THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR THE TRIAL TITLED GENOTYPE-INFORMED VERSUS EMPIRIC MANAGEMENT OF VIREMIA (GIVE MOVE): AN OPEN-LABEL RANDOMISED CLINICAL TRIAL

Version Number: CT20 0003 CPARv2.0

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1. INTRODUCTION

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. Genotypic resistance testing (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

1.1. Study details

Clinical Trial Registration number	TZ20CT0033
Title of the study	Genotype-Informed Versus Empiric Management Of VirEmia (GIVE MOVE): An Open-label Randomised Clinical Trial
Protocol Identification Number/code	NCT04233242
Ethical Clearance Number/ Date of Approval	NIMR, first approval: NIMR/HQ/R.8a/Vol.IX/3442 dated 10th June 2020 NIMR, latest approval: NIMR/HQ/R.8c/Vol.I/2319 dated 3rd May 2023
TMDA Approval Date	First approval: 14th July 2020 Latest approval: 12th April 2023
Name of Investigational Product or Intervention	N/A
Dosage Form(s) and Strength(s) (where applicable)	N/A
Route(s) of Administration (where applicable)	N/A
Name (s) of Comparator Product (where applicable)	N/A
Name and address(es) of the Sponsor	Prof. Niklaus Labhardt Totengaesslein 3, 4051 Basel, Switzerland +41 61 265 38 16; niklaus.labhardt@usb.ch

Name and address(es) of the Principal Investigator (PI)	Country PI, Tanzania: Ezekiel Luoga Ifakara Health Institute P.O Box 53 Ifakara Morogoro Country PI, Lesotho: Isaac Ringera PI: Jennifer Brown, Totengaesslein 3, 4051 Basel, Switzerland +41 61 265 38 16; jennifer.brown@usb.ch
Name and address(es) of Study Site(s)	In Tanzania: - 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 In Lesotho: - 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
Name and address of the manufacturer of Investigational medical product (IMP) if applicable	N/A
Name and address of the manufacturer of the comparator product (if applicable	N/A
Phase of Trial	N/A
Duration of the study	38 months
Primary purpose of the study (Screening, Diagnosis, Prevention, Treatment)	Treatment
Condition or diseases under study	HIV/AIDS
Number of participants intended to be enrolled in the study	276

1.2. Assessment procedure

The application for authorization for a clinical trial titled Genotype-Informed Versus Empiric Management of VirEmia (GIVE MOVE): An Open-label Randomised Clinical Trial was submitted on 18-02-2020. The assessment was completed in two (2) rounds of evaluation. The trial was approved on 14-07-2020.

2. TRIAL INFORMATION

2.1. Study 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 Objective

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 suppression, viral development of drug resistance, and immune recovery without vs with GRT-based management of viremia

2.2. Outcome Measures

2.2.1. Primary Outcome

The primary composite outcome measure of the study is to determine the occurrence of any one or more of the events; -

a) death due to any cause during the follow-up period (36 weeks),
b) HIV- or ART-related hospital admission of ≥24 hours duration (possibly, probably or related to HIV or ART, judged by the endpoint committee blinded to the study arm) during the follow-up period (36 weeks),
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) during the follow-up period (36 weeks), and
d) no documentation of a suppressed VL (<50 c/mL) at 9 months follow-up (window: 32-44 weeks).

2.2.2. Secondary Outcome measures

The following are the secondary outcome measures of the study: -

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 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)

2.2.3. Exploratory outcome

The following are the exploratory outcome: -

a. Time to viral suppression (<50 c/mL; considering VL testing done with samples from the 3-, 6- and 9-month study visit in both arms)
b. 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)
c. Emergence of new drug resistance mutations within the study period (i.e., measured drug resistance at the 9-month visits vs at the baseline visit)

2.3. Investigational Plan

GIVE MOVE is an open-label, two-arm, multicenter, superiority randomized clinical trial. Participants will be randomized in a 1:1 ratio to the intervention or the control arm.

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.

2.4. Type and number of the study participants

The study will be conducted among the pediatric population Age ≥6 months and <19 years. The study plans to enroll about 276 participants. This includes about 138 who will be randomized to the intervention group, and the remaining 138 participants will be enrolled in the control group (standard of care).

2.5. Selection Of Study Population

Inclusion criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply to meet all: -

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

Exclusion criteria

A subject is not eligible for inclusion in this study if any of these criteria meet: -

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

2.6. Drug Formulation

N/A

Instructions for safe handling:

N/A

State the accountability procedures for the investigational product(s), placebos and comparator(s) and disposal:

N/A

2.7. Treatments

Treatments administered in case of biologicals or medicines.

N/A

2.7.1. The name(s) of all the product(s): N/A
2.7.2. Dose(s): N/A
2.7.3. The dosing schedule(s): N/A
2.7.4. The route/mode(s) of administration: N/A
2.7.5. The treatment period(s): N/A

2.7.6. Follow-up period(s) for participants for each investigational product treatment/trial treatment group/arm of the trial: N/A

2.7.7. Concomitant Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial: N/A

2.7.8. Procedures for monitoring participant's compliance: N/A

2.7.9. Wash-out period (Description for pre-, during- and post-trial, as applicable): N/A

2.8. Pre-Study Screening and Baseline Evaluation

Baseline study visit (window: 0-12 weeks after the viral load test date):

- Both arms:
  - Consent procedure (can be completed before the baseline study visit)
  - Screening, enrolment and randomization
  - 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); serum creatinine
  - Blood samples were taken for storage
- Control arm: no further action
- Intervention arm: blood draw for GRT

2.9. Efficacy and Safety Measurements to be Assessed

Efficacy measures to be assessed

See primary endpoint

Safety measures to be assessed

This low-risk trial is expected to have potential health benefits and minimal risks for participants.

Any new WHO stage 4 event and hospitalization lasting 24 hours or longer will be assessed by an independent Endpoint Committee consisting of specialists in paediatrics and/or clinical management of HIV. Once 50% of participants have reached the primary endpoint and/or completed the 9-month study visit, an interim analysis will take place and interim results will be reviewed by a Data Safety Monitoring Board that will recommend the continuation or premature termination of the trial, with the final decision resting with the trial's Steering Committee.

In the case of a Serious Adverse Event (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 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.

3. ETHICAL CONSIDERATIONS

3.1. Ethical Clearance

The study has approved by the National Health Research Ethics Committee on 10th June 2020 with ethical clearance. No. NIMR/HQ/R.8a/Vol. IX/3442, with subsequent renewals. It has also been approved by TMDA and IHI IRB in Tanzania, by NH-REC in Lesotho, and has received a positive review by EKNZ in Switzerland.

3.2. Insurance

The study participants will be insured through:

- Axa, Key Account Management, P.O. Box, Laupenstrasse 19, 3001 Berne via the study titled Genotype-Informed Versus Empiric Management of viremia (GIVE MOVE): An Open-label Randomized Clinical Trial, protocol. No. NCT04233242. The cover validity is from 06.12.2019 to 31.12.2022 with the policy No. 4.746.321 and the amount of 5,000,000 CHF as premium insurance cover
- Jubilee Insurance, policy number P//301/6016/2020/000002, 01.04.2020 – 01.09.2023
- Helvetia, policy number 4.001.396.623 - (967437/2). 01.01.2023 – 01.01.2024.

3.3. Informed Consent

Informed consent for adult participants from version 1.2, of 10th December 2019 and Assent from version: 1.2, 10th December 2019 and informed consent for caregiver version 1.2 of 10th December 2019 were approved by the ethics committee on 10th June 2020.

3.4. Patient Information Leaflet

Patient information leaflet versions for Lesotho and Tanzania, for different age groups, and in different languages (Lesotho: English, Sesotho; Tanzania: English, Swahili have been provided as approved by the ethics committee (as listed above).

3.5. Payment

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. WHAT ARE THE BENEFITS OF BEING IN THE STUDY?

The study 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.

5. WHAT ARE THE RISKS OF THE STUDY?

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, and 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

Details on treatment and/or management of participants and their disease condition(s) after completion of the trial (post-trial medicine access) if provided

N/A

6. PRE-CLINICAL STUDIES (IF APPLICABLE)

N/A

7. HUMAN EXPERIENCE (CLINICAL STUDIES) IF APPLICABLE

N/A

8. PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATION OF THE INVESTIGATIONAL MEDICINAL PRODUCT OF DRUG SUBSTANCE (VACCINES AND DRUGS ONLY)

N/A

8.1. Drug Substance(s)

8.1.1. Description

N/A

8.1.2. Name(s)

N/A

8.1.3. Structural Formula and Molecular Formula

N/A

8.1.4. Physical-Chemical Properties

N/A

8.1.5. Drug Substance Stability

N/A

8.2. Drug Product

8.2.1. Drug Product Formulation

N/A

8.2.2. Placebo Formulation (In case applicable)

N/A

8.2.3. Drug Product Stability

N/A

8.2.4. Drug Product Storage

N/A

9. Benefit-Risk Assessment and Conclusion

Based on the data provided, the current state of knowledge regarding an investigational product, including the non-clinical and clinical information that is currently available, is sufficient to support the proposed clinical trial and compliance with Good Clinical Practice (GCP), and the anticipated benefits of conducting the trial justify the risks associated with its use when done by the approved protocol and ethical principles that have their origin in the Declaration of Helsinki

10. Post-approval updates

10.1. Amendment applications

Reference number	Date submitted	Change Requested	Recommendation	Granting date

PART 5: CHANGE HISTORY

Version number	**Date**	**Description of update**	**Section(s) Modified**	**Approval date**
Only versions and approvals in Tanzania are listed.				
1.2	10.12.2019	Submission IHI-IRB	(version not implemented)	13.03.2020; 08.03.2021
1.3	27.02.2020	Submission IHI-IRB	(first implemented version)	08.03.2021
1.3	27.02.2020	Submission NIMR	(first implemented version)	10.06.2020; 19.05.2021
1.3	27.02.2020	Submission TMDA	(first implemented version)	14.07.2020
1.4	23.08.2021	Submission IHI-IRB	(Inclusion criteria; another minor)	30.01.2023; 06.03.2023

1.4	23.08.2021	Submission NIMR	(Inclusion criteria; another minor)	19.01.2022; 29.11.2022; 03.05.2023
1.4	23.08.2021	Submission TMDA	(Inclusion criteria; another minor)	22.03.2022; 12.04.2023