Effect of a differentiated service delivery model on virological failure in adolescents with HIV in Zimbabwe (Zvandiri): a cluster-randomised controlled trial

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Summary

Background Adolescents living with HIV face challenges to their wellbeing and antiretroviral therapy adherence and have poor treatment outcomes. We aimed to evaluate a peer-led differentiated service delivery intervention on HIV clinical and psychosocial outcomes among adolescents with HIV in Zimbabwe.

Methods 16 public primary care facilities (clusters) in two rural districts in Zimbabwe (Bindura and Shamva) were randomly assigned (1:1) to provide enhanced HIV care support (the Zvandiri intervention group) or standard HIV care (the control group) to adolescents (aged 13–19 years) with HIV. Eligible clinics had at least 20 adolescents in pre-ART or ART registers and were geographically separated by at least 10 km to minimise contamination. Adolescents were eligible for inclusion if they were living with HIV, registered for HIV care at one of the trial clinics, and either starting or already on ART. Exclusion criteria were being too physically unwell to attend clinic (bedridden), psychotic, or unable to give informed assent or consent. Adolescents with HIV at all clinics received adherence support through adult counsellors. At intervention clinics, adolescents with HIV were assigned a community adolescent treatment supporter, attended a monthly support group, and received text messages, calls, home visits, and clinic-based counselling. Implementation intensity was differentiated according to each adolescent's HIV vulnerability, which was reassessed every 3 months. Caregivers were invited to a support group. The primary outcome was the proportion of adolescents who had died or had a viral load of at least 1000 copies per µL after 96 weeks. In-depth qualitative data were collected and analysed thematically. The trial is registered with Pan African Clinical Trial Registry, number PACTR201609001767322.

Findings Between Aug 15, 2016, and March 31, 2017, 500 adolescents with HIV were enrolled, of whom four were excluded after group assignment owing to testing HIV negative. Of the remaining 496 adolescents, 212 were recruited at Zvandiri intervention sites and 284 at control sites. At enrolment, the median age was 15 years (IQR 14–17), 52% of adolescents were female, 81% were orphans, and 47% had a viral load of at least 1000 copies per µL. 479 (97%) had primary outcome data at endline, including 28 who died. At 96 weeks, 52 (25%) of 209 adolescents in the Zvandiri intervention group and 97 (36%) of 270 adolescents in the control group had an HIV viral load of at least 1000 copies per µL or had died (adjusted prevalence ratio 0·58, 95% CI 0·36–0·94; p=0·03). Qualitative data suggested that the multiple intervention components acted synergistically to improve the relational context in which adolescents with HIV live, supporting their improved adherence. No adverse events were judged to be related to study procedures. Severe adverse events were 28 deaths (17 in the Zvandiri intervention group, 11 in the control group) and 57 admissions to hospital (20 in the Zvandiri intervention group, 37 in the control group).

Interpretation Peer-supported community-based differentiated service delivery can substantially improve HIV virological suppression in adolescents with HIV and should be scaled up to reduce their high rates of morbidity and mortality.

Funding Positive Action for Adolescents Program, ViiV Healthcare.

Lancet Glob Health 2020; 8: e264–75

Published Online January 7, 2020 https://doi.org/10.1016/S2214-109X(19)30526-1

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Introduction

The number of adolescents (aged 10–19 years) with HIV globally is growing as more perinatally-infected children survive into adolescence.[1–3] Adolescents have the highest rates of attrition from HIV treatment and care of any age group, resulting in higher rates of treatment failure, morbidity, and mortality compared with children and adults.[3–6] In sub-Saharan Africa, which is home to 85% of adolescents with HIV globally, adolescents are the only population with increasing mortality rates.[1–3,7] Of particular concern are combined data from east and southern African countries showing that only 45% of adolescent girls living with HIV are virologically suppressed (versus the goal of 73% under UNAIDS 90-90-90 targets for 2020),[8] making them more vulnerable to treatment failure and progression to

Research in context

Evidence before this study

Adolescents have the highest rates of attrition from HIV treatment and care of any age group, resulting in higher rates of treatment failure, morbidity, and mortality than that of children and adults. We searched PubMed for articles published in English between database inception and July 31, 2019, using the search terms: "HIV" AND "adolescents" OR "youth" AND "HIV treatment" AND "adherence" OR "retention". Systematic reviews of interventions to improve ART adherence and retention in care among adolescents with HIV have identified specific interventions that show promise, such as individual and group education and counselling, financial incentives, youth-friendly clinic services, and increased accessibility to clinics. However, these reviews also highlight the need for additional studies in this subgroup. To date, only two trials have shown an intervention to be effective against virological outcomes among populations with HIV in low-income and middle-income countries in general and adolescents with HIV, specifically.

Added value of this study

To our knowledge, this is the first youth-led cluster-randomised trial of a multicomponent differentiated service delivery intervention focusing on adolescents' HIV-related and psychosocial outcomes. This study adds to the scant evidence base for comprehensive interventions for adolescents with HIV—a group with disproportionately poor HIV treatment outcomes. Notably, our qualitative data highlight the importance of improving the broader relational context in which adolescents with HIV live in order to support their adherence and retention in care.

Implications of all the available evidence

This study adds to the growing body of evidence to support WHO's recommendations for comprehensive, differentiated service delivery interventions to support ART adherence and retention in care. Our study evaluated the Zvandiri programme as delivered in a real-world and resource-constrained setting, suggesting the Zvandiri intervention can be feasibly implemented in similar settings. Our cost analysis suggests incorporating the Zvandiri intervention into current standard of care would increase the cost of providing HIV treatment to adolescents with HIV in the short term. Policy makers might need to invest in these higher costs to avert the health and economic consequences of not achieving viral suppression in a population likely to require several decades of ART, and in a setting with a scarce number of alternative and more costly drugs.

expensive second-line and third-line regimens than other age groups.

For more on the **Zvandiri programme** see https://www.africaid-zvandiri.org/

WHO recommends antiretroviral therapy (ART) for all individuals with HIV, irrespective of disease stage or CD4-positive T-cell count.[9] For adolescents, WHO additionally recommends community-based interventions to support ART adherence and retention in care, while acknowledging that the evidence to support this recommendation is weak.[9] Few studies have rigorously explored the effectiveness of community-based programmes to improve the wellbeing and longevity of adolescents with HIV, and the current pace of intervention research remains inadequate to their needs.[1–3,10] Systematic reviews highlight the small number of studies done among adolescents with HIV, despite this being the age group that is in greatest need of interventions to support their wellbeing, adherence, and retention in care; these reviews recommend prioritisation of further intervention studies with adolescents.[1,10–12]

Optimisation of the public health impact of ART among adolescents with HIV will require scalable, effective, and cost-effective strategies that provide differentiated support for adolescents with HIV to maximise their wellbeing and facilitate their engagement with treatment and care. Differentiated service delivery has the potential to optimise the effects of ART among vulnerable and key populations.[1,13,14] Differentiated service delivery models simplify and decentralise HIV care by adapting services across the care cascade to the preferences and expectations of different subpopulations of people living with HIV.[14]

The Zvandiri (meaning "As I am" in Shona) programme, which was recommended in 2013 by WHO as a best practice programme,[15] is a theoretically grounded, multicomponent differentiated service delivery model for children, adolescents, and young people with HIV.[16] Zvandiri aims to directly improve the wellbeing of this population and strengthen their engagement with services across the HIV prevention and care cascades.[16] In this cluster-randomised trial, we aimed to evaluate the effectiveness and cost of the Zvandiri programme in relation to clinical and psychosocial outcomes among adolescents with HIV in Zimbabwe.

Methods

Study design and participants

The trial design has been described in detail elsewhere.[7] Briefly, we did a cluster-randomised controlled trial in public clinics in two rural districts (Bindura and Shamva) in Mashonaland Central province, Zimbabwe. Districts were selected in consultation with the Ministry of Health and Child Care in June, 2015, when it was estimated that ART coverage among adolescents with HIV in these districts was the lowest in Zimbabwe (about 29%).

Clinics were eligible for inclusion if they were public primary care facilities and had at least 20 adolescents in pre-ART or ART registers. Eligible clinics were geographically separated by at least 10 km to minimise

contamination. Adolescents were eligible for inclusion if they were living with HIV, registered for HIV care at one of the trial clinics, aged 13–19 years, either starting or already on ART, able to provide informed assent, and their caregiver was able to provide informed consent (those aged 18–19 years did not need caregiver consent). Exclusion criteria were being too physically unwell to attend clinic (bedridden), psychotic, or unable to give informed assent or consent. At each clinic, a list of potentially eligible participants was generated from the pre-ART or ART registers and selected village health workers were asked to contact adolescents with HIV after receiving training on trial objectives, procedures, and importance of maintaining confidentiality.

Ethics approval was granted by the Medical Research Council of Zimbabwe and the ethics committees of the London School of Hygiene & Tropical Medicine (London, UK) and University College London (London, UK). Written informed consent from guardians and age-appropriate assent from participants were obtained before enrolment.

Randomisation and masking

Public clinics were the unit of randomisation. Clinics were randomly assigned (1:1) to receive either enhanced ART adherence support through the Zvandiri programme (the Zvandiri intervention group) or standard of HIV care (the control group). Imbalance between the groups was reduced by matching on district and by using restricted randomisation to minimise imbalance in clinic size (difference in mean clinic size ≤10). For randomisation, we used random-number tables generated in Stata by an independent statistician. The data manager had sole access to the password-protected randomisation file. A public randomisation meeting was held on July 5, 2016.

It was not possible to mask intervention status from the field research team, but laboratory staff who assessed the primary outcome were unaware of intervention status. In addition, statisticians undertaking analyses were masked to allocation. We used non-site specific study ID numbers on all laboratory and data collection forms to maintain masking.

Procedures

At enrolment, all participants completed a questionnaire using interviewer-administered, computer-assisted personal interviews lasting about 60 min. Sensitive questions were self-administered using an audio-computer-assisted survey instrument. Questionnaire domains included sociodemographic, socioeconomic, medical history (including history of opportunistic infections and admission to hospital), HIV testing and history of ART use, information on clinic attendances, adherence, and psychological wellbeing. On completion of the questionnaire, all participants were asked to provide a finger-prick blood spot sample for HIV viral load testing and to undergo a clinical examination to assess WHO stage. All viral load test results were returned to the clinic within 3 months (standard turnaround time) to guide clinical care in the Zvandiri intervention and control groups. Participants were assessed by the research team, in addition to their routine clinic visits, after weeks 42–60 and 96. At the follow-up visits, participants completed another questionnaire (shorter than the previous one) that covered the same topics as the first, had a blood spot sample taken for viral load testing, and had a physical examination to allow clinical staging. Programme data were collected in the communities receiving the Zvandiri intervention and regularly compiled to record uptake and attendance at community intervention and use of clinical services.

All eligible adolescents attending clinics received ART and adherence support, as set out in the Ministry of Health and Child Care guidelines.[17] For participants in the control group, adherence support was provided by adult counsellors and nursing staff. After ART initiation, these participants were seen every 3 months, with CD4 monitoring every 6 months. Prescription refills, pill counts, and consultations with clinical staff were used to measure adherence.

Participants in the Zvandiri intervention group received standard care, as determined by the Ministry of Health and Child Care, plus the Zvandiri intervention. Details of the Zvandiri intervention have been published previously.[7,16] Briefly, up to three trained and supported peer counsellors (community adolescent treatment supporters [colloquially known as CATS] who are adolescents with HIV aged 18–24 years) at each clinic provided adherence counselling and support at clinic visits and through ongoing individualised community-based support. All community adolescent treatment supporters attended a weekly supervision meeting at the clinic with a designated nurse and provided each other with peer-to-peer support (through a Whatsapp group and via Skype) with oversight from a Zvandiri mentor in the district. Up to ten trial participants were allocated to a designated community adolescent treatment supporter according to their residential area and were followed up through text messages, phone calls, home visits, and during their clinic reviews. The type and frequency of contact was determined following assessment of their individual situation (ie, whether they were considered stable so in need of standard support, or in need of enhanced support).

Adolescents with a viral load of less than 1000 copies per µL or a most recent (and within the past 6 months) CD4 count of at least 200 cells per µL, or both, and recorded attendance at all scheduled clinic visits in the past 3 months were offered Zvandiri standard care (ie, a home visit once a month, plus a weekly, individualised text message). The text message was sent by the community adolescent treatment supporters and focused on

motivational reminders related to adherence, attendance at clinic and support groups, and encouragement to contact the community adolescent treatment supporters if any problems arose. An additional home visit was done if an adolescent missed a scheduled clinic appointment or support group meeting.

Adolescents with a viral load of at least 1000 copies per µL or CD4 count of less than 200 cells per µL, or both, who were at risk of common mental disorders or a major depressive disorder, had not attended one or more scheduled clinic visits in the past 3 months, had started ART in the past 3 months, who were pregnant, or had other psychosocial challenges or protection issues were offered Zvandiri enhanced care. This care involved two home visits a week, plus weekly phone calls and daily text messages. During the home visit, the community adolescent treatment supporters did an adherence assessment and gave adherence counselling, as appropriate. A community health nurse or case care worker, or both, accompanied the community adolescent treatment supporters where possible. If adolescents required more than two home visits a week (owing to child protection needs, depression, or ill health), the third visit (and onwards) of the week was done by community adolescent treatment supporters with the caregiver present.

Adolescents were allocated to the appropriate intervention level (standard or enhanced care) at enrolment and reassessed every 3 months by community adolescent treatment supporters in conjunction with clinic nurses. Adolescents were moved between levels of intervention support as indicated by clinic attendance and other clinical or psychosocial factors (table 1). All participants in the Zvandiri intervention group were invited to a monthly support group, facilitated by a support group leader (a volunteer nurse, teacher, or social worker) in conjunction with the community adolescent treatment supporters, with supervision from the Zvandiri mentor. A standardised curriculum was used, focusing on improving health and treatment literacy, HIV disclosure, resilience and coping strategies, sexual and reproductive health, social networks, and awareness of, and linkages to, services as required. Adolescents identified as being at risk of harm were immediately referred to the Zvandiri Intervention Coordinator or clinic nurse for mental health services or management with the Department of Social Services, or both.

Caregivers of adolescents in the Zvandiri intervention group were invited to a 12-session caregiver support group, facilitated by the Zvandiri mentor and community adolescent treatment supporters. Sessions were in Shona, the beneficiaries' language, and focused on improving caregivers' knowledge, skills, and confidence of HIV and treatment literacy, communication and parenting, and available support services. Sessions were planned to be held each month, with each session lasting up to 2 h.

Process evaluation

As part of a process evaluation of the Zvandiri intervention, we did in-depth interviews between June 1, 2017, and Dec 21, 2018, with 54 trial participants (32 female participants, 22 male participants), 34 caregivers (24 women, ten men), 15 health-care workers (13 women, two men), nine support group leaders (three women, six men), and 18 community adolescent treatment supporters (six female supporters, 12 male supporters). We observed 11 support groups meetings, 18 community adolescent treatment supporters' coordination meetings, and eight caregiver information sessions. We sought to understand from multiple perspectives the context of young people's lives (including the community adolescent treatment supporters), their experiences, and their support needs. Iterative qualitative data collection and analysis informed a grounded thematic analytical approach.

Cost analysis

We used standard costing guidelines[18] to estimate the annual cost per adolescent treated on ART and cost per adolescent virally suppressed on ART through the Zvandiri intervention and control clinics. Cost estimates included staff salaries and training, drugs and other consumables, equipment, and overheads. We also did a sensitivity analysis of scenarios in which salaries were public sector-based, start-up costs were excluded, and the two Zvandiri mentors supervised the total number of

	Control group	Standard Zvandiri intervention support	Enhanced Zvandiri intervention support
Eligibility criteria	All eligible	A viral load of <1000 copies per µL in the past 6 months; CD4 count ≥200 cells per µL in the past 6 months; attending all scheduled clinic visits in the past 3 months; psychologically stable; and safe	Commencing ART or switching regimens in the past 3 months; a viral load of ≥1000 copies per µL in the past 6 months; CD4 count <200 cells per µL in the past 6 months; pregnant or breastfeeding; failing to attend at least one scheduled clinic visit in the past 3 months; psychologically distressed; and abused or neglected
Intervention	Adherence support provided by adult counsellors and nursing staff; after ART initiation, participants seen every 3 months, with CD4 monitoring at 6 monthly intervals; and prescription refills, pill counts and consultations with clinical staff used to measure adherence	Monthly support group; monthly home visit; weekly text message reminder; clinic contact; and caregiver workshop	Monthly support group; two home visits a week; daily text message reminder; weekly phone calls; clinic contact; caregiver workshop; referral and linkages; and community outreach visits with other community cadres

ART=antiretroviral therapy.

Table 1: **Intervention components and levels of intervention support**

clinics within their two districts, rather than just the eight per district in our trial. A full description of the costing methods is listed in the appendix (pp 28–29).

Outcomes

The primary outcome, assessed in the modified intention-to-treat population (ie, excluding enrolled participants who were later found to be HIV-negative), was the proportion of participants who had died or had virological failure (defined by an HIV-1 viral load of ≥1000 copies per µL at 96 weeks [window period for inclusion: 88–104 weeks]) after enrolment. HIV viral load was assessed using blood spot samples, which were air dried on filter papers and stored at room temperature until they were taken every week to the Flowcytometry Laboratory (Harare, Zimbabwe). Viral load testing of HIV1 RNA was done via PCR using the NucliSENS EasyQ Director (bioMerieux; Marcy L'Etoile, France).

See Online for appendix

The five secondary outcomes were the proportion of participants who were not retained in clinic services, stratified according to the WHO definition of retention in HIV care;[19] who had discontinued ART (defined as completely stopping taking drugs for at least 3 months), as documented in clinic records; who had depression,

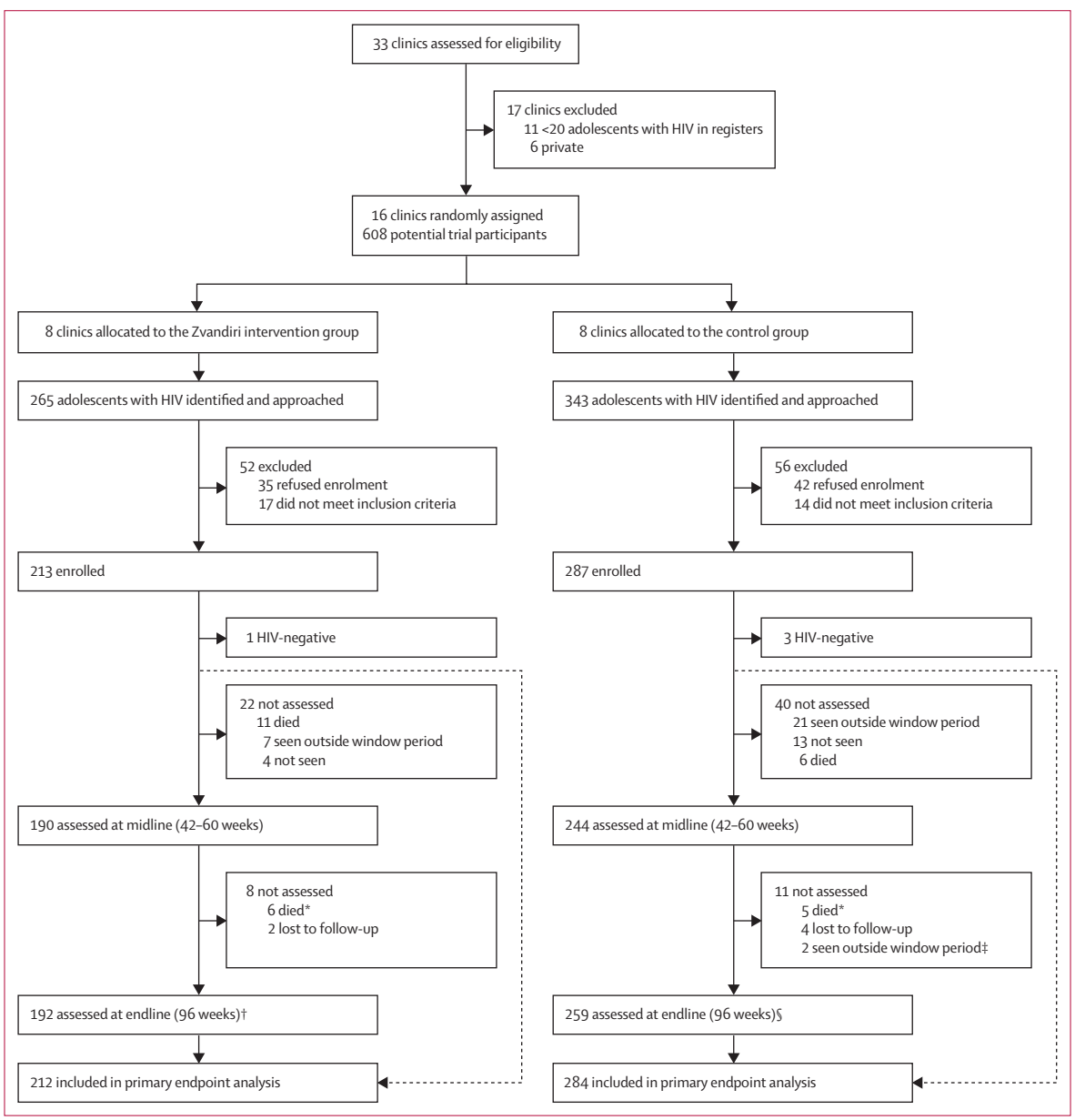

Figure 1: **Trial profile**

*Includes one participant who was not seen at midline. †Includes nine participants who were not seen at midline. ‡Includes one participant who was seen outside of the window period at midline. §Includes 24 participants who were not seen at midline.

	Zvandiri group (n=212)	Control group (n=284)
Sex		
Female	119 (56%)	138 (49%)
Male	93 (44%)	146 (51%)
Age group, years		
13–14	81 (38%)	110 (39%)
15–16	59 (28%)	86 (30%)
17–19	72 (34%)	88 (31%)
Currently in school		
No	133 (63%)	198 (70%)
Yes	79 (37%)	86 (30%)
Orphanhood status		
Not orphan	36 (17%)	54 (19%)
Maternal	49 (23%)	56 (20%)
Paternal	38 (18%)	61 (21%)
Both	84 (40%)	108 (38%)
Data missing	5 (2%)	5 (2%)
Number of children in household		
≤1	63 (30%)	77 (27%)
2	56 (26%)	72 (25%)
3	43 (20%)	54 (19%)
≥4	50 (24%)	81 (29%)
Caregiver attitude*		
Positive	183 (86%)	232 (82%)
Negative	29 (14%)	52 (18%)
Disclosed HIV status		
Yes	55 (30%)	81 (34%)
No or do not know	130 (70%)	159 (66%)
Data missing	27 (13%)	44 (15%)
Stigma		
0–1	76 (36%)	85 (30%)
>1	136 (64%)	199 (70%)
Mean SSQ-14 score (SD)	3·99 (3·37)	4·73 (3·60)
SSQ-14 score		
<8	174 (82%)	221 (78%)
≥8	38 (18%)	63 (22%)
Mean PHQ-9 score (SD)	3·15 (3·11)	3·77 (3·71)
PHQ-9 score		
<8	191 (90%)	242 (85%)
≥8	21 (10%)	42 (15%)
HIV viral load		
Undetectable	55 (26%)	86 (30%)
<1000 copies per µL	54 (25%)	69 (24%)
≥1000 copies per µL	103 (49%)	129 (45%)
(Table 2 continues in next column)		

	Zvandiri group (n=212)	Control group (n=284)
(Continued from previous column)		
Duration on ART		
Not on ART at enrolment	15 (7%)	16 (6%)
<2 years	55 (26%)	60 (21%)
2–3 years	52 (26%)	58 (20%)
4–7 years	75 (37%)	128 (45%)
≥8 years	6 (3%)	17 (6%)
Data missing	8 (4%)	6 (2%)
Median CD4 count at ART initiation (IQR)	281 (232–319)	307 (251–324)

Data are n (%) unless otherwise specified. *Assessed via a positive or negative response to each of the following: my caregiver spoke or speaks to me with a warm and friendly voice; my caregiver seemed or seems emotionally cold to me; my caregiver appeared or appears to understand my problems and worries; my caregiver enjoyed or enjoys talking things over with me; my caregiver made or makes me feel better when I am upset; my caregiver did not or does not talk to me when I was or am upset.

Table 2: **Baseline characteristics, modified intention-to-treat population (n=496)**

defined as scoring at least 10 out of 27 on the Patient Health Questionnaire (PHQ-9);[20] who were at risk of common mental disorders (depression, anxiety, or both), defined as scoring at least 8 out of 14 on the Shona Symptom Questionnaire (SSQ-14);[21] and who had poor quality of life, as measured on the European Quality of Life-5 Dimensions (EQ-5D) scale (which has been previously validated in Zimbabwe).[22] Secondary outcomes were assessed at midline (42–60 weeks) and endline (96 weeks) in the modified intention-to-treat population.

Two exploratory outcomes were the proportion of participants with onward HIV status disclosure and with perceived stigma measured using the HIV/AIDS Stigma Instrument-People living with AIDS (HASI-P).[23]

Severe adverse events (deaths and admissions to hospital) were recorded and reported by type and study group. For all deaths, we used verbal autopsy to determine cause of death. Other, non-severe, adverse events were reported similiarly.

Statistical analysis

In 16 clusters, the sample size of 500 participants provided 80% power to detect a difference in detectable viral load of 35% among participants in the standard care group versus 18% in the Zvandiri intervention group, assuming 20% loss to follow-up and a coefficient of variation (k) between clusters of 0·25, using the sample size formula for cluster randomised trials as outlined by Hayes and Moulton.[24] For secondary outcomes, the trial had 90% power to detect, for example, a difference in non-complete attendance of 26% in the standard care group versus 10% in the Zvandiri intervention group, and 80% power to detect a difference in mean SSQ-14 score of 7·4 (SD 3·74) in the control group and 4·8 (3·74) in the Zvandiri intervention group. Our alpha level was 0·05.

The primary analyses were done in a complete case manner in the modified-intention-to-treat population. Cluster-level summary measures were used owing to the small number of clusters per group.[24] For binary outcomes, the effect was estimated by the prevalence

ratio (PR). Stratum (district)-specific PRs were estimated as the ratio of the geometric mean prevalence between groups for each of the two strata, and the overall PR was estimated as the weighted average of these stratum-specific PRs. An approximate variance for the log (mean prevalence) in each group was estimated from the residual mean square from a two-way analysis of variance of community log-prevalence on strata and group. For outcomes with zero events in at least one cluster,[24] PR was estimated as the ratio of the arithmetic mean prevalence between groups, with variance estimated from analysis of variance of prevalence on strata and groups. A 95% CI for the PR was estimated from this variance using a stratified *t* test with 14 degrees of freedom. For continuous outcomes, the measure of effect was the mean difference between groups, analysed in an analogous method based on mean scores in each facility.

Secondary analyses examined effect modification by baseline viral load, age group, sex, duration on treatment, SSQ-14 score, and PHQ-9 score.[25] Predefined analyses included adjustment for baseline viral load and other variables that were imbalanced at baseline. We did sensitivity analyses to investigate the effect of missing data by using multiple imputation, analysed using an individual level logistic regression model, allowing for within-cluster correlation using fixed effects.

We used STATA software (version 15.0; StatCorp, College Station, TX, USA) for all analyses. A data safety and monitoring board oversaw the study and was responsible for assessing data quality, protocol compliance (participants and investigators), and frequency of adverse events among participants. Details of protocol amendments are included in the appendix (p 9).

This trial is registered with the Pan African Clinical Trial Registry, number PACTR201609001767322.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

In July, 2016, we identified 33 clinics in the two trial districts. Of the 33 clinics, 11 were excluded from the trial because they served fewer than 20 adolescents with HIV and six were private clinics. The remaining 16 primary care clinics were randomly assigned (1:1) to deliver either standard of HIV care plus Zvandiri (the Zvandiri intervention group) or standard of HIV care only (the control group).

Between Aug 15, 2016, and March 31, 2017, 608 adolescents (aged 13–19 years) with HIV from the 16 clinics were identified and approached. Of these, 77 (13%) refused enrolment and 31 (5%) were ineligible, leaving 500 (82%) enrolled into the trial. Four (<1%) of the 500 participants had their data excluded from final analyses after repeat testing using several assays showed that they were HIV negative. 212 adolescents were enrolled in the Zvandiri intervention group and 284 in the control group (figure 1).

At enrolment, the median age of participants was 15 years (IQR 14–17), 52% of adolescents were female, 81% were orphans, 47% had a viral load of at least 1000 copies per µL, and 68% had not disclosed their HIV status to anyone other than health-care staff or caregivers (table 2). There was some imbalance between groups at enrolment, with participants in the Zvandiri intervention group more likely to be female, older, not in school, with a more positive caregiver attitude, less likely to have experienced stigma or to have common mental disorders or depression, more likely to have an unsuppressed viral

	Zvandiri group	Control group	Unadjusted PR or mean difference (95% CI)	Adjusted PR or mean difference (95% CI)*	p value
Primary outcome					
HIV viral load ≥1000 copies per µL or death	22% (52/209)	36% (97/270)	0·61 (0·38 to 0·97)	0·58 (0·36 to 0·94)	0·03
Secondary outcomes					
Discontinuation of ART for ≥3 months†	7% 16/209)	11% (30/270)	0·64 (0·28 to 1·48)	0·68 (0·23 to 1·99)	0·45
Attended <80% of scheduled visits†	13% (28/207)	15% (39/269)	0·83 (0·38 to 1·82)	0·80 (0·32 to 2·02)	0·62
SSQ-14 score ≥8	27% (60/192)	35% (86/259)	0·79 (0·52 to 1·19)	0·86 (0·60 to 1·23)	0·35
PHQ-9 score ≥8†	10% (22/192)	16% (38/259)	0·69 (0·32 to 1·48)	0·80 (0·38 to 1·69)	0·53
Mean SSQ-14 score	5·42 (0·42)	5·90 (0·55)	–0·48 (–2·06 to 1·10)	–0·31 (–1·70 to 1·08)	0·64
Mean EQ-5D Index	0·91 (0·01)	0·92 (0·01)	0·00 (–0·04 to 0·03)	–0·01 (–0·04 to 0·03)	0·65
Exploratory outcomes					
No onward disclosure	62% (134/192)	65% (172/259)	0·96 (0·83 to 1·11)	1·00 (0·85 to 1·18)	0·98
HASI-P stigma index >1	43% (90/192)	43% (119/259)	0·99 (0·79 to 1·22)	1·06 (0·85 to 1·31)	0·56

Data are % (n/N) or mean (SE). % refers to geometric mean of the cluster-level proportions. ART=antiretroviral therapy. EQ-5D=European Quality of Life-5 Dimensions. HASI-P=HIV/AIDS Stigma Instrument-People living with AIDS. PHQ= Patient Health Questionnaire. PR=prevalence ratio. SSQ=Shona Symptom Questionnaire. *Adjusted for district, age, sex, being in school, baseline viral load, and baseline SSQ-14 plus PHQ-9 scores. †Estimated using arithmetic means owing to at least one cluster with zero outcomes.

Table 3: **Effect of the intervention at endline (96 weeks), modified intention-to-treat population (n=496)**

load, and with a shorter duration on ART. Age, sex, being in school, baseline viral load, and baseline SSQ-14 and PHQ-9 scores were adjusted for in all subsequent analyses.

Of the 496 eligible participants enrolled, 479 (97%) had primary outcome data at endline, including 28 participants who died (17 in the Zvandiri intervention group, 11 in the control group). 14 (5%) participants in the control group and three (1%) in the Zvandiri intervention group did not complete 96 weeks of follow-up within the 8-week assessment period (ie, 88–104 weeks). Process evaluation data suggested that two of the three participants in the Zvandiri intervention group who were lost to follow-up had relocated but continued to receive HIV care. The other participant, who had not disclosed her HIV status to her partner, discontinued the study owing to fear of unintentional disclosure.

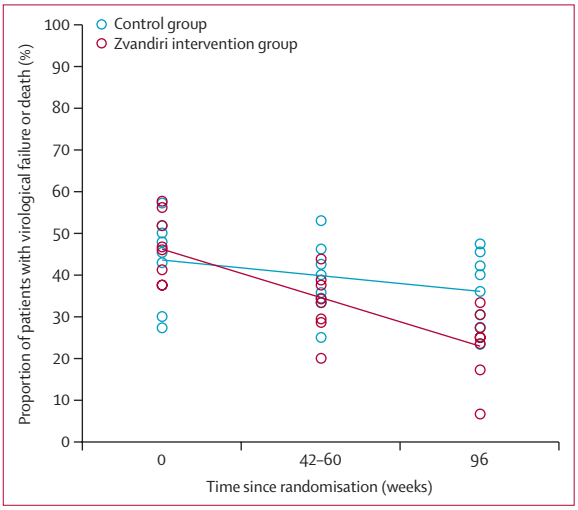

Figure 2: **Proportion of patients reaching the primary outcome during follow-up**

Virological failure or death at endline was less common in the Zvandiri intervention group than in the control group (adjusted PR 0·58, 95% CI 0·36–0·94; p=0·03; table 3, figure 2). The Zvandiri intervention had a favourable effect on all secondary outcomes at endline, but the differences were not significant. The exploratory outcomes did not differ between the two groups (table 3).

There was some evidence of an intervention effect on the primary outcome at midline (adjusted PR 0·84, 95% CI 0·64–1·10; p=0·17); the effect was stronger (0·80, 0·64–1·03; p=0·07) when deaths in the first 3 months after enrolment were excluded (specified as a sensitivity analysis in the analysis plan; table 4). There was also some evidence of an intervention effect on PHQ-9 score at midline (adjusted PR 0·55, 95% CI 0·30–1·03; p=0·06), but not on other secondary outcomes (table 4). There were stronger intervention effects at 96 weeks in participants aged 13–16 years than in those aged 17–19 years, although the effect modification was not significant (table 5). The results for the multiple imputation analysis were similar to the complete case analysis (adjusted PR 0·66, 95% CI 0·51–0·85; p=0·001; data not shown). The coefficient of variation was k=0·24 for the Zvandiri intervention group and k=0·35 for the control group. Adjusted risk differences and the effects on viral load and death separately are shown in the appendix (pp 26–27).

Process evaluation data suggested that the Zvandiri intervention improved the quality of adolescents' lives through a focus on shared experiences, role modelling, and supportive friendship (community adolescent treatment supporters' visits and support group). Their own and their caregivers' HIV and treatment literacy was also improved (via support groups, community adolescent treatment supporters' visits, and caregiver workshops) which, in tandem, enabled adolescents to better manage adherence and build their self-esteem. Adolescents with HIV described the transformative effect of a more

	Zvandiri group	Control group	Unadjusted PR or mean difference (95% CI)	Adjusted PR or mean difference (95% CI)	p value
Primary outcome					
HIV viral load of ≥1000 copies per µL or death	32% (68/201)	38% (98/250)	0·86 (0·66 to 1·11)	0·84 (0·64 to 1·10)	0·17
HIV viral load of ≥1000 copies per µL or death*	31% (65/198)	37% (97/249)	0·83 (0·65 to 1·05)	0·80 (0·64 to 1·03)	0·07
Secondary outcomes					
SSQ-14 score ≥8	33% (70/190)	41% (98/244)	0·82 (0·54 to 1·24)	0·90 (0·61 to 1·31)	0·52
PHQ-9 score ≥8	11% (27/190)	23% (53/244)	0·48 (0·24 to 0·97)	0·55 (0·30 to 1·03)	0·06
Mean SSQ-14 score	6·08 (0·34)	6·91 (0·74)	–0·82 (–2·58 to 0·93)	–0·71 (–2·13 to 0·72)	0·30
Mean EQ-5D Index	0·86 (0·01)	0·84 (0·02)	0·02 (–0·02 to 0·07)	0·02 (–0·02 to 0·06)	0·27
Exploratory outcomes					
No onward disclosure	61% (126/190)	66% (162/244)	0·93 (0·78 to 1·11)	1·00 (0·88 to 1·14)	0·99
HASI-P stigma index >1	55% (111/190)	62% (152/244)	0·89 (0·70 to 1·12)	0·92 (0·74 to 1·16)	0·44

Data are % (n/N) or mean (SE). % refers to geometric mean of the cluster-level proportions. EQ-5D=European Quality of Life-5 Dimensions. HASI-P=HIV/AIDS Stigma Instrument-People living with AIDS. PHQ=Patient Health Questionnaire. PR=prevalence ratio. SSQ=Shona Symptom Questionnaire. *Excluding four deaths in the first 3 months.

Table 4: **Effect of the intervention at midline (42–60 weeks), modified intention-to-treat population (n=496)**

sympathetic household environment, where caregivers, benefitting from the workshops, were better educated about the low transmission risk of HIV in ordinary daily activities and were more responsive in meeting the nutritional and physical needs of adolescents with HIV. These changes were experienced by adolescents with HIV as being better cared for and more cared about. Adolescents described the Zvandiri intervention as a way of relieving their sense of isolation and reducing their fear of the present and future implications of their HIV status. Community adolescent treatment supporters were hosted within local clinics and, over time, this situation influenced the attitudes of health-care workers towards adolescents with HIV, which was reported by health-care workers, community adolescent treatment supporters, adolescents with HIV, and caregivers to create a more open and receptive environment in which to seek care and support. The text messages, alongside the other support provided by the community adolescent treatment supporters, provided practical reminders that improved the capacity of adolescents with HIV to habituate treatment adherence.

The total annual cost per adolescent treated with ART was US$997·00 through the Zvandiri intervention clinics and $163·17 through control clinics (table 6). The annual cost per virally suppressed adolescent on ART was $1340·00 for the Zvandiri intervention clinics and $450·36 for the control clinics. Across all clinics, personnel costs accounted for the largest proportion of the total cost.

Our predefined sensitivity analyses, which assessed scenarios where salaries were public sector-based, start-up costs were excluded, and the two Zvandiri mentors supervised more clinics located within their two districts (22 for Bindura and 16 for Shamva) than the eight in our trial (thus taking the programme to scale across the district), showed that costs were reduced to $602·85 per adolescent treated with ART and $810·00 per virally suppressed adolescent (appendix p 29). Other input parameters, such as discount rate, life of vehicles and equipment, prices of supplies, and building utilities, had little effect on cost (appendix pp 28–29).

Regarding severe adverse events, there were 28 deaths (17 in the Zvandiri intervention group, 11 in the control group) and 57 admissions to hospital (20 in the Zvandiri intervention group, 37 in the control group). We did not collect robust data on non-severe adverse events. Verbal autopsy findings suggested that six (35%) of 17 deaths in the Zvandiri intervention group and eight (73%) of 11 deaths in control group were due to cessation of ART sanctioned by caregivers and were probably motivated by faith healing. No adverse events were judged by the Medical Research Council of Zimbabwe or data safety and monitoring board to be related to study procedures.

	Zvandiri group	Control group	Adjusted PR (95% CI)	p value	$p_{interaction}$
Baseline viral load					
<1000 copies per μL	10% (11/108)	12% (18/146)	0·57 (0·23–1·42)	0·20	0·61
≥1000 copies per μL	35% (41/101)	67% (79/124)	0·56 (0·39–0·82)	0·01	..
Sex					
Female	22% (24/118)	33% (41/129)	0·69 (0·39–1·22)	0·18	0·83
Male	31% (28/91)	39% (56/141)	0·68 (0·48–0·97)	0·04	..
Age, years					
13–16	20% (31/139)	40% (69/187)	0·51 (0·29–0·90)	0·02	0·12
17–19	29% (21/70)	27% (28/83)	1·00 (0·45–2·21)	1·00	..
Duration on antiretroviral therapy, years					
<2	31% (3/21)	56% (17/39)	0·81 (0·37–1·79)	0·55	0·43
≥2	25% (35/134)	37% (73/196)	0·64 (0·45–0·93)	0·02	..

Data are % (n/N) unless otherwise specified. % refers to geometric mean of the cluster-level proportions. PR=prevalence ratio.

Table 5: **Effect modification of selected baseline characteristics on the primary outcome at endline (96 weeks), modified intention-to-treat population (n=496)**

	Zvandiri intervention clinics		Control clinics	
	Cost	Percentage of total cost	Total cost	Percentage of total cost
ART treatment costs				
Capital costs				
Buildings and storage	$1223·43	1%	$1223·43	2%
Equipment	$1001·93	0%	$1001·93	1%
Recurrent costs	$1521·62	1%	$1521·62	2%
Personnel	$73 561·43	35%	$73 561·43	94%
Drug supplies	$603·65	0%	$603·65	1%
Lab supplies	$1223·43	1%	$1223·43	2%
Zvandiri intervention costs				
Capital costs				
Equipment	$2967·96	1%	..	..
Vehicles	$3062·81	1%	..	..
Recurrent costs				
Personnel	$62 933·93	30%	..	..
Materials and supplies	$2364·00	1%	..	..
Vehicle operation	$7660·44	4%	..	..
Building operations	$9024·24	4%	..	..
CATS coordination and training	$44 442·28	21%	..	..
Total annual cost	$210 367·71	100%	$77 912·05	100%
Adolescents on ART, n	211	..	285	..
Virally suppressed adolescents, n*	157	..	173	..
Annual cost per adolescent treated on ART	$997·00	..	$163·17	..
Cost per adolescent virally suppressed on ART	$1340·00	..	$450·36	..

Data are US$ unless otherwise specified. ART=antiretroviral therapy. CATS=community adolescent treatment supporters. *Includes only those known to be virally suppressed at 96 weeks.

Table 6: **Health provider costs of HIV treatment**

Discussion

This cluster-randomised trial of adolescents with HIV in Zimbabwe found 42% lower prevalence of virological failure or death at 96 weeks among participants receiving enhanced ART adherence support through the Zvandiri programme than among those solely receiving standard

HIV care at rural clinics. This finding reinforces previous assertions that ambitious approaches such as the treat all strategy need to be complemented by interventions that actively support adherence to treatment and wellbeing more generally.[3]

To our knowledge, this trial is the first youth-led investigation of a multicomponent differentiated service delivery intervention focusing on adolescents' HIV-related and psychosocial outcomes. Only two other trials[3,26] have shown an intervention's effect on virological outcomes among populations living with HIV in low-income and middle-income countries in general and adolescents with HIV, specifically. Both previous trials had a singular focus: structured adherence support to caregivers of adolescents with HIV[3] and savings-led economic empowerment of adolescents with HIV.[26] An important explanation for the Zvandiri intervention's success was the multicomponent aspect, which addressed the inhibiting context in which adolescents with HIV navigated adherence, by providing them with a supportive peer network and a more receptive household environment. Consequently, adolescents with HIV receiving the Zvandiri intervention were able to benefit from continual support to drive and sustain behaviour change. The effectiveness of this comprehensive wraparound programme is in line with the so-called development accelerators approach advocated in the 2019 UNAIDS Global AIDS update.[27] Modelling clearly shows the synergistic effect of combining three development accelerators (support for parenting, cash transfers, and safe schools) on the lives of adolescents with HIV.[27,28] Notably, the stronger intervention effects we report in 13–16 year-olds than in 17–19 year-olds are consistent with the observed trend of suboptimal adherence as adolescents age and become independent from caregiver supervision.[2,29]

Our trial highlights the importance of the context in which interventions, especially those in children and young people, are implemented. Implementation of interventions in contexts characterised by high youth unemployment, a struggling economy, persistent HIV stigma, considerable faith healing, and a struggling health-care system with weak mental health provision is particularly difficult. We found that ART adherence was sometimes disrupted when caregivers, acting upon faith healers' instructions, ordered adolescents with HIV to temporarily or permanently stop their medication intake, often leading to clinical AIDS events or death. Given the high prevalence of faith healing and continued impact on ART adherence in sub-Saharan Africa,[30] interventions need to continue targeting caregivers but also target faith healers. Further, although studies have shown that text messaging can support ART adherence,[31] its effectiveness is context-dependent. The rural setting of this trial resulted in electricity and mobile network challenges, meaning that text messages were not always sent. Additionally, community adolescent treatment supporters had to use coded messages specific to each adolescent with HIV to counteract the possibility of messages being intercepted and resulting in unintentional disclosure. Although burdensome, this aspect reinforced the differentiated aspect of the Zvandiri programme.

The high proportion (68%) of non-disclosure of HIV status seen in our questionnaire data is consistent with previous findings[29,32] and process evaluation data, wherein adolescents with HIV mentioned that the consequences of disclosure include rejection. Given the potential individual and public health benefits associated with onward disclosure, including ART adherence and reduced levels of unprotected sexual activity,[33] interventions should encourage and empower individuals with HIV to disclose their HIV status, especially to their sexual partners. The undetectable equals untransmittable concept (known as U=U), which signifies that HIV positive individuals who receive ART and have achieved and maintained an undetectable viral load cannot sexually transmit the virus to others,[34] should be properly explained to the adolescents and their caregivers to enhance disclosure, sustained adherence, and acceptance of those with HIV.

Our cost analysis suggests that incorporation of the Zvandiri intervention into current standard of care would increase the cost of providing HIV treatment to adolescents by about three times. Most of this additional cost is due to the additional staff needed to deliver the counselling and adherence support at the clinics and in the community. In our study, each Zvandiri intervention health facility had three additional staff who could provide the same level of care to many more adolescents than the 30 or fewer adolescents accessing treatment at each facility during the study period (as currently happens programmatically). Potential economies of scale, and therefore lower unit costs, could be achieved through provision of both ART and the Zvandiri intervention to larger numbers of adolescents. Costs were lower when assessed in an anticipated national scale-up scenario where salaries were public sector-based, start-up costs were excluded, and the two mentors supervised more clinics located within their two districts (22 for Bindura and 16 for Shamva) than the eight in our trial. Funders and policy makers might need to invest in these higher costs to avert the health and economic consequences of not achieving viral suppression in a population with the worst HIV outcomes, which will probably require many years of ART. A full economic analysis incorporating these long-term health and economic effects is underway to explore cost-effectiveness.

A major strength of this trial is that it evaluated the Zvandiri programme as delivered in a real-world and resource-constrained setting. The Zvandiri intervention can, therefore, be feasibly implemented in similar settings. In fact, the Zvandiri intervention has now (as of October, 2019) been introduced in the control group of this trial and continues to be used in the communities of the intervention group. In October, 2019, the programme

was scaled up in partnership with the Ministries of Health in six countries in sub-Saharan Africa (Eswatini, Mozambique, Nigeria, Rwanda, Tanzania, and Uganda), and now supports 961 community adolescent treatment supporters working with 65 500 beneficiaries in 613 clinics. The finding that the Zvandiri intervention reduces rates of treatment failure strengthens support for further scale-up across the region. The results will likely inform policies and standard of care for young people with HIV in Zimbabwe, regionally, and internationally. Further, despite high rates of orphanhood (81%) and associated changes in households or locations, our trial had high follow-up (97%), providing a high level of confidence in the results and greater power than anticipated to detect differences in outcomes. Moreover, we used rigorous procedures to ascertain objectively measured outcomes; the cluster-randomised controlled trial was complemented by process evaluation including in-depth qualitative data collection to understand the mechanisms of action.

This trial has a few limitations, including that it was difficult to deliver certain intervention components as intended. In addition to text messaging challenges, community adolescent treatment supporters were unable to visit some adolescents' homes—a recurring issue in community-based interventions.[35] Community adolescent treatment supporters were, however, able to meet study participants in neutral spaces, highlighting the value of differentiated service delivery in responding to beneficiaries' preferences.[14] Finally, although process evaluation data suggested the mechanisms of effect of the Zvandiri intervention, it is possible that unmeasured or unassessed variables might also have played a role in the intervention effect.

In our trial, community adolescent treatment supporters were well-supported, including by mentors located in the study districts. If taken to scale, Zvandiri mentors could support more community adolescent treatment supporters than they did in this trial. Additionally, each community adolescent treatment supporter supported a manageable number of adolescents with HIV (up to ten). In non-trial settings, community adolescent treatment supporters support up to 80 adolescents with HIV as a result of financial constraints. Future research should explore the effectiveness of community adolescent treatment supporters when they support relatively large numbers of adolescents with HIV, and how this situation affects the total costs of delivering HIV treatment. How programmes for orphaned and vulnerable children could be strengthened should also be investigated to ensure they are community-based and holistic to support adolescents with HIV and their caregivers with a comprehensive package of services.

Our study is the only youth-led trial so far to show effectiveness of a community-based intervention in improving viral suppression among adolescents with HIV—a group with disproportionately poor HIV treatment outcomes.[3–5] By showing that the sum of a multicomponent differentiated service delivery model is more important than the individual components, our study adds to the growing body of evidence to support WHO's recommendations for community-based interventions to support ART adherence and retention in care. Our findings provide further justification for the scaling up of the Zvandiri intervention in sub-Saharan Africa. Community-based interventions are likely to make a substantial contribution to the UNAIDS 90-90-90 targets if they offer differentiated services, are youth-led, and are multicomponent.

Contributors

FMC led the trial design, with involvement from WMav, WMan, TA, RA, and HAW. FMC and WMav led protocol development, with involvement from WMan, TA, RA, and HAW. NW led intervention implementation. FMC and WMav led trial implementation, with involvement from JM. SB led process evaluation, with involvement from MT. CM led the costing component, with involvement from HM. HAW was responsible for analyses and led data interpretation, with involvement from FMC, WMav, NW, JM, SB, MT, WMan, TA, and RA. WMav wrote the manuscript. All authors reviewed the drafts.

Declaration of interests

We declare no competing interests.

Data sharing

Data from our trial will be made available upon request to the London School of Hygiene & Tropical Medicine data repository.

For the **data repository** see https://datacompass.lshtm.ac.uk/

Acknowledgments

The research reported in this publication was funded by ViiV Healthcare's Positive Action for Adolescents Programme. The content is solely the responsibility of the authors and does not necessarily represent the official views of ViiV Healthcare. We thank the members of the data safety and monitoring board (Diana Gibb, Petrus J de Vries, and Mi-Suk Kang Dufour), study participants, caregivers, health-care workers, and trial steering committee members.

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