

Supplement to the manuscript entitled:

Same-day antiretroviral therapy versus clinic referral and pre-ART counselling during home-based HIV testing in rural Lesotho (CASCADE trial): An open-label randomized controlled trial

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This supplement contains:

- Page 2: First protocol submitted to Ethics Committee (V2.0)
- Page 40: Revised protocol submitted to Ethics Committee (V2.1)
- Page 79: Approval Letter Ethikkommission Nordwestschweiz
- Page 80: Approval Letter National Ethics Committee of Lesotho
- Page 81: Renewal of Ethics Approval by National Ethics Committee of Lesotho
- Page 82: External Monitoring for completeness of Informed Consent Forms and Case-Reporting Forms
- Page 89: Case-Reporting Form SD arm and SOC arm

Please also refer to the published protocol:

<https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-016-2972-6>

And to the study-website:

<https://visibleimpact.org/projects/1197-cascade-trial>

Status of recruitment was publicly updated on weekly basis on this link:

<https://visibleimpact.org/projects/1197-cascade-trial/show/updates>

Same day community-based ART initiation versus clinic-based pre-ART assessment and counselling for individuals newly tested HIV-positive during community-based HIV testing in rural Lesotho – a randomized study

Abbreviated title: CASCADE-Study

Study Proposal submitted to the National Ethics Committee of the Ministry of Health of Lesotho

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CVs of principal investigator and co-investigators are attached to this proposal

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Principal investigator and co-investigators who sign below have approved the study protocol version 2.0, date 10.12.2015, 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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4 Abbreviations

ART	Antiretroviral Therapy
DHMT	District Health Management Team
HIV	Human Immune Deficiency Virus
HTC	HIV Testing and Counselling
MoH	Ministry of Health
Swiss TPH	Swiss Tropical and Public Health Institute
UNAIDS	United Nations Programme on HIV/AIDS
WHO	World Health Organization

5 Proposal Summary

Study Title	Same day community-based ART initiation versus clinic-based pre-ART assessment and counselling for individuals newly tested HIV-positive during community-based HIV testing in rural Lesotho – a randomized study
Study Background	Early start of ART has been shown to be beneficial to the infected individual as well as to prevent further transmission from the individual to other individuals. To link individuals who test HIV-positive to care for start of ART proves however, difficult, particularly in low-resource settings. To achieve the 90-90-90 targets of the United Nations Programme on HIV/AIDS (UNAIDS) 90% linkage to care will be the most difficult target to reach. Innovative approaches that are not too resource-intensive to be implemented at a larger scale are needed. This study aims to assess if in case of a new HIV diagnosis during community-based HTC proposition of same day ART-start improves linkage to care and subsequently viral suppression as compared to standard of care consisting of pre-ART clinic visits for adherence counselling.
Study Objectives	<p>Primary Objectives To compare in both arms</p> <ol style="list-style-type: none"> 1. Linkage to care within 3 months after HIV-diagnosis (participant attends the clinic for HIV care at least once within 3 months after HIV-diagnosis) 2. Viral suppression 12 months after diagnosis of HIV <p>Secondary objectives</p> <ol style="list-style-type: none"> a.) To compare between both groups mortality and loss to follow-up b.) To compare clinical outcomes at 12 months in both groups: haemoglobin, CD4-count, new clinical WHO 3 or 4 events c.) To compare viral suppression rates 6 months after ART-start
Primary purpose	Health Service Delivery Research
Study Category	A, minimal risk to participants
Type of study	Prospective randomized-controlled study
Number of study-arms	2 (1 intervention arm, 1 control arm)
Intervention Model:	Parallel assignment
Masking	Open label
Indication	Diagnosis of previously untreated HIV-infection during community-based HIV testing and counselling (HTC)
Recruitment	From February to May 2016 community-based HTC-campaigns will be

	conducted in randomly selected areas in the district of Butha-Buthe. Participants who test HIV-positive and who have never been on ART will be assessed for eligibility.
Major eligibility criteria	<ul style="list-style-type: none"> - ≥ 18 years of age - never been on triple ART - written informed consent
Intervention and Control	<p>Intervention: Same-day start of anti-retroviral therapy (ART) after diagnosis of HIV and spaced refill follow-up thereafter (2weeks – 6 weeks – 3 – 6 – (9) - 12 months)</p> <p>Control: Standard-of-care: at least 2 pre-ART visits for adherence counselling and laboratory work-up and after ART-start monthly refill-visits.</p>
Primary Endpoints	<ol style="list-style-type: none"> 1. Linkage to care within 3 months after diagnosis of HIV (participants attends the clinic for HIV care within 3 months after diagnosis of HIV) 2. Viral suppression 12 months after the diagnosis of HIV
Study Duration	February 2016 to September 2018

6 Background and literature review

In November 2014 the Joint United Nations Programme on HIV/AIDS (UNAIDS) declared the 90-90-90 targets for 2020 as an intermediate step towards ending the AIDS epidemic as a global health threat by 2030 [1, 2]. The targets are that 90% of HIV-infected individuals know their HIV-status, of these 90% receive sustained ART and 90% of these achieve viral suppression. If achieved, the 90-90-90 targets will result in 73% of all HIV-infected individuals having a suppressed viral load (VL) by 2020. The UNAIDS estimate that achievement of the 90-90-90 goal would result in a reduction of new HIV-infections from 2 million at present to 500'000 per year [3].

The rationale of the 90-90-90 targets lies in the preventive potential of ART. Mathematical modelling concludes that universal ART-coverage could stop the epidemic [4-6]. The landmark HPTN 052 study in 2011 showed that treatment of an HIV infected partner reduced the risk of transmission to the uninfected partner in discordant couples by 96% [7]. Long-term follow-up results from this study presented at the IAS-conference in July 2015 further confirmed the preventive effect of ART [8], but only if ART successfully suppressed VL [9]. Despite knowing since 2011 the preventative benefit of starting ART as early as possible, the positive effect of early ART for the infected individual has only been shown recently. The TEMPRANO trial conducted in Ivory Coast showed that starting ART before CD4-cells dropped below 500 cells/mL resulted in lower rates of severe infections and mortality [10]. The recent START-trial that was conducted in several countries across America, Europe, Africa, and Asia was stopped after an interim-analysis showed net health benefit for those starting ART before CD4-count dropped below 500 cells/mL [11]. Evidence from these two trials led the World Health Organization (WHO) to issue the recommendation on September 30, 2015 that anyone infected with HIV should begin ART as soon as possible after diagnosis [12].

This “treat all” strategy is now endorsed by a broad community of scientists, patient-organizations, donors, non-governmental organisations, civil-rights activists, and politicians, who signed the Vancouver Consensus in 2015 [13]. It bears, however, also unprecedented challenges to resource-limited settings where HIV is hyperendemic. First, there are practical challenges, such as the supply of tests, reagents, and drugs as well as the availability of sufficient human resources in the health sector [14]. Second, the “seek-test-treat” strategy poses implementation and clinical challenges [15], in particular to the Continuum of Care Cascade.

6.1 The Continuum of Care Cascade

The Continuum of Care Cascade (“the cascade”) involves the steps HIV-infected individuals have to take in order to achieve viral suppression. It starts at knowing the HIV-status, continues with linkage to care after a positive HIV-test, initiation of ART, uninterrupted continuation of ART (called retention in care), and ends with viral suppression documented through regular VL monitoring [16]. Already prior to announcement of the “treat all” approach, weaknesses in the care cascade often hampered the effectiveness of HIV-programs in resource-rich as well as resource-poor settings [17-19].

In Sub-Saharan Africa the care cascade is still quite far from the 90-90-90 targets. According to UNAIDS in 2013 only 45% of individuals were aware of their HIV-status, 39% of diagnosed individuals received ART and 29% of infected individuals on ART had achieved viral suppression [2]. Innovative, effective, and practical approaches for improving the treatment cascade are thus urgently needed [20, 21].

Achieving 90% HIV testing coverage

Uptake of HIV testing and counselling (HTC) in a standard clinical setting is usually low [22-24]. Several studies concluded that HTC-provision outside clinical settings in communities is feasible, acceptable and results in a higher uptake of HTC, particularly among populations that are usually hard to reach, such as men or first-time testers [22, 25-28]. Home-based HTC

shows high acceptance in the community [29-33], results in high uptake among hard to reach populations [22-28, 34-36], and is advocated by the WHO [37]. Our group conducted a cluster-RCT comparing home-based HTC to HTC in mobile clinics and found that home-based HTC resulted in an acceptance rate of 92.5% (versus 86.7% in mobile clinics), and reached more children, men, and first-time testers [38]. This trial showed that home-based HTC may be an effective tool to achieve 90% testing coverage but first feasibility, effectiveness, and efficiency of large-scale home-based HTC need to be established.

Achieving 90% linkage to care

Linkage to care after an initial positive HIV-test result has been described as the “Achilles’ heel” of the care cascade [39]. Most studies from Sub-Saharan Africa report linkage rates lower than 50% [40-44]. In the trial on home-based HTC mentioned above, only 25% of newly tested HIV-positive individuals accessed care within one month after the test [38]. Following community-based HTC-campaigns conducted by Population Services International (PSI) in Lesotho, about 45% of newly identified HIV-positive individuals linked to care within 3 months (PSI, personal communication). On the other hand, several observational intervention studies and trials from Sub-Saharan Africa reported that single interventions can indeed improve linkage to care: point-of-care CD4 count directly after a positive HIV-test [45], immediate start of cotrimoxazole prophylaxis [46], incentives such as food-assistance [47], extended post-test counselling, or community-workers accompaniment led to higher linkage rates [48-50]. However, two reviews critically noted in this context that controlled studies testing programmatic intervention-packages for improving linkage to care are still largely missing [51, 52]. Furthermore, it must be noted that interventions, such as intensified patient-accompaniment or food-support are resource intensive and may work in small NGO-driven projects, but are not sustainable on a larger scale [53].

In a systematic review addressing barriers for linkage to care, transport cost and distance were the most frequent factors for patients not enrolling in care after a positive HIV-test [54]. On the rationale of reducing travel-time and cost for patients, the CASCADE-trial will test the effectiveness of same-day home-based ART-initiation after a positive HIV-test together with a reduction of the frequency of follow-up visits to the clinic as a pragmatic and programmatically feasible approach to improve the HIV-cascade in the time of “test-and-treat” policies.

Achieving 90% viral suppression

Data on virologic outcomes from larger cohorts in Sub Saharan Africa are still scarce because of delays in scaling up VL-monitoring [55]. Most studies report viral suppression rates among adult patients between 80 and 90% [56, 57]. In Lesotho our group found a viral suppression rate ranging from 86.7% for adult patients on zidovudin/lamivudin/nevirapin regimen to 93.8% for patients on tenofovir/lamivudin/efavirenz [58]. In line with other studies reporting much lower viral suppression rates in children (likely due to the difficulty of maintaining adherence and drug-dosing especially in small children [59-62]), we found that only 72% of children on first-line ART for ≥ 6 months were virally suppressed [63].

Based on currently available data, 90% viral suppression seems to be the first of the 90-90-90 targets to be in reach – at least among adults. Of note, however, until now most studies reporting viral outcomes were cross-sectional and were conducted at tertiary clinics or in programs with particular support from non-governmental organizations. Moreover, all studies only enrolled patients who had started ART based on old starting criteria, such as CD4 cell count <350 cells/mL. In a treatment-for-all approach with rapid ART-initiation for all individuals after positive HIV-test, irrespective of their CD4-count, a higher share of patients may have poor adherence resulting in higher rates of virologic failures [20, 64, 65].

6.2 Rationale of the proposed study

On the way to achieve the 90-90-90 targets, the second 90, linkage to care, appears to be the most difficult one [39]. Our group recently demonstrated in a cluster-randomized trial that in home-based HTC campaigns in Lesotho more than 90% of the rural population accepts HIV-testing [38]. After a positive test result, however, linkage to care was found to be extremely poor (25%), even though newly tested individuals received on-site-post-test counselling, clinical staging and point-of-care CD4-testing. From a cohort analysis of our research group, we found that only about 80% of patients are retained in care 12 months after ART-initiation [66].

This fact unequivocally stresses the clear need for testing intervention packages that address linkage to and retention in care [52]. Time constraints and transport costs are frequently identified barriers for not accessing ART [54, 67] suggesting that reducing transport costs and travel time for patients prior to starting and while on ART has the potential to improve linkage and retention.

The proposed study will test an intervention package consisting of same-day, community-based ART initiation after a positive HIV test, and subsequently reduced frequency of ART visits during follow-up. Because the final goal of 90-90-90 is to achieve viral suppression in individuals who are HIV-infected, the trial will not only assess linkage to and retention in care but also the rates of viral suppression 12 months after HIV diagnosis.

7 Research Objectives (general and specific)

General aim of the proposed research project

The research project aims to test an intervention package for persons newly tested HIV-positive during community-based HTC campaigns. The intervention package consists of same-day community-based ART-start and subsequently spaced follow-up visits. This intervention package will be compared to standard of care (referring to facility for ART-initiation and subsequently monthly follow-up visits) in terms of linkage to care, one-year retention in care and viral suppression one year after the test result.

7.1 Primary Objectives

To compare between the intervention and the control arms

3. Linkage to care within 3 months after HIV-diagnosis
4. Viral suppression 12 months after HIV-diagnosis

7.2 Secondary objectives

To compare between the intervention and the control arms

- d.) 12-month mortality and loss to follow-up
- e.) Clinical outcomes at 12 months: haemoglobin-level, CD4-cell count, body-weight, diagnosis of new clinical WHO 3/4 events
- f.) Viral suppression rates 6 months after ART-initiation

7.3 Exploratory objective

To explore feasibility of achieving 90-90-90 in the study areas and resources needed.

7.4 Objectives of nested studies 1 & 2

See section -, page 24

8 Research Design and Methods

8.1 Overview of design characteristics

Primary Purpose: Health Services Research

Type of study: prospective randomized-controlled study

Number of study-arms: two (1 intervention arm, 1 control arm)

Allocation: 1:1 randomization

Intervention Model: Parallel Assignment

Masking: Open Label

8.2 Place of study

The study will be conducted in the district of Butha-Buthe, more specifically within the catchment areas of the following six health facilities: Butha-Buthe Government Hospital, Seboche Mission Hospital, Boiketsiso Health Center, Rampai Health Center, Ngoajane Health Center, Linakeng Health Center. All facilities are in an already established close collaboration with SolidarMed.

SolidarMed, the Swiss Organization for Health in Africa, is a not-for-profit organization supporting public and faith-based facilities in Lesotho in the delivery of ART since 2005 in the districts of Butha Buthe and Thaba Tseka. SolidarMed is working within the national health system with the aim to improve health for the population in its intervention area by strengthening integrated primary health care and adding to new knowledge and evidence.

8.3 Intervention and Control

Intervention

The intervention-package entails 2 major interventions. Intervention 1: same-day clinical and laboratory assessment with proposition of same-day ART-start after a new HIV-diagnosis.

Intervention 2: reduced frequency of follow-up visits after ART-initiation (for more detailed description see section 8.10, page 16).

Control:

The control-group follows the standard-of-care in Lesotho that is similar to most settings in Sub Saharan Africa. Participants newly tested HIV-positive who are in the control group receive post-test counselling and a referral letter with an appointment at their health facility. After having received baseline-assessment and at least 2 adherence counselling sessions at different days at the facility, they qualify for starting ART (for more detailed description see section 8.10, page 16).

8.4 Endpoints

8.5 Primary endpoints

1. Linkage to care within 3 months

Definition: participant attends the clinic for follow-up at least once within 90 days after HIV-diagnosis

2. Viral suppression 12 months after the positive HIV-test result during the home-base HTC-campaign

Definition: 11 to 14 months after diagnosis of HIV-infection the participant has a VL<100copies/mL.

8.6 Secondary endpoints

1. 12-month mortality and loss to follow-up

Definition “loss to follow-up”: participant has not attended the clinic for follow-up between months 11 and 14 after the positive HIV-test

Definition “one-year mortality”: participant has died < 365 days after the positive HIV-test result

2. Clinical outcomes 12 months after the positive HIV-test result

Definition “clinical outcomes”: Change in values of body-weight (kg), CD4-cell count (cells/mL), and haemoglobin (g/dL) between day of positive HIV-test result and 12-month follow-up visit (11 to 14 months after positive HIV-test result); Number of newly recorded clinical WHO-stage 3 or 4 events between baseline and 12-month follow-up visit (11 to 14 months after positive HIV-test result)

3. Viral suppression 6 months after ART-initiation (\neq after positive HIV test result)

Definition “viral suppression”: VL < 100copies/mL at 5 to 7 months after ART initiation

8.7 Exploratory endpoints

1. Testing coverage achieved through the community-based HTC-campaigns (see nested study, page 24)
2. ART coverage achieved one year after testing-campaigns
3. Resources needed to achieve the exploratory endpoints 1&2

8.8 Eligibility

Inclusion criteria

- HIV infection newly diagnosed during community-based HTC-campaigns
Comment: In line with the new WHO-recommendations issued in September 2015 [12], in this trial all HIV-infected persons are eligible to start ART, irrespective of their CD4-count.
- Never been on triple-ART (women who once received mono- or bi-therapy as part of previous treatment for prevention of mother-to-child transmission but never received ART consisting of 3 drugs simultaneously are eligible)
- Lives and/or works in the district of Butha-Buthe and declares to seek follow-up at one of the 6 health facilities involved in the study
- Age \geq 18 years
- Signed written informed consent

Exclusion

- Pregnant or breast-feeding
- Already enrolled in chronic care for another disease, such as tuberculosis or diabetes
- Clinical WHO-stage 4 or active tuberculosis
- Positive cryptococcal antigen test
- Currently working in the Republic of South Africa

8.9 Conducting community-based HTC-campaigns

The HTC campaigns serve for recruitment of participants but are at the same time an observational sub-study nested within the CASCADE-study (see nested study 1, section 9.1, page 24). Three types of community-based HTC-campaigns will serve for recruitment: 1) rural home-based HTC; 2) urban home-based HTC; and 3) urban mobile clinic.

Rural home-based HTC campaigns

Except for Butha-Buthe town, other areas are considered as rural. HTC-areas will be selected randomly from a list of eligible villages/sub-villages. To be eligible a village has to be clearly confined to the catchment area of one of the study facilities, have a size of 40 to 80 households, and not been exposed to a large HTC-campaign during the last 12 months. Rural HTC-campaigns will start as of end of February 2016 and are anticipated to last for 12 weeks. Campaigns may, however, be prolonged if the sample-size is not reached after the 12 weeks. The population of the selected areas will be informed through village chiefs two weeks prior the campaign starts. A team consists of 14 persons (8 trained and experienced lay-counsellors, 2 nurses, 2 community-mobilisers or professional/senior counsellors and 2 drivers). Each team visits each area on two different days. The first day will be during the week, from Monday to Friday. The second day will be during the weekend or a holiday to

reach household members who were absent during the first visit. The team has two sub-teams with the following members, roles and responsibilities:

- 1 community-mobiliser or professional/senior counsellor: supervises the lay-counsellors, ensures accurate conduct and documentation of HTC as well as collection of study-variables
- 4 lay-counsellors: visit households, conduct and document HTC
- 1 study-nurse: post-test counselling of newly diagnosed HIV-positive persons, enrolment of participants for CASCADE-study and baseline laboratory (CD4 count, hemoglobine, creatinine) for those allocated to the intervention arm
- 1 driver: responsible for logistics

The structure and functions of 2 sub-teams are similar. The purpose of dividing sub-teams is to have better coverage.

First visit to a testing area during the week:

The team arrives in the study area at 11:30am, informs the village chief about its arrival and then starts systematic testing of all households in the pre-defined area by going from door to door until sunset (around 6pm). Under coordination and supervision of the community mobiliser, households are visited by one lay-counsellor. At the household the lay counsellors proceed as follows:

- 1 Introduction of himself/herself and the HTC-campaign.
- 2 Ask the head of household or representative for written informed consent to assess number of household-members and uptake of HTC among household-members (see section 16.1, page 33). If the head of household refuses his/her household to participate, the lay-counsellor leaves the house and proceeds to the next household.
- 3 Assessment of total number of household members and number of household members currently present
- 4 From each household member the following data will be collected: name, age, sex, currently present in household (see section 8.12, page 19)
- 5 For all household members who are present: HIV-status, previous HIV-tests, information about HTC and proposition of HTC.
- 6 Informed consent to HTC from each household-member who agrees to HTC (this is the national HTC consent form every person has to sign before HTC is conducted)
- 7 Conduct of HTC according to national guidelines [68].
- 8 If HIV test is negative, lay counsellor provides post-test counselling. If HIV-test is positive the lay-counsellor contacts the study-nurse of the team. The study nurse will then assess the participant clinically and propose enrolment in CASCADE-study if eligible (for enrolment CASCADE-trial, see section 8.10 on page 16).
- 9 Before leaving the household the lay-counsellor informs the persons present that he/she will again return next weekend to propose HTC to household members who were not present at the first visit.

Second visit to a testing area during a weekend or holiday

At the second visit to a HTC area, each lay-counsellor goes to the same households he/she attended during the first visit. The lay-counsellor enquires about household members who were absent during the first visit. If household members who were absent during the first visit are now present, the lay-counsellor follows again steps 5 to 8 of the first visit for these household members.

Urban home-based HTC campaigns

Similar to rural areas, areas within Butha-Buthe town will be randomly chosen for home-based HTC. Information about the dates and the campaigns will be spread through urban community councils and the local radio. Again each household will be visited twice (during the week and on the weekend). A team consisting of 1 professional counsellor, 1 study nurse, 4 lay-counsellors and 1 driver starts HTC at 11:30 am, following the same principles as for rural home-based HTC described above. The urban home-based HTC campaigns will be conducted in parallel to the rural campaigns.

Urban mobile clinics HTC

In addition to the home-based approach, HTC is proposed in mobile clinics stationed at different places within Butha-Buthe town (i.e. taxi-rank, in front of the Mall, etc.). Exact localisation of the mobile clinics will be discussed and agreed upon with the local authorities. The mobile clinics consist of 2 tents where 2 lay-counsellors and a nurse provide HTC. The population will again be informed through radio and community councils about exact location and dates for HTC at the mobile clinics. If a person enters the tent and consents to participate, HTC will be conducted according to national guidelines [68].

In case of a positive HIV test result, the nurse will assess the person and propose participation in the CASCADE-study if eligibility criteria are met (see below). HTC-clients from the mobile clinics are only eligible for the CASCADE trial but not for nested study 1 & 2.

8.10 Recruitment for CASCADE-study

In case a person tests positive during the HTC-campaigns, the study nurse assesses if the person presents with any acute illness and if he or she is eligible for participation in the CASCADE-study. In case the person is eligible and consents to participation, they will be randomized using a stratified randomization list, generated by an independent statistician. Randomization will be at household level and stratified by HTC-area. Reason for randomizing at household level is that in case more than one individual tested HIV-positive it would not be feasible for individuals of the same household to participate in different arms due to a high risk of cross-contamination between the arms.

Intervention arm:

The study nurse assesses the participant's clinical WHO-stage and performs CD4-count (PIMA® Alere), creatinine (StatSensor Creat®, Nova® Biomedical) and hemoglobine (Hemocue®, HB301) as point-of-care tests. Thereafter, the participant receives a standardized short adherence counselling. After the adherence counselling, participants are offered to start ART the same day. Choice of ART-regimen follows national guidelines [69, 70]. In addition, and in line with national and WHO guidelines, participants with a CD4-count < 350cells/mL will receive cotrimoxazole prophylaxis. Participants who have a CD4-count < 100cells/mL will receive testing for cryptococcal antigen. In case of a positive result, the participant will be referred for fluconazole therapy according to guidelines and excluded from the study.

The participant will receive one box of his/her ART-regimen containing drugs for 30 days and an appointment for a first clinic visit in 12 to 16 days.

At the first clinic visit, the participant receives a second adherence-counselling. If the participant is clinically stable at this first visit, the next follow-up visits will be 6 weeks, 3, 6, 9 and 12 months after ART-initiation to reduce travel time and transport cost. Participants are; however, encouraged to visit the clinic any time in case of problems or questions.

Control arm:

Management follows national guidelines [68, 69]. After post-test counselling and assessment for any acute illness, the participant receives the national standard referral form, together with an appointment at the nearest clinic.

The day the participant presents the first time at the clinic, he/she receives laboratory baseline-assessment (CD4-cell count, creatinine, haemoglobin) and a first adherence counselling session. The participant has then to return to the clinic a second time for a second adherence counselling and to receive the results of the laboratory baseline tests. If judged as “ready” by the counsellor, the participant may start ART at his/her second clinic visit. Once the participant has started ART, the first and second follow-up visits are 14 and 28 days, respectively, after ART start. Thereafter, follow-up visits are monthly until 6 months after ART start. If the participant is clinically stable, follow-up visits may then be spaced to 3-monthly intervals, but ART refill still must be collected on a monthly basis.

Tracing of participants

In both groups participants will be traced if they did not link to care 90 days after the HIV-test. Tracing will be done using the system in place (contact via village health worker or phone if available)

8.11 Consort flow-chart

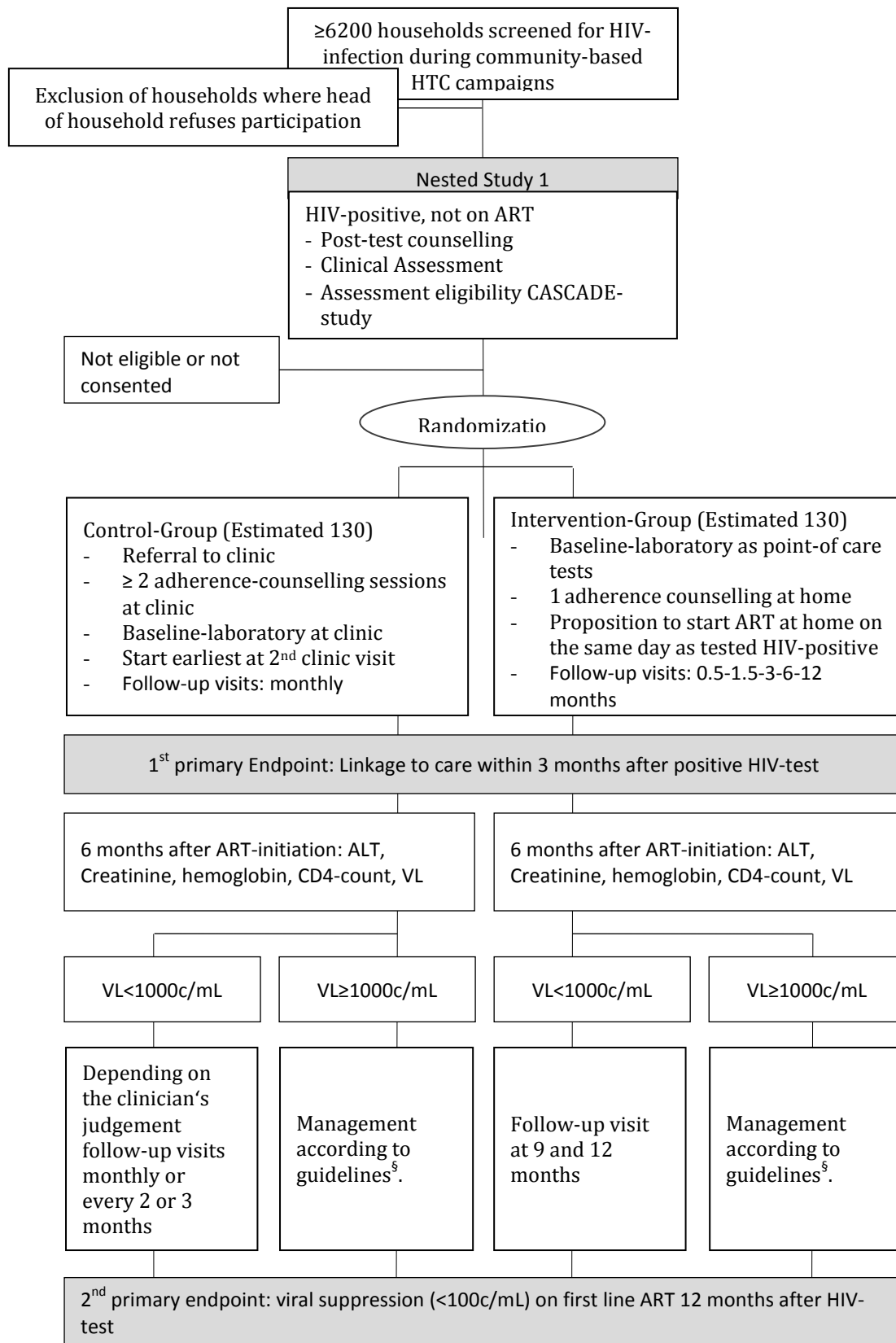


Figure 1 CONSORT flow-chart of the CASCADE-trial. VL: Viral load; HTC: HIV testing and counselling; ART: anti-retroviral therapy; ALT: alanine amino transferase.

§ participants with sustained un-suppressed viral load 8-12 weeks after enhanced adherence counselling will be switched to second-line ART as outlined in WHO- and Lesotho guidelines^{69,70}.

8.12 Data collection and variables collected

Means of data collection

Data during the HTC-campaigns will be collected using a tablet-based electronic database.

Variables collected during HTC-campaigns

Variable	Type of variable	Comment
Household Data		
– Household ID		Anonymous identifier generated for each household
– Household location	GPS-coordinates of the household	To ensure the right household is identified at second visit
– Date of household visit	Date	
– Name head of household	String	The name will be encrypted and deleted after the HTC-campaign (see section 10.6, page 29)
– Consent of head of household or representative for participation of household in nested study 1	Binary (Y/N)	See information and consent form section 16.1, page 33
Data collected for each household members		Only if head of household provides written informed consent to nested study 1
– Name	String	The name will be encrypted and deleted after the HTC-campaign (see section 10.6, page 29)
– Age	Continuous	
– Sex	Binary	
– Current location of household member	Present; not present but in the surroundings of the village (working in the fields, etc.); away for work in Lesotho; away for work in South Africa; away, other; away, unknown where	
If household-member present		
– HIV-status	Categorical (HIV-negative; HIV-positive on ART; HIV-positive defaulted ART; HIV-positive never been on ART; unknown)	
– Previous HIV-test	Categorical (<12 months ago; ≥12 months ago; never)	
– HTC-uptake	Binary (Accepted; Declined)	
– HTC-result	Negative; Positive; Indeterminate	
If tested HIV-positive		
– Eligible for CASCADE-study	Binary (Y/N)	

Baseline-variables collected for persons enrolled in CASCADE-study

Variable	Type of variable	Comment
– Study-ID	Integer	From randomization list
– Education of participant	Ordinal (none, primary, secondary, tertiary)	
– Marital status of participant		
– HIV status of partner	Categorical (not known, tested negative < 3 months ago, positive not on ART, positive on ART, positive, no known if on ART)	
– Partner lives in same household	Binary (Y/N)	
– Number of children	Continuous	
Pre-ART assessment		
– Clinical WHO-stage	Ordinal (I-IV)	Assessed by the study nurse
– Body-weight of participant (kg)	Continuous	
– Clinic where participant wishes follow-up	Categorical	Has to be one of the 6 study-clinics. Otherwise participant is not eligible for study (see section 8.8, page 14)
Laboratory baseline-assessment		
– CD4 cell count (cells/mL)	Continuous	Is done as point-of-care in the intervention group. For the control group laboratory assessment is done at the laboratories of Butha-Buthe or Seboche Hospital, once participant is linked to care.
– Creatinine (mmol/mL)	Continuous	
– Hemoglobine (g/L)	Continuous	
Nested study 2		
– Lipid-panel (total cholesterol, LDL, HDL, triglycerides)	Continuous	See section 9.2, page 26
– Glycosylated hemoglobine (HbA1c)	Continuous	In both groups blood will be drawn and then analysed in the evening.

Follow-up variables for persons enrolled in the CASCADE-trial

Collection of follow-up variables will be paper-based.

Months	Follow-up period after HIV-test			
	0	3	5-6	11-14
Adherence		X	X	X
Body-weight	X	X	X	X
Clinical assessment	X	X	X	X
CD4-cell count	X		X	X
Haemoglobin	X		X	X
Creatinine	X		X	X
ALT	X		X	X
Viral Load			X	X
Lipid-panel	X			X
HbA1c	X			X
Plasma for storage (see section 8.13)	X			X
Assessment first primary endpoint		X		
Assessment second primary endpoint				X

8.13 Collection and storage of biologic material

Participants of the CASCADE-trial undergo phlebotomy at recruitment, 6 and 12 months after having started ART. In case the participant is allocated to the intervention group baseline, tests (CD4-count, haemoglobine and creatinine) are done as point-of-care. In case the participant is in the control group these tests will be done when he or she presents at the clinic for the first time. For nested study 2, blood is taken at enrolment and analysed the same day in the evening at the facility. At recruitment and after 12 months follow-up, one plasma-sample of the participant will be stored at -80 degrees at the laboratory of Butha-Buthe hospital. In case a participant presents with virologic failure at follow-up, genotype resistance testing will be performed. In case of the presence of resistance mutations in the follow-up viral load, the stored baseline plasma sample will be analysed using next generation sequencing to determine if the participant had primary resistance or if the resistance was acquired while on ART. Plasma samples will be stored at -80 freezers in Butha-Buthe Hospital for unlimited time. In will only served for viral analyses. In case researchers wish to do any other additional analysis in the plasma, an amendment will have to be submitted to the Ethics Committee of Lesotho.

8.14 Confidentiality of processed data

Processed data will be coded and anonymous. Stored blood samples will only contain the study-ID.

Handling of participant names during HTC

Because a lay-counsellor visits each household twice, he or she has to know the names of household members to assess presence and absence at each visit. Names of study-participants will be collected but encrypted for storage on tablets. After completion of second household visit the database will delete automatically all names and only keep the anonymous ID codes.

Handling of participant names during CASCADE-study

Apart from the informed consent form, all study documents will only contain the study-coded. Facility records will be handled as all other records for patients on ART.

8.15 Adverse Events (AEs) and Serious Adverse Events (SAEs)

Prescription and use of anti-retroviral drugs will follow current national guidelines of Lesotho [69]. All anti-retroviral drugs used in Lesotho have a well-established safety profile. Most frequent adverse events are summarized on page 40 of the *Lesotho National guidelines on the use of antiretroviral therapy for HIV prevention and treatment*, 4th edition, 2013 [69] and on page 138 of the *Consolidated Guidelines on the Use of antiretroviral Drugs for treating and preventing HIV Infection* of the WHO [70]. Before conduction of the study, nurses of the study-facilities will be re-trained on the national guidelines and potential AEs and SAEs of ART. In case of AEs the nurse has to document the AE and the action taken on the follow-up file. In case of SAEs the facility nurse must inform the study-physician immediately.

8.16 Sample-size and analytic plan

The sample size for this trial was based on the primary endpoint of linkage to care 3 months after HIV diagnosis. We expect 3-month linkage to care rates of 40% in the control arm and 60% in the intervention arm. As the trial is randomized at the household level, we require a total of 260 households with at least one HIV-positive participant to detect a 20% increase in linkage to care assuming a Type I error rate of 5% and power of 90%. With an estimated uptake of HTC of 94%, a prevalence of previously undiagnosed HIV-infection during home-based HTC-campaigns of 5%, and a 10% trial participation refusal rate or choice of alternative health facility, we need to visit 6200 households to achieve the desired sample size of 260 households with at least one HIV-infected person not on ART. In case more than one HIV-positive individual is diagnosed in the household, all individuals meeting eligibility criteria will be included. This will only serve to increase the power of the study. With the proposed sample size above, we will have sufficient power to test the second primary endpoint of viral suppression at 12 months. As those not linking to care will be considered as failures, we expect viral suppression rates of 25% in the control arm and 45% in the intervention arm. With 130 individuals per arm, we will have 93% power to detect a difference of 20% in viral suppression rates.

The study will be analysed using mixed effects models that account for the clustering of the households. Factors used in stratifying the randomization will be included in the models. Linkage and viral suppression rates between the control and intervention arm will be presented with odds ratios and 95% confidence intervals.

8.17 Expected benefit from the study

Community-based HTC campaigns will be one important intervention towards reaching the 90-90-90 goals as it is a key strategy to access “hard-to-reach” populations for HTC [71]. Despite recent popularity of home-based HTC campaigns, linkage after a positive HIV-test continues to be uniformly poor in Sub Saharan Africa [39, 72] and interventions improving linkage are greatly needed [73]. The intervention tested in the CASCADE-study could represent a feasible add-on to the current practice of health-care-provider teams in the villages providing HTC. If proven to be effective, increases in the intervals between follow-up visits in stable patients has the potential of saving resources within the health system. Furthermore, if same day home-based ART start and prolonged intervals between ART visits should prove superior, this strategy will have the potential to be scaled up nationally and internationally in similar settings and to be integrated into guidelines and policies.

8.18 Strengths and limitations

Strengths

- One of the first randomized controlled studies addressing the HIV care cascade
- Assessment of the whole cascade from HTC to viral suppression
- Includes urban (Butha-Buthe town) as well as rural areas
- Includes catchment areas of primary and secondary level facilities

- Is implemented in the context of a district health system and not in a research setting

Weaknesses

- The trial only includes persons tested during community-based HTC. It does not consider persons who receive their test at the facility. The population tested through home-based HTC may therefore differ from the one reached through facility-based HTC.
- The trial is not implemented in the whole district but selected facilities
- Persons, who are not at home during one of the two visits, cannot be enrolled.
- Children are excluded from this study
- After enrolment persons may decide to access treatment outside the district of Butha-Buthe. This may lead to an underestimation of linkage to and retention in care.

9 Nested studies within the CASCADE-trial

The trial embraces two nested studies. Both are observational and do not include any additional intervention.

9.1 Nested Study 1: Feasibility and resources needed for achieving 90% HIV-testing coverage in rural and urban areas in Lesotho

This study is an observational analysis of the home-based HTC-campaigns that are conducted for the recruitment of participants in the CASCADE-study.

Background/rationale

In the cluster randomized trial that our group conducted in the districts of Butha-Buthe and Thaba-Tseka in Lesotho in 2011, home-based HTC achieved > 90% HTC uptake among persons encountered at their homes during the campaigns. However, the trial left some doubt about the appropriateness of home-based testing for achieving high HTC-coverage in the population: Home-based HTC appeared to reach an underexposed population yielding only very few newly detected HIV-infections leading to a high cost per newly detected infection (495 USD) [38]. A likely reason for this is that the campaigns were conducted during weekdays where the working-population was not at home. Additionally, the trial was only conducted in very remote rural areas.

While conducting the home-based HTC-campaigns to recruit participants of the CASCADE-study, this nested study will now specifically assess testing coverage through home-based HTC on week- as well as weekend-days in rural and urban areas of Butha-Buthe district and assess the resources needed to achieve this coverage.

Main objective

To assess the percentage of the population tested for HIV in predefined geographical areas after two days of home-based HTC campaigns per area.

Secondary objectives

1. To assess ART coverage in the areas where the campaigns are conducted
2. To assess resources needed per individual tested and per individual testing HIV-positive
3. To assess HTC uptake
4. To assess clinical and immunological stage of individuals newly tested HIV-positive

Design

Cross-sectional, observational

Eligibility

All households of the randomly selected pre-defined HTC areas

Main outcome

- Testing coverage in a pre-defined area after two one-day visits

Secondary outcomes

- Resources needed to test one person and resources needed to find one HIV-infected person who is not yet enrolled in ART.
- HTC-uptake (acceptance of HTC among persons proposed HTC during the campaigns)

Procedures and data-collection

See section 8.9 on page 14.

Expected benefit from the nested study

This study will provide practical information on the feasibility to conduct home-based HTC on a larger scale and achievability of 90% testing-coverage. It will assist the Ministry of Health of Lesotho as well as its implementing partners in the planning of future HTC-campaigns. Study results will be of interest for governments and non-governmental organizations in similar settings in Southern Africa.

Limitations of the nested study

The assessment of the number of persons living in the households enrolled in the study relies on the reporting of those household-members encountered during the campaigns. Depending on the definition used, household-sizes may vary [74]. As many Basotho frequently migrate for labour to other regions within Lesotho or to South Africa, defining who is a household member may be difficult in some situations. For the purpose of this study, household-members will have to acknowledge the same household-head and to have spent at least one week or at least 3 weekends living in the house during the last 3 months. This accounts for the fact that nowadays most persons who work legally in South Africa, i.e. in the mines, receive regularly prolonged weekends that allow them to visit their families in Lesotho. The situation for those who work without a permit is indeed different. They may be absent from home for longer periods and are not included in the definition for household-members used in this study.

Another limitation is that testing coverage has to be estimated based on persons encountered at one of the two cluster visits. Persons who are absent at both visits will be coded as not tested/not on ART. They may, however, have tested at another occasion, i.e. at their working-place.

9.2 Nested Study 2: Lipid- and glucose profile in adult HIV-infected and non-infected persons in Lesotho and changes after initiation of anti-retroviral therapy

Background/rationale

ART has transformed HIV into a chronic disease that still affects the lives of millions although it no longer necessarily shortens their life expectancy [75]. As a result, the number of HIV-infected persons who are 50 years and older is increasing also in Sub Saharan Africa. In 2014, the UNAIDS estimated there to be about 1.4 million HIV-infected persons aged 50 years and older living in Southern Africa [76]. Therefore monitoring of risk-factors for cardiovascular diseases is becoming increasingly important, particularly for this group. The CART-1 study [77] revealed that among women on first-line ART in Lesotho 25% fulfilled the definition of metabolic syndrome [78] and 9.6% of women and 14.2% of men on first-line ART had an unfavourable lipid-profile, defined as an LDL/HDL ratio > 3.0 (unpublished). Whereas several cross-sectional studies observed an association of ART with metabolic abnormalities in Sub-Saharan Africa [79-84], there are very few longitudinal studies describing changes in lipid-profiles over time in Africa and those that did were in older, often outdated first-line regimens that contained thymidine-analogues such as stavudine or zidovudine [85, 86].

Objectives

- To assess changes in lipid-profile and levels of glycosylated hemoglobin (HbA1c) in HIV-infected individuals after starting first-line ART in the CASCADE-trial;
- Prevalence of impaired fasting glucose, diabetes and dyslipidemia in ART-naïve HIV-infected and non HIV-infected persons

Design

Cross-sectional, followed by prospective cohort study among those participants who start ART

Eligibility

- All persons enrolled in CASCADE-study
- Age- and sex-matched individuals tested HIV-negative during the community-based HTC-campaigns

Main outcomes

- Prevalence of impaired fasting glucose, diabetes and dyslipidemia in ART-naïve HIV-infected and non HIV-infected persons (age- and sex-matched non HIV-infected controls are randomly selected among those who test negative during home-based HTC)
- Changes in pre-ART lipid-profile and HbA1c-level at 12 months post ART initiation

Sampling and data-collection

HIV-infected individuals: As part of the baseline-assessment blood-samples of all participants of the CASCADE-study will be used for measurement of lipid-panel and HbA1c (see page 19). In those starting ART lipid-profile and HbA1c will again be assessed at 12-months follow-up (see table on page 21).

Not HIV-infected individuals: For each individual enrolled in CASCADE-study two age- and sex-matched HIV-negative individuals will be randomly selected for assessment of lipid-status and HbA1c. The tablet-based database used during the HTC-campaigns will randomly select among age- and sex-matched individuals and indicate if measurement of lipid-profile and HbA1c should be conducted.

Impact of the nested study

Description of metabolic changes under the currently recommended first-line ART-regimen will help to plan future interventions aiming at cardiovascular prevention among the ageing HIV-population in similar settings.

Limitations of the nested study

Whereas lipid-profiles are assessed in HIV-infected ART-naïve and non HIV-infected persons during the cross-sectional study, changes in lipid-profiles will only be assessed among HIV-infected persons starting ART and retained in the trial after 12 months. Re-visiting non HIV-infected persons one year later for assessing potential changes would be too resource intensive.

10 Ethical Considerations CASCADE-study

10.1 Ethical conduct of the study

The research project will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki (DoH) and The Principles of Good Clinical Practice (GCP).

10.2 Recruitment

Individuals who test HIV-positive during the HTC-campaign and have never been on ART will be proposed to participate in the study. In the information-form (see page 33, section 16.1) it is emphasized that the individual is entirely free to participate or not and that one can terminate or withdraw consent at any time of the study without any immediate or future negative effects regarding the services provided.

10.3 Risk to participants

Participants of the study do not undergo any experimental therapy. Medical management of HIV-infection will follow national guidelines and standards. No additional risk compared to standard management has to be expected.

The procedure of blood draw for laboratory analyses will be done respecting all hygiene and safety regulations in order to avoid any harm to participants or project staff. Handling of blood samples by the project and the laboratory staff will be done according to standard safety regulations.

10.4 Informed consent

The study-nurse, seconded by a lay-counsellor, will explain the information sheet for participants. Once all open questions have been clarified and if the person agrees to participate, he or she has to sign the informed consent form. In case of illiteracy a thumb-print will be used instead and a witness chosen by the participant has to sign the form (see informed consent form on page 33).

10.5 Handling and storage of Plasma

At enrolment three 4mL blood tubes (3 EDTA) will be collected. One tube will be used for baseline-analyses (CD4 cell-count, haemoglobin, creatinine, lipid-profile, HbA1c, cryptococcal antigen if CD4<100cells/mL). Two tubes will be centrifuged and only plasma will be kept for storage and frozen at -80 degrees at Butha-Buthe laboratory. In case of treatment failure at 6 or 12 months, plasma will be used to do genotype resistance testing (see page 21).

We anticipate that from mid-2016 genotypic resistance testing will be functional at Butha-Buthe laboratory. Only in case resistance testing has to be done in a laboratory outside Lesotho, samples will be prepared in Butha-Buthe and then shipped to Department of Biomedicine – Haus Petersplatz, University of Basel, Switzerland. The same institute performed virologic analyses for the research project entitled “*Chronic non-communicable and selected communicable comorbidities, virologic failure and resistance among patients on antiretroviral therapy in rural Lesotho*” (CART-1 study) that had been reviewed by the National Ethics Committee of the Ministry of Health of Lesotho in 2014 (Protocol Reg. number (for RCU): 01-2014). In case shipment outside Lesotho will be needed, an amendment including a materials transfer agreement will be submitted to the National Ethics Committee prior to shipment.

10.6 Confidentiality of data

Database during HTC-campaigns

As outlined on page 21 the database used during HTC-campaigns will contain the names of the household members. The rationale for having the names is to allow the lay-counsellor at the second visit to know who was absent at the first visit. The tablets that will be used for data-collection will be password-protected. The software developed for tablet-based data-entry during the HTC-campaigns will, however, delete the names once the second household-visit has been completed.

Database for CASCADE-study

The database of the CASCADE-study will be coded and does not contain any names. The study-nurse will have a master-file kept in the SolidarMed office in Butha-Buthe, linking the study-ID to participant's name and address. The master-file will only be accessed in case the study-information is needed for clinical management of the study-participant.

Blood tubes

All blood samples will be labelled with the study-ID.

Medical records of participants

During the HTC-campaign as well as during follow-up of persons tested HIV-positive at their clinics, all regular national medical records will be filled out. All persons who agree to do HTC will have to fill in the national HTC consent form. This form contains the name of the person who provides consent to testing. In case of a positive test-result the person receives a national referral form. This form again contains the name. For those who enrol in care the usual national ART-file will be opened. The file contains pre-ART- and ART-number as well as patient names. National HTC-forms as well as ART-files of study-participants will be handled exactly the same way as those from individuals who are not part of the study, respecting good practice of medical confidentiality.

10.7 Role of sponsor

The study is supported by the Swiss Foundation *Stiftung für Infektiologie beider Basel*. This is an independent foundation aiming at supporting research in the field of infectious diseases. The study is embedded in the SolidarMed country programme and thus benefits from logistics and human resources from SolidarMed Lesotho.

10.8 Compensation

This study causes no substantial additional risk or cost to the participants. Therefore we do not pay compensation to the participants.

11 Ethical considerations nested study 1

Nested study 1 (see section 9.1, page 24) is a purely descriptive study describing number of persons tested per household in the areas where the home-based HTC-campaigns will be conducted. Home-based HTC-campaigns are common in Lesotho and conduct of the campaigns will be according to national and international standards of practice [37, 68]. Conduction of this study needs to respect sovereignty of the household as well as the household members. In a first step the lay-counsellors visiting a household will approach the head of household or – if absent – his or her representative informing about the HTC-campaigns and the data that will be collected at household-level. The head of household/representative has first to provide informed written consent before household data can be included in the study (see section 16.1 on page 33). If the head of household consents

to the participation the lay-counsellor will collect in a second-step information on household members present and absent. HTC is then proposed to each household-member individually. Each household-member has to provide informed written consent to HTC. For this purpose the national HTC consent form will be used (.

12 Ethical considerations nested study 2

International guidelines recommend monitoring of blood-lipids for persons with HIV-infection [87]. For participants of the CASCADE-trial nested study 2 does not lead to any additional blood-draw.

For participants who test HIV-negative during the HTC-campaigns and who are randomly selected for participation in nested study 2, measurement of lipid-panel will require an additional venous blood-draw of one 2ml EDTA-tube. Prior to blood-draw HIV-negative participants will be informed and asked for written informed consent, using a specific informed consent form (see page 33).

13 Plan for distribution of results

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. At national level the national research symposium at the Ministry of Health will serve as a platform to share the results and discuss their implications. International scientific conferences, such as the yearly conference of the International AIDS Society and publications in scientific journals will serve for results dissemination.

14 Timelines of the study

	2015	2016				2017			
	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Start of VL-monitoring in Butha-Buthe									
Planning/preparation of HTC-campaigns									
Pre-test									
HTC-campaigns (recruitment)									
Follow-up									
Assessment 1st primary endpoint									
Assessment 2nd primary endpoint									
Results nested study 1									
Results nested study 2									
Results dissemination									

15 Budget of the study

The research project will benefit from the infrastructure provided by SolidarMed. The budget below provides an overview of additional cost caused specifically by the study. These cost are covered by the independent Swiss Foundation “Stiftung für Infektiologie beider Basel”.

Equipment	LSL
Laboratory point-of-care tests (CD4, hemoglobine, creatinine, lipid panel, HbA1c)	140000
Data-management (programming of database, tablets, etc.)	150000
Viral Load tests	215600
Stationary and other consumables	22000
Human Resources	
Study nurse (18 months)	360000
20 lay counsellors for 3 months (HTC campaigns)	70000
Food, perdiem, accommodation study team during HTC campaigns	150000
Training study-team	22000
Study dissemination at national level	10000
Total	<u>1139600</u>

16 Appendices

16.1 Informed consent of the head of household for participation in the HTC-campaign

For English and Sesotho version of informed consent form please refer to documents attached to this protocol with the following title:

- Informed_Consent_Household_participation_Nested_Study_1_English_V1.1.pdf
- Informed_Consent_Household_participation_Nested_Study_1_Sesotho_V1.1.pdf

16.2 National consent form for HTC

The national HTC consent form of the Ministry of Health of Lesotho will have to be signed by all individuals prior to conduction of HTC. A scan of the form is attached to the submission of this protocol. See National_HTC_Consent_Form.pdf

16.3 Informed consent for participation in the CASCADE study

For English and Sesotho version of the informed consent form please refer to the documents with the following title:

- Informed_Consent_CASCADE_English_V1.1.pdf
- Informed_Consent_CASCADE_Sesotho_V1.1.pdf

16.4 Informed consent for HIV-negative participants of the nested study 2

For English and Sesotho version of the informed consent form please refer to the documents attached to this protocol with the following title:

- Informed_Consent_Nested_Study_2_English_V1.1.pdf
- Informed_Consent_Nested_Study_2_Sesotho_V1.1.pdf

16.5 List of study-staff and responsibilities

Please refer to the document attached to this protocol with the following title:

- Staff_List_V1.0.pdf

16.6 Curriculum Vitae of investigators

The following CVs are submitted together with this protocol

- CV_Niklaus_Labhardt.pdf
- CV_Tracy_Glass.pdf
- CV_Christiane_Fritz.pdf
- CV_Kyaw_Thin.pdf
- CV_Ravishankar_Gupta.pdf
- CV_Thabo_Lejone.pdf
- CV_Isaac_Ringera.pdf
- CV_Bienvenu_Nsakala.pdf

16.7 Approval letter of the Swiss Tropical and Public Health Institute

A scan of the approval letter of the Swiss Tropical and Public Health Institute is submitted together with this protocol. The file name is: Approval_Letter_Swiss_TPH.pdf

17 References

1. UNAIDS: **Fast Track - Ending the AIDS Epidemic by 2030**. *UNAIDS / JC2686* (accessed July 18, 2015 at: http://www.unaids.org/sites/default/files/media_asset/JC2686_WAD2014report_en.pdf) 2014, .
2. **90-90-90 An ambitious treatment target to help end the AIDS epidemic**. *UNAIDS / JC2684* (accessed October 30th 2014 at www.unaids.org) 2014, .
3. Jones A, Cremin I, Abdullah F, Idoko J, Cherutich P, Kilonzo N, Rees H, Hallett T, O'Reilly K, Koechlin F, Schwartlander B, de Zaluondo B, Kim S, Jay J, Huh J, Piot P, Dybul M: **Transformation of HIV from pandemic to low-endemic levels: a public health approach to combination prevention**. *Lancet* 2014, .
4. Hontelez JAC, Lurie MN, Bärnighausen T, Bakker R, Baltussen R, Tanser F, Hallett TB, Newell M-L, de Vlas SJ: **Elimination of HIV in South Africa through expanded access to antiretroviral therapy: a model comparison study**. *PLoS Med* 2013, **10**:e1001534.
5. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG: **Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model**. *The Lancet* 2009, **373**:48-57.
6. Cremin I, Alsallaq R, Dybul M, Piot P, Garnett G, Hallett TB: **The new role of antiretrovirals in combination HIV prevention: a mathematical modelling analysis**. *AIDS* 2013, **27**:447-458.
7. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, Hakim JG, Kumwenda J, Grinsztejn B, Pilotto JHS, Godbole SV, Mehendale S, Chariyalertsak S, Santos BR, Mayer KH, Hoffman IF, Eshleman SH, Piwowar-Manning E, Wang L, Makhema J, Mills LA, de Bruyn G, Sanne I, Eron J, Gallant J, Havlir D, Swindells S, Ribaud H, Elharrar V, Burns D, Taha TE, Nielsen-Saines K, Celentano D, Essex M, Fleming TR, HPTN 052 Study Team: **Prevention of HIV-1 infection with early antiretroviral therapy**. *N Engl J Med* 2011, **365**:493-505.
8. Cohen MH, Chen Y, McCauley M, Gamble T, Hosseinipour M, Kumarasamy N: **Final results of the HPTN 052 randomized controlled trial: antiretroviral therapy prevents HIV transmission**. *J Int AIDS Soc* 2015, (Suppl 4).
9. Eshleman SH, Hudelson SE, Ou SS, Redd AD, Swanstrom R: **Treatment as prevention: characterization of partner infections in the HIV Prevention Trials Network 052 trial**. *J Int AIDS Soc* 2015, **18** (Suppl 4).
10. TEMPRANO ANRS 12136 Study Group: **A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa**. *N Engl J Med* 2015, .
11. INSIGHT START Study Group: **Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection**. *N Engl J Med* 2015, .
12. World Health Organization: **GUIDELINE ON WHEN TO START ANTIRETROVIRAL THERAPY AND ON PRE-EXPOSURE PROPHYLAXIS FOR HIV**. accessed October 2, 2015 at: <http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/> 2015, ISBN 978 92 4 150956 5.
13. International AIDS Society Conference 2015: **The Vancouver Consensus**. available at: <http://vancouverconsensus.org> .
14. Hull M, Lange J, Montaner JSG: **Treatment as prevention--where next?** *Curr HIV/AIDS Rep* 2014, **11**:496-504.
15. Delva W, Abdool Karim Q: **The HIV epidemic in Southern Africa - Is an AIDS-free generation possible?** *Curr HIV/AIDS Rep* 2014, **11**:99-108.
16. MacCarthy S, Hoffmann M, Ferguson L, Nunn A, Irvin R, Bangsberg D, Gruskin S, Dourado I: **The HIV care cascade: models, measures and moving forward**. *J Int AIDS Soc* 2015, **18**:19395.

17. Yehia BR, Stephens-Shields AJ, Fleishman JA, Berry SA, Agwu AL, Metlay JP, Moore RD, Christopher Mathews W, Nijhawan A, Rutstein R, Gaur AH, Gebo KA, HIV Research Network: **The HIV Care Continuum: Changes over Time in Retention in Care and Viral Suppression.** *PLoS One* 2015, **10**:e0129376.
18. Piñeirúa A, Sierra-Madero J, Cahn P, Guevara Palmero RN, Martínez Buitrago E, Young B, Del Rio C: **The HIV care continuum in Latin America: challenges and opportunities.** *Lancet Infect Dis* 2015, **15**:833-839.
19. Kranzer K, Govindasamy D, Ford N, Johnston V, Lawn SD: **Quantifying and addressing losses along the continuum of care for people living with HIV infection in sub-Saharan Africa: a systematic review.** *J Int AIDS Soc* 2012, **15**:17383.
20. Mills EJ, Nachega JB, Ford N: **Can we stop AIDS with antiretroviral-based treatment as prevention?** *Glob Health Sci Pract* 2013, **1**:29-34.
21. Piot P, Abdool Karim SS, Hecht R, Legido-Quigley H, Buse K, Stover J, Resch S, Ryckman T, Møgedal S, Dybul M, Goosby E, Watts C, Kilonzo N, McManus J, Sidibé M, UNAIDS–Lancet Commission: **Defeating AIDS-advancing global health.** *Lancet* 2015, .
22. Chirawu P, Langhaug L, Mavhu W, Pascoe S, Dirawo J, Cowan F: **Acceptability and challenges of implementing voluntary counselling and testing (VCT) in rural Zimbabwe: evidence from the Regai Dzive Shiri Project.** *AIDS Care* 2010, **22**:81-88.
23. Snow RC, Madalane M, Poulsen M: **Are men testing? Sex differentials in HIV testing in Mpumalanga Province, South Africa.** *AIDS Care* 2010, **22**:1060-1065.
24. Bwambale FM, Ssali SN, Byaruhanga S, Kalyango JN, Karamagi CA: **Voluntary HIV counselling and testing among men in rural western Uganda: implications for HIV prevention.** *BMC Public Health* 2008, **8**:263.
25. Baiden F, Akanlu G, Hodgson A, Akweongo P, Debpuur C, Binka F: **Using lay counsellors to promote community-based voluntary counselling and HIV testing in rural northern Ghana: a baseline survey on community acceptance and stigma.** *J Biosoc Sci* 2007, **39**:721-733.
26. Sweat M, Morin S, Celentano D, Mulawa M, Singh B, Mbwambo J, Kawichai S, Chingono A, Khumalo-Sakutukwa G, Gray G, Richter L, Kulich M, Sadowski A, Coates T, Project Accept study team: **Community-based intervention to increase HIV testing and case detection in people aged 16-32 years in Tanzania, Zimbabwe, and Thailand (NIMH Project Accept, HPTN 043): a randomised study.** *Lancet Infect Dis* 2011, **11**:525-532.
27. Suthar AB, Ford N, Bachanas PJ, Wong VJ, Rajan JS, Saltzman AK, Ajose O, Fakoya AO, Granich RM, Negussie EK, Baggaley RC: **Towards universal voluntary HIV testing and counselling: a systematic review and meta-analysis of community-based approaches.** *PLoS Med* 2013, **10**:e1001496.
28. NIMH Project Accept (HPTN 043) Collaborators: **Project Accept (HPTN 043).** *presented in a Special Session at IAS 2013, available at:*
<http://pag.ias2013.org/session.aspx?s=79> .
29. Angotti N, Bula A, Gaydos L, Kimchi EZ, Thornton RL, Yeatman SE: **Increasing the acceptability of HIV counseling and testing with three C's: convenience, confidentiality and credibility.** *Soc Sci Med* 2009, **68**:2263-2270.
30. Obare F, Fleming P, Anglewicz P, Thornton R, Martinson F, Kapatuka A, Poulin M, Watkins S, Kohler H-P: **Acceptance of repeat population-based voluntary counselling and testing for HIV in rural Malawi.** *Sex Transm Infect* 2009, **85**:139-144.
31. Njau B, Watt MH, Ostermann J, Manongi R, Sikkema KJ: **Perceived acceptability of home-based couples voluntary HIV counseling and testing in Northern Tanzania.** *AIDS Care* 2012, **24**:413-419.

32. Doherty T, Tabana H, Jackson D, Naik R, Zembe W, Lombard C, Swanevelder S, Fox MP, Thorson A, Ekström AM, Chopra M: **Effect of home based HIV counselling and testing intervention in rural South Africa: cluster randomised trial.** *BMJ* 2013, **346**:f3481.
33. Sabapathy K, Van den Bergh R, Fidler S, Hayes R, Ford N: **Uptake of home-based voluntary HIV testing in sub-Saharan Africa: a systematic review and meta-analysis.** *PLoS Med* 2012, **9**:e1001351.
34. Mutale W, Michelo C, Jürgensen M, Fylkesnes K: **Home-based voluntary HIV counselling and testing found highly acceptable and to reduce inequalities.** *BMC Public Health* 2010, **10**:347.
35. Sekandi JN, Sempeera H, List J, Mugerwa MA, Asiimwe S, Yin X, Whalen CC: **High acceptance of home-based HIV counseling and testing in an urban community setting in Uganda.** *BMC Public Health* 2011, **11**:730.
36. Lugada E, Levin J, Abang B, Mermin J, Mugalanzi E, Namara G, Gupta S, Grosskurth H, Jaffar S, Coutinho A, Bunnell R: **Comparison of home and clinic-based HIV testing among household members of persons taking antiretroviral therapy in Uganda: results from a randomized trial.** *J Acquir Immune Defic Syndr* 2010, **55**:245-252.
37. World Health Organization: **Planning, implementation and monitoring home-based HIV testing and counselling. A practical handbook for Sub-saharan Africa.** Available at: http://apps.who.int/iris/bitstream/10665/75366/1/9789241504317_eng.pdf. *Planning, implementation and monitoring home-based HIV testing and counselling. A practical handbook for Sub-saharan Africa.* Available at: http://apps.who.int/iris/bitstream/10665/75366/1/9789241504317_eng.pdf.
38. Labhardt ND, Motlomelo M, Cerutti B, Pfeiffer K, Kamele M, Hobbins MA, Ehmer J: **Home-Based Versus Mobile Clinic HIV Testing and Counseling in Rural Lesotho: A Cluster-Randomized Trial.** *PLoS Med* 2014, **11**:e1001768.
39. Nachega JB, Uthman OA, del Rio C, Mugavero MJ, Rees H, Mills EJ: **Addressing the Achilles' heel in the HIV care continuum for the success of a test-and-treat strategy to achieve an AIDS-free generation.** *Clin Infect Dis* 2014, **59 Suppl 1**:S21-S27.
40. Naik R, Doherty T, Jackson D, Tabana H, Swanevelder S, Thea DM, Feeley FG, Fox MP: **Linkage to care following a home-based HIV counselling and testing intervention in rural South Africa.** *J Int AIDS Soc* 2015, **18**:19843.
41. Parker LA, Jobanputra K, Rusike L, Mazibuko S, Okello V, Kerschberger B, Jouquet G, Cyr J, Teck R: **Feasibility and effectiveness of two community based HIV testing models in rural Swaziland.** *Trop Med Int Health* 2015, .
42. Clouse K, Pettifor AE, Maskew M, Bassett J, Van Rie A, Behets F, Gay C, Sanne I, Fox MP: **Patient retention from HIV diagnosis through one year on antiretroviral therapy at a primary health care clinic in Johannesburg, South Africa.** *J Acquir Immune Defic Syndr* 2013, **62**:e39-e46.
43. Gerdt SE, Wagenaar BH, Micek MA, Farquhar C, Kariaganis M, Amos J, Gimbel S, Pfeiffer J, Gloyd S, Sherr K: **Linkage to HIV Care and Antiretroviral Therapy by HIV Testing Service Type in Central Mozambique: A Retrospective Cohort Study.** *J Acquir Immune Defic Syndr* 2013, .
44. Bassett I, Regan S, Luthuli P, Mbonambi H, Bearnot B, Pendleton A, Robine M, Mukuvisi D, Thulare H, Walensky R, Freedberg K, Losina E, Mhlongo B: **Linkage to care following community-based mobile HIV testing compared with clinic-based testing in Umlazi Township, Durban, South Africa.** *HIV Med* 2013, .
45. Wynberg E, Cooke G, Shroufi A, Reid SD, Ford N: **Impact of point-of-care CD4 testing on linkage to HIV care: a systematic review.** *J Int AIDS Soc* 2014, **17**:18809.

46. Kohler PK, Chung MH, McGrath CJ, Benki-Nugent SF, Thiga JW, John-Stewart GC: **Implementation of free cotrimoxazole prophylaxis improves clinic retention among antiretroviral therapy-ineligible clients in Kenya.** *AIDS* 2011, **25**:1657-1661.
47. Cantrell RA, Sinkala M, Megazinni K, Lawson-Marriott S, Washington S, Chi BH, Tambatamba-Chapula B, Levy J, Stringer EM, Mulenga L, Stringer JSA: **A pilot study of food supplementation to improve adherence to antiretroviral therapy among food-insecure adults in Lusaka, Zambia.** *J Acquir Immune Defic Syndr* 2008, **49**:190-195.
48. Muhamadi L, Tumwesigye NM, Kadobera D, Marrone G, Wabwire-Mangen F, Pariyo G, Peterson S, Ekström AM: **A single-blind randomized controlled trial to evaluate the effect of extended counseling on uptake of pre-antiretroviral care in Eastern Uganda.** *Trials* 2011, **12**:184.
49. Franke MF, Kaigamba F, Socci AR, Hakizamungu M, Patel A, Bagiruwigize E, Niyigena P, Walker KDC, Epino H, Binagwaho A, Mukherjee J, Farmer PE, Rich ML: **Improved retention associated with community-based accompaniment for antiretroviral therapy delivery in rural Rwanda.** *Clin Infect Dis* 2013, **56**:1319-1326.
50. Hatcher AM, Turan JM, Leslie HH, Kanya LW, Kwena Z, Johnson MO, Shade SB, Bukusi EA, Doyen A, Cohen CR: **Predictors of linkage to care following community-based HIV counseling and testing in rural Kenya.** *AIDS Behav* 2012, **16**:1295-1307.
51. Okeke NL, Ostermann J, Thielman NM: **Enhancing linkage and retention in HIV care: a review of interventions for highly resourced and resource-poor settings.** *Curr HIV/AIDS Rep* 2014, **11**:376-392.
52. Govindasamy D, Meghij J, Kebede Negussi E, Clare Baggaley R, Ford N, Kranzer K: **Interventions to improve or facilitate linkage to or retention in pre-ART (HIV) care and initiation of ART in low- and middle-income settings--a systematic review.** *J Int AIDS Soc* 2014, **17**:19032.
53. Posse M, Baltussen R: **Costs of providing food assistance to HIV/AIDS patients in Sofala province, Mozambique: a retrospective analysis.** *Cost Eff Resour Alloc* 2013, **11**:20.
54. Govindasamy D, Ford N, Kranzer K: **Risk factors, barriers and facilitators for linkage to antiretroviral therapy care: a systematic review.** *AIDS* 2012, **26**:2059-2067.
55. International AIDS Society: **Expanding Access To Viral Load Monitoring in Resource-Limited Settings - Meeting Report.** (accessed June 01, 2015 at: http://www.infectiousdiseasesonline.com/wp-content/uploads/2014/06/IAS-ILF_INTEREST_VL_in_RLS_Meeting_Report.pdf) .
56. Aghokeng AF, Monleau M, Eymard-Duvernay S, Dagnra A, Kania D, Ngo-Giang-Huong N, Toni TD, Touré-Kane C, Truong LXT, Delaporte E, Chaix M-L, Peeters M, Ayoub A, ANRS 12186 Study Group: **Extraordinary heterogeneity of virological outcomes in patients receiving highly antiretroviral therapy and monitored with the world health organization public health approach in sub-saharan Africa and southeast Asia.** *Clin Infect Dis* 2014, **58**:99-109.
57. McMahon JH, Elliott JH, Bertagnolio S, Kubiak R, Jordan MR: **Viral suppression after 12 months of antiretroviral therapy in low- and middle-income countries: a systematic review.** *Bull World Health Organ* 2013, **91**:377-385E.
58. Labhardt ND, Bader J, Lejone TI, Ringera I, Puga D, Glass TR, Klimkait T: **Is zidovudine first-line therapy virologically comparable to tenofovir in resource-limited settings?** *Trop Med Int Health* 2015, **20**:914-918.
59. Kebe K, Thiam M, Diagne Gueye NR, Diop H, Dia A, Signate Sy H, Charpentier C, Belec L, Mboup S, Toure Kane C: **High rate of antiretroviral drug resistance mutations in HIV type 1-**

- infected Senegalese children in virological failure on first-line treatment according to the World Health Organization guidelines. *AIDS Res Hum Retroviruses* 2013, **29**:242-249.
60. Mulu A, Liebert UG, Maier M: **Virological efficacy and immunological recovery among Ethiopian HIV-1 infected adults and children.** *BMC Infect Dis* 2014, **14**:28.
61. Teasdale CA, Abrams EJ, Coovadia A, Strehlau R, Martens L, Kuhn L: **Adherence and viral suppression among infants and young children initiating protease inhibitor-based antiretroviral therapy.** *Pediatr Infect Dis J* 2013, **32**:489-494.
62. Jobanputra K, Parker LA, Azih C, Okello V, Maphalala G, Kershberger B, Khogali M, Lujan J, Antierens A, Teck R, Ellman T, Kosgei R, Reid T: **Factors associated with virological failure and suppression after enhanced adherence counselling, in children, adolescents and adults on antiretroviral therapy for HIV in Swaziland.** *PLoS One* 2015, **10**:e0116144.
63. Puga D, Cerutti B, Molisana C, Bader J, Faturiyele O, Ringera I, Lejone T, Pfeiffer K, Klimkait T, Labhardt ND: **Outcomes of Children on Anti-Retroviral Therapy in Nurse-Led Clinics in Rural Lesotho.** *Pediatr Infect Dis J* 2015, .
64. Kranzer K, Ford N: **Unstructured treatment interruption of antiretroviral therapy in clinical practice: a systematic review.** *Trop Med Int Health* 2011, **16**:1297-1313.
65. Mills EJ, Funk A, Kanters S, Kawuma E, Cooper C, Mukasa B, Odit M, Karamagi Y, Mwehira D, Nachega J, Yaya S, Featherstone A, Ford N: **Long-term health care interruptions among HIV-positive patients in Uganda.** *J Acquir Immune Defic Syndr* 2013, **63**:e23-e27.
66. Labhardt ND, Keiser O, Sello M, Lejone TI, Pfeiffer K, Davies M-A, Egger M, Ehmer J, Wandeler G: **Outcomes of antiretroviral treatment programmes in rural Lesotho: health centres and hospitals compared.** *J Int AIDS Soc* 2013, **16**:18616.
67. Lankowski AJ, Siedner MJ, Bangsberg DR, Tsai AC: **Impact of geographic and transportation-related barriers on HIV outcomes in sub-Saharan Africa: a systematic review.** *AIDS Behav* 2014, **18**:1199-1223.
68. Ministry of Health and Social Welfare Lesotho: **National Guidelines For HIV Testing And Counselling.** *National Guidelines For HIV Testing And Counselling* 2009, .
69. Ministry of Health of Lesotho: **National guidelines on the use of antiretroviral therapy for HIV prevention and treatment.** *National guidelines on the use of antiretroviral therapy for HIV prevention and treatment* 2013, .
70. World Health Organization: **Consolidated Guidelines on the Use of antiretroviral Drugs for treating and preventing HIV Infection.** available at: www.who.int 2013, .
71. Smith JA, Sharma M, Levin C, Baeten JM, van Rooyen H, Celum C, Hallett TB, Barnabas RV: **Cost-effectiveness of community-based strategies to strengthen the continuum of HIV care in rural South Africa: a health economic modelling analysis.** *Lancet HIV* 2015, **2**:e159-e168.
72. Genberg BL, Naanyu V, Wachira J, Hogan JW, Sang E, Nyambura M, Odawa M, Duefield C, Ndege S, Braitstein P: **Linkage to and engagement in HIV care in western Kenya: An observational study using population-based estimates from home-based counseling and testing.** *Lancet HIV* 2015, **2**:e20-e26.
73. Ferrand R, Ford N, Kranzer K: **Maximising the benefits of home-based HIV testing.** *Lancet HIV* 2015, **2**:e4-e5.
74. Randall S, Coast E, Leone T: **Cultural constructions of the concept of household in sample surveys.** *Popul Stud (Camb)* 2011, **65**:217-229.
75. Rabkin M, Nishtar S: **Scaling up chronic care systems: leveraging HIV programs to support noncommunicable disease services.** *J Acquir Immune Defic Syndr* 2011, **57 Suppl 2**:S87-S90.
76. UNAIDS: **The Gap Report.** *The Gap Report* 2013, .

77. **Comorbidities and Virologic Outcome Among Patients on Anti-retroviral Therapy in Rural Lesotho (CART-1 study).** *www.clinicaltrials.gov* NCT02126696.
78. Labhardt ND, Cheleboi M, Faturyiele O, Motlatsi MM, Pfeiffer K, Lejone TI, Cerutti B, Muser J, Gupta RS, Lynen L, Hatz C: **Higher rates of metabolic syndrome among women taking zidovudine as compared to tenofovir in rural Africa: preliminary data from the CART-1 study.** *J Int AIDS Soc* 2014, **17**:19552.
79. Bekolo CE, Nguena MB, Ewane L, Bekoule PS, Kollo B: **The lipid profile of HIV-infected patients receiving antiretroviral therapy in a rural Cameroonian population.** *BMC Public Health* 2014, **14**:236.
80. Dave JA, Lambert EV, Badri M, West S, Maartens G, Levitt NS: **Effect of nonnucleoside reverse transcriptase inhibitor-based antiretroviral therapy on dysglycemia and insulin sensitivity in South African HIV-infected patients.** *J Acquir Immune Defic Syndr* 2011, **57**:284-289.
81. Omech B, Sempa J, Castelnuovo B, Opio K, Otim M, Mayanja-Kizza H, Colebunders R, Manabe YC: **Prevalence of HIV-Associated Metabolic Abnormalities among Patients Taking First-Line Antiretroviral Therapy in Uganda.** *ISRN AIDS* 2012, **2012**:960178.
82. Abebe M, Kinde S, Belay G, Gebreegziabxier A, Challa F, Gebeyehu T, Nigussie P, Tegbaru B: **Antiretroviral treatment associated hyperglycemia and dyslipidemia among HIV infected patients at Burayu Health Center, Addis Ababa, Ethiopia: a cross-sectional comparative study.** *BMC Res Notes* 2014, **7**:380.
83. Tesfaye DY, Kinde S, Medhin G, Megerssa YC, Tadewos A, Tadesse E, Shimelis T: **Burden of metabolic syndrome among HIV-infected patients in Southern Ethiopia.** *Diabetes Metab Syndr* 2014, **8**:102-107.
84. Ayodele OE, Akinboro AO, Akinyemi SO, Adepeju AA, Akinremi OA, Alao CA, Popoola AA: **Prevalence and clinical correlates of metabolic syndrome in Nigerians living with human immunodeficiency virus/acquired immunodeficiency syndrome.** *Metab Syndr Relat Disord* 2012, **10**:373-379.
85. Liu E, Armstrong C, Spiegelman D, Chalamilla G, Njelekela M, Hawkins C, Hertzmark E, Li N, Aris E, Muhihi A, Semu H, Fawzi W: **First-line antiretroviral therapy and changes in lipid levels over 3 years among HIV-infected adults in Tanzania.** *Clin Infect Dis* 2013, **56**:1820-1828.
86. Buchacz K, Weidle PJ, Moore D, Were W, Mermin J, Downing R, Kigozi A, Borkowf CB, Ndazima V, Brooks JT: **Changes in lipid profile over 24 months among adults on first-line highly active antiretroviral therapy in the home-based AIDS care program in rural Uganda.** *J Acquir Immune Defic Syndr* 2008, **47**:304-311.
87. European AIDS Clinical Society (EACS): **Guidelines Version 7.1.** available at: <http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html> 2014, .

Same day community-based ART initiation versus clinic-based pre-ART assessment and counselling for individuals newly tested HIV-positive during community-based HIV testing in rural Lesotho – a randomized study

Abbreviated title: CASCADE-Study

Revised protocol submitted to the National Ethics Committee of the Ministry of Health of Lesotho (05.02.2016)

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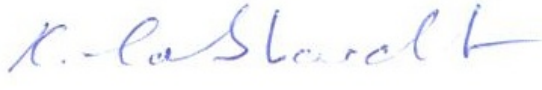
CVs of principal investigator and co-investigators are attached to this proposal

19 Signatures


Principal investigator and all co-investigators who sign below have approved the study protocol version 2.0, date 10.12.2015, 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).

The revised version 2.1 (05.02.2016) has been approved by all investigators. Due to absence of some of the co-investigators approved the revision via email and could not sign the revised version on paper. Their signature has been added electronically. The principal investigator (Niklaus Labhardt) and one of the co-investigators in Lesotho (Christiane Fritz) sign the revised form on behalf of co-investigators.

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21 Abbreviations

ART	Antiretroviral Therapy
CRF	Case reporting form
DHMT	District Health Management Team
HbA1c	Glycosylated Hemoglobine
HIV	Human Immune Deficiency Virus
HTC	HIV Testing and Counselling
MoH	Ministry of Health
NH-REC	National Health and Research Ethics Committee
Swiss TPH	Swiss Tropical and Public Health Institute
UNAIDS	United Nations Programme on HIV/AIDS
VL	Viral Load
WHO	World Health Organization

22 Proposal Summary

Study Title	Same day community-based ART initiation versus clinic-based pre-ART assessment and counselling for individuals newly tested HIV-positive during community-based HIV testing in rural Lesotho – a randomized study
Study Background	Early start of ART has been shown to be beneficial to the infected individual as well as to prevent further transmission from the individual to other individuals. To link individuals who test HIV-positive to care for start of ART proves however, difficult, particularly in low-resource settings. To achieve the 90-90-90 targets of the United Nations Programme on HIV/AIDS (UNAIDS) 90% linkage to care will be the most difficult target to reach. Innovative approaches that are not too resource-intensive to be implemented at a larger scale are needed. This study aims to assess if in case of a new HIV diagnosis during community-based HTC proposition of same day ART-start improves linkage to care and subsequently viral suppression as compared to standard of care consisting of pre-ART clinic visits for adherence counselling.
Study Objectives	<p>Primary Objectives To compare in both arms</p> <ul style="list-style-type: none"> 5. Linkage to care within 3 months after HIV-diagnosis (participant attends the clinic for HIV care at least once within 3 months after HIV-diagnosis) 6. Viral suppression 12 months after diagnosis of HIV <p>Secondary objectives</p> <ul style="list-style-type: none"> g.) To compare between both groups mortality and loss to follow-up h.) To compare clinical outcomes at 12 months in both groups: haemoglobin, CD4-count, new clinical WHO 3 or 4 events i.) To compare viral suppression rates 6 months after ART-start
Primary purpose	Health Service Delivery Research
Study Category	A, minimal risk to participants
Type of study	Prospective randomized-controlled study
Number of study-arms	2 (1 intervention arm, 1 control arm)
Intervention Model:	Parallel assignment
Masking	Open label
Indication	Diagnosis of previously untreated HIV-infection during community-based HIV testing and counselling (HTC)
Recruitment	From February to May 2016 community-based HTC-campaigns will be

	conducted in randomly selected areas in the district of Butha-Buthe. Participants who test HIV-positive and who have never been on ART will be assessed for eligibility.
Major eligibility criteria	<ul style="list-style-type: none"> - ≥ 18 years of age - never been on triple ART - written informed consent
Intervention and Control	<p>Intervention: Same-day start of anti-retroviral therapy (ART) after diagnosis of HIV and spaced refill follow-up thereafter (2weeks – 6 weeks – 3 – 6 – (9) - 12 months)</p> <p>Control: Standard-of-care: at least 2 pre-ART visits for adherence counselling and laboratory work-up and after ART-start monthly refill-visits.</p>
Primary Endpoints	<ol style="list-style-type: none"> 3. Linkage to care within 3 months after diagnosis of HIV (participants attends the clinic for HIV care within 3 months after diagnosis of HIV) 4. Viral suppression 12 months after the diagnosis of HIV
Study Duration	February 2016 to September 2018

23 Background and literature review

In November 2014 the Joint United Nations Programme on HIV/AIDS (UNAIDS) declared the 90-90-90 targets for 2020 as an intermediate step towards ending the AIDS epidemic as a global health threat by 2030 [1, 2]. The targets are that 90% of HIV-infected individuals know their HIV-status, of these 90% receive sustained ART and 90% of these achieve viral suppression. If achieved, the 90-90-90 targets will result in 73% of all HIV-infected individuals having a suppressed viral load (VL) by 2020. The UNAIDS estimate that achievement of the 90-90-90 goal would result in a reduction of new HIV-infections from 2 million at present to 500'000 per year [3].

The rationale of the 90-90-90 targets lies in the preventive potential of ART. Mathematical modelling concludes that universal ART-coverage could stop the epidemic [4-6]. The landmark HPTN 052 study in 2011 showed that treatment of an HIV infected partner reduced the risk of transmission to the uninfected partner in discordant couples by 96% [7]. Long-term follow-up results from this study presented at the IAS-conference in July 2015 further confirmed the preventive effect of ART [8], but only if ART successfully suppressed VL [9]. Despite knowing since 2011 the preventative benefit of starting ART as early as possible, the positive effect of early ART for the infected individual has only been shown recently. The TEMPRANO trial conducted in Ivory Coast showed that starting ART before CD4-cells dropped below 500 cells/mL resulted in lower rates of severe infections and mortality [10]. The recent START-trial that was conducted in several countries across America, Europe, Africa, and Asia was stopped after an interim-analysis showed net health benefit for those starting ART before CD4-count dropped below 500 cells/mL [11]. Evidence from these two trials led the World Health Organization (WHO) to issue the recommendation on September 30, 2015 that anyone infected with HIV should begin ART as soon as possible after diagnosis [12].

This “treat all” strategy is now endorsed by a broad community of scientists, patient-organizations, donors, non-governmental organisations, civil-rights activists, and politicians, who signed the Vancouver Consensus in 2015 [13]. It bears, however, also unprecedented challenges to resource-limited settings where HIV is hyperendemic. First, there are practical challenges, such as the supply of tests, reagents, and drugs as well as the availability of sufficient human resources in the health sector [14]. Second, the “seek-test-treat” strategy poses implementation and clinical challenges [15], in particular to the Continuum of Care Cascade.

23.1 The Continuum of Care Cascade

The Continuum of Care Cascade (“the cascade”) involves the steps HIV-infected individuals have to take in order to achieve viral suppression. It starts at knowing the HIV-status, continues with linkage to care after a positive HIV-test, initiation of ART, uninterrupted continuation of ART (called retention in care), and ends with viral suppression documented through regular VL monitoring [16]. Already prior to announcement of the “treat all” approach, weaknesses in the care cascade often hampered the effectiveness of HIV-programs in resource-rich as well as resource-poor settings [17-19].

In Sub-Saharan Africa the care cascade is still quite far from the 90-90-90 targets. According to UNAIDS in 2013 only 45% of individuals were aware of their HIV-status, 39% of diagnosed individuals received ART and 29% of infected individuals on ART had achieved viral suppression [2]. Innovative, effective, and practical approaches for improving the treatment cascade are thus urgently needed [20, 21].

Achieving 90% HIV testing coverage

Uptake of HIV testing and counselling (HTC) in a standard clinical setting is usually low [22-24]. Several studies concluded that HTC-provision outside clinical settings in communities is feasible, acceptable and results in a higher uptake of HTC, particularly among populations that are usually hard to reach, such as men or first-time testers [22, 25-28]. Home-based HTC

shows high acceptance in the community [29-33], results in high uptake among hard to reach populations [22-28, 34-36], and is advocated by the WHO [37]. Our group conducted a cluster-RCT comparing home-based HTC to HTC in mobile clinics and found that home-based HTC resulted in an acceptance rate of 92.5% (versus 86.7% in mobile clinics), and reached more children, men, and first-time testers [38]. This trial showed that home-based HTC may be an effective tool to achieve 90% testing coverage but first feasibility, effectiveness, and efficiency of large-scale home-based HTC need to be established.

Achieving 90% linkage to care

Linkage to care after an initial positive HIV-test result has been described as the “Achilles’ heel” of the care cascade [39]. Most studies from Sub-Saharan Africa report linkage rates lower than 50% [40-44]. In the trial on home-based HTC mentioned above, only 25% of newly tested HIV-positive individuals accessed care within one month after the test [38]. Following community-based HTC-campaigns conducted by Population Services International (PSI) in Lesotho, about 45% of newly identified HIV-positive individuals linked to care within 3 months (PSI, personal communication). On the other hand, several observational intervention studies and trials from Sub-Saharan Africa reported that single interventions can indeed improve linkage to care: point-of-care CD4 count directly after a positive HIV-test [45], immediate start of cotrimoxazole prophylaxis [46], incentives such as food-assistance [47], extended post-test counselling, or community-workers accompaniment led to higher linkage rates [48-50]. However, two reviews critically noted in this context that controlled studies testing programmatic intervention-packages for improving linkage to care are still largely missing [51, 52]. Furthermore, it must be noted that interventions, such as intensified patient-accompaniment or food-support are resource intensive and may work in small NGO-driven projects, but are not sustainable on a larger scale [53].

In a systematic review addressing barriers for linkage to care, transport cost and distance were the most frequent factors for patients not enrolling in care after a positive HIV-test [54]. On the rationale of reducing travel-time and cost for patients, the CASCADE-trial will test the effectiveness of same-day home-based ART-initiation after a positive HIV-test together with a reduction of the frequency of follow-up visits to the clinic as a pragmatic and programmatically feasible approach to improve the HIV-cascade in the time of “test-and-treat” policies.

Achieving 90% viral suppression

Data on virologic outcomes from larger cohorts in Sub Saharan Africa are still scarce because of delays in scaling up VL-monitoring [55]. Most studies report viral suppression rates among adult patients between 80 and 90% [56, 57]. In Lesotho our group found a viral suppression rate ranging from 86.7% for adult patients on zidovudin/lamivudin/nevirapin regimen to 93.8% for patients on tenofovir/lamivudin/efavirenz [58]. In line with other studies reporting much lower viral suppression rates in children (likely due to the difficulty of maintaining adherence and drug-dosing especially in small children [59-62]), we found that only 72% of children on first-line ART for ≥ 6 months were virally suppressed [63].

Based on currently available data, 90% viral suppression seems to be the first of the 90-90-90 targets to be in reach – at least among adults. Of note, however, until now most studies reporting viral outcomes were cross-sectional and were conducted at tertiary clinics or in programs with particular support from non-governmental organizations. Moreover, all studies only enrolled patients who had started ART based on old starting criteria, such as CD4 cell count <350 cells/mL. In a treatment-for-all approach with rapid ART-initiation for all individuals after positive HIV-test, irrespective of their CD4-count, a higher share of patients may have poor adherence resulting in higher rates of virologic failures [20, 64, 65].

23.2 Rationale of the proposed study

On the way to achieve the 90-90-90 targets, the second 90, linkage to care, appears to be the most difficult one [39]. Our group recently demonstrated in a cluster-randomized trial that in home-based HTC campaigns in Lesotho more than 90% of the rural population accepts HIV-testing [38]. After a positive test result, however, linkage to care was found to be extremely poor (25%), even though newly tested individuals received on-site-post-test counselling, clinical staging and point-of-care CD4-testing. From a cohort analysis of our research group, we found that only about 80% of patients are retained in care 12 months after ART-initiation [66].

This fact unequivocally stresses the clear need for testing intervention packages that address linkage to and retention in care [52]. Time constraints and transport costs are frequently identified barriers for not accessing ART [54, 67] suggesting that reducing transport costs and travel time for patients prior to starting and while on ART has the potential to improve linkage and retention.

The proposed study will test an intervention package consisting of same-day, community-based ART initiation after a positive HIV test, and subsequently reduced frequency of ART visits during follow-up. Because the final goal of 90-90-90 is to achieve viral suppression in individuals who are HIV-infected, the trial will not only assess linkage to and retention in care but also the rates of viral suppression 12 months after HIV diagnosis.

24 Research Objectives (general and specific)

General aim of the proposed research project

The research project aims to test an intervention package for persons newly tested HIV-positive during community-based HTC campaigns. The intervention package consists of same-day community-based ART-start and subsequently spaced follow-up visits. This intervention package will be compared to standard of care (referring to facility for ART-initiation and subsequently monthly follow-up visits) in terms of linkage to care, one-year retention in care and viral suppression one year after the test result.

24.1 Primary Objectives

To compare between the intervention and the control arms

7. Linkage to care within 3 months after HIV-diagnosis
8. Viral suppression 12 months after HIV-diagnosis

24.2 Secondary objectives

To compare between the intervention and the control arms

- j.) 12-month mortality and loss to follow-up
- k.) Clinical outcomes at 12 months: haemoglobin-level, CD4-cell count, body-weight, diagnosis of new clinical WHO 3/4 events
- l.) Viral suppression rates 6 months after ART-initiation

24.3 Exploratory objective

To explore feasibility of achieving 90-90-90 in the study areas and resources needed.

24.4 Objectives of nested studies 1 & 2

See section -, page 24

25 Research Design and Methods

25.1 Overview of design characteristics

Primary Purpose: Health Services Research

Type of study: prospective randomized-controlled study

Number of study-arms: two (1 intervention arm, 1 control arm)

Allocation: 1:1 randomization

Intervention Model: Parallel Assignment

Masking: Open Label

25.2 Place of study

The study will be conducted in the district of Butha-Buthe, more specifically within the catchment areas of the following six health facilities: Butha-Buthe Government Hospital, Seboche Mission Hospital, Boiketsiso Health Center, Rampai Health Center, Ngoajane Health Center, Linakeng Health Center. All facilities are in an already established close collaboration with SolidarMed.

SolidarMed, the Swiss Organization for Health in Africa, is a not-for-profit organization supporting public and faith-based facilities in Lesotho in the delivery of ART since 2005 in the districts of Butha Buthe and Thaba Tseka. SolidarMed is working within the national health system with the aim to improve health for the population in its intervention area by strengthening integrated primary health care and adding to new knowledge and evidence.

25.3 Intervention and Control

Intervention

The intervention-package entails 2 major interventions. Intervention 1: same-day clinical and laboratory assessment with proposition of same-day ART-start after a new HIV-diagnosis.

Intervention 2: reduced frequency of follow-up visits after ART-initiation (for more detailed description see section 8.10, page 16).

Control:

The control-group follows the standard-of-care in Lesotho that is similar to most settings in Sub Saharan Africa. Participants newly tested HIV-positive who are in the control group receive post-test counselling and a referral letter with an appointment at their health facility. After having received baseline-assessment and at least 2 adherence counselling sessions at different days at the facility, they qualify for starting ART (for more detailed description see section 8.10, page 16).

25.4 Endpoints

25.5 Primary endpoints

3. Linkage to care within 3 months

Definition: participant attends the clinic for follow-up at least once within 90 days after HIV-diagnosis

4. Viral suppression 12 months after the positive HIV-test result during the home-base HTC-campaign

Definition: 11 to 14 months after diagnosis of HIV-infection the participant has a VL<100copies/mL.

25.6 Secondary endpoints

4. 12-month mortality and loss to follow-up

Definition “loss to follow-up”: participant has not attended the clinic for follow-up between months 11 and 14 after the positive HIV-test

Definition “one-year mortality”: participant has died < 365 days after the positive HIV-test result

5. Clinical outcomes 12 months after the positive HIV-test result

Definition “clinical outcomes”: Change in values of body-weight (kg), CD4-cell count (cells/mL), and haemoglobin (g/dL) between day of positive HIV-test result and 12-month follow-up visit (11 to 14 months after positive HIV-test result); Number of newly recorded clinical WHO-stage 3 or 4 events between baseline and 12-month follow-up visit (11 to 14 months after positive HIV-test result)

6. Viral suppression 6 months after ART-initiation (\neq after positive HIV test result)

Definition “viral suppression”: VL < 100copies/mL at 5 to 7 months after ART initiation

25.7 Exploratory endpoints

4. Testing coverage achieved through the community-based HTC-campaigns (see nested study, page 24)
5. ART coverage achieved one year after testing-campaigns
6. Resources needed to achieve the exploratory endpoints 1&2

25.8 Eligibility

Inclusion criteria

- HIV infection newly diagnosed during community-based HTC-campaigns
Comment: In line with the new WHO-recommendations issued in September 2015 [12], in this trial all HIV-infected persons are eligible to start ART, irrespective of their CD4-count.
- Never been on triple-ART (women who once received mono- or bi-therapy as part of previous treatment for prevention of mother-to-child transmission but never received ART consisting of 3 drugs simultaneously are eligible)
- Lives and/or works in the district of Butha-Buthe and declares to seek follow-up at one of the 6 health facilities involved in the study
- Age \geq 18 years
- Signed written informed consent

Exclusion

- Pregnant or breast-feeding
Rationale for excluding pregnant women: Pregnant women should start ART as soon as possible to minimize the risk of mother to child transmission. Pregnant women who are tested HIV-positive during recruitment will be cared for as per guidelines, with close follow-up and fast-track start of ART, following the national guidelines of Option B+.
- Already enrolled in chronic care for another disease, such as tuberculosis or diabetes
- Clinical WHO-stage 4 or active tuberculosis
- Positive cryptococcal antigen test

25.9 Conducting community-based HTC-campaigns

The HTC campaigns serve for recruitment of participants but are at the same time an observational sub-study nested within the CASCADE-study (see nested study 1, section 9.1, page 24). Three types of community-based HTC-campaigns will serve for recruitment: 1) rural home-based HTC; 2) urban home-based HTC; and 3) urban mobile clinic.

Rural home-based HTC campaigns

Except for Butha-Buthe town, other areas are considered as rural. HTC-areas will be selected randomly from a list of eligible villages/sub-villages. To be eligible a village has to be clearly confined to the catchment area of one of the study facilities, have a size of 40 to 80 households, and not been exposed to a large HTC-campaign during the last 12 months. Rural HTC-campaigns will start as of end of February 2016 and are anticipated to last for 12 weeks. Campaigns may, however, be prolonged if the sample-size is not reached after the 12 weeks. The population of the selected areas will be informed through village chiefs two weeks prior the campaign starts. A team consists of 14 persons (8 trained and experienced

lay-counsellors, 2 nurses, 2 community-mobilisers or professional/senior counsellors and 2 drivers). Each team visits each area on two different days. The first day will be during the week, from Monday to Friday. The second day will be during the weekend or a holiday to reach household members who were absent during the first visit. The team has two sub-teams with the following members, roles and responsibilities:

- 1 community-mobiliser or professional/senior counsellor: supervises the lay-counsellors, ensures accurate conduct and documentation of HTC as well as collection of study-variables
- 4 lay-counsellors: visit households, conduct and document HTC
- 1 study-nurse: post-test counselling of newly diagnosed HIV-positive persons, enrolment of participants for CASCADE-study and baseline laboratory (CD4 count, hemoglobin, creatinine) for those allocated to the intervention arm
- 1 driver: responsible for logistics

The structure and functions of 2 sub-teams are similar. The purpose of dividing sub-teams is to have better coverage.

First visit to a testing area during the week:

The team arrives in the study area at 11:30am, informs the village chief about its arrival and then starts systematic testing of all households in the pre-defined area by going from door to door until sunset (around 6pm). Under coordination and supervision of the community mobiliser, households are visited by one lay-counsellor. At the household the lay counsellors proceed as follows:

- 10 Introduction of himself/herself and the HTC-campaign.
- 11 Ask the head of household or representative for written informed consent to assess number of household-members and uptake of HTC among household-members (see section 16.1, page 33). If the head of household refuses his/her household to participate, the lay-counsellor leaves the house and proceeds to the next household.
- 12 Assessment of total number of household members and number of household members currently present
- 13 From each household member the following data will be collected: name, age, sex, currently present in household (see section 8.12, page 19)
- 14 For all household members who are present: HIV-status, previous HIV-tests, information about HTC and proposition of HTC.
- 15 Informed consent to HTC from each household-member who agrees to HTC (this is the national HTC consent form every person has to sign before HTC is conducted)
- 16 Conduct of HTC according to national guidelines [68].
- 17 If HIV test is negative, lay counsellor provides post-test counselling. If HIV-test is positive the lay-counsellor contacts the study-nurse of the team. The study nurse will then assess the participant clinically and propose enrolment in CASCADE-study if eligible (for enrolment CASCADE-trial, see section 8.10 on page 16).
- 18 Before leaving the household the lay-counsellor informs the persons present that he/she will again return next weekend to propose HTC to household members who were not present at the first visit.

Second visit to a testing area during a weekend or holiday

At the second visit to a HTC area, each lay-counsellor goes to the same households he/she attended during the first visit. The lay-counsellor enquires about household members who were absent during the first visit. If household members who were absent during the first visit are now present, the lay-counsellor follows again steps 5 to 8 of the first visit for these household members.

Urban home-based HTC campaigns

Similar to rural areas, areas within Butha-Buthe town will be randomly chosen for home-based HTC. Information about the dates and the campaigns will be spread through urban community councils and the local radio. Again each household will be visited twice (during the week and on the weekend). A team consisting of 1 professional counsellor, 1 study nurse, 4 lay-counsellors and 1 driver starts HTC at 11:30 am, following the same principles as for rural home-based HTC described above. The urban home-based HTC campaigns will be conducted in parallel to the rural campaigns.

Urban mobile clinics HTC

In addition to the home-based approach, HTC is proposed in mobile clinics stationed at different places within Butha-Buthe town (i.e. taxi-rank, in front of the Mall, etc.). Exact localisation of the mobile clinics will be discussed and agreed upon with the local authorities. The mobile clinics consist of 2 tents where 2 lay-counsellors and a nurse provide HTC. The population will again be informed through radio and community councils about exact location and dates for HTC at the mobile clinics. If a person enters the tent and consents to participate, HTC will be conducted according to national guidelines [68].

In case of a positive HIV test result, the nurse will assess the person and propose participation in the CASCADE-study if eligibility criteria are met (see below). HTC-clients from the mobile clinics are only eligible for the CASCADE trial but not for nested study 1 & 2.

25.10 Recruitment for CASCADE-study

In case a person tests positive during the HTC-campaigns, the study nurse assesses if the person presents with any acute illness and if he or she is eligible for participation in the CASCADE-study. In case the person is eligible and consents to participation, they will be randomized using a stratified randomization list, generated by an independent statistician. Randomization will be at household level and stratified by HTC-area. Reason for randomizing at household level is that in case more than one individual tested HIV-positive it would not be feasible for individuals of the same household to participate in different arms due to a high risk of cross-contamination between the arms.

Intervention arm:

The study nurse assesses the participant's clinical WHO-stage and performs CD4-count (PIMA® Alere), creatinine (StatSensor Creat®, Nova® Biomedical) and hemoglobine (Hemocue®, HB301) as point-of-care tests. Thereafter, the participant receives a standardized short adherence counselling. **Thereafter the nurse has to judge if the participant has understood the implications of lifelong ART. If yes, the participant is offered to start ART the same day. He/she may however decide to start in the coming days or not to start for the moment (see page 10 of case reporting form of the intervention group with the title: "Documents for participants of the CASCADE-study; Study Arm: Same-day ART start and spaced follow-up visits"). If the participant is ready to start the same day or in the days to come, he/she receives a first box of antiretrovirals.** The participant Choice of ART-regimen follows national guidelines [69, 70]. In addition, and in line with national and WHO guidelines, participants with a CD4-count < 350cells/mL will receive cotrimoxazole prophylaxis. Participants who have a CD4-count < 100cells/mL will receive testing for cryptococcal antigen. In case of a positive result, the participant will be referred for fluconazole therapy according to guidelines and excluded from the study.

The participant will receive one box of his/her ART-regimen containing drugs for 30 days and an appointment for a first clinic visit in 12 to 16 days.

At the first clinic visit, the participant receives a second adherence-counselling. If the participant is clinically stable at this first visit, the next follow-up visits will be 6 weeks, 3, 6, 9 and 12 months after

ART-initiation to reduce travel time and transport cost. Participants are; however, encouraged to visit the clinic any time in case of problems or questions.

Control arm:

Management follows national guidelines [68, 69]. After post-test counselling and assessment for any acute illness, the participant receives the national standard referral form, together with an appointment at the nearest clinic.

The day the participant presents the first time at the clinic, he/she receives laboratory baseline-assessment (CD4-cell count, creatinine, haemoglobin) and a first adherence counselling session. The participant has then to return to the clinic a second time for a second adherence counselling and to receive the results of the laboratory baseline tests. If judged as “ready” by the counsellor, the participant may start ART at his/her second clinic visit. Once the participant has started ART, the first and second follow-up visits are 14 and 28 days, respectively, after ART start. Thereafter, follow-up visits are monthly until 6 months after ART start. If the participant is clinically stable, follow-up visits may then be spaced to 3-monthly intervals, but ART refill still must be collected on a monthly basis.

Tracing of participants

In both groups participants will be traced if they did not link to care 90 days after the HIV-test. Tracing will be done using the system in place (contact via village health worker or phone if available)

25.11 Consort flow-chart

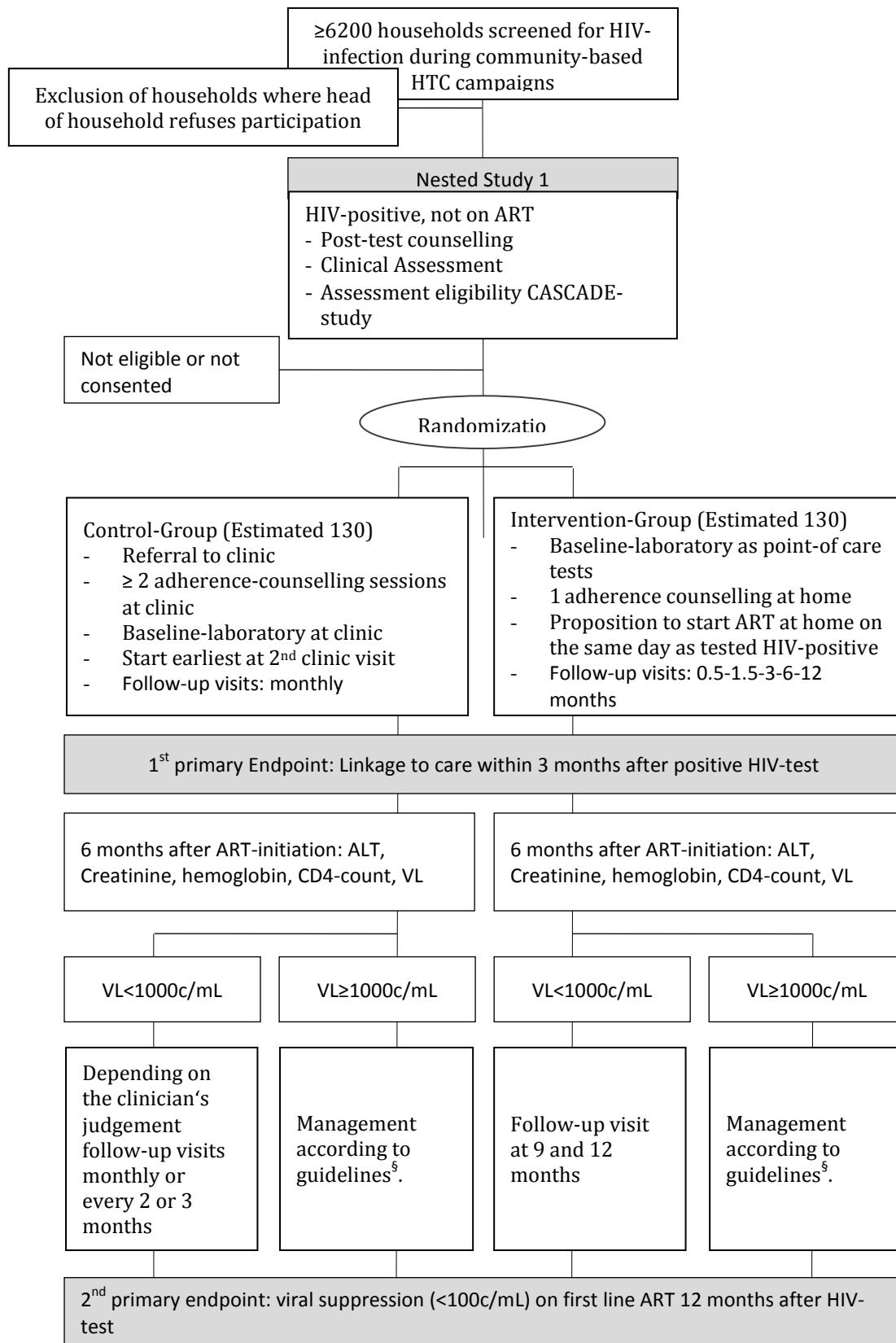


Figure 2 CONSORT flow-chart of the CASCADE-trial. VL: Viral load; HTC: HIV testing and counselling; ART: anti-retroviral therapy; ALT: alanine amino transferase.

§ participants with sustained un-suppressed viral load 8-12 weeks after enhanced adherence counselling will be switched to second-line ART as outlined in WHO- and Lesotho guidelines [69, 70].

25.12 Data collection and variables collected

Means of data collection

Data during the HTC-campaigns will be collected using a tablet-based electronic database.

Variables collected during HTC-campaigns

Variable	Type of variable	Comment
Household Data		
– Household ID		Anonymous identifier generated for each household
– Household location	GPS-coordinates of the household	To ensure the right household is identified at second visit
– Date of household visit	Date	
– Name head of household	String	The name will be encrypted and deleted after the HTC-campaign (see section 10.6, page 29)
– Consent of head of household or representative for participation of household in nested study 1	Binary (Y/N)	See information and consent form section 16.1, page 33
Data collected for each household members		Only if head of household provides written informed consent to nested study 1
– Name	String	The name will be encrypted and deleted after the HTC-campaign (see section 10.6, page 29)
– Age	Continuous	
– Sex	Binary	
– Current location of household member	Present; not present but in the surroundings of the village (working in the fields, etc.); away for work in Lesotho; away for work in South Africa; at school ; away, unknown where	
If household-member present		
– HIV-status	Categorical (HIV-negative; HIV-positive on ART; HIV-positive defaulted ART; HIV-positive never been on ART; unknown)	
– Previous HIV-test	Categorical (<12 months ago; ≥12 months ago; never)	
– HTC-uptake	Binary (Accepted; Declined)	
– HTC-result	Negative; Positive; Indeterminate	
If tested HIV-positive		
– Eligible for CASCADE-study	Binary (Y/N)	

Baseline-variables collected for persons enrolled in CASCADE-study

Please refer to the case-reporting forms attached to the submission of the revised protocol:
Intervention: Documents for participants of the CASCADE-study; Study Arm: Same day ART-start, spaced follow-up visits

Control: Documents for participants of the CASCADE-study; Study Arm: Same day ART-start, spaced follow-up visits

Variable	Type of variable	Comment
– Study-ID	Integer	From randomization list
– Education of participant	Ordinal (none, primary, secondary, tertiary)	
– Marital status of participant		
– HIV status of partner	Categorical (not known, tested negative < 3 months ago, positive not on ART, positive on ART, positive, no known if on ART)	
– Number of children	Continuous	
Pre-ART assessment		
– Clinical WHO-stage	Ordinal (I-IV)	Assessed by the study nurse
– Body-weight of participant (kg)	Continuous	
– Clinic where participant wishes follow-up	Categorical	Has to be one of the 6 study-clinics. Otherwise participant is not eligible for study (see section 8.8, page 14)
Laboratory baseline-assessment		
– CD4 cell count (cells/mL)	Continuous	Is done as point-of-care in the intervention group. For the control group laboratory assessment is done at the laboratories of Butha-Buthe or Seboche Hospital, once participant is linked to care.
– Creatinine (mmol/mL)	Continuous	
– Hemoglobine (g/L)	Continuous	
Nested study 2		
– Lipid-panel (total cholesterol, LDL, HDL, triglycerides)	Continuous	See section 9.2, page 26 In both groups blood will be drawn and then analysed in the evening.
– Glycosylated hemoglobine (HbA1c)	Continuous	

Follow-up variables for persons enrolled in the CASCADE-trial

Please refer to the case-reporting forms (see previous page)

Months	Follow-up period after HIV-test			
	0	3	5-6	11-14
Adherence		X	X	X
Body-weight	X	X	X	X
Clinical assessment	X	X	X	X
CD4-cell count	X		X	X
Haemoglobin	X		X	X
Creatinine	X		X	X
ALT	X		X	X
Viral Load			X	X
Lipid-panel	X			X
HbA1c	X			X
Plasma for storage (see section 8.13)	X			X
Assessment first primary endpoint		X		
Assessment second primary endpoint				X

25.13 Collection and storage of biologic material

Participants of the CASCADE-trial undergo phlebotomy at recruitment, 6 and 12 months after having started ART. In case the participant is allocated to the intervention group baseline, tests (CD4-count, haemoglobine and creatinine) are done as point-of-care. In case the participant is in the control group these tests will be done when he or she presents at the clinic for the first time. For nested study 2, blood is taken at enrolment and analysed the same day in the evening at the facility. At recruitment and after 12 months follow-up, one plasma-sample of the participant will be stored at -80 degrees at the laboratory of Butha-Buthe hospital. In case a participant presents with virologic failure at follow-up, genotype resistance testing will be performed. In case of the presence of resistance mutations in the follow-up viral load, the stored baseline plasma sample will be analysed using next generation sequencing to determine if the participant had primary resistance or if the resistance was acquired while on ART. Plasma samples will be stored at -80 freezers in Butha-Buthe Hospital for unlimited time. In will only served for viral analyses. In case researchers wish to do any other additional analysis in the plasma, an amendment will have to be submitted to the Ethics Committee of Lesotho.

25.14 Confidentiality of processed data

Processed data will be coded and anonymous. Stored blood samples will only contain the study-ID.

Handling of participant names during HTC

Because a lay-counsellor visits each household twice, he or she has to know the names of household members to assess presence and absence at each visit. Names of study-participants will be collected but encrypted for storage on tablets. After completion of second household visit the database will delete automatically all names and only keep the anonymous ID codes.

Handling of participant names during CASCADE-study

Apart from the informed consent form, all study documents will only contain the study-coded. Facility records will be handled as all other records for patients on ART.

25.15 Adverse Events (AEs) and Serious Adverse Events (SAEs)

Prescription and use of anti-retroviral drugs will follow current national guidelines of Lesotho [69]. All anti-retroviral drugs used in Lesotho have a well-established safety profile. Most frequent adverse events are summarized on page 40 of the *Lesotho National guidelines on the use of antiretroviral therapy for HIV prevention and treatment*, 4th edition, 2013 [69] and on page 138 of the *Consolidated Guidelines on the Use of antiretroviral Drugs for treating and preventing HIV Infection* of the WHO [70]. Before conduction of the study, nurses of the study-facilities will be re-trained on the national guidelines and potential AEs and SAEs of ART. In case of AEs the nurse has to document the AE and the action taken on the follow-up file. In case of SAEs the facility nurse must inform the study-physician immediately.

25.16 Sample-size and analytic plan

The sample size for this trial was based on the primary endpoint of linkage to care 3 months after HIV diagnosis. We expect 3-month linkage to care rates of 40% in the control arm and 60% in the intervention arm. As the trial is randomized at the household level, we require a total of 260 households with at least one HIV-positive participant to detect a 20% increase in linkage to care assuming a Type I error rate of 5% and power of 90%. With an estimated uptake of HTC of 94%, a prevalence of previously undiagnosed HIV-infection during home-based HTC-campaigns of 5%, and a 10% trial participation refusal rate or choice of alternative health facility, we need to visit 6200 households to achieve the desired sample size of 260 households with at least one HIV-infected person not on ART. In case more than one HIV-positive individual is diagnosed in the household, all individuals meeting eligibility criteria will be included. This will only serve to increase the power of the study. With the proposed sample size above, we will have sufficient power to test the second primary endpoint of viral suppression at 12 months. As those not linking to care will be considered as failures, we expect viral suppression rates of 25% in the control arm and 45% in the intervention arm. With 130 individuals per arm, we will have 93% power to detect a difference of 20% in viral suppression rates.

The study will be analysed using mixed effects models that account for the clustering of the households. Factors used in stratifying the randomization will be included in the models. Linkage and viral suppression rates between the control and intervention arm will be presented with odds ratios and 95% confidence intervals.

25.17 Expected benefit from the study

Community-based HTC campaigns will be one important intervention towards reaching the 90-90-90 goals as it is a key strategy to access “hard-to-reach” populations for HTC [71]. Despite recent popularity of home-based HTC campaigns, linkage after a positive HIV-test continues to be uniformly poor in Sub Saharan Africa [39, 72] and interventions improving linkage are greatly needed [73]. The intervention tested in the CASCADE-study could represent a feasible add-on to the current practice of health-care-provider teams in the villages providing HTC. If proven to be effective, increases in the intervals between follow-up visits in stable patients has the potential of saving resources within the health system. Furthermore, if same day home-based ART start and prolonged intervals between ART visits should prove superior, this strategy will have the potential to be scaled up nationally and internationally in similar settings and to be integrated into guidelines and policies.

25.18 Strengths and limitations

Strengths

- One of the first randomized controlled studies addressing the HIV care cascade
- Assessment of the whole cascade from HTC to viral suppression
- Includes urban (Butha-Buthe town) as well as rural areas
- Includes catchment areas of primary and secondary level facilities

- Is implemented in the context of a district health system and not in a research setting

Weaknesses

- The trial only includes persons tested during community-based HTC. It does not consider persons who receive their test at the facility. The population tested through home-based HTC may therefore differ from the one reached through facility-based HTC.
- The trial is not implemented in the whole district but selected facilities
- Persons, who are not at home during one of the two visits, cannot be enrolled.
- Children are excluded from this study
- After enrolment persons may decide to access treatment outside the district of Butha-Buthe. This may lead to an underestimation of linkage to and retention in care.

26 Nested studies within the CASCADE-trial

The trial embraces two nested studies. Both are observational and do not include any additional intervention.

26.1 Nested Study 1: Feasibility and resources needed for achieving 90% HIV-testing coverage in rural and urban areas in Lesotho

This study is an observational analysis of the home-based HTC-campaigns that are conducted for the recruitment of participants in the CASCADE-study.

Background/rationale

In the cluster randomized trial that our group conducted in the districts of Butha-Buthe and Thaba-Tseka in Lesotho in 2011, home-based HTC achieved > 90% HTC uptake among persons encountered at their homes during the campaigns. However, the trial left some doubt about the appropriateness of home-based testing for achieving high HTC-coverage in the population: Home-based HTC appeared to reach an underexposed population yielding only very few newly detected HIV-infections leading to a high cost per newly detected infection (495 USD) [38]. A likely reason for this is that the campaigns were conducted during weekdays where the working-population was not at home. Additionally, the trial was only conducted in very remote rural areas.

While conducting the home-based HTC-campaigns to recruit participants of the CASCADE-study, this nested study will now specifically assess testing coverage through home-based HTC on week- as well as weekend-days in rural and urban areas of Butha-Buthe district and assess the resources needed to achieve this coverage.

Main objective

To assess the percentage of the population tested for HIV in predefined geographical areas after two days of home-based HTC campaigns per area.

Secondary objectives

5. To assess ART coverage in the areas where the campaigns are conducted
6. To assess resources needed per individual tested and per individual testing HIV-positive
7. To assess HTC uptake
8. To assess clinical and immunological stage of individuals newly tested HIV-positive

Design

Cross-sectional, observational

Eligibility

All households of the randomly selected pre-defined HTC areas

Main outcome

- Testing coverage in a pre-defined area after two one-day visits

Secondary outcomes

- Resources needed to test one person and resources needed to find one HIV-infected person who is not yet enrolled in ART.
- HTC-uptake (acceptance of HTC among persons proposed HTC during the campaigns)

Procedures and data-collection

See section 8.9 on page 14.

Expected benefit from the nested study

This study will provide practical information on the feasibility to conduct home-based HTC on a larger scale and achievability of 90% testing-coverage. It will assist the Ministry of Health of Lesotho as well as its implementing partners in the planning of future HTC-campaigns. Study results will be of interest for governments and non-governmental organizations in similar settings in Southern Africa.

Limitations of the nested study

The assessment of the number of persons living in the households enrolled in the study relies on the reporting of those household-members encountered during the campaigns. Depending on the definition used, household-sizes may vary [74]. As many Basotho frequently migrate for labour to other regions within Lesotho or to South Africa, defining who is a household member may be difficult in some situations. For the purpose of this study, household-members will have to acknowledge the same household-head and to have spent at least one week or at least 3 weekends living in the house during the last 3 months. This accounts for the fact that nowadays most persons who work legally in South Africa, i.e. in the mines, receive regularly prolonged weekends that allow them to visit their families in Lesotho. The situation for those who work without a permit is indeed different. They may be absent from home for longer periods and are not included in the definition for household-members used in this study.

Another limitation is that testing coverage has to be estimated based on persons encountered at one of the two cluster visits. Persons who are absent at both visits will be coded as not tested/not on ART. They may, however, have tested at another occasion, i.e. at their working-place.

26.2 Nested Study 2: Lipid- and glucose profile in adult HIV-infected and non-infected persons in Lesotho and changes after initiation of anti-retroviral therapy

Background/rationale

ART has transformed HIV into a chronic disease that still affects the lives of millions although it no longer necessarily shortens their life expectancy [75]. As a result, the number of HIV-infected persons who are 50 years and older is increasing also in Sub Saharan Africa. In 2014, the UNAIDS estimated there to be about 1.4 million HIV-infected persons aged 50 years and older living in Southern Africa [76]. Therefore monitoring of risk-factors for cardiovascular diseases is becoming increasingly important, particularly for this group. The CART-1 study [77] revealed that among women on first-line ART in Lesotho 25% fulfilled the definition of metabolic syndrome [78] and 9.6% of women and 14.2% of men on first-line ART had an unfavourable lipid-profile, defined as an LDL/HDL ratio > 3.0 (unpublished). Whereas several cross-sectional studies observed an association of ART with metabolic abnormalities in Sub-Saharan Africa [79-84], there are very few longitudinal studies describing changes in lipid-profiles over time in Africa and those that did were in older, often outdated first-line regimens that contained thymidine-analogues such as stavudine or zidovudine [85, 86].

Objectives

- To assess changes in lipid-profile and levels of glycosylated hemoglobin (HbA1c) in HIV-infected individuals after starting first-line ART in the CASCADE-trial;
- Prevalence of impaired fasting glucose, diabetes and dyslipidemia in ART-naïve HIV-infected and non HIV-infected persons

Design

Cross-sectional, followed by prospective cohort study among those participants who start ART

Eligibility

- All persons enrolled in CASCADE-study
- Age- and sex-matched individuals tested HIV-negative during the community-based HTC-campaigns

Main outcomes

- Prevalence of impaired fasting glucose, diabetes and dyslipidemia in ART-naïve HIV-infected and non HIV-infected persons (age- and sex-matched non HIV-infected controls are randomly selected among those who test negative during home-based HTC)
- Changes in pre-ART lipid-profile and HbA1c-level at 12 months post ART initiation

Sampling and data-collection

HIV-infected individuals: As part of the baseline-assessment blood-samples of all participants of the CASCADE-study will be used for measurement of lipid-panel and HbA1c (see page 19). In those starting ART lipid-profile and HbA1c will again be assessed at 12-months follow-up (see table on page 21).

Not HIV-infected individuals: For each individual enrolled in CASCADE-study two age- and sex-matched HIV-negative individuals will be randomly selected for assessment of lipid-status and HbA1c. The tablet-based database used during the HTC-campaigns will randomly select among age- and sex-matched individuals and indicate if measurement of lipid-profile and HbA1c should be conducted.

Impact of the nested study

Description of metabolic changes under the currently recommended first-line ART-regimen will help to plan future interventions aiming at cardiovascular prevention among the ageing HIV-population in similar settings.

Limitations of the nested study

Whereas lipid-profiles are assessed in HIV-infected ART-naïve and non HIV-infected persons during the cross-sectional study, changes in lipid-profiles will only be assessed among HIV-infected persons starting ART and retained in the trial after 12 months. Re-visiting non HIV-infected persons one year later for assessing potential changes would be too resource intensive.

27 Ethical Considerations CASCADE-study

27.1 Overview on consent forms used in the CASCADE-study

The whole study-project incorporates 4 different consent forms:

1. **Household consent form:** During the HTC-campaigns this form has to be signed by the head of household or his/her substitute to allow the HTC-team to enter the household, ask for present and absent household members and propose HTC to those who are present. (see the household-consent form entitled: “informed consent form: Home-based HIV Testing and Counselling (nested study 1 of CASCADE-study) - V1.1; 08.12.2015”)
2. **National HTC consent form:** This is simply the national consent form any individual in Lesotho has to sign before HTC is conducted.
3. **Informed consent for participation in the CASCADE-study:** This form is for persons who tested HIV-positive during the HTC-campaign and who are enrolled in the CASCADE main study (same-day ART start versus standard of care). This consent form is incorporated in the case-reporting forms submitted with the revised version of the protocol (page 2 to 6 of the case-reporting form with the title “Documents for participants in the CASCADE-study”).
4. **Consent form for nested study 2:** For the nested study 2 (see page 26) HIV-negative controls need to be asked for consent to perform venous blood-draw (see case reporting form entitled “Documents for HIV-negative controls in lipid- and HbA1c survey”)

27.2 Ethical conduct of the study

The research project will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki (DoH) and The Principles of Good Clinical Practice (GCP).

27.3 Recruitment

Individuals who test HIV-positive during the HTC-campaign and have never been on ART will be proposed to participate in the study. In the information-form (see page 33, section 16.1) it is emphasized that the individual is entirely free to participate or not and that one can terminate or withdraw consent at any time of the study without any immediate or future negative effects regarding the services provided.

27.4 Risk to participants

Participants of the study do not undergo any experimental therapy. Medical management of HIV-infection will follow national guidelines and standards. No additional risk compared to standard management has to be expected.

The procedure of blood draw for laboratory analyses will be done respecting all hygiene and safety regulations in order to avoid any harm to participants or project staff. Handling of blood samples by the project and the laboratory staff will be done according to standard safety regulations.

27.5 Informed consent

The study-nurse, seconded by a lay-counsellor, will explain the information sheet for participants. Once all open questions have been clarified and if the person agrees to participate, he or she has to sign the informed consent form. In case of illiteracy a thumb-print will be used instead and a witness chosen by the participant has to sign the form (see informed consent form on page 33).

27.6 Handling and storage of Plasma

At enrolment three 4mL blood tubes (3 EDTA) will be collected. One tube will be used for baseline-analyses (CD4 cell-count, haemoglobin, creatinine, lipid-profile, HbA1c, cryptococcal antigen if CD4<100cells/mL). Two tubes will be centrifuged and only plasma will be kept for storage and frozen at -80 degrees at Butha-Buthe laboratory. In case of treatment failure at 6 or 12 months, plasma will be used to do genotype resistance testing (see page 21).

We anticipate that from mid-2016 genotypic resistance testing will be functional at Butha-Buthe laboratory. Only in case resistance testing has to be done in a laboratory outside Lesotho, samples will be prepared in Butha-Buthe and then shipped to Department of Biomedicine – Haus Petersplatz, University of Basel, Switzerland. The same institute performed virologic analyses for the research project entitled “*Chronic non-communicable and selected communicable comorbidities, virologic failure and resistance among patients on antiretroviral therapy in rural Lesotho*” (CART-1 study) that had been reviewed by the National Ethics Committee of the Ministry of Health of Lesotho in 2014 (Protocol Reg. number (for RCU): 01-2014). In case shipment outside Lesotho will be needed, an amendment including a materials transfer agreement will be submitted to the National Ethics Committee prior to shipment.

27.7 Confidentiality of HTC

Confidentiality of HTC at home

The HTC-team has longstanding experience in providing home-based HTC [38]. Home-based HTC will be conducted following the recommendations of the WHO [37]. In particular in rural places, where houses stand alone, experience showed that ensuring confidentiality of HTC is often easier than in mobile clinics where other persons are queuing outside the tent. A challenge is, however, confidentiality between household members. In practice many families wish to be tested as a group. This approach of family-testing will be encouraged. But there are situations where household members wish to test individually. In these cases the lay-counselor will assess together with the household members in which room or additional house individuals can be tested in a confidential environment.

“Family testing and sero-discordant couples

As mentioned in the paragraph above, family testing and couple testing will be encouraged. In case a couple or family wish to test together, pre-test counseling will address the possibility of sero-discordance and the importance of a supportive attitude towards the HIV-infected partner or family member. During couple-testing individuals are given the opportunity to consent to or refuse sharing of their HTC results. Moreover, even if couples chose to disclose their test results pre-test risk assessment will be done individually and confidentially. In case an individual tests HIV-positive, the study-nurse will be called to assist in post-test counseling. In case of sero-discordance and need for further support of the HIV-infected individual and his/her family, a professional counselor will be involved. In case of sero-discordance post-test counseling will focus on medical aspects, such as condom-use and importance of viral suppression through ART to avoid transmission to the non-infected partner, as well as on the importance that family members support the infected individual. Un-infected partners will be advised to re-test in three and six months.”

Risk of discomfort after positive HTC result

Receiving a positive HIV test result is distressing – no matter if it happens during home-based or clinic based HTC. To ensure good post-test counseling, the lay-counselor will be assisted by the study-nurse for all individuals testing HIV-positive. In situations with particular

distress or problems a professional counselor will be involved. If wished so, the infected individual may be linked to a village health worker.

27.8 Confidentiality of data

Database during HTC-campaigns

As outlined on page 21 the database used during HTC-campaigns will contain the names of the household members. The rationale for having the names is to allow the lay-counsellor at the second visit to know who was absent at the first visit. The tablets that will be used for data-collection will be password-protected. The software developed for tablet-based data-entry during the HTC-campaigns will, however, delete the names once the second household-visit has been completed.

Database for CASCADE-study

The database of the CASCADE-study will be coded and does not contain any names. The study-nurse will have a master-file kept in the SolidarMed office in Butha-Buthe, linking the study-ID to participant's name and address. The master-file will only be accessed in case the study-information is needed for clinical management of the study-participant.

Blood tubes

All blood samples will be labelled with the study-ID.

Medical records of participants

During the HTC-campaign as well as during follow-up of persons tested HIV-positive at their clinics, all regular national medical records will be filled out. All persons who agree to do HTC will have to fill in the national HTC consent form. This form contains the name of the person who provides consent to testing. In case of a positive test-result the person receives a national referral form. This form again contains the name. For those who enrol in care the usual national ART-file will be opened. The file contains pre-ART- and ART-number as well as patient names. National HTC-forms as well as ART-files of study-participants will be handled exactly the same way as those from individuals who are not part of the study, respecting good practice of medical confidentiality.

27.9 Role of sponsor

The study is supported by the Swiss Foundation *Stiftung für Infektiologie beider Basel*. This is an independent foundation aiming at supporting research in the field of infectious diseases. The study is embedded in the SolidarMed country programme and thus benefits from logistics and human resources from SolidarMed Lesotho.

27.10 Compensation

This study causes no substantial additional risk or cost to the participants. Therefore we do not pay compensation to the participants.

28 Ethical considerations nested study 1

Nested study 1 (see section 9.1, page 24) is a purely descriptive study describing number of persons tested per household in the areas where the home-based HTC-campaigns will be conducted. Home-based HTC-campaigns are common in Lesotho and conduct of the campaigns will be according to national and international standards of practice [37, 68]. Conduction of this study needs to respect sovereignty of the household as well as the household members. In a first step the lay-counsellors visiting a household will approach the head of household or – if absent – his or her representative informing about the HTC-

campaigns and the data that will be collected at household-level. The head of household/representative has first to provide informed written consent before household data can be included in the study (see section 16.1 on page 33). If the head of household consents to the participation the lay-counsellor will collect in a second-step information on household members present and absent. HTC is then proposed to each household-member individually. Each household-member has to provide informed written consent to HTC. For this purpose the national HTC consent form will be used.

29 Ethical considerations nested study 2

International guidelines recommend monitoring of blood-lipids for persons with HIV-infection [87]. For participants of the CASCADE-trial nested study 2 does not lead to any additional blood-draw.

For participants who test HIV-negative during the HTC-campaigns and who are randomly selected for participation in nested study 2, measurement of lipid-panel will require an additional venous blood-draw of one 2ml EDTA-tube. Prior to blood-draw HIV-negative participants will be informed and asked for written informed consent, using a specific informed consent form (see case reporting form entitled “Documents for HIV-negative controls in lipid- and HbA1c survey”).

30 Plan for distribution of results

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-Butha. At national level the national research symposium at the Ministry of Health will serve as a platform to share the results and discuss their implications. International scientific conferences, such as the yearly conference of the International AIDS Society and publications in scientific journals will serve for results dissemination.

31 Timelines of the study

	2015	2016				2017			
	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Start of VL-monitoring in Butha-Planning/preparation of HTC-campaigns									
Pre-test									
HTC-campaigns (recruitment)									
Follow-up									
Assessment 1st primary endpoint									
Assessment 2nd primary endpoint									
Results nested study 1									
Results nested study 2									
Results dissemination									

32 Budget of the study

The research project will benefit from the infrastructure provided by SolidarMed. The budget below provides an overview of additional cost caused specifically by the study. These cost are covered by the independent Swiss Foundation “Stiftung für Infektiologie beider Basel”.

Equipment	LSL
Laboratory point-of-care tests (CD4, hemoglobine, creatinine, lipid panel, HbA1c)	140000
Data-management (programming of database, tablets, etc.)	150000
Viral Load tests	215600
Stationary and other consumables	22000
Human Resources	
Study nurse (18 months)	360000
20 lay counsellors for 3 months (HTC campaigns)	70000
Food, perdiem, accommodation study team during HTC campaigns	150000
Training study-team	22000
Study dissemination at national level	10000
<u>Total</u>	<u>1139600</u>

33 Appendices

33.1 Informed consent of the head of household for participation in the HTC-campaign

For English and Sesotho version of informed consent form please refer to documents attached to this protocol with the following title:

- Informed_Consent_Household_participation_Nested_Study_1_English_V1.1.pdf
- Informed_Consent_Household_participation_Nested_Study_1_Sesotho_V1.1.pdf

33.2 National consent form for HTC

The national HTC consent form of the Ministry of Health of Lesotho will have to be signed by all individuals prior to conduction of HTC. A scan of the form is attached to the submission of this protocol. See National_HTC_Consent_Form.pdf

33.3 Informed consent for participation in the CASCADE study

For English and Sesotho version of the informed consent form please refer to the documents with the following title:

- Informed_Consent_CASCADE_English_V1.1.pdf
- Informed_Consent_CASCADE_Sesotho_V1.1.pdf

33.4 Informed consent for HIV-negative participants of the nested study 2

For English and Sesotho version of the informed consent form please refer to the documents attached to this protocol with the following title:

- Informed_Consent_Nested_Study_2_English_V1.1.pdf
- Informed_Consent_Nested_Study_2_Sesotho_V1.1.pdf

33.5 List of study-staff and responsibilities

Please refer to the document attached to this protocol with the following title:

- Staff_List_V1.0.pdf

33.6 Curriculum Vitae of investigators

The following CVs are submitted together with this protocol

- CV_Niklaus_Labhardt.pdf
- CV_Tracy_Glass.pdf
- CV_Christiane_Fritz.pdf
- CV_Kyaw_Thin.pdf
- CV_Ravishankar_Gupta.pdf
- CV_Thabo_Lejone.pdf
- CV_Isaac_Ringera.pdf
- CV_Bienvenu_Nsakala.pdf

33.7 Approval letter of the Swiss Tropical and Public Health Institute

A scan of the approval letter of the Swiss Tropical and Public Health Institute is submitted together with this protocol. The file name is: Approval_Letter_Swiss_TPH.pdf

33.8 Case-reporting forms for CASCADE-study participants

There are two different case-reporting forms (CRF). One for the intervention group and one for the control group. Attached to the revised version of the protocol is one example of each form:

Title of CRF intervention group: Documents for participants of the CASCADE study; Study Arm: Same-day ART-start, spaced follow-up visits

Title of CRF control group: Documents for participants of the CASCADE study; Study Arm: Standard of care

34 References

1. UNAIDS: **Fast Track - Ending the AIDS Epidemic by 2030.** *UNAIDS / JC2686 (accessed July 18, 2015 at: http://www.unaids.org/sites/default/files/media_asset/JC2686_WAD2014report_en.pdf)* 2014, .
2. **90-90-90 An ambitious treatment target to help end the AIDS epidemic.** *UNAIDS / JC2684 (accessed October 30th 2014 at www.unaids.org)* 2014, .
3. Jones A, Cremin I, Abdullah F, Idoko J, Cherutich P, Kilonzo N, Rees H, Hallett T, O'Reilly K, Koechlin F, Schwartlander B, de Zaluondo B, Kim S, Jay J, Huh J, Piot P, Dybul M: **Transformation of HIV from pandemic to low-endemic levels: a public health approach to combination prevention.** *Lancet* 2014, .
4. Hontelez JAC, Lurie MN, Bärnighausen T, Bakker R, Baltussen R, Tanser F, Hallett TB, Newell M-L, de Vlas SJ: **Elimination of HIV in South Africa through expanded access to antiretroviral therapy: a model comparison study.** *PLoS Med* 2013, **10**:e1001534.
5. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG: **Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model.** *The Lancet* 2009, **373**:48-57.
6. Cremin I, Alsallaq R, Dybul M, Piot P, Garnett G, Hallett TB: **The new role of antiretrovirals in combination HIV prevention: a mathematical modelling analysis.** *AIDS* 2013, **27**:447-458.
7. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, Hakim JG, Kumwenda J, Grinsztejn B, Pilotto JHS, Godbole SV, Mehendale S, Chariyalertsak S, Santos BR, Mayer KH, Hoffman IF, Eshleman SH, Piwowar-Manning E, Wang L, Makhema J, Mills LA, de Bruyn G, Sanne I, Eron J, Gallant J, Havlir D, Swindells S, Ribaud H, Elharrar V, Burns D, Taha TE, Nielsen-Saines K, Celentano D, Essex M, Fleming TR, HPTN 052 Study Team: **Prevention of HIV-1 infection with early antiretroviral therapy.** *N Engl J Med* 2011, **365**:493-505.
8. Cohen MH, Chen Y, McCauley M, Gamble T, Hosseinipour M, Kumarasamy N: **Final results of the HPTN 052 randomized controlled trial: antiretroviral therapy prevents HIV transmission.** *J Int AIDS Soc* 2015, (Suppl 4).
9. Eshleman SH, Hudelson SE, Ou SS, Redd AD, Swanstrom R: **Treatment as prevention: characterization of partner infections in the HIV Prevention Trials Network 052 trial.** *J Int AIDS Soc* 2015, **18** (Suppl 4).
10. TEMPRANO ANRS 12136 Study Group: **A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa.** *N Engl J Med* 2015, .
11. INSIGHT START Study Group: **Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection.** *N Engl J Med* 2015, .

12. World Health Organization: **GUIDELINE ON WHEN TO START ANTIRETROVIRAL THERAPY AND ON PRE-EXPOSURE PROPHYLAXIS FOR HIV.** accessed October 2, 2015 at: <http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/> 2015, ISBN 978 92 4 150956 5.
13. International AIDS Society Conference 2015: **The Vancouver Consensus.** available at: <http://vancouverconsensus.org> .
14. Hull M, Lange J, Montaner JSG: **Treatment as prevention--where next?** *Curr HIV/AIDS Rep* 2014, **11**:496-504.
15. Delva W, Abdool Karim Q: **The HIV epidemic in Southern Africa - Is an AIDS-free generation possible?** *Curr HIV/AIDS Rep* 2014, **11**:99-108.
16. MacCarthy S, Hoffmann M, Ferguson L, Nunn A, Irvin R, Bangsberg D, Gruskin S, Dourado I: **The HIV care cascade: models, measures and moving forward.** *J Int AIDS Soc* 2015, **18**:19395.
17. Yehia BR, Stephens-Shields AJ, Fleishman JA, Berry SA, Agwu AL, Metlay JP, Moore RD, Christopher Mathews W, Nijhawan A, Rutstein R, Gaur AH, Gebo KA, HIV Research Network: **The HIV Care Continuum: Changes over Time in Retention in Care and Viral Suppression.** *PLoS One* 2015, **10**:e0129376.
18. Piñeirúa A, Sierra-Madero J, Cahn P, Guevara Palmero RN, Martínez Buitrago E, Young B, Del Rio C: **The HIV care continuum in Latin America: challenges and opportunities.** *Lancet Infect Dis* 2015, **15**:833-839.
19. Kranzer K, Govindasamy D, Ford N, Johnston V, Lawn SD: **Quantifying and addressing losses along the continuum of care for people living with HIV infection in sub-Saharan Africa: a systematic review.** *J Int AIDS Soc* 2012, **15**:17383.
20. Mills EJ, Nachega JB, Ford N: **Can we stop AIDS with antiretroviral-based treatment as prevention?** *Glob Health Sci Pract* 2013, **1**:29-34.
21. Piot P, Abdool Karim SS, Hecht R, Legido-Quigley H, Buse K, Stover J, Resch S, Ryckman T, Møgedal S, Dybul M, Goosby E, Watts C, Kilonzo N, McManus J, Sidibé M, UNAIDS–Lancet Commission: **Defeating AIDS-advancing global health.** *Lancet* 2015, .
22. Chirawu P, Langhaug L, Mavhu W, Pascoe S, Dirawo J, Cowan F: **Acceptability and challenges of implementing voluntary counselling and testing (VCT) in rural Zimbabwe: evidence from the Regai Dzive Shiri Project.** *AIDS Care* 2010, **22**:81-88.
23. Snow RC, Madalane M, Poulsen M: **Are men testing? Sex differentials in HIV testing in Mpumalanga Province, South Africa.** *AIDS Care* 2010, **22**:1060-1065.
24. Bwambale FM, Ssali SN, Byaruhanga S, Kalyango JN, Karamagi CA: **Voluntary HIV counselling and testing among men in rural western Uganda: implications for HIV prevention.** *BMC Public Health* 2008, **8**:263.
25. Baiden F, Akanlu G, Hodgson A, Akweongo P, Debpuur C, Binka F: **Using lay counsellors to promote community-based voluntary counselling and HIV testing in rural northern Ghana: a baseline survey on community acceptance and stigma.** *J Biosoc Sci* 2007, **39**:721-733.
26. Sweat M, Morin S, Celentano D, Mulawa M, Singh B, Mbwambo J, Kawichai S, Chingono A, Khumalo-Sakutukwa G, Gray G, Richter L, Kulich M, Sadowski A, Coates T, Project Accept study team: **Community-based intervention to increase HIV testing and case detection in people aged 16-32 years in Tanzania, Zimbabwe, and Thailand (NIMH Project Accept, HPTN 043): a randomised study.** *Lancet Infect Dis* 2011, **11**:525-532.
27. Suthar AB, Ford N, Bachanas PJ, Wong VJ, Rajan JS, Saltzman AK, Ajose O, Fakoya AO, Granich RM, Negussie EK, Baggaley RC: **Towards universal voluntary HIV testing and counselling: a systematic review and meta-analysis of community-based approaches.** *PLoS Med* 2013, **10**:e1001496.

28. NIMH Project Accept (HPTN 043) Collaborators: **Project Accept (HPTN 043)**. *presented in a Special Session at IAS 2013, available at:* <http://pag.ias2013.org/session.aspx?s=79> .
29. Angotti N, Bula A, Gaydos L, Kimchi EZ, Thornton RL, Yeatman SE: **Increasing the acceptability of HIV counseling and testing with three C's: convenience, confidentiality and credibility**. *Soc Sci Med* 2009, **68**:2263-2270.
30. Obare F, Fleming P, Anglewicz P, Thornton R, Martinson F, Kapatuka A, Poulin M, Watkins S, Kohler H-P: **Acceptance of repeat population-based voluntary counselling and testing for HIV in rural Malawi**. *Sex Transm Infect* 2009, **85**:139-144.
31. Njau B, Watt MH, Ostermann J, Manongi R, Sikkema KJ: **Perceived acceptability of home-based couples voluntary HIV counseling and testing in Northern Tanzania**. *AIDS Care* 2012, **24**:413-419.
32. Doherty T, Tabana H, Jackson D, Naik R, Zembe W, Lombard C, Swanevelder S, Fox MP, Thorson A, Ekström AM, Chopra M: **Effect of home based HIV counselling and testing intervention in rural South Africa: cluster randomised trial**. *BMJ* 2013, **346**:f3481.
33. Sabapathy K, Van den Bergh R, Fidler S, Hayes R, Ford N: **Uptake of home-based voluntary HIV testing in sub-Saharan Africa: a systematic review and meta-analysis**. *PLoS Med* 2012, **9**:e1001351.
34. Mutale W, Michelo C, Jürgensen M, Fylkesnes K: **Home-based voluntary HIV counselling and testing found highly acceptable and to reduce inequalities**. *BMC Public Health* 2010, **10**:347.
35. Sekandi JN, Sempeera H, List J, Mugerwa MA, Asiimwe S, Yin X, Whalen CC: **High acceptance of home-based HIV counseling and testing in an urban community setting in Uganda**. *BMC Public Health* 2011, **11**:730.
36. Lugada E, Levin J, Abang B, Mermin J, Mugalanzi E, Namara G, Gupta S, Grosskurth H, Jaffar S, Coutinho A, Bunnell R: **Comparison of home and clinic-based HIV testing among household members of persons taking antiretroviral therapy in Uganda: results from a randomized trial**. *J Acquir Immune Defic Syndr* 2010, **55**:245-252.
37. World Health Organization: **Planning, implementation and monitoring home-based HIV testing and counselling. A practical handbook for Sub-saharan Africa**. Available at: http://apps.who.int/iris/bitstream/10665/75366/1/9789241504317_eng.pdf. *Planning, implementation and monitoring home-based HIV testing and counselling. A practical handbook for Sub-saharan Africa*. Available at: http://apps.who.int/iris/bitstream/10665/75366/1/9789241504317_eng.pdf .
38. Labhardt ND, Motlomelo M, Cerutti B, Pfeiffer K, Kamele M, Hobbins MA, Ehmer J: **Home-Based Versus Mobile Clinic HIV Testing and Counseling in Rural Lesotho: A Cluster-Randomized Trial**. *PLoS Med* 2014, **11**:e1001768.
39. Nachega JB, Uthman OA, del Rio C, Mugavero MJ, Rees H, Mills EJ: **Addressing the Achilles' heel in the HIV care continuum for the success of a test-and-treat strategy to achieve an AIDS-free generation**. *Clin Infect Dis* 2014, **59 Suppl 1**:S21-S27.
40. Naik R, Doherty T, Jackson D, Tabana H, Swanevelder S, Thea DM, Feeley FG, Fox MP: **Linkage to care following a home-based HIV counselling and testing intervention in rural South Africa**. *J Int AIDS Soc* 2015, **18**:19843.
41. Parker LA, Jobanputra K, Rusike L, Mazibuko S, Okello V, Kerschberger B, Jouquet G, Cyr J, Teck R: **Feasibility and effectiveness of two community based HIV testing models in rural Swaziland**. *Trop Med Int Health* 2015, .
42. Clouse K, Pettifor AE, Maskew M, Bassett J, Van Rie A, Behets F, Gay C, Sanne I, Fox MP: **Patient retention from HIV diagnosis through one year on antiretroviral therapy at a**

primary health care clinic in Johannesburg, South Africa. *J Acquir Immune Defic Syndr* 2013, **62**:e39-e46.

43. Gerdtts SE, Wagenaar BH, Micek MA, Farquhar C, Kariaganis M, Amos J, Gimbel S, Pfeiffer J, Gloyd S, Sherr K: **Linkage to HIV Care and Antiretroviral Therapy by HIV Testing Service Type in Central Mozambique: A Retrospective Cohort Study.** *J Acquir Immune Defic Syndr* 2013, .

44. Bassett I, Regan S, Luthuli P, Mbonambi H, Bearnot B, Pendleton A, Robine M, Mukuvisi D, Thulare H, Walensky R, Freedberg K, Losina E, Mhlongo B: **Linkage to care following community-based mobile HIV testing compared with clinic-based testing in Umlazi Township, Durban, South Africa.** *HIV Med* 2013, .

45. Wynberg E, Cooke G, Shroufi A, Reid SD, Ford N: **Impact of point-of-care CD4 testing on linkage to HIV care: a systematic review.** *J Int AIDS Soc* 2014, **17**:18809.

46. Kohler PK, Chung MH, McGrath CJ, Benki-Nugent SF, Thiga JW, John-Stewart GC: **Implementation of free cotrimoxazole prophylaxis improves clinic retention among antiretroviral therapy-ineligible clients in Kenya.** *AIDS* 2011, **25**:1657-1661.

47. Cantrell RA, Sinkala M, Megazinni K, Lawson-Marriott S, Washington S, Chi BH, Tambatamba-Chapula B, Levy J, Stringer EM, Mulenga L, Stringer JSA: **A pilot study of food supplementation to improve adherence to antiretroviral therapy among food-insecure adults in Lusaka, Zambia.** *J Acquir Immune Defic Syndr* 2008, **49**:190-195.

48. Muhamadi L, Tumwesigye NM, Kadobera D, Marrone G, Wabwire-Mangen F, Pariyo G, Peterson S, Ekström AM: **A single-blind randomized controlled trial to evaluate the effect of extended counseling on uptake of pre-antiretroviral care in Eastern Uganda.** *Trials* 2011, **12**:184.

49. Franke MF, Kaigamba F, Socci AR, Hakizamungu M, Patel A, Bagiruwigize E, Niyigena P, Walker KDC, Epino H, Binagwaho A, Mukherjee J, Farmer PE, Rich ML: **Improved retention associated with community-based accompaniment for antiretroviral therapy delivery in rural Rwanda.** *Clin Infect Dis* 2013, **56**:1319-1326.

50. Hatcher AM, Turan JM, Leslie HH, Kanya LW, Kwena Z, Johnson MO, Shade SB, Bukusi EA, Doyen A, Cohen CR: **Predictors of linkage to care following community-based HIV counseling and testing in rural Kenya.** *AIDS Behav* 2012, **16**:1295-1307.

51. Okeke NL, Ostermann J, Thielman NM: **Enhancing linkage and retention in HIV care: a review of interventions for highly resourced and resource-poor settings.** *Curr HIV/AIDS Rep* 2014, **11**:376-392.

52. Govindasamy D, Meghij J, Kebede Negussi E, Clare Baggaley R, Ford N, Kranzer K: **Interventions to improve or facilitate linkage to or retention in pre-ART (HIV) care and initiation of ART in low- and middle-income settings--a systematic review.** *J Int AIDS Soc* 2014, **17**:19032.

53. Posse M, Baltussen R: **Costs of providing food assistance to HIV/AIDS patients in Sofala province, Mozambique: a retrospective analysis.** *Cost Eff Resour Alloc* 2013, **11**:20.

54. Govindasamy D, Ford N, Kranzer K: **Risk factors, barriers and facilitators for linkage to antiretroviral therapy care: a systematic review.** *AIDS* 2012, **26**:2059-2067.

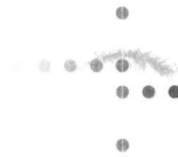
55. International AIDS Society: **Expanding Access To Viral Load Monitoring in Resource-Limited Settings - Meeting Report.** (accessed June 01, 2015 at: http://www.infectiousdiseasesonline.com/wp-content/uploads/2014/06/IAS-ILF__INTEREST__VL_in_RLS__Meeting_Report.pdf).

56. Aghokeng AF, Monleau M, Eymard-Duvernay S, Dagnra A, Kania D, Ngo-Giang-Huong N, Toni TD, Touré-Kane C, Truong LXT, Delaporte E, Chaix M-L, Peeters M, Ayoub A, ANRS 12186 Study Group: **Extraordinary heterogeneity of virological outcomes in patients**

- receiving highly antiretroviral therapy and monitored with the world health organization public health approach in sub-saharan Africa and southeast Asia. *Clin Infect Dis* 2014, **58**:99-109.
57. McMahon JH, Elliott JH, Bertagnolio S, Kubiak R, Jordan MR: **Viral suppression after 12 months of antiretroviral therapy in low- and middle-income countries: a systematic review.** *Bull World Health Organ* 2013, **91**:377-385E.
58. Labhardt ND, Bader J, Lejone TI, Ringera I, Puga D, Glass TR, Klimkait T: **Is zidovudine first-line therapy virologically comparable to tenofovir in resource-limited settings?** *Trop Med Int Health* 2015, **20**:914-918.
59. Kebe K, Thiam M, Diagne Gueye NR, Diop H, Dia A, Signate Sy H, Charpentier C, Belec L, Mboup S, Toure Kane C: **High rate of antiretroviral drug resistance mutations in HIV type 1-infected Senegalese children in virological failure on first-line treatment according to the World Health Organization guidelines.** *AIDS Res Hum Retroviruses* 2013, **29**:242-249.
60. Mulu A, Liebert UG, Maier M: **Virological efficacy and immunological recovery among Ethiopian HIV-1 infected adults and children.** *BMC Infect Dis* 2014, **14**:28.
61. Teasdale CA, Abrams EJ, Coovadia A, Strehlau R, Martens L, Kuhn L: **Adherence and viral suppression among infants and young children initiating protease inhibitor-based antiretroviral therapy.** *Pediatr Infect Dis J* 2013, **32**:489-494.
62. Jobanputra K, Parker LA, Azih C, Okello V, Maphalala G, Kershberger B, Khogali M, Lujan J, Antierens A, Teck R, Ellman T, Kosgei R, Reid T: **Factors associated with virological failure and suppression after enhanced adherence counselling, in children, adolescents and adults on antiretroviral therapy for HIV in Swaziland.** *PLoS One* 2015, **10**:e0116144.
63. Puga D, Cerutti B, Molisana C, Bader J, Faturiyeye O, Ringera I, Lejone T, Pfeiffer K, Klimkait T, Labhardt ND: **Outcomes of Children on Anti-Retroviral Therapy in Nurse-Led Clinics in Rural Lesotho.** *Pediatr Infect Dis J* 2015, .
64. Kranzer K, Ford N: **Unstructured treatment interruption of antiretroviral therapy in clinical practice: a systematic review.** *Trop Med Int Health* 2011, **16**:1297-1313.
65. Mills EJ, Funk A, Kanters S, Kawuma E, Cooper C, Mukasa B, Odit M, Karamagi Y, Mwehira D, Nachega J, Yaya S, Featherstone A, Ford N: **Long-term health care interruptions among HIV-positive patients in Uganda.** *J Acquir Immune Defic Syndr* 2013, **63**:e23-e27.
66. Labhardt ND, Keiser O, Sello M, Lejone TI, Pfeiffer K, Davies M-A, Egger M, Ehmer J, Wandeler G: **Outcomes of antiretroviral treatment programmes in rural Lesotho: health centres and hospitals compared.** *J Int AIDS Soc* 2013, **16**:18616.
67. Lankowski AJ, Siedner MJ, Bangsberg DR, Tsai AC: **Impact of geographic and transportation-related barriers on HIV outcomes in sub-Saharan Africa: a systematic review.** *AIDS Behav* 2014, **18**:1199-1223.
68. Ministry of Health and Social Welfare Lesotho: **National Guidelines For HIV Testing And Counselling.** *National Guidelines For HIV Testing And Counselling* 2009, .
69. Ministry of Health of Lesotho: **National guidelines on the use of antiretroviral therapy for HIV prevention and treatment.** *National guidelines on the use of antiretroviral therapy for HIV prevention and treatment* 2013, .
70. World Health Organization: **Consolidated Guidelines on the Use of antiretroviral Drugs for treating and preventing HIV Infection.** available at: www.who.int 2013, .
71. Smith JA, Sharma M, Levin C, Baeten JM, van Rooyen H, Celum C, Hallett TB, Barnabas RV: **Cost-effectiveness of community-based strategies to strengthen the continuum of HIV care in rural South Africa: a health economic modelling analysis.** *Lancet HIV* 2015, **2**:e159-e168.

72. Genberg BL, Naanyu V, Wachira J, Hogan JW, Sang E, Nyambura M, Odawa M, Duefield C, Ndege S, Braitstein P: **Linkage to and engagement in HIV care in western Kenya: An observational study using population-based estimates from home-based counseling and testing.** *Lancet HIV* 2015, **2**:e20-e26.
73. Ferrand R, Ford N, Kranzer K: **Maximising the benefits of home-based HIV testing.** *Lancet HIV* 2015, **2**:e4-e5.
74. Randall S, Coast E, Leone T: **Cultural constructions of the concept of household in sample surveys.** *Popul Stud (Camb)* 2011, **65**:217-229.
75. Rabkin M, Nishtar S: **Scaling up chronic care systems: leveraging HIV programs to support noncommunicable disease services.** *J Acquir Immune Defic Syndr* 2011, **57 Suppl 2**:S87-S90.
76. UNAIDS: **The Gap Report.** *The Gap Report* 2013, .
77. **Comorbidities and Virologic Outcome Among Patients on Anti-retroviral Therapy in Rural Lesotho (CART-1 study).** www.clinicaltrials.gov **NCT02126696.**
78. Labhardt ND, Cheleboi M, Faturyiele O, Motlatsi MM, Pfeiffer K, Lejone TI, Cerutti B, Muser J, Gupta RS, Lynen L, Hatz C: **Higher rates of metabolic syndrome among women taking zidovudine as compared to tenofovir in rural Africa: preliminary data from the CART-1 study.** *J Int AIDS Soc* 2014, **17**:19552.
79. Bekolo CE, Nguena MB, Ewane L, Bekoule PS, Kollo B: **The lipid profile of HIV-infected patients receiving antiretroviral therapy in a rural Cameroonian population.** *BMC Public Health* 2014, **14**:236.
80. Dave JA, Lambert EV, Badri M, West S, Maartens G, Levitt NS: **Effect of nonnucleoside reverse transcriptase inhibitor-based antiretroviral therapy on dysglycemia and insulin sensitivity in South African HIV-infected patients.** *J Acquir Immune Defic Syndr* 2011, **57**:284-289.
81. Omech B, Sempa J, Castelnuovo B, Opio K, Otim M, Mayanja-Kizza H, Colebunders R, Manabe YC: **Prevalence of HIV-Associated Metabolic Abnormalities among Patients Taking First-Line Antiretroviral Therapy in Uganda.** *ISRN AIDS* 2012, **2012**:960178.
82. Abebe M, Kinde S, Belay G, Gebreegziabxier A, Challa F, Gebeyehu T, Nigussie P, Tegbaru B: **Antiretroviral treatment associated hyperglycemia and dyslipidemia among HIV infected patients at Burayu Health Center, Addis Ababa, Ethiopia: a cross-sectional comparative study.** *BMC Res Notes* 2014, **7**:380.
83. Tesfaye DY, Kinde S, Medhin G, Megerssa YC, Tadewos A, Tadesse E, Shimelis T: **Burden of metabolic syndrome among HIV-infected patients in Southern Ethiopia.** *Diabetes Metab Syndr* 2014, **8**:102-107.
84. Ayodele OE, Akinboro AO, Akinyemi SO, Adepeju AA, Akinremi OA, Alao CA, Popoola AA: **Prevalence and clinical correlates of metabolic syndrome in Nigerians living with human immunodeficiency virus/acquired immunodeficiency syndrome.** *Metab Syndr Relat Disord* 2012, **10**:373-379.
85. Liu E, Armstrong C, Spiegelman D, Chalamilla G, Njelekela M, Hawkins C, Hertzmark E, Li N, Aris E, Muhihi A, Semu H, Fawzi W: **First-line antiretroviral therapy and changes in lipid levels over 3 years among HIV-infected adults in Tanzania.** *Clin Infect Dis* 2013, **56**:1820-1828.
86. Buchacz K, Weidle PJ, Moore D, Were W, Mermin J, Downing R, Kigozi A, Borkowf CB, Ndazima V, Brooks JT: **Changes in lipid profile over 24 months among adults on first-line highly active antiretroviral therapy in the home-based AIDS care program in rural Uganda.** *J Acquir Immune Defic Syndr* 2008, **47**:304-311.

87. European AIDS Clinical Society (EACS): **Guidelines Version 7.1.** *available at:*
<http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html> 2014, .



Präsident
Prof. André P. Perruchoud
Vizepräsidenten
Prof. Gregor Schubiger
Dr. Marco Schärer

Dr. Niklaus Labhardt
Swiss Topical- and Public Health-Institute
Socinstrasse 57
4002 Basel

Basel, 12. Februar 2016 / NJ

EKNZ UBE-15/123:

Same day community-based ART initiation versus clinic-based pre-ART assessment and counselling for individuals newly tested HIV-positive during community-based HIV testing in rural Lesotho - a randomized study (CASCADE-Trial)

Dear Dr. Labhardt

On the occasion of its meeting (20/01/2016), the Ethics Committee of Northwestern and Central Switzerland EKNZ reviewed the research project "*Same day community-based ART initiation versus clinic-based pre-ART assessment and counselling for individuals newly tested HIV-positive during community-based HIV testing in rural Lesotho - a randomized study (CASCADE-Trial)*".

This research project was evaluated according to the ICH-GCP (International-Conference on Harmonisation - Good Clinical Practice) guidelines. It conforms to the conditions that have to be met for research studies in Switzerland, namely:

- scientific validity and relevance of the research project and of the results that are to be expected;
- favourable benefit-risk ratio;
- consent of the study subjects;
- protection of the private sphere and confidentiality;
- professional qualification of the Swiss research scientists involved in the project;
- Definitions of the qualifications that are required of the other research scientists involved.

Whether the project can be accepted from ethical points of view depends on the local circumstances, which could not be assessed. In particular, the present statement does not consider the following points:

- procedure and documentation for recruitment of the study subjects, especially the information sheets and consent forms written in the local language;
- the adequacy of the local infrastructure (material, premises, personnel etc.) with regard to the best possible protection of the study subjects;
- Professional qualification of the non-Swiss research personnel.

The points listed above should be assessed by the responsible ethical research committee(s) of the place(s) where the project is carried out.

The Ethics Committee of Northwestern and Central Switzerland acknowledges the following Documents (Solidar Med, Swiss TPH, Bophelo Contract).

Mit freundlichen Grüßen



Prof. A. P. Perruchoud
Präsident der Ethikkommission
Nordwest- und Zentralschweiz / EKNZ



Ministry of Health
PO Box 514
Maseru 100

REF: ID89-2015

Date: 10 February 2016

To:
Dr. Niklaus Labhardt
Solidarmed
Maseru, Lesotho

Category of Review:

- Initial Review
- Continuing Annual Review
- Amendment/Modification
- Reactivation
- Serious Adverse Event
- Other _____

Dear Dr. Labhardt

RE: Same day community-based ART initiation versus clinic based pre-ART assessment and counseling for individuals newly tested HIV-positive during community-based HIV testing in rural Lesotho – a randomized study (ID 89-2015)

This is to inform you that on 10 February 2016 the Ministry of Health Research and Ethics Committee reviewed and **APPROVED** the above named protocol and hereby authorizes you to conduct the study according to the activities and population specified in the protocol. Departure from the approved protocol will constitute a breach of this permission.

This approval includes review of the following attachments:

- Protocol version 15 September 2015
- English consent forms
- Sesotho consent forms
- Data collection forms
- Participant materials:
- Other materials:

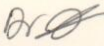
This approval is **VALID** until 09 February 2017.

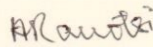
Please note that an annual report and request for renewal, if applicable, must be submitted at least 6 weeks before the expiry date.

All serious adverse events associated with this study must be reported promptly to the MOH Research and Ethics Committee. Any modifications to the approved protocol or consent forms must be submitted to the committee prior to implementation of any changes.

We look forward to receiving your progress reports and a final report at the end of the study. If you have any questions, please contact the Research and Ethics Committee at rcumoh@gmail.com (or) 22226317.

Sincerely,

Dr. Nyane Letsie 
Director General Health Services (a.i)


Dr. A. Ranotsi
Chairperson National Health-Institutional Review Board (NH-IRB)



Ministry of Health
PO Box 514
Maseru 100

REF: ID89-2015 Modification

LESOTHO

Date: 29 June 2017

To
Niklaus Labhardt MD, MPH, DTM&H
MIH; Swiss Tropical and Public Health Institute
SolidarMed

Category of Review:

- Initial Review
- Continuing Annual Review
- Amendment/Modification
- Reactivation
- Serious Adverse Event
- Other _____

Dear Dr. Niklaus,

RE: Same day community based ART initiation versus clinic-based pre-ART assessment and counselling for individuals newly tested HIV positive during community-based HIV testing in rural Lesotho- a randomized study

This is to inform you that on 28 June 2017 the Ministry of Health Research and Ethics Committee reviewed your interim report and **APPROVED** the above named modified protocol and hereby authorizes you to continue the study according to the activities and population specified in the protocol. Departure from the approved protocol will constitute a breach of this permission.

This approval includes review of the following attachments:

- Protocol dated 02/01/2017
- English & Sesotho consent forms dated November 2016
- Data collection forms in Sesotho
- Data collection forms in English
- Participant materials *[insert types, versions, dates]*
- Other materials: Interim report dated 12.05.2017, SAE form V1, Informed re-consent form V1.1& GCP certificates dated 2 April 2017

This approval is **VALID** until 28 June 2018.

Please note that an annual report and request for renewal, if applicable, must be submitted at least 6 weeks before the expiry date.

All serious adverse events associated with this study must be reported promptly to the MOH Research and Ethics Committee. Any modifications to the approved protocol or consent forms must be submitted to the committee prior to implementation of any changes.

We look forward to receiving your progress reports and a final report at the end of the study. If you have any questions, please contact the Research and Ethics Committee at rcumoh@gmail.com (or) 22226317.

Sincerely,

Dr. Nyane Letsie
Director General Health Services

Dr. A. Ranotsi
Chairperson NH-IRB

Quality Control Check – Report

Study acronym: **CASCADE-Study**

Study Title: Same day community-based ART initiation versus clinic-based pre-ART assessment and counselling for individuals newly tested HIV-positive during community-based HIV testing in rural Lesotho – a randomized study

Sponsor : IIT

PI : Niklaus Labhardt

This quality check has been requested by Niklaus Labhardt the principal investigator of this IIT trial.

The study has enrolled 276 patients of whom we have checked one third of informed consent forms (CRFc) (ICF - 90) and 10% of Case report Forms (CRFs - 28) randomly selected from the Excel sheet (see list below).

CRFs: 001, 002, 003, 006, 009, 015, 057, 065, 073, 078, 086, 151, 161, 168, 172, 193, 217, 218, 298, 305, 310, 313, 317, 320, 343, 411, 412, 418

ICF: 001, 002, 003, 006, 015, 016, 018, 019, 023, 026, 029, 034, 035, 039, 045, 047, 051, 058, 062, 064, 065, 067, 070, 071, 072, 073, 074, 077, 079, 080, 084, 085, 086, 088, 149, 151, 155, 156, 157, 159, 161, 168, 172, 187, 193, 195, 198, 201, 204, 206, 210, 217, 218, 229, 237, 298, 301, 305, 308, 310, 313, 315, 316, 317, 318, 320, 323, 325, 327, 330, 334, 343, 347, 350, 352, 353, 404, 405, 409, 411, 412, 415, 418, 419, 421, 423, 430, 431, 441

Informed consent

The informed consent forms were checked for:

- Completeness
- Coherence
- Compliance with Good Clinical Practices (GCP)
- Other

Detailed list of checked points :

- Name of study staff mentioned on page 1 of consent form
- Name of patient and date of informed consent self-entered by patient
- Presence of witness when necessary
- Presence of legal representative when necessary
- Presence of signature, for literate patient
- Quality of finger print, for illiterate patients
- Coherence between patient and staff signature dates

- Coherence between patient initials on page one of CRF and patient name as mentioned on the informed consent form.
- Distribution of birthdates

A graphical summary of the findings is attached to this document:

Critical observations :

1. Three minor patients (between 19 and 20 year old, meeting inclusion criterion Age \geq 18 year old, but not in legal age of majority in Lesotho which is 21 years - The Age of Majority Ordinance (Ordinance No. 62 of 1829)-) have signed without legal representative. One of them is of particular concern as his consent form also lacks signature and thumb print (underlined below), meaning that Legal Representative and witness were missing.

The following ICFs were concerned : 157, 201, 313

2. 4.4% of the ICFs were not signed

The following ICFs were concerned : 198, 201, 353, 421

3. Informed consents for illiterate patients were consistently taken without witness; exceptions are: 065 and 317.

The following ICFs were concerned : 23, 34, 198, 204, 206, 210, 308, 350, 353, 404, 405

4. It is obvious for most of the ICFs (89%, listed in attached file, point 2), that the study staff has prefilled the form by writing themselves the date and patient name on the ICF for the patient:

e.g. patient 015 :

date written by patient : 26-02-16

date written by staff : 26-02-16

This is not a good documentation practice, and ICH GCP section 4.8.8 mentions : "Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion." In addition to be a GCP requirement, it is also a way to control literacy of the patients (13% of the patients of the study declared to be illiterate, which is in agreement with national average, https://www.unicef.org/infobycountry/lesotho_statistics.html) This point should also be addressed in staff training.

Corrective Action/Preventive Action (CA/PA) : The above listed informed consents should be taken again, study staff taking the consent should be trained again with a particular attention to the informed consent procedure for illiterate/minor patients, and appropriate way

to fill in the ICF.

Minor observations

1. Due to their high prevalence (cf. attached table 1), the following birthdates were considered doubtful. 01.01, 02.02, 03.03, 04.04 etc.

The following ICFs were concerned : 001, 002, 009, 023, 045, 051, 058, 067, 079, 088, 149, 155, 156, 204, 206, 210, 217, 218, 301, 308, 317, 327, 350, 353, 404, 405, 421, 423, 441

2. Also raising questions about the accuracy of birth dates :
 - 50% of birthdates are between January and March (normal distribution: 25%).
 - 4 consents taken within 2 days of the informed consent signature anniversary

Comments/Suggestions: Given the lack of accuracy in birthdate recording, the option of just mentioning the age or year of birth should be considered, and day/month only if known. It is actually now a recommendation of Swiss Ethics not to record the full birthdates of a patient in CRFs, but only year (for confidentiality reasons).

Case Report Forms

Completion of the forms is overall of very good quality; the content of the forms themselves was found to be clear and easy to follow.

The CRFs were checked for:

- Completeness
- Coherence
- Compliance with GCP
- Other

Detailed list of checked points :

- Completeness of data entered in socio-demographic forms (2 pages)
- Completeness of information entered in Antiretroviral Treatment (ART) initiation form
- Coherence against source was done for the following laboratory values:
 - HbA1C
 - HbA1C : %
 - Total Cholesterol
 - LDL
 - HDL
 - TriG
 - CD4 count

No source data verification (SDV) was done for Hemoglobin and Creatinine.

Minor observations

Only minor observations were done:

- It should be avoided to leave blank a field when filling the forms :



32 . mmol/l

- 001 : HDL value impossible to check due to low quality of scan.
- 172 : value of HbA1c in mmol/mol not entered in CRF even though source available
- 172 : total value for cholesterol is incorrect (CRF : 5.6mmol/L, source : 4.9 mmol/L)
- 305 : form is not correctly filled in (unrounded value added above field of completion)
- 317 : triglyceride value is incorrect (CRF : 0.9mmol/L, source : 1.5 mmol/L)

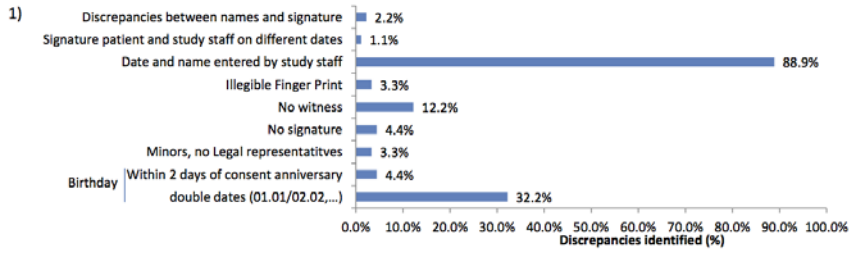
Study design

Concerning the design and handling of ICF & CRF study process the following points could be corrected/clarified

- Allocation to study treatment arm is visible at the top of the informed consent form (standard of care/same day). This should be removed to avoid bias in recruitment, in case participants would be more reluctant to one arm than the other.
- Linked to the previous point, it is unclear whether this is due to the fact that ICF is designed as part of the CRFs. This should not be the case, as clearly ICF is nominative, while the CRF should be anonymous, so the documents should not be kept together for confidentiality reasons
- To ensure the confidentiality of study participants, it should be ensured that the signed informed consent forms or copies thereof should be kept in a secure place.
- Unit for HbA1c should be mmol/mol instead of mmol/L as mentioned in CRF.

Date of report 16.02.2017		
Quality check done by Julie Catusse	Signature 	Date 23 02.2017
Reviewed by Valentina Butoescu	Signature 	Date 23 Feb. 2017

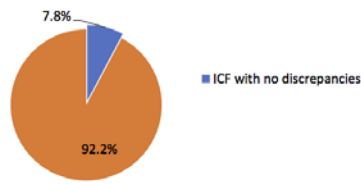
Deviations/flaws identified in ICF (% of total ICFs)



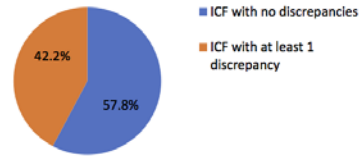
2) Date and patient name entered by study staff:

023, 026, 029, 034, 035, 039, 045, 047, 051, 058, 062, 064, 065, 067, 070, 071, 072, 073, 074, 077, 079, 080, 084, 085, 086, 088, 149, 151, 155, 156, 157, 159, 168, 172, 187, 193, 195, 198, 201, 204, 206, 210, 217, 218, 229, 237, 298, 301, 305, 308, 310, 313, 315, 316, 317, 318, 320, 323, 325, 327, 330, 334, 343, 347, 350, 352, 353, 404, 405, 409, 411, 412, 415, 418, 419, 421, 423, 430, 431, 441

3) % of informed consent forms with identified deviations



% of informed consent forms with identified deviations (without name/date filled in by study staff)



4) Deviations in Informed consents by study staff

	number of consents taken	number of deviations	%	deviations including date/name by study staff	%
NC	37	16	43.24	36	94.59
TL	22	9	40.91	18	81.82
IR	31	14	45.16	30	96.77

