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Clinical Study Protocol

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VIllage-based refill of ART after same-day ART start vs clinic-based ART refill for HIV-positive individuals not on ART during home-based HIV testing – a cluster randomized controlled trial in rural Lesotho

abbreviated title:

VIBRA study („VIllage-Based Refill of ART")

PART B
of GET ON research project

This study is embedded in the overall research project called **GET ON** ("GETing tOwards Ninety") project

Protocol Version Number	6	**Document Date**	20.04.2018
Principal Investigator	**Niklaus Daniel Labhardt** *Swiss Tropical and Public Health Institute,* *Socinstrasse 57, 4002 Basel, Switzerland*		
Protocol authors (so far)	AA, FT, FV, JM, NDL, TIL, TRG		

Signature PI: _____

Date: 20.04.2018

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III. Remarks

1) A list of all other involved staff (lay counsellors, campaign organizers, village health workers) will only be available at the start of the study and is not feasible to include at this stage, because it is more than 100 people. They will all receive a specific training and the study personnel who enrols patients will get an introduction into GCP (without certificates).
2) This is an investigator-initiated trial. The Principal Investigator, the Swiss TPH respectively, acts as Sponsor.
3) This study protocol will be registered on clinicaltrials.gov, the registration number will be provided at a later stage
4) According to Swiss lab (ClinO, Art. 19, 20, App 3, 1.1) this is a Category A trial
5) Conflict of Interest: All authors declare that they have no competing interests.

IV. The "Towards 90-90-90" research consortium

This research protocol has been developed in collaboration with the "Towards 90-90-90 in Butha-Buthe" research consortium.
The project with the full title *Improving the HIV care cascade in rural Lesotho – Towards 90-90-90: A research collaboration with the Ministry of Health* entails operational and clinical research aiming at achieving the 90-90-90 targets in Butha-Buthe and generating evidence on innovative approaches for Lesotho and similar settings. The five institutions that are part of this consortium are introduced below:

1. **District Health Management Team (DHMT) of Butha-Buthe and Mokhotlong, Lesotho:** DHMT has the responsibility for the practical implementation of all activities. It ensures the coordination of the proposed study with other district activities to avoid any negative interference with routine health care activities within the district. The project was set up in collaboration with Dr Lebohang Sao, District Health Manager of Butha-Buthe, and Dr Kabelo Matjeane, District Health Manager of Mokhotlong.
2. **Ministry of Health of Lesotho:** The Research Coordination Unit (RCU) is the Unit responsible for research at the Ministry of Health with extensive experience in supporting the conduct of country-wide surveys and in monitoring studies conducted in Lesotho. The RCU will oversee the implementation of the study, including compliance with the national and ethical standards. The person responsible at RCU is the Unit's Head, Dr. Kyaw Thin, who heads the unit since 2008.
3. **Swiss Tropical and Public Health Institute (Swiss TPH), Basel, Switzerland:** The Swiss TPH has the overall scientific responsibility for design, implementation, and analysis of the study. Swiss TPH is an institute of the University of Basel with longstanding experience in conducting health projects and studies in Sub-Saharan Africa. Dr. Niklaus Labhardt is the principal leader of the Towards 90-90-90 project. He has lived and worked in Lesotho from 2010-12, has successfully conducted studies and trials in Lesotho and has since remained closely connected to the country. He knows the country context very well in terms of clinical work, project management and research. Tracy Glass is the co-investigator of the Towards 90-90-90 project and the principal investigator of HOSENG. She is a biostatistician with 15 years of experience working in clinical and observational studies in HIV, the last 5 years in resource-limited settings. Alain Amstutz is a physician researcher and the local principal investigator. He pursues his PhD in clinical HIV research within the research consortium and currently lives in Lesotho.
4. **SolidarMed, Swiss Organization for Health in Africa, Lesotho:** SolidarMed is a Swiss not-for-profit organization, working in Lesotho for over 50 years (www.solidarmed.ch). Of note, SolidarMed is a longstanding implementing partner of the Ministry of Health in Lesotho, working under a signed Memorandum of Understanding that includes activities related to the project "Towards 90-90-90". SolidarMed has the responsibility to coordinate the proposed project. For implementation of the study SolidarMed will provide infrastructure, such as cars and transport, study personnel, and administrative support. SolidarMed will provide substantial additional funds for the proposed project, i.e. it will cover majority of cost for routine VL monitoring. The person responsible for the project at SolidarMed is Dr. Josephine Muhairwe, Country Director of SolidarMed Lesotho, who has extensive experience in project planning and implementation in Sub-Saharan Africa.
5. **Molecular Virology, Department of Biomedicine (DBM), University of Basel, Switzerland:** The Molecular Virology laboratory contributes all critical laboratory expertise to the proposed project. It provides training, mentoring and quality control for the virologic analyses conducted at the laboratory of Butha-Buthe. The person responsible is Prof. Dr. Thomas Klimkait, who for more than 15 years heads an accredited diagnostic laboratory for clinical diagnostics in Basel, Switzerland. He has experience in molecular test development and in establishing and auditing certified laboratories in Switzerland as well as Sub-Saharan Africa.

V. Signatures

Principal Investigator and Co-Investigators who sign below have approved the current study protocol version 6, date 20.04.2018, and confirm hereby to conduct the project according to the plan, the current version of the World Medical Association Declaration of Helsinki and the principles of Good Clinical Practice (GCP).

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VI. Table of Contents

1. GENERAL INFORMATION

1.1. ABBREVIATIONS / GLOSSARY OF TERMS

3TC	Lamivudine
ABC	Abacavir
ART	Antiretroviral Therapy
AZT	Zidovudine
CHAL	Christian Health Association of Lesotho
CI	Confidence Interval
CAC	Community Adherence Clubs
CAG	Community ART Groups
CAN	Community ART Nurse
COU	Clinical Operations Unit (CRO of Swiss TPH)
CrAg	Cryptococcal Antigen
CRF	Case Report Forms
CTX	Co-trimoxazole (Trimethoprim-Sulfamethoxazole)
DALY	Disability Adjusted Life Years
DBM	Department of Biomedicine, University Basel
DBS	Dried-Blood-Spot
DHMT	District Health Management Team (Lesotho)
DRM	Drug Resistance Mutations
EAC	Enhanced Adherence Counseling
EFV	Efavirenz
eGFR a.CG	estimated creatinine glomerular filtration rate according to Cockroft-Gault
HCG	Human Chorionic Gonadotropin
HDL	High Density Lipoprotein

HIV	Human Immunodeficiency Virus
HIVST	HIV Self-Testing
HTS	HIV Testing and Services
ICF	Informed Consent Form
ITT	Intention To Treat
IPT	Isoniazide Preventive Therapy
IRIS	Immune Reconstitution Inflammatory Syndrome
LDL	Low Density Lipoprotein
LTFU	Loss-To-Follow-Up
LMIC	Low- and Middle-Income Countries
MATI	Models for Accelerating Treatment Initiation
MoH	Ministry of Health (Lesotho)
NNRTI	Non-Nucleoside Reverse-Transcriptase Inhibitors
PIH	Partners In Health
PP	Per Protocol
RCU	Research Coordination Unit (of the Ministry of Health of Lesotho)
(r) VL	(regular/routine) Viral Load (Plasma HIV-1 RNA)
(S) AE	(Serious) Adverse Events
SUSAR	Suspected Unexpected Serious Adverse Reaction
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
VMMC	Voluntary Medical Male Circumcision
WHO	World Health Organization

1.2. SYNOPSIS

study title	Village-based refill of ART after same-day ART start vs clinic-based ART refill for HIV-positive individuals not on ART during home-based HIV testing – a cluster randomized controlled trial in rural Lesotho
abbreviated title	VIBRA study („VIllage-Based Refill of ART")
background & rational	By launching the 90-90-90 strategy UNAIDS has shown a way forward in controlling and finally eradicating the deadly AIDS epidemic. The second UNAIDS target – to link and to retain 90% of those diagnosed HIV-positive on ART – is even more challenging and often referred to as the Achilles' heel of the 90-90-90 strategy. Structural barriers such as the time consuming and expensive (pre-)ART visits and subsequent regular drug refill visits seem to be the main impediment for linkage to and retention in care, and this challenge is likely to increase with more countries implementing the WHO treat-all approach. Same-day ART initiation has shown to significantly improve linkage to care (in a hospital setting as well as during home-based HIV testing campaigns), but is still not reaching the required 90% linkage-to-care-rate and retention in care remains a challenge. In order to address the multiple barriers in the HIV care cascade, we are convinced that only a multicomponent package of differentiated service delivery interventions can be successful. Like different partners, funding agencies and the scientific community we see the way forward in further task-shifting and decentralizing care. Having the longstanding and well-established village health worker (VHW) programme in Lesotho in mind, we developed the "VIBRA model" – a differentiated ART care/delivery model, that was designed to increase care privacy and minimize clinic-based impediments, but most importantly to further reduce structural barriers. The VIBRA model entails an evidence-based intervention (SMS reminders) and the main and innovative intervention pillar: the possibility of village-based ART refill through the VHW – following same-day, home-based ART initiation.
aim/objective(s)	This study aims to evaluate the efficacy of a multicomponent differentiated ART care/delivery model ("VIBRA model") among newly HIV-positive, untreated individuals found during a home-based HIV testing campaign on the 2nd and subsequently 3rd UNAIDS 90-90-90 target. The main pillar of the VIBRA model is the village-based ART refill through VHWs following same-day ART initiation.
study design	The VIBRA study is linked to a another trial, the HOSENG (HOme-based SElf-testiNG) study. Together, HOSENG and VIBRA are called the GET ON ("GETing tOwards Ninety") research project. The HOSENG study, with its home-based HIV testing campaign, provides the recruitment platform for the VIBRA study. The reasons for this interlinked design are: a) for potential study participants for VIBRA trial (HIV-positive individuals not on ART) are to be recruited during the HOSENG study, b) to allow us to assess the entire HIV care cascade in one larger project, and c) because both trials rely on interventions involving VHWs, who need to be randomized and specifically trained. Therefore, it is efficient and feasible to run both trials parallel and randomize at one time point. The VIBRA study is a cluster randomized, parallel-group (1:1:1:1 allocation), open-label, superiority, prospective clinical trial. Clusters are stratified by district, size of village, and village access to the nearest health facility.

<table>
<tr><td>major eligibility criteria</td><td>
Eligibility criteria clusters:
1) the cluster is clearly confined to the catchment area of one of the study clinics
2) the cluster has at least one registered VHW who is willing to participate and fulfills the following criteria:
a) is at least 18 years of age
b) has adequate reading and writing skills
c) successfully passes the training assessment
3) village authority (village chief) is willing to participate in trial
Eligibility criteria individuals:
4) Individual is a household member of the visited households of the respective clusters
5) Individual is confirmed HIV-positive
6) Individual has never taken ART (ART-naïve) or has stopped ART more than 30 days prior (ART-defaulters)
7) Individual is ≥10 years old and has a body weight of ≥35kg
8) Individual is not in care for high blood pressure or diabetes (high blood sugar)
9) HIV-positive individual wishes to get care outside the study districts
</td></tr>
<tr><td>intervention and control</td><td>
<table>
<tr><th></th><th>VIBRA Control
(Standard of care)</th><th>VIBRA Intervention
(Offer of VIBRA model)</th></tr>
<tr><td>1</td><td>Offer of home-based same-day ART initiation</td><td>Offer of home-based same-day ART initiation</td></tr>
<tr><td>2</td><td>Clinic-based ART visit/refill
<u>Who:</u> Nurse
<u>Where:</u> Nurse-led health facility
<u>When:</u> Follow-up interval of max. 3 months
<u>What:</u> TB screening, Screening for other opportunistic infections, Screening for ART-related toxicities, adherence assessment, assessment whether patient visited any medical facility since last appointment, addressing basic psychosocial problems, ART (+CTX/IPT) dispensing
(+ dispensing of other medication & WHO staging)</td><td>Offer of Village-based ART visit/refill
<u>Who:</u> VHW
<u>Where:</u> At VHW’s home*
<u>When:</u> Follow-up interval of max. 3 months
<u>What:</u> TB screening, Screening for other opportunistic infections, Screening for ART-related toxicities, adherence assessment, assessment whether patient visited any medical facility since last appointment, addressing basic psychosocial problems, ART (+CTX/IPT) dispensing
*Except at 6 and 12 months follow-up: visit at health facility for laboratory assessment (viral load)</td></tr>
<tr><td>3</td><td>No SMS intervention
<u>However:</u> SMS might be used to follow-up patients in order to ensure laboratory assessment at 6 and 12 months.</td><td>Offer of Individually customized SMS
<u>Monthly reminder SMS:</u> to pick up ART
<u>A VL results-triggered SMS:</u>
• Undetectable VL (<20 copies/mL): → Message: “Congratulations, your lab test was good. Keep it up!”
• Detectable VL (≥20 copies/mL): → Message: “Your lab test results are back. Make sure to come to the health facility at the next scheduled date and remind the nurse about your lab test.”
• Technical failure of VL measurement → Message: “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.”</td></tr>
</table>
</td></tr>
<tr><td>primary endpoint</td><td>Viral suppression at 12 months, defined as the proportion of all participants with a VL <20 copies/mL 12 months (range: 10 – 15 months) after enrolment.</td></tr>
</table>

secondary endpoints	a) Viral suppression at 6 months, defined as the proportion of all participants with a VL <20 copies/mL 6 months (range 5 – 8 months) after enrolment b) Alternative viral suppression at 12 months, defined as the proportion of all participants with a VL <1000 copies/mL 12 months (range 10 – 15 months) after enrolment. c) Alternative viral suppression at 6 months, defined as the proportion of all participants with a VL <1000 copies/mL 6 months (range 5 – 8 months) after enrolment. d) Sustained viral suppression, defined as the proportion of all participants with a VL <20 copies/mL at 6 (range 5 – 8 months) as well as at 12 months (range 10 – 15 months) after enrolment e) Linkage to care within 1 month, defined as the proportion of all participants attending the first clinic- or VHW-based ART visit at least once within 1 month after enrolment f) Linkage to care within 3 months, defined as the proportion of all participants attending the first clinic- or VHW-based ART visit at least once within 3 months after enrolment g) Retention in care at 6 months, defined as the proportion of all participants active in care at a health facility or at the VHW 6 months (range 5 – 8 months) after enrolment h) Retention in care at 12 months, defined as the proportion of all participants active in care at a health facility or at the VHW 12 months (range 10 – 15 months) after enrolment i) All-cause mortality at 12 months, defined as the proportion of all participants dead 12 months (range 10 – 15 months) after enrolment j) LTFU at 12 months, defined as the proportion of all participants LTFU 12 months (range 10 – 15 months) after enrolment k) Transfer out at 12 months, defined as the proportion of all participants who transferred out to any other health facility (than the initially attached one) with known outcome (documented proof of follow-up visit or laboratory test) at 12 months (range 10 – 15 months) after enrolment
other endpoints & objectives	Further overarching GET ON objectives include safety objectives, exploratory endpoints, a long-term follow-up, a cost-effectiveness & system impact evaluation, qualitative research, as well as biomedical research.
sample size & statistical considerations	Based on preliminary data from the previous CASCADE trial, we expect the proportion of viral suppression in the control arm to be 50%. Given the range of clusters to achieve the varying sample size, we will plan on sampling about 100 clusters/villages therefore expecting approximately n=400 HIV-positive individuals not on ART. Assuming a 20% refusal/ineligible rate, this will provide us with approximately 320 eligible individuals and sufficient power to detect a 20% increase in viral suppression in the intervention group. We plan to recruit a minimum of 262-320 patients to ensure a minimum power of 80%. Of course, if the effect of the intervention is greater – say 0.25 – we will have more than 90% power to detect this under all scenarios. All sample size calculations were done assuming a type 1 error of 0.05 and an intra-cluster correlation coefficient of 0.015. Clusters will be set as unit of stratified randomization, whereas individuals are set as unit of analysis. The primary analysis will use a multi-level logistic regression model based on the intention-to-treat set to assess the difference between viral suppression in the intervention versus control arm, adjusted for a) the pre-specified randomization stratification factors, b) clustering according to village and household and c) other baseline factors found to be unbalanced between intervention and control clusters. We will use 2-sided p-values with alpha 0.05 level of significance and results will be presented as odds ratios and 95% confidence intervals. A detailed data analysis plan will be developed separately.
recruitment & study duration	Based on the experience of previous HTS campaigns and the CASCADE trial, we are confident to reach the required target sample size within 5-6 months. Anticipated start of the entire GET ON project and, thus, recruitment is June/July 2018.
GCP statement	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements.

2. BACKGROUND INFORMATION

2.1. UNAIDS 90-90-90 TARGETS

The Joint United Nations Programme on HIV/AIDS (UNAIDS) launched the 90-90-90 targets for 2020[1] based on the result of newly-acquired scientific evidence that – irrespective of CD4 count – early antiretroviral therapy (ART) for HIV-positive people is beneficial for as individuals and prevents onwards HIV transmission.[2–4] The first target is to ensure 90% of HIV-positive individuals are aware of their status. The second target is to get and keep 90% of those aware of their status on ART. The third target is to achieve 90% viral suppression among those who are taking ART. Based on accumulated evidence that viral suppression through successful ART reduces the risk of transmission[4,5], it is expected that – if achieved – the 90-90-90 targets would lead to a reduction in the yearly global HIV-incidence from 2 million currently to 500,000 by 2020.[6] However, the financial, human and physical resources available to fulfill the UNAIDS targets are unlikely to grow in proportion to the increasing number of people on ART. There is increasing global consensus that in order to successfully treat all persons living with HIV, new differentiated care and service delivery models that increase the capacity, efficiency and cost-effectiveness of delivering ART without reducing quality of care are thus urgently needed.[7,8]

2.2. THE FIRST UNAIDS TARGET

Globally, progress made in improving knowledge of HIV status in 2016 was lower than progress in other areas of the cascade.[9] Most recent data from Eastern and Southern Africa show that the percentage of people living with HIV who know their HIV status has steadily improved in the last years, currently at a level of 62% - 72%, but still leaving a gap of approximately 2.7 million HIV-positive people who do not know their HIV status.[9,10] In order to reach the first UNAIDS target, 90% HIV testing coverage, home-/community-based testing - HIV testing close to where people live or work - is a key strategy endorsed by WHO.[11,12] Many studies have shown that home/community-based testing is highly promising in closing the crucial gap of achieving the first 90. However, it is important to distinguish between HIV test acceptance/uptake and HIV testing coverage. While in most cases uptake of HIV testing is shown to be above 90%, testing coverage remains below 90% because of absent people at the time of the campaign. And this is especially true for men and young adults – both of which have a disproportionately high risk of HIV acquitision and poorer clinical outcomes once infected.[13]

2.3. THE SECOND AND THIRD UNAIDS TARGETS

The second UNAIDS target – to link and to retain 90% of those diagnosed HIV positive on ART – is even more challenging and often referred to as the Achilles' heel of the 90-90-90 strategy.[14–16] Once tested, individuals need to access care and prevention services to maximize the individual and public health benefits of knowledge of HIV status. However, only one-fifth of patients link into care without any periods of loss to follow-up[16–18] and linkage to care after a positive HIV test during community-based HIV testing is far below 50% in the vast majority of studies in sub-Saharan Africa.[13,19] Recently published data from the ANRS 12249 trial in KwaZulu Natal, South Africa, show that less than 33% of ART-naïve individuals linked to facility-care within 3 months after having been tested HIV positive at their home.[20] Structural barriers such as the time consuming and expensive (pre-)ART visits and subsequent regular drug refill visits seem to be the main impediment for linkage to and retention in care.[21–31] These barriers are likely to increase with the new WHO "treat all" approach as asymptomatic individuals may be less motivated to travel long distances to the nearest clinic. Hence, different initiatives, such as the Models for Accelerating Treatment Initiation (MATI) technical consultation consortium, set one of the highest research priorities in the evaluation of simplified clinical algorithms for managing HIV-positive individuals in order to improve linkage to and retention in care, e.g. same-day ART initiation.[21] In a hospital setting, same-day ART initiation has been shown to significantly improve linkage to care, does not require additional resources, and is cost effective.[32,33] As mentioned in the most recent UNAIDS Global AIDS report, besides the treat all strategy, the adoption of same-day initiation along with increasing investment in community-based strategies (incl. increased community management of ART), will be critical to achieve the second UNAIDS target.[9] Most low- and middle-income countries (LMIC) face a severe shortage of nurses and physicians. Thus, the potential benefits of shifting care from skilled facility-based health worker cadres to lay community-based VHWs are evident.[34,35]

The third UNAIDS target (viral suppression) appears to be less challenging once individuals are tested and on ART. In a systematic review on viral suppression among patients on ART in resource-limited settings almost 85% had a viral load (VL) <1000 copies/mL.[36]

2.4. LESOTHO – A HOTSPOT OF ONGOING HIV TRANSMISSION

Lesotho, a small land-locked country surrounded by South Africa, has the second-highest adult HIV prevalence in the

world.[9,37] Among the hyperendemic countries of Southern Africa it has the highest ongoing HIV transmission rate and the lowest ART coverage (below 50%).[38,39] In sub-Saharan Africa young people (aged 15–24 years), especially women, continue to be at great risk of HIV infection, i.e. in 2016 they accounted for 26% of new HIV infections despite making up just 10% of the population.[9] Compared to the other Southern African countries, Lesotho presents one of the highest incidence of HIV among adolescent girls and young women.[10] According to most recent UNAIDS data 72% of people living in Lesotho with HIV knew their status and 74% of them were on ART.[9] No official data for the last UNAIDS target in Lesotho are available, because routine VL was only recently introduced (cf. chapter 2.4.1).

2.4.1. Own accomplished work related to the 90-90-90 targets in Lesotho

Our research consortium, called "Towards 90-90-90", conducts several research projects focusing on achieving the 90-90-90 targets in resource-limited settings. The consortium is headed by The Swiss Tropical and Public Health Institute, but further consists of SolidarMed (Swiss Organization for Health in Africa), the Molecular Virology Group of Department of Biomedicine of the University of Basel, the District Health Management Team of Butha-Buthe and the Research Coordination Unit of the Ministry of Health of Lesotho. The consortium received a CHF 500'000 grant from the Swiss National Science Foundation (R4D Open Call IZ07Z0_160876/1) as well as a cumulative CHF 500'000 from different smaller grants, including ESTHER Switzerland (https://www.esther-switzerland.ch/wordpress/wp-content/uploads/2016/05/ESTHER-Lesotho-Project.pdf). More information about ongoing projects can be found on:

- https://www.swisstph.ch/en/projects/hiv-care-research-in-lesotho/

In a cluster randomized trial comparing home-based HIV testing to testing in mobile clinics we have shown that test uptake may be as high as 92.5% with home-based testing[40], consistent with literature and WHO recommendations (cf. 2.2). However, subsequent linkage to care was only 25%. Experience from this first trial led to the CASCADE trial, that assessed the entire HIV care cascade.[41] In this trial we visited close to 7000 households in rural and semi-rural areas to provide home-based HIV testing and services (HTS). Individuals who tested HIV-positive and were ART naïve were randomized into standard of care (referral to clinic for pre-ART counseling and baseline laboratory tests) and intervention (proposition to start ART the same day at home with a first clinic visit for refill after 4 weeks). Linkage to care, defined as the individual presenting at the clinic within 3 months, was 68.6% in the intervention versus 42.5% in the standard of care group ($p<0.001$). At six months follow-up 63.5% in the intervention and 43.9% in the standard of care group were active in care ($p=0.002$) and 48.2% versus 32.4% had documented viral suppression ($p=0.007$).[42] The results of the CASCADE trial endorse simplified, decentralized access to ART as a good approach to improve linkage to care. However, we still did not reach 90% linkage to care.

Since the beginning of 2016 the district hospital of Butha-Buthe offers VL testing, thanks to a close collaboration between the Ministry of Health of Lesotho, the Swiss Tropical and Public Health Institute (Swiss TPH), Department of Biomedicine University of Basel and SolidarMed, Swiss Organization for Health in Africa. As of November 2015, all patients on ART in Butha-Buthe district have access to routine VL monitoring and VL results are stored in an encrypted and password-protected online database (https://visibleimpact.org/projects/1261-molecular-hiv-monitoring-in-lesotho). This viral load monitoring platform was rolled out to the Mokhotlong district in January 2018. Among those taking ART in the district, viral suppression is > 90% among adults[43], but only 72% in children.[44] Several studies addressing the problem of treatment failure and strategies to switch to second-line ART are currently in preparation.[45,46]

2.5. VIBRA MODEL AND RATIONAL OF THE PROPOSED STUDY

In the CASCADE trial, a significantly higher linkage to care rate (68.6%) has been observed in the intervention group (home-based, same-day ART initiation), showing that same-day ART initiation is not only feasible and effective in a hospital setting[32], but also in a community-based setting. However, although less than 1% declined starting ART at enrolment (home visit), there are still 31.4% who did not link to care for further drug refill and continuation of ART. How could clinical management of HIV-positive individuals be further simplified in order to increase the linkage to care rate and retention in care to 90% - especially in regard to the severe shortage of nurses and physicians in LMIC?

Decentralization of HIV care to community-level and task-shifting to village/lay health workers has shown to be feasible, cost-effective, and has been widely accepted and endorsed – especially regarding the current ambitious goal of universal coverage in rural Africa.[24,47–59] In Zambia, for example, the move to a greater use of community service delivery is helping lower the costs of treatment programmes, contributing to a 32% decline in per-patient treatment costs compared to facility-based services.[60] Since the 2014 supplement to the 2013 WHO guidelines for the treatment of HIV in resource-limited settings the WHO has officially recognised the value of extending ART delivery beyond the facility into the community.[61] With the launch of the 2015 "Treat All" WHO Guidelines, the WHO concurrently recommended a differentiated care/delivery approach. Differentiated care, or differentiated service delivery, is a client-centred approach that responds both to the diversity of needs of people living with HIV and the contraints on the health care system.[62] As part of this, the WHO recommends that clinically stable people living with HIV can have reduced clinical

constulations (every 3-6 months), increased duration of ART refills (3-6 monthly supply) and receive ART refills from trained and supervised lay health workers within communitity settings.

However, at community-level task-shifting usually still focuses on intake monitoring, but not provision of antiretroviral drugs.[53,63–69] Some programs use Coumminity/Village Health Workers (C/VHW) to supply ART at home.[70–77] However, home-based ART supply by C/VHWs is a resource-intensive intervention, requires intensive supervision, encounters difficult disclosure and stigma issues at the home-visit, and most importantly, patients have to be at home during VHW visits and their homes need to be locatable easily. All these factors are very unfavourable in a setting such as Lesotho with limited resources and where the population is scattered around a vast mountainous area. Another wide-spread ART service delivery approach are the community ART groups (CAG) or community adherence clubs (CAC) for collective drug refill in order to reduce travels to clinics.[78–82] As an example, a well-elaborated CAC/CAG project in KwaZulu Natal[78] and another in Lesotho[82] reported retention in care at 12 months of 94% and 98%, respectively. These studies, however, only enrolled patients retained in care and stable on ART. Moreover, setting up CAG/CACs is time and resource-consuming.[78] Furthermore, they are at risk for overestimating the intervention effect, because they are based on the will of patients to join CAC/CAGs (i.e. only 33% of patients in the Lesotho opted to join a CAG).[82] Instead of organizing CAGs/CACs another approach might be to have decentralized posts for ART refill. Vogt et al. studied a promising decentralized ART supply program in Kinshasa, Congo, operating community-based refill centers that solely provided ART refill.[83] However, this trial was a retrospective cohort study (hence subject to all limitations inherent to this kind of analyis), and was conducted in a urban setting and only among stable patients. This model performed considerably better than standard of care and was suitable for heterogeneous patient groups.

All these models usually include only stable patients. However, the definition of a stable patient bears many challenges itself, leading to late inclusion in these models. Meanwhile, many barriers to initiating treatment, particularly among those with high CD4 cell counts at baseline, may hinder linkage to care and early retention in care.[84]

Barriers to linkage to and retention in care entailed in the HIV care cascade are multifactorial. There are health system-level factors such as attitudes of providers, cumbersome clinic procedures with long waiting times, and individual factors, usually categorized into structural, biomedical, and/or behavioural barriers.[23,85,86] In order to address these multiple barriers, we are convinced that a multicomponent package of differentiated care interventions is needed. The most recent systematic review of interventions improving adherence to ART in resource-limited settings supports this statement as well as promising results from other similar recent randomized controlled trials assessing multicomponent care packages.[87–89] As mentioned in chapter 2.3, structural barriers seem to be the biggest impediment.

Therefore, we propose a differentiated ART care/delivery model, called the “VIBRA model”, that is designed to increase care privacy and minimize clinic-based impediments (stigma by health facility staff, congestion at health facility), but most importantly to reduce the structural barriers: time consuming and expensive (pre-)ART visits and subsequent regular drug refill visits. The VIBRA model entails an evidence-based intervention (SMS reminders[90–96]) and the main and innovative intervention pillar: the possibility of village-based ART refill through the VHW – following same-day home-/community-based ART initiation. Despite extensive literature on this topic, a systematic literature research revealed no studies that evaluated such a differentiated ART care/delivery model so far.

This approach utilizes the well-established system of VHWs in Lesotho and similar settings. Moreover, it is in-line with a) the Lesotho national Ministry of Health’s efforts[97], b) the WHO’s strong recommendation[50,98] to decentralize care to a village level, c) the UNAIDS’ global call for 2 Mio VHWs in support of HIV care[99], and d) the Journal of International ADIS Society promotion for a differentiated care research agenda[100].

1. STUDY OBJECTIVES

1.1. OVERALL OBJECTIVE

This study aims to evaluate the efficacy of a multicomponent differentiated ART care/delivery model (“VIBRA model”) among newly HIV-positive, untreated individuals found during a home-based HIV testing campaign on the 2nd and subsequently 3rd UNAIDS 90-90-90 target. The main pillar of the VIBRA model is the village-based ART refill through VHWs following same-day ART initiation.

1.2. PRIMARY OBJECTIVE

As primary objective this study seeks to determine the prevalence in viral suppression rate (3rd UNAIDS 90-90-90 target) 12 months after enrolment between the intervention clusters, who were offered the VIBRA model, and the control clusters, who were offered standard of care.

1.3. SECONDARY OBJECTIVES

Secondary objectives include comparison of prevalence in linkage to care, retention in care, lost-to-follow-up (LTFU), mortality, other definitions of viral suppression, and transfer out between the intervention and control clusters.

1.4. OTHER OBJECTIVES

This study is embedded in an overarching research project, called GET ON, with an interlinked trial called HOSENG (HOme-based SElf-testiNG) study. Further overarching GET ON objectives include safety objectives, a cost-effectiveness and system impact evaluation, qualitative research, as well as biomedical research objectives.

3. STUDY SETTING, DESIGN, AND METHODS

3.1. SETTING

The study will be conducted in the districts of Butha-Buthe and Mokhotlong, in northern Lesotho, Southern Africa, in the catchment areas of total 22 health facilities (10 nurse-led rural health centers, 1 missionary hospital, and 1 governmental hospital in Butha-Buthe district and 9 nurse-led rural health centers, and 1 governmental hospital in Mokhotlong district). Both districts are characterized by mostly rural settings with an estimated population of 220,000, mainly subsistence farmers and mine workers as well as construction or domestic labourers who work in neighbouring South Africa. Each district has only one single mid-size town: Buthe-Buthe with ca. 25,000 inhabitants, and Mokhotlong with ca. 10,000 inhabitants. The remaining population lives in villages scattered over a mountainous area of 5,842 km2. According to the Demographic Health Survey of 2014, the adult HIV prevalence amounts to 21.2% in Butha-Buthe and 17% in Mokhotlong[101], whereas the household-based national survey from 2016-2017 (LePHIA) revealed an adult HIV prevalence of 17.8% in Butha-Buthe and 26.1% in Mokhotlong.

This trial utilizes an existing and long-standing public-sector cadre, called village health workers (VHW). In Lesotho, the VHW project was introduced in 1978 with more than 4000 VHWs currently operating in all districts of the country.[102] VHWs are members of the community, appointed to provide a package of basic services at the household level, but who 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. They are employed either by the Ministry of Health or Partners in Health (PIH), a U.S.-based NGO, and receive a stipend of 300 LSL (approximately 20 USD) per month. Among the tasks of the VHW, which are mostly preventive, are the promotion of antenatal care, the care of children aged 5 years old and under, education about topics such as hygiene and sanitation, HIV testing and counseling, the referral of sick people to the health center or hospital, the organization (together with the village chief) of community meetings and tracing of patients. Specifically regarding HIV service delivery it has been shown that VHW play a pivotal role in reducing stigma and discrimination, increasing demand for services and improve retention in care.[103–105] Moreover, several studies have consistently found that services delivered by VHWs are highly cost effective.[106–108]

3.2. DESIGN

3.2.1. Design of GET ON project

The GET ON ("GETing tOwards Ninety") project entails two sequentially interlinked cluster-randomized trials, HOSENG study and VIBRA study. The HOSENG study is described in a separate study protocol and addresses the first of the UNAIDS 90-90-90 targets. In a nutshell, the HOSENG study aims to significantly improve testing coverage during a home-based HTS campaign using oral self-testing for individuals who are absent or who decline HIV testing during the household visit. Individuals found HIV-positive and not on ART during HOSENG study will thereafter be offered participation in the VIBRA study.

The reasons for this interlinked design are: a) potential study participants for VIBRA trial (HIV-positive individuals not on ART) are identified during the HOSENG study, b) this design allows us to assess the entire HIV care cascade in one larger project, and c) both trials rely on interventions involving VHWs, who need to be randomized and specifically trained. Therefore, it is more efficient and feasible to run both trials parallel and randomize only at one time point.

3.2.2. Design of VIBRA study

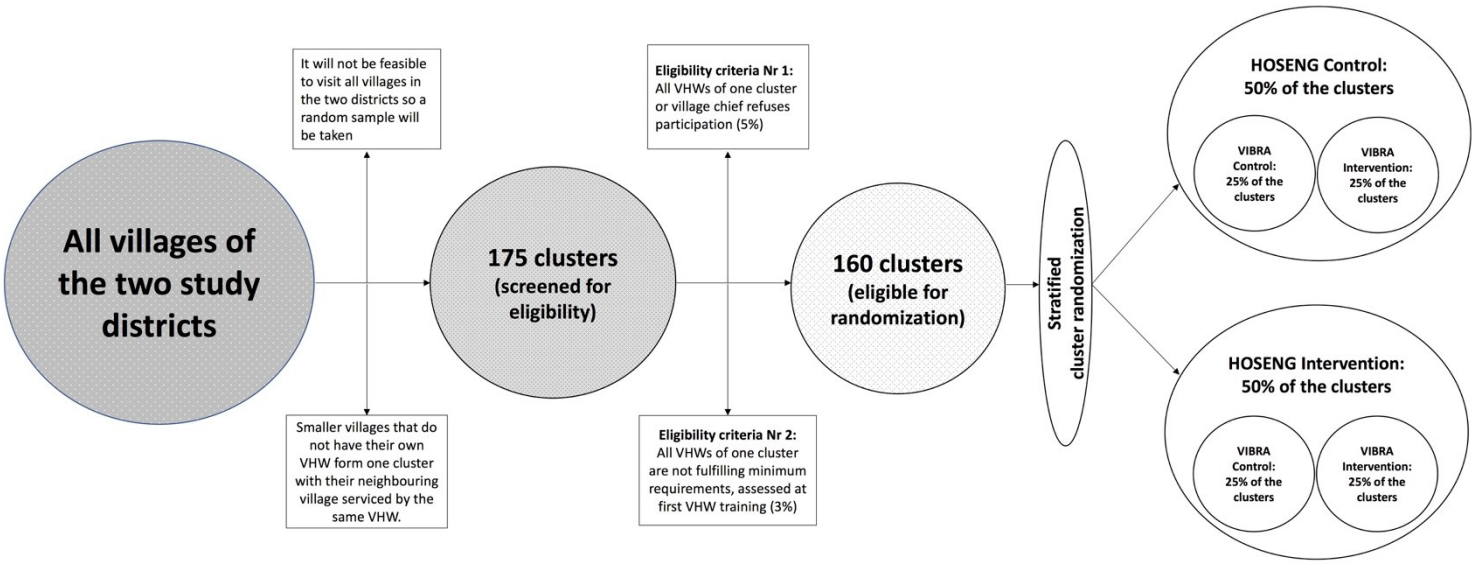
The abbreviated title of this study is "VIBRA study" ("VIllage-Based Refill of ART"). The VIBRA study is a cluster randomized controlled, open-label, superiority trial in a resource-limited setting. The rational for a cluster randomized design is the reliance of the study on the VHWs and, thus, the high risk of cross-contamination between the study arms if randomization would be done at individual level. To ensure a balance in the exposure to the HOSENG intervention in

the two VIBRA arms, the clusters (=villages) will be randomized into 4 potential groups (1:1:1:1 allocation: all combinations of intervention and control group of HOSENG and VIBRA study, see also Figure 1):

- HOSENG Control & VIBRA Control
- HOSENG Control & VIBRA Intervention
- HOSENG Intervention & VIBRA Control
- HOSENG Intervention & VIBRA Intervention

Clusters will be stratified by district, size of village, and village access to the nearest health facility (easy to reach vs hard to reach [i.e. mountain or river to cross or/and more than 10km away from health facility]). Individuals are set as unit of analysis. Potential clustering effects will be adjusted for in the analysis.

FIGURE 1: *GET ON cluster sampling and randomization*



Footnote:

- The VIBRA control and intervention are described in chapter 1.1.1
- The HOSENG control and intervention are described in the HOSENG study protocol
- Eligibility criteria for clusters are described in chapter 3.3.2
- All VHWs in HOSENG or/and VIBRA intervention clusters will receive a second more in-depth training (cf. chapter 3.3.4)

3.3. METHODS

1.4.1. Randomization

Before start of the entire GET ON project that starts with the HTS campaign of HOSENG study, eligible clusters will be randomized into the 4 groups. Hence, the intervention will authomatically be determined by the cluster in which the individual lives. We refer to the HOSENG study protocol for the details of the randomization process, and see also Figure 1.

3.3.1. Procedures in all study clusters

The procedure conducted for all household members encountered during the door-to-door home-based HTS campaign (HOSENG study) is outlined in the HOSENG study protocol and below in Figure 2.

People found HIV-positive and not on ART during the door-to-door HTS campaign of HOSENG study will be screened for eligibility for the VIBRA study. The study nurse (who is part of each campaign team and has the same level of clinical certification as existing primary health care nurses at the local health facilities) or the study physician will assess eligibility (cf. chapter 3.3.3) using a tablet-based questionnaire.

3.3.2. Eligibility – clusters

We refer to the HOSENG study protocol for these details, chapter 4.3.6.

3.3.3. Eligibility – individuals

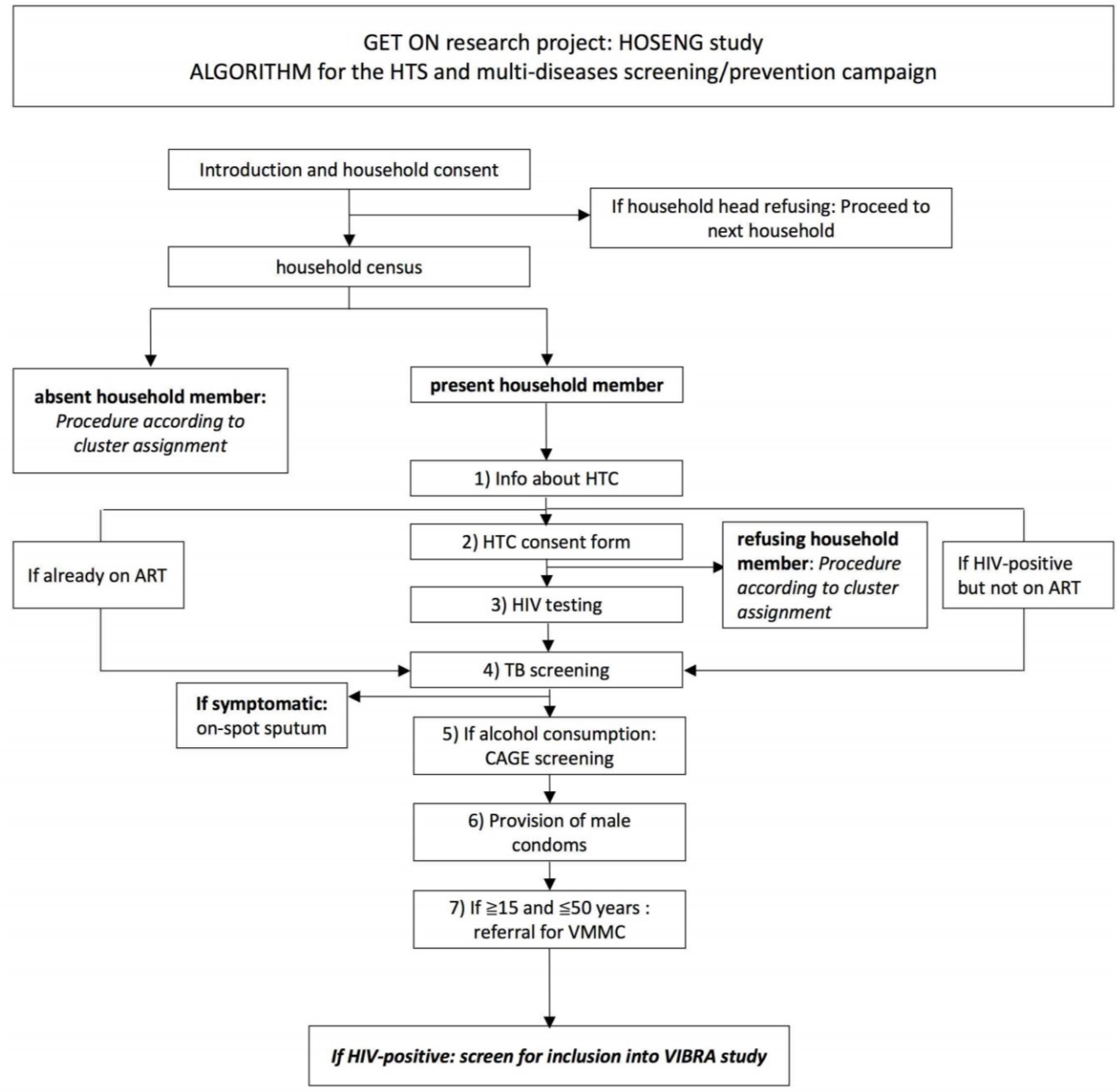
Inclusion criteria:

1) Individual is a present household member of a visited household
    i) Definition of "household member": See HOSENG study protocol, chapter 4.4.1
2) Individual is confirmed HIV-positive
    i) Definition of "confirmed HIV-positive": twice a reactive blood-based HIV test according to national guidelines
3) Individual has never taken ART (ART-naïve) or has stopped ART more than 30 days prior (classified as "defaulter" according to Lesotho National Guidelines)
4) Individual is ≥10 years and body weight ≥35kg

Exclusion criteria:

1) The household member is absent at the time of the campaign
2) HIV-positive individual is taking ART or stopped less than 30 days ago
3) HIV-positive individual is physically, mentally, or emotionally not able to participate in the study, in the opinion of the investigators or study staff
4) HIV-positive individual is in care for high blood pressure (hypertension) or high blood sugar (diabetes) – proof of documentation or medication needed
5) HIV-positive individual wishes to get care outside the study districts

FIGURE 2: *Algorithm HTS and multi-disease screening/prevention campaign (HOSENG study)*



1.1.1. VIBRA study groups

If an individual is eligible for VIBRA study, same-day ART initiation will be proposed as successfully tested and implemented in this setting by our previous study, the CASCADE trial. Hence, we consider same-day ART initiation after home-based HIV testing as standard of care – and hence, same-day ART start is applied in both study groups. Table 1 summarizes the procedures in the two VIBRA study groups.

If an individual is not eligible for VIBRA study, standard of care applies, i.e. referral to health facility for further assessment and ART initiation.

TABLE 1. *Description of VIBRA study groups, including barriers targeted and steps of HIV care cascade addressed*

	VIBRA Control **(Standard of care)**	**VIBRA Intervention** **(Offer of VIBRA model)**	**Barriers targeted by intervention**	**Step targeted in HIV care cascade**
1	Offer of home-based same-day ART initiation	Offer of home-based same-day ART initiation	structural, biomedical[a]	ART initiation, linkage to care
2	**Clinic-based ART visit/refill** Who: Nurse Where: Nurse-led health facility When: Follow-up interval of max. 3 months What: TB screening, Screening for other opportunistic infections, Screening for ART-related toxicities, adherence assessment, assessment whether patient visited any medical facility since last appointment, addressing basic psychosocial problems, ART (+CTX/IPT) dispensing (+ dispensing of other medication & WHO staging) ➔ following the pre-specified checklist (cf. appendix 17.5)	**Offer of Village-based ART visit/refill** Who: VHW Where: At VHW's home* When: Follow-up interval of max. 3 months What: TB screening, Screening for other opportunistic infections, Screening for ART-related toxicities, adherence assessment, assessment whether patient visited any medical facility since last appointment, addressing basic psychosocial problems, ART (+CTX/IPT) dispensing ➔ following the pre-specified checklist (cf. appendix 17.5) *Except at 6 and 12 months follow-up: visit at health facility for laboratory assessment (viral load)	structural	retention in care, viral suppression
3	**No SMS intervention** However: SMS might be used to follow-up patients in order to ensure laboratory assessments at 6 and 12 months.	**Offer of Individually customized SMS** Monthly reminder SMS: to pick up ART A VL results-triggered SMS: • Undetectable VL (<20 copies/mL): → Message: "Congratulations, your lab test was good. Keep it up!" • Detectable VL (≥20 copies/mL): → Message: "Your lab test results are back. Make sure to come to the health facility at the next scheduled date and remind the nurse about your lab test." • Technical failure of VL measurement → Message: "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."	structural	retention in care, viral suppression

Footnotes:

- [a] by using point-of-care tests to avoid waiting for baseline laboratory tests before ART initiation

3.3.3.1. All study clusters: Home-based same-day ART initiation

In both groups (VIBRA intervention and VIBRA control clusters) same-day ART initiation will be proposed. Features of same-day ART initiation are outlined below in Table 2. Before initiating ART the study nurse/physician will re-test the participant as per national guidelines[97], using Alere Determine® HIV1/2 and UniGold® HIV1/2 from a different batch specifically labelled as re-test batch.

TABLE 2. *Features of same-day ART initiation*

Component	Description	Comments / Rational
Medical history	The study nurse assesses the patients medical history using a pre-specified checklist • 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 may contact the study physician	See pre-specified checklist in appendix 17.2
Physical examination	The study nurse conducts a structured physical examination using a pre-specified checklist • 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 may contact the study physician	See pre-specified checklist in appendix 17.3
WHO stage	The study nurse performs clinical WHO staging according to physical examination and medical history	
CD4 measurement	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: ▪ If CD4-count < 350 cells/mcL: Co-trimoxazole (CTX) prophylaxis, 960mg o.d., p.o., 1 tbl o If participant < 14 years: ½ tbl o.d., p.o. ▪ If CD4-count < 200 cells/mcL: Cryptococcal Antigen (CrAg) point-of-care measurement (Lateral Flow Assay, IMMY©) o If CrAg positive: Immediate referral to nearby district hospital by study team, no same-day ART initiation	Although baseline CD4-counts are no longer used according to national guidelines to establish ART eligibility, they continue to be performed for all patients initiating ART. 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. The national guidelines suggest to screen for CrAg only if CD4-count < 100 cells/mcL.[97] However, data is scarce, hence, we will extend screening to those CD4-count < 200 cells/mcL in order to gain more data for exploratory reasons. 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 (Boulware et al., NEJM 2014), same-day ART initiation will not be done in CrAg positive individuals until cryptococcal meningitis has been excluded.
Creatinine measurement	The study team performs point-of-care creatinine, using StatSensor Creat™ Nova™ Biomedical (fingerprick test), that gives results within 2min. • If estimated creatinine glomerular filtration rate according to Cockroft-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 can decide if referral to health facility and no same-day ART initiation	According to national guidelines, before initiating standard first-line ART containing tenofovir disoproxil fumarate (TDF), a baseline creatinine is needed.[97]
Haemoglobin measurement	The study nurse performs point-of-care haemoglobin, using HemocueTM, HB301 (fingerprick test), that gives results within 2min. • If haemoglobin < 8 g/dL: zidovudine contraindicated and nurse can decide if referral to health facility and no same-day ART initiation	According to national guidelines, before initiating ART regimen containing zidovudine, a haemoglobin is needed.[97]
Adherence counseling and education session	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.	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).[41]
Readiness assessment	Before dispensing ART the study nurse confirms readiness and answers remaining questions, using a pre-specified checklist • If patient not ready: referral to health facility and no same-day ART initiation	See pre-specified checklist in appendix 17.4
Dispensing of ART	The study nurse prescribes a 1-month supply of the standard 1st-line ART according to national guidelines[97]: TDF / lamivudine (3TC) / efavirenz (EFV) as fixed-dose combination, once daily. • 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	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, chapter 3.3.3). Thus, TDF/3TC/EFV is the standard treatment, that almost everybody will get unless we discover renal impairment or an active psychosis.
Follow-up visit	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), for a next ART visit.	The study nurse documents the entire process in the patients booklet ("bukana"), incl. drugs prescribed and follow-up date.

Notes:

1. TB screening will be performed for all household members that we encounter during the home-based HTS campaign (HOSENG study), irrespective of HIV-status. See also chapter 4.3.2.1 in HOSENG study protocol about sputum collection. If an individual with presumptive TB is eligible for VIBRA study (i.e. HIV-positive and not on ART): The nurse will decide, after conducting above mentioned medical history and physical exam, if the HIV-positive individual is referred to the nearby health facility and ART initiation is being delayed.

2. Besides above mentioned features of same-day ART initiation, for all VIBRA study participants a) a demographics and b) HIV-knowledge questionnaire will be filled-in, using the validated survey measurement scale for HIV-related knowledge[109]. See "GET ON_CRF" for more details.
3. For all study participants of VIBRA study, a venous blood draw will be performed at enrolment during the home-visit. These samples will be transported the same day to the hospital laboratories of our study sites (either Butha-Buthe or Mokhotlong Government Hospital) and stored in a -80°C freezer and used for Genotypic Resistance Testing (GRT), if applicable, see chapter 6.
4. If patient needs to be referred, the study team provides details about the nearest health facility, provides a transport voucher if needed, and might decide to accompany the patient.
5. Dispensation of IPT (Isoniazid Preventive Therapy): According to national guidelines every individual with HIV greater than 1 year of age who has no signs or symptoms of active TB should be started on IPT as soon as possible - given the high prevalence of latent TB infection in Lesotho.[97] On the other hand, initiating ART, CTX and IPT at the same time correlates with higher risk of drug toxicity and if side-effects occur it's hard to distinguish which drug caused the side-effect. Therefore, IPT will not be initiated at enrolment, but should be started as early as possible during the first 6 months on ART.
6. If, by the time of the study start, Dolutegravir is available in country, we will adapt the study protocol accordingly in order to supply a Dolutegravir-based first-line ART. In that case an amendment will be submitted to the ethics committees.

3.3.3.2. Intervention clusters: VIBRA model

After same-day ART initiation the participants in the intervention clusters are offered the VIBRA model. There are two features of the VIBRA model. The first feature of VIBRA model is the possibility of village-based ART visit/refill at the VHW with clinic-based ART visits only every 6 to 12 months – following same-day ART initiation at home during the HTS campaign. The second feature of VIBRA model is the possibility to receive a standardized, short text-message (SMS) intervention.

3.3.3.2.1. VIBRA model, feature 1: Village-based ART visit/refill

In the VIBRA model, participants have the possiblity to receive village-based ART visits incl. ART dispensing by their VHWs. Participants will 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 pre-specified checklist (cf. appendix 17.5) written in the local language (Sesotho). By following the checklist the VHW documents on a standardized paper-based form patient's symptoms (to alert for drug toxicity, opportunistic infections, IRIS, etc.) along with adherence to ART questions, addressing basic psychosocial problems, and whether the patient visited any health facility since the last appointment.

In order to ensure safe and high-quality clinical management, participants in intervention clusters will not only be linked to their VHW, but also under responsibilty of the Community ART Nurse (CAN) of the corresponding district. See detailed description of the CAN and his tasks below in chapter 3.3.3.2.3. The VHW and the CAN will have a list of the participants they are responsible for.

If the visit triggers any alert, indicated on the checklist, the VHW must immediately inform her/his CAN. If the visit triggers no alert, the VHW dispenses a supply of the patient's medications. Similar to the local health facilites, depending on the VHWs judgement and the patients preference he/she can provide one up to a maximum of three months drug-supply. For example in case the patient is working in South Africa, a three months supply may be provided. Participants are, however, encouraged to visit the VHW or the clinic at any time in case of problems or questions. Six months after ART initiation the participant has to attend the first clinic-based visit for laboratory assessment.

All VHWs of the catchment area of one health facility have a monthly meeting at the health facility together with a designated staff member of the health facility. These pre-existing meetings will be used for VIBRA model and strengthened. Moreover, the CAN (or his representative) will join the meeting as well and provide support as needed. These meetings will provide the platform to review the patient's medical data and patients can be up-referred (to the health facility) or down-referred (to the VHW) as appropriate. If the patient misses an ART visit, either village-based or clinic-based, he/she will be traced by the VHW with a standardized tracking tool (cf. appendix 17.6), that provides clear guidance.

3.3.3.2.2. VIBRA model, feature 2: SMS intervention

In the VIBRA model, participants may choose to receive standardized, short text-message (SMS), that are individually customized:

a) Monthly reminder SMS to adhere to ART: "Take your medication regularly as prescribed and don't run out of medication."

b) a VL results-triggered SMS:

- Undetectable VL (<20 copies/mL): Message: "Congratulations, your lab test was good. Keep it up!"

- Detectable VL (≥20 copies/mL): Message: "Your lab test results are back. Make sure to come to the health facility at the next scheduled date and remind the nurse about your lab test."
- Technical failure of VL measurement: Message: "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, cellular appointment reminders do not refer to HIV or HIV care services directly. Participants are not asked to confirm receipt or reply to any messages. The SMS reminders are translated into the local language. The SMS reminders are sent out automatically from our VL database (VisibleImpact, see also chapter 1.5).

3.3.3.2.3. Community ART Nurse (CAN)

The Community ART Nurse (CAN) is a health professional position within the study project,that will be held by a trained ART nurse. The nurse has to be registered by the Nurses Council of Lesotho and experienced in HIV care as per National HIV guidelines of Lesotho.[97] The CAN will closely monitor and supervise all VHWs of the VIBRA model for an entire district, and is responsible for all participants initiated on ART in the VIBRA model. The CAN will be in close contact with the corresponding health facilites, i.e. to ensure ART procurement and management of study participants at the clinic.

One CAN per district is needed; one for Butha-Buthe district and one for Mokhotlong district. They are specifically trained in the study procedures and in tablet-based electronic data collection and management. They receive a tablet and will enter all follow-up data electronically. The CANs attend the monthly VHW meetings at the health facility in order to facilitate down- and up-referral of VIBRA participants, collect the paper-based Case Report Forms (CRFs) of the VHWs, update ART stock of VHWs, assure documentation of participants in the health facility files (patient file and registers), and go through the individiual patient list with each VHW to detect any irregularities.

3.3.3.2.4. ART procurement

In the VIBRA model ART procurement is organized via the health facility the VHW is affiliated to. Before the health facility places its monthly ART order, the VHW has to submit his/her list to the health center – usually at the monthly meeting. Together with the order the VHW brings a list of all refills provided during the last month to allow the health center to incorporate the VHWs dispensed ART into its monthly statistics. The CAN will supervise correct storage of ART, monitor stock-outs and assist the VHW in case of problems with stock management/ordering of ARTs.

3.3.3.2.5. Modification of intervention

If a participant is being referred to the health facility at the home-visit or after by the VHW, CAN, or self-referral, he/she will be primarily monitored by the health facility. Once the health facility staff considers the patient to be clinically stable again, he/she can again be down-referred to the VHW for ART refill.

3.3.3.3. Control clusters: Standard of Care

Individuals who start ART in the control clusters will not receive the offer of VIBRA model, and, thus, have to attend the health facility to get their ART visit/refill. They will be given an appointment for a first clinic visit in 12 to 16 days after the home-visit. The health facility staff will fill-in the same pre-specified checklist as the VHWs do. The study participants will not be offered any other differentiated care/delivery models such as CAG or CACs.

3.3.4. VHW – training and responsibility

Details about training number 1, which is the basic training for all randomly selected VHWs in the study districts, is outlined in HOSENG study protocol. The VIBRA-specific training is training number 2: All VHWs in the intervention clusters are trained to deliver the VIBRA model, i.e. trained to a) dispense ART (and CTX), b) screen for ART-related adverse events and drug-toxicities, c) screen for co-infection (especially TB), d) assess adherence and basic vital signs, e) understand referral algorithm in case of clinical deterioration of their patients, f) address disclosure and keep confidentiality, g) perform basic data entry/management. This training takes place prior to the start of the trial and lasts for 2-3 days.

The VHWs will receive continuous monitoring by the CAN (cf. 3.3.3.2.3), and are additionally supported by supervisory staff from the nearest health facility. All those not having a cellphone will receive a cellphone in order to stay in close contact with their responsible CAN. Every VHW has a list of patients he/she is responsible for and will only

be allowed to dispense ART to participants on the list. Based on data from CASCADE trial, we estimate a maximum of 5 patients per VHW.

3.3.5. Assignment of national (pre)ART numbers and adherence to local health registers

If a HIV-positive participant newly tested during the HTS campaign starts ART, the campaign team will make sure that this participant is registered in the ART register of the responsible clinic and he/she receives an official pre-ART (if applicable) and ART number. This process has been successfully implemented in the CASCADE trial.[41,42] If a VHW tests a participant newly HIV-positive after the oral HIVST, the CAN has to ensure that this participant is correctly registered at and reported to the health facility. Moreover, the campaign team provides a monthly summary of all people tested HIV-negative during the HTS campaign to the District Health Management Team (DHMT) in order to keep the government statistics up-to-date.

3.3.6. Recruitment

Given the range of clusters to achieve the varying sample size, we will plan on sampling 100 clusters in order to reach a target sample size on an individual level of n=262 HIV-positive individuals who are not on ART. Based on the experience of previous HTS campaigns and the CASCADE trial[41,42] (> 10'000 individuals tested in > 70 villages and 267 individuals newly tested HIV-positive enrolled) we are confident to reach the required target sample size within 5-6 months. Anticipated start of the entire GET ON project and, thus, recruitment is June/July 2018.

3.3.7. Blinding

This is a pragmatic implementation trial, assessing the effectiveness of a new strategy for increasing testing coverage. Due to the nature of the trial it is not possible to fully blind participants nor staff to the intervention. But allocation will be concealed due to the design of a cluster randomization, which implies randomization before participant inclusion.

4. ENDPOINTS

4.1. PRIMARY ENDPOINT

Viral suppression at 12 months, defined as the proportion of all participants with a VL <20 copies/mL 12 months (range: 10 – 15 months) after enrolment

i. *Rational for VL suppression level at 20 copies/mL: VL determination will be done on COBAS TaqMan® HIV-1 Test, v2.0 (Roche Diagnostics) using plasma, and has a reliable lower limit of detection of 20 copies/mL*

4.2. SECONDARY ENDPOINTS

a) Viral suppression at 6 months, defined as the proportion of all participants with a VL <20 copies/mL 6 months (range 5 – 8 months) after enrolment
b) Alternative viral suppression at 12 months, defined as the proportion of all participants with a VL <1000 copies/mL 12 months (range 10 – 15 months) after enrolment
   i. *Rational for alternative VL suppression definition at 1000 copies/mL: All health facilities in our study districts send their blood for VL measurement to Butha-Buthe government hospital laboratory, that uses the above mentioned COBAS TaqMan® HIV-1 Test, v2.0 (Roche Diagnostics). Some of the remote health facilities, however, 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.*[11]
c) Alternative viral suppression at 6 months, defined as the proportion of all participants with a VL <1000 copies/mL 6 months (range 5 – 8 months) after enrolment
d) Sustained viral suppression, defined as the proportion of all participants with a VL <20 copies/mL at 6 (range 5 – 8 months) as well as at 12 months (range 10 – 15 months) after enrolment
e) Linkage to care within 1 month, defined as the proportion of all participants attending the first clinic- or VHW-based ART visit at least once within 1 month after enrolment
f) Linkage to care within 3 months, defined as the proportion of all participants attending the first clinic- or VHW-based ART visit at least once within 3 months after enrolment
g) Retention in care at 6 months, defined as the proportion of all participants active in care at a health facility or at the VHW 6 months (range 5 – 8 months) after enrolment
   i. *Definition of "active in care": at least one ART visit in the defined window*

   I. *Including patients who have stopped ART*
   II. *Including participants who transferred out to any other health facility with known outcome (documented proof of follow-up visit or laboratory test)*
   III. *Excluding 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.)*
  ii. *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*

h) Retention in care at 12 months, defined as the proportion of all participants active in care at the health facility or at the VHW 12 months (range 10 – 15 months) after enrolment

i) All-cause mortality at 12 months, defined as the proportion of all participants dead 12 months (range 10 – 15 months) after enrolment
   i. *Verbal autopsy to capture cause of death whenever possible. No death certificate or autopsy report required.*

j) LTFU at 12 months, defined as the proportion of all participants LTFU 12 months (range 10 – 15 months) after enrolment
   i. *We define participants lost to follow-up if they were more than 2 months late for a scheduled consultation or medication pick-up and no information was found about the participant*

k) Transfer out at 12 months, defined as the proportion of all participants who transferred out to any other health facility (than the initially attached one) with known outcome (documented proof of follow-up visit or laboratory test) at 12 months (range 10 – 15 months) after enrolment

4.3. SAFETY ENDPOINT

We specifically assess safety of our VIBRA model, defined as proportion of all participants experiencing a Serious Adverse Events (SAE) within 12 months (range 10 – 15 months) after enrolment. See chapter 10.4 for detailed description of SAEs.

4.4. EXPLORATORY ENDPOINTS

We will assess several exploratory endpoints.

1) Coverage of differentiated ART delivery:
   a. Proportion of ART refills per participant according to protocol schedule, at the VHW and the health facility, within 12 months after enrolment
   b. Number of visits (clinic or VHW) at which medication pickup occurs per HIV-positive person on ART of the study districts witihin 12 months after end of recruitment period
   c. Number of clinical visits per HIV-positive person on ART of the study districts witihin 12 months after end of recruitment period
2) Overall effect of combined interventions HOSENG and VIBRA (Arm 4 vs Arm 1) on viral suppression (<20 c/mL) 12 months (range 10 – 15 months) after enrolment
3) Assessment of acceptance of same-day ART initiation: How many were same-day initiated, reason for not same-day initiaiton, reasons for referral, etc.
4) Assessment of acceptance of VIBRA model

TABLE 3. *Summary of endpoints*

	Following enrolment			
endpoints	**By 1 month**	**By 3 months**	**At 6 months** (range: 5-8)	**At 12 months** (range: 10-15)
Viral suppression <20 copies/ml			Secondary	Primary
Viral suppression <1000 copies/ml			Secondary	Secondary
Sustained viral suppression <20 copies/ml			Secondary	Secondary
Linkage to care (attending first clinic or VHW visit)	Secondary	Secondary		
Retention in care (either health facility or VHW)			Secondary	Secondary
All cause mortality				Secondary
LTFU				Secondary
Transfer out				Secondary
SAE				Safety
Coverage of differentiated ART delivery				Exploratory
Overall effect of HOSENG + VIBRA				Exploratory
Assessment of acceptance of interventions	Exploratory			

Note: we consider 1 month = 30 days for all endpoints

5. LONG-TERM FOLLOW-UP

We consider assessing long-term follow-up outcomes at 24 months (range: 22 – 28 months) after enrolment: viral suppression, retention in care, and SAEs. A detailed follow-up plan will be developed at a later stage.

6. BIOMOLECULAR RESEARCH

We will include biomolecular research in GET ON. This part will be developed in detail with our research consortium partners from the Department of Biomedicine (University of Basel, Switzerland) under the lead of Prof. Thomas Klimkait (cf. page 3). So far it is planned to assess prevalence of major drug resistance mutations (DRM) a) on all baseline samples (primary DRM) and b) on all samples with unsuppressed VL (>100 copies/mL) at 12 months (range: 10 – 15 months). Moreover, all participants who start ART at the home-visit during the HTS campaign, but subsequently default treatment will be traced to assess development of DRM. Definition of DRM follows the Stanford University HIV Resistance Database (http://hivdb.stanford.edu)

7. QUALITATIVE RESEARCH

Qualitative studies are planned alongside the GET ON project to provide important contextual data and a more in-depth exploration of community response to the HOSENG and VIBRA interventions. A detailed qualitative research plan will be developed at a later stage. Concerning the VIBRA study the following qualititative studies are planned:

1. A qualitative case-control study that examines uptake of village-based ART refill among participants. A random sample of e.g. 20 cases and 20 controls would be chosen from the VIBRA intervention clusters. Cases would be participants who refuse village-based ART refill at the VHW and controls would be participants who accept village-based ART refill at the VHW. A standardized questionnaire would be used to explore reasons for not accepting village-based ART refill, and motivation to accept village-based ART refill, respectively. Participants who accepted the VIBRA model would be asked to identify whether each intervention of the VIBRA model was helpful in terms of assisting in retention in care, reducing structural barriers, respect, stigma, discrimination, overall satisfaction, and what aspects of each intervention were useful and not useful. Besides standardized multiple choice questions, we would leave space for open questions to capture unexpected associations. A separate informed consent to participate in the qualitative research would have to be obtained and would be submitted together with the research plan as an amendment.
2. Standardized interviews will be conducted with a random sample of all stakeholders involved in delivering the VIBRA model, i.e. VHWs, Community ART Nurse, staff at the health facility, and members of the District Health Management Team (DHMT). Focus lies on feasibility assessment, i.e. about overall satisfaction with VIBRA model and time spent with ART patients, but also a brief questionnaire capturing stigma and discrimination within the new model.

8. COST-EFFECTIVENESS ANALYSIS AND SYSTEM IMPACT EVALUATION

For the cost-effectiveness analysis, we will create a model to estimate the effect of the VIBRA intervention on health benefits and costs. First we will assess the direct costs of the interventions. Secondly, we will assess a cost-effectiveness of the intervention (=VIBRA model) tested. Thirdly, we will assess the economic burden of the interventions to patients – the opportunity costs of their time. The economic analyses will address the following questions:

- Which are the direct costs (to both health systems and patients) of delivering the interventions?
- Are there direct cost-savings to the health system and to patients of the new model of care?
- Are there differences across interventions in opportunity costs of time of patients?
- Are the new interventions cost-effective?

The direct costs for the health system of delivering the intervention and for the patients that wiil be estimated include:

a. Personnel
   - Staff costs (home-visit campaign staff, clinical staff, laboratory staff, VHW, CAN)
     i) Including fringe benefits (e.g. medical and dental insurance, housing allowance, educational assistance, vacation pay, sick pay, meals and employee discounts)
     ii) The appropriate approach to measuring personnel time will differ between study personnel. For example, for the CAN who specifically is hired for this intervention, costs can be obtained directly from compensation data. All the other service providers (nurses and physician at health facility, VHWs, etc.) have multiple responsibilities, hence, the time dedicated to the VIBRA model can be obtained via interviews supplemented by direct "time and motion" observations, including completion of logs by staff recording major activities for one week periods approximately six months apart.
   - Costs of training of all involved personel
b. Equipment
   - Costs of HIV tests (blood-based point-of-care tests and oral HIVST)
   - Costs of ART
   - Costs of drugs for prevention of opportunistic infections and other concomitant medications
   - Other costs associated with home-based testing (logistics, multi-disease screening tests, etc.)
   - Other laboratory costs (CD4 cell count, VL, blood chemistry, blood count and other)
c. Non medical costs to patients
   - Cost of transportation; food, drinks, airtime while accessing care

Potential direct cost savings:
VIBRA model is hypothesised to reduce the number of clinic visits, due to a) less scheduled visits because VHW-based ART refill and b) less unscheduled visits because intervention leads to better sustained clinical outcome. This would decrease costs for the health facility and the patient. The direct cost savings related to reduction in use of health service due to better viral suppression and less opportunistic infections, will be assessed and included in the cost-effectiveness analysis. To this end the estimates of the reduced need for health services will be taken from the trial resutls and the literature. The reduction in utilization rates will be then multiplied by the unit cost of the services using available cost estimates.

Patient time opportunity costs:
These estimates will include the value of the time required to patients to get access to the interventions and the working time lost by them of by another member of the households providing assistance related to the interventions. Different methods to value patient time will be used, consistently with the human capital approaches

Examples of Outcomes:

1. The health outcomes considered by the cost-effectiveness analysis will be the primary endpoints of HOSENG and VIBRA study, but the cost-effectiveness will be also expressed in terms of incremental net cost per DALY (Disability Adjusted Life Years) averted.
2. Mean time for a clinical consultation per person living with HIV per visit
3. Mean total time spent by the patient to receive HIV treatment services (including transportation and waiting) per person living with HIV per 6 months period
4. Mean out-of-pocket cost to patient to receive HIV treatment services (including clinic, medication, transportation) per person living with HIV per 6 months period
5. Number of person living with HIV receiving clinical consultations per day per health care worker

6. Number of patients (of any condition other than HIV) receiving clinical consultations per day per health care worker
7. Mean cost of treatment services from a provider perspective per person living with HIV per year
8. Mean cost of treatment services from a provider perspective per virally suppressed person living with HIV per year

Data collection and Analysis:
Cost data will be collected from expenditure records as well as through interviewing key staff involved in the VIBRA model. The average cost to the provider per patient achieving the primary outcome will be compared between intervention and control clusters to provide an estimate of the cost-effectiveness of the two interventions. Costs will be reported as means (incl. SD) and medians (incl. IQRs) in local currencies and 2018 US dollars and International Dollars. If possible, we will document changes in unit cost (most relevant program cost divided by numbers of patients receiving study intervention) over time as the intervention probably will achieve greater scale and administrative efficiency. These findings are intended to provide insights into costs structures that may be used to enhance the models efficiency in future.

A separate detailed plan will be outlined for this cost-effectiveness analysis and system impact evaluation.

9. SAMPLE SIZE AND ANALYTIC PLAN

9.1. SAMPLE SIZE CALCULATION

In the previous comparable CASCADE trial we found 524 HIV-positive individuals (median 4 per village, IQR: 2-6) who were not currently on ART. If we consider only the rural villages and those aged 12 or older, there were 289 who would be eligible for this study. The primary endpoint is viral suppression at 12 months after offer of same-day ART initiation. Based on preliminary data from the CASCADE trial, we expect the proportion of viral suppression in the control arm to be 50%. The Table 4 below provides estimates of the sample size under varying conditions. Given the range of clusters to achieve the varying sample size, we will plan on sampling 100 clusters/villages therefore expecting approximately n=400 HIV-positive individuals. Assuming a 20% refusal/ineligible rate, this will provide us with approximately 320 eligible individuals and sufficient power to detect a 20% increase in the intervention group. We plan to recruit a minimum of 262 patients to ensure a minimum power of 80%. Of course, if the effect of the intervention is greater – say 0.25 – we will have more than 90% power to detect this under all scenarios. 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. *Sample Size estimations*

Control	Intervention	Power	Total sample size	Total clusters
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)

9.2. ANALYSIS

All analyses will be done using R (the R Foundation for Statistical Computing) or Stata (version 14, Stata Corporation, Austin/Texas, USA). For all tests, we will use 2-sided p-values with alpha 0.05 level of significance. A detailed data analysis plan will be developed separately.

Clusters will be set as unit of randomization (stratified by district, size of village, and village access to the nearest health facility), whereas individuals are set as unit of analysis. Multilevel statistical models will be used to adjust for the clustered data. We will present a CONSORT flowchart of the participants, including screening, enrollment and follow-up. 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

9.2.1. Primary analysis

The primary analysis for VIBRA study will be the comparison of viral suppression rates between the intervention and the control clusters. Analyses will be performed following CONSORT guidelines[110] using the ITT set. The primary analysis will use a multi-level logistic regression model to assess the difference between viral suppression rate in the intervention versus control arm, adjusted for a) the pre-specified randomization stratification factors, b) clustering according to village and household and c) other factors found to be unbalanced between intervention and control clusters. Results will be presented as odds ratios and 95% confidence intervals.

1.4.2. Snapshot analyses

Our protocol foresees a predefined snapshot analysis once all participants have completed 6-months follow-up. The 6-months snapshot analysis will entail the following of the above defined secondary endpoints:

a) Viral suppression at 6 months, defined as the proportion of all participants with a VL <20 copies/mL 6 months (range 5 – 8 months) after enrolment
b) Alternative viral suppression at 6 months, defined as the proportion of all participants with a VL <1000 copies/mL 6 months (range 5 – 8 months) after enrolment.
c) Linkage to care within 1 month, defined as the proportion of all participants attending the clinic- or VHW-based ART refill at least once within 1 month after enrolment
d) Linkage to care within 3 months, defined as the proportion of all participants attending the first clinic- or VHW-based ART visit at least once within 3 months after enrolment
e) Retention in care at 6 months, defined as the proportion of all participants active in care at a health facility or at the VHW 6 months (documented refill 5 – 8 months after enrolment) after enrolment

1.4.3. Baseline characteristics; secondary, subgroup and sensitivity analyses

Baseline characteristics will be presented according to randomized groups: categorical variables will be described as absolute and relative frequencies and continuous variables as medians and interquartile ranges (IQRs).

As with the primary analysis, secondary endpoints will be analyzed with multi-level logistic regression model and results will be presented as odds ratios and 95% confidence intervals. The effect of sociodemographic and clinical determinants (e.g. age, sex, WHO stage, CD4-count, tuberculosis status) on key study outcomes will be assessed in subgroup analyses. Sensitivity analyses will be conducted in order to provide evidence that the result seen from the primary analysis are robust. These analyses will center on the deviations in model assumptions. The statistical analysis plan will provide all further details.

10. DATA COLLECTION AND MANAGEMENT

1.5. DATA FORMS, DATA ENTRY, DATA MONITORING, DATA STORAGE, CONFIDENTIALITY

Details about data collection during the HTS campaign (recruitment platform for VIBRA study) are outlined in the HOS-ENG study protocol. The VHWs and the health care staff at the health facilities collect data from the scheduled and any other unscheduled ART visits on standardized paper study forms (Case Report Forms), that act as source documents. These data will be collected regularly by the study team (i.e. the CAN) using a tablet-based CRF (MACRO, Elsevier). Data from the tablet devices will be uploaded onto an password-protected online platform/database and transferred regularly via a secure electronic transfer to our server.

Similarly, relevant data for the SMS intervention will be uploaded and stored in another encrypted and password-protected online database (https://visibleimpact.org/projects/1261-molecular-hiv-monitoring-in-lesotho), our viral load monitoring platform, that was mentioned previously (cf. chapter 2.4.1), because this platform offers the possibility to send out SMS automatically. The viral load monitoring platform was developed by Visible Solutions AG, Switzerland. The platform and data are stored on a Visible Solutions' dedicated server in a data center in Switzerland (Interxion, managed by Hostpoint AG). The data center meets FINMA-RS 08/07 requirements and is ISO-27001-certified. Data in-transit is encrypted with SSL. All patient names are encrypted at-rest using OpenSSL with AES-256-CTR cipher method. One half of the encryption key is stored on the server, the other half is stored on the client (browser). Access to the platform is limited and regulated through personal user profiles (username and password). Access to patient names is further regulated and restricted through a 2-factor authentication procedure. Personally identifiable information (such as names) or identifiable health information (such as HIV status) are not dispatched as part of the SMS text. SMS are dispatched using the trusted third-party provider Twilio. Twilio is headquartered in the United States. Twilio (www.twilio.com) has certified with the EU-U.S. Privacy Shield Framework and the Swiss – U.S. Privacy Shield Framework as set forth by the U.S. Department of Commerce regarding the collection, use, and retention of "personal data" (as defined under the Privacy Shield principles).

Besides the CRF, data for the follow-up period comes from routinely collected medical records at the health facilites, primarily from the patient file, if necessary also from patients health booklet (bukana), antenatal care register, postnatal care register, under 5 register, HTS register, ART register, ART treatment card and file, TB treatment register, TB treatment card, pharmacy register/dispensing logs, and the viral load monitoring platform. All the above mentioned documents act as source documents. For additional information that is not part of these documents, data is taken specifically for the study and the CRFs act as source document.

Following an initial period of weekly quality review, a study data manager will monitor data quality and completeness on a bi-monthly/monthly basis. Queries about the data will be sent to the local Principal Investigators for follow-up and correction, as needed. Data integrity checks will be written into the database to limit the entry of incorrect data and ensure entry of data into required fields. The type of activity that an individual user in the online study database may undertake, is regulated by the privileges associated with his/her user identification code and password.

Apart from the informed consent form and the list for the VHWs/CANs and the follow-up CRFs, study documents will not contain any names but solely the study-ID. The VHWs in the VIBRA model arm and their CANs need to keep an overview of their responsible patients. Hence, a list with the corresponding names and contact details is needed for them. After printing the names and storing them on the confidential master list, the database will automatically delete all names and only keep the anonymous study-ID. There will be one confidential electronic master list with the subject identification code and the names. The informed consent forms will be stored in a secure way in the headquarter of the study center (SolidarMed Office in Butha-Buthe, Lesotho) and the master list will be stored in an encrypted online cloud with password controlled access and only accessible for pre-defined study personnel, i.e. all investigators (cf. staff list in appendix). Participant files will be maintained in storage for a period of at least 10 years after completion of the study.

10.1. COLLECTION AND STORAGE OF BIOLOGIC MATERIAL

Participants in all clusters undergo HIV testing and phlebotomy at enrolment, and phlebotomy at 6 and 12 months. No additional blood collection is planned according to the study procedure, but if it is done due to clinical standard of care reasons (i.e. abnormal laboratory results or a high VL at the 6 month visit), we will collect these results as part of this study. Figure 3 displays the SPIRIT flow diagram with the overview of data collection, laboratory assessments and follow-up visits.

For each participant, study-ID-coded blood samples will be stored at -80 °C at the laboratory of Butha-Buthe government hospital. All samples collected in the GET ON project fall under the biobank agreement ("Biobanking regulations, v2.0") approved by the ethics committee Lesotho, and under the Material Transfer Agreement (cf. appendix 17.7) submitted together with this study protocol.

FIGURE 3. *SPIRIT Flow Diagram of VIBRA study*

	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 (set by cluster)	X					
INTERVENTIONS:						
VIBRA model (Intervention)	♦———	———	———	———	———♦	·····♦
Standard of care (Control)	♦———	———	———	———	———♦	·····♦
ASSESSMENTS:						
Socio-demographic factors	X					
HIV knowledge[1]	X					
tuberculosis screening[2]	X	X	X	X	X	X
medical history[3]	X	X	X	X	X	X
physical examination[4]	X	X	X	X	X	X
WHO staging[5]	X	X	X	X	X	X
CD4	X				X	(X)
CrAg[6]	(X)					
Creatinine	X			X	X	X

Haemoglobin	X			(X)	(X)	(X)
adherence counseling	X	X	X	X	X	X
readiness assessment[7]	X					
dispensing of ART[8]	X	X	X	X	X	X
viral load	X			X	X	X
plasma for storage (=3 EDTA tubes for GRT)[9]	X			(X)	(X)	(X)

[1] using the validated survey measurement scale for HIV-related knowledge[109]
[2] cf. appendix 17.1
[3] cf. appendix 17.2 for enrolment and appendix 17.5 for follow-up visits
[4] cf. appendix 17.3 for enrolment and appendix 17.5 for follow-up visits
[5] only at clinic follow-up visit
[6] for all participants with a baseline CD4-count <200 cells/mcL
[7] cf. appendix 17.4
[8] incl. CTX and IPT (+B6) and other co-infection (prophylaxis) medication if appropriate
[9] cf. chapter 6

10.2. MONITORING AND AUDITING – GET ON PROJECT

During the entire GET ON project at least one external monitoring visit will assess compliance with the approved trial protocol, accuracy of completed CRFs, and the electronic dataset. The Clinical Operations Unit (COU) at the Swiss Tropical and Public Health Institute, which acts as an independent academic contract research organization, will perform the monitoring. The Principal Investigator agrees to allow inspectors from regulatory agencies to review records and will assist the inspectors in their duties, if requested.

10.3. DATA AND SAFETY MONITORING COMMITTEE – GET ON PROJECT

The GET ON project represents implementation research, the recruitment is projected to happen fairly quickly, safety profiles of all used drugs are well-known, and the intervention does not include any new drugs. We do not expect major adverse effects on patients' health from this intervention given the encouraging results from the trials in Uganda, Kenya and Tanzania.[70,73,111] Moreover, participants in the VIBRA model can opt to switch back or being referred to facility-based care at any time during the trial period. Therefore it is not planned to establish a data safety and monitoring committee (DSMB). Nevertheless, a detailed safety monitoring plan for (Serious) Adverse Events complementing chapter 10.4 will be outlined in collaboration with COU before the trial start and we may decide to install a DSMB based on their input.

10.4. ADVERSE EVENTS (AES) AND SERIOUS ADVERSE EVENTS (SAES) – GET ON PROJECT

Prescription and use of ART will follow current national guidelines of Lesotho.[97] All ART used in Lesotho have a well-established safety profile. The most frequent adverse events are summarized on page 54 of the Lesotho National guidelines on the use of antiretroviral therapy for HIV prevention and treatment, 5th edition, 2016[97] and on page 138 of the Consolidated Guidelines on the Use of antiretroviral Drugs for treating and preventing HIV Infection of the WHO[11]. AE and SAE will be graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0., November 2014[112], and managed according to study sites standard procedure following the national guidelines.[97]

Before start of the study, the study personel will be re-trained on the national guidelines and potential AEs and SAEs of ART. In case of AEs, the study personel documents the AE on a separate form. In case of SAEs, the study personel must inform the study physicians within 72 hours of his/her awareness of the SAE. SAEs are defined as following: a) life-threatening event, b) hospitalization, c) persistent or significant disability or incapacity, d) congenital anomaly / birth defect, e) death. The study physicians must then inform the Sponsor/PI and COU within 24h. The Sponsor/PI will inform the local ethics committee in Lesotho within 24h. COU informs the ethics committee in Switzerland (EKNZ) according to Swiss regulations (HFG, VKlin Art 40, 41): a) within 7 days after notice to the Sponsor/PI in case of death and b) within 15 days after notice to Sponsor/PI in case of a suspected unexpected serious adverse reaction (SUSAR). A SUSAR is an event that exceeds the nature, severity, or frequency described in the protocol, consent form and investigator brochure (when applicable). COU informs the respective Pharmaceutical compagny by sending a copy of the safety report submitted to EKNZ. An annual safety report (listing all SAEs with seriousness criteria, causality assessment) will be submitted yearly to EKNZ (HFG, VKlin Art 43).

A separate, safety monitoring plan will be developed to handle (S)AEs, in-line with swiss and basotho ethics regulations. The study physicians are responsible for all direct safety procedures among study participants. If a participant develops an AE of Grade 2 or higher at last study visit, he/she remains under observation by the study physicians until the AE is resolved or stabilized.

11. ETHICAL CONSIDERATIONS

11.1. RESEARCH ETHICS APPROVAL / INFORMED CONSENT / AMENDMENTS

This trial will be conducted in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice E6 and the current version of the Declaration of Helsinki. Ethics approval will be sought from the National Health Research and Ethics Committee of Lesotho and the Ethikkomission Nordwest- und Zentralschweiz (EKNZ) in Switzerland and the trial will only commence once both committes have awarded approval.

The informed consent process for the cluster randomized GET ON project has several layers, based on two fundamental principles that need to be balanced in a cluster-randomized health systems implementation research trial[113,114]: First, specific ethical requirements (e.g., informed consent, confidentiality, avoidance of harm) should be fulfilled. Second, a generally accepted claim is that a study being methodologically sound constitutes a necessary condition for its being ethically sound. Because only sound design can produce valid findings, and, in general, only valid findings can bring about therapeutic benefits, methodological demands carry moral weight. Prior consent to randomization by individual cluster participant is not feasible in cluster randomized trial such as ours. In such circumstances, once clusters have been randomly assigned, participants in the clusters can no longer be asked for their consent to be randomized to receive either of the interventions, only for consent to receive the intervention to which their group has been assigned, and for consent to follow-up. If participants are aware of this (i.e. know that there is another treatment arm) it would introduce the possibility of post-randomization selection bias and would compromise the methodology. Some even argue that no individual informed consent should be obtained in a cluster-randomized trial in order to sustain a high-quality and sound methodology.[114] However, in our view we value individual consent higher and hence propose the following approach:

- Before cluster randomization (more details about the randomization process in HOSENG study protocol), verbal consent from all village chiefs will be obtained, similar to any HTS campaign done by SolidarMed in Lesotho, because the GET ON project starts with an HTS campaign (see HOSENG study protocol).
- At the day of the HTS campaign, a general household consent (to collect household data, to assess number of household members and uptake of HTS among household members) will be obtained. Allocation to treatment arm will be concealed in order to keep the risk of selection bias as low as possible.
- As requested per national HIV testing guidelines, we will obtain individual HTS consent to perform blood-based point-of-care HIV testing (see HOSENG study protocol). If a participant uses the oral HIVST on his own (i.e. an absent person during the day of the HTS campaign) this implies consent for testing. However, prior to every blood-based HIV test a signed national HTS consent form is needed. No copy of this national HTS consent form will be provided.
- Before inclusion into VIBRA study we will obtain individual informed consent, but using two different Informed Consent Forms (ICF), again, in order to keep the risk of selection bias as low as possible by concealing the allocation: One ICF for participants in VIBRA intervention clusters and one ICF for participants in VIBRA control clusters.

The study team will obtain the verbal consent from the village chiefs. One person from the HTS campaign team (lay counselor or study nurse) will obtain the informed consent from the houshold head or representative and finally, the study nurse will obtain the individual informed consent from the participant before inclusion into VIBRA study.

Iliterate study participants will provide a thumb-print and a witness (independent to the trial and >21 years old), chosen by the participant, will co-sign the form. For study participants aged <18 years, a literate caregiver >21 years old (person that takes care of the child/young adult) will provide oral and written informed consent. The informed consent is provided in the local language, Sesotho, and the participant will receive a copy of the consent form. The village chief, the household head, and/or the individual 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, identifyer removed).

All communities will benefit from strengthened HTS intervention and VHW programme that will improve access to HIV care and long-term ART management. This study is embedded within the national governmental health system to ensure that these benefits are sustained.

Any modifications to the protocol which may impact on the conduct of the study, potential benefit to the patient or patient safety, including changes of study objectives, study design, patient population, sample sizes, study

procedures, or significant administrative aspects, will require a formal amendment to the protocol and will be submitted to the Ethics Committee of Lesotho and the EKNZ and the trial register (clinicaltrials.gov) will be updated accordingly.

11.2. PUBLICATION AND DISSEMINATION POLICY

Results of this research project will be shared at three levels. At district level, health care workers and stakeholders will be informed about the findings during district meetings headed by the DHMT of Butha-Buthe and Mokhotlong. At national level, the national research symposium of the Ministry of Health will serve as a platform to share the results and discuss their implications among the policy makers. International scientific conferences, such as the conference of the International AIDS Society, and publications in scientific peer-reviewed journals will serve for wider results dissemination. The requirements of the CONSORT statement[115] will be fulfilled. The study will be registered on ClinicalTrials.gov prior to the start of the trial and the study protocol will be published in a peer-reviewed journal. The current version of the ICMJE recommendations is applicable regarding authorship eligibility.[116] The use of professional writers is not intended.

11.3. COMPENSATION

11.3.1. Study participants

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.

11.3.2. Study personel

The VHWs and the CANs and the lay counsellors will receive free AirTime (prepaid money for cellphone usage) for the duties of the study. Moreover, each CAN will receive a tablet and each VHW, who has no cellphone, a cellphone. We will consider a remuneration for nurses at the health facilities for the clinic-based ART visits of our study participants during the follow-up of the study. The team who performs the HTS campaign will be equipped with basic supplies (raincoats, gumboots, backpack). The VHW has a central role in this new differentiated ART care/delivery model. Besides basic supplies required for 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 VHW and the health facility is guaranteed (150.- LSL quarterly per VHW in intervention clusters).

12. CRITERIA FOR DISCONTINUATION OF TRIAL

12.1. DISCONTINUATION OF A PARTICIPANT

The study participant has the right to withdraw from the study 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, identifyer removed). Discontinued participants will not be replaced. A subject or cluster (if applicable) can be discontinued from the study by the Principal Investigator for the following reasons:

1. withdrawal of informed consent
2. ethical concerns
3. major violation of the study protocol
4. intolerable side-effects, adverse events
5. any conditions that might jeopardize the patient's health if they were to continue in the study

12.2. DISCONTINUATION OF THE ENTIRE STUDY

The Sponsor-Investigator may terminate the study prematurely according to certain circumstances, for example:

1. ethical concerns
2. insufficient participant recruitment
3. when the safety of the participants is doubtful or at risk, respectively
4. alterations in accepted clinical practice that make the continuation of a clinical trial unwise

The Prinicipal Investigator would provide the study site written notice submitted at a reasonable time in advance of the intended termination. If the Sponsor/Principal Investigator chooses to terminate the study for safety reasons, it will immediately notify all investigators and subsequently provide written instructions for study termination.

13. FUNDING SOURCES AND ROLE OF THE FUNDING SOURCES

The study will be predominantly funded by a grant from the Swiss National Science Foundation (Grant Number IZ07Z0_160876/1), obtained by NDL. The Swiss TPH acts as sponsor of the study. AA receives his salary through a grant from the MD-PhD programme of the Swiss National Science Foundation (Grant number 323530_177576). The study is embedded in the SolidarMed country programme and thus benefits from logistics and human resources from SolidarMed Lesotho.

The funding sources will 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.

14. EXPECTED OUTCOMES OF THE STUDY – GET ON PROJECT

14.1. BENEFIT / STRENGTHS

- First randomized controlled health systems implementation trial assessing the effectiveness and feasibility of village-based ART supply after home-based HIV testing and same-day ART initiation in rural sub-Saharan Africa.
- This trial is one of few RCTs that assesses the whole care cascade from home-based HIV testing to viral suppression, with viral suppression as primary endpoint. This trial will provided data which are currently lacking.[117,118]
- The research we will undertake is expected to reveal whether our differentiated ART care/delivery model can improve treatment outcomes at a cost that is affordable for treatment service providers and funding agencies – in a "real life" service delivery system. The results of the study may thus lead to improvements in HIV care and keep patients in care and hence alive longer. The results will also provide evidence about the feasibility of test-and-treat strategies in a low-resource setting and thus contribute to efforts to improve HIV prevention. If effective, this model has the potential to be easily scaled up, as the VIBRA model requires little additional human resources and logistics added to the current VHW programme. If this intervention is proven to be effective and cost-effective, the position of the CAN can be easily scaled up (only 1 per district).
- Specific benefits of our differentiated ART care/delivery model ("VIBRA model"):
    - It is embedded in an existing district health system and does not create an artificial research setting
    - It utilizes the well-established system of VHWs in Lesotho and similar settings and strengthens it
    - It reduces structural barriers for patients (time-consuming, expensive ART visits at the clinic)
    - It reduces the burden (=patient load) at healthcare facility, which helps alleviate the severe shortage of skilled healthcare workers in sub-Saharan Africa
    - It reduces clinic-based impediements, i.e. stigma by health facility staff, congestion at health facility
    - It is in-line with a) the Lesotho national Ministry of Health's attempt and WHO's strong recommendation to decentralize care to the village level, c) UNAIDS' global call for 2 million VHWs in support of HIV care, and d) Journal of International ADIS Society promotion for a differentiated care research agenda
- The long-term follow-up offers more robust long-term result
- Eligibility criteria were selected to be broad with the aim to include as many patients as possible forgeneralizability
- Through our planned cost-effectiveness analysis and the qualitative research we will be able to make an assumption about the feasibility of our proposed differentiated ART care/delivery model
- We follow a strict and precise definition of retention and LTFU
- A team experienced in community-based HIV testing and ART initiation and a functional molecular laboratory on site, including a plasma bank, the research consortium has both the know-how and infrastructure required to conduct the research project proposed
- The results of this trial will not only inform ART programs in sub-Saharan Africa but also contribute an important piece of evidence to the ongoing policy debate on how to task-shift chronic disease care from facility- to community-based healthcare workers, as the burden of chronic non-communicable diseases in LMICs grows.[119]

14.2. CHALLENGES / LIMITATIONS

- Slow/poor recruitment during the door-to-door HTS campaign of HOSENG study resulting in not achieving targeted sample size for VIBRA study, therefore risking (a) premature discontinuation of the trial or (b) an underpowered trial and an inconclusive result.
    - Due to previous experience of the research consortium (esp. CASCADE trial), assumptions about recruitment rates are reliable.
    - If needed: Extension of HTS campaign possible or HTS campaign during holidays (e.g. Easter)
- Participants may decide to access HIV care at a clinic that is not part of the study sites ("transfer out"). Other reasons for LTFU might occur.
    - By the nature of randomization, these participants should be equally distributed across all study arms, therefore transfers out should not introduce bias in our primary outcomes estimates. In addition, we have explicitly allowed for LTFU in our sample size calculation.
    - We have included transfer out as a secondary endpoint, including seeking participants at other health facilities if possible, in order not to underestimate linkage to and retention in care.
- The trial is not implemented in the whole country but selected districts
    - These districts, however, are representative for the country
- Children below 10 are excluded from the VIBRA model, hence it will not be possible to draw conclusions about the possible impact of the intervention on this age group
- The trial only includes persons tested during community-based HTS. It does not consider persons who receive their test at the facility. The population tested through home-based HTS may differ from the one reached through facility-based HTS.
- As in most operational research studies, we will have little control over what happens in our standard care arm. Standard of care continues to evolve rapidly in Africa. Guideline revisions are frequent, and clinicians and nurses at the study sites may learn from the intervention and make adjustments to routine care before the study is completed. E.g. risk of bias through introduction of other differentiated care/delivery models (e.g. CAG/CACs)
    - Training for health facility staff not to include any study patient into another differentiated ART care/delivery model such as CAC/CAGs
    - Any changes that occur will be reported by study staff and taken into consideration for analysis.
- The health facilities will serve both patients from the intervention and control clusters. Standard of care for the patients coming from control clusters might be affected due to less patient load, because the patients from intervention clusters are primarily served by the VHW and hence, quality of standard of care might increase
- Risk of overburdening the VHW, which might lead to a reduction in quality and/or quantity of care (esp. for non-ART patients)
    - we carefully monitor the visits of patients at the VHW, the CAN supports them closely and we will assess their job satisfaction and perception of the intervention through semi-structured qualitative interviews
- Cost of establishing and running this differentiated care/delivery model
    - Cost consideration only minor, because VHW program exists already and likely to continue to run independently of whether VHW are tasked with ART supply.
    - Only position of CAN is new. But only 1 per district needed. Cost-Effectiveness Analysis will show if this added position is cost-effective.
- Model depends on performance of VHW and his/her trustworthyness within the community
    - We are confident that this is the case, because the VHW programme is a well-established, long-standing system, and the VHWs are selected by community themselves
- Generalizability of the results to other settings and to non-research conditions is uncertain
- Village-based ART refill by the VHW requires close clinical monitoring.
    - A specific safety and monitoring procedure has been developed with a pre-specified checklist that has to be followed by the VHW. Moreover, all VHW will undergo an intensive training before trial start.
    - Reassuringly Woodd et al. in a subanalysis in patients who started ART with a low CD4-cell count (<50 cells/µL) as part of the cluster-randomized trial in Uganda did not find an increased rate of mortality among those who received ART at home after ART initiation as compared to those who received standard clinic-based care.[120]

- Although the same-day ART initiation strategy is expected to increase the proportion of patients who do initiate ART, there is a possibility that patients who accept same-day ART initiation will subsequently discontinue treatment. Results from CASCADE trial, however, suggest that the loss of treatment-eligible patients before starting ART exceeds loss after initiation. It is also likely that patients who discontinue treatment soon after same-day initiation may never have started at all, if only standard initiation had been offered. From CASCADE trial we suggest therefore that the intervention will have a net positive impact and hence, offer this approach in both study arms.
- The study design does not allow for evaluation of the effectiveness of each component of the VIBRA model which would require a study of substantially larger size.
- Challenge of keeping the confidentiality of a person's HIV status:
    - VHW are dealing with this issue since a long time. They will all receive a lockable drawer cabinet to lock away confidential information.
    - All confidentail study documents will be stored securely (cf. chapter 1.5)
    - To protect against other violations of confidentiality, study staff will be trained in expectations that they are not to disclose any information collected in the study to anyone outside the study team.
    - All study participants will be encouraged to contact the study personel to report any undesirable conduct associated with the study. These reports will be brought to the attention of the PI, and appropriate steps will be taken to solve the problems, including reporting to relevant ethical review boards.
- Assessing testing coverage implies that we know the total number of household members for our denominator. If this is not being assessed thoroughly by the campaign team or a household head does not mention all household members, we will underestimate the population
    - Before the trial starts, all study staff will undergo a in-depth training about the study and applying our definition of a household member will be one of the training aspects

15. STUDY TIMELINE

The study protocol of the VIBRA study is to be submitted for review for ethical approval. Ethics approval is sought from the National Health Research and Ethics Committee of Lesotho and the "Ethikkomission Nordwest- und Zentralschweiz" (EKNZ) in Switzerland and the trial will only commence once both committes have awarded approval. We expect recruitment to start June/July 2018 and a total study duration of approximately 18 months.

Time line VIBRA study (excluding long-term follow-up)

Calendar year	*2017*				*2018*				*2019*			
Quarter of year	*1*	*2*	*3*	*4*	*1*	*2*	*3*	*4*	*1*	*2*	*3*	*4*
Preparation of study protocol and ethic approval, briefing of stakeholders, logistics preparation, recruitment of CAN, training of VHWs			x	x	x	x						
HTS campaign with recruitment of participants						x	x	x				
Follow-up visits							x	x	x	x	x	x
Assessment of outcomes							x	x	x	x	x	x
Data management, analysis, writing of report, dissemination of results							x	x	x	x	x	x

Note: Dissemination of results through different stakeholder meetings and publications will obviously continue in 2020.

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17. APPENDIX

17.1. TB SCREENING

TB screening tool, adapted from "NATIONAL GUIDELINES ON THE USE OF ANTIRETROVIRAL THERAPY FOR HIV PREVENTION AND TREATMENT (May 2016), ANNEX 17: TB SCREENING TOOL[97]:

For HIV-negative individuals:

Adults / Adolescents YES NO
1. Are you coughing, persistently since 2 weeks?
2. Have you lost weight (without trying) of more than 1.5 kg in a month?
3. Do you have drenching/soaking sweats at night, persistently since 2 weeks?
4. Do you have fevers, persistently since 2 weeks?

Infants / Children YES NO
1. Has the child been coughing, persistently since 2 weeks?
2. Has the child had a fever, persistently since 2 weeks?
3. Failure to thrive / faltering growth or signs of severe malnutrition?
4. Has the child been in contact with someone with TB disease?

[__] If "Yes" to any question above, then the patient is a TB suspect.

For HIV-positive individuals:

Adults / Adolescents YES NO
1. Are you coughing?
2. Have you lost weight (without trying) of more than 1.5 kg in a month?
3. Do you have drenching/soaking sweats at night?
4. Do you have fevers?

Infants / Children YES NO
1. Has the child been coughing?
2. Has the child had a fever?
3. Failure to thrive / faltering growth or signs of severe malnutrition?
4. Has the child been in contact with someone with TB disease?

[__] If "Yes" to any question above, then the patient is a TB suspect.

17.2. MEDICAL HISTORY CHECKLIST

Feature of same-day ART initiation: Medical history checklist
1. Is the patient pregnant? Yes/No/not applicable
   - If yes,
     - expected date of delivery?
     - next scheduled ANC visit?
2. Have you been on ART before ? Yes/No
   - If yes,
     - when did you start taking ART before and when did you stop taking ART before?
     - why did you stop taking ART? (options available)
     - what was the ART regimen? (options available)
3. Have you been on PMTCT, PrEP or PEP before? Yes/No
   - If yes,
     - when did you start taking PMTCT, PrEP or PEP before and when did you stop taking PMTCT, PrEP or PEP before?
     - what was the PMTCT, PrEP or PEP regimen? (options available)
4. History of TB? Yes/No
5. Are you currently on TB treatment? Yes/No

- If yes,
    - when did you start taking TB treatment?
        - (if within last two weeks, then no same-day ART initiation and management by health facility)

6. Have you been told that you have other diseases or health problems besides HIV? Yes/No
    - If yes,
        - what other diseases or conditions do you have?
7. Are you currently taking any medication? Yes/No
    - If yes,
        - specify
            - (specifically ask for a) anti-epilepsy medication, b) metformin, c) incl. traditional herbal medication)
8. Do you currently smoke dagga? Yes/No
9. Do you currently smoke cigarettes/nicotin? Yes/No

17.3. PHYSICAL EXAMINATION CHECKLIST

Feature of same-day ART initiation: Physical examination checklist

1. Body weight
2. Does the patient report any diarrhoea? Yes/No
    - If yes,
        - specify (date of onset, frequency, colour)
    - If yes: After examination, do you suggest referral with further consultation before starting ART? Yes/No
3. Does the patient report any headache? Yes/No
    - If yes,
        - specify (date of onset, location, pain intensity)
    - If yes: After examination, do you suggest referral with further consultation before starting ART? Yes/No
4. Does the patient report any symptoms (other than the above mentioned)? Yes/No
    - If yes,
        - Specify
    - If yes: After examination, do you suggest referral with further consultation before starting ART? Yes/No
5. Does the patient present oral thrush? Yes/No
6. Does the patient present any abnormal skin lesions (incl. lips, scalp)? Yes/No
    - If yes,
        - specify
7. Does the patient present any lymphadenopathie? Yes/No
    - If yes,
        - specify location
8. Does the patient present any other condition? Yes/No
    - If yes,
        - Specify
    - If yes: Does this condition(s) suggest referral with further consultation before starting ART is needed? Yes/No
9. WHO stage

17.4. READINESS ASSESSMENT CHECKLIST

Feature of same-day ART initiation: Readiness assessment

1. What do you think: How will you remember to take your medication every day? (choose from below)
    - Mobile phone reminder
    - Alarm on a clock or watch
    - Ask someone to remind me
    - Use a calendar or diary
    - Take my tablets at the same time as I do something else every day (like brushing my teeth)
    - No reminders, I'll just remember
    - Other way (specify)
2. Is there anything that will stop you from taking your tablets every day? Yes/No
    - If yes,
        - specify
3. If you should start ART today, how ready are you? (choose from below)
    - Ready today

- Thinking about starting in the coming days -> If yes: indicate date of suggested ART start
- Not ready

4. Did the patient raise any issues or serious concerns that lead you to think that ART should be delayed? Yes/No
   - If yes,
     - specify

17.5. FOLLOW-UP CHECKLIST

Feature of VIBRA model: medical checklist for the follow-up, that will be filled in by VHWs and staff at the health facilities. This checklist will be translated into Sesotho, the local language.

put sticker here

GET ON SOLIDAR MED

VIBRA study

Follow-up checklist

Date today	☐☐.☐☐.☐☐☐☐ (DD.MM.YYYY)
Name of patient	
ART Number of patient	☐ - ☐☐ / ☐☐☐☐☐
Date of positive HIV test	☐☐.☐☐.☐☐☐☐ (DD.MM.YYYY)
What visit is this? (tick one)	☐6 month ☐12 month ☐other
	6 month visit = a visit **between 5-8 months** since positive HIV test 12 month visit = a visit **between 10-15 months** since positive HIV test

➢ **If this is a 6 month or 12 month visit: Patient needs a blood draw for viral load:**
- If you are a **VHW**: Send patient to health facility
- If you are a **clinical staff**: Draw blood for VL

If any of these events happened to the patient since the last visit:

- Death: date of death: ☐☐.☐☐.☐☐☐☐ (DD.MM.YYYY)
- hospitalization
- life-threatening event
- significant disability
- newborn birth defect if patient gave birth

=> Call CAN now:
- **For Butha-Buthe: Thabo Lejone (62000584 / 59936334)**
- **For Mokhotlong: Lefu Khesa (63166525 / 56425205)**

Transfer out

Does patient want to transfer out?	☐ YES: date of expected transfer out: ☐☐.☐☐.☐☐☐☐ (dd.mm.yyyy) where does patient want to transfer out:_____ ➔ **Inform CAN now** ☐ NO

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put sticker here

Date today: ☐☐.☐☐.☐☐☐☐ (dd.mm.yyyy)

GET ON SOLIDARMED

Pregnancy

Is the patient currently pregnant?	☐ YES: date of last menses: ☐☐.☐☐☐☐ (mm.yyyy) ➔ **Inform CAN now** ☐ NO: .. but pregnant at last visit? If yes, please specify outcome: ☐ live birth ☐ stillbirth ☐ spontaneous abortion ☐ induced abortion

Tuberculosis screening

Does the patient report a cough?	☐ YES: specify: since how many days:_____ productive? (yes/no):_____ ☐ NO
Does the patient report weight loss (without trying)?	☐ YES ☐ NO
Does the patient report drenching/soaking sweats at night?	☐ YES ☐ NO
Does the patient report having fevers?	☐ YES ☐ NO

⇨ **If any of the above 4 questions (TB screening) answered with <u>YES</u>:**
- **Collect 1 sputum!**
- **and Inform CAN now!**

Medical history

Does the patient report any headache, dizziness, disturbing dreams or a confused behaviour?	☐ YES: since how many days:_____ ➔ **Inform CAN now** ☐ NO
Does the patient report any abdominal pain or nausea?	☐ YES: decrease of food intake? (yes/no):_____ ➔ **Inform CAN now** ☐ NO
Does the patient report any vomiting?	☐ YES: specify: since how many days: _____ frequency (episodes per day): _____ with blood? (yes/no):_____ ➔ **Inform CAN now** ☐ NO
Does the patient report any diarrhoea?	☐ YES: specify: since how many days: _____ frequency (episodes per day): _____ with blood? (yes/no):_____ ➔ **Inform CAN now** ☐ NO

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Date today: ☐☐.☐☐.☐☐☐☐ (dd.mm.yyyy)

Does the patient report any other symptoms?	☐ YES: specify: _____ ➔ **Inform CAN now** ☐ NO

Physical examination

Does the patient present oral thrush?	☐ YES ➔ **Inform CAN now** ☐ NO
Does the patient present any skin rash?	☐ YES: specify: itchy? (yes/no):_____ painful? (yes/no):_____ location:_____ ➔ **Inform CAN now** ☐ NO
Does the patient present any lymphadenopathie?	☐ YES: location:_____ ➔ **Inform CAN now** ☐ NO
Does the patient present any other new condition?	☐ YES: specify: _____ ➔ **Inform CAN now** ☐ NO

Other

Did the patient miss any ARTs at any day during the last month (last 30 days)?	☐ YES: specify: ☐ 1 day ☐ 2 - 4 days ☐ 5 - 7 days ☐ more than 7 days specify reason for missing:_____ ☐ NO
Did the patient miss ARTs at two consecutive days or more in the last month?	☐ YES ☐ NO
Did the patient go to any other health facility since last visit?	☐ YES: specify: clinic name:_____ reason:_____ ➔ **Inform CAN now** ☐ NO
Did the patient disclose his/her HIV-status to others?	☐ YES ☐ NO ☐ Refused to answer
According to you: How well is the patient coping with the disease?	☐ very good ☐ good ☐ bad ☐ very bad

put sticker here

Date today: ☐☐.☐☐.☐☐☐☐ (dd.mm.yyyy)

Drugs

ART regimen modified today?	☐ YES: specify reason: ☐ Side-effects ☐ Pregnancy ☐ Treatment failure (clinical, CD4 or VL) ☐ Other: _____ ☐ NO
ART regimen provided today:	☐ **TDF/3TC/EFV** ☐ **ABC/3TC/EFV** ☐ **AZT/3TC/EFV** ☐ other: _____
Isoniazid Preventive Therapy (IPT) given today?	☐ YES ☐ NO
Co-trimoxazole (CTX) given today?	☐ YES ☐ NO
Any other drugs given today?	☐ YES: specify: _____ ☐ NO
Blood drawn today?	☐ YES ☐ NO

Follow-up

Next appointment date:	☐☐.☐☐.☐☐☐☐ (DD.MM.YYYY)

Print name of person that did the follow-up visit:_____

Signature:_____

17.6. TRACKING TOOL

Feature of VIBRA model: tool for standardized tracking system (excerpt, will be translated into Sesotho)

If patient does not show up for ART visit, make a first attempt 1-2 days later:

Nr	Date of attempt	What kind of attempt?	Outcome (if successful)
1	□□.□□.□□□□ (dd.mm.yyyy)	□ Phone call □ SMS/WhatsApp □ Home visit □ info via family member / close friend	□ will come back to care □ died; Date: □□.□□.□□□□; Cause of death:_____ □ decided to get care somewhere else; clinic name: _____ date of transfer out: □□.□□.□□□□ □ Lost to follow-up (no info found about the patient) □ other: _____

If attempt unsuccessful, make a second attempt 1 day later:

Nr	Date of attempt	What kind of attempt?	Outcome (if successful)
2	□□.□□.□□□□ (dd.mm.yyyy)	□ Phone call □ SMS/WhatsApp □ Home visit □ info via family member / close friend	□ will come back to care □ died; Date: □□.□□.□□□□; Cause of death: _____ □ decided to get care somewhere else; clinic name: _____ date of transfer out: □□.□□.□□□□ □ Lost to follow-up (no info found about the patient) □ other: _____

If attempt unsuccessful, make a third attempt 1 day later:

Nr	Date of attempt	What kind of attempt?	Outcome (if successful)
3	□□.□□.□□□□ (dd.mm.yyyy)	□ Phone call □ SMS/WhatsApp □ Home visit □ info via family member / close friend	□ will come back to care □ died; Date: □□.□□.□□□□; Cause of death: _____ □ decided to get care somewhere else; clinic name: _____ date of transfer out: □□.□□.□□□□ □ Lost to follow-up (no info found about the patient) □ other: _____

If attempt still unsuccessful, inform your CAN

1.6. STAFF LIST (INCL. CVS, DIPLOMA, GCP)

We refer to attached document, called “VIBRA study_staff list”
All necessary and available CVs, diploma and GCP certificates are attached, too.

1.7. INFORMED CONSENT FORMS

We refer to attached documents, called “VIBRA_ICF-CG” and “VIBRA_ICF-IG”

1.8. CASE REPORT FORM

We refer to attached document, called “GET ON_CRF”

17.7. MATERIAL TRANSFER AGREEMENT

We refer to attached document, called “GET ON_MTA”