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Clinical Study Protocol

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Peer-Educator-coordinated vs nurse-coordinated ART refill for adolescents and young adults living with HIV in Lesotho – a cluster randomized clinical trial

abbreviated title:

PEBRA study („Peer-Educator Based Refill of ART")

This study is embedded in a research project called **GET ON IT** ("GETing tOwards Ninety In Teens")

Protocol Version Number	3	**Document Date**	24.05.2019
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IV. Remarks

1) A list of all other involved staff (i.e. peer-educators) will only be available at the start of the study and is not feasible to include at this stage. They will all receive a specific training and those who enrol patients will get an introduction into GCP (without certificates).
2) This is an investigator-initiated trial. The Principal Investigator, the Swiss TPH respectively, acts as Sponsor.
3) This study protocol will be prospectively registered on clinicaltrials.gov, before the first study participant is included, the registration number will be provided at a later stage.
4) According to Swiss lab (ClinO, Art. 19, 20, App 3, 1.1) this is a Category A trial, study type “other clinical trial”.
5) Conflict of Interest: All authors declare that they have no competing interests.

V. Signatures

Principal Investigator and Co-Investigators who sign below have approved the current study protocol version 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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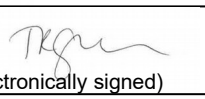
Signature	 (electronically signed)		12.03.2019
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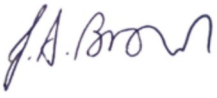
Signature	 (electronically signed)		12.03.2019
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VI.Table of Contents

1. GENERAL INFORMATION

1.1 Abbreviations / Glossary of Terms

AYPLHIV	Adolescent & Young People Living with HIV
CAC	Community Adherence Clubs
CI	Confidence Interval
CYC	Community Youth Club
CPP	Cluster Per Protocol
CRF	Case Report Forms
DHMT	District Health Management Team
DSD	Differentiated Service Delivery
DSMB	Data Safety Monitoring Board
EAC	Enhanced Adherence Counseling
FGD	Focus Group Discussion
HIV	Human Immunodeficiency Virus
ICC	Intra-cluster Correlation Coefficient
ICF	Informed Consent Form
ITT	Intention To Treat
KII	Key Informant Interviews
LIS	Laboratory Information System
LTFU	Loss-To-Follow-Up
PE	Peer-Educator
PEBRA	Peer-Educator-Based Refill of ART
PHC	Primary Health Care
PI	Principal Investigator
PP	Per Protocol
QoC	Quality of Care
QoL	Quality of Life
(S) AE	(Serious) Adverse Events
SCC	Saturday Clinic Club
SSA	Sub-Saharan Africa
Swiss TPH	Swiss Tropical and Public Health Institute
UNAIDS	United Nations Programme on HIV/AIDS
VHW	Village Health Worker
VL	Viral Load (Plasma HIV-1 RNA)
VS	Viral Suppression
WHO	World Health Organization

1.2 Synopsis

study title	Peer-Educator-coordinated vs nurse-coordinated ART refill for adolescents and young adults living with HIV in Lesotho – a cluster randomized clinical trial
abbreviated title	PEBRA study (Peer-Educator-Based Refill of ART)
background & rational	Sub-Saharan Africa (SSA) is home to 85% of the adolescents and young people living with HIV (AYPLHIV) globally. AYPLHIV in SSA are the only population group for whom HIV-related mortality continues to increase, and they have overall poorer outcomes than all other age groups. Lesotho has the second-highest HIV prevalence and shows a viral suppression rate among AYPLHIV of only 49%. In order to address the multiple barriers in the adolescent HIV care cascade and their unique

	needs, multicomponent packages of differentiated service delivery (DSD) are a promising approach. In close collaboration with different local stakeholders, we designed a DSD model specifically for AYPLHIV, called the PEBRA model. In the PEBRA model the peer-educator (PE) plays a pivotal role, by coordinating the ART refill/care according to the patients' preferences using a tablet-based application, called PEBRApp. The PEBRApp helps the PE to assess each participants' preference, to adapt the ART refill according to these preferences in a feasible manner, to keep track of the ART refill, and to ensure regular contact between the PE and the participant. The model includes key innovative options such as individualized automatic SMS notifications and decentralized ART delivery.
primary aim	This study aims to evaluate the feasibility and effectiveness of a DSD model ("PEBRA model") among AYPLHIV.
study design	PEBRA study is a cluster randomized, open-label, superiority trial in a resource-limited setting. The rational for a cluster randomized design with health facilities as clusters, is the high risk of cross-contamination between the study arms if randomization would be done at individual level. The clusters (health facilities) will be randomized (randomly-varying block sizes, 1:1 allocation) into the 2 groups using a computer-generated randomization list, stratified by district. The study will be conducted at 20 health facilities in three districts of Lesotho (Leribe, Butha-Buthe, Mokhotlong).
major eligibility criteria	**Eligibility – clusters** *Inclusion criteria*: 1) the cluster is a public or missionary health center from the study districts, that offers ART services 2) the cluster has at least one PE who is willing to participate and fulfills the following criteria: a) underwent the Sentebale Peer-Educator two-weeks training b) attended and successfully passed the training assessment *Exclusion criteria*: 1) health facility authority opposed to trial participation (verbal assent) 2) the health facility is a hospital 3) the health facility is situated in an area without cellphone signal **Eligibility – individuals** 1) Individual is living with HIV and in care in a participating cluster 2) Individual is 15-24 years old (AYPLHIV) 3) Informed consent given 4) Declares to seek the next follow-up visit at the same health facility
intervention and control	Participants in the *intervention clusters* are offered the PEBRA model. In the PEBRA model the ART visit/refill is coordinated by the PE according to the participants' preferences, using a tablet-based application, called PEBRApp. The preference assessment entails the following three domains of DSD: 1) ART Refill 2) SMS notifications 3) Support In each of the domains, the participants' preferences will be assessed and the most feasible option will be selected. The PEBRApp not only helps the PE to assess each participants' preference, but also to keep track of the ART refill, and to ensure regular contact between the PE and the participant. The model includes key innovative options such as individualized automatic SMS notifications and decentralized ART delivery Participants in the *control clusters* are offered standard of care: ART visit/refill is coordinated by the nurse, is mostly clinic-based, not adapted to youth, and differentiated according to clinical values (i.e. if VL suppressed then option of ART Refill in a Community Adherence Club).
primary endpoint	In care with documented viral suppression at 12 months, defined as the proportion of participants in care with a documented VL <20 copies/mL 12 months (range: 9 – 15 months) after enrolment out of all participants enrolled.

secondary endpoints	a) Adherence to ART at 3 months, 6 months and 12 months after enrolment b) Quality of Life at 6 months and 12 months after enrolment c) Perceived quality of ART Care / patient service satisfaction at 6 months and 12 months after enrolment d) Engagement in care at 6 months e) Alternative viral suppression level at 12 months f) Engagement in care at 12 months g) All-cause mortality at 6 and 12 months h) LTFU at 6 and 12 months i) Transfer out at 6 and 12 months
sample size & statistical considerations	An overall target sample size of 300 AYPLHIV in 20 clusters (10 per arm) will provide us 90% power (design effect of 1.7) to detect a 20% increase of viral suppression in the intervention group, assuming a type 1 error of 0.05, and an intra-cluster correlation coefficient (ICC) of 0.05. Clusters, i.e. clinics, will be set as unit of randomization (stratified by district), whereas individuals are set as unit of analysis. The primary analysis will use multi-level logistic regression models (on the intention-to-treat set) including clinic as random effect to assess the difference between viral suppression rate in the intervention versus control arm, adjusted for the pre-specified randomization stratification factor, baseline VL, and relevant baseline factors that may be randomly unbalanced between intervention and control clusters. All results will primarily be presented as odds ratios and their respective 95% confidence intervals.
recruitment & study duration	We expect recruitment to start August/September 2019 and a total study duration of approximately 18 months. We anticipate a recruitment period of 4-5 months. A pilot trial, assessing PEBRA model at one health facility, will form the basis for the main trial.
GCP statement	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements.

2 BACKGROUND

2.1 The HIV/AIDS epidemic among adolescents and young people in sub-Saharan Africa

The latest UNAIDS report showed encouraging progress towards an AIDS-free generation by 2030. This progress is, however, counterbalanced by persistent challenges among young people in sub-Saharan Africa (SSA). SSA accounts for 85% of the adolescents and young people living with HIV (AYPLHIV) globally and they represent one of the population groups most affected by the HIV/AIDS epidemic: Almost a third of new HIV-infections are among individuals aged 15–25 years, mostly female.[1,2] AYPLHIV are more likely to drop out of HIV-care, both before and after starting antiretroviral therapy (ART), are the only population group for whom HIV-related mortality continues to increase, and have overall poorer outcomes than all other age groups. AIDS remains the leading cause of death among young people in SSA.[3–6]

AYPLHIV face particular challenges in accessing and adhering to ART. The distinct rapid physical, psychological and emotional changes that occur during adolescence impact on how AYPLHIV view their health, make decisions, perceive risk and interact with health and related services.[7] Thus, barriers of the adolescent HIV care cascade are multifactorial: Psychological and social barriers such as heightened stigma both within the community and health system, structural barriers such as time-consuming expensive ART visits (especially in remote rural areas of SSA), individual behavioral barriers such as non-disclosure, as well as policy barriers such as the requirement for parental consent to access HIV and broader sexual and reproductive health services.[8–12]

2.2 The HIV/AIDS epidemic in Lesotho

Lesotho, a small land-locked country surrounded by South Africa, has the second-highest adult HIV prevalence in the world with 25.6%.[1,13] Compared to the other Southern African countries, Lesotho presents one of the highest HIV-incidence among adolescent girls and young women.[14] According to the recent household-based national survey (LePHIA) overall viral suppression (VS), the final target in the HIV care cascade, among people living with HIV is 67.7%. VS is highest among people living with HIV aged 45 to 59 years (80.9%), and significantly lower among AYPLHIV (50.9% among female and 46.1% among male).[13]

The geographic characteristics of Lesotho impose an extra impediment on the HIV/AIDS epidemic. About 70% of Lesotho's population lives in rural mountainous areas (>1500m) characterized by widespread poverty, poor transport infrastructure and hard-to-reach villages. Thus, access to the health care facilities remains a major barrier for engagement in care.

2.3 Differentiated Service Delivery and the Rational of the PEBRA model

In order to address the multiple barriers in the adolescent HIV care cascade, multicomponent packages of differentiated service delivery (DSD) are a promising approach.[15,16] Unlike service delivery models that apply standardized care for all people living with HIV, the idea of DSD models is to consider the specific needs of different groups of people living with HIV, while facilitating service scale-up by reducing the burden on health systems and increasing efficiency. Among AYPLHIV with their unique and heterogenous needs, DSD models may provide an opportunity to ensure better outcomes.

In 2018, Paediatric-Adolescent Treatment Africa, in collaboration with other key stakeholders, undertook a situational analysis of DSD for AYPLHIV in neighboring South Africa. They report a lack of published literature documenting adolescent-specific DSD models in the Southern African region, including Lesotho. Moreover, the analysis shows that most adolescents are not accessing DSD models even where they exist, an indicator that the few existing DSD models are not tailored according to adolescent-specific preferences. DSD models usually include stable patients. However, differentiated care should not only be designed for stable patients, but include patients who would otherwise not engage in care. The definition of a "stable patient" bears challenges itself, leading to late inclusion in these models.[17]

The South African situation analysis identified key principles to make DSD work for AYPLHIV: a) to remove structural barriers (decentralized community-based and fast-track ART refills), b) to develop and deliver DSD models with young people using youth-friendly communication (i.e. social media, cellphone), c) to include psychosocial support as an essential component in any DSD model, and d) to make the surrounding health framework more youth-friendly. Overall, there is a strong emphasis on the diverse needs and preferences of AYPLHIV while planning DSD models.[18]

In close collaboration with different local stakeholders, especially Sentebale and their existing Peer-Educator program, we designed a DSD model specifically for AYPLHIV, called the PEBRA (Peer-Educator

Based Refill of ART) model. In the PEBRA model the peer-educator (PE) plays a pivotal role, by coordinating the ART refill/care according to the patients preferences using a tablet-based application, called PEBRApp. The PEBRApp helps the PE to assess each participants' preference, to adapt the ART refill according to these preferences in a feasible manner, to keep track of the ART refill, and to ensure regular contact between the PE and the participant. The model includes key innovative options such as individualized automatic SMS notifications and the option of decentralized ART delivery.

3 STUDY OBJECTIVES

3.1 Overall objective

This study aims to evaluate the feasibility and effectiveness of a DSD model ("PEBRA model") among AYPLHIV.

3.2 Primary objective

As primary objective this study seeks to assess the rate of viral suppression among AYPLHIV 12 months after enrolment between the intervention clusters, where AYPLHIV were offered the PEBRA model, and the control clusters, where AYPLHIV were offered standard of care.

3.3 Secondary objectives

Secondary objectives include a comparison of adherence to ART, the level of perceived quality of ART care and patient service satisfaction, engagement in care, viral suppression, lost-to-follow-up (LTFU), mortality, and transfer out between the intervention and control clusters.

3.4 Other objectives

Further objectives include a cost-effectiveness evaluation and qualitative research regarding acceptance, scalability and feasibility of the DSD model.

4 STUDY SETTING, DESIGN, AND METHODS

4.1 Setting

The study will be conducted in northern Lesotho, in the districts of Leribe, Butha-Buthe and Mokhotlong. Butha-Buthe and Mokhotlong districts are both characterized by mostly rural settings with an estimated population of 220,000, mainly subsistence farmers and mine workers as well as construction or domestic labourers who work in neighbouring South Africa. Each district has only one single mid-size town: Butha-Buthe with ca. 25,000 inhabitants, and Mokhotlong with ca. 10,000 inhabitants. The remaining population lives in villages scattered over a mountainous area of 5,842 km^2. Leribe has an estimated population of approximately 330,000 inhabitants and two bigger cities: Maputsoe with 55,000 and Hlotse with 40,000 inhabitants. Butha-Buthe district comprises 12 public/missionary health facilities (10 health centers, 2 hospitals), Leribe district 26 public/missionary health facilities (24 health centers, 2 hospitals) and Mokhotlong district 10 public health facilities (9 health centers, 1 hospital), that offer ART services. The HIV prevalence among individuals 15 to 59 years old ranges from 17.8% (Butha-Buthe), 23.7% (Leribe) to 26.1% (Mokhotlong).[13]

4.2 Design of PEBRA study

The PEBRA study is embedded in an overarching research project, called GET ON IT ("GETing tOwards Ninety In Teens"). The abbreviated title of this study is "PEBRA study" and stands for "Peer-Educator Based Refill of ART". The PEBRA study is a cluster randomized, open-label, superiority trial in a resource-limited setting. The rational for a cluster randomized design with health facilities as clusters, is the high risk of cross-contamination between the study arms if randomization would be done at individual level.

4.3 Methods

4.3.1 Cluster sampling and randomization

The clusters (health facilities) will be randomized (randomly-varying block sizes, 1:1 allocation) into intervention and control clusters using a computer-generated randomization list, stratified by district (Leribe vs Butha-Buthe vs Mokhotlong). The randomization list will be prepared by a statistician not involved in the study.

4.3.2 Eligibility – clusters

Inclusion criteria:

1) the cluster is a public or missionary health center from the study districts, serving a rural population and offering ART services
2) the cluster has at least one PE who is willing to participate and fulfills the following criteria:
   a) underwent the Sentebale Peer-Educator training
   b) attended and successfully passed the study training assessment

Exclusion criteria:

1) health facility authority opposed to trial participation (verbal assent)
2) the health facility is situated in an area without cellphone signal

4.3.3 Eligibility – individuals

1) Individual is living with HIV and in care in a participating cluster
2) Individual is 15-24 years old (AYPLHIV)
3) Informed consent given
4) Declares to seek the next follow-up visit at the same health facility

4.3.4 Procedures in all study clusters

A trained PE per cluster will actively screen all AYPLHIV for eligibility. If eligible, the PE will continue with the baseline assessment, using a tablet-based application. The following data will be collected (from medical records and patient interview):

- Consent documentation (and if not consenting, then reason for refusal and stop data collection)
  - Details about consent process see in section 13.1
- ART number
- Clinic/Cluster
- Year of birth
- Gender
- Village
- Cellphone number
- Date of ART initiation
- WHO-stage at ART initiation
- Laboratory information: CD4 at ART initiation, last CD4, VL history and baseline VL*
- Co-morbidities
- TB history
- Co-medication
- ART regimen history
- Socio-demographic data including age, gender, level of education, employment status, marital status, pregnancy
- Structural data incl. distance and time and costs (incl. opportunity costs) to visit the health facility
- HIV/AIDS knowledge and stigma[19]
- Adherence: Pill count and setting- & age-validated treatment adherence questions[20–22]
- Quality of Life (QoL): WHO HIV QoL questionnaire (whoqol_hiv_bref questionnaire)[23–25]
- Quality of Care (QoC): a setting-validated perceived QoC & patient satisfaction questionnaire[26]

*Note: Baseline VL is defined as the last VL within the previous 12 months, taken from the medical records (bukana, patient file, laboratory databases). If no VL within previous 12 months available, then the participant will be sent to the nurse for blood draw for routine VL measurement. This is not a study-specific procedure, but standard of care. If the patient is new in care and due for 6 months VL, then the 6m routine VL will be taken as baseline VL.

4.3.5 Intervention clusters: PEBRA model

The participants in the intervention clusters are offered the PEBRA model. In the PEBRA model the ART visit/refill is coordinated by the PE, as much as feasible according to the participants' preferences. Thus, the preferences of each participant are captured at enrolment and after a strict schedule thereafter. The PE conducts the preference assessment using a tablet-based application, called PEBRApp. The PEBRApp will automatically alert the PE when the next preference assessment of each participant is due. The preference assessment interval is independent from the ART refill interval and can be performed via phone as well. Participants with a suppressed VL will get a preference assessment every 3 months and participants with unsuppressed VL a preference assessment every month. As a strict part of the preference assessment, the PE asks two psychosocial questions ("Is there anything you would like to share with me today?" / "How do you think you are doing today?") and for those patients with unsuppressed VL an additional third question ("Do you have a safe environment to take your medication?").

The preference assessment works as a two-step approach: First, the participant will be asked his/her preference regarding different domains of DSD (see below) and this will be entered into the PEBRApp. Secondly, the chosen preferences are assessed regarding feasibility with specific questions, as not all preference options are available to everyone all the time, e.g. no nearby Village Health Worker (VHW) available who could dispense ART, or no Community Youth Club (CYC) established in the participants' community, or home-delivery by PE not feasible.

The preference assessment entails the following three domains of DSD:

1) ART Refill
2) SMS notifications
3) Support

For each domain, the following options can be chosen:

1) ART Refill (one option possible):
    a. At the clinic
    b. Village Health Worker (VHW) in the community
    c. Home-delivery by the PE
    d. Through a Community Adherence Club (CAC)
    e. Through a Treatment Buddy
2) SMS notifications (several options possible):
    a. Adherence reminder: Frequency (to be chosen) and pre-defined message (to be chosen)
    b. Refill visit reminder: Frequency (to be chosen) and pre-defined message (to be chosen)
    c. VL-triggered message after blood draw as soon as VL result is available: pre-defined message for "unsuppressed" and "suppressed" (to be chosen)
3) Support (several options possible):
    a) By the nurse at the clinic
    b) Saturday Clinic Club (SCC)
    c) Community Youth Club (CYC)
    d) Phone Call by PE
    e) Home-visit by PE
    f) School visit and health talk by PE
    g) Pitso visit and health talk by PE
    h) Condom demonstration
    i) More information about contraceptives
    j) More information about VMMC
    k) For pregnant: Linkage to young mothers group (DREAMS or Mothers-to-Mothers)
    l) For females: Linkage to a female WORTH group (Social Asset Building Model)
    m) Legal aid information
    n) Show me tuneme.org (teenage topics)
    o) Show me Ntlafatso Foundation Facebook (HIV stigma/discrimination topics)
    p) No support wished

Every PE who delivers PEBRA model receives a tablet, that has a calling function and the PEBRApp installed. PEBRApp is protected by a password, only known to the PI and the PE, and does not entail confidential patient information, i.e. names. PEBRApp serves as a data collection tool (baselines assessment, preference assessment, etc.) and as a patient management tool to keep track of the ART refill of each participants (WHERE and WHEN) and his/her chosen support. PEBRApp will keep overview of all due dates (next ART refill date, next preference assessment date) and automatically alert the PE for an action.

The PEBRApp helps the PE to assess each participants' preference, to adapt the ART refill according to these preferences in a feasible manner, to keep track of the ART refill, and to ensure regular contact between the PE and the participant. The chosen SMS notifications will be sent automatically through an external platform (VL platform, www.lstowards909090.org/db), and always include a call-back option to the PE's number.

The PEBRA model as well as the PEBRApp have been developed and refined in several multi-stakeholder workshops together with adolescents and young people (Sentebale PEs, Sentebale Youth staff, AYPLHIV, various youth club members from urban and rural areas, international and national App developers).
Figures 1a and 1b illustrate the PEBRA model and Figures 2a and 2b the PEBRApp. Under the following link (https://bit.ly/2TA5RA5) a prototype version of PEBRApp can be accessed.

FIGURE 1a. Schematic description of PEBRA model for AYPLHIV

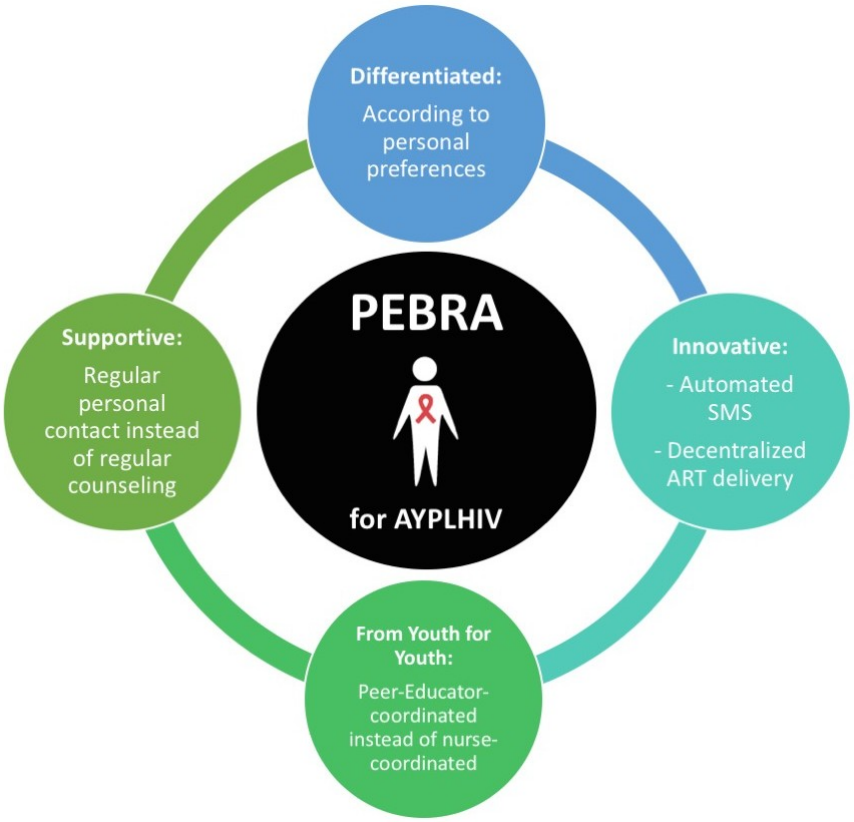


FIGURE 1b. Schematic description of PEBRA model delivered by PEBRApp

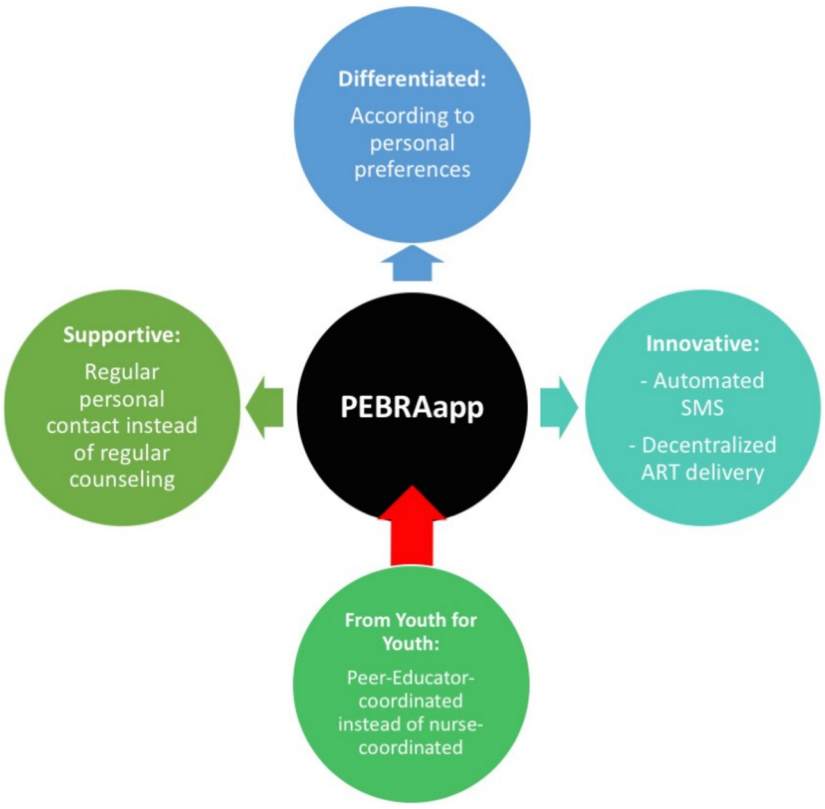


FIGURE 2a. Screenshot of PEBRApp: Main Screen

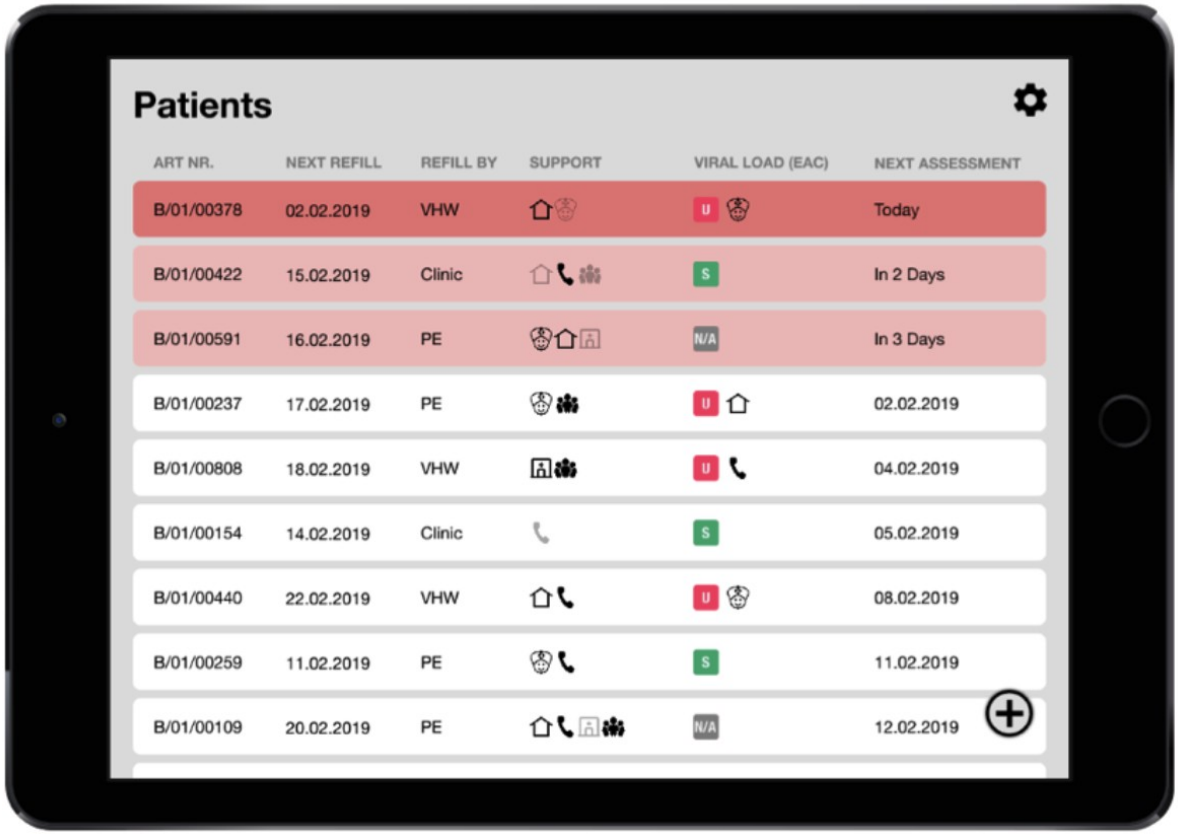
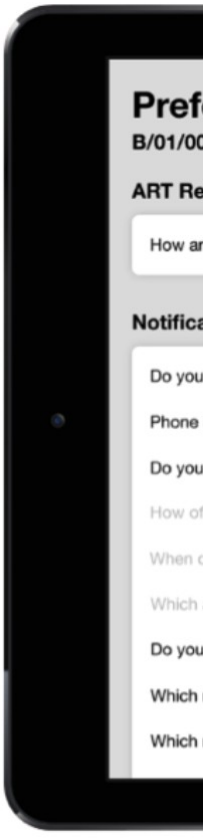


FIGURE 2b. Screenshot of PEBRApp: Excerpt from Preference Assessment Screen



4.3.6 Control clusters: Standard of Care

Participants in the control clusters are offered standard of care: ART visit/refill is coordinated by the nurse, is mostly clinic-based and not specifically adapted to youth. Currently the Ministry of Health is piloting an SMS notification system that alerts patients once their VL result is out and entered into the LIS (Laboratory Information System). Thus, the standard of care at the health facilities in our study districts nowadays entails several options, however not all option are available at all health facilities:

1) ART Refill:
    a. Nurse at the clinic
    b. Through a Community Adherence Club
    c. Through a Treatment Buddy
2) SMS notifications:
    a. VL-triggered message: “Your laboratory result is out. Please come to the health facility to collect it”
3) Support:

a. Nurse at the clinic
b. Community Youth Club
c. Saturday Clinic Club

4.3.7 Peer-Educators – training and responsibility

The PEs for this research project will be recruited within the existing network of Sentebale (www.sentebale.org). The Sentebale PEs are young people (18-24 years) living in a community from their attached health facility catchment area. All Sentebale PEs received at the beginning of their volunteering work a one-week training on general issues around HIV/AIDS and youth-related health topics with focus on psychosocial support. All PEs involved in PEBRA study will receive an additional training on the PEBRApp, the use of the tablet, reporting & documentation system, obtaining of informed consents and other study-specific procedures.

4.3.8 Blinding

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

5 ENDPOINTS AND DEFINITIONS

Table 1 summarizes all endpoints.

5.1 Primary endpoint

In care with documented viral suppression at 12 months, defined as the proportion of participants in care with a documented VL <20 copies/mL 12 months (range: 9 – 15 months) after enrolment out of all participants enrolled

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

ii. Definition of "in care": at least one ART visit in the defined window

I. Including participants who transferred out to any other health facility with known outcome (documented proof of follow-up visit or laboratory test)

II. Excluding participants who died (all-cause), were lost to follow-up (LTFU), or were known defaulters/refusers, i.e. were more than 2 months late for ART refill with a reason available (e.g. currently no money for clinic-visit, busy working in South Africa, etc.)

iii. The study will use VL results from routine VL monitoring. To synchronize routine VL monitoring and study VL monitoring, study staff will help ensure each site has the capacity to collect these samples and will support existing systems that help to provide results back to sites. VLs will only be performed on individuals who return for visits and no tracking will be performed by the study staff to obtain VLs.

5.2 Secondary endpoints

a) Adherence to ART at 3 months (range 2.5 – 3.5), 6 months (range 5 – 8) and 12 months (range 9 – 15) after enrolment

i. Assessed by 4 different setting- and age-validated ART adherence questions[20–22]*:*

a. pill count: change in percentage

b. "When was the last time you missed any medications?" [i) past week, ii) 1-2 weeks ago, iii) 3-4 weeks ago, iv) never]: Dichotomous outcome missed doses vs. no missed doses in the past month

c. "ART missed at two or more consecutive days within last month?" ("drug holiday" question)

d. "How would you rate your adherence over the last month" [i) very poor, ii) poor, iii) fair, iv) good, v) very good, vi) excellent]: Dichotomous outcome adherent vs non-adherent (anything less than 'excellent')

b) Quality of Life (QoL) at 6 months (range 5 – 8) and 12 months (range 9 – 15) after enrolment

i. Assessed by WHO QoL in PLHIV: WHO HIV QoL questionnaire (whoqol_hiv_bref questionnaire with 31 five-point Likert Scale items with categorical outcome)[23–25]

c) Perceived quality of ART Care (QoC) / patient service satisfaction at 6 months (range 5 – 8) and 12 months (range 9 – 15) after enrolment

i. Assessed by a setting-validated QoC and patient service satisfaction questionnaire (12 five-point Likert Scale items with categorical outcome)[26] *by an external data collector, not the PE*

d) Engagement in care at 6 months, defined as the proportion of participants engaged in care 6 months (range 5 – 8) after enrolment out of all participants enrolled
   i. Definition of "in care": at least one ART visit in the defined window
      I. Including participants who transferred out to any other health facility with known outcome (documented proof of follow-up visit or laboratory test)
      II. Excluding participants who died (all-cause), were lost to follow-up (LTFU), or were known defaulters/refusers, i.e. were more than 2 months late for ART refill with a reason available (e.g. currently no money for clinic-visit, busy working in South Africa, etc.)

e) Alternative viral suppression at 12 months, defined as the proportion of participants with a documented VL <1000 copies/mL 12 months (range 9 – 15) after enrolment out of all participants enrolled
   i. Rational for alternative VL suppression definition at 1000 copies/mL: According to the currently used Lesotho national guidelines, an unsuppressed VL is defined as a 1000 copies/mL or more

f) Engagement in care at 12 months, defined as the proportion of participants engaged in care 12 months (range 9 – 15) after enrolment out of all participants enrolled (definitions see above under d)

g) All-cause mortality at 6 and 12 months, defined as the proportion of participants dead 6 months (range 5 – 8) and 12 months (range 9 – 15) after enrolment, respectively, out of all participants enrolled
   i. Verbal autopsy to capture cause of death whenever possible. No death certificate or autopsy report required.

h) LTFU at 6 and 12 months, defined as the proportion of participants LTFU 6 months (range 5 – 8) and 12 months (range 9 – 15) after enrolment, respectively, out of all participants enrolled
   i. We define participants lost to follow-up if they or their treatment buddies were more than 2 months late for a scheduled consultation or medication pick-up and no information was found about the participant

i) Transfer out at 6 and 12 months, defined as the proportion of participants who transferred out to any other health facility (than the initially attached one) with known outcome (documented proof of follow-up visit or laboratory test) 6 months (range 5 – 8) and 12 months (range 9 – 15) after enrolment, respectively, out of all participants enrolled

5.3 Safety Endpoint

We specifically assess the safety of our PEBRA model, defined as the proportion of participants experiencing a Serious Adverse Events (SAE) within 12 months after enrolment out of all participants enrolled. See chapter 12.4 for a detailed description of SAEs.

TABLE 1. Summary of PEBRA study endpoints

	Following enrolment		
endpoints	***At 3 months (range: 2-5 – 3.5)***	***At 6 months (range: 5-8)***	***At 12 months (range: 9-15)***
In care with documented viral suppression <20 copies/ml			Primary
Adherence to ART	Secondary	Secondary	Secondary
QoL	Secondary	Secondary	Secondary
QoC	Secondary	Secondary	Secondary
In care with documented viral suppression <1000 copies/ml			Secondary
Engagement in care		Secondary	Secondary
All-cause mortality		Secondary	Secondary
LTFU		Secondary	Secondary
Transfer out		Secondary	Secondary
SAE			Safety

Note: we consider 1 month = 30 days

6 BIOMOLECULAR RESEARCH

In the frozen 12-month follow-up blood samples, we may assess ART drug levels as a marker for adherence. This analysis would be done in collaboration with Department of Biomedicine at University of Basel that are part of this research consortium. These samples would fall under attached Material Transfer Agreement, submitted together with this study protocol (see Appendix 18.4) for approval.

7 QUALITATIVE RESEARCH

Besides above outlined qualitative research (QoL, QoC, longitudinal description of participants' preference assessments) we will explore the acceptability of the PEBRA model in a) Focus Group Discussions (FGD) with study participants from the intervention clusters, and b) key informant interviews (KII) with the main stakeholders (District Health Management Team and different health center staff). We plan to conduct at least 2 FGD (with about 5 study participants) per district and 3 KII per district, according to the concept of saturation. Data will be collected by trained facilitators using piloted interview questionnaires and discussion guides, in the local language (Sesotho). Qualitative data will be recorded, transcribed, translated into English and coded and analyzed using the Framework Method.[27] All participants in this qualitative research will be required to sign a separate consent form to participate and to be recorded. These consent forms and interview questionnaires will be submitted as an amendment to the ethics committee in Lesotho at a later stage.

8 COST-EFFECTIVENESS ANALYSIS AND SYSTEM IMPACT EVALUATION

We will perform a system impact evaluation and cost-effectiveness analysis, in order to estimate the impact of the PEBRA model on health benefits and costs. First, we will assess the direct costs of the PEBRA model. Secondly, we will assess the cost-effectiveness of the PEBRA model. Thirdly, we will assess the economic burden of the PEBRA model to the study participants, i.e. including both direct costs and the opportunity costs of their time. The assessment of direct costs includes staff costs (PEs, clinic staff, VHWs), personnel training costs (especially for the PEs), the cost of equipment needed (PEBRApp, logistics), medical costs to the participant (medication, laboratory tests, consumables, etc.), and non-medical costs to the participant (i.e. cost of transportation to ART service). Data to assess patient level costs will be collected from a randomly selected sub-sample of study participants from each cluster arm, using medical expenditure records and interviews. Cost outcomes will include:

i) The average cost to the service provider per patient achieving the primary endpoint at 12 months in each cluster arm ('per patient suppressed provider cost')
ii) The average cost to the patient per patient achieving the primary endpoint at 12 months in each cluster arm ('per patient suppressed patient cost')
iii) The annual cost per patient in each cluster arm ('per patient year cost')
iv) The cost-effectiveness of the PEBRA model with respect to viral suppression and engagement in care

Costs will be reported as means (incl. standard deviations) and medians (incl. interquartile range) in local currency and US dollar and International Dollar.

9 PREFERENCE AND FEASIBILITY ASSESSMENT

We will systematically assess the following exploratory analyses regarding feasibility and youth ART service preference:

1) Youth ART service preferences: Longitudinal description of participants' preference assessments
2) Feasibility of youth ART service according to preferences: Percentage of ART service delivered according to participants' preferences
3) Differentiated Impact of the different support options on key study outcomes

10 PILOT TRIAL

PEBRA model will be piloted at one representative health facility in Butha-Buthe district, that will be pragmatically chosen in collaboration with the District Health Management Team. The pilot trial will be crucial to assess feasibility of the PEBRA model and the study procedures. The same procedures apply in the pilot trial as outlined in section 4.3.4 and 4.3.5, using the same consent process and baseline data collection. One PE will be specifically trained for the pilot. Recruitment for the pilot will be closed once 3-5 study participants are enrolled and follow-up will last for 2.5 months after having enrolled the last participant. All endpoints that are mentioned in Table 1 under "At 3 months (range 2.5 – 3.5)" will be assessed and analyzed. The aim of the pilot trial is to give a first insight into PEBRA model and provide detailed information for the main trial.

11 SAMPLE SIZE AND ANALYSIS PLAN

11.1 Sample size calculation

Based on data from our database with VL results from all health facilities of Butha-Buthe and Mokhotlong district (VL platform, www.lstowards909090.org/db), there are on average 15 AYPLHIV per health center with an overall viral suppression rate of 70%, thus, we expect this proportion of viral suppression for the control clusters. An overall target sample size of 300 AYPLHIV in 20 clusters (10 per arm) will provide us 90% power (design effect of 1.7) to detect a 20% increase of viral suppression in the intervention group, assuming a type 1 error of 0.05, and an intra-cluster correlation coefficient (ICC) of 0.05, an ICC based on similar studies[28,29].

11.2 Analyses

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

Clusters will be set as unit of randomization (stratified by district), whereas individuals are set as unit of analysis. Multilevel random effects models will be used to analyze the data. We will present a CONSORT flowchart of the participants, including screening, enrollment and follow-up. The following analysis sets will be used in this trial:

1. Intention-to-treat (ITT) set: All study participants will be evaluated according to cluster assignment at randomization
2. Per-protocol (PP) set: This set includes all participants who completed the study without a major protocol deviation

11.2.1 Primary analysis

The primary analysis will use multi-level logistic regression models (on the intention-to-treat set) including clinic as random effect to assess the difference between viral suppression rate in the intervention versus control arm, adjusted for the pre-specified randomization stratification factor, baseline VL, and relevant

baseline factors that may be randomly unbalanced between intervention and control clusters. All results will be presented as odds ratios and their respective 95% confidence intervals (CI).

11.2.2 Baseline characteristics; secondary, exploratory, subgroup and sensitivity analyses

Baseline characteristics will be presented according to randomized groups, no formal testing will be performed. Categorical variables will be described as absolute and relative frequencies and continuous variables as medians and interquartile ranges. As with the primary analysis, secondary (binary and categorical) endpoints will primarily be analyzed with multi-level logistic regression models and presented as odds ratios and their respective 95% CI. To estimate incidence of attrition (defaulting from care), a poisson regression will be used. We will do a quadature check of the model fit and it found to be unreliable, we will utilize generalized estimating equations. The effect of sociodemographic and clinical determinants (age groups, gender, employment status, WHO-stage, CD4-count, HIV/ART history, HIV/AIDS knowledge, HIV/AIDS stigma) on key study outcomes will be assessed by including interaction terms in the model. If the interaction term is found to be significant, effect estimates will be summarized descriptively by subgroup. As the study is not powered for these pre-planned subgroup analyses, these results will be considered exploratory.

12 DATA MANAGEMENT, BIOLOGIC MATERIAL, MONITORING, SAE

12.1 Data entry, data monitoring, data storage, data confidentiality

The PEs collect data directly in two tablet-based applications: PEBRApp (patient management tool and data collection tool) and KoboToolbox (data collection tool, incorporated in PEBRApp). The PEBRApp is password-protected and only accessible to the peer-educator that is responsible for the participant. All data will be regularly uploaded into at a password-protected database. Similarly, relevant data for the SMS intervention will be entered and stored in a separate encrypted and password-protected online database, that offers the possibility to send out SMS automatically and is connected to the district laboratory database containing the VL results (VL platform, www.lstowards909090.org/db). The VL platform data are stored on a dedicated server in a data center, which meets FINMA-RS 08/07 requirements, is ISO-27001-certified, encrypts data in-transit with SSL and all patient names at-rest using OpenSSL with AES-256-CTR cipher method. SMS are dispatched using the trusted third-party provider Twilio, certified with the Privacy Shield Framework. Access to all data collection tools and databases are strictly limited and regulated through personal user profiles.

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

Following an initial period of weekly quality review, a study data manager will monitor data quality and completeness on a bi-monthly/monthly basis. Queries about the data will be sent to the local team for follow-up and correction, as needed. Data integrity checks will be written into the data collection tools to limit the entry of incorrect data and ensure entry of data into required fields.

Apart from the informed consent form, the study documents and data collection tools will not contain any names but solely the study-ID or unique ART number. There will be one confidential electronic master list with the subject identification code and the names. The informed consent forms will be stored in a secure way in the headquarter of the study center (SolidarMed Office in Butha-Buthe, Lesotho) and the master list will be stored in an encrypted online cloud with password controlled access and only accessible for predefined study personnel. Participant files will be maintained in storage for a period of at least 10 years after completion of the study.

12.2 Management of biologic material

Additionally, collected standard-lab-ID-coded blood samples would be stored at -80°C at the laboratory of Butha-Buthe government hospital. All samples that are stored at Butha-Buthe Government Hospital Laboratory fall under the current biobanking regulation agreement (“Biobanking regulations, v2.0”), approved by the ethics committees in Switzerland and Lesotho, and under the attached Material Transfer Agreement, submitted together with this study protocol (see Appendix 18.4) for approval. Remaining sample material after analysis of the ART drug levels will be destroyed.

12.3 Monitoring and Data Safety Monitoring Board (DSMB)

At least one external monitoring visit will assess compliance with the approved trial protocol, accuracy of completed data entries, and the electronic dataset. The Principal Investigator agrees to allow inspectors from regulatory agencies to review records and will assist the inspectors in their duties, if requested.

The PEBRA study represents implementation research, safety profiles of all used drugs are well-known, and the intervention does not include any new drugs. We do not expect major adverse effects on patients' health from this intervention. Moreover, participants in the PEBRA model can opt to switch back or be referred to facility-based care at any time during the trial period. Therefore it is not planned to establish a DSMB. Nevertheless, a safety monitoring plan for (Serious) Adverse Events has been outlined (see chapter 12.4) before the trial start.

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

Prescription and use of ART will follow current national guidelines of Lesotho. All ART used in Lesotho have a well-established safety profile. The most frequent adverse events are summarized on page 54 of the Lesotho national guidelines on the use of antiretroviral therapy for HIV prevention and treatment, 5th edition, 2016[30] and on page 138 of the consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection of the WHO[31]. AE and SAE will be graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0., November 2014[32] and managed according to study sites standard procedure following the national guidelines. SAEs are defined as follows: a) life-threatening event, b) hospitalization, c) persistent or significant disability or incapacity, d) congenital anomaly / birth defect, e) death. In case of SAEs, any study personel must inform one of the study physicians within 72 hours of his/her awareness of the SAE. The study physicians must then inform the Principal Investigator within 24 hours of his/her awareness of the SAE. The Principal Investigator will inform the local ethics committee in Lesotho within 48 hours. The study physicians are responsible for all direct safety procedures among study participants. If a participant develops an AE of Grade 2 or higher at last study visit, he/she remains under observation by the study physicians until the AE is resolved or stabilized.

13 ETHICAL CONSIDERATIONS

13.1 Research ethics approval / Informed consent / Amendments

This trial will be conducted in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice E6 and the current version of the Declaration of Helsinki. Ethics approval will be sought from the National Health Research and Ethics Committee of Lesotho and the Ethikkomission Nordwest- und Zentralschweiz (EKNZ) in Switzerland and the trial will only commence once both committes have awarded approval. This is a cluster randomized health systems implementation research trial, thus its informed consent process is based on two fundamental principles that need to be balanced[33,34]:

First, specific ethical requirements (e.g., informed consent, confidentiality, avoidance of harm) should be fulfilled. Second, a generally accepted claim is that a study being methodologically sound constitutes a necessary condition for its being ethically sound. Because only sound design can produce valid findings, methodological demands carry moral weight. In cluster-randomized trials, if participants would be aware of their cluster assignment and would know that there is another cluster arm with a different intervention, it would introduce the possibility of post-randomization selection bias and compromise the methodology. Some even argue that no individual informed consent should be obtained in a cluster-randomized trial in order to sustain a high-quality and sound methodology.[34] However, in our view we value individual consent higher and hence propose the following approach:

- Before cluster randomization, verbal consent from all health facility managers and the respective District Health Management Team will be obtained
- Before inclusion into PEBRA study we will obtain individual informed consent (for data collection and blood draw during follow-up), but using two different Informed Consent Forms (ICF) to keep the risk of selection bias as low as possible by concealing the allocation: One ICF for participants in PEBRA intervention clusters and one ICF for participants in PEBRA control clusters.

The trained PEs will obtain the individual informed consent from the participant before inclusion into PEBRA study. The investigator will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. All participants will receive an information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study before signing the consent form. Iliterate study participants will provide a thumb-print and a literate witness (independent to

the trial and chosen by the participant) will co-sign the form. The informed consent is provided in the local language, Sesotho, and the participant will receive a copy of the consent form. The participant has the right to withdraw consent at any time without giving reasons. In case of withdrawal, only data collected until the time of withdrawal will be used for research purposes (fully anonymized, identifyer removed) and the participant will be managed according to standard of care.

This research includes adolescents and young people from the age of 15 years and older, a key group that is often neglected in research projects. One reason is that the consent process for people below 18 years is more complicated and usually requires a caregiver. This leads to decreased feasibility (e.g. most AYPLHIV do not come with their caregivers to the health facility) and to a negative bias in the study (e.g. caregivers not consenting although the AYPLHIV would agree). This is an operational research project, that does not test any new medication or experimental substances, but tries to tailor the services more according to the preferences of the AYPLHIV with the help of peer-educators and an electronic application. We strongly feel that it is feasible, justifiable and very important that these young people living with HIV give consent without parental consent, as it is being discussed in other research projects.[35–39] Hence, we apply for a waiver of the parental consent for this specific research project.

Any modifications to the protocol which may impact on the conduct of the study, potential benefit to the patient or patient safety, including substantial changes of the study protocol, will require a formal amendment to the protocol and will be submitted to the Ethics Committee of Lesotho and the trial register (clinicaltrials.gov) will be updated accordingly.

13.2 Publication and Dissemination policy

Results of this research project will be shared at three levels. At the district and community level, during meetings headed by the District Health Management Team, such as at the PHC (primary health care) meeting where - in addition to the District Health Management Team - also representatives from all health centres are present. At the national level, at the national research symposium of the Ministry of Health, and at the international level through presentations at conferences (especially at the conferences of the International AIDS Society) and publications in peer-reviewed journals. The current version of the ICMJE recommendations[40] is applicable regarding authorship eligibility and the use of professional writers is not intended. Before trial start, PEBRA study will be registered in the trial register ‘clinicaltrials.gov’.

13.3 Compensation

13.3.1 Study participants

Participation in this study is not anticipated to cause any substantial additional risk or cost to the participant. Therefore, we will not pay compensation to the participants.

13.3.2 Study personel

As the incentive for PEs currently differs, we will ensure that all involved PEs receive a minimum stipend per month. They will receive an android-based tablet with the two applications (PEBRApp & KoboToolbox) installed, a simcard, and regular AirTime (prepaid money for calling and for data usage) for the duties of the study.

14 Withdrawal of participants and Discontinuation of trial

14.1 Withdrawal

The study participant has the right to withdraw from the study at any time without giving reasons. In case of withdrawal, only data collected until the time of withdrawal will be used for research purposes (fully anonymized, identifyer removed). Discontinued participants will not be replaced. A participant or cluster (if applicable) can be withdrawn from the study by the Principal Investigator for the following reasons:

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

14.2 Discontinuation of the entire study

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

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

The Sponsor/Prinicipal Investigator would provide written notice and instructions for study termination submitted at a reasonable time to all involved stakeholders.

15 FUNDING SOURCES AND ROLE OF THE FUNDING SOURCES

This trial is predominantly funded by a CIPHER grant from the International AIDS Society, obtained by AA. AA receives his salary through a grant from the MD-PhD programme of the Swiss National Science Foundation (Grant number 323530_177576). Further funding came from a grant of the Stiftung für Infektiologie beider Basel and two grants from the Swiss National Science Foundation (Grant Number IZ07Z0_160876/1 and Grant Number PCEFP3_181355), all obtained by NDL. The Swiss TPH acts as sponsor of the study. The study is embedded in the SolidarMed country programme and thus benefits from logistics and human resources from SolidarMed Lesotho. The same applies for Sentebale Lesotho.

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

16 STUDY TIMELINE

We expect recruitment to start August/September 2019 and a total study duration of approximately 18 months. Figure 3 illustrates the time-line of PEBRA study, incl. preparation and pilot phase. We anticipate a recruitment period of 4-5 months.

FIGURE 3. Time-line of PEBRA study incl. preparation and pilot phase

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18 APPENDIX

18.1 Staff List (incl. CVs, diploma, GCP)

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

18.2 Informed Consent Forms

We refer to attached documents, called “PEBRA study_ICF-Intervention” and “PEBRA study_ICF-Control”, both in english and sesotho.

18.3 Case Report Form

We refer to attached document, called “PEBRA study_CRF/Codebook”

18.4 Material Transfer Agreement

We refer to attached document, called “PEBRA study_MTA”