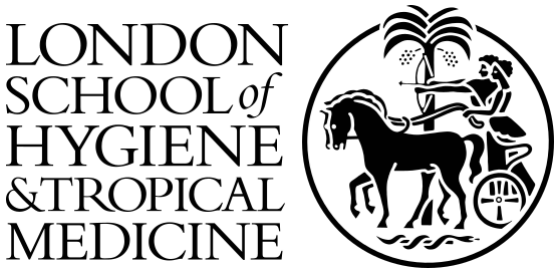

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Effects of parenting classes and economic strengthening for caregivers on the cognition of HIV-exposed infants: a pragmatic cluster randomised controlled trial in rural Zimbabwe

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ABSTRACT

Introduction HIV-exposed children show signs of developmental delay. We assessed the impact of a pragmatic multicomponent intervention for caregivers of HIV-exposed children aged 0–2 years in Zimbabwe.

Methods We conducted a cluster-randomised trial from 2016 to 2018. Clusters were catchments surrounding clinics, allocated (1:1) to either National HIV guidelines standard of care or standard care plus an 18-session group intervention comprising i) early childhood stimulation (ECS) and parenting training with home visits to reinforce skills and retention in HIV care; ii) economic strengthening. Primary outcomes measured 12 months after baseline (4.5 months postintervention completion) included: i) global child development measured using the Mullen early learning composite score; ii) retention in HIV care. Analysis used mixed effects regression to account for clustering and adjusted minimally for baseline prognostic factors and was by intention to treat.

Results Thirty clusters, 15 in each arm, were randomised. 574 dyads were recruited with 89.5% retained at follow-up. Ninety one of 281 (32.4%) were recorded as having received the complete intervention package, with 161/281 (57.3%) attending ≥14 ECS sessions. There was no evidence of an intervention effect on global child development (intervention mean 88.1 vs standard of care mean 87.6; adjusted mean difference=0.06; 95% CI −2.68 to 2.80; p=0.97) or infant retention in care (proportion of children who had missed their most recent HIV test: intervention 21.8% vs standard of care 16.9%, p=0.18). There was weak evidence that the proportion of caregivers with parental stress was reduced in the intervention arm (adjusted OR (aOR)=0.69; 95% CI 0.45 to 1.05; p=0.08) and stronger evidence that parental distress specifically was reduced (intervention arm 17.4% vs standard of care 29.1% scoring above the cut-off; aOR=0.56; 95% CI 0.35 to 0.89; p=0.01).

Conclusion This multicomponent intervention had no impact on child development outcomes within 4.5 months of completion, but had an impact on parental distress. Maternal mental health remains a high priority.

Trial registration number PACTR201701001387209.

Key questions

What is already known?

- HIV-exposed children in resource-limited settings face multiple and complex stressors associated directly and indirectly with HIV infection.
- Early interventions for HIV-exposed children have led to documented improvements in child outcomes in the short term and long term.

What are the new findings?

- The intervention trialled here did not have an impact on child cognitive development, but reduced parental distress which could directly and indirectly impact child trajectories.
- The prevalence of reported symptoms of common mental disorder was extremely high among participating caregivers.

What do the new findings imply?

- Cognitive development outcomes may take longer to improve following parental child stimulation training.
- Comprehensive interventions to address childhood development may need to include screening and intervention for poor mental health in caregivers.

INTRODUCTION

Early childhood development (ECD) covering the first 3 years of a child's life marks a time of gradual development of a child's sensorimotor, social-emotional, cognitive and language capacities. These processes are shaped by many factors, including interactions between the child and their environment, exposure to experiences and genetics.[1] During this period of rapid physical growth, the child acquires a complex set of skills and functional competencies facilitating achievement of their potential in life and laying the

foundation for long-term physical, emotional and psychological health in childhood and adulthood.

During this period, children's brains develop rapidly and can be modified by their environment[2] influencing their ability to learn and develop over time.[3] Thus, early childhood is a key time to maximise the opportunity for children to develop their full potential. Researchers have shown that appropriate stimulation, good quality parenting provided by a consistent, responsive caregiver, coupled with adequate nutrition and access to health and psychosocial care can contribute to optimal development.[4 5] Conversely, adversities during this period, such as poverty, malnutrition, poor health, low stimulation, exposure to stressful conditions and impoverished environment can disrupt brain development, attachment, and early learning.[2]

HIV infection in both the parent and the child represents a multifaceted life challenge.[6] HIV can impact child growth and development in a variety of ways including their cognitive development.[7 8] Several studies have described the risk of developmental delay and impairment in both children living with HIV,[9] and HIV-exposed uninfected (HEU) infants[7] compared with HIV-unexposed infants,[8] with the risk apparently heightened in low-income and middle-income countries (LMICs).[10] Children infected with HIV perinatally face greater risk of neurological and neuropsychological deficits compared with HEU infants, either due to direct effects of HIV on the central nervous system,[9] exposure to treatment or other HIV-related factors. These risks can be mitigated; research illustrates the importance of early antiretroviral therapy (ART) initiation, and virological suppression during infancy or early childhood and its association with improved neurocognitive outcomes in children with perinatally acquired HIV.[11 12] HIV can also impact the neurodevelopment of children indirectly through its influence on the child's living environment,[8] including community stigma and discrimination, caregiver unemployment, caregiver illness and bereavement or caregiver mental health.[10 13 14] However, in some cases despite facing significant adversities, HEU children can develop resiliency and demonstrate positive developmental trajectories, similar to those HIV-unexposed uninfected.[15]

Early interventions for disadvantaged children have led to documented improvements in child outcomes such as survival, health, growth and cognitive and social development.[16] Several studies have demonstrated the benefits of caregiver or child targeted interventions over the long term and showed improvements in developmental outcomes of children from LMICs.[2 4] Home visits and support to HIV-positive caregivers by community health workers was found to improve developmental outcome for HEU children.[17] Parenting and child stimulation programmes taught to the caregiver can significantly improve cognitive and motor development in young children infected with HIV.[18] In addition, microfinance programmes (which includes the provision of loans, savings and insurance) in rural settings can have a positive impact on various household indicators, improve food security and the health of children.[19] Research shows that combination interventions can have accelerated benefits.[20 21] Theoretical models[22] suggest that internal assets, family resources and community support can promote the resilience process and temper negative impacts of parental HIV. The need for an evaluation of more complex, broader and integrated interventions is timely.

Zimbabwe is one of the countries most severely affected by HIV globally, with prevalence estimated at 14.6% among those aged 15–64 years.[23] Over a million children have been orphaned due to AIDS-related deaths since the start of the epidemic.[24] Prevention of mother to child transmission (PMTCT) programmes have dramatically reduced perinatal transmission and ART rollout has reduced mortality and morbidity in caregivers.[25] However, despite improved health and survival of infants born to mothers living with HIV, interventions to improve the well-being and development of these children are needed. The Child Health Intervention for Developmental Outcomes (CHIDO) trial aimed to determine the real-world effectiveness of a multicomponent community-based intervention on child development and HIV.

METHODS

The methods have been previously published.[26] A brief overview is provided here.

Study design and participants

The CHIDO trial is a pragmatic parallel-arm cluster randomised controlled trial conducted in 30 primary care clinic catchment areas in two districts in Zimbabwe (Goromonzi and Mudzi). Detailed mapping of all health facilities and their communities was conducted to select trial sites, which are at least 15 km apart.

Community sensitisation was carried out in phases. First, the local leaders (including traditional and political leaders, health and educational professionals) were given information about the study, its objectives, the target population and encouraged to ask questions or raise any concerns. They were then invited to take part in the site randomisation process. The caregivers were identified from the HIV-exposed infant registers kept at trial clinics and were eligible for inclusion if they were the primary caregivers (biological and non-biological), the biological mother had been living with HIV and cared for a child aged 0–24 months. Caregivers who gave written informed consent/assent in English or Shona were enrolled into the trial, completed a baseline assessment and were followed up after 12 months. In intervention communities, caregiver-infant dyads were encouraged to engage in all CHIDO intervention activities. While they attended the clinic specifically for the intervention sessions, they could also attend clinic services if scheduled/required.

Extended Consolidated Standards of Reporting Trials guidelines were followed for reporting the results of this trial.

Patient involvement

Patients and village health workers were involved in formative work undertaken at which the CHIDO intervention was developed.

Randomisation and masking

Clinics were randomised in a 1:1 allocation ratio to the CHIDO intervention or Ministry of Health and Child Care (MoHCC) standard of care. Restricted randomisation was used to ensure balance by district (20 in Goromonzi district and 10 in Mudzi district) and on the number of HIV-exposed infants aged between 0 and 24 months per clinic by stratifying the clinics into those able to run one group of 12 dyads (12 clusters) and those of sufficient size to run two groups of 12 dyads (18 clusters). To maximise transparency and buy-in from stakeholders, a public randomisation procedure was undertaken in each district (on 19 January 2016 in Goromonzi and on 31 May 2016 in Mudzi) involving MoHCC, and district-level government and medical representatives. Assessors conducting the endline survey procedures were blind to trial arm.

Intervention components

The intervention included three elements: (i) an 18-session health, nutrition and early childhood stimulation (ECS) parenting programme (table 1); (ii) an internal savings and lending scheme (ISALS) with ISALS sessions held immediately after each ECS session and (iii) village health workers who visited participants at home each month (or more frequently in the case of non-attendance at group sessions or other problems). The parenting programme content evolved out of formative work and the number of sessions was set after piloting and feedback from participants about preferred length and frequency of sessions.

Baseline and endline assessments and data collection

Participant enrolment was conducted in parallel in intervention and standard of care communities between 16 January and 8 September 2016. At enrolment, all participating caregiver-child dyads were allocated a unique identifier. Questionnaire data which included demographic, socioeconomic, maternal mental health and household food security information were collected using an interviewer-administered questionnaire with data entered directly onto tablets preprogrammed using Open Data Kit with range and consistency checks incorporated. Maternal mental health was measured using the Edinburgh Postnatal Depression Scale (EPDS),[27 28] which is a diagnostic tool that has been locally validated in Zimbabwe,[28] plus the 8-item Shona Symptoms Questionnaire (SSQ-8), a locally developed and validated scale which determines risk of common mental disorders (including anxiety and depression).[29] Finally, parental stress was measured using the Parental Stress Index Short Form (PSI-SF).[30]

Table 1 Parenting programme content

Session number	Delivered by	Parenting programme content
1	CHW	Relationships with people around you and your child
2	CHW	The role of good parent—responsive parenting practices (session I)
3	CHW	The role of good parent—responsive parenting practices (session II)
4	Nurse	A healthy infant and young child (session I)
5	Nurse	A health infant and young child (session II)
6	Nurse	A well-nourished infant and young child
7	CHW	Physical/motor development (session I)
8	CHW	Physical/motor development (session II)
9	CHW	Social and emotional development (session I)
10	CHW	Social and emotional development (session II)
11	Nurse	A health infant and young child (focus on PMTCT and treatment adherence)
12	Nurse	Complementary feeding (session I)
13	Nurse	Complementary feeding (session II)
14	CHW	Communication and language development (session I)
15	CHW	Communication and language development (session II)
16	CHW	Developing thinking and understanding of the world (cognitive) (session I)
17	CHW	Developing thinking and understanding of the world (cognitive) (session II)
18	CHW	Positive discipline

CHW, Community Health Worker; PMTCT, Prevention of mother to child transmission.

The more sensitive questions were self-completed using audio computer-assisted survey instrument to maximise validity. This was followed by a developmental assessment of the child conducted by one of two trained research nurses. Developmental assessments were videoed, and a small randomly selected sample was reviewed by a highly experienced assessor. This was done as part of quality control and assurance, and to minimise differences between assessors.

Intervention implementation commenced within 3 months of participant enrolment in all communities and ran over 12 months between 7 March 2016 and 7 July 2017.

An endline assessment was conducted between 10 April 2017 and 18 January 2018 among enrolled caregiver-child dyads 12 months after the baseline survey and within 0–5 months after completion of intervention delivery. The endline survey was conducted in parallel, with pairs of intervention and control trial sites being assessed at the same survey venue to minimise unblinding of assessors. Survey procedures were as described at baseline.

At endline a dried blood spot sample was collected from all biological mothers to determine HIV viral load and infants to test for HIV antibody status and viral load. Programme attendance records and village healthcare worker diaries were reviewed, and data double entered into password protected Access databases.

Laboratory assessments

Dried blood spot samples were air dried, stored at room temperature and submitted weekly to the respective laboratories. Infant samples were sent to the National Microbiology Reference Laboratory in Harare for HIV-1 antibody testing using COBAS AmpliPrep/COBAS TaqMan. Samples confirmed HIV positive were sent for viral load testing. Caregiver samples were sent to flow cytometry laboratory for viral load testing using Biomerieux NucliSENS easyMag and EasyQ.

Outcome measures

There were two primary outcomes for the trial: (i) change in the mean age-standardised Mullen early learning composite (ELC) score[31] of children; (ii) the proportion of HIV-exposed or HIV-positive children with full retention in care (>80%) of scheduled HIV treatment and care visits at 12 months. In the absence of locally validated robust child development measures, the Mullen ELC score was chosen as it had been used to determine impact of caregiver interventions over a similar time period in Africa.[32 33] We assessed seven prespecified secondary end points as previously reported, reflecting factors intended to be affected by the intervention, which were analysed by the same analytical framework as the primary outcome (table 2).

Statistical analysis

Our sample-size calculations have been described previously.[26] We estimated that we would need 15 clusters per arm with a harmonic mean of 16 caregiver-child dyads per cluster at endline, and assuming 20% loss to follow-up over 12 months to have 80% power to detect an effect size (difference in means/SD) of 1.23 for the Mullen ELC score and 82% power to detect a risk difference in retention in care of HIV-exposed children of at least 17% assuming 65% are retained in the control arm. The overall recruitment target was therefore

Table 2 Secondary outcomes of the CHIDO trial

Outcome measures	Assessment tools used
Child HIV outcomes: viral load	Viral load tests conducted using Biomerieux NucliSENS easyMag and EasyQ on dried blood spot samples
Child development outcomes: ► Visual reception ► Fine motor ► Receptive language ► Expressive language	Mullen early learning composite score
Nutritional outcomes: weight-for-age, height-for-age, weight-for-height (BMI) z-scores	Midupper arm circumference tape measure, height mate/board
Parental stress	Parental Stress Index Short Form
Adherence outcomes: ► Retention in care ► Viral load	Medical Adherence Rating Scale Viral load tests conducted using Biomerieux NucliSENS easyMag and EasyQ on dried blood spot samples
Food security outcome	Household hunger (food deprivation) scale—modified HFIAS (one item from each domain of the scale: i) uncertainty about household food supply; ii) insufficient quality and iii) insufficient food intake
Mental health outcomes: ► Postnatal depression ► Common mental disorders	Edinburgh Postnatal Depression Scale Shona Symptom Questionnaire 8

BMI, body mass index; CHIDO, Child Health Intervention for Developmental Outcomes; HFIAS, Household Food Insecurity Access Scale.

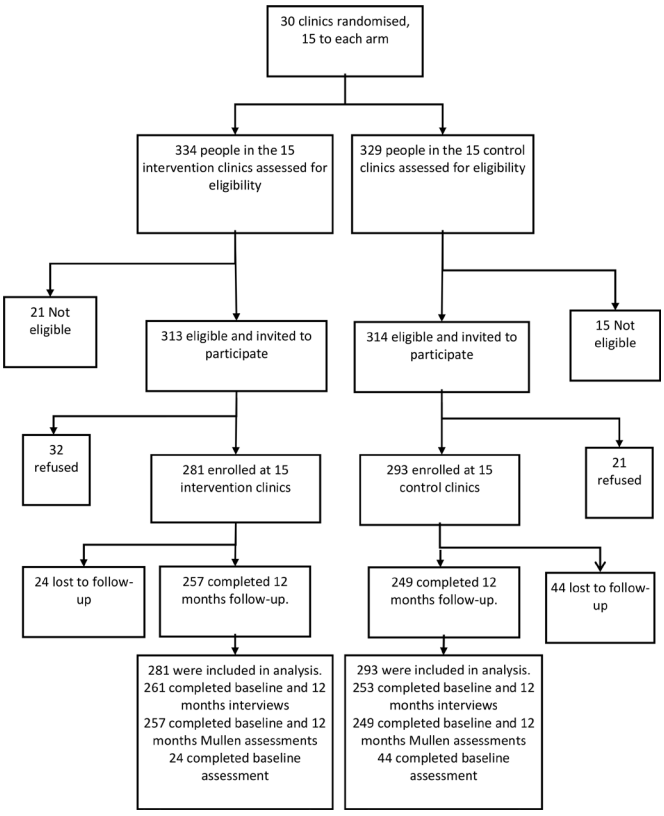

Figure 1 Recruitment and enrolment.

528 caregiver-child dyads in total from 30 clinics. We recruited 574 dyads to ensure a harmonic mean of 24 dyads was enrolled from the larger seven clinics (to allow two groups to run at these sites) and a harmonic mean of 12 dyads was enrolled from the smaller eight clinics, where just one ECS/ISALS group was run.

The statistical analysis followed a prespecified analytical plan differing from the published protocol by using individual-level analysis (see online supplementary materials), which allowed for greater flexibility. Data were analysed in STATA V.15.1 (StataCorp, College Station, Texas, USA) using intention-to-treat principles incorporating random effects for clusters and adjusting minimally for baseline prognostic factors. Mean differences and 95% CIs were used to estimate the effect of the intervention for quantitative outcomes using mixed effects linear regression. ORs and 95% CI were used to estimate the effect of the intervention for binary outcomes using mixed effects logistic regression. Mental health questions were categorised as at risk or not at risk, with cut-points of 12/30 for the EPDS,[28] 6/8 for the SSQ-8[29] and at the 90th percentile of the reference range for PSI-SF domain and total scores.[30] Baseline factors adjusted for a priori were the baseline measurement, strata in Goromonzi (two groups based on the number of children on the clinic register), district (Goromonzi or Mudzi), infant age (0 to <6 months, 6 to <12 months and 12–24 months) and for quantitative Mullen outcomes, a categorical covariate representing the assessor at baseline. Sensitivity analyses were performed using a cluster-level analysis for the ELC score.[34] Evidence for effect modification in the ELC score was assessed by incorporating interaction terms with baseline Mullen ELC score or with baseline caregiver's mental health as measured by EPDS, SSQ-8 and PSI-SF. The effect of the intervention was also examined in a per-protocol analysis comparing those in the intervention arm who attended most ECS sessions (either at least 14/18 sessions in total, or at least 7/9 sessions addressing child development) with those in the standard of care arm.

RESULTS

All 30 clusters were randomised (15 to each trial arm) and all remained in the trial until the end (figure 1). Number of participants recruited (n=574) exceeded target enrolment (n=528). Retention was 89.5% (514/574) (261: 91.5% in the intervention arm and 253: 85.0% in the standard of care arm), of whom 506 of 514 had endline data on the Mullen score. Six Mullen scores were missing because the child had died. The other two children were found and tested for HIV but the Mullen test was not performed. At follow-up, 18 children had a different primary caregiver from the person who completed the baseline interview.

Descriptive characteristics at baseline

Baseline characteristics were generally comparable between trial arms (table 3); the intervention arm had a greater percentage of infants aged under 6 months (26.3% vs 15.0%), infants stunted at baseline (38.4% vs 34.3%) and households of lower socioeconomic status (37.0% vs 30.0%). Only two of seven HIV-infected babies had been started on ART within 6 weeks of birth. Almost all caregivers (562/574; 97.9%) were biological mothers, and about half (304/574; 53.0%) had secondary education or higher. Reported food insecurity was high. Mental health of caregivers was poor with 230/574 (40.1%) caregivers at risk of common mental disorders (SSQ-8 >6) and about half of mothers (284/562; 49.5%) above the threshold for postnatal depression (EPDS >12) at baseline. High parental distress (PSI-SF parental distress subscale >90th percentile) was reported by 185/574 (32.2%) caregivers.

Infants were 291/574 (50.1%) female, and 207/574 (36.1%) were stunted (WHO height-for-age z-score <–2). The mean composite score on the Mullen ELC score at baseline was 102.3 (95% CI 98.6 to 106.0), which was similar to the US reference norms (table 3). Characteristics of those lost to follow-up were similar to those who completed follow-up (online supplementary appendix table 1).

Programme implementation

The CHIDO intervention was initiated in all 15 intervention clusters, with 281 participants enrolled. There are missing attendance data from one cluster. In the 14 clusters with attendance data, 21 ECS groups were run with each group intended for up to 12 participants. Seven clusters ran one group and seven clusters ran two groups.

Table 3 Descriptive characteristics of participants at baseline by trial arm

	Measure and level	Intervention arm	Standard of care arm
Total	N (% of total)	281 (49.0%)	293 (51.0%)
Infant's characteristics			
Age (years)	Median (IQR)	1.04 (0.48–1.49)	1.00 (0.68–1.47)
Age (months)	0 to <6	74 (26.3%)	44 (15.0%)
	6 to <12	61 (21.7%)	100 (34.1%)
	12–24	146 (52.0%)	149 (50.9%)
Sex	N (%)		
	Male	141 (50.2%)	142 (48.5%)
	Female	140 (49.8%)	151 (51.5%)
HIV status as reported at baseline	N (%)		
	True positive	2 (0.7%)	3 (1.0%)
	False positive	7 (2.5%)	1 (0.3%)
	Unconfirmed positive	3 (1.1%)	2 (0.7%)
	True negative	155 (55.2%)	184 (62.8%)
	False negative	6 (2.1%)	2 (0.7%)
	Unconfirmed negative	11 (3.9%)	31 (10.6%)
	Prefers not to say	2 (0.7%)	0 (0%)
	Unknown	95 (33.8%)	70 (23.9%)
HIV status as reported at 12 months	N (%)		
	True positive	5 (1.8%)	4 (1.4%)
	False positive	1 (0.4%)	2 (0.7%)
	True negative	236 (84.0%)	231 (78.8%)
	False negative	5 (1.8%)	2 (0.7%)
	Unconfirmed negative	1 (0.4%)	2 (0.7%)
	Prefers not to say	1 (0.4%)	2 (0.7%)
	Unknown (negative)	9 (3.2%)	7 (2.4%)
	Lost to follow-up	23 (8.2%)	43 (14.7%)
HIV status as known at 12 months	N (%)		
	Infected	10 (3.6%)	6 (2.0%)
	Exposed uninfected	247 (87.9%)	242 (82.6%)
	Unknown	1 (0.4%)	2 (0.7%)
	Lost to follow-up	23 (8.2%)	43 (14.7%)
Birth weight (kg)	Mean (95% CI)	2.99 (2.90 to 3.08) n=272	2.93 (2.86 to 3.00) n=283
Weight-for-age z-score	Mean (95% CI)	−0.86 (−1.15 to −0.57)	−0.86 (−0.99 to −0.72)
Underweight (z-score <−2)	Yes	44 (15.7%)	43 (14.7%)
	No	237 (84.3%)	250 (85.3%)
Length-for-age z-score	Mean (95% CI)	−1.56 (−1.87 to −1.25)	−1.46 (−1.71 to −1.21)
Stunted (z-score <−2)	Yes	107 (38.4%)	100 (34.3%)
	No	172 (61.7%)	192 (65.8%)
BMI z-score			
Low BMI z-score	Yes	15 (5.4%)	17 (5.8%)
	No	264 (94.6%)	275 (94.2%)
MUAC z-score			
Low MUAC z-score <-2	Yes	14 (6.0%)	15 (5.8%)

Continued

Table 3 Continued

	Measure and level	Intervention arm	Standard of care arm
	No	218 (94.0%)	246 (94.3%)
Mullen scales (T-scores)	Mean (95% CI)		
	Expressive language	52.4 (49.7 to 55.1)	53.1 (51.3 to 55.0)
	Fine motor	51.1 (47.9 to 54.4)	50.2 (47.4 to 53.0)
	Gross motor	50.1 (47.7 to 52.6)	50.8 (49.2 to 52.4)
	Receptive language	47.6 (44.5 to 50.8)	47.6 (44.8 to 50.4)
	Visual reception	53.5 (49.3 to 57.8)	52.6 (50.2 to 55.1)
	Early learning composite score	102.6 (96.5 to 108.7)	102.0 (97.8 to 106.3)
Caregiver's characteristic			
Caregiver type	N (%)		
	Mother	272 (96.8%)	290 (99.0%)
	Other	9 (3.2%)	3 (1.0%)
Age (years)	Median (IQR)	32 (27–36)	32 (27–36)
Marital status	N (%)		
	Married	227 (81.1%)	228 (77.8%)
	Divorced/separated	32 (11.4%)	42 (14.3%)
	Widowed	16 (5.7%)	15 (5.1%)
	Never married	5 (1.8%)	8 (2.7%)
Education	N (%)		
	Secondary or above	152 (54.1%)	152 (51.9%)
Employment	N (%)		
	Employed	90 (32.0%)	120 (41.0%)
SES	N (%)		
	Lowest	104 (37.0%)	88 (30.0%)
	Middle	100 (35.6%)	91 (31.1%)
	Highest	77 (27.4%)	114 (38.9%)
Parental stress score (PSI-SF)	N (%)		
Parental distress subscale n=565	Not stressed (<90th percentile)	188 (68.4%)	192 (66.2%)
	Stressed (≥90th percentile)	87 (31.6%)	98 (33.8%)
Parent-child interaction dysfunction subscale n=565	Not stressed (<90th percentile)	169 (61.2%)	182 (63.0%)
	Stressed (≥90th percentile)	107 (38.8%)	107 (37.0%)
Difficult child subscale n=563	Not stressed (<90th percentile)	241 (87.3%)	240 (83.6%)
	Stressed (≥90th percentile)	35 (12.7%)	47 (16.4%)
PSI-SF total score n=564	Not stressed (<90th percentile)	180 (65.7%)	185 (63.8%)
	Stressed (≥90th percentile)	94 (34.3%)	105 (36.2%)
Mother's viral load copies/mL n=485	Geometric mean (SD)	126.2	108.0
	N (%) failure (≥1000 copies/mL)	33/246 (13.4%)	25/239 (10.5%)

Continued

Table 3 Continued

	Measure and level	Intervention arm	Standard of care arm
Maternal mental health (EPDS) n=562	N (%)		
	Not depressed (score 0–11)	132 (48.5%)	146 (50.3%)
	Depressed (score≥12)	140 (51.4%)	144 (50.0%)
Common mental disorders (SSQ-8) n=573	N (%)		
	No CMD (score 0–5)	168 (60.0%)	175 (60.0%)
	CMD (score 6–8)	112 (40.0%)	118 (40.0%)
Household food security (HFIAS)	N (%)		
	Little to no hunger	116 (41.3%)	126 (43.0%)
	Moderate-to-severe hunger	165 (58.7%)	167 (57.0%)
Medical Adherence Rating Scale n=560	Not adherent	8 (3.0%)	5 (1.7%)
	Adherent	263 (97.1%)	284 (98.3%)

BMI, body mass index; CMD, Common mental disorders; EPDS, Edinburgh Postnatal Depression Scale; HFIAS, Household Food Insecurity Access Scale; MUAC, mid-upper arm circumference; PSI-SF, Parental Stress Index Short Form; SES, socioeconomic status; SSQ-8, 8-item Shona Symptoms Questionnaire.

Of 268 caregivers in the intervention arm from the 14 clusters with records, 232 (86.6%) attended any ECS session. There were 43/268 (16.0%) participants who attended all 18 ECS sessions, and 118/268 (44.0%) who attended 14–17 sessions. Of the nine sessions addressing child development (table 1 and figure 2), 79/268 (29.5%) participants attended all nine sessions, and 79/268 (29.5%) attended seven or eight sessions, median per group who attended seven to nine child development sessions was 7.5 (IQR 6–9).

ISALS ran immediately after the ECS sessions and all women who attended an ECS session were assumed to have attended an ISALS session. Women were recorded in the ISALS register if they made a financial contribution to the ISALS (ie, actively participated in the ISALS process). The target was for women to participate in 12 ISALS over the course of the trial. ISALS registers were not available for five clusters. Where records were kept, 184 of the 232 caregivers (79.3%) participated in at least one ISALS session and 155 (67%) made a financial contribution. The median number of sessions attended at which a financial contribution was made was 5 (IQR 2–9), and 14/232 (6.0%) made a financial contribution at least 12 times (equivalent to once monthly). Overall, 198/232 (85.3%) received at least one home visit and the median number of home visits per caregiver was seven (IQR 0–9). Impact evaluation was assessed a median 134 (IQR 98–163) days after participants attended their last ECS session among 232 participants who attended any session and were followed up.

Among all intervention participants, only 32.4% (91/281) were recorded as having received the full intervention package as devised (>14 ECS, >6 ISALS and >6 home visits) (figure 3).

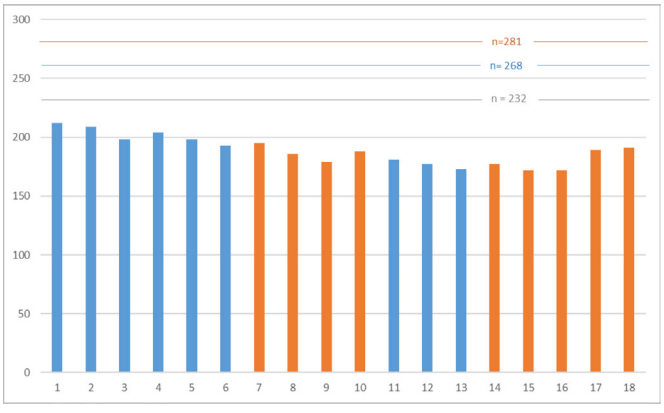

Figure 2 Early childhood stimulation (ECS) session attendance. Orange bars indicate sessions focusing on child development (n=281 all trial participants; n=268 trial participants in communities that recorded ECS; n=232 who ever enrolled in a session).

Primary outcomes

Early learning composite score

At the endline survey the Mullen ELC mean score was 87.9, a reduction of 14.4 points from baseline. There was no evidence of a difference in Mullen composite score after programme implementation between trial arms (mean of 88.1 in the intervention arm and 87.6 in standard of care arm; adjusted mean difference (aMD)=0.06; 95% CI −2.68 to 2.80). The estimated coefficient of variation (k) was 0.09. Cluster-level means showed departure from normality, but results were comparable (aMD=0.11; 95% CI −2.90 to 3.11). There was also no evidence of difference in Mullen subscales by trial arm (table 4). Individual child trajectories showed that 80% of infants had lower ELC scores at follow-up compared with baseline in both arms.

There was no evidence for effect modification for the prespecified baseline covariates on the intervention

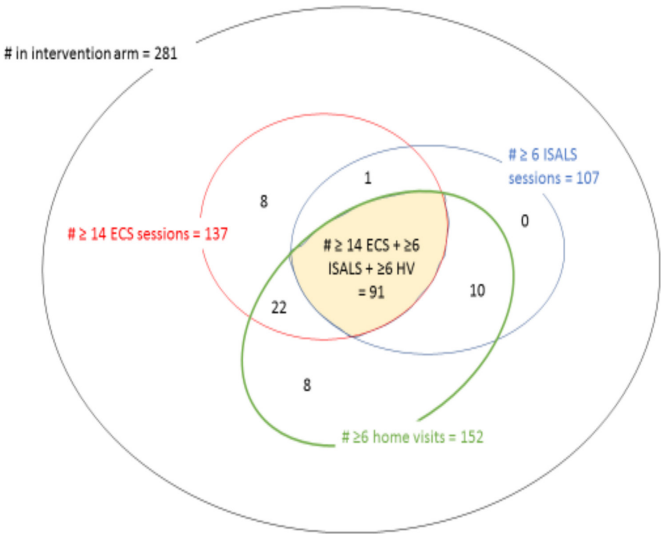

Figure 3 Venn diagram of trial participant attendance at intervention sessions. ECS, early childhood stimulation; HV, home visit; ISALS, internal savings and lending scheme.

effect on the Mullen score (table 5). Defining adequate provision of ECS as attendance at 14 or more sessions, there was no evidence of an intervention effect among those receiving adequate provision (aMD=0.57; 95% CI −2.39 to 3.53) compared with the standard of care arm.

Child HIV retention in care

At follow-up, infant HIV prevalence was 3.9% (10/257) in the intervention arm and 2.4% (6/248) in the standard of care arm. Clinic attendance data were not collected. Two proxy measures for HIV care retention were used. First, in HIV-positive children the prevalence of virological failure (viral load >1000 copies/mL) was 4/8 (50.0%) in the intervention arm (with two missing test results) and 4/6 (66.6%) in the standard of care arm. The numbers were too small to detect any difference between arms in HIV prevalence or viral suppression. Second, the date of the most recent HIV test was recorded at baseline and follow-up. Children were recorded as not retained in care if they had missed an HIV test in the PMTCT schedule (at 6 weeks, 9 months and weaning).

Table 4 Primary outcomes

Outcome	Intervention arm	Standard of care arm	Adjusted mean difference* (95% CI)	Measure of effect (95% CI)	Coefficient of variation (k)
Mullen scales (T-scores), mean (95% CI), adjusted mean difference	n=257	n=249			
Early learning composite score	88.1 (84.0, 92.2)	87.6 (83.1, 92.1)	0.06 (–2.68 to 2.80) p=0.97	–	0.09
Expressive language Mullen scale	44.9 (43.1, 46.7)	45.3 (43.3, 47.3)	–0.44 (–2.03 to 1.14) p=0.58	–0.44 (–2.03 to 1.14) p=0.58	
Receptive language Mullen scale	45.3 (43.1, 47.5)	45.8 (43.1, 48.4)	–0.11 (–1.82 to 1.60) p=0.90	–0.11 (–1.82 to 1.60) p=0.90	
Fine motor Mullen scale	41.7 (39.3, 44.2)	41.0 (38.5, 43.6)	–0.23 (–2.38 to 1.92) p=0.83	–0.23 (–2.38 to 1.92) p=0.83	
Gross motor Mullen scale	50.2 (47.7, 52.6) n=196	48.2 (45.4, 51.0) n=201	1.99 (–0.54 to 4.51) p=0.12	1.99 (–0.54 to 4.51) p=0.12	
Visual reception Mullen scale	42.8 (40.1, 45.5)	41.5 (38.6, 44.4)	0.84 (–1.44 to 3.12) p=0.47	0.84 (–1.44 to 3.12) p=0.47	
Child retention in HIV care	201/257 (78.2%)	207/249 (83.1%)	–	OR=0.73 (0.47 to 1.14 p=0.16	
Virological failure children as proportion of those HIV positive	4/8 (50%)	4/6 (67%)	–	–	
Virological failure mothers	33/246 (13.4%)	25/239 (10.5%)	–	OR=1.33 (0.72 to 2.46) p=0.36	

*Positive mean difference indicates that those in the intervention arm have higher Mullen scores.

Table 5 Effect modification of the intervention effect by baseline characteristics

Covariate	Level	Mean Mullen ELC after programme implementation		
		Intervention arm	Standard of care arm	P value for effect modification
Baseline ELC score	Below average (Mullen ELC <85)	78.5	79.2	
	Average+(Mullen ELC≥85)	90.1	89.1	0.91
Baseline EPDS	Not showing signs of depression (EPDS score <12)	89.7	88.5	
	Showing signs of depression (EPDS score≥12)	86.5	86.5	0.78
Baseline SSQ-8	No CMD (SSQ-8<6)	89.7	88.6	
	CMD (SSQ-8≥6)	85.7	86.1	0.51
Baseline PSI-PDparental distress subscale	Not showing signs of distress (PSI-PD<90th percentile)	87.7	88.3	
	Showing signs of distress (PSI-PD≥90th percentile)	89.2	85.9	0.54
Baseline infant's age (month)	0 to <6	88.5	89.1	
	6 to <12	89.6	86.7	
	12–24	87.3	87.8	0.70

ELC, early learning composite; EPDS, Edinburgh Postnatal Depression Scale; PSI-PD, Parental Stress Index parental distress subscale; SSQ-8, 8-item Shona Symptoms Questionnaire.

In the intervention arm 21.8% of infants had missed the most recent test, compared with 16.9% in the standard of care arm (adjusted OR (aOR)=1.25; 95% CI 0.77 to 2.01, p=0.37).

At baseline, 165/574 (28.7%) of caregivers said they did not know the child's HIV status and by follow-up only 16/506 (3.1%) said they did not know (table 3). There was no difference between arms in reported knowledge of HIV status at follow-up. At follow-up in the intervention arm 79/85 (92.9%) of caregivers who at baseline reported not knowing child's status reported they now knew it, compared with 55/58 (94.8%) in the standard of care arm.

Secondary outcomes

Nutritional outcomes

There was no evidence of any impact of the intervention on weight-for-age z-score, height-for-age z-score or body mass index (table 6), although there was strong evidence that infants in the intervention arm had a reduced mean MUAC for z-score (−0.60 vs −0.49; aMD=−0.20; 95% CI −0.35 to 0.06; p=0.01).

Parenting stress

There was weak evidence of an intervention effect on parental stress overall (aOR=0.69; 95% CI 0.45 to 1.05; p=0.08). There was strong evidence that the intervention had an impact on the parental distress subscale of the PSI (17.4% vs 29.1%; aOR=0.56; 95% CI 0.35 to 0.89; p=0.01).

Maternal adherence outcomes

The proportion of women with viral loads of >1000 copies/mL was similar by arm (13.4% in the intervention arm vs 10.5% in the standard of care arm; aOR=1.33; 95% CI 0.72 to 2.46). Self-reported adherence on the Medical Adherence Rating Scale was high at follow-up and also similar between trial arms (97.6% in the intervention arm vs 98.4% in the standard of care arm; online supplementary appendix table 1).

Household food security

There was no evidence of difference in household food security by trial arm, with 24.9% in the intervention arm and 21.7% in the standard of care arm reporting experiencing food insecurity (aMD=1.19; 95% CI 0.62 to 2.26; p=0.52).

Maternal mental health outcomes

There was no evidence of a difference between trial arms in the proportion of biological mothers with at least mild postnatal depression measured using the EPDS (39.8% vs 43.9%; aOR=0.79; 95% CI 0.50 to 1.25; p=0.32), despite symptoms of postnatal depression being common (table 6). There was also no difference observed among

Table 6 Secondary outcomes

Outcome	Intervention arm n=257	Standard of care arm n=249	Measure of effect (95% CI)
Weight-for-age z-score, mean (95% CI), adjusted mean difference	−0.96 (−1.09 to −0.84)	−0.85 (−0.97 to −0.72)	−0.13 (−0.28 to 0.03) p=0.10
Underweight, n (%), adjusted OR			
No	224 (86.8%)	222 (88.8%)	1
Yes	34 (13.2%)	28 (11.2%)	1.24 (0.62 to 2.47) p=0.54
Height-for-age z-score, mean (95% CI), adjusted mean difference	−1.36 (−1.61 to −1.12)	−1.34 (−1.49 to −1.20)	−0.06 (−0.24 to 0.11) p=0.49
Stunted, n (%), adjusted OR			
No	184 (71.3%)	189 (75.6%)	1
Yes	74 (28.7%)	61 (24.4%)	1.23 (0.79 to 1.93) p=0.36
BMI-for-age z-score, mean (95% CI), adjusted mean difference	−0.16 (−0.48 to 0.15)	−0.01 (−0.20 to 0.18)	−0.14 (−0.39 to 0.10) p=0.26
Low BMI-for-age z-score, n (%), adjusted OR			
No	239 (92.6%)	237 (94.8%)	1
Yes	19 (7.4%)	13 (5.2%)	1.45 (0.68 to 3.05) p=0.34
MUAC-for-age z-score, mean (95% CI), adjusted mean difference	−0.60 (−0.75 to −0.45)	−0.49 (−0.61 to −0.38)	−0.20 (−0.35 to −0.06) p=0.006
Low MUAC-for-age z-score, n (%), adjusted OR			
No	245 (95.0%)	244 (97.6%)	1
Yes	13 (5.0%)	6 (2.4%)	1.63 (0.53 to 496) p=0.39
PSI-SF percentile≥90%, n (%), adjusted OR			
No	185 (71.7%)	161 (63.6%)	OR=1
Yes	73 (28.3%)	92 (36.4%)	OR=0.69 (0.45 to 1.05) p=0.08
PSI-SF percentile, mean (95% CI), adjusted mean difference	76.8 (73.0 to 80.4)	76.2 (70.5 to 81.9)	0.44 (−5.18 to 6.05) p=0.88
Parental distress subscale percentile>90%, n (%), adjusted OR			
No	213 (82.6%)	178 (70.9%)	OR=1
Yes	45 (17.4%)	73 (29.1%)	OR=0.56 (0.35 to 0.89) p=0.01
Parental distress subscale, mean (95% CI), adjusted mean difference	65.0 (60.1to 70.0)	66.6 (60.2 to 72.9)	−0.15 (−7.16 to 6.86) p=0.97
Parent-child dysfunctional interaction subscale percentile≥90%, n (%), adjusted OR			
No	157 (60.6%)	152 (60.1%)	OR=1
Yes	102 (39.3%)	101 (39.9%)	OR=1.00 (0.63 to 1.59)
Parent-child dysfunctional interaction subscale, mean (95% CI), adjusted mean difference	74.0 (68.3 to 79.7)	72.7 (65.8 to 79.6)	−0.02 (−6.16 to 6.12) p=0.99

Continued

Table 6 Continued

Outcome	Intervention arm n=257	Standard of care arm n=249	Measure of effect (95% CI)
Difficult child subscale percentile≥90%, n (%), adjusted OR			
No	203 (78.3%)	186 (73.5%)	OR=1
Yes	56 (21.6%)	67 (26.5%)	OR=0.79 (0.46 to 1.38) p=0.41
Difficult child subscale, mean (95% CI), adjusted mean difference	70.0 (65.5 to 74.5)	70.0 (66.0 to 73.2)	0.73 (–4.34 to 5.79) p=0.78
High EPDS, n (%), adjusted OR			
No	148 (60.2%)	134 (56.1%)	1
Yes	98 (39.8%)	105 (43.9%)	0.79 (0.50 to 1.25) p=0.32
High SSQ-8, n (%), adjusted OR			
No	144 (55.2%)	138 (54.6%)	1
Yes	117 (44.8%)	115 (45.5%)	0.90 (0.62 to 1.32) p=0.59
Household food security (HFIAS), n (%), adjusted OR			
Little to no hunger	196 (75.1%)	198 (78.3%)	1
Moderate-to-severe hunger	65 (24.9%)	55 (21.7%)	1.19 (0.62 to 2.26) p=0.52

BMI, body mass index; EPDS, Edinburgh Postnatal Depression Scale; HFIAS, Household Food Insecurity Access Scale; MUAC, mid-upper arm circumference; PSI-SF, Parental Stress Index Short Form; SSQ-8, 8-item Shona Symptoms Questionnaire.

those at risk for common mental disorders (44.8% vs 45.5%; aOR=0.90, 95% CI 0.62 to 1.32; p=0.59).

DISCUSSION

We undertook a pragmatic evaluation of a multicomponent group intervention combining sessions addressing early childhood stimulation and more general childcare with household economic strengthening to improve food security and economic barriers to clinic attendance. We aimed to improve global child development and retention in HIV care of infants born to HIV-positive mothers both by targeting these outcomes and some of their structural drivers. There was no effect of the intervention on global child development within 4.5 months of completing the intervention. HIV retention in care was almost universal in both arms of the trial by endline. Only 32% of those in the intervention arm were confirmed to have received the full intervention package. Participants reported high levels of food insecurity, symptoms of anxiety and depression and parenting stress at baseline, all factors which are likely to impede participation. The intervention had no effect on any of these secondary outcomes except parental distress. Of note, the intervention was evaluated in rural communities requiring some participants to travel considerable distances to attend sessions.

Although evidence from LMIC is limited, studies have demonstrated that ECS programmes targeting young children in these settings can improve global child development both in the short term and long term.[4 35] However, few have been delivered to HEU children. Many of these interventions have focused just on single interventions (such as nutrition, positive parenting practices) while this trial has looked at a more comprehensive package which addressed the wider structural barriers to early childhood development in addition to global chid development per se.

This intervention implemented by the Bantwana Initiative of World Education was innovative in seeking to reach groups of caregivers rather than individuals and combine ECS training with training on more general child care issues. In addition, the intervention aimed to strengthen household economic security through ISALS both to improve food security (and thereby nutritional status of the child) and reduce economic barriers to clinic attendance. In practice, uptake of the intervention was suboptimal possibly reflecting the acceptability of the intervention to some of the potential beneficiaries. Process evaluation suggested that using a group approach for mothers living with HIV was potentially stigmatising, in that some women feared participation might result in deductive disclosure within the community. The distance caregivers had to travel to take part in intervention sessions in some sites also undermined attendance. In addition, although the majority of women attended ISALS sessions relatively few opted to participate in the savings and lendings process perhaps reflecting their

reluctance to trust women in a group they were assigned to. Outside of the trial this intervention is offered to all mothers/caregivers of small children in a community and mothers are free to choose whether or not to join an ISALS and with whom. By evaluating the intervention we imposed artificial constraints on its delivery.

The trial occurred while the Zimbabwe Ministry of Health and Child Care and partners were strengthening prevention of mother to child transmission programmes. Option B+ was scaled up across Zimbabwe in 2014 and several studies have shown increasing engagement of mothers with services although engagement of infants in the care cascade has been less marked. Our findings suggest substantial improvements in knowledge of infant HIV status over the trial with knowledge of status near universal after 12 months in both arms. Reassuringly few children are HIV positive (3%) post-breast feeding, although among the few with HIV, a substantial proportion in both arms had a detectable viral load, implying suboptimal engagement with care. Over 90% of women in both arms were virologically suppressed, higher than among women living with HIV in Zimbabwe generally (86%).[36] This suggests that Zimbabwean mothers are optimally engaged in care and that our intervention could not substantially contribute to this.

There was some evidence of an intervention effect on parenting stress overall and distress specifically. However, the intervention did not affect risk of other common mental disorders. Of note, the intervention was not designed to address maternal mental health specifically. Caregivers in this trial had a high prevalence of risk of common mental disorder symptoms; around 50% of women were above the cut-off for mild postnatal depression at baseline and endline. Previous studies suggest that maternal depression negatively impacts both parenting and child development and this may have undermined our ability to demonstrate an impact. Future interventions may need to incorporate a specific mental health component. The treatment gap for mental health in much of Africa is extremely high community-based lay health worker problem-solving therapy, such as the Friendship Bench which has been widely scaled up in urban Zimbabwe presents a method of closing the gap. Implementation of an adapted Friendship Bench through primary health clinics in rural areas is currently being explored.

We assessed global child development using the Mullen ELC score which is widely used but not validated or normed among African children of this age. It is a complex instrument and despite comprehensive training and limiting the number of trained assessors our independent review of instrument implementation found that assessment of children was suboptimal. Of note though, the Mullen ELS has been successfully used elsewhere in Africa to determine the impact of a caregiver intervention after 12 months.[32] When compared with normative data (US-based), the baseline data on child development score ranges were comparable, but by 12 months follow-up the scores were lower than normative groups. All children in the study were, by definition, HIV-exposed and there is a solid evidence base that both HIV exposure and infection are associated with child development challenges.

Although there were no short-term effects on cognitive development for children, the fact that the endline data collection occurred a median of 4.5 months after intervention completion may be important. The child development benefit of parenting training may need more time to influence child development outcomes, particularly as the child stimulation components of the course were scheduled at the end of the package and the impact of reduced parental stress on parenting behaviours may take time to be observed.

Strengths of our study included that we piloted research and intervention components to optimise our implementation and evaluation approach. We ran a large trial and had a high retention rate (90%) over 12 months. The trial was conducted independently of programme implementers. We measured child development outcomes using assessors blinded to trial arm and undertook an independent validation of these measures. HIV retention in care was validated using biological markers. Mental health outcomes were all assessed using locally validated scales.

However, there are some limitations. By recruiting from the HIV-exposed infant registry, children who were not engaged in care were not included. This could have introduced some bias, excluding those least engaged in care and potentially most vulnerable. Measurement of global child development was suboptimal and we are uncertain as to what impact this has had on the global child development outcomes. However, we minimised number of Mullen ELC assessors and assessors determined outcomes in intervention and control arms. More time and resources for training and validation of assessment procedures was required. Programme uptake was measured using programme implementer data and the apparently low programme uptake may reflect incomplete data collection by lay facilitators rather than poor attendance. As outlined above, the intervention design was adapted to fit the constraints of the trial evaluation design which may have adversely affected outcomes. A shorter ECS programme may be more practical to implement. The nature of the intervention was ambitious both in complexity and duration. Our study suggests that fidelity to the lengthy programme may be a challenge, but that the intertwining of interventions was feasible. Single interventions may flounder when real-life complexity is not addressed. Parenting in poverty and the presence of HIV is a complex reality. Our hypothesis was that a multicomponent intervention which addresses both ECD and its structural drivers was feasible and acceptable to some; the data on attendance can serve as a guide to future intervention planning. HIV-specific interventions, even if they are not labelled as such, may be stigmatising and may hinder attendance.

Our trial has important implications for programmers and policy makers. Causes of poor child development in HIV-affected children are clearly multifactorial, but the feasibility and scalability of addressing multiple factors in a single multicomponent intervention is challenging. Given the high rates of poor mental health, effective community-based mental health interventions need to be scaled up beyond urban areas and potentially run alongside ECS interventions. Design and implementation of evaluations of real-world interventions face several challenges including fitting within donor funding cycles, limited by implementer priorities and political realities, all of which are crucial factors.

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Contributors LS and FMC led the trial design, with involvement from VS and HAW. FC and LS conceived and designed the study protocol. PN and FMC developed the intervention programme. FMC, RC, PN, RM and ZM led the trial implementation, data collection and process evaluation. AMR carried out the statistical analysis. VS and HAW oversaw trial analysis and data interpretation. LS and FMC led data interpretation with involvement from HAW, VS, AMR, HM, RC and ZM. HM, LS and FMC wrote the paper and all authors were involved in the review of drafts. All authors have approved the final manuscript.

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