIC

Parenting interventions that support caregivers and provide guidance on practices and skills that help caregivers to support their young child's development have been beneficial in improving early childhood development (ECD) outcomes and reducing risks of developmental delay. The most recent global meta-analysis of parenting interventions, comprising 90 RCTs, found small (β=0.19, socioemotional) to medium (β=0.31-0.34, cognitive and language) effects on ECD. It is noteworthy that interventions that included strategies to support responsive caregiving had stronger

effects on children's development (34). However, there are evidence gaps. Firstly, only a small number of parenting interventions implemented in LMIC evaluated children's early socioemotional development. Secondly, fewer interventions have assessed caregiver mental health. In a review that examined care outcomes for parenting interventions in LMIC, nine of the 15 interventions assessed maternal depressive symptoms and the meta-analyses did not report any significant reduction in depressive symptoms (35). Parenting interventions that include components of promoting mental health, rather than focusing only on the needs of the child, are likely to be beneficial for children and their caregivers (36). However, more research is needed on how these interventions can be effectively combined and tailored to the needs of at-risk families.

To our knowledge, the present study is the first to test a home-based integrated intervention specifically targeting HIV-positive, depressed pregnant women, which combines treatment for depression with a parenting intervention delivered by lay counsellors.

The Insika Yomama intervention

In this trial, we test a novel integrated intervention to treat HIV-positive perinatally depressed women and enhance child development, using a combination and adaptation of two evidence-based interventions: (i) Behavioural Activation (BA) for depression and (ii) and the WHO/UNICEF Care for Child Development (CCD) package.

Behavioural Activation (BA) is being trialled because it has been shown to be as effective as cognitive-behavioural (CBT) therapy in high-income settings (37–39). BA is easier to deliver than CBT since it does not require extensive training or complex counselling skills. Studies suggest that BA delivered by non-specialists appear similar to those with formal therapy qualifications (40). Importantly, studies report that BA is effective in treating depression in LMICs when delivered by a range of non-specialist health care workers (41). As a result, BA lends itself to task-shifting (42,43). In South Africa, the National Mental Health Policy Framework (2013-2020), acknowledges task-shifting as a critical approach to improving mental health nationally (Chowdhary et al., 2014; Dennis, 2005). Furthermore, BA is considered to be suitable for cross-cultural delivery because it targets behavioural change rather than beliefs and attitudes. To date, BA has not been tested among HIV-positive women in the perinatal period.

The WHO/UNICEF CCD package was developed to promote early childhood development, especially cognitive development, through responsive caregiving and early stimulation (44,45). Evaluations of CCD implementation have shown that the CCD strategy can be feasibly delivered by community health workers and there are acceptance and demand from families (23,46,47). Meta-analyses have shown significant benefits from programmes that support parents to enhance early stimulation as a means to improve early child cognitive development, including language development (48). The CCD package has also been adapted and evaluated in several LMICs with positive results although it has not yet been tested in the context of perinatal depression or HIV, nor does it include content for pregnant women (49,50). Thus, the present trial is the first to adapt the CCD package for perinatally depressed, HIV-positive women. Furthermore, in this study CCD has been augmented with specific content to begin during pregnancy including visual aids for lay counsellors, including, information sheets and handouts.

Objectives

The primary objective is to test whether a home-based intervention, integrating behavioural activation for depression with a parenting programme adapted from CCD, for HIV-positive women with perinatal depression compared to Enhanced Standard of Care (ESoC) improves:

1. Maternal perinatal depression at 12 months postnatal
2. Child cognitive development at 24 months of age

Secondary objectives:

To identify if the combined intervention compared to the ESoC:

1. Improves maternal depression at end of pregnancy[1] and 24 months postnatal.
2. Improves maternal anxiety at the end of pregnancy and 24 months postnatal.
3. Increases maternal adherence to ART (measured as viral load (VL) and viral suppression post-initiation of treatment) over the trial period.
4. Increases rates of exclusive breastfeeding to six months postnatal.
5. Improves adherence to immunisation schedule over the 24-month postnatal period.
6. Reduces episodes of diarrhoea over the postnatal period[2].
7. Improves maternal contingent responsiveness to infant cues at 12 and 24 months postnatal.
8. Improve the quality of infants' cognitive and emotional stimulation within the home environment at 12 and 24 months.
9. Reduces child behavioural difficulties at 12 and 24 months postnatal.
10. Improves child language development at 24 months postnatal.
11. Improves child growth at 24 months postnatal.

Trial design

A cluster randomised controlled superiority trial with two parallel groups. The trial comprises 48-60 neighbourhood clusters, randomly allocated to the combined intervention or ESoC using a 1:1 allocation ratio with approximately 9-11 participants (mothers) per cluster, totalling 528 mother-infant pairs.

[1] 'End of pregnancy' refers to ~35 weeks of gestation in this paper.

[2] Episodes of diarrhoea are defined as maternal report of diarrhoea in the previous 14 days (86).

Methods: Participants, Interventions And Outcomes

Study setting

The trial is being conducted at the Africa Health Research Institute (AHRI) Somkhele Research Campus in rural Northern KwaZulu-Natal, South Africa, within AHRI's Population Intervention Platform demographic surveillance area. The study area covers 845km^2 and the community is predominantly rural but contains an urban township and informal peri-urban settlements (51,52). The resident population is approximately 100,000 people (~20,000 households) of which the majority are isiZulu-speaking. The area includes one district-level hospital and 17 primary health-care facilities. A 2019 study of a prospectively followed, population-based cohort from the study area estimated that HIV-prevalence amongst women aged 15-54 years of age in the study area increased from 25% to 41% between 2005 and 2017 (53). Despite high HIV prevalence, the incidence of HIV infection declined between 2012 and 2017 with men experiencing the biggest declines. Prevention of Mother-to-Child Transmission services were implemented in the sub-district in 2001 along with an HIV treatment programme in 2004 providing ART through public health facilities (54). ART treatment is delivered in a decentralised model at primary health care clinics. Consistent with WHO guidance, all pregnant women not already on ART are initiated on ART treatment for life, irrespective of CD4+ count.

Eligibility criteria

Participants provide written, informed consent both before screening and again if they fulfil all eligibility criteria before any trial activities, including randomisation, proceed. Minors (<18 years of age) provide guardian/parental consent as well as their assent to participate. The participant flow is outlined in Figure 1.

Inclusion Criteria:

- Pregnant women, ≤33 weeks of gestation at the time of enrolment;
- Participant willing and able to give informed consent for participation in the trial;
- Aged 16 years and above;
- Diagnosed HIV-positive;
- Participant meets the criteria for antenatal depression as defined by a score of ≥9 on the EPDS;
- Living, or planning to live, within the study area at the time of delivery and for at least 9 months after delivery (the intensive therapy period);
- Participant is conversant in isiZulu or English.

Exclusion criteria:

The participant may not enter the trial if any of the following apply:

- Any significant disease, disorder or disability which, in the opinion of the Principal Investigator, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial. This includes hospitalisation for at least three days for severe psychiatric illness (specifically bipolar disorder, schizophrenia and any other psychoses), or a life-threatening or other serious physical illness (excluding HIV and tuberculosis).
- Current suicidal ideation/thoughts with specific plans and means identified.
- Substance or alcohol use disorder.

- Currently receiving psychological treatment for mental health problems.
- Participant planning to move away from the study area before 9 months postnatal.
- Participant not planning to cohabit with the infant.

Who will take informed consent?

Screening consent is obtained before screening procedures. If potential participants are not able to be screened at the first meeting, initial consent to contact is obtained. The full informed consent is explained at the enrolment visit at the clinic and confirmed at the baseline assessment. For participants <18 years, full guardian consent is obtained in addition to adolescent assent. Informed consent, confidentiality and data handling comply with Good Clinical Practice (GCP) regulations. The consent processes are conducted by trained recruiters who are supervised and monitored by a recruitment supervisor and the trial coordinator.

Additional consent provisions for collection and use of participant data and biological specimens

No biological specimens will be collected on the trial.

Interventions

Explanation for the choice of comparators

Eligible participants are randomised in clusters to either the intervention or the Enhanced Standard of Care (ESoC).

Intervention description

Therapy intervention

The intervention, integrating a psychological treatment for maternal depression and a parenting intervention to enhance early child development, is based on two evidence-based interventions delivered at the home:

- Behavioural Activation (BA) is a structured therapeutic approach that emphasises environmental causes of depression (37). It is based on the evidence that increased activity (i.e., activation), and the resulting positive consequences, leads to a reduction of depressive symptoms. BA helps people understand the interaction between individual and environmental sources of their depression, and targets behaviours that might maintain or worsen the depression. Thus, BA aims to increase behaviours that are personally rewarding to improve mood and quality of life and decreases behaviours that maintain or worsen depression, such as passivity, avoidance and rumination. BA introduces small behavioural changes, building up the level of activity gradually towards long-term goals, making it feasible for perinatal women with little time to spare.
- WHO/UNICEF Care for Child Development (CCD) package is a parenting intervention that aims to enhance early child development, especially cognitive development, through improving parenting skills. The Insika Yomama

parenting intervention tested in this study is adapted from the evidence-based CCD programme and aims to promote responsive caregiving and early stimulation. In this trial, we include specific pregnancy modules and visual aids to assist the delivery of the parenting content. The parenting component is designed to be integrated complementary to the BA component by ensuring that parenting activities enhance access to positive reinforcement through rewarding caregiving experiences, especially around responsiveness, thus potentially improving both mood and quality of parenting concurrently.

The participant is allocated a lay counsellor who provides all 10 sessions and the booster session.

Session structure:

The combined intervention is delivered by lay-counsellors in the participants' homes across 10-sessions, starting in pregnancy (between 26 and 33 weeks of gestation) through to nine months postnatal, along with an additional booster session at 16 months postnatal. The initial session lasts up to 2 hours and focuses on orientation to BA and assessment of behaviours around depression using a BA diagram to conceptualise problem behaviours. The session focuses on BA only. The remaining sessions last approximately 1.5 hours each, compromising combined mother-focused BA modules and infant-focused parenting components. The therapy arm also receives a 'keep in contact call' at 36-38 weeks of gestation between therapy session four and delivery.

Materials:

Electronic tablets assist the lay-counsellors in delivering the combined intervention and keeping track of participants' developments and session content. The tablets contain visual aids and a treatment manual. The treatment manual has been developed to guide the lay-counsellors in providing standardised BA activities. This is accompanied by handouts containing exercises and health information relating to antenatal care, breastfeeding, management of infant crying and HIV treatment are provided for participants to accompany the sessions.

The BA comprises four major components:

- Assessment – Session 1 is an orientation to BA (explanation of core concepts); psychoeducation around self-care, routines, and nourishing activities (i.e., activities one enjoys doing); and setting of treatment goals.
- Activating activities - Sessions 2-6 cover the core BA content. The treatment manual includes modules on self-care (sleep, eating, exercise), routines, nourishing activities (e.g., bath with privacy), and problem-solving. Each module focuses on behavioural change that increases positive reinforcement and reduces avoidance behaviour. By the end of each session, homework is discussed (e.g., activation goals, mood monitoring and avoidance behaviours in the period leading up to the next session).
- Planning for the future – Session 7 involves identifying strategies that have been helpful and setting goals for the future.
- Review and consolidation sessions – Sessions 8-10 review progress, reinforce maintenance of changes and set further goals.
- The core principles of BA are reviewed during the booster session (16 months postnatal) and any new difficulties that arise are dealt with using skills developed in the earlier sessions.

The Parenting Intervention components focus on:

- Increasing attention to infant facial and verbal cues.
- Increasing “contingent responding”, by guiding the participant to attend to her baby’s signals and efforts at communication, and to respond to her baby’s communication in a way that is synchronous with the baby’s signals and focus.
- Increasing opportunities for early stimulation.

The behaviour change techniques employed include:

- Providing opportunities for participants to try age-appropriate play interactions with their infants and receive coaching and feedback on ways to enhance the interaction.
- Using visual aids such as home-made/low-cost toys, illustrated case studies and prompts.
- Problem-solving with participants about ways to overcome barriers to providing early stimulation and nurturing care.

The session content is distributed as follows (see Figure 2):

Antenatal (sessions 1-4) - Core parenting principles and activities are introduced through audio-visual material to prepare the participant for the baby. Activities include attending to and recognising infant facial and vocal expressions, contingent responsiveness, and communication through singing.

Postnatal (sessions 5-10) – Extends the core principles and activities introduced antenatally and supports the participants in applying these during interactions with their baby. Additionally, new modules are introduced, including guidance around breastfeeding (including an emphasis on EBF); different types of play (developmentally appropriate activities, e.g., simple face-to-face games and “peek-a-boo”) with emphasis on contingent responding; and supporting the participants in consulting their Road to Health Book to recognise signs of serious illness in the infant.

These sessions are delivered from 2 weeks postnatal until 9 months postnatal.

In the booster session, age-appropriate opportunities for a range of play activities are provided, because of the rapid advances in development in the second year. The core principles of the parenting intervention are also reviewed and any new difficulties that arise are dealt with using skills developed in the earlier sessions.

Personnel; recruitment, training, and supervision: The intervention is delivered by experienced lay-counsellors who have at least 2 years of counselling experience, including working with women and children and HIV counselling. Intervention counsellors receive 2 weeks of intensive training based on the treatment manual, followed by a period of supervised practice. No counselling sessions are attempted by the counsellors until they have been assessed as competent by the supervising psychologist (using standardised checklists and through observation of role-playing). The lay-counsellors' first sessions are reviewed, and any competency issues addressed through additional training. The counsellors receive weekly supervision from the trial psychologist as well as added supervision from therapy supervisors who are more senior therapists/counsellors. Ongoing training is also conducted through workshops.

Fidelity: The fidelity and competency of the lay-counsellors are monitored through several measures:

- The lay-counsellors complete a Fidelity Checklist for every module.
- Sessions are audio-recorded (if participants consent) and a sample of audio recordings is scored by the supervising psychologist and feedback is provided as needed.
- The trial psychologist conducts periodic in-person therapy-observation with all therapists to identify any additional training needs.
- A sample of audio recordings is scored by an independent assessor to provide a formal assessment of fidelity to the intervention.
- Weekly supervision meetings are conducted by an experienced psychologist who records fidelity and competence. Retraining is conducted as needed.

Enhanced Standard of Care (ESoC):

The ESoC arm receives four support and advice phone calls in addition to the standard of care provided to them through the Department of Health (DoH) services. Through supportive listening, the ESoC caller assesses the participant's current health and based on responses, provides advice around managing their health and relationships. Three scripts have been developed to support the caller in dealing with common problems reported by participants. These include partner, family, and health problems. The caller also guides participants to use the services and support provided by the standard of care services. Training and monthly supervision support the ESoC caller to be empathetic and responsive to the participants. The caller also identifies risk situations that have arisen and reports and refers these in line with the trial risk management protocol for further action. ESoC participants receive all four support calls from the same support caller.

Session structure:

The support calls last 15 minutes. Participants receive two antenatal calls (2 weeks post-enrolment and 36 weeks of gestation) and two postnatally (2-weeks and 4-months postnatal). Each call follows the same structure:

1. **Connect and check-in** - with the participant to see how they are doing
2. **Suggestions and advice -** Based on how the participant is doing, the ESoC caller uses scripts to s offer suggestions and advice on actions the participant can take to manage health or social challenges they disclose.

3. **Health information –** ESoC caller offers health information messages linked to the participants' stage of pregnancy or parenting and offers advice on the availability of make referrals to services where needed.

Brief health information is provided to the participant during each call:

1. Early Pregnancy Call – Attending antenatal visits, managing HIV treatment
2. Late Pregnancy Call - Managing HIV treatment, planning for delivery, healthy pregnancies
3. Early Postnatal Call – Feeding infant; managing infant's sleep and routines;
4. Late Postnatal Call - Feeding infant baby; managing infant's sleep and routines; managing HIV treatment; parenting

Materials:

Electronic tablets assist the ESoC caller with scripts to deliver the ESoC calls and to keep a record of session content.

A parenting leaflet developed by UNICEF South Africa (with the Department of Education) is given to all participants in the study at the clinic at enrolment.

Personnel; recruitment, training, and supervision: The ESoC is delivered by an experienced ESoC caller who has at least 2 years of counselling experience, including working with women and children and providing HIV counselling. The ESoC caller attends a 2-day training workshop followed by a mock telephone call competency assessment. The ESoC caller receives fortnightly supervision and debriefing with the trained counselling supervisor, to support and facilitate referrals in risk cases and in managing the logistical aspects of the ESoC.

Fidelity: The fidelity and competency of the ESoC callers are monitored through several measures including supervision, debriefing, and recordings and rating of ESoC calls (if participants consent).

Criteria for discontinuing or modifying allocated interventions

Criteria for discontinuation of allocated interventions include situations where participants have requested discontinuation or have or have developed another major physical illness or injury which makes it too challenging for the participant to continueIn specific situations, such as following bereavement or a major life event, the Principal Investigators can agree to a limited number of additional therapy sessions or ESoC calls.

Strategies to improve adherence to interventions

Several strategies are implemented to improve adherence, including clear communication to the participants about intervention timing and structure (including provision of an intervention schedule and homework sheets). Text reminders and/or calls to participants are made when therapy/ESoC sessions are missed. Data is routinely collected

during each intervention session using checklists to monitor adherence to intervention content which are reviewed frequently by the trial coordinator.

Relevant concomitant care permitted or prohibited during the trial

Concomitant psychopharmacological treatment is not commonly prescribed in the population under study, however, where it is deemed necessary by a health care provider, this will be permitted, and carefully documented and monitored. Additional care in the form of psychological therapy or treatment delivered by a professional therapist or counsellor is permitted in circumstances to manage risks such as significant suicidality or significant social harm, such as domestic violence (according to the Trial Risk Management Protocol). In such cases, we make appropriate referrals to health or social services following well-established referral pathways and risk management protocols. Careful records will be kept of all referrals. Provision and participation in supplementary child stimulation activities, and/or attendance at childcare or educational centres or nursery school will be permitted across both allocations.

Provisions for post-trial care

A trial clinical psychologist is employed on a full-time basis to supervise intervention delivery and to provide ancillary psychological care to participants in emergencies who meet criteria, including those expressing suicidal thoughts and intent, those experiencing life-threatening trauma, violence and/or close family bereavement. In cases of infant death or stillbirth, additional bereavement sessions are offered. Following the final trial outcome assessment (24 months postpartum), all participants with high-risk profiles who require additional and ongoing care will be referred to the local Department of Health and Department of Social Security services as necessary. Additional, psychological sessions may also be offered to participants by the trial psychologist. If the therapy intervention is shown to be successful, in line with the pre-trial consultations, we will train local primary healthcare workers to provide the combined therapy locally.

Outcomes

Primary outcomes

1. Child cognitive development at 24 months of age, assessed using the Bayley Scales of Infant and Toddler Development III (BSID-III) cognitive subscale.
2. Maternal perinatal depression at 12 months postnatal assessed using the Edinburgh Postnatal Depression Scale (EPDS).

Secondary outcomes:

The 11 secondary outcomes and the associated measures are summarised in Table 1 and 2.

Table 1 – Secondary outcomes

	Secondary outcome	Measure	Timepoint
1	Maternal Depression	EPDS	End of pregnancy, 24m
2	Maternal Anxiety	Generalized Anxiety Disorder 7-item (GAD-7) scale	End of pregnancy, 24m
3	Maternal ART Adherence (Maternal HIV outcomes)	Viral load and CD4+ count. (measured as viral load (VL) and viral suppression post-initiation of treatment).	Baseline, end of pregnancy, 12wk, 12m, 24m
4	Exclusive Breastfeeding to six months postnatal	Self-report questionnaire	6m
5	Adherence to immunisation schedule over the 24-month postnatal period	Road to Health Book[1], Health questionnaires and clinical records	12wk, 12m, 24m
6	Episodes of Infant Diarrhoea over the 24-month postnatal period	Road to Health Book, Health questionnaires. Episodes of diarrhoea are defined as maternal report of child diarrhoea in the previous 14 days.	12wk, 6m, 12m, 24m
7	Maternal contingent responsiveness to infant cues	Mother and infant interaction assessed by video observation	12M, 24m
8	Cognitive and emotional stimulation within the home environment	Multiple Indicator Cluster Surveys (MICS)	12m, 24m
9	Infant behaviour	Parenting Stress Index Short Form (PSI/SF) (12m) parent-child dysfunctional interaction subscale and difficult child scale; Externalising sub-scale of Child Behaviour Checklist (CBCL) (24m);	12m, 24m
10	Child language development	Language subscale of the BSID-III	24m
11	Child growth	Road to Health Book, study Weight and length measurements (head circumference at birth only)	12wk, 12m, 24m

Table 2: Mediators, including measures and timepoints

	Mediators	Measure	
	Family, Relationship support and Conflict	Relationship conflict questions adapted from the Romantic Partner Conflict Scale (55). Support questions used from social support measure previously validated in South Africa (56).	Baseline, end of pregnancy, 12 weeks, 12 and 24 months
	Rumination	Brief Rumination Response Scale (57)	Baseline, end of pregnancy, 12 weeks, 12 and 24 months
	Maternal recognition of infant faces and sounds	Stimuli task	Baseline, 12 months

Participant timeline

Table 3 – Participant timeline

Assessment (A)		**A1**	**Allocation**	**A2**	**Birth**	**A3**	**A4**	**A5**	**A6**	**A7**
	Enrolment & Screening			**Post-Allocation Period**						
Timepoint	Screening & Enrolment	Baseline		End of pregnancy		6-12 days	12w	6m	12m	24m
Screening form and eligibility checklist	X									
Demographic & socioeconomic status		X								
Tracing and location information	X	X		X			X	X	X	X
GPS capture of home		X								
Allocation			x							
Primary Outcomes										
BSID-III cognitive										X
EPDS									X	
Secondary Outcomes										
EPDS	X			X			X			X
GAD-7		X		X					X	X
Maternal ART adherence		X		X			X		X	X
Breastfeeding								X		
Infant immunisations							X		X	X
Infant diarrhoea							X	X	X	X
Maternal contingent Responsiveness (video observation)									X	X
Cognitive & emotional stimulation (MICS)									X	X
PSI-SF									X	
Externalising subscale CBCL										X
BSID-III language										X
Child Growth							X		X	X

[1] The Road to Health booklet is produced by the Department of Health and given to new mothers at delivery or the child's first contact with the healthcare system. It is used to record a child's growth, immunisations, and health interventions.

Sample size

The first primary outcome is the cognitive subscale on the BSID-III at 24 months of age. To achieve a power of over 90% (two-sided t-test with a significance level of 0.05), and assuming an estimated difference of 6 points (SD 15), a

total sample size of 396 women (198 per arm) is required. This calculation takes into account geospatial clustering (28 clusters per arm with an intra-cluster correlation coefficient (ICC) of 0.05) and 'counsellor effect' in the intervention arm (4 lay counsellors with an ICC of 0.05). To take account of attrition of up to 25% a total sample size of 528 women are being recruited (264 per arm, 48-60 geospatial clusters, 9-11 women per cluster).

Using the EPDS assessment with a standard deviation of 5, with the same assumptions of clustering as above, a difference of 2 points between trial arms (not adjusting for baseline or repeated measurements) could be detected with 90% power and a 5% two-sided significance level. Analysis using repeated measures, taking into account within-participant correlation over time, would allow smaller differences to be detected with the same power

Recruitment

Recruitment and screening take place from 15 DoH Primary Health Care Clinics within a sub-district in KwaZulu-Natal offering maternity services.

Recruitment strategy:

The recruitment process is led by recruiters from the trial team with support from DoH antenatal nurses and clinic clerks.

Recruitment into the trial occurs through a four-stage process:

1. **Identification of potential participants -** Clinic records are reviewed by antenatal nurses and clinic clerks at antenatal clinics to identify HIV-positive, pregnant women (gestational age 18-33 weeks) over the age of 16 years. The nurses and clerks reassure the potential participants that their clinical care will not be compromised by participation.
2. **Referral to recruiter -** If the identified potential participants consent, they are referred to a trial recruiter who explains the trial procedures and screen for additional eligibility criteria.
3. **Depression screen -** Administration of the EPDS if the potential participant meets all other eligibility criteria.
4. **Consent processes -** Written consent and scheduling of baseline assessment at home for participants who fulfil all inclusion criteria, including an EPDS $\geq$9.

The baseline assessment is conducted at the home at which point the GPS location is verified. The participant is randomised (based on their geospatial cluster) following the baseline assessment.

Only participants who were diagnosed with HIV at least 2 weeks previously and have been initiated on ART are recruited.

Assignment of interventions: allocation

Sequence generation

The unit of randomisation is the cluster using the geospatial location of the participant's home. There are approximately 300 neighbourhoods in the region included in this trial; these are defined by geographical area as well as

population density so that they are equivalent in terms of sample size. The distinct neighbourhoods have been merged into 48-60 clusters to ensure comparable clusters in terms of key indicators, including population size. This clustering approach, and the important role of randomisation in this trial, has been presented to, and approved by, the Africa Health Initiative Research Institute (AHRI) Community Advisory Board.

Concealment mechanism

Allocation concealment is ensured by a two-step enrolment procedure whereby neither the recruiter nor the assessor establishing eligibility know to which arm the clusters have been allocated.

Implementation

The 48-60 geospatial clusters are randomly allocated to the integrated intervention or ESoC with an allocation ratio of 1:1 using a random sequence generated by a senior statistician at the National Perinatal Epidemiology Unit (NPEU), University of Oxford (using Stata/SE version 13 for windows). The randomisation schedule is sent to the AHRI using a secure web-link and implemented by the local data management team. None of these parties is involved in the implementation of trial activities (recruitment, assessments, therapy).

Assignment of interventions: Blinding

Who will be blinded

Participants are not informed at enrolment to which arm they are allocated to ensure the blindness of the recruiters and assessors. Rather, participants are informed that a trial counsellor will contact them. The intervention counsellors or the ESoC caller reveal the arm to which participant has been allocated when they first make contact.

The recruiters and assessors are blinded to the treatment allocation arm. Furthermore, the assessors are independent of the lay-counsellors performing the counselling sessions and blind to treatment allocation. The two primary endpoints are assessed by different independent assessors (at 12 and 24 months).

Procedure for unblinding if needed

In the event of inadvertent unblinding of an assessor, standard operating procedures are in place to reduce the impact and ensure that the assessor is never allocated to the given participant in future assessments.

Minimisation of contamination

Recruitment staff are located at clinics while intervention staff operate from a separate AHRI campus to minimise contact between recruitment and other staff. ESoC caller and lay-counsellors operate separately within different scopes of work in distinct offices, are line-managed and supervised by different individuals, use separate transport services and attend separate meetings to reduce the risk of unblinding. They are trained not to share information that could compromise the blinding or the integrity of the trial. Any instances of unblinding are recorded and assessed at the conclusion of the trial.

Data collection and management

Plans for assessment and collection of outcomes

Participants in both arms receive 6 assessments following the baseline assessment: 1) End of pregnancy; 2) 6-day postnatal screener, 3) 12-week postnatal, 4) 6-months; 5) 12-months, 6) 24-months. The points at which primary and secondary outcome data are collected are outlined in Table 1 and Table 2. Assessments take place at home, except for the mother-child interaction assessments (videotaped) and the primary end-point BSID-III assessment, which take place in participating clinics.

Table 4 outlines the standardised data collection tools used in the study. Below we outline tools specific to this study.

Table 4 – Data collection tools

Maternal Recognition of Infant Faces and Sounds

The participants' ability to accurately interpret and respond to infants' emotional cues are assessed using a subset of stimuli baby faces developed by rigorous validation methods in Brazil (77) and a sample of standardised baby vocalisations (78,79). Mothers are asked to indicate their interpretation of both the facial expressions ('happy', 'neutral' 'sad') and the vocalisations (positive 'laughs' neutral 'babbles' and 'negative 'cries) on an electronic tablet screen using a vertical visual analogue scale. The faces used for this sample include Caucasian, African and mixed-race infant faces and the images are presented in greyscale and matched in size and luminosity (80). The task takes around 15 minutes to complete.

Videoed Mother-Child Interaction

Video recordings of the maternal-child interaction are conducted to assess maternal sensitivity, responsivity and contingent responsiveness (responding to the baby's cues in a timely and appropriate manner) and the child's attention and emotional tone (mood). The video-recorded interaction consists of three scenarios (free-play, reading a book together and playing with a toy) each taking about 2.5 minutes to complete. A single-camera is used to obtain a view of the face and upper body of both mother and infant. Ratings are made by independent raters blind to arm allocation using a predefined and agreed rating scale, with regular interrater reliability established. This method of analysis is widely used within early child development research (81,82)

Economic Evaluation

Costing is conducted from a societal perspective, including financial costs to providers, opportunity costs of diverted provider resources (such as time of staff not paid on the trial, space) and financial (e.g., travel, time off work) and opportunity costs (e.g., time away from unpaid productive activities) to participants. We distinguish between research costs and operational costs to allow estimation of the cost of replication in non-research settings. The analysis involves three levels with increasing complexity. The first level involves a cost-utility analysis of the intervention with the primary and secondary outcome included in turn: the cost per improvement in cognitive development; the cost per improvement in maternal depression. The second level involves cost-effectiveness analysis using disability-adjusted life years (DALYs) averted. Improvements in child cognitive development and maternal depression are converted to

Instrument	Description	Outcome	Contextual Validity
The Bayley Scales of Infant Development-Third Edition (BSID-III) (58)	A comprehensive objective assessment administered face-to-face by a qualified independent assessor to assess child development. Only the cognition and language subscales are administered.	Child cognitive and language development	Validated in South Africa (59,60) with reported values similar to the reference population in the USA. (58)
Edinburgh Postnatal Depression Scale (EPDS) (61)	10-item questionnaire of perinatal depressive symptoms over the last 7 days assessed on a scale of 0 to 3.	Maternal depressive symptoms	Widely used and validated in Africa and South Africa, including use among antenatal populations (62). Has been validated in the study population against a structured clinical interview for depression (DSM-IV) showing good specificity (93%) and sensitivity (68%) for detecting clinical depression (63,64)
Child Behaviour Checklist (1.5-5-year-old) (65)	Externalising subscale (attention problems and aggressive behaviour syndrome scales) of the CBCL. 24 items, assessed on a scale of 0 to 2. Parental self-report.	Child externalising behaviour	Has been shown to be reliable in Africa (66), and to have high (>90%) sensitivity and specificity for identifying behavioural emotional problems compared to a clinical diagnosis by a psychiatrist in other LMICs (67) Widely used and well-validated in South Africa (68,69).
Parenting Stress Index Short Form (70,71)	Measure of parenting stress related to three domains: the parental role, the parent-child relationship and the degree to which the parent finds the child difficult. The scale comprises 36 statements, which are scored 1 (strongly disagree) to 5 (strongly agree) and can be summed to reflect the total score for each domain.	Maternal perception of child behaviour (Dysfunctional Interaction and Difficult Child subscales)	Has been shown to be reliable in South Africa (72)
Brief Rumination Response Scale	A 5-item questionnaire assessing depressive rumination assessed on a scale of 0 (never) to 4 (always).	Maternal rumination	A validated and reliable measure of depressive rumination (57,73)
The Generalized Anxiety Disorder Scale (GAD-7)	7-item questionnaire assessing symptoms of generalised anxiety disorder over the previous 2 weeks. Scores	Maternal anxiety	Has been widely used in the study setting and has shown good reliability (72,74).
Multiple Indicator Cluster Survey (MICS)	Specific questions from the Early Child Development module of the UNICEF 'Multiple Indicator Cluster Surveys' (MICS) under five are used to assess cognitive and emotional stimulation at home. Items are mostly scored on a dichotomous scale of 0 and 1 except for the question about how many children's books or picture books a mother has for her child (0=none, 1=a number of books and 2=ten or more books).	Cognitive and emotional stimulation.	Validated survey used in over 100 countries over the past two decades, also used in large scale surveys in 27 African countries. (75,76)

DALYs based on assumptions regarding the duration of the observed benefit. The cost per DALY is then calculated. The

third level compares costs to a vector of benefits, including indicative estimates of long-term gains (based on simple models), such as improved education outcomes and increased income in adulthood.

Nested Qualitative Study

A qualitative sub-study is conducted alongside the trial, using semi-structured interviews with both the lay-counsellors who delivered the intervention and with a sample of participants from each study arm. The sub-study aims to investigate the acceptability, challenges, enablers and potential benefits of the combined intervention compared to ESoC. The sub-study also investigates the acceptability and effectiveness of the therapist training and therapy supervision for this intervention. The data will be analysed using grounded theory principles and thematic content analysis (83,84).

Plans to promote participant retention and complete follow-up

We have developed a standard operating procedure to guide and promote retention and follow-up. This includes maintaining a regular schedule of assessments. Tracing and follow-up methods include text, telephone calls and in-person track and tracing. Participants are encouraged to notify the trial staff if they change their telephone number or address. Retention in the study community in previous clinical trials using these strategies have resulted in high retention rates. If participants discontinue the intervention (therapy/ESoC), they continue to receive assessments, including the primary outcome assessments (providing their consent).

Data management

Study data are collected and managed using a secure, web-based data collection platform on encrypted tablet computers which are securely uploaded to a central server hosted at AHRI. The platform is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trials for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages, and 4) procedures for data integration and interoperability with external sources. The tablets are encrypted, and all documents are stored safely under confidential conditions. On all trial-specific documents, other than the signed consent forms, the participant is referred to by the trial participant number, not by name.

Confidentiality

The trial staff ensure that the participants' anonymity is protected as far as possible. The trial complies with GCP and established practice which requires data to be anonymised as soon as it is practical to do so. Audio- and video-recordings are stored on a secure server with very limited access (to senior research team members and researchers working directly with a particular participant or directly involved in coding data). Participants are informed that audio-visual recordings will not be used outside of the team of researchers, and this is outlined in the consent form. Following the completion of the trial, the data will be downloaded and de-identified.

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

Not applicable, no biological samples collected.

Statistical methods

Statistical methods for primary and secondary outcomes

The primary inference will be based on the BSID-III cognitive score at 24 months and the EPDS at 12 months. For the primary outcomes and other continuous outcomes, the mean (SD) will be presented by the allocation group, and the mean difference (plus 95% confidence interval) will be estimated using mixed-effects linear regression. For binary outcomes, the number and percentage with the outcome will be presented by the allocation group, and the risk ratio (plus 95% confidence interval) will be estimated using a mixed-effect binomial or Poisson regression model.

The unit of randomisation is a geospatial cluster. As outcomes are collected at the individual level, hence the unit of analysis is the mother and the infant(s). There is also an additional level of clustering by counsellor delivering the intervention. The lack of independence among individuals in the same cluster and standard methods of analysis will underestimate the standard error of the treatment difference yielding p-values that are too small. To account for the correlation of outcomes within clusters, the geospatial cluster and counsellor identifier will be fitted as random effects, with counsellor nested within the geospatial cluster. The intra-class correlation coefficients for geospatial cluster and counsellor will be estimated.

For the EPDS and the GAD-7, a repeated measures model will be fitted, including the baseline, end of pregnancy, 12-month and 24-month score. For the maternal contingent responsiveness to infant cues and cognitive and emotional stimulation at home outcomes, a repeated measures model will be fitted including the 12- and 24-month scores. Mixed-effects models with maximum-likelihood estimation, allow participants with incomplete repeated measures data to be included in the model, contributing to the estimation of model parameters. The mean scores with 95% confidence intervals will be plotted over time by the allocation group.

In addition to adjusting for important baseline differences between randomised groups, any differences between participants followed-up to 24 months and those lost to follow-up will be adjusted for in the final models. Both unadjusted and adjusted models will be fitted, but the primary inference will be based on the adjusted model which provides unbiased estimates if the outcome data is missing at random (i.e., only dependent on observed characteristics).

Interim analyses

A Data Monitoring and Safety Board (DSMB), independent of the trial organisers and sponsors, has been established with the remit to review trial progress. The terms of reference for the DMSB were agreed at their first meeting and documented in the DSMB charter. The DSMB is chaired by a senior clinical trialist, and members include two statisticians and a clinician. Interim data analyses are supplied, in strict confidence, to the DSMB, as frequently as the chair requests and meetings are held at least annually. Based on interim data on the trial's outcomes, adverse event data, accumulating evidence from other trials and any other relevant evidence, the DSMB will inform the Trial Steering

Committee (TSC) if, in their view, there is proof beyond a reasonable doubt that the data indicate that any part of the protocol under investigation is either clearly indicated or contra-indicated, either for all trial participants or for a particular subgroup of trial participants. A difference of at least 3 standard errors in the interim analysis of a major endpoint may be needed to justify halting, or modifying, such a study prematurely.

Methods for additional analyses (e.g., subgroup analyses)

Pre-specified subgroup analysis of factors known to be associated with infant cognitive development - maternal education, socio-economic class, the severity of depression at trial entry and infant sex - will be performed for the infant cognitive development outcome at 24 months using the statistical test of interaction. Sub-group analysis based on maternal education, socio-economic class, and infant sex concerning maternal depression at 12 months will also be performed. The subgroups will be categorised as follows:

- Maternal education (primary completed or below; grade 10; matriculation or above).
- Socio-economic status (paid employment yes/no).
- Severity of depression at trial entry (continuous).
- Infant sex (male/female).

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data

Women with outcome data will be analysed in the groups to which they are randomly assigned, regardless of deviation from the protocol or treatment received (modified ITT population). Women whose infant died during the trial will also be included unless they withdrew consent to participate further in the trial.

The number and percentage of individuals missing data for outcome measurements that are based on summing items to give overall scores (e.g., EPDS, GAD-7, and subscales of the PSI/SF and CBCL) will be described. Missing items will be imputed if ≤20% are missing using the median score of completed scale items unless alternative guidance is provided in the scoring manual.

A multiple imputation analysis will be performed for the primary infant and maternal outcome if attrition exceeds 5%. The multiple imputation model will include baseline characteristics and outcome measures collected before the missing assessment, which are associated with missing status.

Plans to give access to the full protocol, participant level-data and statistical code

Data will be available beginning 9 months and ending 36 months following main article publication to researchers who provide a methodologically sound proposal that purposes to achieve aims in the approved proposal and /or for individual participant data meta-analysis. Data is documented and stored on the Africa Health Research Institute (AHRI) Data Repository (https://data.ahri.org) with a digital object identifier (doi) and can be accessed with permission

and in line with AHRI policies and procedures. Data requestors will need to sign a data access agreement before any data can be shared. In addition, Study Protocol and Statistical Analysis Plan documents will be available. Data sets associated with publications will be made available in line with Wellcome Trust data policies and journal requirements.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee

This trial is managed and coordinated by a trial group (management, operational and data management sub-groups) with regular advice and consultation from the investigators' group and the AHRI Clinical Research Department.

The trial group composes of management, operational, and data management sub-groups. The management sub-group consists of the principal investigators, trial coordinator(s), and trial psychologist. The group meets at least once a week virtually to discuss and manage major trial operational challenges (screening, recruitment, assessments, therapy/ESoC), logistics, AEs and SAEs, staffing, and trial reporting and monitoring. Trial reporting and monitoring include the management and reporting of AEs and SAEs and trial progress using summary statistics and graphs**.** The operational sub-group includes the four trial components (recruitment, assessment, therapy, ESoC) and is managed by the trial coordinator. The operational teams meet at least once a week, with individual meetings and contact points as needed. The four teams are operated separately to ensure blinding.

The investigators' group consist of the trial management group and experts (investigators) in maternal health and early child development. The investigators are consulted regularly dependent on their specific roles and small sub-group meetings are organised as needs be. The whole group meets formally every 3 months. Trial Progress Reports containing updates, summary statistics and graphs, and discussion points are submitted for these meetings.

The trial group confers regularly with the AHRI Clinical Research Department, primarily regarding SAE and AE management. The trial coordinator has frequent meetings with the head of the Clinical Research Department and attends regular AHRI wide project coordination meetings to ensure that the trial implementation coordinated with awareness of other research activities in the study community.

The Trial Steering Committee (TSC) act as the oversight body for this trial on behalf of the Sponsor/Funder and it should also provide advice through its independent Chair on all aspects of the trial. All substantial issues regarding the trial must go to the TSC for consideration. The Data Safety Monitoring (DSMB) is advisory to the TSC and the DSMB makes recommendations to the TSC based on the interim data. The TSC oversee the timely analysis, writing up and publication of the main trial results. The independent members of the TSC will have the opportunity to read and comment on the proposed main publications of trial data before submission. The TSC is made up of the chair, three independent members, including an experienced trials statistician. The TSC meets with the trial management team and an independent observer from the funding body at least annually and ad hoc as required to discuss trial issues.

Composition of the data monitoring committee, its role and reporting structure

The Data Monitoring and Safety Board (DSMB) consists of a chair (senior clinical trialist), two statisticians and a clinician. Interim data analyses are supplied, in strict confidence, to the DSMB, as frequently as the chair requests and meetings are held at least annually. The DSMB is independent of the trial organisers and sponsors. The terms of reference for the DMSB were agreed at their first meeting and documented in the DSMB charter. Based on interim data on the trial's outcomes, adverse event data, accumulating evidence from other trials and any other relevant evidence, the DSMB will inform the Trial Steering Committee (TSC) if, in their view, there is proof beyond a reasonable doubt that the data indicate that any part of the protocol under investigation is either clearly indicated or contra-indicated, either for all trial participants or for a particular subgroup of trial participants. A difference of at least 3 standard errors in the interim analysis of a major endpoint may be needed to justify halting, or modifying, such a study prematurely.

Adverse event reporting and harms

The processes of risk identification and management have been developed and tested. The trial has, in collaboration with the AHRI Clinical Research Department, identified and established referral pathways for the management of risk, including referrals to the local Department of Health and social development services. The AHRI Clinical Research Department assists with the management of medical SAEs. We have developed a protocol for the management of these events and reporting at appropriate times to the DSMB.

The trial distinguishes between Severe Adverse Events (SAEs) and Adverse Events (AEs). SAEs pose a high risk to the mother and/or enrolled child and require urgent attention and management. SAEs include maternal/child death; physical illness requiring hospitalisation ≥5 days; severe psychological or psychiatric illness (may require hospitalisation; current suicidal ideation with intention and/or a plan; self-harm; serious social harm (e.g., interpersonal violence-causing immediate danger or risk); stigma, emotional harm or risk of displacement/insecure housing (as a direct result of trial participation); and inadvertent disclosure of participants HIV status or breach of confidentiality (intentionally or unintentionally by research staff). Details of the SAE and a brief management plan are communicated to the DSMB Chair within 24 hours of the team being notified of the SAE. Furthermore, SAEs are reported to the HSRC and OxTREC ethics committees within 7 days of the team being notified of the SAE.

In contrast, AEs are defined as events that do not pose an immediate risk to the mother/infant but require management and attention to prevent escalation into a high-risk event (SAE). These include relationship problems/conflicts, feelings of hopelessness and suicidal thoughts without serious intent or plans. These are monitored and recorded and reported to the ethics committees and the DSMB as AEs.

Frequency and plans for auditing trial conduct

The trial is being conducted in accordance with the current approved protocol, GCP, relevant regulations and SOPs. The risk management protocol and operational SOPs are reviewed as necessary over the course of the trial to reflect significant changes to the protocol or outcomes of monitoring activities.

The AHRI research data management team conducts frequent checks of the trial, including recruitment patterns and the quality and completeness of data using relevant software as well as manual checks. Lists of missing data will be generated automatically for regular checks. Furthermore, the data collection software is designed to optimise correct data capture by specifying the data and values required.

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

Any protocol modifications which may influence the study conduct, potential benefit of the participants, participants' safety, study objectives, study design, participant population, sample sizes, study procedures, interventions, assessments or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed upon by the Principal Investigators and the Investigators and submitted to OxTREC and HSRC for formal ethical approval before implementation. Participants will be informed of any important protocol amendments if deemed necessary.

Dissemination plans

The trial results will be disseminated to participants, the public, researchers, healthcare professionals, and policymakers. The study participants will be informed of the findings from the trial. The trial results and their implications for policy and practice will be presented in the form of a technical brief to the district, provincial and national departments of health and disseminated nationally through webinars. The technical brief will also be disseminated to relevant mental health and public health charities and non-governmental organisations. With support from the AHRI community advisory board and public engagement office, we will disseminate the findings to the local community. The trial results will be presented at national and international conferences. Publications will be submitted to peer-reviewed, open-access journals in line with funder requirements.

Discussion

There is a considerable treatment gap for mental health disorders amongst people living with HIV in LMICs (85), of which HIV-positive women in the perinatal period are considered especially vulnerable to poor mental health (3). Addressing this treatment gap requires innovative programmes that can be integrated sustainably into existing primary care programmes to create a holistic approach. Importantly, treating both maternal perinatal depression and enhancing child development has the potential to result in positive health and human capital benefits. If the integrated intervention is found to be effective, the ultimate aim is that it will be scalable at different levels, including local, provincial, national and international, and critically include users, stakeholders, the general public, policy-makers and academic beneficiaries.

The intervention is potentially generalisable to countries with high levels of HIV as part of initiatives to prioritise antenatal and postnatal health care for mothers and children within fragile health systems.

The trial has developed an electronic treatment manual that guides the lay-counsellors as they deliver BA and parenting support. There is a demand for improving the competencies and skills of the mental health and early child development workforce. Building capacity entails not only training frontline workers, many of whom are lay workers but contributing

to an evidence-based body of knowledge that will be informative for future implementation strategies in community systems. The knowledge base will also contribute to supervision and training systems.

Trial status

The trial started recruitment on 04/04/2018. Recruitment was suspended on 16/03/2020 due to the COVID-19 pandemic and was resumed briefly for six weeks in November and December 2020 but had to be paused in December 2020 due to further COVID-19 restrictions. Recruitment resumed again in March 2021. We expect to complete recruitment by October 2021. The trial is currently operating on protocol version V1.04 (15 October 2020).

Abbreviations

AE	Adverse Event
ART	Antiretroviral Therapy
AHRI	Africa Health Research Institute
BA	Behavioural Activation
BSID-III	Bayley Scales of Infant and Toddler Development III (BSID-III) cognitive subscale.
CBCL	Child Behaviour Checklist
CBT	Cognitive Behavioural Therapy
CCD	Care for Child Development
CD4	Cluster of Differentiation 4 (T-cells or T-helper cells)
CHW	Community Health Worker
DALY	Disability-Adjusted Life Years
DfID	Department for International Development, UK
DoH	Department of Health (South Africa)
DOI	Digital Object Identifier
DSMB	Data and Safety Monitoring Board
EBF	Exclusive Breast Feeding
ECD	Early Child Development
EPDS	Edinburgh Postnatal Depression Scale
ESoC	Enhanced Standard of Care
GAD-7	Generalized Anxiety Disorder Scale 7-item

GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HSRC	Human Sciences Research Council, South Africa
ICC	Intra-cluster Correlation Coefficient
LMIC	Low- and Middle-Income Country/ies
MICS	Multiple Indicator Cluster Surveys (Cognitive and Emotional Stimulation)
MRC	Medical Research Council
OxTREC	Oxford Tropical Research Ethics Committee
PI	Principal Investigator
PSI/SF	Parenting Stress Index Short Form
RCT	Randomised Controlled Trial (RCT)
REC	Research Ethics Committee
SAE	Serious Adverse Event
SD	Standard Deviation
SoC	Standard of Care
TSC	Trial Steering Committee
UNICEF	United Nations International Children's Emergency Fund
VL	Viral Load
WHO	World Health Organization

Declarations

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Author contributions

AS and TJR conceptualised the study with contributions from the LR, RB, KH, CD, LL, EJ, MA, and AY, and MC. LL drafted the statistical analysis section and SD leads the implementation. The paper was drafted by CH and AS with input from SR, TJR, and LL. All authors reviewed and commented on the manuscript and approved the final version.

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Availability of data and material

Data will be available beginning 9 months and ending 36 months following main article publication to researchers who provide a methodologically sound proposal that purposes to achieve aims in the approved proposal and /or for individual participant data meta-analysis. Data is documented and stored on the Africa Health Research Institute (AHRI) Data Repository (https://data.ahri.org) with a digital object identifier (DOI) and can be accessed with permission and in line with AHRI policies and procedures. Data requestors will need to sign a data access agreement before any data can be shared. In addition, Study Protocol and Statistical Analysis Plan documents will be available. Data sets associated with publications will be made available in line with Wellcome Trust data policies and journal requirements.

Ethics approval and consent to participate

The University of Oxford is the sponsor of the trial. Ethical approval has been obtained from the Human Sciences Research Council (HSRC, #REC 5/23/08/17), South Africa, and the Oxford Tropical Research Ethics committee (OxTREC #31-17), UK. The HSRC provides annual review and re-certification for the trial, whilst OxTREC has certified the trial for 5 years.

Consent for publication

Not applicable, no participant data is used in this protocol

Competing interests

The authors, including the Principal Investigators, declare no financial or non-financial competing interests.

Authors' information (optional)

NA

Authors' contributions

AS and TJR conceptualised the study. The paper was drafted by CH and AS with input from SR, TJR, and LL. All authors reviewed and commented on the manuscript and approved the final version.

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Consent for publication

Not applicable, no participant data is used in this protocol

Competing interests

The authors, including the Principal Investigators, declare no financial or non-financial competing interests.

Authors' information (optional)

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Figures

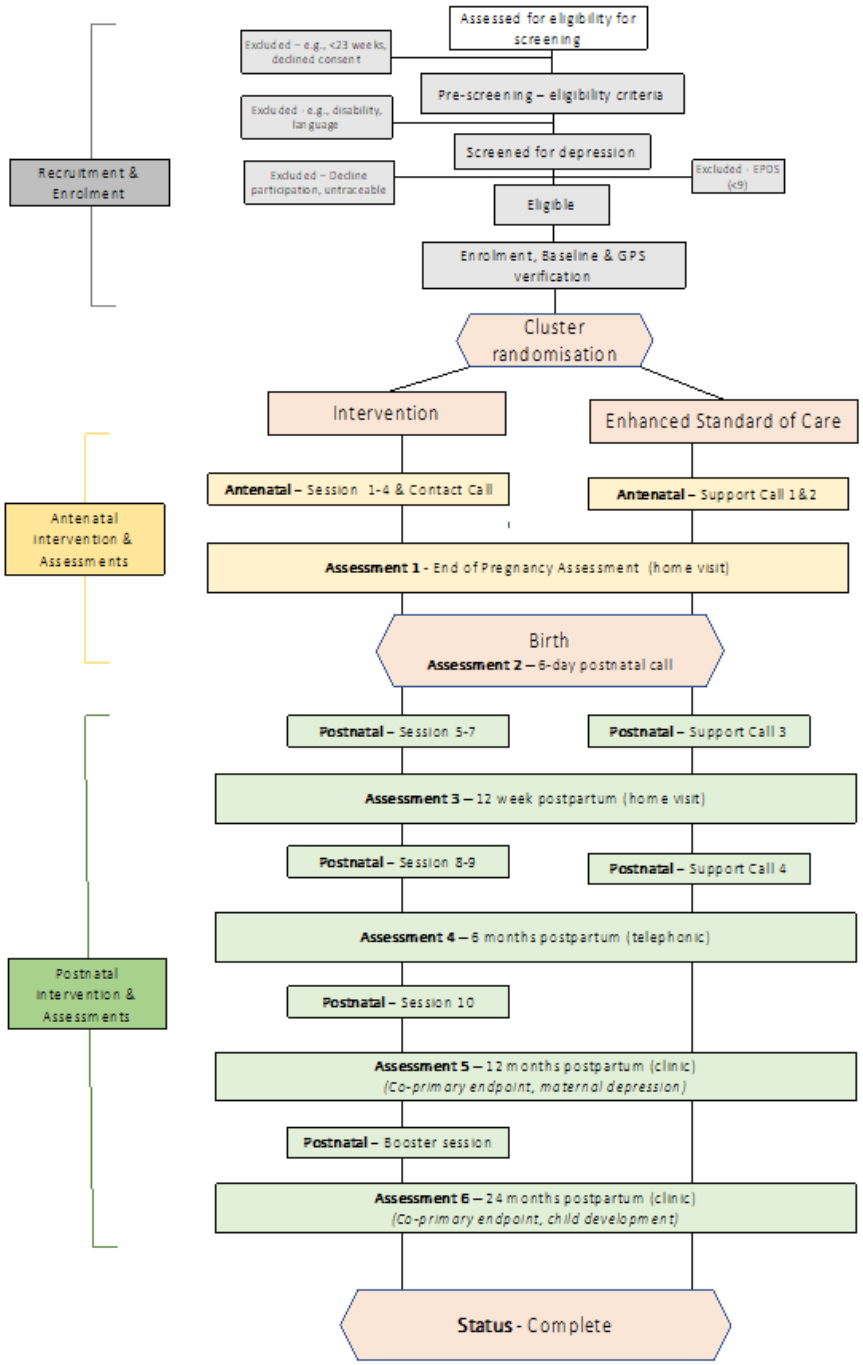

Figure 1

Participant Flow

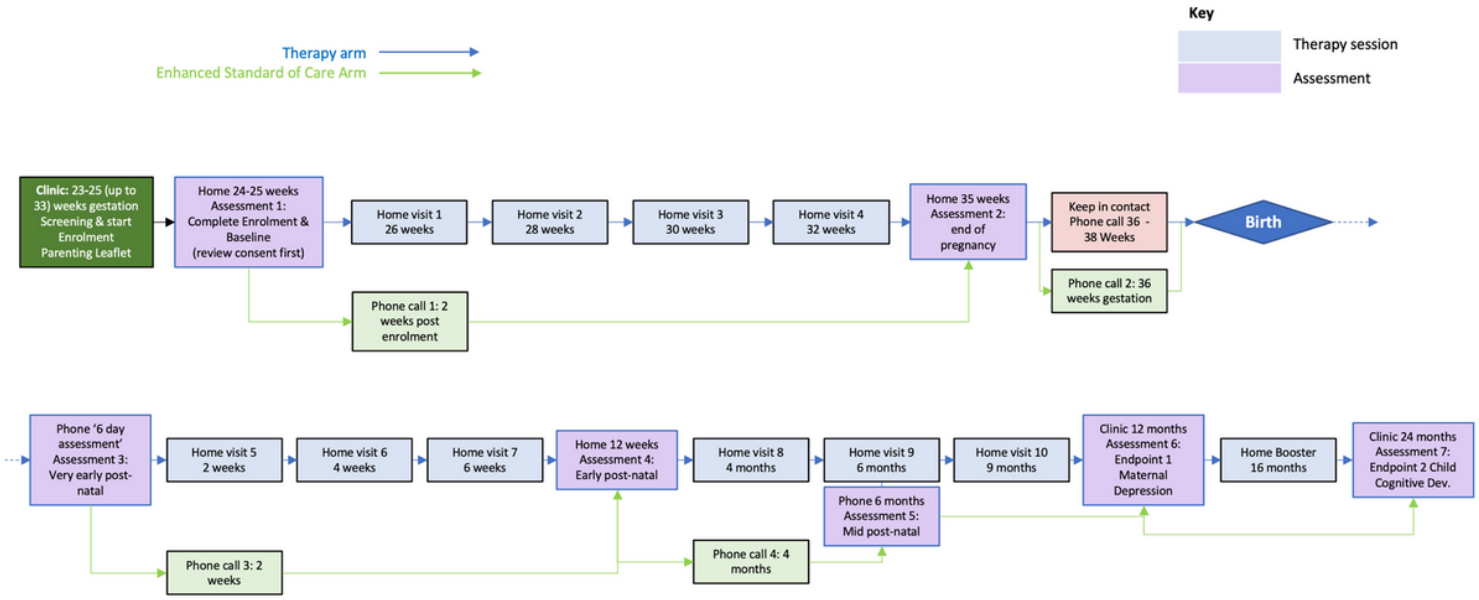

Figure 2

Participant timeline