

Title: Impact of community antiretroviral therapy delivery on clinical outcomes among children and adolescents living with HIV: an emulated target trial

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Abstract

Background

Antiretroviral therapy (ART) delivery through community pick-up points (“community ART”) simplifies clients’ HIV care and reduces the need for clinical visits. Clinical outcomes of adults using community ART are good, however evidence of its effect on children and adolescents living with HIV (CALWH) is lacking.

Methods

We outlined a 12-month target trial to evaluate the effect of first referral to community ART on retention and viral load (VL) outcomes among CALWH aged 5-18 years and eligible for community ART in KwaZulu-Natal, South Africa. We then emulated sequential target trials using routine, de-identified data from 567 primary care clinics from 2020-2025, to estimate the association between community ART referral and the co-primary outcomes of 12-month retention-in-care and viral load (<50 copies/mL, >50 copies/mL [viraemic] or not done). We used logistic and multinomial logistic regression models incorporating inverse-probability-of-treatment and censoring weights to estimate risk differences (RD) by age groups.

Findings

From 32,009 CALWH, we constructed 121,061 person-trials. Across all person-trials, 54.2% of CALWH were female and 39.3% used dolutegravir-based regimens. During follow-up, those referred for community ART and those not referred had a median (interquartile range) of 2 (2-3) and 6 (4-7) clinical visits, respectively. Overall, 7.7% were not retained, 19.4% were viraemic and 9.8% had no VL measurement. The estimated RD (95% confidence interval [CI]) of not being retained for those in community ART versus those not was -0.04% (-2.89%;2.95%) for 5-9-year-olds, 0.47% (-1.04%;2.04%) for 10-14-year-olds, and -3.18% (-4.30%;-2.05%) for 15-18-year-olds. The RD (95% CI) for viraemia and for no VL measurement was 1.62% (-1.60;7.63%) and 2.55% (-1.07%;8.03%) respectively for 5-9-year-olds, -1.10% (-3.73;1.02%) and 1.49% (-0.55%;3.59%) for 10-14-year-olds and -2.78% (-3.73%;-1.00%) and 1.95% (0.57%;3.38%) for 15-18-year-olds.

Interpretation

Community ART reduced clinical visit frequency, with no change in retention and viraemia in younger CALWH, and evidence of improvement in older CALWH.

Funding

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Research in Context

Evidence before this study

We searched PubMed for articles on differentiated service delivery models (DSD) providing antiretroviral therapy (ART) delivery at pick-up points within communities ("community ART") for children and adolescents living with HIV (CALWH) in high-burden countries. We identified additional studies using hand searches of reference lists and cited papers. From these, we selected studies measuring clinical outcomes of retention and viral suppression.

There is a paucity of evidence available on the effect of community ART on outcomes of CALWH. In a systematic review by *Tao et al* of studies conducted between January 2015 and September 2024 of interventions for adolescents in HIV high-burden countries, only one study examined interventions with community ART as a component, and none measured the impact of community ART alone. An additional study, published in 2025 and using observational data of 10-19-year-olds from a rural setting in South Africa, estimated the effect of referral into one of three DSD programmes, of which community ART was one, on retention and viral suppression. Although it found that retention was similar and viral suppression better among 646 CALWH who were referred to DSD compared to 1282 who were not, it did not measure the effect of community ART alone and included CALWH who were ineligible for DSD in the comparator group.

Added value of this study

We present the largest study to date quantifying the impact of referral to community ART among CALWH aged 5-18 years. We show that community ART referral reduced clinical visit frequency from approximately 6 to 2 times per year and improved 12-month retention and viral suppression in 15-18-year-olds, with no negative impact in 5-14-year-olds. Among 15-18-year-

olds, however, those referred to community ART had a slightly lower probability of completing their 12-month viral load.

Implications of all the available evidence

These results provide support for the ongoing roll-out of community ART for CALWH who are stable on first-line ART in low- and middle-income countries. CALWH referred to these models are likely to benefit from a less burdensome ART collection process and have similar, or better, retention and viral suppression outcomes as in traditional clinic-based care.

Introduction

Differentiated service delivery (DSD) programmes for antiretroviral therapy (ART) provide a client-centred approach to ART delivery, with the aim of improving client experiences and treatment outcomes¹. Among adults living with HIV who are stable on ART, DSD has been readily adopted, with referred clients showing similar or better clinical outcomes compared to those in traditional clinic-based care^{2,3}. Although DSD now includes children and adolescents living with HIV (CALWH) in several countries^{4,5}, evidence on its uptake and effect on clinical outcomes among CALWH remains limited⁶.

As of 2025, South Africa had an estimated 150,000 children <15 years living with HIV, accounting for approximately 11% of all global infections among children⁷. To facilitate ART delivery to persons living with HIV, the South African National Department of Health offers three DSD models, namely out-of-facility individual models, facility-based individual models, and healthcare worker managed groups (or “adherence clubs”)⁸. Of these, the out-of-facility individual model, requiring ART collection at community pick-up points between bi-annual clinic consultations (hereafter termed “community ART”), is widely used^{9,10}. Adults enrolled in this programme have shown good clinical outcomes¹¹⁻¹³ while also reporting saving time and money through less frequent clinical visits^{14,15}. However, little is known about the uptake or impact of community ART among CALWH, and to date there have been no randomised controlled trials assessing its effect on treatment outcomes among CALWH.

In this study, we use routinely-collected data from South African primary care clinics to evaluate the uptake of community ART among CALWH and emulate a target trial to measure the impact of community ART on clinical outcomes among CALWH.

Methods

Study design

We used observational data on CALWH aged 5 to 18 years who were collecting ART from clinics in KwaZulu-Natal (KZN), South Africa, between April 2020 and April 2024 to report uptake of community ART. Among those CALWH who were eligible for community ART, we emulate a target trial assessing the effect of referral to community ART on clinical outcomes.

This study is reported according to the Transparent Reporting of Observational Studies Emulating a Target Trial (TARGET) guidelines¹⁶ (Supplementary Table 1).

Setting

HIV prevalence among children <15 years in KZN is the second-highest in the country at 1.1%¹⁷. Since 2016, all CALWH in South Africa have been eligible for ART¹⁸. ART is typically dispensed in 1-3 months' supply and can be collected from primary care clinics. From 2020, CALWH have also been able to collect ART using DSD models, if eligible. CALWH are eligible for DSD if they are 5 to 18 years old, have been on ART for at least 6 months with no regimen or dosage changes in last 3 months, have had an HIV viral load value <50 copies/ml taken in the last 6 months, and have no current medical condition requiring frequent medical consultation. In KZN, community ART models that use community pick-up points are the predominant form of DSD and therefore the focus of this analysis. Those referred to community ART receive a 6-month ART prescription for collection at a prespecified community pick-up point. Once the prescription has expired, CALWH should return to the clinic for a clinical consultation, during which they can be referred to community ART again if still eligible. Among CALWH aged ≥ 5 years who are clinically stable, viral load testing is required annually¹⁹.

Data source and data management

Data was extracted from TIER.Net, an electronic register capturing health record data on clients collecting ART from South African primary care clinics²⁰. Data captured in TIER.Net includes basic demographic data such as birth year and sex, dates of clinic visits, ART regimens, prescription lengths, referral into DSD models, pregnancy and tuberculosis status, viral load and CD4 count test results and dates, clinic transfer dates and death dates. We analysed de-identified person-level data using R 4.6 (R Foundation for Statistical Computing, Vienna, Austria) and SAS, version 9.4 (SAS Institute Inc).

Target Trial Emulation

We aimed to measure the effect of first community ART referral on CALWH eligible for community ART through emulating a target trial with two treatment strategies, community ART referral and no referral. We specifically state that the treatment is *referral* into community ART

and not use of community ART, as CALWH may transition out of community ART during follow-up. The target trial specifications are provided in Table 1. We excluded CALWH who were ineligible for community ART, and those on uncommon ART regimens, as referrals amongst these were few. We also removed CALWH who had a recent (within 2 years) CD4 count below 500 cells/mm³, to exclude children who were more likely to be unwell and need close clinical monitoring.

Since CALWH were eligible at many timepoints, rather than selecting one baseline timepoint randomly, we emulated 16 sequential trials, each with a 3-month enrolment period and a 12-month follow-up period following treatment assignment. The first emulated trial enrolled from April-June 2020, with follow-up ending in April-June 2021 and the last trial enrolled from January-March 2024, with follow-up ending in January-March 2025. Each child could be included in multiple trials if they remained eligible, though not referred, for community ART. However, once referred, they were excluded from future trials. CALWH were assigned to the community ART arm if they had been referred to community ART at one of their clinic visits during the 3-month enrolment period, and to the no referral arm otherwise. The baseline visit (or trial “time-zero”) was chosen to be the community ART referral visit for those in the community ART arm and the first visit in the 3-month enrolment period for those in the no referral arm.

Outcome variables

We had two clinical outcome variables, retention-in-care and a viral load outcome. Retention was a dichotomous variable indicating whether a CALWH was late by more than 90 days for any visit scheduled in the 12 months follow-up or not. CALWH who were transferred to another clinic before end of follow-up were assigned a missing value for the retention variable.

For the 12-month viral load outcome variable, we defined three possible values: suppressed (<50 copies/ml), viraemic ($\geq$ 50 copies/ml) or not done. The ‘not done’ category was included because we wanted to assess whether reduced clinic visit frequency through community ART impacted the probability of completing viral load measurements. Although missing viral load values in TIER.Net could result from either no test being done or test data not being captured in TIER.Net, a recent analysis using data from KZN clinics showed that 99% of viral load data was captured in TIER.Net in 2022²¹. We therefore assumed if CALWH were still in follow-up but

missed a viral load outcome that it was because the test was not done, rather than not captured. For those who did not have a viral load and were lost-to-follow-up, we assumed that the CALWH was viraemic. For those who were transferred to another clinic during follow-up, we classified the viral load outcome as missing.

Annual viral loads for CALWH in the trial were due between 6- and 12-months during follow-up because eligibility viral loads were measured 0- to 6-months before baseline. For measuring the viral load outcome, we therefore included viral loads taken from 3-15 months after baseline to account for viral loads performed earlier or later than the 12-month due date. If multiple viral loads were recorded, the result closest to 12 months from baseline was selected.

Confounders

Among variables included in TIER.Net, we considered age, sex, ART regimen, time on ART, date of trial enrolment and district as possible confounders as they are likely to be associated with both community ART referral and outcomes. Possible confounders that are not measured in TIER.Net include child health and caregiver support. Poor child health may lower the willingness for a healthcare worker to refer a child to community ART and lower the probability of subsequent viral suppression. Less caregiver support may impact retention (due to inability/unwillingness to take children to attend their visit), and through its possible impact on child health and previous retention-in-care, may also affect the probability of referral. To reduce this unmeasured confounding, we included a variable measuring history of missing a clinic visit as a proxy for caregiver support, and we removed CALWH who had a recent CD4 count below 500 cells/mm³.

Statistical analysis

We used pooled data from the 16 sequential trials, censoring those who were transferred to other clinics, for the modelling of our two outcome variables. The outcome regressions were weighted using inverse probability of treatment weights (IPTW) to approximate exchangeability between the two arms as community ART referral was not random. Regressions were also weighted by inverse-probability-of-censoring weights (IPCW) to reduce possible selection bias due to censoring of CALWH transferred to other clinics.

IPTW were derived as the inverse probability of community ART referral / no referral for those who were referred to community ART/ not referred respectively. The probability of community ART referral at baseline was estimated using the pooled data with age (in years), sex, ART regimen (non-nucleoside reverse transcriptase inhibitors [NNRTI]-, integrase inhibitor [INSTI]-or protease inhibitor [PI]- containing regimens), years on ART, a polynomial of order 2 for year quarters since April 2020, district and history of previously missing a visit by more than 90 days (Yes/No, measured using historical visit data) as covariates. IPTW were stabilized by setting the numerator of each weight equal to the marginal probability of the individual's observed value for community ART referral. The same approach and the same model covariates were used for estimation of the IPCW except that the outcome was an indicator for *not* transferring to another clinic and the regression additionally included an indicator for trial arm as a covariate.

The association between community ART referral and the odds of missing one or more visits over 12 months was estimated using IPTW- and IPCW-weighted pooled logistic regression and included a second order polynomial of year quarters since April 2020 as a proxy for trial. Age category (5-9, 10-14 and 15-18 years) and an interaction term between age category and community ART referral was also included in the model as we hypothesized that the effect of referral may differ across age groups. The derived model was used to predict the risk of missing at least one visit in 12 months for CALWH assuming community ART referral and then assuming no referral strategies. The risk difference (RD) was computed to express the marginal difference in the probability of missing a visit. We used nonparametric bootstrapping based on 500 bootstrap samples to obtain percentile-based 95% confidence intervals (CI) for the risk difference, accounting for within child correlation. The regression weights were re-estimated for every bootstrap sample. Since CALWH can return to clinic-based collections or be referred to community ART during follow-up, our risk difference represents an intention-to-treat (ITT) effect of community ART referral. We describe the time spent in community ART referral after trial enrolment to understand the degree of switching across arms.

The steps taken to build the outcome regression for the viral load outcome were the same, except that multinomial regression was used for the outcome regression instead of logistic regression. We estimated the marginal difference in the risk of viraemia for community ART

versus no community ART referral and the marginal difference in the risk of missing a viral load measurement for community ART referral versus no referral. As a sensitivity analysis, we used a viral load outcome threshold of 1000 copies/ml. Statistical significance was measured using a significance level of 0.05.

Ethical Approval

This work was approved by University of KwaZulu-Natal Biomedical Research Ethics Committee (BE646/17) and the University of Cape Town Faculty of Health Sciences Human Research Ethics Review Committee (822/2024), the KwaZulu-Natal Department of Health's Provincial Health Research Ethics Committee (KZ_201807_021), and the eThekweni Municipal Health Department Research Committee, with a waiver for informed consent for analysis of de-identified, routinely collected data. No emulated target trial protocol was registered.

Results

Between 1 April 2020 and 1 April 2024, 80,237 CALWH collected ART from the 567 clinics with data accessible for this study. During this period, 27.9% of CALWH were referred to community ART at least once, with referrals increasing with age and calendar time (Figure 1). A total of 32,009 CALWH were eligible for community ART (based on predefined trial criteria) at least once before 1 April 2024. The most common reason for being ineligible was failing to meet viral load criteria (Figure 2). Among those found eligible, 5,741 (17.9%) were referred to community ART.

From the 32,009 eligible CALWH we constructed 16 sequential trials with 121,061 person-trials, 5,741 person-trials in the community ART arm and 115,320 in the no referral arm. The median (interquartile range [IQR]) number of trials per child was 3 (2-5). Eligibility viral loads were measured a median (IQR) of 81 (29-120) days before trial enrolment among those referred for community ART and 60 (0-119) days among those not. The distribution of baseline characteristics varied across the trial arms with respect to age, calendar time, and variables associated with age and time (Table 2). Those referred to community ART were more likely to be older and on a dolutegravir (DTG) based regimen (DTG use in community ART arm: 67.8% vs DTG use in non-referral arm: 37.9%; 39.3% overall). Once weighted using IPTW

(Supplementary Table 2), baseline characteristics were well-balanced across the trial arms, indicating that our weighting procedure created a comparable pseudo-population with regards to known confounders (Table 2). The median (IQR) number of clinical visits during the 12 months of follow-up was 2 (2-3) and 6 (4-7) among those referred to community ART and those not referred, respectively. The median (IQR) time in community ART during follow-up for those in the community ART arm was 93% (53%-100%), whereas only 2% of those not referred at enrolment were later referred to community ART.

Across all trials, there were 6,462 clinic transfers, 291 (5.1%) from the community ART referral arm and 6,171 (5.4%) from the no referral arm, leaving a total of 114,599 person-trials with measured outcome data. Among these, there were 8,711 (7.6%) CALWH who were not retained, 338 (6.2%) among those referred to community ART and 8,373 (7.7%) among participants not referred. In total, 113 of these events were due to death, 8 (0.1%) among those referred to community ART and 105 (0.1%) among participants not referred. Most (78%) who were not retained returned to care before the data cut-off of June 2025, and, among them, the median (IQR) time between their first missed visit and return to care was 140 (108-257) days. Without adjusting for confounding or censoring, the estimated RD (95% CI) for the 12-month probability of not being retained for those referred to community ART versus those not was -1.24% (-3.41 to 0.87%) for 5-9-year-olds, 0.73% (-1.78 to 0.41%) for 10-14-year-olds, and -3.77% (-4.69 to -2.92%) for 15-18-year-olds (Table 3). After incorporating IPTW and IPCW, the RD (95% CI) was -0.04% (-2.89% to 2.95%) for 5-9-year-olds, 0.47% (-1.04% to 2.04%) for 10-14-year-olds, and -3.18% (-4.30% to -2.05%) for 15-18-year-olds.

Follow-up viral loads were measured a median (IQR) of 10 (8-12) months after baseline for both CALWH referred to community ART and those not. A total of 20,948 (18.3%) CALWH were classified as viraemic during follow-up, 16,647 (14.5%) based on a viral load ≥ 50 copies/ml and 4,301 (3.8%) owing to them missing a visit and viral load measurement. A further 11,917 (10.4%) did not have viral load measured during follow-up although they consistently attended all visits. The percentage with viraemia by 12 months was 16.0% among those referred to community ART and 18.4% among those not, and the percentage missing a viral load was 11.5% and 10.3% respectively. The unweighted estimated RD (95% CI) of being viraemic and of not having a viral load done for those referred for community ART compared to those not was 1.15% (-1.86 to 3.57%) and 0.42% (-1.72 to 2.74%), respectively, for 5-9 year-olds, -2.23% (-

3.83 to -0.89%) and 0.49% (-0.58 to 1.70%) for 10-14 year-olds and -2.82% (-3.61 to -2.01%) and 1.62% (0.71 to 2.55%) for 15-18 year-olds (Table 3). After weighting, the RD (95% CI) for viraemia and for no viral load measurement was 1.62% (-1.60 to 7.63%) and 2.55% (-1.07% to 8.03%) respectively for 5-9-year-olds, -1.10% (-3.73 to 1.02%) and 1.49% (-0.55% to 3.59%) for 10-14-year-olds and -2.78% (-3.73% to -1.00%) and 1.95% (0.57% to 3.38%) for 15-18-year-olds. In a sensitivity analysis using a threshold of 1000 copies/ml for viraemia, 10,019 (8.7%) CALWH were classified as viraemic. The percentage with viral load >1000 copies/mL was 7.2% among those referred to community ART and 8.8% among those not, and associations by age group were similar to the 50 copies/mL analysis (Supplementary Table 3).

Discussion

In this study, we examine the uptake of community ART in a large cohort of CALWH and measure its impact on outcomes over 12 months using a target trial framework. Though uptake was slow, community ART referral approximately halved the number of clinical visits attended in a year. Overall retention was high, with >90% of CALWH attending all required visits in a year. Using a threshold of 50 copies/mL, viraemia was 18.3% but using the WHO threshold of 1000 copies/mL²², it was 8.7%. Retention and viral suppression were similar across arms among CALWH aged 5-14 years, and slightly higher in those referred for community ART among 15-18-year-olds. Viral load monitoring was similar across arms except among 15-18-year-olds, where monitoring was slightly poorer in the community ART arm.

Our results provide evidence that community ART can maintain, and possibly improve, outcomes among CALWH while significantly reducing clinical visit frequency. Although this has been observed among adults, there is limited evidence among CALWH. A smaller study from a rural setting in South Africa used observational data from CALWH aged 10-19 years to compare retention and viral suppression between those referred to DSD programmes (of which community ART was one) and those not²³. Like ours, they found no evidence that a reduction in clinical visits compromised outcomes. However, they did not measure the effect of community ART alone and included some CALWH ineligible for DSD in the comparator group. Several studies examining outcomes of CALWH using a different DSD intervention, multi-month dispensing (MMD), have also shown that favourable outcomes can be maintained following transition to MMD with less frequent visits²⁴⁻²⁶. Collectively, these results provide reassuring evidence that CALWH who are stable in care can achieve favourable clinical outcomes with

clinical consultation frequency of up to 6 months, in line with WHO guidelines²⁷. Although regular clinical monitoring may be perceived as preferable for CALWH, the impact of it may be limited in this context. Many determinants of clinical outcomes among CALWH in sub-Saharan Africa²⁸, particularly sociodemographic ones, cannot be influenced by healthcare workers. Opportunities for meaningful interaction with healthcare workers at interim visits may also be minimal, if for example, caregivers collect ART on behalf of their children, or if contact with healthcare workers is brief owing to the constraints of an over-burdened health system.

More needs to be done to understand barriers to uptake and accelerate referrals to community ART among CALWH, particularly among those aged 15-18 years for whom community ART had significant benefits. Policy makers and healthcare workers should be assured that community ART referral will not negatively impact outcomes of CALWH who are stable in care while likely providing benefits that were not measurable here, namely cost and time savings for clients and reduced clinic congestion. As DSD expands, however, it will be important to continue to prioritise viral load monitoring. Our study showed that 10% of all CALWH, over and above those that were not retained, missed viral load measurements, and this proportion was slightly higher among 15-18-year-olds who were referred to community ART. A recent study from Mozambique also found that consistent MMD was associated with lower odds of having a viral load measured²⁹. Further research to identify factors contributing to missed viral load measurements among CALWH is warranted.

Our study has some limitations. The results of this study are relevant to children who are stable-in-care, and not generalizable to those who are newly initiated on ART or viraemic. While we used target trial methods, IPTW and IPCW to infer causal effects, we cannot rule out bias due to unmeasured confounding, most importantly from not being able to measure child health and caregiver support. To try address this, we limited the study to children with a CD4 count ≥ 500 copies/ml, and we included an indicator for history of ever missing a clinical visit as a proxy for caregiver support.

Conclusion

In summary, in a large cohort of CALWH who were eligible for community ART, our analysis showed that uptake has been poor, but that CALWH referred for community ART, had

approximately half as many clinical visits, with as good or better clinical outcomes compared to those not referred to community ART. Scale-up of community ART amongst CALWH could reduce the burden of ART collections on families while maintaining or improving retention-in-care and viral suppression.

Authors' contributions: JD, NG, and LL conceptualised the study. YS and LM oversaw data collection. JvdM and TK oversaw data curation. LL and JvdM analysed the data, with inputs on the design and implementation from RK, JB, JD, FC, SM and FL. LL drafted the manuscript. All authors contributed to interpretation of results, critically reviewed and edited the manuscript, and consented to final publication.

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Data availability: The data used for this analysis cannot be shared publicly because of legal and ethical requirements regarding use of routinely collected clinical data in South Africa. The analysis code is available on request from the first author.

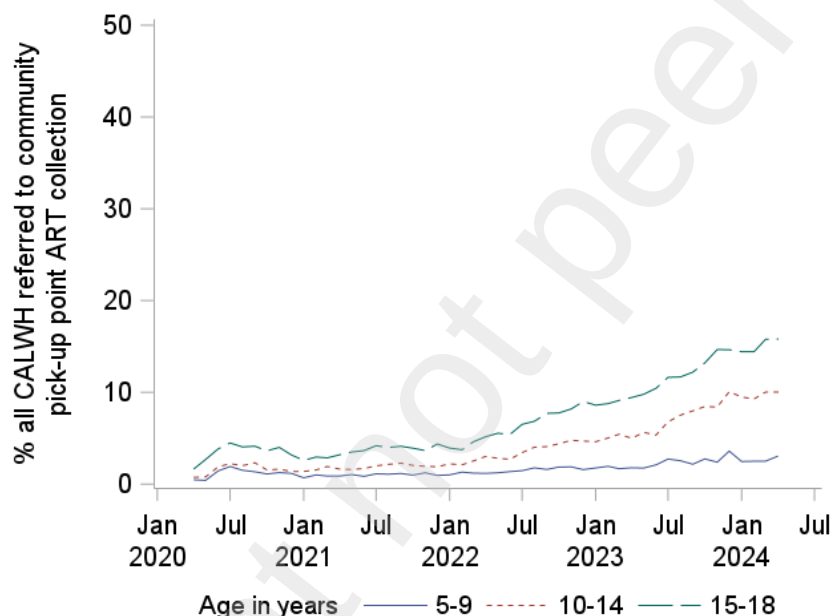


Figure 1: Percentage of all children and adolescents living with HIV (CALWH) at the respective calendar time referred for ART collection through community pick-up points, disaggregated by age-group

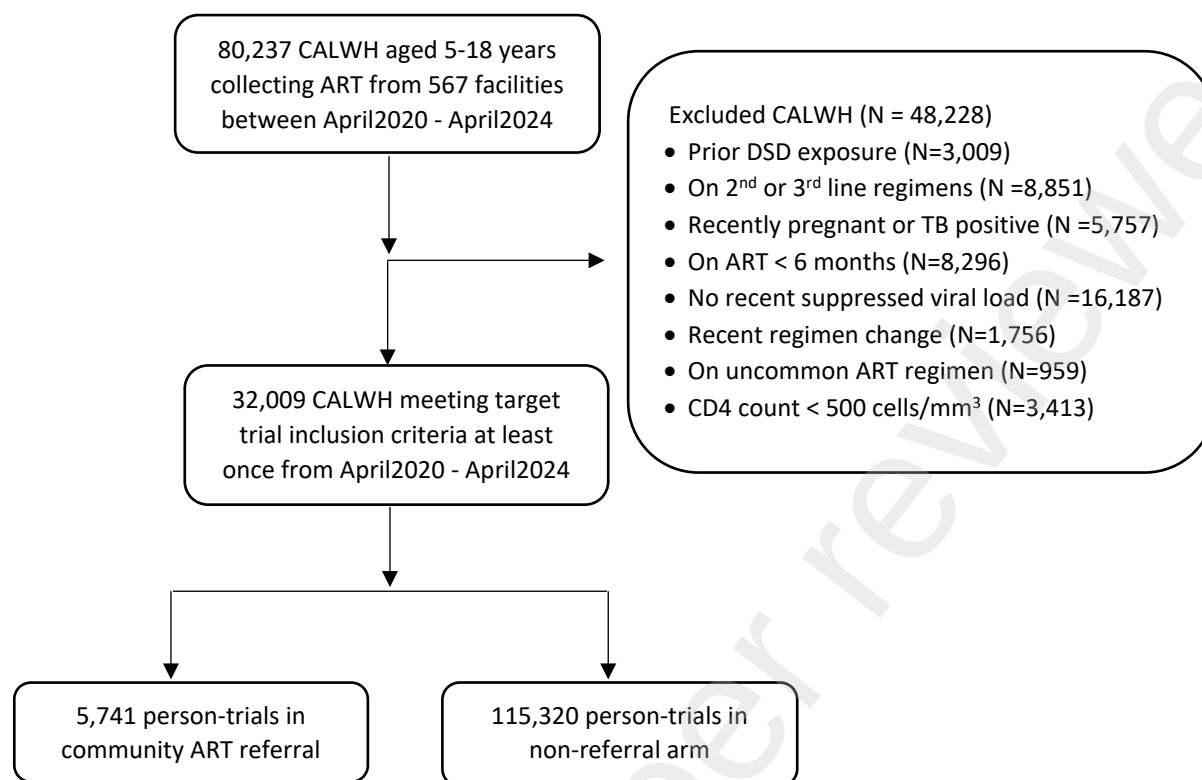


Figure 2: Participant flowchart

Table 1: Specification of the target trial

Protocol	Target trial	Emulated trial
Eligibility criteria	Children aged 5-18	Same
	On first-line ART for at least 6 months	Same
	No regimen or dosage changes in the last 3 months	No history of ART regimen changes in the last 3 months
	Most recent viral load <50 copies/ml taken in last 6 months	Recorded VL available from previous 6 months and <50 copies/ml
	Not pregnant	No record of positive pregnancy test
	No TB	No record of TB treatment
	No other medical condition requiring regular care	Did not have a recent (from last 2 years) CD4 count below 500 cells/mm ³ . This approximation was used as there were no variables capturing medical condition over and above TB and pregnancy in observational dataset.
	No reported previous community ART exposure	No record of community ART referral
	On one of the following common regimens: ABC/XTC/DTG, ABC/XTC/EFV, ABC/XTC/LPV/r, and for those aged 10+ years, TDF/XTC/DTG, TDF/XTC/EFV	Same

Treatment strategies	Referred to DSD through community pick-up points ("community ART")	Same
	Not referred to community ART	Same
Treatment assignment	Participants randomised to either community ART / no community ART as soon as they are enrolled in study. It is an open label trial.	Community ART referral based determined by clients and healthcare workers at each clinic visit
Follow-up period	12-month follow-up period per participant from treatment assignment.	Same
Primary endpoints	12-month retention in care: a binary variable capturing whether a client was >90 days late for any scheduled visit in year after enrolment or not.	Same, but there will be some missing outcomes due to clinic transfers.
	12-month viral suppression: a binary variable capturing whether the viral load at 12 months after enrolment was ≤ 50 copies/mL or not. There will be missing viral loads among those lost to follow-up.	Same, but there will be additional viral loads that were not done. This necessitates that we use a viral load outcome variable with 3 levels: ≤ 50 copies/mL, > 50 copies/mL or not done. There will be some with missing outcomes due to clinic transfers. There will be some with missing values because they became lost to follow-up before viral load measurement, and for these we assign a value of > 50 copies/mL.
Causal contrasts	Risk difference using an intention-to-treat population (i.e., include all randomised participants, analysed in the groups that they were assigned)	Same
Identifying assumptions	We assume exchangeability due to randomization.	Treatment assignment was not random, and our two treatment groups may not be exchangeable. Those transferred to other clinics will be missing outcomes, and their exclusion may introduce selection bias. We assume that treatment assignment / censoring and outcomes were independent conditional on: - Sex - Age (in years) - ART Regimen - Time on ART - Time of trial - District of trial - History of retention - Community ART referral (censoring only)
Data analysis		There is no unique time-zero for the clients included in the study, because clients are eligible at multiple times in the observation dataset. We use sequential trials approach to deal with this. Create 16 trials with a 3-month enrolment period, the first trial starting in April 2020 and the last starting in Jan 2024. Pool data for analysis.

Retention outcome: Use logistic regression with community ART as a fixed effect and other prognostic variables in the regression. Then use standardization to obtain the marginal treatment effect. Bootstrapping used for 95% CI.	Retention outcome: Logistic regression weighted for the inverse probability of being treated and the inverse probability of being censored due to transferring to another clinic. Risk difference estimated using standardization. To account for the repeated use of individuals, nonparametric bootstrapping with 500 samples to calculate 95% CIs.
Viral suppression outcome: The same approach will be used as with retention outcome, but those missing viral loads at 12 months because they are lost to follow-up will be assumed viraemic. We cannot assume the data is missing at random as we know that this data is missing because participants were not retained.	Viral suppression outcome: There will be missing viral loads due to loss to follow-up, due to transfers, and due to no viral load test being done. As in the target trial, we will assume those who are lost to follow-up are viraemic. Weighted multinomial regression will be used to model outcome variable with 3 levels and bootstrapping with 500 samples to calculate 95% CIs.

Note: ABC=Abacavir; DTG=Dolutegravir; EFV=Efavirenz; LPV/r=Lopinavir/ritonavir; TDF=Tenofovir disoproxil fumarate; XTC=Lamivudine or emtricitabine; TB=Tuberculosis

Table 2: Characteristics of children and adolescents living with HIV referred and not referred for Community ART at the start of trial follow-up

Characteristic	Level	Unweighted %(N)		Weighted by IPTW %(N)	
		Community ART referral	No Community ART referral	Community ART referral	No Community ART referral
Age category	5-9 years	8.1(464)	22.0(25411)	22(1197)	21.4(23309)
	10-14 years	30.0(1725)	39.3(45303)	36.9(2014)	38.9(42435)
	15-18 years	61.9(3552)	38.7(44606)	41.1(2242)	39.8(43405)
Sex	female	56.7(3257)	54.1(62424)	55.1(3004)	54.2(59210)
	male	43.3(2484)	45.9(52896)	44.9(2449)	45.8(49939)
ART regimen	Dolutegravir	67.8(3892)	37.9(43743)	39(2127)	39.4(42950)
	Efavirenz	25.7(1473)	45.3(52272)	45.1(2457)	44.4(48453)
	Lopinavir/ritonavir	6.5(376)	16.7(19305)	15.9(869)	16.3(17746)
Time on ART	<2 years	10.4(597)	9.4(10796)	8.8(482)	9.3(10122)
	2-9 years	53.9(3092)	65.4(75378)	65(3544)	65(70986)
	10+ years	35.7(2052)	25.3(29146)	26.2(1427)	25.7(28040)
KZN district	Amajuba	3.2(184)	4.1(4683)	4(219)	4(4384)
	Harry Gwala	7(401)	5.3(6153)	6.4(349)	5.4(5934)
	King Cetshwayo	7.6(437)	11.3(13024)	9.6(521)	11.1(12137)
	Ugu	11.9(682)	9(10416)	8.5(464)	9.2(10000)
	Umkhanyakude	4.5(258)	9.3(10716)	9.5(520)	9.1(9890)
	Umzinyathi	4.8(277)	3.9(4446)	4.9(266)	3.9(4270)
	Uthukela	7.7(440)	7.5(8641)	6.4(349)	7.5(8178)
	Zululand	11.8(677)	10.5(12092)	9.9(539)	10.5(11506)
	eThekweni	29.4(1686)	26.1(30130)	26.9(1469)	26.3(28676)
	iLembe	4.8(274)	6.8(7854)	7.4(405)	6.7(7335)
	uMgungundlovu	7.4(425)	6.2(7165)	6.5(352)	6.3(6839)

Characteristic	Level	Unweighted %(N)		Weighted by IPTW %(N)	
		Community ART referral	No Community ART referral	Community ART referral	No Community ART referral
Trial year	2020	14.1(812)	23.4(26961)	27.3(1487)	22.9(25014)
	2021	19.9(1143)	28.3(32677)	24.2(1321)	28.1(30641)
	2022	28.6(1641)	24.2(27908)	24.1(1315)	24.3(26507)
	2023	29.8(1710)	19.8(22802)	19.6(1071)	20.2(22071)
	2024	7.6(435)	4.3(4972)	4.7(259)	4.5(4916)
History of missed visit	No	93.5(5368)	93.8(108122)	92.7(5057)	93.2(101731)
	Yes	6.5(373)	6.2(7198)	7.3(396)	6.8(7418)

Table 3: Measured association between community ART referral and outcomes

Outcome	Age (in years)	% (N) outcome Community ART referral	% (N) outcome no Community ART	Risk difference % (95% CI) Community ART vs. no Community ART	
				Unweighted	Weighted with IPTW and IPCW
Not retained	5-9	5.09% (22)	6.22% (1489)	-1.24% (-3.41 to 0.87%)	-0.04% (-2.89 to 2.95%)
	10-14	5.51% (90)	5.99% (2572)	-0.73% (-1.78 to 0.41%)	0.47% (-1.04 to 2.04%)
	15-18	6.68% (226)	10.20% (4312)	-3.77% (-4.69 to -2.92%)	-3.18% (-4.30 to -2.05%)
Viraemia (≥ 50 copies/ml)	5-9	18.75% (81)	17.77% (4253)	1.15% (-1.86 to 3.57%)	1.62% (-1.60 to 7.63%)
	10-14	15.97% (261)	18.42% (7911)	-2.23% (-3.83 to -0.89%)	-1.10% (-3.73 to 1.02%)
	15-18	15.60% (528)	18.72% (7914)	-2.82% (-3.61 to -2.01%)	-2.78% (-3.73 to -1.00%)
VL not done	5-9	10.42% (45)	9.98% (2389)	0.42% (-1.72 to 2.74%)	2.55% (-1.07 to 8.03%)
	10-14	10.16% (166)	9.90% (4252)	0.49% (-0.58 to 1.70%)	1.49% (-0.55 to 3.59%)
	15-18	12.32% (417)	10.99% (4648)	1.62% (0.71 to 2.55%)	1.95% (0.57 to 3.38%)

References

1. Duncombe C, Rosenblum S, Hellmann N, et al. Reframing HIV care: putting people at the centre of antiretroviral delivery. *Trop Med Int Health* 2015; **20**(4): 430-47.
2. Bwire GM, Njiro BJ, Ndumwa HP, et al. Impact of differentiated service delivery models on retention in HIV care and viral suppression among people living with HIV in sub-Saharan Africa: A systematic review and meta-analysis of randomised controlled trials. *Rev Med Virol* 2023; **33**(6): e2479.
3. Long L, Kuchukhidze S, Pascoe S, et al. Retention in care and viral suppression in differentiated service delivery models for HIV treatment delivery in sub-Saharan Africa: a rapid systematic review. *J Int AIDS Soc* 2020; **23**(11): e25640.
4. Abelman R, Alons C, Stockman J, et al. Implementation of differentiated service delivery for paediatric HIV care and treatment: opportunities, challenges and experience from seven sub-Saharan African countries. *Fam Med Community Health* 2020; **8**(3).
5. Differentiated Service Delivery. Eligibility of Children for DSD and Inclusion in Less-Intensive DSD Models: National Policy. Differentiated Service Delivery; August 2024. <https://www.differentiatedservicedelivery.org/wp-content/uploads/DSD-Eligibility-in-Children-Aug24-WEB.pdf> (accessed June 19, 2026).
6. Tao Y, Byrne M, Ho D, et al. HIV interventions across the care continuum for adolescents in high-burden countries: a systematic review and meta-analysis. *EClinicalMedicine* 2024; **78**: 102989.
7. Joint United Nations Programme on HIV/AIDS (UNAIDS). AIDSinfo: UNAIDS data 2025. 2025. <https://aidsinfo.unaids.org/databook>.
8. South Africa National Department of Health. Differentiated Models of Care Standard Operating Procedures. South Africa: National Department of Health, 2023.
9. Project Last Mile. 2023 Annual Report. 2024. <https://www.projectlastmile.com/wp-content/uploads/2024/06/2023-PLM-Annual-Report-240605s.pdf>.
10. Engelbrecht J, Tajeer C, O'Connor C, Rees K. Differentiated antiretroviral distribution: Implementation in five South African districts. *Afr J Prim Health Care Fam Med* 2025; **17**(1): e1-e9.
11. Lewis L, Sookrajh Y, van der Molen J, et al. Long-term usage patterns and clinical outcomes in a community-based differentiated antiretroviral therapy delivery programme in South Africa. *Journal of the International AIDS Society* 2023; **26**(7): e26141.
12. Lewis L, Sookrajh Y, Gate K, et al. Differentiated service delivery for people using second-line antiretroviral therapy: clinical outcomes from a retrospective cohort study in KwaZulu-Natal, South Africa. *J Int AIDS Soc* 2021; **24** Suppl 6(Suppl 6): e25802.
13. Huber AN, Jamieson L, Fox MP, et al. Evaluating the impact of differentiated service delivery (DSD) on retention in care and HIV viral suppression in South Africa: A target trial emulation using routine healthcare data. *PLoS Med* 2025; **22**(8): e1004489.
14. Dorward J, Msimango L, Gibbs A, et al. Understanding how community antiretroviral delivery influences engagement in HIV care: a qualitative assessment of the Centralised Chronic Medication Dispensing and Distribution programme in South Africa. *BMJ Open* 2020; **10**(5): e035412.
15. Bassett IV, Yan J, Govere S, et al. Uptake of community- versus clinic-based antiretroviral therapy dispensing in the Central Chronic Medication Dispensing and Distribution program in South Africa. *J Int AIDS Soc* 2022; **25**(1): e25877.
16. Cashin AG, Hansford HJ, Hernán MA, et al. Transparent Reporting of Observational Studies Emulating a Target Trial—The TARGET Statement. *JAMA* 2025; **334**(12): 1084-93.
17. Hall K. HIV prevalence in children. 2024. <https://childrencount.uct.ac.za/indicator.php?domain=5&indicator=29> (accessed July 10, 2026).
18. UNAIDS. South Africa takes bold step to provide HIV treatment for all. 2016. https://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2016/may/20160513_UTT (accessed July 10, 2026).
19. South Africa National Department of Health. 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. South Africa: National Department of Health, 2023.
20. Osler M, Hilderbrand K, Hennessey C, et al. A three-tier framework for monitoring antiretroviral therapy in high HIV burden settings. *J Int AIDS Soc* 2014; **17**.

21. Naidu L, van der Molen J, Jugathpal V, et al. Quality assessment of data for decentralised antiretroviral therapy referrals and laboratory results in the South African national electronic HIV management register TIER.Net. *PLOS Global Public Health* 2026; **6**(3): e0005534.
22. World Health Organization. The role of HIV viral suppression in improving individual health and reducing transmission. Policy brief. 22 July 2023.
23. Shaku PM, Rees K, Mutasa B, Maluleke C, Mashele S, Njuguna C. Programmatic outcomes of adolescents in differentiated service delivery models in South Africa. *S Afr J Infect Dis* 2025; **40**(1): 733.
24. Casalini C, Bateganya M, Akolo C, et al. Increasing multimonth dispensing of antiretrovirals and assessing the effect on viral load suppression among children and adolescents receiving HIV services in Nigeria. *PLOS ONE* 2023; **18**(6): e0286303.
25. Kim MH, Wanless RS, Caviness AC, et al. Multimonth Prescription of Antiretroviral Therapy Among Children and Adolescents: Experiences From the Baylor International Pediatric AIDS Initiative in 6 African Countries. *J Acquir Immune Defic Syndr* 2018; **78 Suppl 2**(Suppl 2): S71-S80.
26. Mugo C, Zubayr B, Ezeokafor N, et al. Effect of Dolutegravir and Multimonth Dispensing on Viral Suppression Among Children With HIV. *J Acquir Immune Defic Syndr* 2023; **93**(3): 229-36.
27. WHO. Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring: Recommendations for a Public Health Approach. Geneva, 2021.
28. Mukuku O, Govender K, Wembonyama SO, Kiakuvue YN. Magnitude and characteristics of unsuppressed HIV viral load in children and adolescents on antiretroviral therapy in sub-Saharan Africa: a systematic review and meta-analysis. *The Lancet HIV* 2025; **12**(7): e506-e21.
29. Meque I, Herrera N, Gill MM, et al. Consistency of Multi-Month Antiretroviral Therapy Dispensing and Association with Viral Load Coverage among Pediatric Clients Living with HIV in Mozambique. *Trop Med Infect Dis* 2024; **9**(7).