Full title:

Improving **RET**ention and viral load outcomes for people taking **A**ntiretroviral therapy through early **I**dentificatioN of missed doses.

Short title:

The RETAIN study

(nested within the SUSTAIN study – UCT Ethics reference 568/2021).

Funder:	EDCTP2 Senior Fellowship Grant
Sponsor:	Desmond Tutu Health Foundation
Protocol version:	Version 1
Protocol date:	15 November 2021

STUDY TEAM:

Principal Investigator

Name	Catherine Orrell
Title	Professor
Qualifications	MBChB, MSc, MMed, PhD
Institution	Desmond Tutu Health Foundation and Desmond Tutu HIV Centre University of Cape Town, Cape Town
Email	Catherine.Orrell@hiv-research.org.za

Co-Investigators

Research site investigator

Name	Lauren Jennings
Title	Doctor
Qualifications	MBChB, MPH
Institution	Desmond Tutu Health Foundation and Desmond Tutu HIV Centre University of Cape Town, Cape Town
Email	Lauren.Jennings@hiv-research.org.za

Collaborating investigator

Name	Lora Sabin
Title	Associate Professor
Institution	School of Public Health, Boston University

Project study coordinator

Name	Tebogo Mosina
Title	Professional Nurse
Institution	Desmond Tutu Health Foundation and Desmond Tutu HIV Centre University of Cape Town, Cape Town

Statistical support

Name	Francesca Little
Title	Professor
Institution	Department of Statisitcal Sciences, University of Cape Town

SPONSOR

Desmond Tutu Health Foundation

FUNDER

EDCTP TMA2019SFP-2812

Contents

SUMMARY

Although advances in antiretroviral therapy (ART) have reduced illness and death for people living with HIV (PLWH), recent evidence has highlighted gaps in the HIV continuum, including poor adherence and low retention in care, particularly in resource-poor, high-burden African settings. This emphasises the need to address two critical priorities: first, PLWH at risk of treatment failure must be identified more rapidly than current systems allow, before they leave care or develop drug resistance; and, second, these patients need support to keep them in care at optimal adherence levels.

This study is one of two inter-linked studies which together aim to address both problems: a highly efficient, locally-informed, randomised study called SUSTAIN (UCT Ethics reference 568/2021, approved 10Nov21), together with this project (RETAIN). Both will be conducted in resource-poor communities in Cape Town, South Africa.

The parent SUSTAIN study will evaluate three feasible methods of identifying (flagging) those with poor adherence earlier than the current standard of care; and then offering them a supported version of the packaged adherence intervention already in place at antiretroviral clinics (enhanced standard of care). Primary outcomes will include retention in care and viral suppression at 24 months. The RETAIN study, described here, will add an intensive therapeutic monitoring component to those flagged with adherence lapses during SUSTAIN; and will review the impact of the early flagging and adherence intervention on immediate adherence behaviour, drug concentration (short and long half- life moieties) and the longer term outcome of viral suppression at 12 months.

Both studies will contribute to the implementation of an enhanced version of the packaged adherence intervention already in place in antiretroviral clinics.

Key words: HIV; drug concentrations; therapeutics; virological failure; retention; adherence

BACKGROUND AND RATIONALE

Although advances in antiretroviral therapy (ART) have reduced illness and death for people living with HIV (PLWH), recent evidence highlights major gaps in the HIV continuum, including poor adherence and low retention in care, particularly in resource-poor, high-burden settings such as Southern Africa.(1) This underscores the need to address two critical priorities: first, PLWH at risk of treatment failure must be identified more rapidly than current systems allow, before they leave care or develop drug resistance; second, these patients need support to keep them in care at optimal adherence levels from the day they start ART.

We have proposed to address both problems by conducting two highly efficient, inter-linked studies based on local quantitative and qualitative data; and designed with the involvement of City of Cape Town senior management staff. The first study will recruit people commencing ART at three clinics and evaluate three feasible methods of identifying (flagging) those with poor adherence, and then offering them a supported version of the packaged adherence intervention already in place in antiretroviral clinics (enhanced standard of care) comparing retention and virological outcomes at 24 months. The study is called SUpporting Sustained HIV Treatment Adherence after INitation (SUSTAIN).

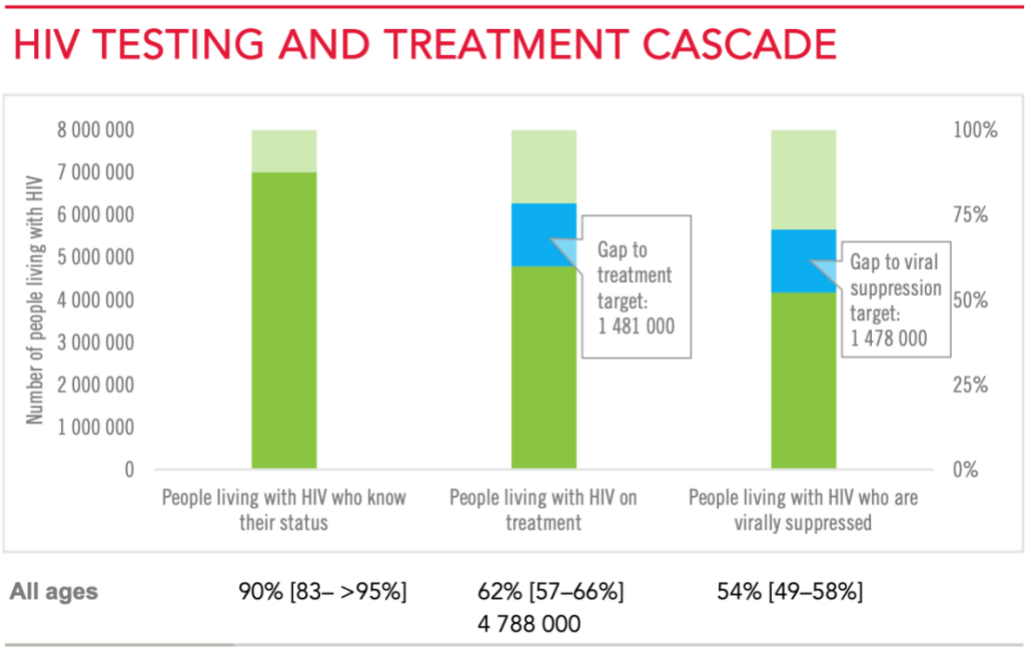
The second study, described here (RETAIN), will review the impact of this early flagging and adherence intervention both on immediate adherence behaviour, drug concentrations (short and long half-life moieties) and viral load outcomes; as well as on the longer-term outcome of viral suppression at 12 months.

Too few South Africans living with HIV achieve viral suppression:

UNAIDS introduced the 90-90-90 goal in 2013; aiming to encourage 90% of people living with HIV to know their status; 90% of people who know their status to start ART; and 90% of those on ART to achieve viral suppression by 2020; with a secondary goal of achieving 95-95-95 by 2030.(2, 3) In Eastern and Southern Africa the average 90-90-90 scorecard in 2019 stood at 85-67-58; a substantial way off achieving the 90-90-90 targets, as compared to many better resourced countries with over 90% in all three areas e.g. 90-93-94 in the Netherlands.

In South Africa, where, while currently achieving some success in the first 90, only 68% of those who know their status are linked into care and only 54% of those who commence ART are achieving viral suppression (Figure 1).(1) More recent UNAIDS reports show that this poor viral suppression rate is largely due to the loss of patients to care i.e. poor retention, rather than directly due to missed doses: as 87% of those who are in care and have a viral load drawn do achieve suppression.(1)

Figure 1: UNAIDS 90-90-90 statistics for South Africa.



We face a challenge: adherence to ART in Africa, and South Africa in particular, is low (4-7) and is accompanied by poor ART retention which declines over time.(8, 9) In South Africa, with 18.9% HIV prevalence and the world's greatest HIV burden, over 4 million people have started ART. Local data shows that 17% of these people are lost to care before 16 weeks on treatment; and over 20% are lost within the first year.(6, 7, 10) While viral suppression in those who continue to attend local clinics and have a viral load drawn seems reasonable; when reviewed in the context of all those who started ART, only 47- 60% of PLWH are virally suppressed, matching national statistics.(4, 11, 12) Recent unpublished data from the Gugulethu ART cohort monitored by my team supports this: of 1961 HIV-positive adults who commenced ART with tenofovir/emtricitabine/efavirenz as a single tablet regimen between April 2014 and March 2019, only 1295 (66%) received a viral load at month 12, with 1173 (90%) of those suppressed – representing only 59.8% (1173/1961) of those entering care (David Huang, unpublished data). These poor outcomes undermine the individual and public health impact of ART as well as the likelihood of achieving of the World Health Organization's "End HIV/AIDS by 2030" goals.(1, 12)

Those who miss doses are later lost to care.

Non-suppression of virus occurs due to missed doses (poor adherence) and missed visits (poor retention) and contributes to poor outcomes. Literature across a number of disease states shows that people who initially miss doses, progress to missing visits and are later lost to care. Data from our Gugulethu cohort showed that PLWH who had a single raised viral load (>1000 copies/ml), indicating an episode of poor adherence, were more likely to be lost to care over subsequent years than those who remained virally suppressed.(13, 14) Such ART treatment interruptions to date have been associated with HIV-1 viral failure and resistance, and although these adverse consequences might reduce with the introduction of integrase-inhibitor-based regimens; gaps in treatment will continue to have individual health and disease transmission consequences (15-17). In tuberculosis treatment, poor treatment adherence contributes to lower rates of treatment completion and to higher rates of loss to follow-up

among TB patients, followed by an increased rate of TB relapse.(18-19) In a modelling study, poor adherence was identified as the strongest predictor for the emergence of MDR-TB in previously treated patients. (20) Similar data can be shown for other chronic diseases such as osteoporosis, where poor adherence results in worsening outcomes; and, in people with hypertension, poor adherence was associated with increased rates of loss to care / poor retention.(21, 22)

There are objective and effective methods to monitor ART adherence that are feasible in a resource limited primary care setting, but these are not being utilised.

Many adherence measures overestimate adherence to some degree, especially the more subjective measures such as patient self-report or counting of tablets in returned bottles. While easy and cheap to implement, these methods are variably delivered and susceptible to the "white coat" effect: allowing adjustments by patients to please their health care worker. Although asking about adherence (self-report) adds individual clinical value, these assessments rarely accurately predict virological outcomes.(23, 24)

Other objective measures of adherence more reliably predictive of viral and resistance outcomes. Pharmacy refill (PR) data, through review of patient pharmacy drug collections, and calculation of time without medication in hand, has been proven to be a reliable predictor of outcomes in both adult and paediatric populations.(25-27) Pharmacy refill data is collected electronically throughout South Africa, but although proven predictive of virological outcomes, is not routinely linked to clinical care.(28) As these pharmacy systems are in place in most ART clinics, relatively little investment would be required to implement useful pharmacy-clinic linkage and make this data available to clinicians at the time of patient visits. Electronic adherence monitoring, using a device such as the Wisepill (www.wisepill.com), is another objective adherence monitoring system, with the additional benefit of observing dosing in real-time. This allows immediate and effective intervention through a call or message.(25, 29) These systems have been extensively used in South Africa and implementation is feasible in a local setting. While highly predictive of virological outcomes, these devices are currently costly and would require substantial investment in time and infrastructure.(4, 25, 30)

Measuring drug concentrations of tenofovir in biospecimens (plasma, dried blood spots [DBS], hair) appears a promising strategy for objectively monitoring ART adherence, because it directly measures drug ingestion. However, drug plasma concentrations for ART have not accurately predicted virological outcomes in the past due to "white coat" dosing on the day of blood draw, and HIV-drug resistance in those with intermittent adherence altering the relationship between drug concentration and viral suppression. Therapeutic drug monitoring was thus not recommended routinely, until recent work by Castillo-Mancilla et al exploring the use of longer half-life drug metabolites, such as tenofovir diphosphate (TFV-DP) collected as dried blood spots (DBS), showed strong association with viral suppression.(23, 31-33) These moieties give a picture of adherence over the past 30 days, similar to measuring the HbA1c in a patient with diabetes, and when considered with viral load may add clinical value (Figure 2). Recent and novel work at our site, measuring TFV-DP in dried blood spots, shows reduced drug TFV-DP concentrations are also *predictive* of future viral breakthrough, up to two months in advance (Orrell, data from the ADD-ART study, in review). Disadvantages of this method include cost ($100) and the delay in turn-around (3 weeks) as the analysis is laboratory intensive.

Figure 2: Relationship between viral load, adherence and resistance when monitoring ART drug concentrations.

High viral load, low adherence = poor **ADHERENCE**	High viral load, high adherence = likely **RESISTANCE**
Low viral load, low adherence = **COUNSELL** to avoid failure	Low viral load, high adherence = **ALL GOING WELL**

Other new methodologies, such as lateral flow assays for tenofovir parent drug, called Urine Tenofovir Rapid Assays (UTRA), could overcome these disadvantages (instant results and $5 each), but we may lose the benefit of the long half-life moiety and the assay might again be susceptible to "white coat" dosing. Data on the value of these assays is limited in a resource-poor HIV treatment setting and will be explored in this proposal.

Current local health systems only intervene to improve adherence once a viral load is raised.

Low patient-provider ratios in many resource limited settings (ranging from 800:1 to 1000:1), can make it extremely challenging to identify those patients at greatest risk for poor health outcomes and intervene in time. Although there are published national guidelines for HIV, TB and Non-Communicable Diseases, that advocate for monitoring adherence, the focus is on patient self-report and viral load monitoring.(34) In practice even self-reported adherence questions are poorly implemented, giving unreliable data, and in the average busy ART clinic it is not noticed if a patient misses a visit or an appointment to collect ART or have a viral load drawn. Poor adherence is only noted if the viral load is raised at the month 4 or month 12 (or subsequent annual) measurement; and, in some clinics raised viral load data is not acted upon until the following visit, some 1-2 months after testing.

At this late stage, even with an adherence intervention, only 50% of PLWH resuppress their virus.(14, 35, 36) These people are all at risk of HIV-1 resistance, requiring more complex and harder to maintain second-line ART regimens and will have poorer clinical outcomes.(12) Not identifying those with adherence issues early has consequences beyond individual health: through increasing the chances of HIV-transmission and increasing the burden on the health care system (more expensive second-line drugs, and more illness).(14)

Adherence interventions can be efficacious, but are delivered too late.

Two decades of research have identified a range of tools to improve ART outcomes, including approaches using electronic adherence devices, but translating interventions into clinical practice has been slow, especially where resources are constrained.(23, 30, 37, 38) Adherence is understood to be a multi- dimensional phenomenon determined by many factors including denial, fear of drug side effects, poor knowledge of the importance of adherence, stigma, depression, symptom reduction during the course of treatment and forgetfulness.(23).

Meta-analyses and systematic reviews highlight the effectiveness of relatively simple interventions such as peer-based support, education and counselling interventions, electronic/mobile phone technologies (short message services, SMS), health care delivery changes, and incentives.(12, 23, 38-42)

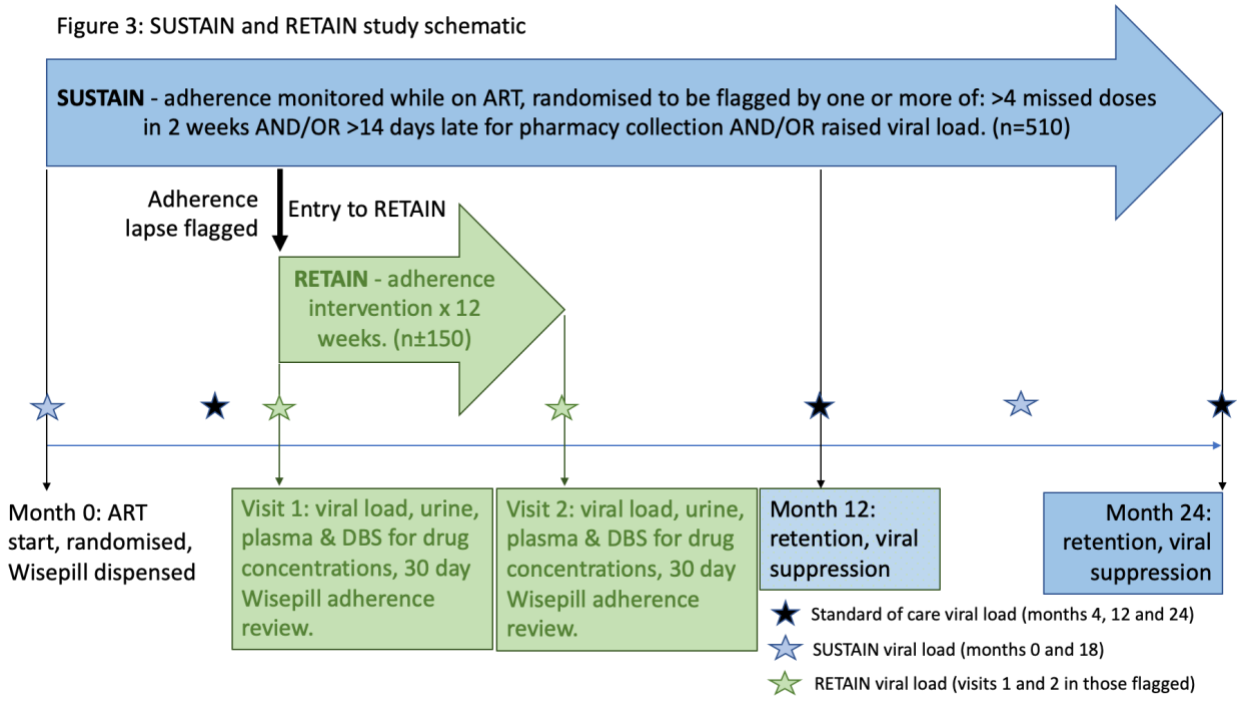
In Cape Town, city health officials are acting to apply the lessons of research, establishing the Risk of Treatment Failure clinics (RoTF – see details below) as an adherence support intervention for ART patients known to be struggling with adherence. Currently, when a viral load is raised, the patient will be informed of this result at his/her next clinic visit and referred. The RoTF clinic comprises two components, both evidence- based adherence interventions: peer support groups and structured data-driven adherence and clinical support. Recent work at our site using a modified Delphi process to determine adherence intervention preferences supported the RoTF programme: when ranking nine locally feasible and evidence-based methods, local clinicians preferred data-driven support, and patients at risk of viral failure preferred peer group support and also liked the idea of messaging. While information on the consistency of delivery of the RoTF programme is sparse; and the impact likely lessened by delivery too late in the adherence-failure sequence, current local viral re-suppression data ranges from 30-70% among those referred at local community level clinics (CoCT data, September to November 2019, personal communication with Beth Harley) and 50% across resource poor settings.(14, 35, 36, 39)

In summary, even though adherence to ART is critical to long term treatment success, when ART is delivered in an under-resourced community setting, individuals who are struggling to adhere and maintain treatment access are often neglected. Only 54 of every 100 people who commence ART in South Africa achieve viral suppression: damaging to the individual and to the country HIV programme. Simple and generalisable systems are required to identify these individuals reliably, and early enough to offer them differentiated care to support and improve their adherence before they develop HIV-1 drug resistance and adverse health consequences. These adherence interventions should be simple, feasible and acceptable to the community, as are those already in place, but need to be delivered and assessed with quality and consistency.

AIMS and OBJECTIVES

The overall aim of these combined research projects is to increase the proportion of South African individuals commencing ART in a community clinic who remain in care and achieve viral suppression 12 and 24 months after starting treatment. The interlinkage of SUSTAIN and RETAIN are shown in the study schematic (Figure 3).

Figure 3: SUSTAIN and RETAIN study schematic



1. SUSTAIN: SUpporting Sustained HIV Treatment Adherence after INitation.

The SUSTAIN protocol has been approved by UCT Research Ethics (reference number 568/2021). In summary, SUSTAIN is a Multiphase Optimisation Strategy study. The primary objective is to to evaluate three feasible methods of identifying (flagging) those with poor adherence earlier than the current standard of care, and to offer this subset a basic or enhanced version of the standard of care adherence intervention already in place in local antiretroviral clinics with or wouthout weekly text-message support; and measure the impact on the primary outcome of **viral suppression at 24 months** (inter-individual analyses). We will also examine retention in care (any evidence of clinic attendance) by arm at 24 months, and the presence of HIV-drug resistance in those with viral failure.

2. RETAIN: Improving RETention and viral load outcomes for people taking Antiretroviral therapy through early IdentificatioN of missed doses.

The primary objective of RETAIN is to explore the more immediate impact of the adherence intervention on **individual adherence behaviour** through monitoring changes in daily dosing behaviour and drug concentrations (short and long half-life moieties) immediately before and shortly after the intervention is delivered (intra-individual analyses); as well as the immediate impact on viral load.

The primary outcomes of RETAIN will include the change in 30-day daily dosing (using Wisepill®) immediately before and within 4 weeks after completion of the adherence intervention; and a change in drug concentrations (plasma tenofovir concentrations, and tenofovir diphosphate from dried blood spot sampling as well as presence of urine tenofovir using a new lateral flow assay) immediately before and within 4 weeks after completion of the adherence intervention (Figure 3 and Tables 1 and 2).

Secondary outcomes include the impact of the adherence intervention on viral load, as well as retention in care and viral suppression rates at month 12.

HYPOTHESES

1. Identifying poor adherence early or very early through noting missed pharmacy refills or missed daily doses (monitored by Wisepill®), and managing this poor adherence immediately, will result in improved rates of retention and viral suppression, as well as reduce HIV-1 drug resistance at month 12 and 24; compared to noting poor adherence at the time of a raised viral load (standard of care).

2. A properly implemented or enhanced standard of care adherence intervention comprising a structured data-driven clinical adherence session and 4 peer support groups will immediately improve daily adherence as monitored by Wisepill® and reduce the proportion of individuals with sub-optimal drug concentrations as measured by urine tenofovir rapid test and by dried blood spot tenofovir diphosphate.

STUDY DESIGN

PARENT STUDY (SUSTAIN): We will recruit 510 HIV-positive people into SUSTAIN from three City of Cape Town ART clinics and randomise them into one of 16 conditions at the time of commencing ART. Poor ART adherence will be identified by three different methods with varying degrees of sophistication and will be compared head-to-head: 1) real-time electronic adherence monitoring (EAM), a technology-based approach previously used in this setting 2) pharmacy refill (PR) data, leveraging current infrastructure; and 3) standard of care viral load testing indicating unsuppressed virus. Feasibility and evidence for proposed study components are described in the SUSTAIN protocol.

All participants will be issued with and taught how to use a Wisepill device. Adherence data (openings) from the device will only be utilised in the 50% of the cohort who are assigned to Wispill flagging condition (active monitoring). In the other 50% this data will be collected in the background and not be reviewed by or available to study staff (passive monitoring). A study viral load will be drawn at baseline and month 18, and standard of care viral loads will be drawn at months 4, 12 and 24. Retention in care will be assessed using clinical, pharmacy and laboratory records at month 12 and 24.

Table 1 – Summary of key procedures for the **parent study (SUSTAIN)**: participants will be seen for study procedures at screening (day -7 to -21), baseline (day 0) and months 4, 8, 12 and 18 on study.

Procedure:	Screen	Month 0	Month 4	Month 8	Month 12	Month 18	Month 24
Informed Consent (SUSTAIN and RETAIN)	X						
Demographic and disease data	X						
Confirm ART regimen		X					
Randomisation to condition		X					
Wisepill dispensing		X					
Viral load (Study)**		X				X	
Viral load (SoC)			X		X		X*
Wisepill monitoring throughout		X					
Pharmacy collection and clinic visits monitored throughout		X					

* A study viral load will be drawn month 24 if no SoC viral load result is available.

** Plasma will be stored for genotyping for all with a raised viral load or no viral load available after the month 24 SoC visit.

Once flagged, each participant will be invited to enter the RETAIN study.

RETAIN is a single arm pharmacokinetic sub-study contained within a randomised prospective cohort study (SUSTAIN), involving enhanced identification of reduced adherence (flagging) followed by a interventions to improve adherence. RETAIN adds intense pharmacokinetic and adherence monitoring during the period of adherence improvement (Figure 3).

SUSTAIN participants are randomised to a combination of different methods of flagging poor adherence to ART including: 1) Electronic Adherence Monitor (EAM) flagging (missing more than 3 consecutive doses or 4 doses in a 14 day window); 2) Pharmacy Refill or Clinic Visit (PR) flagging (being more that 14 days late for a drug refill or clinic visit); and 3) Viral load (VL) flagging (Vial Load >50 copiesl/ml as per Standard of Care). To minimize bias all data will be collected across all arms.

After flagging for poor adherence on any arm, the participant will be invited back to the clinic, where they will enter the RETAIN study, for intense PK sampling, prior to receiving enhanced standard of care adherence support, including a data-driven discussion of adherence and an offer of four peer support group sessions.

RETAIN study procedures will include informed consent (conducted at the same time as SUSTAIN concent processes); sampling for a viral load, plasma tenofovir (TDF), tenofovir diphosphate (TDF-DP) dried blood spot and urine tenofovir rapid assay (UTRA) at visit 1, before participant receives the enhanced standard of care adherence support as described in the SUSTAIN protocol. After the intervention (visit 2), the same three samples will be collected and the participant offered participation in a qualitative interview to explore acceptability of the flagging methodology and adherence process (Table 2).

Table 2 - Schedule of events for the invention process (RETAIN).

	Visit 1	Adherence Intervention					Visit 2
Study procedures							
Urine Tenofovir Rapid Assay (UTRA)	X						X
Tenofovir diphosphate (TDF-DP)	X						X
Study viral load	X						X
Plasma for drug concentrations & HIV-1 genotype	X						X
Monitor Wisepill (last 30 days)	X						X
Adherence questionnaire	X						X
Qualitative interview							X
Standard of care procedures (monitored)							
Data-driven counselling*		X					
Peer support groups*			X	X	X	X	

*Described in detail in the SUSTAIN protocol.

RECRUITMENT AND ENROLMENT

The study will recruit a subset of 510 HIV-positive people from three City of Cape Town ART clinics, in the Klipfontein Health district: Mzamomhle, Phumlani and Weltevreden Valley. Study staff (Community Research Workers) based at the clinics will identify and approach people who appear to meet the inclusion and exclusion criteria below. The study visits will occur in parallel to their ART visits and

enrolment in the study will not alter the ART dispensed, which will be dispensed through the standard of care programme at their clinic.

Study timelines are given in Appendix 1.

Inclusion criteria:

- ≥16 years old
- Signed informed consent for RETAIN at enrolment into SUSTAIN
- Enrolled onto the SUSTAIN study (meeting all eligibility criteria)
- Flagged as poorly adherent by one of the three study adherence methodolgies
- Able to sign written informed consent

Exclusion criteria:

- Unable to understand study procedures

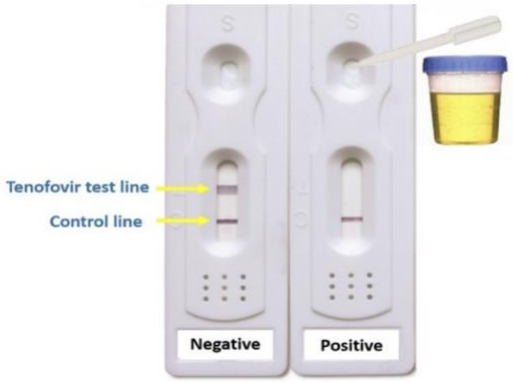
The study will recruit participants regardless of gender. Older adolescents ages 16 and above will be included as a vulnerable population, as they are more prone to adherence discrepancies. The study will also not exclude pregnant women, although these women are unlikely to be commencing ART at our recruiting clinics.

Study Procedures

Tables 1 and 2 above describe the schedule of events for the RETAIN study.

Visit procedures

Screening: this will occur at the SUSTAIN screening visit. Informed consent for RETAIN will be added to the SUSTAIN screening process; as a separate short infomed consent document (Appendix 2).



Visits 1 and 2:

1. **Urine sample for UTRA:** Urine will be collected into a cup at each study visit. The urine will be analysed by the lateral flow assay, as illustrated in the figure, to provide a yes/no value for adherence to tenofovir over the past 4 days.
2. **Blood sample for drug concentrations and genotype:** 5ml blood will be drawn by venipuncture into a purple top EDTA tube.

    - 50 µl of whole blood without centrifugation will be pipetted onto a Whatman 903 protein saver card (five 50 µl spots per card) or equivalent card The pipetting onto the protein saver cards should be done within 1 hour of collection of whole blood into the EDTA. The protein saver card will be air dried at room temperature for at least two hours prior to storing in a sealed bag with desiccant sachets and humidity indicators. The sealed bags will be stored at -20°C before transport to the laboratory for TDF-DP assay.

- The remaining whole blood will be centrifuged at 2000rpm for ±10 minutes and the plasma pipetted into 2 cryovials (one for immediate analysis of tenofovir concentrations in plasma and the other for storage at -80°C for possible HIV-1 genotyping should the viral load be raised).

3. **Blood sample for viral load:** 5ml venous blood will be drawn into a white top PPT tube, and sent to the National Health Laboratory Service (NHLS) for analysis.

4. **Review of Wisepill data:** community research worker or data clerk will access the participant Wisepill profile and record:
   a. the number of doses taken in the past 30 calendar days*
   b. the number of missed doses in the past 30 calendar days*
   c. the number of >= 3 day periods with consecutive missed doses.

   (* a + b must = 30.)

5. Adherence questionnaire: participants will be asked to give a short self-report of their adherence using the following questionnaire:

1. In the last 30 days, on how many days did you miss at least one dose of any of your HIV medicines? Xhosa: Kwintsuku ezi-30 ezidlulileyo,zimini ezingaphi okhe walibala ukutya amchiza akho entsholongwana?
   Range 0–30
2. In the last 30 days, how good a job did you do at taking your HIV medicines in the way that you were supposed to? Xhosa: Kwintsuku ezi-30 ezidlulileyo,zimini ezingaphi okhe walibala ukutya amchiza akho entsholongwana?
   Range "very poor" to "excellent" (1–6)
3. In the last 30 days how often did you take your HIV medicines in the way that you were supposed to? Xhosa: Kwezi ntsuku zi-30 zidlulileyo,kukangaphi usitya amachiza akho entsholongwane ngendlela omele kuwatya ngayo?
   Range "never" to "always" (1–6)

Only at Visit 2:

Qualitative Interview: At visit 2, participants will be offered an option to attend a qualitative interview, until a total of 24 participants, balanced by gender, have been interviewed using a semi-structured interview guide. The qualitative data will explore individual reasons for adherence and describe acceptability of the intervention and adherence flagging processes in this community. Interviews will explore perceptions of the adherence measures, advantages and disadvantages of each, potential challenges, and their recommendations for how it might be integrated into clinical care.

VISIT WINDOWS

Visit 1 should be conducted within 28 days of the participant being flagged for poor adherence.

Visit 2 should be conducted at 12 weeks (±4 weeks) after Visit 1.

RECRUITMENT STRATEGY

The Desmond Tutu Health Foundation (DTHF) maintains multiple community relationships and supports a number of clinical sites providing access for recruitment of our target population, in partnership with the City of Cape Town. There are 3 community sites that will recruit for our target population in the Klipfontein / Mitchell's Plain health sub district, all within easy distance of our DTHF research sites. These are Mzamomhle, Phumlani and Weltevreden Valley clinics. These clinics do not offer full curative adult care, but treat patients in disease programmes: HIV care, including antiretroviral therapy, tuberculosis, contraception ("family planning") and sexually transmitted diseases. Potential participants for SUSTAIN will be first approached either at the point of HIV diagnosis, in the HIV Counselling and Testing (HCT) room, or when presenting for the first time to the ART clinic, and thus opening a folder.

All participants enrolled in SUSTAIN will be informed of the RETAIN study at the time of their SUSTIAN enrollment and, if interested, will sign a RETAIN informed consent form. At the time of flagging, study staff will confirm with the participant if they are still willing to participate in RETAIN. Patient information leaflets and informed consent / assent documents will be provided in their language of choice. For adolescents, this same process will take place with the approval and agreement of both the adolescent and a guardian. The former will provide informed assent, and the guardian will provide full informed written consent.

Should they agree to participate, they will be asked to attend a study visit at the clinic or at the Gugulethu Research Offices (within 3km of the clinics)..

Recruitment approach

Permission has been obtained from the City of Cape Town to recruit at the above facilities. Potential participants attending the antiretroviral services will be approached by the SUSTAIN/RETAIN recruiting team and verbally offered participation in the study, with a request to review their folder. Should they agree, and initial folder review indicate likely eligibility, the potential participant will be invited for a full informed consent process. If eligible for SUSTAIN, the participant will automatically be offered entry to RETAIN should poor adherence be flagged.

The proposed clinics have large numbers of new HIV treatment patients every year. In 2019, Phumlani, Mzamomhle and Weltevreden clinics had 585, 653 and 510 new ART starts respectively. We plan to recruit 170 patients to SUSTAIN from each clinic over 15 -18 months (<50% of those eligible); which is feasible and supported by the numbers starting care there, allowing for an over 50% refusal rate; and will allow for ±180 people to enrol into RETAIN during the enrolment period and over

Sub-optimal recruitment

We will review our recruitment rates during our weekly study team management meeting. With input from the recruiters and other study team members we will revise our recruitment strategy and approach to meet our recruitment targets. One strategy would be to expand our recruitment sites from the three clinics to other clinic facilities near the main study site. We have built in 6 months in our time

line to manage unforeseen circumstances, including poor recruitment, which might well be impacted by the SARS-CoV-2 pandemic.

Participant retention

To date we have had excellent retention at site (>90%). Retention strategies included: employing recruiters and community research workers from the local community who have a cultural and a location connection with participants; home visits by CRWs when needed; scheduling intensive visits early in the study to build a relationship between study staff and participants; regular locator detail checks; and providing a caring study site environment. For these nested studies, retention in care is a study outcome and retention efforts are built in to the study procedures.

Enrolment, consent and baseline activities

We will screen potential participants for willingness to participate in a 2-year study with 10 visits requiring study porcedures (9 of which will occur during booked ART clinic visits). We will fully inform (written and verbal communication) participants of the commitment and requirements of the study. It is essential to collect participant tracing information, such as address, phone number, clinic number and contact information of next of kin at each visit.

Data management

Each participant will receive a unique participant identification number, which will be used for identification for the duration of the study on all source, case report forms (CRFs) and transcript documents, with the exception of the locator information form that contains their address and contact information, which will be kept separately in a locked cupboard at the research office / clinic site.

Data will be collected for this study on an open access electronic data capture system (RedCap) using a password protected platform, with a limited number of paper-based documents. The study visit case record form will be completed as soon as possible during or immediately after the study visit. The principal investigators have overall responsibility for ensuring the data collected are complete, accurate, and recorded in a timely manner. Confidentiality of records will be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirements.

Once the electronic case report form (eCRF) is completed data staff will monitor the data for completeness and accuracy. Any discrepancies either manual or automatic will be corrected by site staff. Corrections to eCRFs will only be possible by study personnel with sufficient authorisation to make changes. All changes will have an electronic date stamp. Corrections to paper-based forms can only be done by study staff and must be signed and dated. All hard copies of source and CRF's documents will be kept in a locked cupboard at the research office or secure long-term storage facility for five years.

Qualitative data: will be recorded on a digital recorder and downloaded daily to an encrypted hard drive. The digital recorder will be cleared once the interview is downloaded. Transcripts will be deidentified and stored electronically on the DTHF secure server with password protection.

Electronic data will be stored in a password-protected folder on the secure company server.

STUDY WITHDRAWAL

Participants are free to withdraw from the study at any stage, without prejudice to them or affecting their rights to care in any way. The following participants will be withdrawn from the study:

1) If the investigator deems it in the best interest of the participant to withdraw from the study;
2) No longer able to provide full informed consent.

Withdrawn participants will not be replaced and will be included in the intention to treat analysis.

ADVERSE EVENT MANAGEMENT

As we will not be altering the standard of care ART given by the CoCT clinics, we will not be collecting drug-related adverse events for the RETAIN study. We will minimize all risks associated with study participation to the greatest extent possible, as detailed in the SUSTAIN procotol (section G2).

DATA SAFETY AND MONITORING BOARD

We will establish a Data Safety and Monitoring Board (DSMB) as part of the requirements for the SUSTAIN study funding. The RETAIN study in itself does not require the use of a DSMB as there are no drug products being administered to the study particpants.

The Trial Management Committee (TMC) will meet bi-weekly leading up to study start and weekly during the recruitment window of RETAIN; and will comprise, at a mimimum, the Senior Fellow, the Site Medical Officer, and an external consultant with an interest in the study outcomes. The role of the TMC will be to monitor day to day functioning of the study, take responsibility for overall participant safety and to act as the oversight body for this trial. The TMC will report immediately to the funders and the UCT Ethics Committee should a breach of study integrity occur.

STATISTICAL DESIGN AND POWER

Work from prior studies at the proposed site shows that ±20% of individuals are lost to care at 12 months, and a further ±20% who remain in care are not virally suppressed. We anticipate that all these individuals would be flagged by SUSTAIN: ±180 of 510 enrolled individuals. For the intra-individual analysis of the adherence intervention component in RETAIN, ±53 people receiving the adherence intervention per flagging method has 85% power to detect a decrease in non-adherence from 20% at Visit 1 to 0% at Visit 2 at a 5% level of significance using McNemar's test, and assuming that 97% (almost all) adherent individuals remain adherent.

Baseline demographic factors will be described with simple proportions for categorical variables and means (± standard deviation) or medians (±inter-quartile range) for continuous variables. Intra-individual adherence and drug concentration data will be compared using the paired T-test for paired data (normally distributed) or the Wilcoxon signed-rank test (not normally distributed) data. An intention-to-treat analysis of any viral failure (viral non-suppression) as a categorical variable, using logistic regression,

controlling for age, sex, baseline CD4 cell count and baseline viral load. Patients with viral suppression will be compared to the remainder of the cohort by assessing associations of categorical variables (such as sex, presence of depression or anxiety, substance use and stigma), and continuous variables (such as age, weight, HIV VL, CD4 count and electronic adherence and drug concentrations) using Fisher exact tests or Wilcoxon rank-sum tests respectively.

ETHICAL CONSIDERATIONS AND INFORMED CONSENT

ETHICAL CONDUCT

This study will be conducted in accordance with the ethical principles laid out in the National Statement on Ethical Conduct in Research Involving Humans, the Declaration of Helsinki (most current version issued, available at www.wma.net), and will be consistent with GCP and applicable regulatory requirements.

The rights, safety, and wellbeing of the study participants are the most important consideration and will prevail over interests of science and society. All personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s).

Institutional review board/independent ethics committee (IRB/IEC) and local regulatory approval will be documented and kept in the investigator site file, specifying the version number of the protocol and informed consent as well as the date of approval. Any amendments will require IRB/IEC and regulatory approval.

The principal investigator will comply with all IRB/EC and regulatory authorities, reporting requirements for all safety reporting, annual updates, safety updates, end of study reports and any other important information relevant to the conduct of the study.

COMPLIANCE WITH THE PROTOCOL

The study will be conducted as described in this protocol. The principal investigator will not implement any deviation or change to the protocol without prior review and documented approval/favourable opinion from the IRB/IEC and regulatory authorities of an amendment, except where necessary to eliminate an immediate hazard(s) to study participants. Any significant deviation will be reported to sponsor, IRB/IEC, and local regulatory authority.

PROTOCOL AMENDMENTS

When revisions to the protocol are made by the sponsor, if the revision is an administrative letter, the principal investigator will submit this for the information of their IRB/IEC. Study documents will be updated in line with the changes required in the protocol amendment.

INFORMED CONSENT AND PROCEDURES

A study specific informed consent and assent document will include all elements required by GCP as well as all local ethics and regulatory requirements.

The principal investigator will ensure that participants are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they participate and that their

participation is voluntary. A copy of the informed consent will be given to the participant in a language of their choice. Informed consent process will be conducted as per the trials site standard operating procedures. A copy of the signed informed consent will be given to the participant.

If the patient is illiterate, an impartial witness will be present during the entire consent discussion. A thumb print may be used as a signature.

The informed consent and assent documents will be updated with any pertinent information that becomes available during the study.

POTENTIAL RISKS

Risks to participants

Given that this is a behavioural study, we do not have grave concerns about the safety of the study procedures. The risk of blood draw is minimal. The site staff have experience in HIV care and can mitigate risks of status disclosure. All participant stand to gain health benefits from the support in improving their adherence to ART.

Vulnerable subjects:

Pregnant women will be included in this study, as they are a group at increased risk, across sub-Saharan Africa of poor ART outcomes, usually due to poor adherence during pregnancy. It is essential that continuous care in this group is improved, in order to protect their own life as well as the lives of their current and future babies. Including these women is scientifically appropriate.

The pregnant women and their unborn babies will be at no increased risk through study participation. The study will not impact on the choice of ART made for the pregnant women. Through potentially improving adherence to ART, this research holds the prospect of direct benefit to both the mother and her unborn baby.

Similarly, we are including older adolescents aged 16 and above. These individuals are also at increased risk of poor ART retention and adherence and thus are being included purposefully. During the informed consent process, we will endeavour to be very clear what study participation entails so that these adolescents make an informed decision understanding the risks involved—and with their guardians make the best choice for them.

Confidentiality:

Participants will be anonymised and allocated a study number to protect their identity. The identity of participants will be protected, respecting the privacy and confidentiality rules in accordance with regulatory requirements. All data generated will be linked to a participant study number and not a patient name. Only the investigators will have access to an identity log which links the participant study number to the participant name. All request forms, blood sample and imaging reports will therefore be labelled using the participant's study number and not details that may identify the participant.

Protection Against Risks

Informed Consent

Informed consent / assent will be obtained from all participants prior to conducting any study related procedures. The University of Cape Town Human Research Ethics Committee and GCP informed consent principles have been used to develop the informed consent template for this study. The informed consent will detail the potential benefits of participating in the research as well as the potential risks of the experimental interventions. Those who express interest will undergo the consenting process, which assures that the participants have understood the overall reasons for the investigation, its risk and benefits. The participant signing the consent and receiving a copy completes the process.

We will obtain informed consent in the following manner: the investigator or a designated study team member will fully explain the nature, conditions and possible consequences including risks and inconveniences of the study to the study participants.

We will ask simple questions to assess the ability of potential participants to provide informed consent such as: *What is this study about? Will you get any study treatment to take with your antiretroviral drugs? How long will you have to take the study treatment? Will you need to come to study visits extra to your clinic visits? What will happen at the study visits? Do you want to participate in this study?*

We will record the participant's ability to provide informed consent in the source documents. A competent translator, familiar with the study will assist in the informed consent process when necessary. The translator will be able to translate the conversation between the investigator and the participant should there be any questions from the participant. Subject information and consent documents will be available in Xhosa and English and participants will have the opportunity to discuss whether to enrol with family or friends before screening. A witness independent of the study will countersign the consent documents of illiterate participants. The independent witness will be signing to the effect that the information was read to the participant, who understood and freely gave their consent. Each participant will be given a copy of the signed information and consent document, a copy will be placed in the participant's medical record (if applicable) and the original stored in the trial files. Consenting will be a continuous process requiring on-going assessment during the course of the study. If a study participant is determined to have lost decision-making capacity after initially consenting, he or she will be withdrawn from the study. We will exclude participants who are unable to provide informed consent.

Incidental findings

The results of any viral load blood draw will be communicated to participants. Copies of reports will be given to participants to provide to their regular health care provider. Drug concentrations will not be provided to the particiapnts in real-time, but will be offered at the end of their study participation. If the

study team notes any incidental findings these will be communicated to participant, and if needed, we will refer participants appropriately to specialist care in the public sector.

Participant identification

Research data will be collected in accordance with the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2015. No data will be collected without written approval of Univiersity of Cape Town Human Research Ethics Committees that complies with the South African National Health Act No.61 2003 as it pertains to health research. Only data relevant to the study will be collected and data to be collected will be specified in the protocol. Participants will be anonymised and allocated a study number to protect their identity. All data generated will be linked to a participant study number and not a patient name. Only the study investigators will have access to an identity log which links the participant study number to the participant name. Only coded samples or imaging data, with no identifying characteristics, will be disseminated for analyses.

Data storage and access to participant records

We will keep participant files containing study-related source documents (screening notes / ICF or assent documents, any blood test result reports, and adherence questionnaire documents, etc.) securely at the study site. Access to the participant files will be limited to the study team. Steps involved in data management, including those relating to the development and management of a database will be performed in accordance with standard operating procedures consistent with regulatory requirements. The confidentiality of records that can identify participants will be protected, respecting the privacy and confidentiality rules in accordance with regulatory requirements. The principal investigator will provide direct access to source data/documents for trial-related monitoring, audits, ethics committee review, and regulatory inspection.

The principal investigator agrees that the Desmond Tutu Health Foundation, the study funder (EDCTP), IRB/EC or regulatory authorities may consult and/or copy study documents to verify information in the CRF. By signing the consent form the participant agrees to these processes. Participant confidentiality will be maintained at all times and no documents containing the participant's name or other identifying information will be collected by the funding organisation. It may be necessary for the funder's representatives, the IRB/EC and regulatory authority representatives to have direct access to the participant's medical records. If study documents need to be photocopied during the process of verifying CRF data, the participant will be identified by a unique code only; full names and other identifying information will be masked.

The principal investigator also agrees to maintain confidentiality with all study information and only divulge necessary information to the staff, ethics committee and regulatory authorities. The data generated by this study will be considered confidential, except where it is included in a publication as agreed in the publication policy of this protocol.

All study-related documents will be stored for at least 5 years following study completion. The raw data

may be shared with other researchers if the investigators, sponsor, funder and University of Cape Town Human Research Ethics Committees agree. The underlying principle of sharing of data should be that it is in the interest of advancing scientific knowledge. Data will not be shared with any party that infringe the rights of the study participants or the intellectual property.

POTENTIAL BENEFITS

Participants may benefit personally from taking part in this study. Participating in a study with intensive adherence monitoring and support may benefit participants who may not receive such care routinely. The study team may detect or be told incidental findings which may otherwise be missed or be delayed in diagnosed.

The risks exposure of participants in this trial are considered to be minimal; amounting to extra blood draws and urine sampling at two visits.

POTENTIAL PROBLEMS AND ALTERNATIVE STRATEGIES

The study PI will take responsibility for all aspects of data safety for both studies. Because both studies are largely behavioural, and neither involve any testing of medications, or any type of procedure that is outside the usual care provided to HIV-positive individuals in South Africa, risk is minimal. The study team's role in monitoring patient safety will be limited to noting any severe adverse events or serious adverse events that might have occurred and alerting the clinics to unexpected test findings or conditions identified during subject participation.

Reporting of adverse events and unanticipated problems:

- Adverse events will include reactions to blood draws related to the study, as well as any reported stigma or physical and/or mental harm as a result of participation in the study, including disclosure of HIV status. We will also record any clinical adverse event leading to a change in antiretroviral therapy. All adverse events will be recorded on designated forms and rated for both severity and seriousness.

- Any serious adverse or unanticipated event that occurs during the course of the study which might be related to study participation will be reported immediately to the PI/Trainee Fellow. If the SAE is directly related to study participation or an unexpected drug reaction, these events will be reported to the IRB within 2 weeks of their occurrence; otherwise they will be reported on a 6-monthly line listing. The two-week period is necessary to allow the investigators to examine and clarify the full circumstances surrounding serious adverse events or unanticipated events. In collaboration with the local and Nigerian study teams, the PI/Trainee Fellow will make a determination as to whether these events are probably, possibly, or unlikely to be related to study procedures. While all these events will be reported, they will need to be managed locally. When necessary, the study teams can arrange for hospitalisation and treatment at the nearest district hospital, though this is likely to be managed by the patient's own local clinic team.

- All mild to moderate adverse events will be reported during the annual renewal of the protocol. Any events deemed by the study team to be possibly related to the study will be carefully reviewed and, if necessary, modifications to the protocol or informed consent will be made in order to protect the safety of study subjects.

A Data and Safety Monitoring Board will not be appointed for this study. The study leadership team (Senior fellow, MO and data manager) will constitute the Trial Management Committee and monitor safety closely and work with our institutional Ethics Committees. Our data management plan carefully considers any findings and events that would bring safety concerns. As a behavioural intervention study, we determined an external board would not be necessary.

Monitoring will be conducted by the GRO internal monitor after the first month of recruitment and thereafter on a quarterly basis. Documents to be monitored will include 100% of Informed Consent Forms, 100% of eligibility criteria checklists and 10% of all participants who receive the intervention. Recruitment will take approximately 12 months and proposed monitoring visits will be frequent enough to identify trends and provide feedback on progress and for necessary changes and improvements to be implemented.

Study staff will be responsible for real-time quality control of their work and the on-site data manager and study management team will be responsible for quality control of the flagging methods and implementation of the intervention for flagged participants.

DISSEMINATION PLAN

SCIENTIFIC COMMUNITY

The study will be registered on the South African National Health Research Ethics Council (NHREC) and Pan African Clinical Trials Registry (PACTR). We will widely share our positive and negative research findings by presenting the data at appropriate conferences and publish the results in reputable journals, preferable open access journals. The timeline of sharing of data will be 12 months from study completion. The raw study data will be made available to individuals or organisations who make legitimate and appropriate requests, provided that permission from the PI, the EDCTP and the University of Cape Town Human Research Ethics Committee have been obtained.

We plan to publish the outcomes of the SUSTAIN and RETAIN studies in open access academic journals to add our findings to the research literature and so potentially impact on the ideas and future research of other scientists. We expect to publish at least five manuscripts from the combination of the two nested studies: analysis of the intra-individual components, examining changes in electronic adherence data and drug concentrations before and after the intervention; as well as using the detailed granular electronic adherence and daily dosing data from the Wisepill to conduct modelling analyses exploring the impact of these variables on short and long half-life drug concentrations. Other work will have an epidemiological flavour, and detail the primary study outcomes of viral suppression; also exploring factors impacting on retention vs loss to care; and patterns of adherence impacting on drug resistance. The qualitative data will explore individual reasons

for adherence and describe acceptability of the intervention and adherence flagging processes in this community.

We will further share our data through presentations at appropriate conferences – both local and international. Abstracts from these manuscripts will be presented at local conferences such as INTEREST and the Southern African HIV Clinicians Society conference, as well as internationally, at the IAPAC Adherence Conference, the EDCTP Forum and potentially at the Conference on Retroviral and Opportunistic Infection (CROI). These conferences will provide an opportunity for the mentee researchers and other in the team to present the results to a broader audience. These conferences will allow us both to contribute to and to learn from recent advances in the HIV adherence and therapeutic fields, as well as to meet other researchers. In order to foster existing and create new collaborations.

Oral presentations will be given by the team to the City of Cape Town (CoCT) and the Provincial Department of Health (DoH) Management Teams, to keep them aware of the study's progress and outcomes. In mid and late 2019, the applicant met with the CoCT TB/HIV team to explore this project; and gain their support.

STUDY PARTICIPANTS

At the end of the study, we will plan a community dissemination event. These have been well-received in the past with 25-35% of previous participants attending feedback of the other community adherence studies. Staff will contact participants to invite them to the event. There are often challenges in terms of contacting the participants using their study locator information, as many will have changed their contact details. We will use all forms of possible outreach including social media platforms, calls, messages and home visits to reach the participants. We will also place an invite to the dissemination meeting in the local community newspapers and use our local staff and Community Advisory Board to invite local community members to attend.

The results will be communicated at the annual research day of the research site (Desmond Tutu Health Foundation). We will approach the press to communicate the finding in publications targeted at the public.

APPENDIX 1: TIMELINE

Workpackage	Activity	Year 1 (Nov21-Oct22)				Year 2 (Nov22-Oct23)				Year 3 (Nov23-Oct24)				Year 4 (Nov24-Oct25)				Year 5 (Nov-Dec25)	
		Q1	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q 4**	**Q1**	**Q2**
	SENIOR FELLOW RESEARCH PROPOSAL																		
WP 1	Assess and improve current RoTF adherence intervention at clinics		X	X															
	Protocol completion	X																	
	UCT Ethics approval	X																	
	Approvals from clinics / CoCT	X	X																
	Staff training	X	X																
	Recruitment at clinics		X	X	X	X	X	X	X	X									
	Enrolment at clinics or DCAT offices		X	X	X	X	X	X	X	X									
	Follow-up		X	X	X	X	X	X	X	X	X	X	X	X					
	Adherence intervention (if flagged)		X	X	X	X	X	X	X	X	X	X	X	X					
	CAPACITY BUILDING COMPONENT																		
WP 2	Masters student						X	X	X	X	X	X	X	X					
	PhD student		X	X	X	X	X	X	X	X	X	X	X	X					
	Trainee Fellow	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
	TRAINEE FELLOW RESEARCH PROPOSAL																		
	Protocol completion	X																	
	Ethics approvals	X																	
	Site approvals	X	X																
	Staff training		X																
	Recruitment at clinics			X	X	X	X	X	X										
	Follow-up			X	X	X	X	X	X	X	X	X	X	X					
	DATA MANAGEMENT AND WRITING																		
WP 4	Data cleaning			X	X	X	X	X	X	X	X	X	X	X	X				
	Data analysis											X	X	X	X	X			
	Manuscript writing and submission												X	X	X	X	X	X	
	Dissemination of findings															X	X	X	

CoCT - City of Cape Town; RoTF – Risk of Treatment Failure; D-CAT – DTHF Centre for Adherence and Therapeutics

APPENDIX 2: Informed consent document – attached separately.

REFERENCES

1. United Nations Programme on HIV/AIDS (UNAIDS). UNAIDS Data 2019. 2019. Available from: https://www.unaids.org/sites/default/files/media_asset/2019-UNAIDS-data_en.pdf. Accessed 10Feb2020.
2. United Nations Programme on HIV/AIDS (UNAIDS). 90-90-90 An ambitious treatment target to help end the AIDS epidemic. 2014. Available from: http://www.unaids.org/sites/default/files/media_asset/90-90-90_en_0.pdf. Accessed 05Feb2020.
3. United Nations Programme on HIV/AIDS (UNAIDS). Understanding Fast-Track: Accelerating Action to End the AIDS Epidemic by 2030. 2014. Available from: https://www.unaids.org/sites/default/files/media_asset/JC2686_WAD2014report_en.pdf. Accessed 05Feb2020.
4. Haberer JE, Bwana BM, Orrell C, Asiimwe S, Amanyire G, Musinguzi N, et al. ART adherence and viral suppression are high among most non-pregnant individuals with early-stage, asymptomatic HIV infection: an observational study from Uganda and South Africa. Journal of the International AIDS Society. 2019;22(2):e25232.
5. Phillips TK, Clouse K, Zerbe A, Orrell C, Abrams EJ, Myer L. Linkage to care, mobility and retention of HIV- positive postpartum women in antiretroviral therapy services in South Africa. Journal of the International AIDS Society. 2018;21 Suppl 4:e25114.
6. Orrell C CK, Mauff K, Bangsberg D, Maartens G, Wood R. . A randomised controlled trial of real-time electronic adherence monitoring with text message dosing reminders in people starting first-line antiretroviral therapy. JAIDS. 2015; 70(5):495-502.
7. Katz IT, Kaplan R, Fitzmaurice G, Leone D, Bangsberg DR, Bekker LG, et al. Treatment guidelines and early loss from care for people living with HIV in Cape Town, South Africa: A retrospective cohort study. PLoS medicine. 2017;14(11):e1002434.
8. Fox MP, Rosen S. Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007-2009: systematic review. Tropical medicine & international health : TM & IH. 2010;15 Suppl 1:1-15.
9. Fox MP, Rosen S. Retention of Adult Patients on Antiretroviral Therapy in Low- and Middle-Income Countries: Systematic Review and Meta-analysis 2008-2013. Journal of acquired immune deficiency syndromes (1999). 2015;69(1):98-108.
10. Nglazi MD, Lawn SD, Kaplan R, Kranzer K, Orrell C, Wood R, et al. Changes in programmatic outcomes during 7 years of scale-up at a community-based antiretroviral treatment service in South Africa. Journal of acquired immune deficiency syndromes (1999). 2011;56(1):e1-8.
11. Takuva S, Brown AE, Pillay Y, Delpech V, Puren AJ. The continuum of HIV care in South Africa: implications for achieving the second and third UNAIDS 90-90-90 targets. AIDS (London, England). 2017;31(4):545-52.
12. Ford N GE, Ellman T, Orrell C, Ehrenkranz E, Sikazwel I, Jahn A, Rabkin M, Addo SA, Grimsrud A, Rosen S, Zulu I, Reidy W, LejoneI T, Apollo T, Holmes C, Kolling AF, Lesihla RP, Nguyen HH, Bakashaba B, Chitembo L, Tiristel G, Doherty M, Bygrave H. . Emerging priorities for HIV service delivery. PLOS Medicine. 2020;In press.
13. Orrell C, Kaplan R, Wood R, Bekker LG. Virological breakthrough: a risk factor for loss to followup in a large community-based cohort on antiretroviral therapy. AIDS research and treatment. 2011;2011:469127.
14. Orrell C, Harling G, Lawn SD, Kaplan R, McNally M, Bekker LG, et al. Conservation of first-line antiretroviral treatment regimen where therapeutic options are limited. Antiviral therapy. 2007;12(1):83-8.
15. Ncaca LN, Kranzer K, Orrell C. Treatment interruption and variation in tablet taking behaviour result in viral failure: a case-control study from Cape Town, South Africa. PloS one. 2011;6(8):e23088.
16. Parienti JJ, Barrail-Tran A, Duval X, Nembot G, Descamps D, Vigan M, et al. Adherence profiles and therapeutic responses of treatment-naive HIV-infected patients starting boosted atazanavir-based therapy in the ANRS 134-COPHAR 3 trial. Antimicrobial agents and chemotherapy. 2013;57(5):2265-71.
17. Parienti JJ, Das-Douglas M, Massari V, Guzman D, Deeks SG, Verdon R, et al. Not all missed doses are the same: sustained NNRTI treatment interruptions predict HIV rebound at low-to-moderate adherence levels. PloS one. 2008;3(7):e2783.
18. Vijay S, Kumar P, Chauhan LS, Vollepore BH, Kizhakkethil UP, Rao SG. Risk factors associated with default among new smear positive TB patients treated under DOTS in India. PLoS One. 2010;5(4):e10043.

19. Thomas A, Gopi PG, Santha T, Chandrasekaran V, Subramani R, Selvakumar N, et al. Predictors of relapse among pulmonary tuberculosis patients treated in a DOTS programme in South India. Int J Tuberc Lung Dis. 2005;9(5):556-61.
20. Cadosch D, Abel Zur Wiesch P, Kouyos R, Bonhoeffer S. The Role of Adherence and Retreatment in De Novo Emergence of MDR-TB. PLoS computational biology. 2016;12(3):e1004749.
21. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. BMJ (Clinical research ed). 2008;336(7653):1114-7.
22. Hiligsmann M, Cornelissen D, Vrijens B, Abrahamsen B, Al-Daghri N, Biver E, et al. Determinants, consequences and potential solutions to poor adherence to anti-osteoporosis treatment: results of an expert group meeting organized by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the International Osteoporosis Foundation (IOF). Osteoporos Int. 2019;30(11):2155-65.
23. Thompson MA, Mugavero MJ, Amico KR, Cargill VA, Chang LW, Gross R, et al. Guidelines for improving entry into and retention in care and antiretroviral adherence for persons with HIV: evidence-based recommendations from an International Association of Physicians in AIDS Care panel. Ann Intern Med. 2012;156(11):817-33, w-284, w-5, w-6, w-7, w-8, w-9, w-90, w-91, w-92, w-93, w-94.
24. Deschamps AE, De Geest S, Vandamme AM, Bobbaers H, Peetermans WE, Van Wijngaerden E. Diagnostic value of different adherence measures using electronic monitoring and virologic failure as reference standards. AIDS patient care and STDs. 2008;22(9):735-43.
25. Orrell C, Cohen K, Leisegang R, Bangsberg DR, Wood R, Maartens G. Comparison of six methods to estimate adherence in an ART-naive cohort in a resource-poor setting: which best predicts virological and resistance outcomes? AIDS Res Ther. 2017;14(1):20.
26. Court R, Leisegang R, Stewart A, Sunpath H, Murphy R, Winternheimer P, et al. Short term adherence tool predicts failure on second line protease inhibitor-based antiretroviral therapy: an observational cohort study. BMC infectious diseases. 2014;14(1):664.
27. Nachega JB, Hislop M, Dowdy DW, Lo M, Omer SB, Regensberg L, et al. Adherence to highly active antiretroviral therapy assessed by pharmacy claims predicts survival in HIV-infected South African adults. Journal of acquired immune deficiency syndromes (1999). 2006;43(1):78-84.
28. Orrell C, Dipenaar R, Killa N, Tassie JM, Harries AD, Wood R. Simplifying HIV cohort monitoring-- pharmacy stock records minimize resources necessary to determine retention in care. Journal of acquired immune deficiency syndromes (1999). 2013;62(3):e106-8.
29. Sabin LL, Bachman DeSilva M, Gill CJ, Zhong L, Vian T, Wubin X, et al. Improving Adherence to Antiretroviral Therapy with Triggered Real Time Text Message Reminders: the China through Technology Study (CATS). Journal of acquired immune deficiency syndromes (1999). 2015;69(5):551-9.
30. Haberer JE, Sabin L, Amico KR, Orrell C, Galarraga O, Tsai AC, et al. Improving antiretroviral therapy adherence in resource-limited settings at scale: a discussion of interventions and recommendations. Journal of the International AIDS Society. 2017;20(1):1-15.
31. Kredo T, Van der Walt J-S, Siegfried N, Cohen K. Therapeutic drug monitoring of antiretrovirals for people with HIV. Cochrane Database of Systematic Reviews [Internet]. 2009; (3). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007268.pub2/abstract.
32. Liu X, Ma Q, Zhang F. Therapeutic drug monitoring in highly active antiretroviral therapy. Expert opinion on drug safety. 2010;9(5):743-58.
33. Castillo-Mancilla JR, Morrow M, Coyle RP, Coleman SS, Gardner EM, Zheng JH, et al. Tenofovir Diphosphate in Dried Blood Spots is Strongly Associated with Viral Suppression in Individuals with HIV nfection. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2018.
34. South African National Department of Health. Adherence Guidelines for HIV, TB and NCDs. 2016 [Available from: https://www.nacosa.org.za/wp-content/uploads/2016/11/Integrated-Adherence-Guidelines-NDOH.pdf
35. Ford N, Orrell C, Shubber Z, Apollo T, Vojnov L. HIV viral resuppression following an elevated viral load: a

systematic review and meta-analysis. Journal of the International AIDS Society. 2019;22(11):e25415.
36. Bonner K, Mezochow A, Roberts T, Ford N, Cohn J. Viral load monitoring as a tool to reinforce adherence: a systematic review. Journal of acquired immune deficiency syndromes (1999). 2013;64(1):74-8.
37. Barnighausen T, Chaiyachati K, Chimbindi N, Peoples A, Haberer J, Newell ML. Interventions to increase antiretroviral adherence in sub-Saharan Africa: a systematic review of evaluation studies. The Lancet infectious diseases. 2011;11(12):942-51.
38. Kanters S, Park JJ, Chan K, Socias ME, Ford N, Forrest JI, et al. Interventions to improve adherence to antiretroviral therapy: a systematic review and network meta-analysis. The lancet HIV. 2017;4(1):e31-e40.
39. Harvey K. SL, Orrell C. Challenges to antiretroviral therapy adherence and treatment retention among HIV+ adults in South Africa: Qualitative investigations in the Locally-tailored, Evidence-based, And Personalized (LEAP) ART support study. Maternal and Child Health Fellowship Program at the Maternal and Child Health Center of Excellence, BUSPH; December 06, 2019.; Boston, MA.: . 2019.
40. Liu X, Blaschke T, Thomas B, De Geest S, Jiang S, Gao Y, et al. Usability of a Medication Event Reminder Monitor System (MERM) by Providers and Patients to Improve Adherence in the Management of Tuberculosis. Int J Environ Res Public Health. 2017;14(10).
41. Orrell C, Hagins DP, Belonosova E, Porteiro N, Walmsley S, Falco V, et al. Fixed-dose combination dolutegravir, abacavir, and lamivudine versus ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate and emtricitabine in previously untreated women with HIV-1 infection (ARIA): week 48 results from a randomised, open-label, non-inferiority, phase 3b study. The lancet HIV. 2017;4(12):e536-e46.
42. Orrell C, Felizarta F, Nell A, Kakuda TN, Lavreys L, Nijs S, et al. Pharmacokinetics of Etravirine Combined with Atazanavir/Ritonavir and a Nucleoside Reverse Transcriptase Inhibitor in Antiretroviral Treatment- Experienced, HIV-1-Infected Patients. AIDS research and treatment. 2015;2015:938628.
43. Waitt C OC, Walimba S, Singh Y, Simmons B, Kaboggoza J, Sihlangu M, Coombes J-A, Malaba T et al. Safety and pharmacokinetics of dolutegravir in pregnant mothers with HIV infection and their neonates: a randomised trial (DOLPHIN-1 study). PLoS medicine. 2019;in press.
44. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. The New England journal of medicine. 2010;363(27):2587- 99.