

A Digital Adherence Tools randomised trial among children living with HIV: lessons learnt

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Abstract

Challenges that arise during the implementation of (clinical) trial activities in African settings can consume substantial resources for participants, investigators, and the funding agency. The literature on these aspects of the challenge is relatively scarce, although it could help prevent similar errors in future studies. We conducted a trial (registered as PACTR202301844164954) to test the effectiveness of digital adherence tools (DAT) on medicine adherence and viral suppression among children living with HIV (CLHIV). We encountered critical operational challenges, which we present as a case study to illustrate their consequences for primary outcomes and for predicting viral suppression. Then, we evaluate and extract lessons learnt to inform future DAT studies.

Our case was a pragmatic two-arm trial investigating the effectiveness of DAT in Tanzania, in which we followed participants for 12-months. We measured self-reported adherence, pharmacy refill adherence, and viral suppression. We performed a chi-square test and a quasi-Poisson regression analysis to analyze the significance of differences between the two arms. We also determined the ability of our DAT data to predict viral suppression.

We enrolled 154 children; 151 children had at least one follow-up visit during which refill information was collected from source documents. While 145 children had contact with the research team, during which self-reported adherence and viral load data were collected. Operational challenges related to the research team, infrastructure, data collection and management, and quality oversight led to inefficiency and inconsistency in implementing study procedures and to poor-quality adherence data. As a result, no conclusions could be drawn regarding the effect of DAT on adherence. However, there was a weak effect of on improving viral suppression among CLHIV. Adherence, as measured by DAT, was a strong predictor of viral suppression (AUC = 0.84 on the ROC curve).

For the successful implementation of study procedures in pragmatic trials, it is essential to involve healthcare facility leadership in trial management from the planning stage, thereby facilitating the smooth integration of research activities into routine practice. Moreover, it is crucial to select measurable, objectively quantifiable endpoints sensitive enough to detect the intervention's effect, regardless of logistical constraints.

Introduction

The world has been fighting against Human Immunodeficiency Virus (HIV) and acquired immunodeficiency syndrome (AIDS) since its detection in the early 1980s. (1, 2) Global HIV & AIDS statistics by UNAIDS in 2023 reported that 88.4 million people have acquired the virus globally since the start of the epidemic. About 39.9 million people were living with HIV in 2023. Among those, 1.4 million were children aged 0–14 years, and 120,000 children were newly diagnosed in 2023. (3) Mother-to-child transmission of HIV remains the primary source of HIV transmission among children under 5 years old. (4) Much success against HIV/AIDS has been achieved since the discovery and advancement of highly active antiretroviral therapy (ART). Children living with HIV (CLHIV) who started on ART on time showed

an increase in CD4 cell counts, suppressed viral load, accelerated immunity recovery, and growth improvement. (5, 6)

For any medication, including ARTs, to be effective, it must be taken as prescribed. People living with HIV are required to take 95% or more of the prescribed dose (not miss more than one pill per month) to avoid consequences of suboptimal drug exposure, including low-level viremia and development of resistance strains. (7, 8) Although there is evidence that lower adherence rates may be sufficient for integrase inhibitor-based regimens.(9) Maintaining such levels of adherence for prolonged time periods is challenging.(10–12) A meta-analysis assessing ART adherence among orphaned children showed adherence ranged from 76% to 95%, with a pooled mean of 78% (95% CI: 67.4–87.7; $p < 0.001$). (13) A cross-sectional study in Uganda, conducted among children under five years of age, reported 57.3% non-adherence (i.e., 42.6% adherence) using a multi-measurement adherence assessment scale.(14) In contrast, a cross-sectional study in Tanzania reported mean adherence rates of 82.9%, 79.6%, and 72.2% based on clinic attendance, self-report, and plasma drug levels, respectively. (15) Interventions are needed to help children and their caregivers overcome barriers to ART adherence.

Accurate adherence measurements and early detection of non-adherence are crucial to enabling timely interventions before adverse clinical manifestations, ART resistance, and treatment failure. However, there is no single golden standard for adherence. The most commonly used adherence measures include pharmacy refill counts, pill counts, self-reports, electronic monitoring, plasma concentration measurements, and viral load measurements. Although self-report is cheap and easy to use, it has the disadvantage of being subjective. It might not provide an accurate estimate of the participant's adherence due to a high level of social desirability bias. (16) While pharmacy refill methods are superior to self-report, their accuracy depends on the quality of the refill documentation.(17, 18) More objective measures, like plasma concentration measurements of ARTs, are challenging to assess and do not belong to the standard of HIV treatment and care in resource-poor settings. Also, viral load counts provide an objective measure of disease progression; however, they are expensive, cannot be performed regularly at short intervals, may require months of unnoticed non-adherence before they detect it, which would delay the initiation of adherence interventions, and actually represent the undesirable consequence of non-adherence that should be avoided. (19)

Digital adherence tools (DATs) have shown promise in helping PLHIV overcome some adherence barriers. Electronic adherence monitoring devices, such as real-time medication monitoring (RTMM) devices, use smart pillboxes that detect openings and transmit real-time signals to a web-based server, indicating possible pill intake. (20) These devices can be used to monitor patient adherence, and by identifying non-adherence patterns, they provide a basis for adherence counselling where possible solutions can be discussed. (21) DATs also provide a more objective tool in measuring adherence compared to other measures.

Several studies have reported that RTMM-based DATs are acceptable and feasible, even in remote settings. (22–24) However, only eight published studies have examined the effectiveness of RTMM-

based DATs in improving adherence and/or viral suppression among PLHIV. Among them, only one trial has shown a significant effect on adherence, and none have reported significant results on viral suppression. Also, no trial has been conducted to assess the effectiveness of DAT among children living with HIV.(25, 26)

Randomised clinical trials are essential for evidence-based health interventions. However, if clinical trials are not adequately designed and conducted, they may fail to achieve their objectives. Studies show that many investigational products fail at late clinical development stages (phase 3) due to safety, efficacy, and funding-related issues.(27) A systematic review encompassing 640 trials revealed that 57% failed in phase 3 to demonstrate that the investigational product was statistically significantly superior to the comparator. (28) Among the factors that may have contributed to trials failing to demonstrate the efficacy of potentially efficacious drugs or other interventions were flawed study designs, inappropriate outcomes, and insufficient statistical power. (28, 29)

Additionally, challenges related to participant or site-level factors, study team infrastructure, intervention-related factors, or the longitudinal study design that arise during trial implementation may hinder trial success. (30) Trials are demanding and consume the time, energy, and money of participants, investigators, and funders. It is essential to learn from unsuccessful trials to avoid similar errors in future studies. However, negative trial findings and the reasons for failures are less often published. Hence, little is known about the implementation challenges encountered during trials, as well as the key measures and strategies required for successful planning and execution. This is particularly true of trials in Africa.

In our case, we conducted a trial to assess the effectiveness of a DAT on treatment adherence (primary outcome) and viral suppression (secondary outcome) among CLHIV. We encountered several operational challenges that prevented us from drawing sound conclusions on the effectiveness of the DAT. In this paper, we aim to describe challenges faced and their consequences. We first present our DAT trial as a case study to illustrate the implications for the primary outcome and the predictive ability of our adherence data for viral suppression (Part A). We then evaluate the challenges faced and the lessons we learnt from them to inform future DAT studies. (Part B)

Part A: Our case (the REMIND-KID Trial)

Design and study population

We conducted a two-armed, randomised, non-blinded pragmatic trial among children living with HIV subjectively judged to be non-adherent, aged six months to 14 years, with their caregivers. Participants were randomised to either the intervention or the standard care arm. Participants in the intervention arm received a DAT throughout the study period, in addition to standard care, whereas participants in the control arm received only standard care, in accordance with Tanzanian HIV care and treatment guidelines. The intervention was a DAT, in which participants used (1) a Wisepill box, an internet-enabled

medication dispenser, that detects and records every opening as an intake, (2) received customised reminder Short Message Service (SMS) texts 30 minutes before their medication intake time,(23) and (3) received feedback on adherence in each follow-up visit during the 12-month duration of the study. More details on the intervention and trial sample size calculations are provided in the published REMIND KID protocol. (31)

The trial was approved by the College Research and Ethical Review Committee (CRERC) of Kilimanjaro Christian Medical University College and the National Health Research Ethics Subcommittee (NATREC) of the National Institute of Medical Research in Tanzania. Trial is registered as PACTR202301844164954 (31) We obtained informed consent from the child's caregivers/parents, and assent from children aged 8–14 years after confirming the HIV status had been disclosed to the child. If the child was not aware of the HIV status, we only involved the parent/caregiver in the study procedures.

Recruitment and Data Collection

We recruited participants from 12 different healthcare facilities and followed them for 12 months. The personnel who enrolled participants and assigned them to interventions had no access to the allocation sequence. The randomisation sequence was generated by the data manager, who is an off-site statistician. Our trial follow-ups adhered to the standard clinic schedule, in which patients were grouped by viral load (VL < 50 or ≥ 50 copies/mL). Suppressed children had ARV drug refill clinics every 84 days (3 months), while unsuppressed children had monthly visits (every 28 days). During the trial, guidelines changed, allowing suppressed participants to receive six-month (168-day) refills. (32) However, we still asked them to attend every 84 days. We collected refill details from the patient files for visits outside our trial schedule and documented them as out-of-schedule visits.

During follow-up visits, we collected self-reported adherence data and pharmacy refill counts. We therefore asked participants about the number of pills taken per day and the number of missed pills during the past month (self-report). For pharmacy refills, we collected the number of dispensed pills from the current and previous visits, obtained from patients' files, Care and Treatment Centre cards (CTC1), and pharmacy dispensing books. We asked participants to bring their leftover pills, which we counted during refill visits. In addition to adherence measures, we collected viral load data at study entry and at the last follow-up visit. Data were collected by our study team in collaboration with healthcare workers at the Care and Treatment Center (CTC). Participants in the intervention arm received feedback on their adherence patterns, generated by the Wisepill dashboard, during refill visits. We collected health-related adverse events at each visit and any device-related risks during the exit interviews.

Measurement of adherence in the trial

We calculated self-reported adherence as = $\{[(\text{Number of days in the past month} \times \text{pills to take per day}) - (\text{number of missed pills in the past month})] / (\text{number of days in the past month} \times \text{pills to take per day})\} \times$

100%.

We calculated the Medication Possession Ratio (MPR) as = $\{[(\text{number of pills given in previous visit} / \text{number of pills to take per day})] / (\text{number of days between visits})\} \times 100\%$.

For participants in the intervention arm, we measured DAT adherence as $((\text{Total number of days with intakes} / \text{number of days the device was used}) \times 100)$.

Trial analysis

We compared baseline characteristics of the included participants between the two arms and summarised the results as medians and proportions.

To compare differences between the intervention and control arms in self-report, MPR, and viral load, we used a modified intention-to-treat analysis, including only participants who attended at least one follow-up visit at which the outcome of interest could be measured. For self-reported adherence and MPR, we calculated adherence at each clinic visit during the observation period, capping values at 100%. We then computed the mean adherence across all observations for each participant and classified participants as adherent ($\geq 95\%$) or non-adherent ($< 95\%$). We categorized viral suppression as viral load < 50 copies/mL, as this is the cutoff for initiating intensive adherence counselling in our study regions. (32)

We conducted a chi-square test to compare adherence and viral suppression across the study arms, using the proportions of participants classified as adherent or virally suppressed, respectively. As a sensitivity analysis, we also employed a quasi-Poisson regression model with robust standard errors to compare adherence across study arms, accounting for repeated adherence measurements within individuals over time. We also used a quasi-Poisson regression model to estimate the adjusted risk ratio (ARR) for viral suppression at the last visit.

To evaluate the ability of self-report, MPR, and DAT adherence measurements to predict viral suppression, we calculated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for each adherence measure. We plotted sensitivity and (1-specificity) in a receiver operating characteristic (ROC) curve as a function of the cut points of the most accurate specific adherence measure for predicting viral suppression. An area under the ROC curve (AUC) value of 1.0 indicates perfect discriminatory capacity, while an AUC of 0.5 indicates poor discriminatory capacity.

We defined (i) sensitivity as the percentage of unsuppressed participants (having viral load ≥ 50 copies/mL) that were correctly identified by the specific adherence method as being non-adherent ($< 95\%$ adherence cut point); (ii) specificity as the percentage of suppressed participants (viral load < 50 copies/mL) that were identified as adherent ($> 95\%$ adherence cut point); (iii) positive predictive value (PPV) as the percentage of non-adherent participants with unsuppressed viral load; and the (iv) negative predictive value (NPV) as the percentage of adherent participants with suppressed viral load.

Trial Results

Description of the study population

We enrolled 154 children with their caregivers; 76 were randomised to the control arm and 78 to the intervention arm. The median age was 10 years (IQR = 6.6, 12.1), and 87 (56%) of the included children were girls (Appendix 1). The median time since the first HIV diagnosis was 4.7 (IQR 2.0-7.9) years. All children were on a dolutegravir-based regimen. For 87(56%) children, their parents reported suboptimal adherence, 80(52%) had leftover medication, and 51 (33%) had missed clinic visits in the past, suggesting adherence issues for many children. Eighty-two percent had a suppressed viral load at baseline. One hundred forty-five children, 74 (51%) in the intervention arm and 71 (49%) in the control arm, completed the 12 months.

Effect of the intervention on adherence to ART and viral suppression

During the 12-month follow-up, 151 children had at least one visit at which refill information was collected from source documents. Of those, 145 children had contact with the research team, during which self-reported adherence and viral load data were collected (Appendix 2). Data on self-reported adherence and leftover pills were not available in the source documents and could only be obtained from the participants.

There was no statistically significant difference in the proportion of participants achieving 95% adherence between the intervention and control arms, as measured by self-reporting (84% vs 90%, $p = 0.26$) and pharmacy refills (82% vs 85%, $p = 0.58$). Additionally, Poisson regression analysis showed no difference between the two arms, neither for self-reported adherence (ARR = 0.97; 95% CI: 0.90–1.05) nor for medication possession ratio adherence (ARR = 0.99; 95% CI: 0.93–1.07), as shown in Appendices 2 and 3. Of note, in part B, we state that these findings cannot be trusted because the adherence measures were deemed inaccurate or unreliable.

The chi-square test showed a borderline effect on viral suppression at 12 months, with 85% of children in the intervention arm suppressed compared with 72% in the control arm ($p = 0.046$). This effect was weaker in the Poisson regression analysis, with an ARR of 1.14 (95% CI: 0.98–1.34; $p = 0.08$). (Appendices 3 & 4)

Ability of different adherence measures to predict viral suppression

We compared the accuracy of the three adherence methods (self-report, MPR, and DAT) in predicting viral suppression. Both self-report and MPR had lower sensitivities (32% and 45%, respectively) than DAT, which had the highest sensitivity (90.9%) at 95% adherence, as shown in Appendix 5. Also, DAT had the highest discriminative capacity, with an AUC of 0.84 on the ROC curve, compared with MPR (0.56) and self-report (0.54), which performed poorly in predicting viral suppression. The optimal AUC cut-off points

for DAT, MPR, and self-report adherence were 58%, 98.9%, and 100%, respectively, as shown in Appendix 6. Of note, MPR and self-report data were not considered accurate or reliable (see part B).

Part B: Trial implementation challenges and lessons learnt

To evaluate the operational challenges faced and the lessons learnt, we assessed the implementation of our study procedures and reviewed study documents and data tools. We used a framework for assessing clinical trial site readiness to evaluate trial implementation practices and to describe our experiences in addressing the methodological and logistical challenges we encountered.⁽³³⁾ This framework has six domains, which include: (1) research team, (2) infrastructure, (3) study management, (4) data collection and management, (5) quality oversight, and (6) ethics and safety. For each of the first five domains, we described the challenges encountered during the trial implementation process, the consequences for the data, the lessons learnt, and possible strategies for future studies. We did not encounter any ethical or safety challenges, so we will not discuss this domain in this paper.

Results

We encountered several challenges during the conduct of the trial, including the following:

Table 1
Trial implementation challenges and lessons learnt

Challenge	Study consequence	Lessons learnt and possible strategies for the future
1. Research team 1.1 Deficiency in the number of delegated staff for study activities 1.2 Unrealistic expectations for the clinic staff	-Inefficiency and inconsistency in the implementation of study procedures -Missed study visits and fewer adherence feedback sessions when research assistants are not at the site	-It is essential to ensure that staff delegated to the research activities have and can dedicate enough time to trial activities
2. Infrastructure 2.1 Poor coordination and communication of study procedures between the research assistant and clinic staff	-Inefficiencies and inconsistency in the implementation of study procedures	-The successful execution of study procedures requires good collaboration between the research staff and clinical staff involved in the study
3. Study management 3.1 Poor planning and the approach to introducing the study in clinical settings	-Failure to fully integrate our protocol/study procedures into daily clinical site practices -lacked full support from the clinic staff, and struggled with implementing study procedures	-Discuss the implementation strategies with the clinical site leadership, include them in the management of the study, and work together to integrate the study into the clinical site's schedule
4. Data Collection and Management 4.1 Complex data collection tools 4.2 Changes in the standard of care guideline from 3 to 6 monthly refills 4.3 Participants not bringing leftover pills	-Failure of clinic staff to collect study data during a busy schedule -Few contacts with participants and hence fewer feedback sessions -Couldn't calculate pharmacy refill, accounting for the leftover pills	-Have simple tools for easy data collection among clinic staff or to divide tools between clinic staff and the research team -Being flexible to adapt to the changes in the standard of care -Efforts to have participants adhere to the study procedures (eg, incentives for only those who brought back the leftover pills)
5. Quality oversight 5.1 Relying on public health data for trial use 5.2 Inaccurate source document selection due to poor understanding of the documentation practices at the facilities.	-Poor quality of adherence data collected from three different source documents	-It is a risk to rely on public health data for trial purposes. -A clear understanding of practices at the facilities is needed to identify the accurate source document for the study. -It is crucial to conduct regular data quality checks and introduce simple monitoring and evaluation tools to

1. Research team:

Deficiency in the number of delegated staff for study activities

We had a team of junior researchers (research assistants) with diverse backgrounds in research-related fields, who had successfully executed our previous DAT studies. The research team members were based at the research centre (KCRI), and, in addition to their other responsibilities, one team member was assigned to each recruiting site to lead trial implementation activities. Due to budget constraints, we could have research assistants physically present at the sites only two days a week. However, having one research assistant per site for only two days a week appeared insufficient to execute study procedures efficiently. This was partly because we had two other parallel trials among adolescents and breastfeeding women, and their scheduled refill visits were on different days from the children's. Additionally, the research assistants had responsibilities beyond data collection; consequently, less time was devoted to data collection.

Unrealistic expectations for the clinic staff

Since we conducted a pragmatic trial, we designed the study to encourage clinic staff at CTC centres to participate actively in study procedures. We identified and trained 2–3 healthcare workers at each recruitment site to work with research assistants in conducting study procedures. However, it was challenging for clinic staff to prioritize trial activities (even when compensated for the additional time required) because they already had busy schedules with standard-of-care responsibilities.

As a result of these challenges with the research team and time constraints, the study protocol was implemented inefficiently and inconsistently. Most importantly, it led to missed study visits (meaning children attended the facility for medication refills, but study data were not collected and feedback sessions were not held), thereby hampering our intervention. Clearly, it is essential to ensure that staff delegated to research activities have sufficient time to dedicate to trial activities.

2. Infrastructure

Poor coordination and communication of study procedures between the research assistants and clinic staff

There was inadequate communication and insufficient allocation of responsibilities between the two teams, leading each team to believe the other was responsible for conducting the study procedures. We worked as separate teams, with clinic staff included in research activities only during data collection. This resulted in inadequate support and dedication from the clinic staff, prompting the research assistants to assume additional responsibilities at the sites, including remotely.

The successful execution of study procedures requires good collaboration between the research staff and clinical staff involved in the study. Efforts should be made to ensure that all parties involved in the research function as a unified team in day-to-day activities, such as integrating the study protocol into the treatment guidelines or manuals of the participating sites. (30)

3. Study management

Poor planning and the approach to introducing the study in clinical settings

The study management was done by the steering team, which consisted of a principal investigator, a post-doc, a data manager, study coordinators, a PhD student, and master students, whereas most of this steering team also functioned as research assistants. The steering team was responsible for planning, training, evaluating the trial process, conducting data quality checks, and managing finances. Given that we were conducting a pragmatic trial aimed at generating evidence on DAT effectiveness that could be applied to the general population and routine practice, our steering team lacked key personnel, specifically clinical site leadership. Without clinical site leadership on the management team, we lacked a clear understanding of how the general practice functioned and the best way to introduce our study to the sites to maximize collaboration. As a result, we were unable to fully integrate our protocol/study procedures into daily site practices, lacked full support from the clinic staff, and struggled to implement them. Although we obtained entry to the sites through healthcare facilities and the CTC unit leadership, the research team still had to lead research activities at the site level. We believe the right approach would have been to introduce and discuss the implementation strategies with the clinical site leadership, include them in the management of the study, and work together to integrate the study into the clinical site's clinical schedule from the top leadership level, and have the management of the study at the site level done in collaboration with the medical officers in charge of the facilities. (34–37)

4. Data collection and management

Complex data collection tools

In addition to medication refills and treatment information, we collected data for other secondary objectives, including cost-effectiveness and psychosocial aspects (stigma, depression, quality of life, HIV status disclosure, and social support). (31) Hence, during busy clinic periods, nurses could not allocate sufficient time to collect data on more than 100 questions. Using less demanding questionnaires and assigning additional data-collection tasks to research assistants could have improved data-collection efficiency.

Changes in the standard of care

We designed the trial to collect data in accordance with the standard-of-care schedule in Tanzania. As described under Part A, virologically unsuppressed children had monthly visits, and suppressed children had ARV drug refill clinics every three months. When guidelines changed to six-month refills for the virologically suppressed participants, most of them did not show up since they already had enough pills,

even though we asked the participants to keep visiting every three months for the study procedure. Because most recruited participants were suppressed at baseline (82%), we had fewer study visits than initially planned, which affected the implementation of the intervention in the intervention arm. Study protocols should be flexible to accommodate changes in the standard of care and should select an outcome sensitive enough to detect effects despite contamination in pragmatic trials. (30)

Collection of leftover pills

As described in the trial protocol, we aimed to estimate adherence using pharmacy refills by counting dispensed pills and accounting for leftover pills at scheduled refill clinics. However, most participants did not bring their leftover pills to the refill clinics (even after repeated requests), and it is not routine for the standard of care to document leftovers; therefore, we did not have a source for this data. We decided to use the medication possession ratio (MPR) as a measure of pharmacy refill adherence, based solely on the number of dispensed pills and accounting for carryover pills from previous periods. In this way, one of our adherence outcome measures was less credible.

5. Quality oversight

Use of public health data for trials

In addition to missed visits due to changes in the standard of care, we also missed study visits in which participants attended the health facility for refills but had no contact with the study team, and trial data were not collected directly from them. In this case, we later retrieved the refill details from the patient's file (CTC2), patient card (CTC1), and the pharmacy dispensing logs. (Fig. 1). Although these documents contain the necessary data for our study, the quality and accuracy of the data across the three sources were poor. We observed inconsistencies in refill data obtained from different source documents at health facilities. We selected the most accurate source document for each of the twelve recruiting sites. Early identification and selection of a trusted source document for each site would have saved us this trouble. However, it is also essential to implement regular quality control measures to improve the accuracy of public health data used in practice-based research.

Interestingly, based on adherence feedback reports, we observed that participants in the DAT arm were more likely to report nonadherence than those in the control arm. During feedback, participants in the DAT arm were first asked to rate themselves on a percentage scale of how well they had taken their medication, before the feedback graph was presented. As a result, we believe they were more likely to report nonadherence when asked about self-reported adherence in subsequent visits, knowing that this would be compared with their Wisepill adherence records. Based on this, we discourage using self-reported adherence as an outcome in DAT trials.

Discussion

The methodological and logistical challenges encountered during our trial implementation affected the number of study visits and feedback sessions in the intervention arm. They compromised the accuracy and credibility of adherence outcome measures, resulting in inconclusive findings for the primary adherence endpoint. As to the secondary endpoint on viral suppression, valid conclusions could, however, be drawn that there was a weak effect of the DAT intervention on improving viral suppression among children living with HIV. In addition, DAT adherence was an adequate predictor of viral suppression.

We measured adherence using self-report and the medication possession ratio, both of which are less sensitive for detecting non-adherence. Self-reported adherence is prone to social desirability bias and overestimation. (16) As observed in our trial results, a lower proportion of children achieved optimal adherence in the DAT (84%) arm than in the control arm (90%). Since viral suppression results from optimal adherence, we expected a higher proportion of participants in the intervention arm to achieve it. We believe this is because participants in the DAT arm were more likely to report non-adherence than those in the control arm due to the adherence feedback report provided during counselling sessions. In addition, our MPR adherence data depended on the quality of documentation in medication refill records, which varied across the 12 recruiting healthcare facilities. Although pharmacy refills generally provide better adherence estimates than self-reports, the accuracy of documented refill data in public health is indeed limited, especially in low-income settings. (17, 18)

On the contrary, studies in high-income countries show that both self-report and pharmacy records are strongly correlated with viral suppression. (38) A study conducted in the Netherlands, among migrant people living with HIV, showed that self-report measured using a 4-item questionnaire and pharmacy refill adherence (both when leftover pills are included or excluded) could predict viral suppression. (39) Social, economic, and cultural background, the type of tools used to measure adherence, and the way adherence questions are asked and recorded, as well as the recording of pharmacy refills, all affect the levels of social desirability bias and the accuracy of dispensing documents. (40)

Accurate measurement of ART adherence is complex, and the validity of results varies across contexts and data-collection settings. (16, 41) Using RTMM-based DATs provides a more accurate assessment of adherence. Our study found that DAT adherence had high sensitivity and performed well at predicting viral suppression. Similarly, a machine learned analysis of real-time medication adherence data provided a good prediction of viremia with an AUC of 0.88 in a study among people living with HIV in Uganda. (42, 43) Since Wisepill provides better adherence measurement, trials assessing the effectiveness of DAT could design studies that use RTMM in both arms to avoid non-differential misclassification errors. An example of such a trial was conducted in China. This is the only trial that has reported positive results on the effectiveness of DAT on adherence among people living with HIV. The trial in China was designed to measure adherence using the Wisepill box in both the intervention and control arms. They found that a larger proportion of participants in the intervention arm (87.3%) achieved optimal adherence compared to 51.8% in the control arm, with RR 1.7 (95% CI 1.3–2.2), when comparing participants who received a

triggered reminder SMS after a missed dose and counselling on adherence using Wisepill-generated reports (intervention) versus those who did not receive SMS or data-informed counselling (control).(25)

Our trial found that more children in the intervention arm were virologically suppressed at the end of the follow-up period than in the control arm. The proportion of children with a suppressed viral load in the intervention arm remained at 85% at both baseline and endline, whereas in the control arm it declined from 79% to 72%. This indicates that digital tools helped the children to maintain viral suppression. This is the first trial to show promising results on DAT in improving viral load suppression, as none of the currently published studies have shown a positive effect on viral suppression. (25,26,43–45)

In retrospect, we consider self-report and pharmacy refills to have been suboptimal adherence endpoints in our pragmatic trial in a resource-poor setting. Given the dilution and contamination of real-world data, studies that use hybrid effectiveness-implementation designs should employ a robust intervention and a strong, objectively measurable outcome that can detect minor effects, despite methodological challenges. (34,36,44,45) This could be adherence, as measured by DAT, or viral suppression. As observed in our study, viral suppression (a secondary outcome) detected a slight difference between the study arms, while our adherence outcome measures were significantly compromised. We discourage the use of subjective adherence measures, such as self-report and pharmacy refills, as outcomes in DAT or pragmatic trials conducted in low- and middle-income countries with a similar context to ours.

In most low-income settings, there is no established support system for practice-based research, and healthcare workers have tight schedules with less time and experience for research. (34, 44) When collaborating on research, it is crucial to have simple data-collection tools, clear communication, and well-defined responsibilities. It is also essential to identify ways to encourage ownership of the study, such as involving clinical staff in progress meetings and managing research funds allocated to their site. (29, 30, 34) Additionally, implementing robust, regular data quality checks is necessary to enhance data accuracy and credibility. (34)

Strengths and limitations

A limitation of our study is that the lessons learnt were evaluated only after trial data analysis, when we realized we couldn't trust the validity of our adherence outcome measures. Therefore, we relied on document review, recall, and the subjective judgment of team members and co-authors. However, our strength lies in having thoroughly evaluated the operational challenges that may have contributed to the unreliable trial results, using the site-readiness framework, whose themes applied to our trial.

Additionally, our quantitative data revealed the consequences of trial misconduct and the limitations of self-report and pharmacy refill adherence as outcome measures, enabling us to offer lessons learnt and recommendations to inform the design of future DAT trials.

Conclusion

For the successful implementation of study procedures in pragmatic trials, it is crucial to involve healthcare facility leadership in trial management from the planning stage, enabling the smooth integration of research activities into everyday practice. Moreover, using simple data-collection tools, clear communication, and transparent assignment of responsibilities between clinical and research assistants will enhance collaboration and ensure that neither research nor clinical activities are compromised.

Our trial yielded results regarding the effectiveness of DAT on adherence among children living with HIV that could not be trusted, in view of compromised adherence outcome measures that were not accurate or credible. The methodological and logistical challenges encountered during trial implementation affected adherence (the primary outcome) but did not affect viral suppression. We discourage the use of subjective adherence measures as outcomes in DAT or pragmatic trials conducted in low- and middle-income countries with a similar context to ours.

Declarations

Ethics and consent

We obtained ethical clearance (Ref No: 2589) from the College Research and Ethical Review Committee (CRERC) of Kilimanjaro Christian Medical University College (KCMUCo), now known as KCMC University, and a certificate (Ref. NIMR/HQ/R.8a/Vol.IX/4141) from the National Health Research Ethics Sub-Committee (NathREC) of the National Institute for Medical Research (NIMR) in Tanzania. We obtained written informed consent from the caregivers, followed by the child's written assent for children who were aware of their HIV status. If a child was not aware of their HIV status, we only used the caregiver's written consent and collected data from the caregiver.

Competing Interests

The authors declare no financial or non-financial interests.

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Author Contribution

Conceptualization, data analysis, and writing of the original draft: IUS, TM, MSBInvestigation: IUS, BM, RM, LVM, NE, AM, PCM, KN, MSB,Supervision, conceptualization, writing, review, and editing: KN, BTM, MSB, RA, TRWFunding acquisition, resources, and project administration: KN, BTM, MSB,

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Data Availability

The datasets generated and/or analysed during the current study are not publicly available, as Tanzania's regulations do not allow data sharing without a data transfer agreement with the recipient. But they are available from the corresponding author (i.swai@kcri.ac.tz) or the principal investigator (m.sumari@kcri.ac.tz) on reasonable request. We will then need to comply with Tanzanian data-sharing laws, and the authorities will require approval of the data-sharing request by signing a data transfer agreement.

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