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

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Study Type:	Other Clinical Trial according to the Swiss Human Research Act (HRA) 2014, Ordinance on Clinical Trials in Human Research (ClinO), Chapter 4
Risk Categorisation:	Risk Category A (lowest risk category; according to HRA, ClinO, Chapter 4)
Study Registration:	ClinicalTrials.gov: NCT04233242
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Investigated Intervention:	Genotype-informed management of unsuppressed viremia in children and adolescents living with HIV
Protocol ID	*Lesotho:* National Health Research Ethics Committee: ID 229-2019 *Tanzania:* Ifakara Health Institute Institutional Review Board: IHI/IRB/No. 12-2020; IHI/IRB/EXT/No. 10-2021 National Institute for Medical Research: NIMR/HQ/R.8a/Vol IX/3442; NIMR/HQ/R.8a/Vol I/1768 Tanzania Medicines and Medical Devices Authority: TMDA0020/CTR/0003/03 *Switzerland:* Ethikkommission Nordwest- und Zentralschweiz: Req-2019-01275
Version and Date:	Version 1.4 (23.08.2021)

CONFIDENTIALITY STATEMENT

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PROTOCOL SIGNATURE FORM

The following persons have approved the GIVE MOVE protocol version 1.4 (23.08.2021) and confirm hereby to conduct the study according to the protocol, the current version of the World Medical Association Declaration of Helsinki, and ICH GCP E6R2 guidelines as well as the local legally applicable requirements.

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GLOSSARY OF ABBREVATIONS

AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ASR	Annual Safety Repot
BASEC	Business Administration System for Ethical Committees
CALHIV yearsCDCI	Children and Adolescents Living with HIV; defined as ≥6 months and <19 Chronic Diseases Clinic Ifakara (at St. Francis Referral Hospital; affiliated with IHI)
ClinO	Ordinance on Clinical Trials in Human Research
CRF	Case Report Form
FBC	Full Blood Count
EAC	Enhanced Adherence Counselling
eCRF	electronic Case Report Form
EKNZ	Ethikkommission Nordwest- und Zentralschweiz
EVAg	European Virus Archive global
FAS	Full Analysis Set
FPFV	First Participant First Visit
FPLV	First Participant Last Visit
GCP	Good Clinical Practice
GIVE MOVE	Genotype-Informed Versus Empiric Management of Viremia
GRT	Genotypic Resistance Testing
HBV	Hepatitis B Virus
HIV	Human Immunodeficiency Virus
HRA	Swiss Human Research Act
IAF	Informed Assent Form
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IHI	Ifakara Health Institute
INSTI	Integrase Strand Transfer Inhibitor
IRB	Institutional Review Board
LPFV	Last Participant First Visit
LPLV	Last Participant Last Visit
MDH	Management and Development for Health (Tanzania)
NIMR	National Institute for Medical Research (Tanzania)
NNRTI	Non-nucleoside reverse transcriptase inhibitor
PI	Protease Inhibitor
RCT	Randomised Clinical Trial
SAE	Serious Adverse Event
Swiss TPH	Swiss Tropical and Public Health Institute
UNAIDS	United Nations Programme on HIV/AIDS
USB	University Hospital Basel (Universitätsspital Basel)
VL	Viral Load
WHO	World Health Organisation

1 STUDY SYNOPSIS

Sponsor / Chief Investigator	Prof. Niklaus Labhardt Clinical Research Unit, Department of Medicine, Swiss Tropical and Public Health Institute Socinstrasse 55, 4051 Basel, Switzerland +41 79 870 18 59; n.labhardt@swisstph.ch
Study Title	Genotype-Informed Versus Empiric Management Of VirEmia (GIVE-MOVE): An Open-Label Randomised Clinical Trial
Short Title / Study ID	GIVE MOVE
Protocol Version and Date	Version 1.4 (23.08.2021)
Study Registration	ClinicalTrials.gov: NCT04233242
Study Category and Rationale	Category A (lowest risk category according to the Swiss Human Research Act (HRA) 2014, Ordinance on Clinical Trials in Human Research (ClinO), Chapter 4). Rationale for risk categorisation: The trial's intervention, Genotypic Resistance Testing (GRT) and GRT-informed treatment, is part of standard care for people living with HIV in most high-income countries. The intervention is not expected to pose any risks beyond those present in standard care. Additional blood collection required by the study will be limited to age-appropriate volumes. Data collection and questionnaires are expected to pose only minimal risks. All study participants will be treated with antiretroviral drugs licenced in Lesotho and Tanzania, using indications and dosages as defined in WHO guidelines as well as Tanzania and Lesotho guidelines.
Background and Rationale	Children and adolescents are highly vulnerable to adverse health consequences (including impaired growth and neurocognitive development) caused by HIV. Unlike adults, children and adolescents living with HIV (CALHIV) and receiving antiretroviral therapy (ART) in sub-Saharan Africa suffer high rates of treatment failure (approx. 25-40%). Treatment failure may be caused by non-adherence to therapy, incorrect drug dosing, or viral drug resistance. GRT is a diagnostic test to detect drug resistance, allowing for an informed selection of drugs that will be effective in the respective patient. GRT-informed patient management is routine in high-income countries but rarely available in sub-Saharan Africa. We intend to assess the effect of GRT-informed management of unsuppressed viremia on subsequent health outcomes in CALHIV.
Risk / Benefit Assessment	Risks to study participants are minimal (see "Study Category and Rationale" above). Participants in the intervention group will receive and are expected to benefit from GRT-informed onward therapy (optimized drug regimen based on testing the drug resistance profile) already during the study period. In case this study shows that GRT-informed management is superior to standard care, at study closure all participants with an elevated viral load (VL) will receive GRT and GRT-informed onward therapy.
Objective(s)	**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.
Endpoint(s)	**Primary endpoint:** The composite primary endpoint is the occurrence of any one or more of the events 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 one or more of the composite endpoints.

	Secondary endpoints: 1. Separate analyses of the four components of the primary endpoint, namely: a. Death due to any cause b. 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) c. 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) d. No documentation of a suppressed VL (<50 c/mL) at 9 months follow-up (window: 32-44 weeks) 2. Loss to follow-up, defined as no documented clinic visit in the window period (32-44 weeks) of the 9-month study visit 3. 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 4. 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 availability of a follow-up VL result in the control arm or after the availability of a GRT result in the intervention arm) **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)
Study Design	Open-label two-arm randomised clinical trial
Statistical Considerations	Analyses will follow CONSORT guidelines and intention-to-treat principles. Outcomes will be described by arm using summary statistics. The primary outcome, the proportion of individuals not having experienced the primary endpoint, will be assessed using a logistic regression model, reporting odds ratios. Binary secondary outcomes will be evaluated in the same way. Continuous secondary outcomes will be assessed using linear regression models, reporting adjusted mean differences between arms. Time to event outcomes will be assessed using appropriate methods, such as Kaplan-Meier estimation and Cox proportional hazards models. All estimates will be reported with 95% confidence intervals (CI). All models will be adjusted for the stratification factors of country, age, and ART regimen at enrolment. Subgroup analyses are planned by country, age, sex, and ART regimen at enrolment. An interim analysis is planned once 50% of the study participants have completed the 9-month study visit and/or reached the primary endpoint, and stopping criteria for success or futility have been defined.
Inclusion- / Exclusion Criteria	**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 **Exclusion criteria:** - Indication for treatment switch according to WHO guidelines at screening - 1st enhanced adherence counselling (EAC) 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 randomisation - 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 hospitalisation at screening (no exclusion based on hospitalisation after enrolment) - Received a resistance test within the last 12 months Members of vulnerable populations, specifically children and adolescents, will be enrolled in this study. This is justified by i) the minimal risk of the study, ii) the potential benefits through participation in this study, and iii) the fact that there is a shortage of research assessing ways to improve HIV treatment for these age groups. While pregnant and breastfeeding adolescents will not be enrolled, becoming pregnant during the study period will not lead to exclusion given the low risk and potential benefits through participation.
Number of Participants with Rationale	276 participants (138 participants per arm). Taking into account the best available data from the study sites and the literature, we considered various realistic and clinically relevant scenarios. A rate of 20% vs 35% of participants reaching the primary endpoint in the intervention vs control arm necessitates a sample size of 276 participants to reach 80% power.
Intervention arm	The VL ≥400 c/mL before enrolment triggers genotypic resistance testing (GRT), followed by GRT-informed patient management and counselling. Onward treatment is informed by this GRT result.
Control arm	Standard of care according to national guidelines (though using a more conservative cut-off for viral suppression, and enforcing 3 sessions of EAC): The VL ≥400 c/mL before enrolment is followed by 3 sessions of EAC and a follow-up VL test. Onward treatment is informed by this follow-up VL result.
Study procedures	**Baseline study visit** (window: 0-12 weeks after VL test date): - Both arms: o Consent procedure (can be completed before the baseline study visit) o Screening, enrolment and randomisation o Demographic data, medical history o EAC session 1 (if not already completed) o Laboratory: CD4 testing; hepatitis B virus (HBV) testing (if not already known to be HBV-positive), full blood count (FBC) or haemoglobin, serum creatinine o Blood samples taken for storage - Control arm: no further action - Intervention arm: blood draw for GRT **EAC 2 study visit** (window: 3-5 weeks after baseline study visit) - Control arm: EAC session 2 - Intervention arm: GRT-informed EAC session 2; GRT-informed decision on onward therapy **Control arm EAC 3 and follow-up VL study visit** (window: 6-10 weeks after baseline study visit) - Control arm: EAC session 3; blood draw for follow-up VL test - Intervention arm: no visit **3-month study visit** (window: 10-14 weeks after baseline study visit): - Both arms: blood samples taken for storage - Control arm: VL-informed decision on onward therapy - Intervention arm: EAC session 3 **6-month study visit** (window: 20-28 weeks after baseline study visit): - Both arms: blood samples taken for storage **9-month study visit** (window: 32-44 weeks after baseline study visit): - Both arms: blood samples taken for storage; CD4 testing; **VL testing (part of composite primary endpoint)** **Decision follow-up visit** (window: 20-28 weeks after decision, i.e. after availability of the follow-up VL result in the control arm or after availability of the GRT result in the intervention arm): - Both arms: blood samples taken for storage and VL testing - Notes:

	○ Where possible, this study visit may be combined with a study visit described above ○ If required (i.e., if delays occur in the real-life study setting), this visit may also take place after the window period of the 9-month study period Clinical assessments, documentation of ART and co-medication, and adherence assessments will take place at each visit. Additional visits may take place according to standard care (e.g. additional visits after switching drug regimen, depending on the drug regimen selected; clinically indicated visits; etc.) and will be documented. Participants may be asked to return for additional visits if the purpose of a study visit was not fulfilled, e.g. if laboratory results were not ready or phlebotomy was not possible. Missing participants will be traced, contacted and encouraged to return back to care. Serious Adverse Events (SAEs) will be documented, reported, and followed up.
Study Duration and Schedule	29 months: 18-month enrolment period plus up to 11-month follow-up (follow-up window: 32-44 weeks). Planned first participant first visit (FPFV): 03.03.2020 (actual) Planned first participant last visit (FPLV): 10.11.2020 (actual) Planned last participant first visit (LPFV): 03.05.2022 Planned last participant last visit (LPLV): 02.04.2023
Steering Committee	**Sponsor and Chief Investigator:** Prof. Dr Niklaus Labhardt, MD, MIH +41 79 870 18 59 n.labhardt@swisstph.ch **Principal Investigator:** Jennifer Brown, MSc, MAS +41 79 512 97 16 jennifer.brown@unibas.ch **Expert Virology and Diagnostics:** Prof. Dr Thomas Klimkait, PhD +41 61 207 32 72 thomas.klimkait@unibas.ch **Clinical Advisor:** Dr Josephine Muhairwe, MD, MPH +266 5325 9839 j.muhairwe@solidarmed.ch **Clinical Coordinator Baylor (1), Lesotho:** Dr Buntshi Paulin Kayembe, MD +266 5977 5684 bkayembe@baylorlesotho.org **Clinical Coordinator Baylor (2), Lesotho:** Dr Mosa Molapo Hlasoa, MD +266 5896 2045 mmolapohlasoa@baylorlesotho.org **Lesotho Principal Investigator / Study Manager:** Isaac Ringera, MPH, RN +266 5677 1018 i.ringera@solidarmed.ch **Clinical Coordinator CDCI, Tanzania:** Prof. Dr Maja Weisser, MD +41 61 328 67 42 maja.weisser@usb.ch **Tanzania Principal Investigator / Local Principal Investigator, Ifakara Tanzania:** Dr Ezekiel Luoga, MD +255 768 351 248

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Study Centres	**Countries:** Lesotho and Tanzania **Number of centres:** 10 **Centres:** One-Stop Clinic and Chronic Diseases Clinic Ifakara (CDCI) at St. Francis Referral Hospital (affiliated with the Ifakara Health Institute (IHI)) Address: Off Mlabani Passage, P.O. Box 53, Ifakara, Tanzania Temeke Regional Referral Hospital Address: Box 45232, Dar es Salaam, Tanzania Mbagala Rangi Tatu Hospital Address: Box 45232, Dar es Salaam, Tanzania Upendano Dispensary Address: Box 70225, Dar es Salaam, Tanzania Baylor Clinic Butha-Buthe Address: Butha-Buthe Government Hospital Compound, Butha-Buthe 400, Lesotho Baylor Clinic Mokhotlong Address: Mokhotlong Government Hospital Compound, Main Road, Mokhotlong, Lesotho Baylor Clinic Leribe Address: Motebang Hospital Compound, Hlotse, Leribe, Lesotho Seboche Mission Hospital Address: P.O. Box 304, Butha-Buthe, Lesotho Baylor Clinic Maseru Address: Baylor COE Maseru, Maseru, Lesotho Baylor Clinic Mohale's Hoek Address: Ntsekhe Hospital Compound, P.O. Box 29, Mohale's Hoek, Lesotho
Data privacy	Data will be captured with the MACRO electronic data capture software (Elsevier), which creates an audit trail. The relevant study team members have received and/or will receive GCP training as well as training on using the MACRO software. Paper-based CRFs may be used as a back-up, in which case data will be transferred to MACRO.. All data and biological samples will be coded and stored securely, and only key authorised study team members as well as authorised auditors and monitors may be granted full access to source data and to all study-related files and samples. All involved parties will keep the patient data strictly confidential. Study data will be archived for at least 10 years after study termination. Biological material will be labelled with a unique identifier. Biological material and data may be used for further research. Transfer agreements will be requested from the respective IRBs / ethics committees in each project country. After publication of the study findings, a dataset from which all identifying information has been removed will be made publicly available using a public data repository platform. For quality assurance, monitoring is planned at key stages in the study. Sites in Lesotho will be monitored by the Clinical Operations Unit at the Swiss Tropical and Public Health Institute (Swiss TPH); the site in Tanzania will be monitored by the IHI.
Ethical considerations	GIVE MOVE attempts to answer clinically relevant questions relating to populations for whom targeted research is lacking. This trial entails minimal risks and may benefit participants' health

	through providing access to diagnostic tests (GRT) that can play an important role in clinical decision-making but are not routinely available at the study sites. Participation is voluntary, and consent/assent can be withdrawn at any time without affecting the patient's clinical care. Measures to ensure confidentiality and protect patient rights include the use data capture software that creates an audit trail, GCP training for key study team members, and monitoring activities at key stages in the study in order to ensure quality and ICH GCP E6R2 adherence.
GCP Statement	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH GCP E6R2, the Swiss Human Research Act (HRA) 2014, as well as other locally relevant legal and regulatory requirements.

2 BACKGROUND AND RATIONALE

2.1 Scientific background and knowledge gaps

Three million children and adolescents worldwide are living with HIV, and over 350 die from HIV/AIDS-related causes every day (2017)[1,2]. Sub-Saharan Africa remains the most heavily affected region, accounting for almost 90% of children and adolescents living with HIV (CALHIV)[2]. However, paediatric HIV is vastly understudied[3–5] and is listed as a neglected disease[6].

Substantial progress has been made towards providing life-saving antiretroviral therapy (ART) to all people living with HIV. ART can suppress viral replication and prevent HIV transmission to sexual partners and own children[7–9], and early, successful ART is key to child development as it reduces mortality and morbidity, improves neurocognitive and growth outcomes[10,11], lowers the risk of drug resistance, and preserves future therapy options. However, unlike adults, CALHIV suffer high treatment failure rates of 25—40%[3,12–21], with adolescents having the poorest outcomes of all age groups[3,15,22]. Treatment failure can result in AIDS, death and further transmission of HIV at the onset of sexual activity.

Most ART failure is caused by non-adherence to therapy and/or HIV drug resistance, though the underlying factors differ by age group. In younger children, main drivers include: transmitted drug resistance from mothers; acquired drug resistance from previous or ongoing incomplete viral suppression[23–26], ongoing poor adherence[27], the lack of child-friendly medication, and the need for regular drug dose adjustments with increasing weight[13]. In adolescents, psychological and stigma-related issues further contribute to poor adherence[28,29].

Despite increasing monitoring of treatment success through viral load testing, most diagnosed treatment failures do not trigger a timely and suitable response[17]. Without resistance testing, healthcare providers cannot determine if treatment failure is caused by drug resistance, necessitating an urgent switch of therapy regimen, or by poor adherence to therapy, in which case unnecessary switching must be avoided to preserve limited treatment options.

Genotypic resistance testing (GRT) provides reliable information on whether unsuppressed viremia is caused by ongoing poor adherence or HIV drug resistance. With increasing levels of HIV drug resistance to first-line ART[30], GRT is likely to become increasingly important in the provision of optimised HIV care. However, since GRT remains unavailable in many low- and lower middle income settings[31], little is known on the clinical value and cost-effectiveness of GRT in these settings. Previous modelling studies[32–34] on the cost-effectiveness of GRT in various countries in sub-Saharan Africa have had discrepant conclusions, and focused only on adults. Likewise, one ongoing randomised clinical trial in South Africa and Uganda, the REVAMP trial, is only enrolling adults[35]. Furthermore, the trial includes only participants on a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based first-line drug regimen, rapidly becoming outdated[36]. Finally, one registered trial in Tanzania employs GRT only upon sustained viremia after counselling[37], potentially missing the opportunity to reduce time to clinical action.

2.2 Research question and intervention

CALHIV on ART in sub-Saharan Africa face high rates of treatment failure, yet evidence on the causes and optimal management of treatment failure in resource-limited settings is lacking. The *Genotype-Informed Versus Empiric Management Of VirEmia* (GIVE MOVE) study attempts to address this gap by assessing the clinical value of GRT-informed management in CALHIV with viremia while on ART. Participants will be randomized to an intervention or a control arm. Participants in the intervention arm will receive GRT-informed clinical management, whereas those in the control arm will receive standard care as per current guidelines of the World Health Organization[38,39].

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 (few WHO stage 4 conditions excluded) or HIV-related hospital admission, and are in care with a suppressed viral load – 9 months after randomisation.

The intervention is described in detail in Chapters 3.4 (Study design) and 3.5 (Study intervention); the objectives, research questions, and endpoints are described in Chapters 3.1 (Hypothesis and objectives) and 3.2 (Primary and secondary endpoints).

2.3 Rationale for study design

We plan an open-label randomised clinical trial for the following two reasons: First, a randomised design will provide the highest level of evidence on the value of GRT in the population studied. Second, the study will be open-label due to the nature of the intervention (GRT results provided to the health care providers) which cannot be blinded. However, laboratory technologists performing viral load (VL) testing and endpoint committee members deciding if a WHO stage 4 event or HIV- or ART-related hospitalisation fulfils the criteria to be considered an endpoint will be blinded.

Lesotho and Tanzania differ greatly along many parameters, including their burden of HIV (adult HIV prevalence: 24.4% in Lesotho[40] vs 4.5% in Tanzania[41]) and their other dominant infectious diseases (high tuberculosis burden in Lesotho vs malaria, tuberculosis and other tropical diseases in Tanzania). Thus, inclusion of both settings will imply external validity of findings for similar resource-limited African settings.

We plan to conduct this study in CALHIV (age range ≥6 months to <19 years) since these population groups are particularly vulnerable to treatment failure and especially children and adolescents have often been neglected in previous HIV research[3–6].

3 STUDY OBJECTIVES AND DESIGN

3.1 Hypothesis and objectives

Hypothesis

We hypothesise that providing resistance information will allow for care to be customised 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.

Based on our available data from the study sites as well as published literature[17,18,42–47], we considered various realistic scenarios for the ratio of participants in either arm that might reach the primary endpoint (i.e., reach one or more of the composites to the primary endpoint) described in Chapter 3.2 (Primary and secondary endpoints). In order to avoid missing a true and clinically relevant effect, we selected a scenario in which 20% vs 35% of participants in the intervention vs control arm reach the primary endpoint as the hypothesis on which we based our calculation of the required sample size.

Objectives

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.

3.2 Primary and secondary endpoints

Primary endpoint

The composite primary endpoint is the occurrence of any one or more of the events 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 one or more of the composite endpoints.

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

Participants who experience a WHO stage IV event (with the noted exceptions) or hospitalisation of ≥24 hours duration (possibly, probably or definitely related to HIV or ART) before 9 months of follow-up may then, if judged beneficial by the clinician in charge and the endpoint committee, receive GRT for the benefit of their health even if they are randomised to the control arm.

Secondary endpoints

1. Separate analyses of the four components of the primary endpoint, namely:
    a. Death due to any cause
    b. 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)
    c. 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)
    d. No documentation of a suppressed VL (<50 c/mL) at 9 months follow-up (window: 32-44 weeks)
2. Loss to follow-up, defined as no documented clinic visit in the window period (32-44 weeks) of the 9-month study visit
3. 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
4. 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 availability of a follow-up VL result in the control arm or after the availability of a GRT result in the intervention arm)

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)

3.3 Randomisation considerations

Potential effect modifiers

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

- Country (Lesotho or Tanzania)
- Age ([≥ 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, sex is unlikely to have a major impact on outcomes. Given the sample size and the relatively even sex distribution (expected female:male ratio approx.3:2), a strong clustering effect is unlikely. However, sex will be considered in the planned subgroup analysis.

Randomisation procedure

Eligible and consented patients will be consecutively enrolled and randomised in a 1:1 ratio to the intervention and control arms. Randomisation will be stratified by country (Lesotho or Tanzania), age ([≥ 6 months to <12 years] vs [≥12 years to <19 years]), and ART regimen at enrolment (NNRTI-, PI-, or INSTI-based regimen), using permuted blocks with varying block size. Randomisation will be 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 will be performed once eligibility and consent have been confirmed and entered into the database, thereby maintaining concealment of allocation.

3.4 Study design

GIVE-MOVE is an open-label, two-arm, multicentre, superiority randomised clinical trial. 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 and the decision on whether a treatment switch or optimisation of the ART backbone is indicated, as well as the choice of the new regimen (if applicable), will be based on GRT results. Participants in the control arm will be managed according to the standard of care based on the current WHO recommendations[38,39], with minor changes: there will be 3, rather than 2-3, sessions of enhanced adherence counselling (EAC); and the viral load cut-off will be set to 400 c/mL, rather than 1000 c/mL. Participants in the control arm will receive 3 EAC sessions at monthly intervals, with a follow-up VL test at the 3rd EAC session. In line with the national guidelines[48,49], the follow-up VL test can be delayed if there is clear evidence of poor adherence to therapy, defined here as i) a pill count of <90%, and/or ii) a self-reported period of no drug intake of ≥2 days in the last 4 weeks. Onward treatment will be informed by the follow-up VL in line with standard care. The composite primary endpoint will be assessed latest 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 hospitalisations and potential WHO stage 4 events constitute an endpoint.

Setting

The sites of enrolment are:

- Baylor Clinic Leribe, Leribe, Lesotho
- Baylor Clinic Butha-Buthe, Butha-Buthe, Lesotho
- Baylor Clinic Mokhotlong, Mokhotlong, Lesotho
- Baylor Clinic Maseru, Maseru, Lesotho
- Baylor Clinic Mohale's Hoek, Mohale's Hoek, Lesotho

- Seboche Mission Hospital, Butha-Buthe, Lesotho
- One-Stop Clinic, Chronic Diseases Clinic Ifakara at St Frances Referral Hospital, Ifakara, Tanzania
- Temeke Regional Referral Hospital, Dar es Salaam, Tanzania
- Mbagala Rangi Tatu Hospital, Dar es Salaam, Tanzania
- Upendano Dispensary, Dar es Salaam, Tanzania

GRT will take place at Seboche Mission Hospital Laboratory, Butha-Buthe, Lesotho; Ifakara Health Institute (IHI) Laboratory, Ifakara, Tanzania. Other laboratory diagnostics will take place at the routine laboratories for the respective sites. If required, sample referral to other laboratories will be acceptable (notably: Pathcare laboratory, South Africa; Lancet laboratory, Tanzania with referral to South Africa; Temeke referral laboratory, Tanzania; others possible if required). Participants give consent for the further use of the provided biological samples for any other biomedical analysis that has been approved by the respective Institutional Review Boards (IRBs) / ethics committees (samples from Lesotho: National Health Research and Ethics Committee (NH-REC); samples from Tanzania: IHI IRB and National Institute for Medical Research (NIMR)). For this purpose, samples labelled with a unique identifier may be transferred to Switzerland if the respective analyses cannot be performed in the GIVE MOVE GRT laboratory in the respective project country (Seboche Mission Hospital Laboratory, Butha-Buthe, Lesotho / IHI Laboratory, Ifakara, Tanzania).

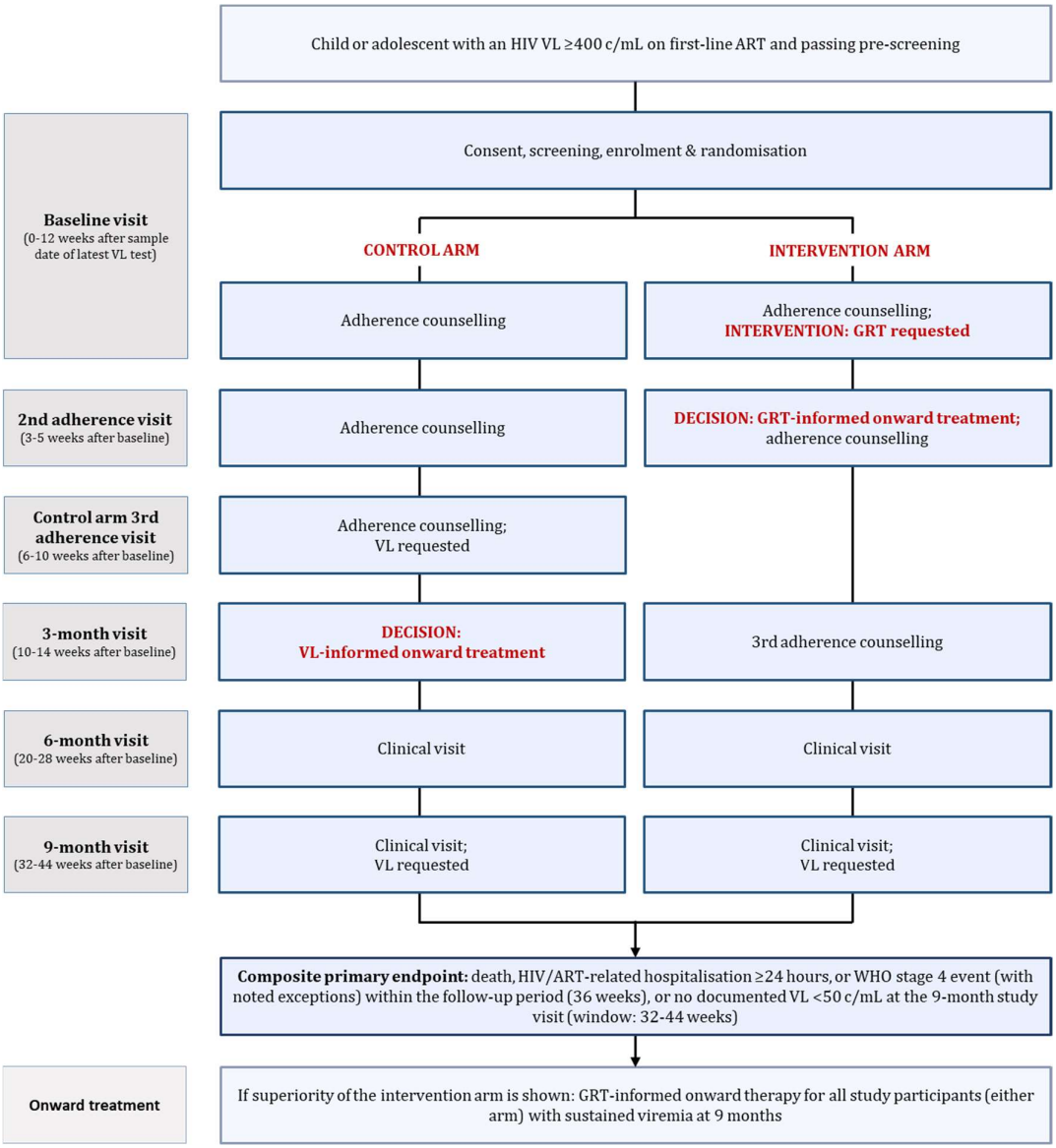

Figure 1: Overview of GIVE MOVE treatment algorithm and study visits. The decision follow-up visit is not shown. Further visits may be indicated, e.g. for follow-up testing upon drug regimen switches (dependent on the choice of new drug regimen) or in the case of pregnancy/breastfeeding, and will be documented. EAC: enhanced adherence counselling; GRT: genotypic resistance testing; VL: viral load. For detailed procedures at each study visit, see Table 3.

3.5 Study intervention

The study intervention will consist of the following components:

1. Genotypic resistance testing (GRT);
2. Secure forwarding of GRT results to an expert committee for review;
3. Secure forwarding of GRT results with the expert committee's treatment recommendation to the healthcare provider, ensuring GRT triggers rapid clinical action;
4. GRT-based decision on further therapy (switch or maintain current ART regimen; choice of regimen); and
5. GRT-informed adherence support.

3.6 Nested Study on Cost-Effectiveness

In a nested study, we intend to assess the cost and cost-effectiveness of GRT for CALHIV with viremia while on ART if superiority of the intervention arm is shown. Costs to the healthcare facilities will be documented (cost of GRT, cost of ART, estimated average number and cost of visits, and hospitalisation costs) and used to estimate the average costs in each arm and the difference in costs per additional virally suppressed CALHIV.

3.7 Nested Study on Other Drivers of Viremia

In a mixed methods analysis, we intend to assess further drivers of viremia beyond viral resistance from a patient-centred perspective. GIVE MOVE participants who have completed the study, as well as their caregivers, will be invited to participate in interviews that will address their individual situation as well as any structural, treatment-related, social, or other barriers that have prevented them from adhering to ART as prescribed. An interview guide will be submitted to the relevant ethics committees before the start of this study.

4 STUDY POPULATION AND STUDY PROCEDURES

4.1 Inclusion and exclusion criteria, justification of study population

Inclusion and exclusion criteria

The study population will consist of CALHIV receiving ART in one of the study sites.

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 Chapter 4.2 Recruitment, screening and informed consent procedure)

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 randomisation
- 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 hospitalisation at screening (no exclusion based on hospitalisation after enrolment)
- Received a resistance test within the last 12 months

Participant number and participant replacement

The study will enrol 276 participants (138 per arm) in a 1:1 allocation. Participants prematurely leaving the study will not be replaced.

Rationale for including vulnerable participants (i.e. minors, pregnant/breastfeeding participants) in the study:

Minors are included in the study for the following reasons:

- The risk to participants is minimal
- There are high potential health benefits: participants in the intervention arm will receive GRT-informed care shortly after randomisation; in case this study shows that GRT-informed management is superior to standard care, at study closure participants in both study arms with an elevated VL will receive GRT-informed care.
- There is a need for HIV research in children: paediatric HIV is classified as a neglected disease[6] since most research is conducted on adults, and there is a lack of data on optimising HIV care for CALHIV in low- and lower middle income countries.
- Children and adolescents have a greater need (compared to adults) for rapid management of therapy failure:
    - Unmanaged HIV infection can negatively impact growth and neurocognitive development in children and adolescents
    - Children and adolescents have a longer prospective lifetime on ART, necessitating an optimised choice of drug regimen
- In children and adolescents, there is a greater potential (compared to adults) to improve treatment outcomes:
    - Treatment success is poorer in children and adolescents, necessitating action and leaving a wider margin for improvement
    - Treatment failure caused by incorrect drug dosing and/or suboptimal adherence is more common in children and adolescents, meaning that there is a greater potential for GRT to prevent unnecessary treatment switches

Patients who are known to be pregnant or breastfeeding will not be enrolled. However, if pregnancy or breastfeeding occurs or becomes known after enrolment, no exclusion will take place. Pregnant or breastfeeding participants in either study arm will receive additional follow-up visits and additional viral load tests in accordance with national guidelines. These additional visits will be recorded.

4.2 Recruitment, screening and informed consent procedure

CALHIV fulfilling the inclusion criteria and/or their caregivers will be informed about the study, complete the consent procedure (see below), and will be screened, enrolled, and randomised. All these processes will generally take place at the routine visit one month after phlebotomy for viral load testing. This will be considered the baseline visit. In cases where caregiver consent is required (see below), the caregiver may be asked to accompany the eligible patient to the clinic. If required, consent can take place before the baseline visit, either in an additional clinic visit or outside the clinic (e.g. in a home visit).

Informed consent will be obtained with the following algorithm:

- Adult participants (Lesotho: ≥16 years; Tanzania: ≥18 years):
    - Study information read to or by the participant
    - Participant Informed Consent Form (ICF) signed by the participant
- Adolescent participants (Lesotho: ≥12 and <16 years; Tanzania: ≥12 and <18 years):
    - Study information read to or by the caregiver and the participant
    - Caregiver ICF signed by the caregiver
    - Adolescent Informed Assent Form (IAF) signed by the participant
- Older child participants (≥6 years and <12 years):
    - Study information read to or by the caregiver
    - Simplified study information with no disclosure of HIV status read to or by the participant (note: more detailed information than included in the Child IAF may be given depending on the child's level of understanding and HIV disclosure)
    - Caregiver ICF signed by the caregiver
    - Child IAF signed or name written by the participant
- Younger child participants (<6 years):
    - Study information read to or by the caregiver
    - Caregiver ICF signed by the caregiver

For both countries, for the purpose of this study a caregiver is defined as a parent, a legal guardian, or an adult aged ≥18 years and living in the same household as the participant.

In the case of illiteracy, the signature can be replaced by a thumb print and a witness must co-sign the form. The witness must be a literate adult aged ≥18 years who is not part of the study team and who, where possible, should be chosen by the participant/caregiver giving consent/assent.

The investigators will explain to each participant and/or caregiver (see algorithm above) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant/caregiver will be informed that participation in the study is voluntary and that he or she may withdraw from the study at any time and that withdrawal of consent will not affect his or her subsequent medical assistance and treatment. The participant/caregiver will be informed that the participant's medical records may be examined by authorised individuals other than their treating physician, either at the study site or remotely after a confidential transfer of the data.

All participants and/or caregivers will be given an ICF (and IAF where applicable; see above) describing the study and providing sufficient information to make an informed decision about participation in the study.

It is foreseen that most participants will be enrolled in a single joint screening, enrolment and baseline visit. If the potential participant/caregiver needs more time to decide about participation, they can take as much time as needed so long as the time windows for eligibility are not exceeded; thereafter, they will no longer be able to participate.

The formal consent of a participant/caregiver will be obtained according to the algorithm above before the participant is submitted to any study procedure and before recording any patient data in the electronic data capture tool.

The ICF (and IAF where applicable) will be signed and dated by an authorised study team member at the same time as the participant/caregiver signs. A copy of the signed ICF/IAF will be given to the study participant or their caregiver. The ICF/IAF will be retained as part of the study records. The informed consent process will be documented in the patient file and any discrepancy to the described process described in the study protocol will be documented and explained.

Participants will not be reimbursed for their participation in the study. However, transport costs for any study-related visits will be compensated. Compensation includes the cost of transport for the participant and, if the participant is a minor, for up to one caregiver. A snack or meal can be provided at study visits.

4.3 Study procedures

Study duration

The trial was launched at the first site (Baylor Clinic Leribe) on 20.02.2020 and is expected to continue until early/mid-2023 (excluding preparation and analysis). The expected total duration is 37 months, consisting of an 26-month enrolment period and up to 11-month follow-up (window for 9-month follow-up: 32-44 weeks corresponding to 8-11 months).

The following visit dates are foreseen / have occurred:

First patient first visit (FPFV; actual date): 03.03.2020
First patient last visit (FPLV; actual date): 10.11.2022
Last patient first visit (LPFV): 03.05.2022
Last patient last visit (LPLV): 02.04.2023

Study procedures

An overview of study procedures is shown in Figure 1. Detailed procedures at each study visit are shown in Chapter 12.1 (Appendix 1: Schedule of study procedures).

Baseline study visit (window: 0-12 weeks after VL test date):

- Both arms:
  - Consent procedure (can be completed before the baseline study visit)
  - Screening, enrolment and randomisation
  - Demographic data, medical history
  - EAC session 1 (if not already completed)
  - Laboratory: CD4 testing; hepatitis B virus (HBV) testing (if not already known to be HBV-positive); full blood count (FBC) or haemoglobin; serum creatinine
  - Blood samples taken for storage
- Control arm: no further action
- Intervention arm: blood draw for GRT

EAC 2 study visit (window: 3-5 weeks after baseline study visit):

- Control arm: EAC session 2
- Intervention arm: GRT-informed EAC session 2; GRT-informed decision on onward therapy

Control arm EAC 3 and follow-up VL study visit (window: 6-10 weeks after baseline study visit):

- Control arm: EAC session 3; blood draw for follow-up VL test
- Intervention arm: no visit

3-month study visit (window: 10-14 weeks after baseline study visit):

- Both arms: blood samples taken for storage
- Control arm: VL-informed decision on onward therapy
- Intervention arm: EAC session 3

6-month study visit (window: 20-28 weeks after baseline study visit):

- Both arms: blood samples taken for storage

9-month study visit (window: 32-44 weeks after baseline study visit):

- Both arms: blood samples taken for storage; CD4 testing; VL testing (part of composite primary endpoint)

Decision follow-up visit (window: 20-28 weeks after decision, i.e. after availability of the follow-up VL result in the control arm or after availability of the GRT result in the intervention arm):

- Both arms: blood samples taken for storage and VL testing
- Notes:
  - Where possible, this study visit may be combined with a study visit described above
  - If required (i.e., if delays occur in the real-life study setting), this visit may also take place after the window period of the 9-month study period

Clinical assessments (including: WHO stage, co-morbidities, symptoms and side-effects; at the baseline and 9-month visit: height, middle upper arm circumference in children <5 years, nutritional status and supplementation; at baseline, decision and 9-month visit: weight), documentation of ART and co-medication, and adherence assessments will take place at each visit. Additional visits may take place according to standard care (e.g. additional visits after switching drug regimen, depending on the drug regimen selected; clinically indicated visits; etc.) and will be documented. Participants may be asked to return for additional visits if the purpose of a study visit was not fulfilled, e.g. if laboratory results were not ready or phlebotomy was not

possible. Missing participants will be traced, contacted and encouraged to return back to care. Serious Adverse Events (SAEs) will be documented, reported, and followed up.

The sites will receive written guidance defining the prioritisation of tests/blood use in the event that insufficient blood is available, the use of paediatric vials where appropriate, as well as safe blood volumes in paediatric patients. Study-related phlebotomy will be limited to age-appropriate volumes per blood draw[50], defined here as: ≤5 mL for participants <5 years; ≤10 mL for participants ≥5 and <10 years; ≤15 mL for participants ≥10 and <15 years; and ≤25 mL for participants ≥15 years.

Stopping criteria

Criteria for the Sponsor/Chief Investigator to prematurely terminate the study are listed in Chapter 4.4 (Withdrawal).

An interim analysis will be conducted and allow for premature termination of the study in the case of clear futility or success. The criteria for premature study termination are detailed in Chapter 5.1 (Statistical analysis plan and sample size calculation).

Sample storage

Biological samples will be stored at -80 °C. Further use of remaining biological samples will be possible if approved by the respective IRBs / ethics committees (samples from Lesotho: NH-REC; samples from Tanzania: IHI IRB and NIMR), including but not limited to: genetic sequencing of other HIV-1 genetic sequences; drug level testing; testing for other viral infections; etc. Samples may be transported to Switzerland (Molecular Virology group, Department of Biomedicine, University of Basel) for further analyses if the respective analyses cannot be performed in the GIVE MOVE GRT laboratory in the respective project country (Seboche Mission Hospital Laboratory, Butha-Buthe, Lesotho / IHI Laboratory, Ifakara, Tanzania). Material Transfer Agreements will be requested from the respective IRBs / ethics committees in both project countries; a Data Transfer Agreement will additionally be requested in Tanzania.

Data Management and Confidentiality

A study specific Data Management Plan will be in place before the start of data collection that describes all data management products and procedures in detail. This includes but is not limited to software details and procedures specific to data collection, management and review. All study team members that are responsible for data entry will receive training for data capture and management. The Principal Investigator is responsible for data quality and will take reasonable measures to ensure complete and accurate data. Study data will be reviewed regularly by monitors and data managers and queries will be raised within the electronic data capture system to clarify inconsistencies, incoherencies and missing data for the purpose of data cleaning. A computer-generated time stamped audit trail will keep track of all user-specific data processing operations such as creation, modification and deletion.

All data will be stored securely in a way that allows future access for the research team. Only study team members (as listed in the delegation log/study team log), as well as the data manager, monitors and IRBs / ethics committees / regulatory authorities, will be given access to the study data. All data will be owned by the Sponsor/Chief Investigator. Data will be kept in compliance with local legal requirements, for a minimum of ten years. All relevant recorded data will be encrypted and password secured, using the MACRO electronic data capture software, which generates an audit trail. A master list linking the participant unique identifier and the participant details such as name will be kept at the respective study site under lock and key.

Swiss TPH servers are located in Basel with a defined policy in place for server set-up, maintenance and security. This includes processes regarding server qualification, back-ups, disaster recovery and restricted server access.

The study database in MACRO allows for database freeze and database lock for either interim or final statistical analyses. Database lock will prevent any further changes after final data entry and query resolution and will be implemented according to agreed timelines.

After the end of the study and once trial results have been published, a dataset from which all identifying information has been removed will be made publicly available using a public data repository platform.

4.4 Withdrawal of consent

Enrolled participants will only be removed from the study upon withdrawal of consent, and will then continue to receive standard care for onward therapy, with the responsibility for further follow-up and management lying with the clinic in which the patient is in care. Participants withdrawing consent will not be replaced. In the case of withdrawal of consent, data and materials collected up to that point may still be used but no further data or sample collection will be permitted.

5 STATISTICS AND METHODOLOGY

5.1 Statistical analysis plan and sample size calculation

Null hypothesis

The null hypothesis is that patients in the intervention have the same odds ratio for the composite primary endpoint as patients in the control arm.

Determination of 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[17,18,42–47] 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]	P_{Int}	P_C	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 276 was calculated (see Table 1).

Planned analysis

Statistical analysis will be performed by the trial statistician using Stata. Analyses will follow CONSORT guidelines[51–53] and intention-to-treat principles. A flowchart will describe the inclusion and follow-up of participants by study arm. Baseline characteristics will be described by study arm with summary statistics such as median and interquartile range or number and percentage; no formal testing between arms will be performed[54]. Outcomes will be described by arm using summary statistics. The primary outcome, the proportion of individuals having experienced the primary endpoint, will be assessed using a logistic regression model, reporting odds ratios. Binary secondary outcomes will be evaluated in the same way. Continuous secondary outcomes will be assessed using linear regression models, reporting adjusted mean differences between arms. Time to event outcomes will be assessed using appropriate methods, such as Kaplan-Meier estimation and Cox proportional hazards models. All estimates will be reported with 95% confidence intervals (CI). All models will be adjusted for the stratification factors of country, age, and ART regimen at enrolment[55]. We will compare each endpoint between the intervention and control arms. Further details will be provided in the statistical analysis plan.

Subgroup analysis

Effect modification of the primary outcome by country (Lesotho or Tanzania), sex (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.

Datasets to be analysed, analysis populations

The full analysis set (FAS) will include all participants as randomised. All statistical analyses will be performed on the FAS according to the intention-to-treat principle (i.e. all participants will be analysed on the basis of the intervention to which they were randomly allocated).

A per-protocol analysis set will include all randomised participants who completed the study without a protocol violation. The primary endpoint will be performed on the per-protocol analysis set.

Interim analysis

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.

The trial may be concluded early for success if a significant difference between the two trial arms for the composite primary endpoint is achieved. Also, 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 interim analysis will be performed by an external independent statistician at an external data analysis centre, 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.

5.2 Handling of missing data, withdrawals, and loss to follow-up

Missing baseline and outcome data will be summarised by study arm. As outlined above, the primary analyses will be the intention-to-treat population. In the case of missing data or drop-outs, we may adjust for further baseline variables which are associated with missing outcome data (which is analogous to performing multiple imputation in the case of a single endpoint)[56]. We may

consider multiple imputation as sensitivity analyses if necessary. Details will be provided in the statistical analysis plan.

6 REGULATORY ASPECTS AND SAFETY

6.1 Local regulations / Declaration of Helsinki

This study is conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH GCP E6R2, the HRA as well as other locally relevant legal and regulatory requirements.

Serious Adverse Events (SAEs)

An SAE (ClinO, Art. 63 / ICH GCP E6R2) is any untoward medical occurrence that

- Results in death or is life-threatening,
- Requires in-patient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity, or
- Causes a congenital anomaly or birth defect

The Sponsor/Chief Investigator will consult with the Principal Investigator and/or Local Principal Investigator as well as with the respective Study Physician and will make i) an assessment of causality of the intervention, and ii) a severity assessment according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (2017; see Table 2)[57].

Table 2: Grading of (Serious) Adverse Events.

Grading	Description
Relationship of the SAE with the trial intervention	
(Possible) relationship	Causal relationship cannot be ruled out
No relationship	Causal relationship can be ruled out
Severity of the SAE (assessed using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, 2017)[57]	
Grade 1	Mild event
Grade 2	Moderate event
Grade 3	Severe event
Grade 4	Potentially life-threatening event
Grade 5	Death

Reporting of SAEs

In the case of an SAE, any study personnel must inform the Local Principal Investigator within 72 hours of his/her awareness of the SAE. The Local Principal Investigator must document and report to SAE to the Sponsor/Chief Investigator and the Principal Investigator immediately (within a maximum of 24 hours). The Sponsor/Chief Investigator is responsible for reporting of the SAE to the respective IRBs / ethics committees within 72 hours (for authorities relevant to the country in which the SAE took place) or 15 days (for all other authorities relevant to the trial):

SAEs in Lesotho:

- Will be reported to the NH-REC Lesotho within 72 hours of reporting to the Sponsor/Chief Investigator
- Will be reported to NIMR Tanzania and the IHI IRB within 15 days of reporting to the Sponsor/Chief Investigator

SAEs in Tanzania:

- Will be reported to NIMR Tanzania and the IHI IRB within 72 hours of reporting to the Sponsor/Chief Investigator

- Will be reported to the NH-REC Lesotho within 15 days of reporting to the Sponsor/Chief Investigator

The Sponsor/Chief Investigator may delegate reporting of SAEs to IRBs / ethics committees to the Principal Investigator.

Follow up of SAEs

SAEs will be documented in a separate form within the eCRF. Further details relating to SAEs will be captured separately from the eCRF. SAEs (excluding death) will be followed up in one or more visits until resolution or stabilisation takes place, even if this exceeds the study period.

6.2 (Periodic) safety reporting

An annual safety report (ASR) will be submitted once a year to the local Ethics Committee by the Sponsor/Chief Investigator or a (Local) Principal Investigator (ClinO, Art. 43 Abs).

The ASR contains information from all sites. The Sponsor/Chief Investigator distributes the ASR to all the participating Investigators.

6.3 Pregnancy

Participants who are pregnant (pregnancy test) or breastfeeding at screening will not be enrolled; however, pregnancy after the baseline study visit will not lead to exclusion. Female participants who become pregnant during the study period will receive standard care (including more frequent clinic visits) according to the national guidelines[48,49]. Additional visits due to pregnancy will be recorded as such. If births occur within the study period, the HIV status and health of the new-born will be recorded.

6.4 Amendments

Substantial changes to the study setup, study organisation, study protocol or relevant study documents will be submitted to the relevant IRBs / ethics committees for approval before implementation. Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the relevant IRBs / ethics committees. Such deviations will be documented and reported to the relevant IRBs / ethics committees as soon as possible. The definition of substantial amendments includes: changes that affect the safety, health, rights and obligations of participants; changes in the study protocol that affect the study's objectives or central research topic; changes of study sites (excluding those already mentioned in this document as potential additional study sites); and changes of the Sponsor/Chief Investigator or Principal Investigator (ClinO, Art. 29).

A list of all non-substantial amendments will be submitted once a year to the relevant IRBs / ethics committees, together with the ASR.

6.5 (Premature) termination of study

The Sponsor/Chief Investigator may prematurely terminate the study. Reasons for premature termination may include:

1) Ethical concerns
2) Insufficient participant recruitment
3) Risks to participant safety or doubtful participant safety
4) Alterations in accepted clinical practice that make the continuation of the trial unwise
5) Criteria for success or futility reached in the interim analysis, as defined in Chapter 5.1 (Statistical analysis plan and sample size calculation; only if decided by the Steering Committee)

Upon regular study termination, the IRBs / ethics committees (Lesotho: NH-REC; Tanzania: IHI IRB and NIMR; Switzerland: EKNZ) will be notified within 90 days. Upon premature study termination or study interruption, the same IRBs / ethics committees will be notified within 15 days.

Participant data and samples will not be anonymised upon the end of data analysis (however, at no time point will they be directly associated with the participant's name). Biological materials labelled with a unique identifier may be stored beyond the end of the study for further use. ICFs/IAFs will be stored under lock and key for at least 10 years. Participant data marked with a unique identifier will be stored digitally for further use.

6.6 Insurance

In the event of study-related damage or injuries, the liability of the Swiss TPH provides compensation, except for claims that arise from misconduct or gross negligence. Given the low risk of the study, no additional insurance is required.

7 FURTHER ASPECTS

7.1 Risk-benefit assessment

The risk to participants is minimal and is limited to risks related to phlebotomy, which are rare (pain or bruising at the site of puncture; in very rare cases, risks may include fainting, nerve damage, bacterial infection and haematoma). All healthcare-related procedures (notably, phlebotomy, diagnostic testing, interpretation of GRT results) will be conducted by experienced personnel. The eCRFs and patient samples will be labelled with a unique identifier and will not contain the participant's name, ensuring confidentiality.

Participants in the intervention arm will potentially benefit from GRT and GRT-informed onward therapy (ensuring an optimal drug regimen) at baseline, and all participants will receive GRT if they still have an elevated VL at study closure in case the intervention proves beneficial.

The evidence generated in this trial is intended to inform future national and international clinical guidelines, potentially benefitting CALHIV in many resource-limited countries. Furthermore, additional evidence generated (e.g. on current local drug resistance profiles) may inform local/national policies.

7.2 Overall ethical considerations

CALHIV suffer high rates of virologic failure despite ART, yet research to guide the management of viremia in these age groups is lacking [3–6]. GIVE MOVE aims to inform national and international (WHO) clinical guidelines and policies to improve HIV care. In order to increase the generalisability of results (including feasibility and cost-effectiveness), this trial is conducted in two different African settings with very distinct features.

This trial entails minimal risks and has potential health benefits for participants. Participation is entirely voluntary, and informed consent can be withdrawn at any time.

All data and biological samples obtained in Lesotho will belong jointly to the Clinical Research Unit, Department of Medicine, Swiss TPH and to SolidarMed. All data and samples obtained in Tanzania will belong jointly to the Clinical Research Unit, Department of Medicine, Swiss TPH and to IHI. The Sponsor/Chief Investigator may make the data and samples available to GIVE MOVE study team members or external researchers for GCP-conform further use if approved by the relevant IRBs / ethics committees (Lesotho: NH-REC; Tanzania: IHI IRB and NIMR).

8 QUALITY CONTROL AND DATA PROTECTION

8.1 Quality measures

Study personnel will be trained on all important study related aspects, including a trial-specific training, GCP training, training on data entry and handling and study interventions (e.g. laboratory technologists will receive further training on resistance testing; physicians, other healthcare professionals, and laboratory technologists will receive trainings on interpreting resistance results). Monitoring visits are planned in both countries at key stages of the trial. In addition to onsite monitoring, central monitoring checks will be built into the MACRO study database that flag inconsistent and erroneous data in real-time fashion.

For quality assurance the Sponsor/Chief Investigator, representatives of the relevant IRBs / ethics committees / regulatory authorities, and trial monitors may visit the research sites. Direct access

to the source data and all study related files is granted on such occasions. All involved parties will keep the participant data strictly confidential.

8.2 Data recording and source data

All data collected during the study period will be captured online in electronic case report forms (eCRFs) into the MACRO Electronic Data Capture (EDC) tool on tablets or computers at each study site. Paper-based CRFs may be used as a back-up, in which case data will be transferred to MACRO eCRFs. Source data includes the original records and copies of original records of information relating to the study and can be electronic or paper-based. The eCRF will be considered the source for some data, which will be identified accordingly in the monitoring plan. For laboratory tests, laboratory reports will be considered as source data. If MACRO cannot be used temporarily, e.g. if the internet is not working, data normally entered straight into MACRO will be captured on paper forms until electronic upload is possible, in which case the paper forms will be the source data.

8.3 Confidentiality and coding

Trial and participant data will be handled with uttermost discretion and will only be accessible to authorised personnel who require the data to fulfil their duties within the scope of the study, as well as to authorised auditors and monitors. On the eCRF and other study specific documents, participants are only identified by a unique participant number. Since age is an important consideration in children and adolescents (e.g. to assess potential stunting), the date of birth will be recorded on the eCRF.

The participant identification list will be securely stored at each site as described above. The ICFs/IAFs will be stored under lock as hard copies at the respective study sites. Traceability will be ensured by use of a unique study number, which will be linked to the participant's ART number for participants in Lesotho and their Unique CTC ID Number for participants in Tanzania (in the participant identification list, the eCRFs and the ICFs/IAFs), date of birth (in the participant identification list, ICFs/IAFs and CRFs), and participant name (in the participant identification list and ICFs/IAFs only). Key study documentation will be stored on a shared folder only accessible to key study team members. An automatic safety back-up of the data on this shared folder will be made at least once per week.

Biological material in this study is not identified by participant name but by a unique identifier. Biological material is appropriately coded and stored in a restricted area only accessible to the authorised personnel. After study closure, biological material may be further used for biomedical research, including genetic analyses, though only if approved by the respective IRBs / ethics committees (Lesotho: NH-REC; Tanzania: IHI IRB and NIMR). For analyses that cannot be performed by the GIVE MOVE GRT laboratories (Seboche Mission Hospital Laboratory, Butha-Buthe, Lesotho / IHI Laboratory, Ifakara, Tanzania), samples may be transported to Switzerland. Material Transfer Agreements may be requested from the NH-REC (Lesotho) and NIMR (Tanzania) for the export of biological material, and biological material will only be transferred as outlined within these agreements.

8.4 Retention and destruction of study data and biological material

All study data will be archived for at least 10 years after study termination (including in the event of premature termination of the study).

Biological material will be labelled with a unique identifier and stored at i) the Butha-Buthe Government Hospital laboratory, Butha-Buthe, Lesotho; ii) the Seboche Mission Hospital laboratory, Butha-Buthe, Lesotho, iii) the Ifakara Health Institute laboratory, Ifakara, Tanzania; or iv) Haus Petersplatz, Department of Biomedicine, University of Basel, Basel, Switzerland. Biological material may be used for further biomedical research beyond the scope of the present study, so long as this use preserves the rights and safety of study participants, and if approved

by the relevant IRBs / ethics committees (Lesotho: NH-REC; Tanzania: IHI IRB and NIMR).

9 MONITORING AND REGISTRATION

The trial will undergo monitoring to ensure compliance with the study protocol and good clinical practice (GCP) principles. Sites in Lesotho will be monitored by the Clinical Operations Unit of the Swiss TPH; sites in Tanzania will be monitored by IHI. Monitoring procedures are outlined in the Monitoring Plan (see Chapter 12.6 Appendix 6: Monitoring Plan).

The Sponsor/Chief Investigator agrees to allow inspectors from IRBs / ethics committees / regulatory agencies to review study records and to assist them in their duties, if requested. Monitors and regulators will have access to source data as well as all study documentation, and the Sponsor/Chief Investigator, Principal Investigator, and/or other central members of the study team will assist them in all their queries.

The trial is registered at ClinicalTrials.gov: NCT04233242.

10 FUNDING / PUBLICATION / DECLARATION OF INTEREST

The major funding for the study will come from a grant from Fondation Botnar (grant number REG-19-008; obtained by NDL). Further funding will come from the Swiss National Science Foundation (grant number PCEFP3_181355; obtained by NDL), the University Hospital of Basel (contribution to salaries of co-investigators; confirmed), and potentially the Federal Commission for Scholarships for Foreign Students (funding application planned for a PhD programme for a study team member from one of the project countries). The minor funding that has yet to be obtained according to the current budget is not critical to the completion of the study. The funding sources are/will not be not involved in the study design, data collection, data analysis, interpretation of the results, or writing the manuscript.

The study will be embedded in the SolidarMed Lesotho country programme, the Baylor College of Medicine Children's Foundation Lesotho (BCMCFL) country programme, and in operations of the Clinical Diseases Clinic Ifakara (CDCI) and Management and Development for Health (MDH) in Tanzania, and will thus benefit from logistics and human resources of these organisations.

The listed co-investigators declare the following conflicts of interest:

Thomas Klimkait reports advisory board membership fees from ViiV and Gilead for work outside this study. NDL reports having received travel grants to attend scientific conferences from Gilead Sciences Sarl. All other team members have no conflicts of interest to declare.

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12 APPENDIX

12.1 Appendix 1: Schedule of study procedures

Table 3: Schedule of study procedures.

Time	**- 1 month**	**0** (window: 0-12 weeks after sample date for latest VL test)	**1 month** (window: 3-5 weeks after baseline study visit)	**2 months** (window: 6-10 weeks after baseline study visit)	**3 months** (window: 10-14 weeks after baseline study visit)	**6 months** (window: 20-28 weeks after baseline study visit)	**9 months** (window: 32-44 weeks after baseline study visit)	**6 months <u>after decision on onward therapy</u>** (window: 20-28 weeks after availability of follow-up VL (control) or GRT (intervention) result [a]
Visit name	Pre-study visit	Baseline study visit	EAC 2 study visit	Control arm EAC 3 and follow-up VL study visit	3-month study visit	6-month study visit	9-month study visit	Decision follow-up visit
Consent / assent [b]		X [c]						
Screening and enrolment		X						
Randomisation		X						
Collection of participant's general and contact information		X						
Collection of medical history [d]		X						
Weight		X	Intervention arm (at decision)		Control arm (at decision)		X	
Assessment of height, MUAC (in children <5 years), nutritional status, and of nutritional supplements		X					X	
Clinical assessment [e]		X	X	Control arm	X	X	X	X [a]
Documentation of ART and co-medication		X	X	Control arm	X	X	X	X [a]
Adherence assessment [f]		X	X	Control arm	X	X	X	X [a]
EAC		X [c]	X [g]	Control arm	Intervention arm [g]			
Phlebotomy [h]								
VL testing	X [i]			Control arm [j]			X	X [a]
GRT		Intervention arm						
CD4		X					X	
FBC or haemoglobin		X						
HBV [k] **and serum creatinine**		X						
Post-hoc VL testing					X	X		
Post-hoc GRT		Control arm					X [l]	
Storage for further use		X			X	X	X	X [a]
Pregnancy test [m]		X					X	
Decision on onward therapy			Intervention arm [g]		Control arm [j,n]			

Additional clinic visits and laboratory testing [o]	As required by standard of care

MUAC: middle upper arm circumference; VL: viral load; EAC: enhanced adherence counselling; FBC: full blood count; GRT: genotypic resistance testing; HBV: Hepatitis B virus

[a] Where possible, will be planned to coincide with another study visit; will be collected even after the 9-month study visit
[b] Oral and written participant and/or caregiver information; written informed consent (and assent if applicable)
[c] If not previously completed
[d] Clinical information at ART initiation; previous ART regimens/exposure; exposure to prevention to mother-to-child transmission strategies
[e] WHO stage; co-morbidities; symptoms and side-effects
[f] Contentedness with ART; pill count; self-reported adherence
[g] In intervention arm: informed by GRT result
[h] Written guidance will define prioritisation of tests/blood use in the event that insufficient blood is available, the use of paediatric vials where appropriate, as well as safe blood volumes in paediatric patients. Phlebotomy will be limited to age-appropriate volumes per blood draw, defined here as: ≤5 mL for participants <5 years; ≤10 mL for participants ≥5 and <10 years; ≤15 mL for participants ≥10 and <15 years; and ≤25 mL for participants ≥15 years.
[i] VL test before trial begin; result ≥400 c/mL is an inclusion criterion
[j] If there is a clear indication of poor adherence (defined as a pill count of <90% and/or a self-reported period of no drug intake of ≥2 days in the last 4 weeks), monthly EAC can continue and VL testing and the decision on onward therapy can be delayed until there is no longer clear evidence of poor adherence
[k] Except if already known to be HBV positive
[l] If viral load permits (approx. ≥100 c/mL)
[m] Female participants aged ≥12 years, unless already known to be pregnant
[n] Based on empirical guidelines
[o] Including (but not limited to) additional visits/tests due to: ART regimen substitutions or switches necessitating laboratory safety testing (e.g. alanine transaminase, full blood count, etc.); pregnancy/breastfeeding; clinical indication

12.2 Appendix 2: Electronic Case Report Forms (eCRF)

12.3 Appendix 3: Informed Consent Forms

Forms Lesotho

- English Informed Consent Form for participants aged ≥16 years, Lesotho
- English Informed Consent Form for caregivers of participants aged <16 years, Lesotho
- English Assent Form for participants aged ≥12 and <16 years, Lesotho
- English Assent Form for participants aged ≥6 and <12 years, Lesotho
- Sesotho Informed Consent Form for participants aged ≥16 years, Lesotho
- Sesotho Informed Consent Form for caregivers of participants aged <16 years, Lesotho
- Sesotho Assent Form for participants aged ≥12 and <16 years, Lesotho
- Sesotho Assent Form for participants aged ≥6 and <12 years, Lesotho

Forms Tanzania

- English Informed Consent Form for participants aged ≥18 years, Tanzania
- English Informed Consent Form for caregivers of participants aged <18 years, Tanzania
- English Assent Form for participants aged ≥12 and <18 years, Tanzania
- English Assent Form for participants aged ≥6 and <12 years, Tanzania
- Swahili Informed Consent Form for participants aged ≥18 years, Tanzania
- Swahili Informed Consent Form for caregivers of participants aged <18 years, Tanzania
- Swahili Assent Form for participants aged ≥12 and <18 years, Tanzania
- Swahili Assent Form for participants aged ≥6 and <12 years, Tanzania

The above-mentioned forms are attached to this document.

12.4 Appendix 4: Staff List

The staff list is attached to this document.

12.5 Appendix 5: CVs of Main Investigators

The CVs of Steering Committee members, Site Co-Investigators, Clinical Co-Investigators, Statistics and Data Co-Investigators, and Diagnostic Co-Investigators (see Chapter 12.4 Appendix 4: Staff List) are attached to this document.

12.6 Appendix 6: Monitoring Plan

The monitoring plans for both countries are attached to this document.