Genotype-Informed Versus Empiric Management
Of VirEmia (GIVE MOVE):
An Open-Label Randomised Clinical Trial

STATISTICAL ANALYSIS PLAN

Version 1.0, 28 April 2022

Trial registration: ClinicalTrials.gov, NCT04233242,

18 January 2020

Current protocol version: 1.4, dated 23 Aug 2021

(Statistical analysis plan contents following Gamble et al [1])

1. Administrative information

Revision history

Version	Date	Changes and reasons
0.1	2 March 2021	First draft reviewed by Jennifer Brown and Niklaus Labhardt
0.2	28 March 2021	Second draft reviewed by Moniek Bresser
1.0	28 April 2022	Signed version prior to interim analysis

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Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
CALHIV	Children and Adolescents Living with HIV; defined as ≥6 months and <19
CDCI	Chronic Diseases Clinic Ifakara (at St. Francis Referral Hospital; affiliated with IHI)
eCRF	Electronic Case Report Form
EAC	Enhanced Adherence Counselling
eCRF	eCRF electronic Case Report Form
EKNZ	Ethikkommission Nordwest- und Zentralschweiz
FAS	Full Analysis Set
HGIVE MOVE	Genotype-Informed Versus Empiric Management of Viremia
GRT	Genotypic Resistance Testing
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
IHI	Ifakara Health Institute
INSTI	Integrase Strand Transfer Inhibitor
NNRTI	Non-nucleoside reverse transcriptase inhibitor
PI	Protease Inhibitor
Swiss TPH	Swiss Tropical and Public Health Institute
UNAIDS	United Nations Programme on HIV/AIDS
VL	Viral Load
WHO	World Health Organisation

Data management and sharing

Key trial data will be made available upon publication of the main manuscript through an appropriate data repository such as Zenodo, and will be referenced accordingly in the main manuscript.

Contents

2. Introduction (from protocol synopsis)

2.1 Background and rationale

Almost three million children and adolescents worldwide are living with HIV [1]. Every day, almost 1000 children and adolescents are newly infected and over 300 die from HIV/AIDS-related causes [1]. Eastern and Southern Africa are particularly affected, accounting for 65% of the epidemic in children and adolescents [1]. While substantial progress has been made towards providing antiretroviral therapy (ART) to all people living with HIV, which can suppress viral replication and prevent onward transmission of HIV [2–4], children and adolescents suffer high rates of treatment failure: among those younger than 15 years who receive ART, reported rates of treatment failure in Eastern and Southern Africa range from 10% (Eswatini) to over 50% (Eritrea, Mozambique, South Sudan) [5].

Treatment failure can be caused by non-adherence to therapy, viral drug resistance, or a combination of both, requiring differentiated clinical management. Without resistance testing, healthcare providers cannot definitively determine whether treatment failure is caused by drug resistance, necessitating an urgent switch of drug regimen, or non-adherence, in which case underlying causes must be addressed and unnecessary switching must be avoided to preserve the limited future treatment options.

Access to genotypic resistance testing (GRT) to detect viral drug resistance is lacking in most low-income settings [6]. As national HIV programs in sub-Sahara Africa struggle with limited resources, the question if resistance testing is of real clinical benefit or rather a “nice to have” is important as it impacts resource allocation within programs. The World Health Organisation (WHO) recommends resistance testing only upon confirmed treatment failure on second-line ART and/or protease-inhibitor-based ART, and even then only after a lengthy process of enhanced adherence counselling followed by a confirmatory viral load (VL) test [7].

A systematic review on the impact of genotypic and/or phenotypic resistance testing in ART-experienced individuals only found randomised clinical trials published before 2007, all conducted in Europe, the USA, or South America, only two of which included children and/or adolescents [8]. This review reported a potential slight reduction of virologic failure where resistance testing was available, but little or no difference in mortality, CD4 cell count, progression to AIDS, or adverse events. Among three modelling studies on the cost-effectiveness of GRT in southern Africa, published between 2011 and 2014, conclusions differed greatly [9–11].

The REVAMP trial did not observe a difference in viral suppression following clinical management informed by viral load versus genotypic resistance testing; however, this trial was conducted among adults taking NNRTI-based first-line ART and its results are thus not necessarily transferrable to children and adolescents taking newer ART regimens. A trial in Tanzania, including all age groups, implements GRT upon confirmation of treatment failure after enhanced adherence counselling [13]. Finally, the Opt4Kids trial assesses the impact of a combination of point-of-care VL testing and targeted resistance testing among children on first-line ART in Kenya [14].

2.2 Objectives

The primary research question is whether GRT improves clinical management and results in improved clinical outcomes – i.e. a higher proportion of participants who are alive, have no new clinical WHO stage 4 events[1] or HIV- or ART-related hospital admission, and are in care with a suppressed viral load – 9 months after randomisation.

We hypothesize that providing resistance information will allow for care to be customized according to the individual child/adolescent's health situation and needs, i.e. targeted adherence support for those without drug resistance and a rapid switch to an optimised ART regimen (with differentiated adherence support) for those with drug-resistant HIV, and thus lead to better clinical and virologic outcomes.

3. Study methods

3.1 Trial design

Full details of the trial are available in the current version (V 1.4) of the trial protocol as well as in summary version in the published protocol[2].

GIVE MOVE is an open-label, two-arm, multi-center, superiority randomised clinical trial conducted in Lesotho and Tanzania. Enrollment takes place in 10 sites (6 in Lesotho, 4 in Tanzania). Participants will be randomized in a 1:1 ratio to the intervention or the control arm. In the intervention arm, GRT (Sanger sequencing) will be performed. Based on the GRT and clinical information, an international expert committee issues a recommendation on the ART regimen and management. Taking this recommendation, the GRT as well as availability of drug formulations into account, the health care provider in charge of the

[1] WHO stage 4 events that are excluded: lymph node tuberculosis, stunting, oral or genital herpes simplex infection and oesophageal candidiasis

participant then takes the final decision on the composition of the ART regimen. Participants in the control arm will be managed according to the standard of care. Onward treatment will be informed by the follow-up VL in line with standard care and without performing resistance testing. The composite primary endpoint will be assessed 9 months (window: 32-44 weeks) after randomization (see Figure 1).

Although participants and treating healthcare professionals will not be blinded, laboratory technologists measuring the viral load (a key component of the primary and some secondary endpoints) will be blinded, as will the endpoint committee assessing if hospitalizations and potential WHO stage 4 events constitute an endpoint.

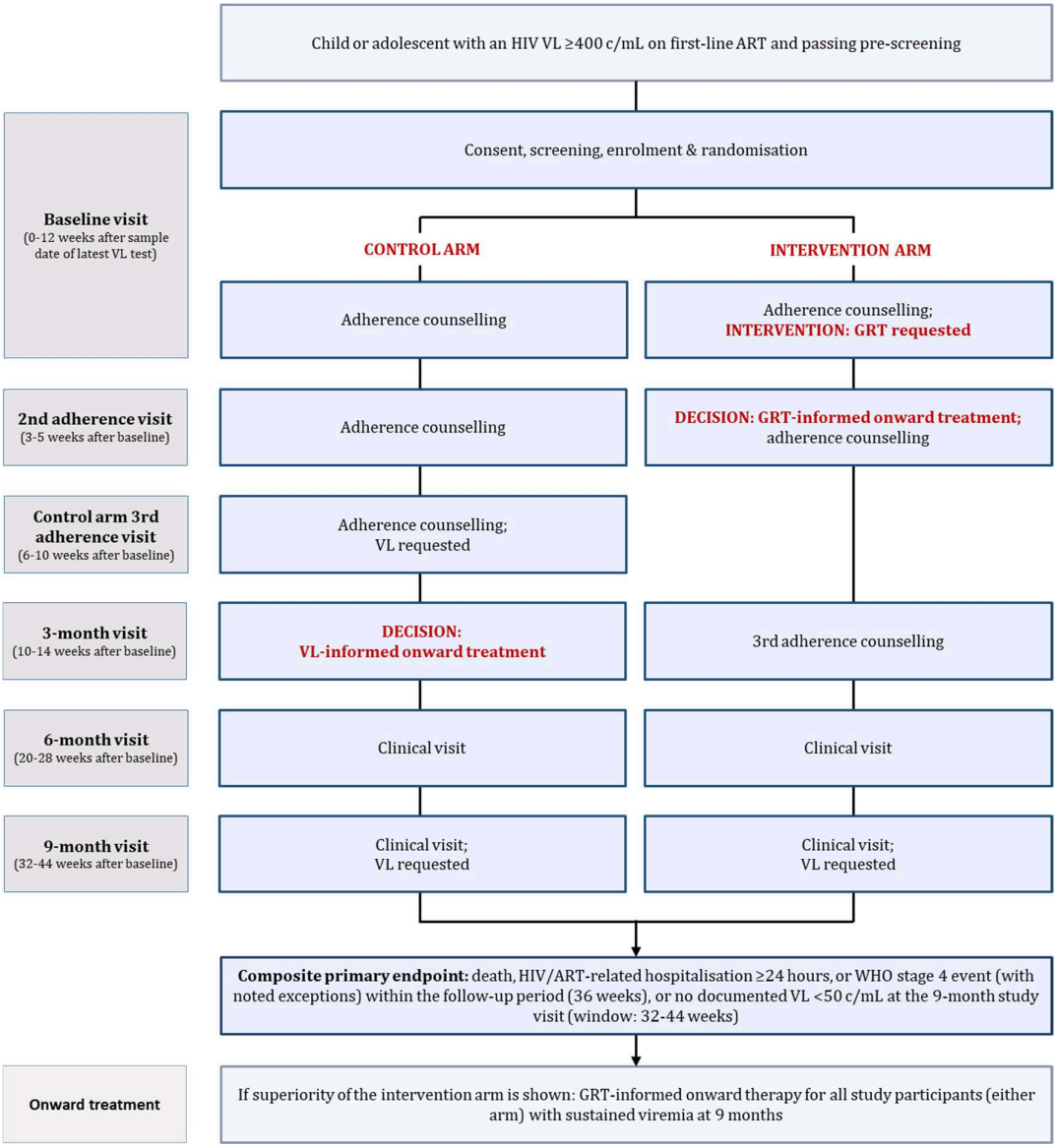

Figure 1: Overview of GIVE MOVE treatment algorithm and study visits. The decision follow-up visit is not shown. GRT: genotypic resistance testing; VL: viral load.

3.1.1 Eligibility

Eligibility criteria are as follows:

Inclusion criteria:

- In care in a study site
- Age ≥6 months and <19 years
- Latest HIV VL result ≥400 c/mL
- On an unchanged ART regimen for ≥6 months
- Phlebotomy for latest VL test <4 months before screening
- Consent given (see section 4.2)

Exclusion criteria:

- Indication for treatment switch according to WHO guidelines at screening
- 1st enhanced adherence counselling session initiated >2 weeks prior to screening
- Intention to transfer out of the study site (and not into a different study site) within 3 months after randomization
- Already enrolled in another study if judged as non-compatible by the (Local) Principal Investigator
- Pregnant or breastfeeding at screening (no exclusion based on pregnancy or breastfeeding after enrolment)
- Acute illness requiring hospitalization at screening (no exclusion based on hospitalization after enrolment)
- Received a resistance test within the last 12 months

3.1.2 Objectives and Endpoints

The trial objectives are:

Primary Objective: To assess if GRT-based management of viremia in CALHIV on ART in resource-limited settings improves overall health outcomes. The results of this trial are intended to inform future WHO and national guidelines on the use of GRT in CALHIV.

Secondary Objectives: To assess the impact of GRT-based management of viremia in CALHIV on various individual health outcomes including mortality, morbidity, and virologic status.

Exploratory Objectives: To assess the dynamics of viral resuppression and the viral development of drug resistance without vs with GRT-based management of viremia.

The primary and secondary endpoints of the trial are:

Primary endpoint

The trial is powered to detect a significant reduction of the composite primary endpoint in the intervention arm compared to the control arm. The composite primary outcome is comprised of: i) death due to any cause during the follow-up period (36 weeks), ii) HIV- or ART-related hospital admission of ≥24 hours duration (possibly, probably or definitely related to HIV or ART, judged by the endpoint committee blinded to the study arm) during the follow-up period (36 weeks), iii) new clinical WHO stage IV event (excluding lymph node tuberculosis, stunting, oral or genital herpes simplex infection and oesophageal candidiasis; judged by the endpoint committee blinded to the study arm) during the follow-up period (36 weeks), and iv) no documentation of a suppressed VL (<50 c/mL) at 9 months follow-up (window: 32-44 weeks).

The primary endpoint will be assessed as an event ratio of participants reaching any of the above-mentioned composite endpoints.

An endpoint committee whose members are unaware of study arm assignments will review all reported WHO stage IV events and hospitalizations and determine if the events in question qualify as endpoints.

Secondary endpoints

- Separate analyses of the four components of the primary endpoint, namely:
  - Death due to any cause
  - HIV- or ART-related hospital admission of ≥24 hours duration (possibly, probably or definitely related to HIV or ART, judged by the endpoint committee blinded to the study arm)
  - New clinical WHO stage IV event (excluding lymph node tuberculosis, stunting, oral or genital herpes simplex infection and oesophageal candidiasis, judged by the endpoint committee blinded to the study arm)
  - No documentation of a suppressed VL (<50 c/mL) at 9 months follow-up (window: 32-44 weeks)
- Loss to follow-up, defined as no documented clinic visit in the window period (32-44 weeks) of the 9-month study visit
- Observed virologic failure, defined as a VL ≥50 c/mL, at the 9-month study visit (window: 32-44 weeks) among participants who had a viral load result at the 9-month study visit
- Composite endpoint (see primary endpoint above) assessed at 6 months (window: 20-28 weeks) after the decision on the regimen for onward treatment (i.e. after the follow-up VL result in the control arm or a GRT result in the intervention arm should be available)

Exploratory endpoints

1. Time to viral resuppression (<50 c/mL; considering VL testing done with samples from the 3-, 6- and 9-month study visit in both arms)
2. Drug regimen switches in the absence of major drug resistance mutations and non-switches in the presence of major drug resistance mutations (as identified by Sanger sequencing, according to the Stanford HIV drug resistance database)
3. Emergence of new drug resistance mutations within the study period (i.e. measured drug resistance at the 9-month visit vs at the baseline visit)

3.2 Randomization

Certain baseline factors may have an effect on the primary and secondary endpoints, including the site, age, gender, and the participant's ART regimen at enrolment. In order to minimise bias, randomisation was stratified by:

- Country (Lesotho or Tanzania)
- Age at enrollment ([≥ 6 months to <12 years] vs [≥12 years to <19 years])
- ART regimen at enrolment (NNRTI-based, protease inhibitor (PI)-based, or integrase strand transfer inhibitor (INSTI)-based regimen)

In children, gender is unlikely to have a major impact on outcomes. Given the sample size and the relatively even gender distribution (expected female to male ratio approximately

3:2), a strong clustering effect is unlikely. However, gender will be considered in the planned subgroup analysis.

Eligible and consented patients are consecutively enrolled and randomised in a 1:1 ratio to the intervention and control arms. Randomisation is stratified according to the factors listed above, using permuted blocks with varying block size. Randomisation is automated using the MACRO electronic data capture software (Elsevier; see chapters 4.3 Study procedures, and 8.2 Data recording and source data). Randomisation of a participant is performed once eligibility and consent have been confirmed and entered into the database, thereby maintaining concealment of allocation.

3.3 Sample size

The sample size was estimated with the aim of showing a significant reduction of the composite primary endpoint in the intervention arm compared to the control arm. The significance level was chosen to be 5%, while the power was chosen to be at least (1-β) = 80%.

Based on the available literature and own experience at the study sites, we compared various realistic scenarios of what ratio of participants would reach the primary endpoint in each study arm (see Table 1).

Table 1: Sample size for different scenarios with 80% power and α = 0.05.

Difference[a]	**PInt**	**PC**	**n (per arm)**
20%			
	0.25	0.45	89
	0.20	0.40	82
	0.15	0.35	73
15%			
	0.25	0.40	152
	0.20	0.35	138
	0.15	0.30	121

[a] Reduction of the event rate for the treatment group compared to the control group. P_{Int}: Probability of event in the intervention group; P_C: Probability of event in the control group.

As our hypothesis for the sample size calculation, we selected the scenario in which 20% vs 35% of participants reach the primary endpoint in the intervention vs the control arm. Using a Pearson's chi-squared test with a significance level of 5% and a power of 80%, a required sample size of calculated (see Table 1).
Participants prematurely leaving the study will not be replaced.

3.4 Framework

This is a superiority trial.

3.5 Statistical interim analyses and stopping guidance

One formal interim analysis is planned. The cut-off for this interim analysis is planned when 138 participants (50% of the intended sample size) have completed the 9-month study visit and/or reached the primary endpoint. The same analysis as planned for the final analysis will be performed for the composite primary endpoint. However, only stratification variables will be included in the analysis and no sensitivity analyses will be done.

The trial may be concluded early for success if a significant difference between the two trial arms for the composite primary endpoint is achieved at the time of the interim analysis. We will use the conservative Haybittle-Peto stopping level of p=0.001 [3].

In addition, premature stopping due to futility will be considered if obtaining a difference of ≥10 percentage points between the study arms is unlikely to be demonstrated. The trial will be stopped for inefficacy if the odds ratio is greater than 1 and the two-sided 95% confidence interval does not contain the alternative hypothesis (i.e., odds ratio of 0.57) [4].

The interim analysis will be performed by an external independent statistician at an external data analysis center, who will not be involved in the study conduct and will be blinded for the treatment allocation. The results will be reviewed by a Data Safety Monitoring Board, who will issue a recommendation to continue or stop the trial to the Steering Committee. The Steering Committee will vote on and thereby determine the continuation or termination of the trial. In the event of a tie, the Sponsor/Chief Investigator will cast the deciding vote.

3.6 Timing of final analysis

Outcomes will be analysed after the last participant has completed the study.

3.7 Timing of outcome assessments

Table 2 shows the timing of outcome assessments, the permitted ranges according to the protocol, and the ranges that will be used for analysis. The protocol provides all times in months and weeks. The lower and upper limits of the analysis windows correspond to the lower and upper protocol-defined limit, respectively.

If more than one value of the viral load outcome is collected during the analysis window, the first one in the analysis window will be used.

Table 2. Follow-up and permitted windows for endpoints.

Follow-up, months	Follow-up, weeks	Range according to the protocol, weeks	Analysis window, days
3	12	10 – 14	>=70 and <98
6	24	20 – 28	>=140 and <196
9	36	32 – 44	>=224 and <308
9	44	Up until study completion*	<308

4. Statistical principles

4.1 Confidence intervals and p-values

Statistical tests and confidence intervals will be two-sided. All estimates will be presented with 95% confidence intervals. P-values will be presented where appropriate. No adjustments will be made for multiple testing; interpretations will be based on the strength of evidence of effect size and consistency of results for related outcomes.

4.2 Adherence protocol violation and deviation

We follow the standard definition of protocol violations and deviations.

Specifically we consider the following as major deviations:

- Not attending the decision visit within six months (defined as 24 weeks) after randomization
- Individuals in the control arm not receiving a VL to inform the decision visit
- Individuals in the intervention arm not receiving GRT to inform their decision visit, except for cases where GRT was not possible due to resuppression to <400 copies/mL
- Not having a VL result within the 9-month window and not having reached the primary endpoint before or at the 9-month visit (Figure 1)
- Individuals in the control arm receiving a GRT before completing the study

As violations we consider any enrolment of an individual not fulfilling the eligibility criteria at the moment of enrolment.

4.3 Analysis populations

Analyses will be performed following the CONSORT guidelines [5]. Individuals are the unit of analysis. The following analysis sets will be used in this trial:

The full analysis set (FAS) will include all participants as randomised. All statistical analyses will be performed on the modified intention-to-treat (mITT) set, which will exclude participants found to be ineligible for the study only after randomization (i.e., with violations).

A per-protocol (PP) analysis set will include all randomized participants who completed the study without a protocol violation or major deviation. The primary endpoint will also be performed on the PP analysis set.

5. Trial population

5.1 Eligibility

Screening/eligibility data will be summarized in a CONSORT flowchart, showing the total number of individuals screened and the reasons for screening failures as per eligibility criteria in section 3.1.1.

5.2 Recruitment

The CONSORT flowchart will include the numbers of participants randomized to each of the two trial arms.

5.3 Withdrawal/follow-up

The CONSORT flowchart will summarize enrolment, decision, 6, and 9-month study visit for each participant, by randomized group. Reasons will be given for participants who did not complete follow-up as expected.

5.4 Baseline patient characteristics

Baseline characteristics will be summarized by randomized group, using medians and interquartile ranges for continuous variables and numbers and percentages for categorical variables. Shell tables showing the variables and categories are included in section 8. Assessment will be made for baseline imbalances between the randomization groups by visual inspection only, by the trial team before looking at outcome data. In analyses, we will further adjust the outcome analyses for any covariates found to be imbalanced and potentially relevant to the outcome (erring on the side of inclusivity). There will be no formal testing of baseline characteristics across randomized groups [6].

6. Analysis

Time will be measured from the date of the baseline/enrolment visit.

Programming of the data analysis will be done by the trial statistician. This code for the primary outcome analysis will be checked for validity by the external independent statistician who will then use the final validated code to conduct the interim analysis.

6.1 Outcome definitions

The VL of participants who did not have a VL measured for the primary and secondary endpoints within the required window will be considered as missing. This includes not having a visit within the respective window, visits without a blood draw, and blood draws with no result available. Missing VL will be counted as having achieved the primary endpoint, i.e. considered as an unsuppressed VL. Clarification of secondary and other outcome definitions are provided in section 3.1.2.

6.2 Analysis methods

Continuous variables will be inspected using histograms: 1) to assess for outliers which may be queried for accuracy, and 2) to assess whether appropriate transformations are required for modeling.

Endpoints will be summarized using medians and interquartile ranges for continuous variables and numbers and percentages for categorical variables, by randomized group. Percentages will be reported to one decimal place.

We will present numbers and proportions of participants achieving each of the four components of the composite endpoint separately. Those with missing VL results will be handled as

described in section 6.1 and reasons for missing VL results will be provided.

For the analysis of the primary outcome, we will use a logistic regression model adjusted for the randomization stratification factors (country, age, and ART regimen; see section 3.2) and relevant baseline characteristics found to be unbalanced between intervention and control clusters (as described above in section 5.5). Results will be reported as odds ratios with 95% confidence intervals. Further, we will estimate the absolute risk difference, with 95% confidence intervals estimated using the delta method [7].

Sensitivity analyses

In a first sensitivity analysis for the primary outcome, we will analyze the PP set (see section 4.2). Protocol violations and deviations will be described. We will summarize the data (numbers and proportions of participants included in this analysis, and meeting the primary endpoint), and fit logistic regression models as for the main primary outcome analysis.

As a second sensitivity analysis of the primary outcome, we will also consider an additional two definitions of viral suppression - <400 and <1000 copies/mL.

Subgroup analysis

Effect modification of the primary endpoint by country (Lesotho or Tanzania), gender (male or female), age ([≥6 months to <12 years] or [≥12 years to <19 years]), and ART regimen at enrolment (NNRTI-, PI-, or INSTI-based regimen) will be assessed by incorporating an interaction between arm and the effect modifier acknowledging that power will be low. Regimens at enrolment containing more than one of the above-mentioned ART types will be classified as INSTI-based if they contain at least one INSTI as well as one or more PI(s) and/or NNRTI(s), and as PI-based if they contain at least one PI and one or more NNRTI(s). If there are small numbers of participants within certain subgroups, then such an approach may not be feasible and instead we would restrict the model to the subgroups of sufficient size. If the interaction term is found to be significant, effect estimates will be summarized by subgroup. As the study is not powered for these pre-planned subgroup analyses, these results will be considered exploratory.

Secondary endpoints

For the secondary endpoints defined by the individual components of the composite outcome, we will summarize the number and proportion of participants meeting each endpoint definition as described in 3.1.2. We will follow the same approach as for the main primary outcome analysis if numbers allow, otherwise we will compare the endpoints between the study arms using a chi-squared or Fischer's exact test (in the case of limited events).

For the remaining secondary endpoints, we will follow the same approach as for the main primary outcome analysis if numbers allow. All analyses of secondary outcomes will be done on the mITT set.

Exploratory endpoints

If the number of events is sufficient, the exploratory endpoint of time to documented viral suppression will be assessed using Kaplan Meier estimation and Cox proportional hazard models adjusted for the stratification factors, reporting hazard ratios and 95% confidence intervals.

The exploratory endpoints of drug regimen switches and emergence of new drug resistance mutations will be compared between the study arms using a chi-squared or Fischer's exact test (in the case of limited events).

6.3 Missing data

Where applicable, percentages of baseline and endpoint data will be of non-missing values, with the number (%) of missing values given if data are not complete. As detailed in section 6.2, main analyses of the primary and the secondary outcomes (with the exception of virological failure) will include all participants as randomized with missing virological data counted as failures.

For the secondary outcome of unobserved virologic failure, only individuals with a valid viral load result in the specified window will be included in the analysis.

Where significant amounts of data are missing in important covariates, we may consider multiple imputation as sensitivity analyses if necessary and compare results to models ignoring missing data [8].

6.4 Additional analyses

Two nested studies about cost-effectiveness and drivers of viremia will be analysed separately.

6.5 Harms

Safety data is collected and serious adverse events will be summarized by study arm. Further details about safety procedures and reporting are described in the protocol.

6.6 Statistical software

Analyses will be conducted in Stata version 16.

7. References

1. C G, A K, D S, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA **2017**; 318. Available at: https://pubmed.ncbi.nlm.nih.gov/29260229/. Accessed 30 June 2020.
2. Brown JA, Ringera I, Luoga E, Cheleboi M, Kimera N, Muhairwe J, Kayembe BP, Molapo Hlasoa M, Kabundi L, Yav CWD, Mothobi B, Thahane L, Amstutz A, Bachmann N, Mollel GJ, Bresser M, **Glass TR**, Paris DH, Klimkait T, Weisser M, Labhardt ND. Genotype-Informed Versus Empiric Management Of VirEmia (GIVE MOVE): study protocol of an open-label randomised clinical trial in children and adolescents living with HIV in Lesotho and Tanzania. BMC Infect Dis. 2020 Oct 19;20(1):773.
3. UNICEF . *Key HIV epidemiology indicators for children and adolescents aged 0–19, 2000–2018.* 2019. [Google Scholar]
4. Bavinton BR, Pinto AN, Phanuphak N, Grinsztejn B, Prestage GP, Zablotska-Manos IB, et al. Viral suppression and HIV transmission in serodiscordant male couples: an international, prospective, observational, cohort study. *Lancet HIV.* 2018;**5**:e438–e447. doi: 10.1016/S2352-3018(18)30132-2. [PubMed] [CrossRef] [Google Scholar]
5. Rodger AJ, Cambiano V, Bruun T, Vernazza P, Collins S, van Lunzen J, et al. Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. *JAMA.* 2016;**16**:171–181. doi: 10.1001/jama.2016.5148. [PubMed] [CrossRef] [Google Scholar]
6. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med.* 2011;**365**:493–505. doi: 10.1056/NEJMoa1105243. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
7. UNAIDS . *UNAIDS data 2020.* Geneva: UNAIDS; 2020. [Google Scholar]
8. Inzaule SC, Ondoa P, Peter T, Mugyenyi PN, Stevens WS, de Wit TFR, et al. Affordable HIV drug-resistance testing for monitoring of antiretroviral therapy in sub-Saharan Africa. *Lancet Infect Dis.* 2016;**16**:e267–e275. doi: 10.1016/S1473-3099(16)30118-9. [PubMed] [CrossRef] [Google Scholar]
9. World Health Organisation . *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach.* 2. Geneva: WHO; 2016. [Google Scholar]
10. Aves T, Tambe J, Siemieniuk RA, Mbuagbaw L. Antiretroviral resistance testing in HIV-positive people. *Cochrane Database Syst Rev.* 2018;**11**:CD006495. [PMC free article] [PubMed] [Google Scholar]
11. Levison JH, Wood R, Scott CA, Ciaranello AL, Martinson NA, Rusu C, et al. The clinical and economic impact of genotype testing at first-line antiretroviral therapy failure for HIV-infected patients in South Africa. *Clin Infect Dis Off Publ Infect Dis Soc Am.* 2013;**56**:587–597. doi: 10.1093/cid/cis887. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
12. Rosen S, Long L, Sanne I, Stevens WS, Fox MP. The net cost of incorporating resistance testing into HIV/AIDS treatment in South Africa: a Markov model with primary data. *J Int AIDS Soc.* 2011;**14**:24. doi: 10.1186/1758-2652-14-24. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
13. Phillips A, Cambiano V, Nakagawa F, Mabugu T, Magubu T, Miners A, et al. Cost-effectiveness of HIV drug resistance testing to inform switching to second line antiretroviral therapy in low income settings. *PLoS One.* 2014;**9**:e109148. doi: 10.1371/journal.pone.0109148. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

14. Siedner MJ, Bwana MB, Moosa M-YS, Paul M, Pillay S, McCluskey S, et al. The REVAMP trial to evaluate HIV resistance testing in sub-Saharan Africa: a case study in clinical trial design in resource limited settings to optimize effectiveness and cost effectiveness estimates. *HIV Clin Trials.* 2017;**18**:149–155. doi: 10.1080/15284336.2017.1349028. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
15. ClinicalTrials.gov . *Impact of HIV drug resistance testing, and subsequent change to an individualized therapy in Tanzania.* 2018. [Google Scholar]
16. ClinicalTrials.gov . *Optimizing viral load suppression in Kenyan children on antiretroviral therapy.* 2019. [Google Scholar]
17. Schulz KF, Grimes DA. Multiplicity in randomised trials II: subgroup and interim analyses. Lancet (London, England) **2005**; 365:1657–61. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15885299. Accessed 13 August 2020.
18. Freidlin B, Korn EL, Gray R. A general inefficacy interim monitoring rule for randomized clinical trials. Clin Trials **2010**; 7:197–208. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20423925. Accessed 13 August 2020.
19. Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med. 2010;152(11):726-732. doi:10.7326/0003-4819-152-11-201006010-00232
20. Pocock SJ, Assmann SE, Enos LE, Kasten LE. Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practiceand problems. Stat Med **2002**; 21:2917–2930. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12325108. Accessed 21 August 2019.
21. Norton E, Miller M, Kleinman L. Computing Adjusted Risk Ratios and Risk Differences in Stata. Stata J Promot Commun Stat Stata **2013**; 13:492–509.
22. Sullivan TR, White IR, Salter AB, Ryan P, Lee KJ. Should multiple imputation be the method of choice for handling missing data in randomized trials? Stat Methods Med Res **2018**; 27:2610–2626. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28034175. Accessed 30 June 2020.

8. Shell tables

Presented below are the shell tables for the baseline characteristics, to illustrate the variables included.

Table 8.1. Baseline characteristics by group: demographic

	Variable	Control	Intervention	Total
Number randomized (mITT)	arm			
Country	Stsite_der			
Tanzania				
Lesotho				
Age, years	age			
≥6 months to <12 years	agegr_der			
≥12 years to <19 years				
ART regimen	regimen_der2			
NNRTI-based				
PI-based				
INSTI-based[1]				
Sex, female	sex			
Primary caregiver	care			
Both parents				
Mother				
Father				
Grandparent(s)				
Other				
Parent vital status				
Mother alive	mothervit			
Father alive	fathervit			
Treatment supporter (other than caregiver)	trtsup			
Yes				
No				
Unknown				
Main transportation to health facility	travmod			
Walk				
Ride horse/donkey				
Taxi/Public transport				
Bicycle				
Own or borrowed motorized vehicle				
Other				
Cost of health facility visit				
One-way travel time	travtim			
One-way travel cost	travcost			
Tanzania (TZS)	curr			
Lesotho (LSL/ZAR)				

Results are n (% of those with non-missing data) for categorical variables and median (IQR) for continuous variables.
[1] In cases where an individual was on a PI and INSTI, they were categorized as being on an INSTI-based regimen.

Table 8.2. Baseline characteristics by group: clinical

	Variable	Control	Intervention	Total
Number randomized (mITT)				
Time since HIV diagnosis (years)	time_since_hiv_yrs			
Time since ART start (years)	time_on_art_yrs			
WHO stage at ART initiation	whoart			
T1				
T2				
T3				
T4				
Uknown				
CD4-based immunodeficiency at ART initiation	Cd4artyn, cd4artpcyn			
Available				
No/no significant				
Mild				
Advanced				
Severe				
Weight, kg	wt			
Height, cm	ht			
MUAC (cm) [1]	muac			
Nutritional status	nutrst			
Not malnourished				
Mild				
Moderate				
Severe				
Overweight/obese				
Nutritional supplement	nutrsup			
Therapeutic				
Supplemental				
Both				
Neither				

Results are n (% of those with non-missing data) for categorical variables and median (IQR) for continuous variables.

Table 8.3. Baseline characteristics by group: laboratory.

	Variable	Control	Intervention	Total
Number randomised				
CD4-based immunodeficiency at baseline				
Available				
No/no significant				
Mild				
Advanced				
Severe				
HbsAg				
Positive				
Negative				
Haemoglobin				
Leucocyte				
Platelets				
Serum Creatinine				

Results are n (% of those with non-missing data) for categorical variables and median (IQR) for continuous variables.
[1] Only measured in those aged 6 months to 5 years.

Table 8.4. Primary outcome

	N	Control N (%)	Intervention n (%)	Odds Ratio (95% CI)	Risk difference (95% CI)
Number randomized					
mITT					
PP set					