

VIBRA trial – Effect of village-based refill of ART following home-based same-day ART initiation vs clinic-based ART refill on viral suppression among individuals living with HIV: protocol of a cluster-randomized clinical trial in rural Lesotho

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Abstract

Background: There is a need for evaluating community-based antiretroviral therapy (ART) delivery models to improve overall performance of HIV programs, specifically in populations that may have difficulties to access continuous care. This cluster-randomized clinical trial aims to evaluate the efficacy of a multicomponent differentiated ART delivery model (VIBRA model) after home-based same-day ART initiation in remote villages in Lesotho, Southern Africa.

Methods: VIBRA (Village-Based Refill of ART) trial is a cluster-randomized, parallel-group, superiority clinical trial conducted in two districts of Lesotho, Southern Africa. Clusters (i.e. villages) are randomly assigned to either the VIBRA model or standard of care, stratified by district, village size, and village access to the nearest health facility. Eligible individuals (HIV-positive, aged 10 years or older, not taking ART) found during community-based HIV testing campaigns are offered same-day home-based ART initiation. Intervention clusters offer a differentiated ART delivery package with two features: Firstly, drug-refill and follow-up through trained and supervised village health workers. Secondly, the option of receiving individually tailored adherence reminders and viral load result notifications via SMS. Standard of care applies for the control clusters, i.e. ART visits at the clinic and no SMS. The primary endpoint is viral suppression 12 months after enrolment. Secondary endpoints include linkage to and engagement in care. Furthermore, safety and cost-effectiveness analyses plus qualitative research are planned. Minimum target sample size is 262 participants. Statistical analyses will follow CONSORT guidelines. VIBRA trial is linked to another trial, the HOSENG (HOMe-based SELF-testiNG) trial, in the GET ON (GETing tOWards Ninety) research project.

Discussion: VIBRA trial is among the first to evaluate ART delivery through VHW immediately after ART-initiation and it assesses the entire HIV care cascade from testing to viral suppression. As most countries in sub-Saharan Africa have cadres similar to the VHW program in Lesotho, this model – if shown to be effective – has potential to be scaled up. The system impact evaluation will provide valuable cost estimations, and the qualitative research will suggest how the model could further be modified to optimize impact.

Trial Registration: This trial has been registered at clinicaltrials.gov (NCT03630549) on August 15, 2018.

Keywords: HIV, cluster randomized controlled trial, village health worker, community health worker, home-based, differentiated care and delivery, antiretroviral therapy, Lesotho, Southern Africa, multi component intervention.

Background

Multiple studies conducted in sub-Saharan Africa (SSA) report high attrition from HIV testing to linkage to care and suboptimal engagement in care.^{1–7} The barriers leading to these gaps are multifactorial, but structural barriers such as the time-consuming and expensive (pre-) antiretroviral therapy (ART) visits and subsequent regular drug refill visits represent major impediments especially in rural settings.^{8–16} Therefore, the World Health Organization (WHO), international funders, national policies in SSA, and the research community is calling for differentiated ART delivery models, adapted to the local context, and including further task-shifting and decentralizing of care.^{17–23}

In a randomized clinical trial, CASCADE trial, we evaluated same-day ART initiation in the community and found significantly improved outcomes along the entire HIV care cascade.²⁴ Although, CASCADE trial did not quite reach the targeted 90% linkage and engagement in care rates after testing positive and being offered same-day ART initiation at home. VIBRA trial builds on these findings, specifically addressing the challenges after same-day home-based ART initiation.

For patients who are stable on ART, decentralization of care to community-level and task-shifting to lay health workers has been shown to be feasible, cost-effective and acceptable.^{25–42} The WHO thus endorse recruitment of community health workers as a strategy to mitigate the impact of the severe shortage of nurses and doctors in rural Africa on health care coverage⁴³ and the UNAIDS launched a recruitment plan for 2 million community health workers in Africa to support its strategy.⁴⁴ Lesotho, a small land-locked country surrounded by South Africa, has the second-highest adult HIV prevalence globally (25.6%) with more than 70% of the population living in rural areas that are facing a shortage of doctors and nurses.^{45,46} A long-standing public sector cadre of lay personnel, called village health workers (VHW), was introduced in 1978 with more than 4000 VHWs currently successfully operating in all districts of Lesotho.⁴⁷

In close collaboration with local stakeholders we designed the VIBRA (Village-Based Refill of ART) model, a multicomponent differentiated ART delivery package that builds on the VHW program and SMS technology. In this manuscript we describe the protocol for a cluster-randomized clinical trial that aims to evaluate the efficacy of the VIBRA model following same-day home-based ART initiation in rural communities of Lesotho.

Methods

1.1 Setting

The VIBRA trial will be conducted in the districts of Butha-Buthe and Mokhotlong, in northern Lesotho, in the catchment areas of 22 health facilities. Both districts are characterized by mostly rural settings with an estimated population of 220,000, mainly living in villages scattered over a mountainous area of 5,842 km².

This trial utilizes the longstanding VHW country program. VHWs are members of and appointed by the community to provide a package of basic services at the household level, although they have no formal professional health education. They are elected by the village members, complete a 2-weeks training followed by periodic refresher courses, and are supported and supervised by the health center staff of the corresponding catchment area. Most are employed by the Ministry of Health, and receive a monthly stipend of USD 20.

1.2 Design

The VIBRA trial is a cluster-randomized superiority trial. The trial is linked to another trial, the HOSENG (HOMe-based SELF-testiNG) trial. Together, HOSENG and VIBRA constitute the GET ON (GETing tOWards Ninety) research project. Reasons for this interlinked design are that both trials rely on interventions involving VHWs, who need to be randomized and specifically trained, and that the HOSENG trial provides one of the recruitment platforms for VIBRA. Thus, the two trials are based on the same cluster-randomization and run in parallel. This design allows us to assess the entire HIV care cascade in one larger project.

The rationale for a cluster-randomized design are the reliance on the VHWs and the high risk of cross-contamination between the study arms if randomization would be done at individual level.

1.3 Cluster-randomization, screening of study participants, eligibility and interventions

Before trial start, the eligible clusters (i.e. villages) are randomized into VIBRA control or VIBRA intervention clusters, stratified by district, village size (≥ 30 versus < 30 households) and access to the nearest health facility (easy versus hard to reach, defined by needing to cross a mountain or river, or > 10 km away from health facility). Details about cluster eligibility, cluster sampling, cluster-randomization and the HIV testing campaign are described in detail in the HOSENG study protocol published separately. In short, different campaign teams consisting of counsellors and one study nurse visit rural villages in the two study districts. The teams will propose HIV testing and counselling and multi-disease screening and prevention. Household members who are eligible for and consent to testing undergo HIV testing by the counselors according to national HIV testing guidelines.⁴⁸ All household members with a confirmed HIV-positive result and not taking ART, will be screened by the study nurse for VIBRA eligibility according to the criteria in Table 1.

If a patient is eligible for VIBRA, the study nurse will offer same-day home-based ART initiation and propose follow-up care according to the assigned respective cluster. As successfully implemented through our previous trial and recommended by the national guidelines, same-day home-based ART initiation, using the national standard first-line ART regimen, will be performed in both arms.^{19,24} If individuals are not eligible for the VIBRA trial and, thus, not eligible for same-day standard first-line ART initiation, they are referred to the health facility. Features of same-day ART initiation are outlined in Table 2.

1.3.1 Intervention clusters

The participants in the intervention clusters are offered the two features of VIBRA model: The first feature is the possibility of village-based ART visit/refill through the VHW with routine clinic visits only at 6 and 12 months after ART initiation. The second is the offer of receiving a tailored short text-message (SMS) intervention. Figure 1 summarizes the VIBRA model.

If participants in the intervention clusters choose the village-based ART visit/refill, they receive an appointment for a first clinical visit at the VHW 12 to 16 days after the home-based ART initiation. At each visit the VHW follows the same paper-based pre-specified checklist (provided as online supplement 1: p34-37) written in the local language (Sesotho). By following the checklist the VHW documents a) patient's symptoms to alert them to a potential drug toxicity, opportunistic infections, immune reconstitution inflammatory syndrome, b) adherence to ART, and c) any visits at other health facilities. In order to ensure safe and high-quality clinical management, participants in intervention clusters will not only be linked to their VHW, but will also be under responsibility of the Community ART Nurse (CAN) of the corresponding district. CANs are nurses who are experienced in HIV care. One CAN per district has been hired. The

VHWs and CANs will have a list of the participants, for whom they are responsible. If any question on the checklist triggers an alert, the VHW informs her/his CAN. Similar to the health facilities, the VHW provides drug supply for 1-3 months at each visit. Participants are, however, encouraged to visit the VHW or the clinic at any time when problems or questions arise. Six months after ART initiation the participant must attend the clinic for the first time for laboratory assessment. VHWs have monthly meetings at the health facility together with a designated facility staff member. The VIBRA model will utilize these existing meetings and the CAN (or representative) will join and provide support. These meetings provide the platform for review of patient files and patients can be up-referred (to the health facility) or down-referred (to the VHW). If a patient misses an ART visit, he/she will be traced by the VHW using a standardized tracking tool (provided as online supplement 1: p39). All VHWs in the intervention clusters will be trained to deliver the VIBRA model: a) dispense ART (and other co-medication such as cotrimoxazole), b) screen for ART-related adverse events and drug-toxicities, c) screen for co-infection (especially tuberculosis), d) assess adherence, e) understand referral algorithm in case of clinical deterioration, f) address disclosure and keep confidentiality, and g) perform basic data entry on the checklists. This training will last for 2-3 days. Every VHW keeps a list of patients he/she is responsible for and will only be allowed to dispense ART to participants on the list.

If participants in the intervention clusters choose the SMS intervention, they will receive monthly reminder SMS in Sesotho to adhere to ART (“Take your medication regularly as prescribed and don’t run out of medication”) and a viral load (VL) result-triggered SMS after the 6- and 12-months follow-up visit:

- If undetectable VL (<20 copies/mL): “Congratulations, your lab test was good. Keep it up!”
- If detectable VL (≥ 20 copies/mL): “Your lab test results are back. Make sure to come to the health facility as soon as possible and remind the nurse about your lab test.”
- If technical failure of VL measurement: “The lab test was unsuccessful. Make sure to come to the health facility as soon as possible and remind the nurse about your lab test.”

In order to maintain participant confidentiality, messages will not explicitly mention HIV or HIV care. Participants are not asked to confirm receipt of messages or to reply and can at any time choose to opt out from receiving messages.

1.3.2 Control clusters

Participants in the control clusters are offered standard of care, i.e. ART visits/refill at the health facility and no SMS intervention. They receive an appointment for a first clinic visit within 12 to 16 days of the home-based ART initiation. The health facility staff fills in the same pre-specified checklist as the VHWs at every visit. Study participants will not be offered any other differentiated delivery models.

1.4 Endpoints

The primary endpoint is viral suppression (<20 copies/mL) at 12 months, defined as the proportion of all participants with a suppressed VL 12 months (range: 10 – 15 months) after enrolment. VL will be measured in plasma using

COBAS TaqMan® HIV-1 Test, v2.0, Roche Diagnostics. Secondary and exploratory endpoints as well as the long-term follow-up are outlined in Table 3.

1.5 Additional research within the project

We will conduct biomolecular research within this project. We will assess prevalence of major drug resistance mutations (DRM) in baseline samples and on all samples with unsuppressed VL at 12 months. Participants who start ART at home during the testing campaign but subsequently never link to care will be specifically traced to assess development of DRM.

Qualitative research is planned alongside the project to provide important contextual data and an in-depth exploration of community response to the intervention. For a qualitative case-control study a random sample from the VIBRA intervention clusters will be chosen. Cases will be participants who refuse village-based ART refill through the VHW, controls will be participants who accept village-based ART refill through the VHW. Moreover, we will conduct standardized interviews with a random sample of all stakeholders involved in delivering this new ART care/delivery model.

We will perform a system impact evaluation and cost-effectiveness analysis, in order to estimate the impact of the VIBRA intervention on health benefits and costs. First, we will assess the direct costs of the interventions. Secondly, we will assess the cost-effectiveness of the VIBRA model. Thirdly, we will assess the economic burden of the interventions to the participants, i.e. including both direct costs and the opportunity costs of their time. The assessment of the direct costs evaluated includes staff costs (campaign staff, clinical staff, laboratory staff, VHWs, CANs), personnel training costs, the cost of equipment needed (costs of HIV tests, ART and other used drugs, laboratory costs including the point-of-care tests at enrolment), and non-medical costs to the participant. The VIBRA model is expected to reduce the number of clinic visits, due to VHW-based ART refill and fewer unscheduled visits because intervention leads to better sustained clinical outcome. This would decrease costs for the health system and the participants (i.e. time required to access care, lost working time while accessing care, additional expenses while accessing care).

1.6 Data collection and management, biologic material, and follow-up

The VHWs and the health care staff at the health facilities collect data from scheduled and unscheduled ART visits on standardized paper study forms (Case Report Forms [CRF]), that act as source documents. CRFs will be collected regularly by the study team and entered into a password-protected database (MACRO, Elsevier). Similarly, relevant data for the SMS intervention will be entered and stored in a separate encrypted and password-protected online database, that offers the possibility to send out SMS automatically and is connected to the district laboratory database containing the VL results. The platform and data are stored on a dedicated server in a data center in Switzerland (Interxion, managed by Hostpoint AG), which meets FINMA-RS 08/07 requirements, is ISO-27001-certified, encrypts

data in-transit with SSL and all patient names at-rest using OpenSSL with AES-256-CTR cipher method. Access to both platforms is strictly limited and regulated through personal user profiles. SMS are dispatched using the trusted third-party provider Twilio, headquartered in the United States and certified with the EU-U.S. and Swiss-U.S. Privacy Shield Framework. The consent forms will be stored in a secure way in the headquarter of the study center (SolidarMed Office in Butha-Buthe, Lesotho). Participant files will be maintained in storage for a period of at least 10 years after completion of the study.

Participants in all clusters undergo HIV testing and phlebotomy at enrolment, and phlebotomy at 6 and 12 months. For each participant, study-ID-coded blood samples will be stored at -80 °C at the laboratory of Butha-Buthe hospital. All samples collected fall under the biobank and material transfer agreement, approved by the ethics committees in Switzerland and Lesotho. Figure 2 displays the SPIRIT flow diagram with the overview of data collection, laboratory assessments and follow-up visits.

1.7 Sample-size

Based on data from the CASCADE trial, we expect the proportion of patients engaged in care with documented viral suppression 12 months after same-day ART initiation in the control arm to be approximately 50%. Assuming a 20% refusal/ineligibility rate, about 400 individuals need to be screened in order to identify 320 eligible individuals and 90% power to detect a 20% increase in the intervention group. We plan to enrol a minimum of 262 patients to ensure a minimum power of 80%. All sample size calculations were done assuming a type 1 error of 0.05 and an intra-cluster correlation coefficient of 0.015. Table 4 provides estimates of the sample size under varying conditions.

1.8 Analyses

Analyses will be performed following CONSORT guidelines for cluster-randomized trials⁴⁹ and an intention-to-treat principle including all participants as randomized per cluster-randomization. Clusters are as unit of randomization, but individuals are set as unit of analysis. Multi-level statistical models will be used to adjust for the clustered data. The following analysis sets will be used in this trial:

1. Intention-to-treat (ITT) set: All study participants will be evaluated according to cluster assignment at randomization
2. Cluster per-protocol (CPP) set: This set includes all participants from clusters who completed the study without a major protocol deviation
3. Individual per-protocol (IPP) set: This set includes all participants who completed the study without a major protocol deviation

The primary analysis for VIBRA study will be the comparison of viral suppression rates 12 months after offer of same-day ART initiation. The primary analysis will use a multi-level logistic regression model to assess the difference between the arms, adjusted for the pre-specified randomization stratification factors, the clustering according to village and other factors found to be unbalanced between intervention and control clusters.

Baseline characteristics will be presented according to randomized groups, no formal testing will be performed. Categorical variables will be described as absolute and relative frequencies and continuous variables as medians and interquartile ranges. As with the primary analysis, secondary endpoints will be analyzed with multi-level logistic regression model. All results will be presented as absolute differences, risk ratios and their respective 95% confidence intervals. Sensitivity analyses will be conducted as measure for robustness and will center on the deviations in model assumptions. The effect of sociodemographic and clinical determinants (age groups, gender, education status, employment status, WHO stage, CD4-count, TB status, CAGE status, HIV/ART history, HIV knowledge) on key study outcomes will be assessed in subgroup analyses. As the study is not powered for these pre-planned subgroup analyses, these results will be considered exploratory. Where data are missing in important covariates, multiple imputation will be utilized and results compared to models ignoring missing data.

The study protocol foresees a predefined snapshot analysis once all participants have completed 6-months follow-up. The snapshot analysis will entail all secondary endpoints assessed within the 6-month study period. All analyses will be done using Stata (version 14, Stata Corporation, Austin/Texas, USA), using 2-sided p-values and a significance level of 0.05.

1.9 Monitoring, auditing, and data safety and monitoring board

At least one external monitoring visit will assess adherence to the approved trial protocol, accuracy of completed CRFs, and the electronic dataset. VIBRA trial represents implementation research, safety profiles of all used drugs are well-known, and the intervention does not include any new drugs. Thus, major adverse effects on patients' health from this intervention are not expected, also given the encouraging results from similar trials in Uganda, Kenya and Tanzania⁵⁰⁻⁵² and participants in the VIBRA model can opt to switch back or be referred to facility-based care at any time during the trial period. Therefore, it is not planned to establish a data safety and monitoring board. However, a separate, detailed safety monitoring plan has been developed to handle (Serious) Adverse Events ([S]AE), in-line with Swiss and Basotho ethics regulations. (S)AE will be graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0., November 2014⁵³ and managed according to study sites standard procedure following the national guidelines.¹⁹ The study physicians are responsible for all safety procedures. If a participant develops an AE of Grade 2 or higher at last study visit, he/she will remain under observation by the study physicians even after study termination, until the AE is resolved or stabilized.

Discussion

Effective and differentiated strategies are needed to improve the HIV care cascade, especially in rural settings. Despite successful upscaling of ART, the financial, human and physical resources available to fulfill the UNAIDS targets are unlikely to grow relative to the increasing number of people on ART.^{54,55} Therefore, there is global consensus that new

differentiated care and service delivery models that increase the capacity, efficiency and cost-effectiveness of delivering ART without reducing quality of care are urgently needed.^{22,41,56}

Task-shifting to lay health workers in the community is a promising approach and in line with the current UNAIDS initiative.⁴⁴ However, at community-level, task-shifting usually focuses on adherence monitoring, not provision of antiretroviral drugs.^{29,57–63} A few programs use community/village health workers to supply ART at home to patients.^{50,51,64–69} This is, however, a resource-intensive intervention, encounters difficult disclosure and stigma issues at the home-visit, patients have to be at home during these visits, and their homes need to be easily located. These factors are unfavourable in a setting as Lesotho with limited resources and the population scattered around a vast mountainous area. Moreover, these models include only stable patients. Differentiated care should not only be designed for stable patients, but include also patients who would otherwise not engage in care.²³ And the definition of a “stable patient” bears challenges itself, leading to late inclusion in these models, and to losing patients already at linkage to care after diagnosis.

The VIBRA model entails a second feature, the SMS reminders and notifications. These have been studied widely in SAA and led to increased adherence and engagement in care.^{70–75} However, sustainability is questionable, especially when reminders have to be implemented manually. Our setting in Lesotho allows sending out SMS automatically from an established database that is connected to the governmental district laboratory database with access to VL results from all study districts. Moreover, while most studies use standardized messages reminding the patient about drug-intake or clinic visits, the SMS intervention in VIBRA model will go one step further. It will automatically generate and send notifications that are individually tailored according to the VL level, indicating the next steps of action for the patient.

In summary, the VIBRA trial evaluates a unique differentiated ART delivery model with community-based drug refill and follow-up after home-based diagnosis and ART initiation in combination with a tailored SMS service. As most countries in SAA have cadres similar to the VHW program in Lesotho, this model – if shown to be effective – has potential to be scaled up. The system impact evaluation will provide valuable cost estimations, and the qualitative research will suggest how the model could further be modified to optimize impact.

Abbreviations

3TC	Lamivudine
ABC	Abacavir
ART	Antiretroviral Therapy
AZT	Zidovudine
CAN	Community ART Nurse
CPP	Cluster per-protocol
CrAg	Cryptococcal Antigen
CRF	Case Report Forms
CTX	Co-trimoxazole (Trimethoprim-Sulfamethoxazole)
DHMT	District Health Management Team
DRM	Drug Resistance Mutations
EAC	Enhanced Adherence Counseling
EFV	Efavirenz
eGFR a.CG	estimated creatinine glomerular filtration rate according to Cockcroft-Gault
GET ON	GETting tOWards Ninety
HIV	Human Immunodeficiency Virus
HOSENG	HOme-based SElftestiNG
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
ITT	Intention To Treat
IPT	Isoniazide Preventive Therapy
IRIS	Immune Reconstitution Inflammatory Syndrome
LTFU	Loss-To-Follow-Up
PP	Per Protocol
(r) VL	(regular/routine) Viral Load (Plasma HIV-1 RNA)
(S) AE	(Serious) Adverse Events
SMS	Short text-Messages
sub-Saharan Africa	SAA
Swiss TPH	Swiss Tropical and Public Health Institute
TB	Tuberculosis
TDF	Tenofovir Disoproxil Fumarate
UNAIDS	United Nations Programme on HIV/AIDS
VHW	Village Health Worker

Declarations

6 Trial status and recruitment

The trial has been launched on August 16, 2018 in both study districts. Based on the experience of previous HIV testing campaigns and the CASCADE trial we assume to reach the required minimum target sample size in about 6-8 months, by visiting approximately 100-120 villages.

6.1 Ethics approval and consent to participate

This trial has been approved by the National Health Research and Ethics Committee of the Ministry of Health of Lesotho (ID06-2018) and the Ethics committee in Switzerland (Ethikkommission Nordwest- und Zentralschweiz; 2018-00283).

Details about the consent process of the testing campaign are provided in the HOSENG study protocol publication. If a household member is eligible for inclusion into VIBRA trial, the study nurse obtains a separate written informed consent, to collect participants' data and to draw blood for storage and additional analyses. The Informed Consent Forms (ICF) for control and intervention clusters are different and do not indicate the cluster allocation. Allocation to cluster arm is concealed in order to minimize the risk of selection bias. Illiterate participants provide a thumb-print and a witness (independent from the trial and >21 years old), chosen by the participant, will co-sign the ICF. For participants aged <18 years, a literate caregiver (person that takes care of the child/young adult) >21 years old provides consent. The ICF is provided in the local language, Sesotho, and the participants receive a copy. Study participants have the right to withdraw consent at any time without giving reasons. In case of withdrawal, only data collected until the time of withdrawal will be used for research purposes (fully anonymized, identifier removed).

Participation in this study is not anticipated to cause any substantial additional risk or cost to the participant. Therefore, we will not pay compensation to the participants. Free AirTime (local prepaid money for cellphone usage) will be provided to the VHWs for the duties of the study. The VHWs have a central role in this new differentiated ART care/delivery model. Besides basic supplies required for their work (i.e. lockable drawer cabinet to store medication and patient documents), we will support them with transport money to make sure the link between VHWs and the health facility is guaranteed. All VHWs who don't have a cellphone will receive a cellphone in order to stay in close contact with their responsible CAN. We will consider a step-wise remuneration for nurses at the health facilities for the clinic-based ART visits of our study participants during the follow-up.

Results of this research project will be shared at three levels. At district level, during meetings headed by the District Health Management Team. At national level, at the national research symposium of the Ministry of Health, and at the international level through presentations at conferences and publication in peer-reviewed journals. The current

version of the ICMJE recommendations⁷⁶ is applicable regarding authorship eligibility and the use of professional writers is not intended.

6.2 Consent for publication

Not applicable

6.3 Availability of data and materials

The datasets used and/or analysed during the study will be available from the corresponding author on reasonable request.

6.4 Competing interests

The Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, under the lead of MB receives unrestricted education and research grants from Gilead, MSD, Janssen, and ViiV. All other authors declare that they have no competing interests.

6.5 Funding

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The funding sources have no role in the design of the study, and will not be involved in data collection, data analysis, interpretation of the results and writing of the manuscript.

6.6 Author's contribution

NDL is the Principal Investigator of this trial. AA, JM, LK, NDL, TIL and TRG conceived and designed the trial. BLN, FT, MB, MBa, MK, MKa were involved in critical revision of the article for important intellectual content. KT and TK provide laboratory expertise. All authors read, revised, and approved the final manuscript.

6.7 Acknowledgements

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Tables

Table 1. *Eligibility criteria for VIBRA trial*

	<i>Inclusion Criteria</i>	<i>Exclusion Criteria</i>
1	Individual is a present household member of a visited household a. Definition: present individual is a) acknowledged by the household head or the representative as part of the household and b) sleeps in the household regularly (at least once a month)	HIV-positive individual is on ART or stopped less than 30 days ago
2	Individual is confirmed HIV-positive a. Definition: twice a reactive blood-based HIV antibody-test according to national guidelines	HIV-positive individual is physically, mentally, or emotionally not able to participate in the study, in the opinion of the study nurse/physician
3	Individual has never taken ART (“ART-naïve”) or has stopped ART more than 30 days prior (“ART-defaulter” according to national guidelines)	HIV-positive individual is in care for high blood pressure (hypertension) or high blood sugar (diabetes). Proof of documentation or medication needed.
4	Individual is ≥ 10 years and body weight ≥ 35 kg	HIV-positive individual wishes to get care outside the two study districts

Table 2. *Components of same-day ART initiation in VIBRA trial*

	<i>Component</i>	<i>Description</i>	<i>Remarks</i>
1	<i>Medical history</i>	<p>The study nurse assesses the patients medical history using a pre-specified checklist</p> <ul style="list-style-type: none"> If any warnings on medical history checklist: Nurse can decide if referral to health facility and no same-day ART initiation. In case of doubt, the nurse contacts the study physician 	<i>See pre-specified checklist in online supplement 1: p23-24</i>
2	<i>Physical examination</i>	<p>The study nurse conducts a structured physical examination using a pre-specified checklist</p> <ul style="list-style-type: none"> If any warnings on physical examination checklist: Nurse can decide if referral to health facility and no same-day ART initiation. In case of doubt, the nurse contacts the study physician 	<i>See pre-specified checklist in online supplement 1: p25-26</i>
3	<i>WHO stage</i>	The study nurse performs clinical WHO staging according to physical examination and medical history	
4	<i>CD4 measurement</i>	<p>The study team performs point-of-care CD4-count, using PIMA Alere™ (fingerprick test), that gives results within 20min. The following consequences depending on the CD4-count result are applied:</p> <p>§ If CD4-count < 350 cells/mcL: Co-trimoxazole (CTX) prophylaxis, 960mg o.d., p.o., 1 tbl</p> <ul style="list-style-type: none"> If participant < 14 years: ½ tbl o.d., p.o. <p>§ If CD4-count < 200 cells/mcL: Cryptococcal Antigen (CrAg) point-of-care measurement (Lateral Flow Assay, IMMY®)</p> <ul style="list-style-type: none"> If CrAg positive: Immediate referral to nearby district hospital by study team, no same-day ART initiation 	<p><i>Although baseline CD4-counts are no longer used according to national guidelines to establish ART eligibility, baseline CD4-count remains a strong indicator of early outcomes on ART and is therefore a) an important variable for the study analysis and b) an important clinical monitoring measurement for the prevention of opportunistic infections.</i></p> <p><i>The national guidelines suggest to screen for CrAg only if CD4-count <100 cells/mcL. However, data is scarce, hence, we will extend screening to those CD4-count <200 cells/mcL.</i></p> <p><i>For CrAg-positive patients, preventive or therapeutic antifungal treatment is indicated and a lumbar puncture is required. Thus, referral to the hospital is needed. Due to evidence that early ART initiation should be avoided in case of cryptococcal meningitis, same-day ART initiation will not be done in CrAg positive individuals until cryptococcal meningitis has been excluded.</i></p>
5	<i>Creatinine measurement</i>	<p>The study team performs point-of-care creatinine, using StatSensor Creat™ Nova™ Biomedical (fingerprick test), that gives results within 2min.</p> <ul style="list-style-type: none"> If estimated creatinine glomerular filtration rate according to Cockcroft-Gault (eGFR a.CG) < 50 ml/min: Substitution of tenofovir disoproxil fumarate (TDF) with abacavir (ABC) or zidovudine (AZT) depending on the haemoglobin result If eGFR a.CG < 30 ml/min: Nurse decides if referral to 	<i>According to national guidelines, before initiating standard first-line ART containing tenofovir disoproxil fumarate (TDF), a baseline creatinine is needed.</i>

		health facility and no same-day ART initiation	
6	<i>Haemoglobin measurement</i>	<p>The study nurse performs point-of-care haemoglobin, using HemocueTM, HB301 (fingerprick test), that gives results within 2min.</p> <ul style="list-style-type: none"> If haemoglobin < 8 g/dL: zidovudine contraindicated and nurse can decide if referral to health facility and no same-day ART initiation 	<i>According to national guidelines, before initiating ART regimen containing zidovudine, a haemoglobin is needed.</i>
7	<i>Adherence counseling and education session</i>	The study nurse conducts a structured education/adherence session. It is delivered, using a leaflet, in a one-on-one session in approximately 5-10min.	<i>A condensed version of the education and counseling typically provided over the course of the former pre-ART visits has been developed and successfully tested in the previous trial (CASCADE trial).</i>
8	<i>Readiness assessment</i>	<p>Before dispensing ART the study nurse confirms readiness and answers remaining questions, using a pre-specified checklist</p> <ul style="list-style-type: none"> If patient not ready: referral to health facility and no same-day ART initiation 	<p><i>See pre-specified checklist in online supplement 1:</i></p> <p><i>p29</i></p>
9	<i>Dispensing of ART</i>	<p>The study nurse prescribes a 1-month supply of the standard 1st-line ART according to national guidelines: TDF / lamivudine (3TC) / efavirenz (EFV) as fixed-dose combination, once daily.</p> <ul style="list-style-type: none"> If TDF contraindicated, substitution with ABC or AZT depending on haemoglobin If uncontrolled mental disease, e.g. active psychosis: referral to health facility and no same-day ART initiation Depending on CD4-count, additionally 1-month supply for CTX will be dispensed 	<p><i>The study nurses, like other qualified nurses in Lesotho, are authorized to write prescriptions for ART. We only include patients 10yrs and older and 35kg or above (cf. eligibility criteria). Thus, TDF/3TC/EFV is the standard treatment, that everybody will receive unless we discover renal impairment.</i></p> <p><i>Before dispensation of ART, the study nurse will re-test again for HIV as per national ART guidelines.</i></p>
10	<i>Follow-up visit</i>	The study nurse provides a follow-up date in 12-16 days, either at the health facility (VIBRA control) or with the VHW (VIBRA intervention, if the participant agrees), for a next ART visit.	<i>The study nurse documents the entire process in the patients booklet ("bukana"), incl. drugs prescribed and follow-up date, and fills in all government documents (patient file, registers) at the health facility responsible for the catchment area.</i>

Table 3. Secondary and exploratory endpoints of VIBRA trial

	<i>Definition</i>	<i>Time point following enrolment</i>	<i>Remarks</i>
Secondary endpoints			
Viral suppression <20 copies/ml	Proportion of all participants with viral suppression (<20 copies/mL)	6 (range: 5-8) months	
Viral suppression <1000 copies/ml	Proportion of all participants with viral suppression (<1000 copies/mL)	6 (range: 5-8) and 12 (range: 10-15) months	<i>Some of the remote health facilities in our study districts face regular challenges in sending the blood to the government hospital. To ensure sufficient VL measurements among our study participants, these health facilities will be equipped with dried-blood-spot (DBS) as a backup for VL measurement. According to the WHO the recommended threshold for treatment failure using DBS is 1000 copies/mL</i>
Linkage to care	Proportion of all participants attending the first clinic- or VHW-based ART visit at least once within given time point	a) Within 1 month b) Within 3 months	
Engagement / Retention in care	Proportion of all participants active in care at a health facility or at the VHW	6 (range: 5-8) and 12 (range: 10-15) months	<i>Definition of “active in care”: at least one ART visit in the defined window.</i> a) <i><u>Including</u> patients who have stopped ART and participants who transferred out to another health facility with known outcome (documented proof of follow-up visit or laboratory test)</i> b) <i><u>Excluding</u> participants who died, were lost to follow-up (LTFU), or were more than 2 months late for a scheduled consultation or medication pick-up with a reason available (e.g. currently no money for clinic-visit, busy working in South Africa, etc.)</i> c) <i>Participants who transferred out to any other facility without known outcome (no documented proof of follow-up visit or laboratory test) are excluded from both the numerator and denominator of calculations of retention</i>
All cause mortality	Proportion of all participants dead	12 (range: 10-15) months	<i>Verbal autopsy to capture cause of death whenever possible. No death certificate or autopsy report required.</i>
Lost-to-follow-up (LTFU)	Proportion of all participants LTFU	12 (range: 10-15) months	<i>We define participants lost to follow-up if they or their treatment buddies were more than 2 months late for a scheduled consultation or medication pick-up and no information was found about the participant</i>
Transfer out (TO)	Proportion of all participants who transferred out to any other health facility (than the initially attached one) with known outcome	12 (range: 10-15) months	<i>Definition of “known outcome”: Documented proof of follow-up visit or laboratory test of the new health facility</i>
Serious Adverse Events (SAE)	Proportion of patients with SAE	Within 12 months	<i>SAE graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0., November 2014</i>
Exploratory endpoints			
Compliance	Proportion of ART	12 (range:	

to protocol procedure	refills and ART visits per participant according to protocol schedule, at the VHW and the health facility	10-15) months	
Overall effect of HOSENG + VIBRA	Overall effect of combined interventions HOSENG and VIBRA (Arm 4 vs Arm 1) on viral suppression (<20 copies/mL)	12 (range: 10-15) months	
Assessment of acceptance of interventions	a) Acceptance of same-day ART initiation b) Acceptance of VIBRA model	Within 1 month	
Long-term follow-up			
Long-term follow-up	Proportion of participants that are active in care and virologically suppressed (<20 copies/mL)	24 (range: 22-28) months	

Table 4. Sample size estimations for VIBRA trial

<i>Control</i>	<i>Intervention</i>	<i>Power</i>	<i>Total sample size</i>	<i>Total clusters</i> <i>median (interquartile range)</i>
0.5	0.7	0.9	478	120 (80 - 236)
0.5	0.7	0.8	262	65 (44 -130)
0.5	0.75	0.9	195	25 (33-100)
0.5	0.75	0.8	130	35 (22-65)

Figures












VIBRA Control (Standard of care)		VIBRA Intervention (Offer of VIBRA model)	
1	Offer of home-based same-day ART initiation	Offer of home-based same-day ART initiation	
	Clinic-based ART visit/refill	Offer of village-based ART visit/refill	
	 WHEN Follow-up interval of max. 3 months	 WHEN Follow-up interval of max. 3 months	
	 WHERE Nurse-led health facility	 WHERE At the VHW <i>Except at 6 and 12 months follow-up: visit at health facility for laboratory assessment (esp. VL=viral load)</i>	
	 WHO Nurse	 WHO VHW	
2	 WHAT Screening for opportunistic infections (esp. TB) and ART-related toxicities, adherence assessment, ART (+CTX/IPT) dispensing	 WHAT Screening for opportunistic infections (esp. TB) and ART-related toxicities, adherence assessment, ART (+CTX/IPT) dispensing	
	No SMS intervention		
	<i>However, SMS might be used to follow-up patients in order to ensure laboratory assessments at 6 and 12 months.</i>		
	Offer of Individually customized SMS		
3	 WHEN Monthly and after VL measurement		
	 WHO Automatically sent out from VL database		
	 WHAT a) Monthly reminder to adhere to ART b) Individually tailored SMS according to VL result		

Figure 1

Description of procedure in VIBRA intervention and control clusters.

	Enrolment	Post-allocation			Close-out	Long-term Follow-up
TIMEPOINT	0	Within 1 month (linkage to care)	Within 3 month (linkage to care)	6 months (range: 5-8 months)	12 months (range: 10-15 months)	24 months (range: 22-28 months)
ENROLMENT:						
eligibility screen	X					
allocation (preset by cluster)	X					
INTERVENTIONS:						
VIBRA model (Intervention)	◀──▶.....◆					
Standard of care (Control)	◀──▶.....◆					
ASSESSMENTS:						
Socio-demographic factors	X					
HIV knowledge ¹	X					
tuberculosis screening ¹	X	X	X	X	X	X
medical history ¹	X	X	X	X	X	X
physical examination ¹	X	X	X	X	X	X
WHO staging ²	X	X	X	X	X	X
CD4	X				X	(X)
CrAg ³	(X)					
creatinine	X			X	X	X
haemoglobin	X			(X)	(X)	(X)
adherence counseling	X	X	X	X	X	X
readiness assessment ¹	X					
dispensing of ART ⁴	X	X	X	X	X	X
viral load	X			X	X	X
plasma for storage (=3 EDTA tubes for GRT) ⁵	X			(X)	(X)	(X)

Figure 2

SPIRIT Flow Diagram of VIBRA trial - 1 see online supplement 1; 2 only at clinic-based follow-up visits; 3 for all participants with a baseline CD4-count <200 cells/mcL (see also Table 2); 4 incl. CTX and IPT (+B6) and other co-infection (prophylaxis) medication if appropriate; 5 See chapter Additional research within the project.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [supplement1.pdf](#)
- [supplement2.pdf](#)