# Title of Proposal

**Can Undetectable (viral load) = Untransmissible (virus) change the life course of adolescents living the HIV in Africa?**

# Acronym

CUUA

# Protocol Team

Dr Zivai Nenguke
Prof Frances Cowan
Dr Sarah Bernays

# Organization

Centre for Sexual Health and HIV AIDS Research Zimbabwe (CeSHHAR Zimbabwe)
4 Bath Road
Belgravia

**Protocol version 2.0**

# Table of Contents


Title of Proposal ..... 1
Abstract ..... 3
Introduction ..... 4
Background and significance ..... 4
Research question ..... 5
Rationale ..... 5
Aim ..... 5
Methods ..... 6
Study design and setting ..... 6
Procedures ..... 8
Quantitative interviews ..... 8
Qualitative interviews ..... 9
Inclusion criteria ..... 9
Exclusion criteria ..... 9
Data management and analysis procedures ..... 9
Quantitative data management ..... 9
Qualitative data management. ..... 9
Managing, storing and curating data. ..... 10
Metadata standards and data documentation. ..... 10
Data preservation strategy and standards. ..... 10
Data security and confidentiality of potentially disclosive information ..... 11
Main risks to data security ..... 11
Data sharing and access ..... 11
Responsibilities ..... 11
Ethical Considerations ..... 11
Informed consent ..... 12
Voluntary participation ..... 12
Confidentiality ..... 12
Potential Risks to participants ..... 12
Benefits ..... 12
Child protection and safeguarding ..... 12
Expected outcomes and impact on programmes and policies ..... 13
Dissemination and exploitation of results ..... 13
REFERENCES ..... 15

## Abstract

Rationale: Adolescents living with HIV (ALHIV) have the worst outcomes of all ages because of sub-optimal adherence driven by structural factors associated with poverty. This is exacerbated for adolescents by the limited opportunities to address mental health problems arising from the intersection of growing up in poverty and with HIV. The scientific breakthrough related to Undetectable (viral load) = Untransmissible (virus) has had a major impact on motivation to take up and adhere to antiretroviral therapy among people living with HIV all over the world. However, the discussion remains remarkably silent in high burden, low-income countries (LIC). Very few ALHIV in LIC are aware that having an undetectable viral load (VL) substantially reduces the risk of transmitting HIV to their sexual partners and children.

***Aims:*** The aim of the study is to work with MoHCC and other stakeholders to explore whether routine VL testing using DBS can provide sufficiently robust evidence of 'undetectability' to support introduction of U=U messaging in ALHIV.

***The specific objectives are:***

1. To determine viral load fluctuation between routine annual VL testing and the extent to which annual VL using DBS reflects short term fluctuations that occur in the interim.
2. To determine what proportion of ALHIV with VL <1000 copies/uL on DBS have a plasma VL less than 200 copies/uL
3. To explore the reasons for and adolescent's understandings of fluctuations in VL and what a VL<1000 copies/mL means to ALHIV

***Methods:*** This mixed method study will be conducted in conjunction with key stakeholders. We will enrol 300 ALHIV with a recent VL<1000 copies/uL in three HIV clinics in Harare and follow them for 12 months. Of these, 100 will be randomly selected to undergo repeat VL testing, using both DBS and plasma samples at enrolment, 6 and 12 months. A purposive sample of twenty will be selected for a longitudinal qualitative study. Additionally, up to eight participatory workshops will be conducted with key stakeholders over the course of the study to co-develop a 'safe' way to message U=U for LIC.

***Potential impact:*** The study will provide scientific evidence on whether routine VL testing using DBS as available in LIC can provide sufficiently robust evidence of 'undetectability' and on the variability of an individual's virological response over 12 months. It will provide contextually orientated evidence to inform U=U messaging which has the potential to change the motivation of ALHIV to engage with their treatment and care.

# Introduction

## Background and significance

Adolescents living with HIV (ALHIV) have the highest HIV-related morbidity and mortality of any age group as a result of suboptimal adherence to ART (1-4) and are falling far behind the global targets of 90-90-90 (5, 6). The majority of ALHIV live in East and Southern Africa where poverty is an overarching factor that increases vulnerability to, and the impact of, HIV. Poverty includes deprivation, constrained choices, and unfulfilled capabilities, and refers to interrelated features of well-being that impact upon the standard of living and the quality of life (7). Combined data from East and Southern African countries show that only 45% of adolescent girls living with HIV have attained the UNAIDS 90-90-90 virological suppression target (73% of those diagnosed and on treatment should be virologically suppressed) (8). As a result, they are more vulnerable to antiretroviral resistance, treatment failure and progression to expensive second- and third-line regimens than other age groups (9, 10) as well as AIDS related illness and death. A major driver of these high rates of morbidity and mortality is suboptimal adherence, which is in turn driven by a complex web of social and structural factors. It is the poorest and most vulnerable ALHIV who are most at risk of treatment failure (11).

There is now convincing evidence from HIC that people living with HIV who are virologically suppressed are at minimal risk of HIV transmission (12, 13), providing PLHIV with added motivation to optimize their adherence to antiretroviral therapy and enabling them to have intimate sexual relationships without fear of transmitting HIV (13). Despite the transformative effects of U=U, very few ALHIV are aware of the clinical relationship between having an undetectable viral load and rendering the virus untransmissible (13, 14).
To date major operational, funding, logistical and developmental concerns have influenced the absence of the U=U discussion at a policy level within LIC. There is increasing opportunity for these concerns to be overcome, which means that the reticence to explain the implications of viral suppression to adolescents needs to be revisited and adjusted. To capitalize on the value of achieving an undetectable viral load we need to do much more to explain the benefits of this to adolescents to incentivise optimal adherence, but also potentially to support their wellbeing and mental health by highlighting the opportunities that accompany viral suppression. We need to do so by discussing virological suppression/failure within the context of their personal goals and priorities, which are focused on their social and sexual relationships and their capacity for future productivity and reproductivity, goals which may seem more achievable in the context of U=U.

Zimbabwe and many other sub-Saharan countries are transitioning to Tenofovir Disoproxil Fumarate, Lamivudine and Dolutegravir (TLD) from TLE as a first-line regimen in line with the World Health Organization (WHO) recommendation. The transition was due to be completed by December 2020 but may be delayed (or possibly accelerated) in light of COVID19. Recent systematic reviews and meta-analysis conducted have shown that TLD is more potent, suppressing viral load more quickly compared to EFV-based regimens (15, 16). Eighty-one percent of individuals who started with a DTG-based regimen presented a viral load below 50 copies/ml after 3 months of treatment, compared to 61% for those on an EFV-based regimen (15). Furthermore, TLD is more durable, featuring a higher drug-resistance barrier compared to NNRTIs and older integrase inhibitors and thereby reducing the risk of drug resistance (17). Although studies from high income countries have shown an improvement in viral suppression, this is not universal and evaluations to determine TLD's place as first-line and second-line therapy in adolescent and paediatric HIV treatment in low-income setting are ongoing. Of relevance is that adolescent adherence is often related to wider structural concerns rather than simply forgetting to take tablets and so adherence may be poor for prolonged periods of time which TLD may be less able to mitigate. Understanding whether U=U in the context TLD will be critical going forward.

Zimbabwe adopted the WHO guidelines on routine VL testing as standard practice in 2015 amidst several resource and logistical challenges (18-20). These include unsuitable laboratory infrastructure, complex sample collection procedures, transportation of samples to central laboratories from all over the country, unreliable power supply, water supply and air-conditioning; non-adherence to cold chain transportation of the reagents, lack of experienced laboratory personnel and the absence of maintenance contracts for the equipment (19). Although routine coverage of VL testing and monitoring is still erratic the Zimbabwean government has made a commitment to increasing laboratory capacity and aggressively scaling-up VL testing to ensure access to VL testing services by at least 90% of people living with HIV (PLHIV) receiving ART by December 2020. Through support for universal VL testing

from GFATM and PEPFAR, strides have been made in strengthening the laboratory infrastructure, sample transportation, data management, procurement and supply chain management, training and mentorship, quality assurance and monitoring and evaluation which are crucial areas to the success of VL testing scale up (19).

## Research question

The main research question for this study is:
Can messaging relating to Undetectable (viral load) = Untransmissible (virus) change the motivations and adherence of adolescents living the HIV in Africa?
The study therefore aims to answer three key questions: i) what is the evidentiary robustness of a VL 1000c/uL measured using a DBS sample to be considered 'undetectable? ii) what are the perceived risks and opportunities of incorporating U=U into routine HIV treatment and care for adolescents in LIC and iii) can locally acceptable and appropriate ways to integrate the discussion about undetectability into standard of care for ALHIV be developed for Zimbabwe in partnership with stakeholders?

## Rationale

Adolescents living with HIV (ALHIV) have the worst outcomes of all ages because of suboptimal adherence driven by structural factors associated with poverty (2, 8). This is exacerbated for adolescents by the limited opportunities to address mental health problems arising from the intersection of growing up in poverty and with HIV (21). The scientific breakthrough related to Undetectable (viral load) = Untransmissible (virus) has had a major impact on motivation to take up and adhere to antiretroviral therapy among people living with HIV all over the world (13) although even in high income settings the messaging is variable (22). However, the discussion remains remarkably silent in high burden, low-income countries (LIC). Very few ALHIV in LIC are aware that having an undetectable viral load (VL) substantially reduces the risk of transmitting HIV to their sexual partners and children. The study will provide scientific evidence on whether routine VL testing using DBS as available in LIC can provide sufficiently robust evidence of 'undetectability' and on the variability of an individual's virological response over 12 months and between those considered undetectable (<1000) and those undetectable and untransmissible (<200).

U=U messaging has potential enabling effects on adherence and onward disclosure of HIV status but there is very little evidence in Zimbabwe or sub-Saharan Africa on how best the importance of viral load levels and the message of U=U can be communicated to young people and with what implications. There has been limited discussion on whether or how this can be incorporated into routine care in LIC, even for adults. This is in part explained by two things. Firstly, the scarce availability of viral load testing in LIC, where quality of both sampling and testing may be variable. In HIC the U=U message is supported by regular VL testing using plasma samples with a cut off for 'undetectability' of <200copies/uL (although the PARTNER study which looked at transmission in 551 heterosexual partners also found no transmission between partners where the index case had a VL of 200-1000 c/uL (14)).

Secondly, the lack of U=U discussions may reflect reticence and possibly stigma among the community delivering HIV care and support to ALHIV about whether young people would respond responsibly to this information; they are uneasy about the potential disruptive effects of this message (22). Whether it is advisable to promote U=U also rests on young people's likely understanding of the messaging; currently there is little knowledge of how an undetectable VL might be interpreted by ALHIV in LIC, what it means for them and their futures and whether it motivates or undermines their intention to adhere. With limited opportunity for ongoing or more nuanced discussion about their illness, their understanding of HIV is often static and may not be updated in response to scientific advances or to meet their evolving needs, depriving ALHIV of the opportunity to develop their understanding of the changing nature of the management of HIV or the benefit of the changing meanings of HIV. U=U may ameliorate stigma associated with it (22). This study will provide contextually orientated evidence to inform U=U messaging to guide both policy makers and healthcare workers on how U=U can be integrated in the routine care of ALHIV in Zimbabwe. The study will also be relevant to other comparable LIC in the region.

## Aim

The study aims to provide scientific evidence on whether routine VL testing using DBS as available in LIC can provide sufficiently robust evidence of 'undetectability' and on the variability of an individual's

virological response over 12 months and between those considered undetectable (<1000) and those undetectable and untransmissible (<200). We therefore propose to conduct a longitudinal study to i) determine at what 'threshold' U=U might be safely promoted in this setting; ii) explore ALHIV's understanding and or interpretation of the VL results. The study will also explore responsible ways to disseminate this message to ALHIV living in Zimbabwe, and across the Southern African region.

Our specific objectives are:

1. To determine viral load fluctuation between routine annual VL testing and the extent to which annual VL using DBS reflects short term fluctuations that occur in the interim.
2. To determine what proportion of ALHIV with viral load <1000 copies/uL on DBS have a plasma VL less than 200 copies/uL
3. To explore the reasons for and adolescent's understandings of fluctuations in VL (measured using standard of care DBS) and what a VL<1000 copies/mL means to ALHIV
4. To explore the perceived risks and opportunities of incorporating U=U into routine HIV treatment and care for ALHIV in LIC
5. To explore with key stakeholders the implications of our findings for the feasibility and framing of the U=U message in LIC for ALHIV.

# Methods

## Study design and setting

A longitudinal mixed method study will be conducted in Harare City Health Department at three high volume clinics (BRIDH, Kuwadzana and Rujeko). All the clinics provide care as part of the Paediatric Opportunistic Infection and Antiretroviral Therapy program (OI/ART) and started conducting routine viral load testing in 2016. BRIDH has capacity for onsite VL testing. The three clinics are situated in the low-income and overpopulated residential suburbs which are ranked among the poorest residential areas in Harare (Mbare, Kuwadzana and Dzivarasekwa). The clinics mainly serve people from poor households. BRIDH is located in Mbare residential suburb which is one of the oldest and most impoverished residential suburbs in Zimbabwe.

**Aim 1 and 2: To determine viral load fluctuation between routine annual VL testing and the extent to which annual VL using DBS reflects short term fluctuations that occur in the interim and to determine what proportion of ALHIV with viral load <1000 copies/uL on DBS have a plasma VL less than 200 copies/uL**

The study will explore the sensitivity of viral load testing so that decisions can be made on the best use of resources in optimizing the care and support that can be given to ALHIV in the region. This component will utilize primary and secondary data. Three hundred ALHIV with a recent VL<1000 copies/uL will be randomly selected from clinic registers complete a structured questionnaire. Interviews will explore demographic characteristics, self-reported ART adherence and knowledge of U=U. In depth analysis of ALHIV' VL trajectories will be conducted on a randomly selected sub sample of 100 ALHIV using 6 monthly finger prick DBS and plasma VL sampling to provide evidence on the fluctuation in an individual's virological response over 12 months and how this differs between those considered virologically suppressed (<1000 copies/uL) and those undetectable and untransmissible (<200 copies/uL). Secondary data will be collected from clinic records on HIV treatment history, drug regimens, VL testing (include VL at enrolment and 12 months).

**Aim 3: To explore the reasons for and adolescent's understandings of fluctuations in VL (measured using standard of care DBS) and what a VL<1000 copies/uL means to ALHIV.**

A purposive and theoretical subsample of 20 ALHIV will be selected to participate in longitudinal qualitative interviews at enrolment, 6 and 12 months after receiving their VL result. The subsample will be selected from the quantitative sample. Theoretical sampling is defined as interviewing directed by evolving themes rather than focusing on predetermined populations. Purposive and theoretical sampling are strategies employed to ensure that the participants involved have a wide range of experiences, relevant to answering the research question, but also limit the scale of the data collection so that detailed analyses could be conducted. Interesting dynamics such as duration on ART, current regimen (first/second line), mode of transmission among other things will be considered among other characteristics.

Interviews will explore reasons for consistent/fluctuating VL and their understandings of why and what is happening. We will explore whether having a VL<1000copies/uL motivates them to adhere and whether and how learning that they have a fluctuating or high VL affects their subsequent motivation to adhere and or their wellbeing, as well as the influence, if any, on their experience of HIV stigma. The interviews will also explore what being undetectable means for ALHIV and what influence it has, if any, on their adherence motivation and behaviour alongside developing a broader understanding of the effects of social context, including events in their daily life, on their engagement with and adherence to ART and their understandings of the social meanings of living with HIV. These in-depth interviews will also explore whether and how learning that they have a fluctuating or high VL affects their subsequent motivation to adhere and or their wellbeing, as well as the influence, if any, on their experience of HIV stigma. Interpretations of how the VL results are described to ALHIV by clinic staff will also be explored. Data collection will be an iterative process, where all the interviews will be transcribed and translated in order to inform individualized guides for subsequent in-depth interviews.

**Aim4: To explore the perceived risks and opportunities of incorporating U=U into routine HIV treatment and care for ALHIV in LIC**

Up to four participatory workshops will be conducted with healthcare workers and ALHIV to explore perceived risks and opportunities of incorporating U=U into routine treatment and care for ALHIV in LIC. It is well documented that adolescents' understanding and acceptance of their HIV status and engagement in their treatment is also critical to attaining U=U. The workshops will unpack some of the key challenges that undermine ALHIV's engagement. The first two workshops will be with policy makers to discuss the findings and explore their perceptions on the feasibility of implementing policies related to U=U in this age group. Additionally, their views will be elicited around whether they consider there is 'safe' U=U messaging for LIC that could be implemented logistically, clinically and socially. The last two workshops will include policy makers, healthcare workers and ALHIV to explore the social understandings of and the health system response to the role of undetectable VL results in supporting care to ALHIV.

**Aim 5: To explore with key stakeholders the implications of our findings for the feasibility and framing of the U=U message in LIC for ALHIV.**

Working with the Ministry of Health and Child Care to develop locally appropriate ways of incorporating U=U into routine HIV treatment and care among ALHIV in Zimbabwe. I have already set up a technical working group comprising members from the MoHCC, Africaid Zvandiri and UNICEF. This was made possible through a UNICEF supported small-scale resource development project which is supporting development of resources for ALHIV to improve their HIV literacy and particularly their literacy related to viral load testing, which has been relatively recently introduced into routine HIV care in Zimbabwe. The UNICEF supported project aims to increase understanding about the importance of achieving, monitoring and maintaining viral suppression primarily for prevention of disease progression but also for prevention of mother to child transmission and potentially sexual transmission. Although UNICEF is supporting the small project viral load data will not be collected so the messaging will largely relate to understanding what viral load means rather than whether U=U is a valid message to promote. The study proposed here will provide opportunity for more in-depth exploration of issues and generation of biological evidence to support or refute perceptions and be integrated into materials so that the messaging is clinically sound for what is feasible and deliverable in the Zimbabwean context (and potentially other similar settings within the region).

This study will benefit from the technical working group established as part of the UNICEF project. The participatory workshops will include members from the technical working group and other key stakeholders (policy makers and healthcare workers) to discuss the findings from ALHIV interviews and explore their perceptions on the feasibility of implementing policies related to U=U in this age group. Additionally, their views will be elicited around whether they consider there is 'safe' U=U messaging for LIC that could be implemented logistically, clinically and socially. The workshops will explore the social understandings of and the health system response to the role of undetectable VL results in supporting care to ALHIV, which may or may not include the feasibility of adopting and adapting the U=U message in the Zimbabwean context. We aim to establish the implications of the health systems variation in provision of VL testing between clinics with or without onsite VL. A range of methodological approaches will be used.

## Procedures

### Quantitative interviews

The sample size for ALHIV will be calculated with reference to the total number of ALHIV aged 13-19 years on ART with a VL <1000copies/uL taken within 6 weeks of study launch from the 3 sampled clinics according to the clinic records. A list of all ALHIV aged 13-19 on ART will be drawn from the ART registers from this, a systematic random sample will be selected to recruit 300. The sample sizes will be calculated using a margin of error of 5 %; confidence interval of 95% and response distribution of 50% (http://www.raosoft.com/samplesize.html). The figure obtained will be shared among the 3 clinics using Probability Proportionate to Size (PPS) sampling. ALHIV taking account age, recency of disclosure, duration on ART and current ART regimen and will be shared among the three clinics using Probability Proportionate to Size (PPS) as in figure 1 below.

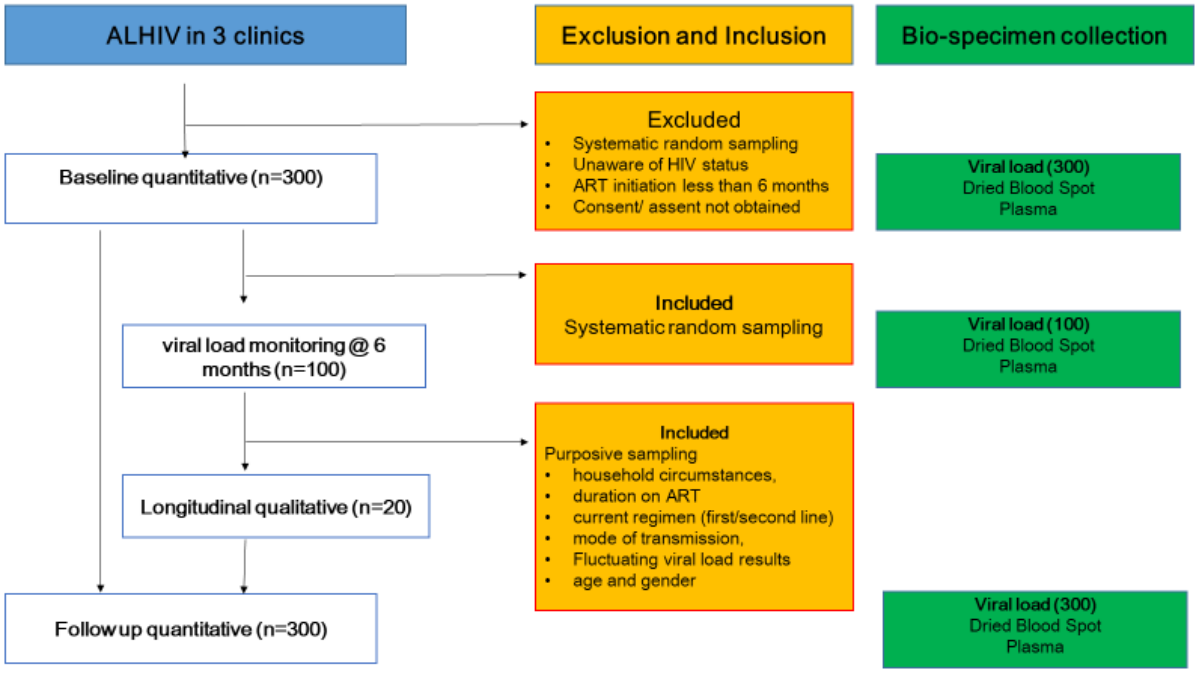


*Figure 1: Recruitment flow chart*

The quantitative subset of 100 ALHIV who will have intensive follow up and will provide plasma and DBS samples VL testing at enrolment, 6 and 12 months will be randomly selected. Ideally, we wanted to have intense follow up on all 300 participants however due to limited resources we reduced the sample size for intense follow up to 100 participants.

Eligible participants will be drawn from the clinic records with the assistance of the clinic nurses. A list of potential eligible participants per clinic containing the residential suburb, name and contact details will be given to the Africaid Zvandiri Community Adolescent Treatment Supporters (CATS) working in the clinics for recruitment during regular support group meetings or through the phone. CATS are ALHIV aged 18-24 years who are trained by Africaid and MOHCC to provide support to other ALHIV. All the clinics are supported by Africaid and offer psychosocial support services to ALHIV through a combination of home visits and support groups. Willing participants will be invited to the clinic and will be introduced to the research team. After being given study information, interested participants who met the inclusion criteria and willing to provide written informed consent were recruited.

Subject to feasibility, all interviews will be conducted in ALHIV's HIV clinics in private and conducive interview rooms. In exceptional cases, where the public sector clinics have limited space interviews will be conducted at the CeSHHAR office. All participants and their parents/caregivers will be reimbursed for their transport costs and given a token of appreciation in line with local ethics committee guidelines for participating. Were possible interviews will be scheduled around the same time ALHIV attend their routine clinic visits to minimise visits to the clinics. No direct household or community contact will be

made by the research team in order to avoid inadvertent disclosure of their HIV status and to prevent the risk of stigma and discrimination of participants.

Participants will complete a structured questionnaire using Audio Computer-Assisted Self- Interview (ACASI) at enrolment and after 12 months. Interviews will explore demographic characteristics, self-reported ART adherence, changes in treatment and illness and knowledge of U=U. Data will be collected from clinic records on HIV treatment history, drug regimens, routinely collected VL results.

### Qualitative interviews

The longitudinal qualitative subsample of 20 participants will be theoretically selected from the baseline cohort. As part of the mixed method study design, the quantitative analysis will inform the dimensions of the qualitative sample. Key sampling characteristics which emerge as being pertinent for inclusion and exploration within the qualitative sample will be identified from the quantitative analysis. Household circumstances, duration on ART, current regimen (first/second line), mode of transmission may be considered among other characteristics. Theoretical sampling is based on specific characteristics and directed by evolving themes rather than focusing on predetermined populations (25). Our sampling will ensure participants have a wide range of experiences, relevant to answering the research questions.

A sample of 20 participants for in-depth qualitative studies is anticipated to be large enough to ensure a broad coverage of the specific questions and to ensure theme saturation. Given the interview design (enrolment, 6 and 12 months), the proposed sample size (20 x 3 phases) will enable the quantity of data collected to remain manageable (n=60 interviews) within the timeframe to allow thorough and rich analyses. The longitudinal approach will allow the study to capture changes over time with regards to how adolescents understand VL testing. Eight (8) participatory workshops will be conducted with 20 key stakeholders including healthcare workers with direct contact with the ALHIV and have been involved in viral loaf results counselling and participating clinics.

## Inclusion criteria

ALHIV aged 13-19 years who are aware of their HIV status for at least six months before enrolment (i.e., know the infection by its name and understand some of its implications).
ART initiation of not less than 6 months.
**Adolescents aged 13-19 with viral load threshold of <1000/uL.**
ALHIV accessing ART within the participating clinics.
Healthcare workers with direct contact with ALHIV and have been involved in viral load result counselling in participating clinics.

## Exclusion criteria

Unable to provide informed assent/ and parental informed consent.
Requires urgent medical attention or has severe mental health problems that would invalidate the informed assent/consent process or else contraindicate participation.

## Data management and analysis procedures

Quantitative data will be collected on password protected and encrypted tablets. Qualitative interviews will be audio recorded; hand-written notes will be taken down as back-up. The Principal applicant will train, supervise and support data collection.

### Quantitative data management.

Data management will take place at CeSHHAR Zimbabwe under the direction of Jeffrey Dirawo and Zivai Nenguke. JD will be responsible for all data management protocols and quality assurance (QA) processes. Most data on this project will be computer-entered, with appropriate consistency and completeness checks to minimize errors and missing data. This allows data to be transmitted in real time to a central database, thus reducing concerns about data safety and problems with data storage.

### Qualitative data management.

Audio files and notes taken during interviews will be stored securely in a folder on the server. Only authorised research team members will have access to this folder. All data will be stored securely in a manner proportionate to the volume and the sensitivity of records involved and will ensure compliance

with the CeSHHAR General Data Protection Regulation (GDPR), national and EU guidelines. All identifiers (address, telephone and names) will be stored separately and linked by a project key. They will be archived and released for use only for data linkage that has been approved by the participant and relevant ethical bodies (e.g. MRCZ), and for re-contact, where permission has been given. All identifiers (such as name, date of birth, location) will be removed from all internal analytical products. All identifiers and potentially disclosive information (such as unusual combinations of occupation and location) will be removed from external products. We will have written permission from participants to collect, store and share all types of data.

## Managing, storing and curating data.

Data will be collected using tablet computers and consecutively uploaded to a cloud. To minimize errors, range checks and skip patterns within data entry screens will be used. The computing system is password protected, encrypted and only accessible to authorised study team members. Any access to the system is automatically recorded. Data will be managed according to International Conference on Harmonisation guidelines for Good Clinical Practices. Participants will receive a unique study identification number recorded on all forms using a pre-printed bar code and QR code. Numbers will be maintained by the data manager on a password protected, secure computer. Data will be uploaded into a password-protected database.

Database files will be exported in Stata format for bi-weekly batch error checking, monthly reporting and analysis by the data manager. Data will be backed-up daily onto a local machine and on an external hard-drive weekly. Audio files will be transcribed into electronic records which will be backed-up on an external hard-drive after each session. All data will be kept confidential, under lock-and-key, accessible only to trained study staff. Participants' data will be identified by an ID number/barcode only, and a link between names and ID numbers will be kept separately under lock-and-key. Paper copies of locator information and consent forms linked to the data through the project-generated identification will be stored in locked file cabinets. Participant locator information will be destroyed within 1 year of the conclusion of the study unless funding for long-term follow-up is sought, and consent forms within five years of the conclusion of the study.

All samples will be labelled by an ID number/barcode that links the samples to the participant's quantitative and qualitative data. Names, contact details, and other personal information will be removed. The results of tests will not be included on the participants' health records. Every effort will be made to keep personal information confidential.

All qualitative data will be collected on digital recording devices. Audio-recorded qualitative data will be transcribed, including relevant non-verbal communications. The audio files will be stored on the principal applicant and research assistant's password-protected laptop computers. No identifying information will be provided to individuals transcribing the data and they will also sign confidentiality agreements. The transcripts will be translated verbatim into English. After translation, interview summaries will be written for each interview – these will be both a descriptive and analytic synopsis of the interview. Names and other personal identifiers will be removed from transcripts before they are entered into NVivo 10, a qualitative data storage and retrieval program. Transcripts will then be coded using the modified coding framework. Codes will be grouped and emerging themes will be identified. Analytic memos will be written for each theme.

## Metadata standards and data documentation.

The database will be available in STATA, and can be exported to other formats. A codebook will accompany the data to provide secondary users with any necessary details to prevent misuse, misinterpretation or confusion.

## Data preservation strategy and standards.

The database for the study will be maintained on the server at CeSHHAR Zimbabwe. The data manager will also have password protected copies of the master database of the quantitative data. The data manager and principal applicant (ZN) will have password protected copies of the qualitative data. Data will be stored electronically for at least 5 years after the end of the study.

## Data security and confidentiality of potentially disclosive information

The data will be will be analysed at CeSHHAR Zimbabwe and will adhere to the CeSHHAR Information Management and Security Policy which seeks to ensure information security and protect the confidentiality, integrity and availability of the data. The database will not store any identifying information.

## Main risks to data security.

The main risk to the confidentiality of the information related HIV status and behaviours contained in the database. These risks will be managed firstly by ensuring that all copies of the quantitative database and qualitative data files are password protected, with access to the password restricted to those trial staff who need to work with the data. Secondly the data will not contain any personal identifiers and will use anonymised ID numbers as the unique participant identifier. The risks associated with disclosure of data are minimal because most data will be collected using tablets in which assessment data are only identified by a unique study identifier. Also, we will report study results only at the aggregate level. To further minimize the risk of breaching confidentiality, all study staff will be trained and certified using the NIH online training course in Protecting Human Subject Research Participants and will be required to sign a staff confidentiality agreement form, and Participant confidentiality will be ensured at screening, recruitment, follow-up, data entry, storage, retrieval, and analysis stages.

## Data sharing and access

The study data will be suitable for sharing. We will ensure that all publications are open access to achieve maximum impact and that our data and dissemination materials are available at a reputable online data repository. Potential users will learn about the data on our CeSHHAR website and websites of the collaborating institutes. Our intended policy will be to make data available to bona fide researchers, within 12 months of completion of the study. This is to make maximum use of data collected using public funding while protecting the intellectual property rights of the study team (so allowing the study team to publish the main study results paper). We will ensure that the study information sheet and participant consent forms contain the information that the study data might later be made available to bona fide researchers to maximize the knowledge gained from this study. All researchers given access to the data will sign data sharing agreements which will restrict the use to answering pre-specified research questions. The steering committee will be responsible for overseeing requests for data sharing and that the researchers granted access to the data comply with the terms of the data sharing agreement.

## Responsibilities

Data management will take place at CeSHHAR Zimbabwe led by JD under the direction of principal applicant. The principal applicant and research team will be responsible for ensuring good quality data are collected.

***Data analysis:*** Quantitative data will be analysed using STATA 15.0. Descriptive summaries and frequencies of social, clinical and demographic characteristics by different VL trajectories will be conducted. All qualitative interviews will be conducted by the PI in Shona, audio-recorded, transcribed verbatim, and translated into English. Iterative data collection and analysis will be conducted. Preceding interviews will inform subsequent interviews. Data will be uploaded, coded and summarized using a qualitative software package (NVivo 9.0, QSR International). Data analysis will be conducted using thematic and constant comparison analytical approaches (23). In the initial stages I will adopt a thematic approach to explore emerging themes followed by adopting a constant comparison approach within and across and between different participants.

## Ethical Considerations

The protocol target ALHIV and healthcare workers and consent procedures will strictly adhere to the considerations contained in the principles of good clinical practise (GCP). The study will be conducted to the highest ethical standards. Ethical permission will be obtained from Medical Research Council of Zimbabwe. All the approvals will be sought prior to the initiation of research.

## Informed consent

Participants will be provided with accurate information about the study; its purpose, procedure and duration, including known risks and benefits by a research assistant and will have the opportunity to ask questions as part of the informed consent/assent process. Participants will be given at least 72 hours to consider whether they would like to be involved in the study. If the participant is willing to take part in the study, researchers will schedule for an interview. Written informed consent/assent will be obtained from all participants and all adolescents below age 18 years will also have parents/caregivers' consent. All discussions of VL testing will be based on results of DBS testing which is standard of care. Given that plasma VL testing is unlikely to become available it seems potentially undermining of existing treatment services to share these results. Ongoing psychological support will be available through the Africaid Zvandiri programme including with CATS and clinic-based counsellors if any participants get distressed during or after the interviews.

## Voluntary participation

Participation in the study will be voluntary and participants are free to withdraw from the study at any given time without giving a reason. If participants decide not to participate or withdraw their participation in this study, the decision will not affect their daily life, regular care or future relations with CeSHHAR Zimbabwe in any way.

## Confidentiality

Information that obtained from all participants will be stored in a locked filing cabinet and separately from any information that identifies them personally (such as consent forms). We will use a unique participant identification number instead of names on the study information. Only participants and the study team will know this number. A link log, which links the unique ID to name, will be kept in a locked and secure place. The information we collect may be shared with other researchers who are involved in this study but if shared, it will be shared anonymously. Also, research regulatory bodies (Medical Research Council of Zimbabwe and Research Council of Zimbabwe) can have access to research records. The information participants tell us will be used to come up with ideas on how to improve viral load testing in Zimbabwe especially around incorporating U=U into routine HIV care and support for ALHIV. It is anticipated that these ideas will be published and presented to CeSHHAR/EDCTP and their partners in order to improve the understanding of the scientific community about these issues. In any publication or presentation, information will be presented in such a way that participants cannot be identified. After study completion, information collected will be kept securely at the project office for a period of 5 years after all analyses and their resulting publications are complete and will then be destroyed. Stored blood specimens will also be destroyed then. All staff will undergo Good Clinical Practice (GCP) and ethics training. All people working with CeSHHAR sign a confidentiality agreement. This Oath requires research teams not to tell people who are not connected with this study, information about participants or any other information related to the study. CeSHHAR has very strict confidentiality procedures in place.

## Potential Risks to participants

This study has minimal risks associated with participation. Participants will not be exposed to any additional risks from this study. Participants may be uncomfortable answering some of the questions but can refuse to answer any or all of the questions during the interview at any point and/or can choose to stop participating in the study at any time. One possible risk of being in the study could be loss of privacy. All the information from participants will be handled with as much privacy as possible.

## Benefits

There are no direct benefits for participating in the study. Information obtained in this study will be used to shed more light on the whether the U=U has the potential to change the life course of ALHIV in Zimbabwe and on how best to incorporate it into routine HIV treatment and care. Participants will receive a token of appreciation valued at USD $5 for their participation in the study. The value of $5 was gazetted and approved by the Medical Research Council of Zimbabwe.

## Child protection and safeguarding

CeSHHAR has robust and monitored safeguarding procedures in place (UNICEF and USAID). CeSHHAR has a ZERO TOLERANCE policy to cases of sexual exploitation and abuse of beneficiaries,

including children, particularly in the implementation of this research project. The study team and data collectors are expected to behave ethically and responsibly at all times and follow the CeSHHAR code of conduct. This means that they must not ask participants for any financial, physical or sexual favours or child safeguarding violations in return for taking part in this research. Its mandatory for research teams to successfully undertake and complete training on prevention of sexual exploitation and abuse and safeguarding of children. In addition, regular background checks are conducted on all who work on the project. If participants experience any abuse, harassment or neglect by a research team member that are free to contact the study Safeguarding Lead. They may also raise a safeguarding concern directly with CeSHHAR Designated Safeguarding Officer or with the Medical Research Council of Zimbabwe. All the contact details will be provided on the consent/assent forms. Should any illegal or reportable activities related or not related to the study be identified during the study period, research assistants will be instructed to report these events to the relevant authorities including the Medical Research Council of Zimbabwe in accordance with CeSHHAR guidelines and the incidental findings policy guidelines. CeSHHAR is ethically obligated to report any instances of child abuse.

## Expected outcomes and impact on programmes and policies

The study will provide scientific evidence on whether routine VL testing using DBS as available in LIC can provide sufficiently robust evidence of 'undetectability' and on the variability of an individual's virological response over 12 months and between those considered undetectable (<1000) and those undetectable and untransmissible (<200). The study will assist in developing an evidence-base to support the U=U integration into standard of care and to maximise the opportunities that the investment in viral load monitoring could bring for adapting and strengthening care and support to improve adolescent HIV outcomes. It will generate peer-reviewed publications and educational resources.

## Dissemination and exploitation of results

The World Health Organization (WHO) and more than 750 other organisations have endorsed the U=U message, leading to calls for healthcare providers to routinely talk to their patients about U=U although even in high income setting stigma remains a barrier to dissemination. To date very few ALHIV in Zimbabwe are aware of the U-U message and very few service providers are confident to routinely communicate U=U to their patients. Such widespread unawareness and misinformation surrounding U=U makes knowledge dissemination critical and urgent. The findings of this study will be disseminated at district, national, regional and international level to health care providers, people including adolescents living with HIV and to the broader public.

At district level the findings will be first disseminated through a series of participatory workshops (n= maximum of 4), with healthcare workers, policy makers, carers and ALHIV in the study areas. The workshops will be facilitated by the research team to present the findings, including diversity and disagreement in what would constitute an appropriate approach of sharing the information with a wider population. The aim of this stage would be to collaboratively develop a working consensus on how this information could be disseminated. The participatory workshops will also explore the format in which the findings, for example, whether to produce electronic or hard copies of graphic novels. At national level the findings will be disseminated through the existing MoHCC partners' forum meetings with the participation of key stakeholders, including Joint UN Team on HIV/AIDS (JUTA), NAC, MoHCC, and NGOs. We will work with MoHCC to get the messaging incorporated into their implementation guidelines. The findings will be disseminated to service providers at various medical professional societies across the spectrum of care from Nursing (Zimbabwe Nursing Association) to general practitioner and specialist medical bodies such as the Zimbabwe Medical Association (ZIMA). This will be done through sessions at the annual conferences or presentations during monthly CME meetings.

The findings will also be disseminated to the research community in Zimbabwe using the UNICEF supported Brown bag meetings and the Medical Research Council of Zimbabwe annual forum. The report of the findings will be shared widely and made available in both soft and hard copies and will be produced in diverse versions, fact sheets and briefs to accommodate the needs of diverse audiences. Presenting the findings in different formats will help policy makers and program implementers to critically analyse and identify potential service delivery needs as well as linkages with other services for ALHIV.

Central to making U=U a reality for ALHIV the principal applicant will work with the MoHCC AIDS/TB technical working group under the mentorship of Dr Sarah Bernays who has considerable expertise in translating research findings among young people into relevant and accessible formats to disseminate the U=U messages into differentiated models of care (DMOC) for ALHIV. The findings will be disseminated to ALHIV countrywide through our partner Africaid Zvandiri's CATS/YMM programmes. Africaid is currently supporting 960 trained, mentored Community Adolescent Treatment Supporters (CATS) across 51 districts of Zimbabwe. The CATS are integrated within 613 health facilities and each manage a caseload of children, adolescents and young people living with HIV. CATS use a range of adolescent-focused IEC materials which have been developed by Africaid in partnership with MoHCC and UNICEF and these have now been housed on the newly developed app for CATS, known as The Hub. Developed educational resources will be uploaded on the HUB. Africaid currently has active relationships with multiple stakeholders at district, provincial, national and regional levels, who will serve as strategic partners as the new innovation is rolled out.

CeSHHAR runs the Sisters with a Voice programme, on behalf of National AIDS Council and Ministry of Health and Child Care. In 2014, CeSHHAR developed a programme for younger women who sell sex (the Young Sisters Programme) up to 40% of who are HIV positive, reaching over 29500 adolescent girls and young women by June 2020. The Young Sisters Programme works with younger peer educators and has age specific and relevant community mobilization materials to encourage younger women to attend services. The findings will also be incorporated into the mobilization materials used by the peer educators.

At regional and international level results will be disseminated at regional forums, including making publications in recognized international journals and international conferences. Including the biennial EDCTP Forum in 2022.

## REFERENCES


1. Kouamou V, Manasa J, Katzenstein D, Mcgregor AM, Ndhlovu CE, Makadzange AT. Drug resistance and optimizing dolutegravir regimens for adolescents and young adults failing antiretroviral therapy. AIDS. 2019; Publish Ahead of Print.
2. Casale M, Carlqvist A, Cluver L. Recent Interventions to Improve Retention in HIV Care and Adherence to Antiretroviral Treatment Among Adolescents and Youth: A Systematic Review. AIDS Patient Care STDS. 2019;33(6):237-52.
3. Martelli G, Antonucci R, Mukurasi A, Zepherine H, Nostlinger C. Adherence to antiretroviral treatment among children and adolescents in Tanzania: Comparison between pill count and viral load outcomes in a rural context of Mwanza region. PLoS One. 2019;14(3):e0214014.
4. Boerma RS, Boender TS, Bussink AP, Calis JC, Bertagnolio S, Rinke de Wit TF, et al. Suboptimal Viral Suppression Rates Among HIV-Infected Children in Low- and Middle-Income Countries: A Meta-analysis. Clin Infect Dis. 2016;63(12):1645-54.
5. Webb D, Cluver L, Luo C. Evolution or extinction? Paediatric and adolescent HIV responses in the Agenda 2030 era. Journal of the International AIDS Society. 2018;21 Suppl 1(Suppl Suppl 1):e25071.
6. Nachega JB, Sam-Agudu NA, Mofenson LM, Schechter M, Mellors JW. Achieving Viral Suppression in 90% of People Living with Human Immunodeficiency Virus on Antiretroviral Therapy in Low- and Middle-Income Countries: Progress, Challenges, and Opportunities. Clinical Infectious Diseases. 2018;66(10):1487-91.
7. Mbirimtengerenji ND. Is HIV/AIDS epidemic outcome of poverty in sub-Saharan Africa? Croat Med J. 2007;48(5):605-17.
8. Mavhu W, Willis N, Mufuka J, Bernays S, Tshuma M, Mangenah C, et al. Effect of a differentiated service delivery model on virological failure in adolescents with HIV in Zimbabwe (Zvandiri): a cluster-randomised controlled trial. The Lancet Global Health. 2020;8(2):e264-e75.
9. Brown K, Williams DB, Kinchen S, Saito S, Radin E, Patel H, et al. Status of HIV Epidemic Control Among Adolescent Girls and Young Women Aged 15-24 Years - Seven African Countries, 2015-2017. MMWR Morbidity and mortality weekly report. 2018;67(1):29-32.
10. Natukunda J, Kirabira P, Ong KIC, Shibanuma A, Jimba M. Virologic failure in HIV-positive adolescents with perfect adherence in Uganda: a cross-sectional study. Tropical Medicine and Health. 2019;47(1):8.
11. Ngarina M, Popenoe R, Kilewo C, Biberfeld G, Ekstrom AM. Reasons for poor adherence to antiretroviral therapy postnatally in HIV-1 infected women treated for their own health: experiences from the Mitra Plus study in Tanzania. BMC Public Health. 2013;13(1):450.
12. The Lancet HIV. U=U taking off in 2017. The Lancet HIV. 2017;4(11):e475.
13. Calabrese SK, Mayer KH. Providers should discuss U=U with all patients living with HIV. The Lancet HIV. 2019;6(4):e211-e3.
14. Eisinger RW, Dieffenbach CW, Fauci AS. HIV Viral Load and Transmissibility of HIV Infection: Undetectable Equals UntransmittableHIV Viral Load and Transmissibility of HIV InfectionHIV Viral Load and Transmissibility of HIV Infection. JAMA. 2019;321(5):451-2.
15. WHO. Dolutegravir (DTG) and the fixed dose combination of tenofovir/lamivudine/dolutegravir (TLD). Briefing Note, April 2018. Briefing Note [Internet]. 2018.
16. Paul N, Ugwu R. Dolutegravir (DTG) Based Fixed Dose Combination (FDC) of Tenofovir/Lamivudine/Dolutegravir (TLD) and Viral Load Suppression in Children in Port Harcourt, Nigeria. Journal of Scientific Research and Reports. 2020:52-9.
17. Ndashimye E, Arts EJ. The urgent need for more potent antiretroviral therapy in low-income countries to achieve UNAIDS 90-90-90 and complete eradication of AIDS by 2030. Infectious Diseases of Poverty. 2019;8(1):63.
18. Sithole Z, Mbizvo E, Chonzi P, Mungati M, Juru TP, Shambira G, et al. Virological failure among adolescents on ART, Harare City, 2017- a case-control study. BMC Infectious Diseases. 2018;18(1):469.
19. Nyagadza B, Kudya N, Mbofana E, Masaka S, Garone D, Chen CY, et al. Scaling up HIV viral load monitoring in Manicaland, Zimbabwe: challenges and opportunities from the field. Public Health Action. 2019;9(4):177-81.

20. Kilmarx PH, Simbi R. Progress and Challenges in Scaling Up Laboratory Monitoring of HIV Treatment. PLOS Medicine. 2016;13(8):e1002089.
21. Vreeman RC, McCoy BM, Lee S. Mental health challenges among adolescents living with HIV. Journal of the International AIDS Society. 2017;20(Suppl 3):21497-.
22. Calabrese SK, Mayer KH. Stigma impedes HIV prevention by stifling patient–provider communication about U = U. Journal of the International AIDS Society. 2020;23(7):e25559.
23. Braun V, Clarke V. Using thematic analysis in psychology Qualitative Research in Psychology. 2006;3(2):77-101.
24. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Antiretroviral Therapy for the Prevention of HIV-1 Transmission. New England Journal of Medicine. 2016;375(9):830-9.
25. Rodger AJ, Cambiano V, Bruun T, Vernazza P, Collins S, Degen O, et al. Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a multicentre, prospective, observational study. The Lancet. 2019;393(10189):2428-38.
26. Rodger AJ, Cambiano V, Bruun T, Vernazza P, Collins S, van Lunzen J, et al. Sexual Activity Without Condoms and Risk of HIV Transmission in Serodifferent Couples When the HIV-Positive Partner Is Using Suppressive Antiretroviral Therapy. JAMA. 2016;316(2):171-81.
27. Bavinton BR, Pinto AN, Phanuphak N, Grinsztejn B, Prestage GP, Zablotska-Manos IB, et al. Viral suppression and HIV transmission in serodiscordant male couples: an international, prospective, observational, cohort study. The Lancet HIV. 2018;5(8):e438-e47.
28. Chandra-Mouli V, Armstrong A, Amin A, Ferguson J. A pressing need to respond to the needs and sexual and reproductive health problems of adolescent girls living with HIV in low- and middle-income countries. Journal of the International AIDS Society. 2015;18(6S5):20297.
29. Alliance. IHA, Zvandiri. A. Supporting children, adolescents and young people living with HIV to start and stay on HIV treatment. Harare, Zimbabwe International HIV/AIDS Alliance; 2017.
30. Willis N, Frewin L, Miller A, Dziwa C, Mavhu W, Cowan F. “My story”—HIV positive adolescents tell their story through film. Children and Youth Services Review. 2014;45:129-36