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An Adhe.ence Feedback Pilot of Integrating DBS Results into Clinic Practice

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Use of ARV Drug Levels in DBS to Assess and Manage ART Adherence in South Africa

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Use of ARV Drug Levels in DBS to Assess and Manage ART Adherence in South Africa (ADD-ART): An Adherence Feedback Pilot of Integrating DBS Results into Clinic Practice (ADD-ART Aim #2)

Study Protocol Version 1.0
03/17/2020

Protocol Signature Page

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

09Apr2020

Signature of Investigator of Record

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3. LIST OF ABBREVIATIONS

ART	Antiretroviral treatment
CAB	Community Advisory Board
CCW	Community Care Workers
DBS	Dried blood spot
DoH	Department of Health
DTHF	Desmond Tutu HIV Foundation
EC	Ethics Committee
EMD	Electronic Monitoring Device
FDW	Feedback Development Workgroup
FGD	Focus Group Discussions
FTC-TP	Emtricitabine-triphosphate
GRO	Gugulethu Research Office
HCW	Health care workers
IRB	Institutional Review Board
NIMART	Nurse Initiated and Managed Anti-Retrovrial Treatment
MO	Medical Officer
NHLS	South African National Health Laboratory Service
PLWH	People Living With HIV
PID	Participant identification number
POC	Point-of-care
PrEP	Pre-exposure prophylaxis
PRO	Protocol Registration Office
RBC	Red blood cells
SA	South Africa
SCO	Study coordinator
SMS	Short message service
SoC	Standard of care
SOP	Standard Operating Procedure
TFV	Tenofovir
TFV-DP	Tenofovir-diphosphate
US	United States
VL	Viral load

4. PROTOCOL SUMMARY

Full Title: An Adherence Feedback Pilot: Integrating DBS Results into Clinic Practice

Title of Main Protocol: Use of **A**RV **D**rug Levels in **D**BS to Assess and Manage **ART** Adherence in South Africa

Short Title: ADD-ART Protocol – Adherence Feedback Pilot

Sample Size: 60

Study Population: HIV-infected adults who have been on an ART regimen containing tenofovir for at least 4 months.

Participating Sites: Desmond Tutu HIV Foundation Gugulethu Research Offices, Cape Town, South Africa; NY State Psychiatric Institute/RFMH, New York, NY

Study Design: This is a prospective, pilot study of HIV-positive individuals who have been on tenofovir-containing antiretroviral therapy for at least 4 months. The overall goal of this research is to determine the feasibility of giving patients and their providers monthly feedback about Tenofovir-Diphosphate (TFV-DP) drug levels and to examine patient and provider behaviors in response to receiving this information. This study will build upon the Aim 1 observational study and the subsequent patient and provider Feedback Development Workgroups (FDWs).

We will consent a sample (N=60) of HIV-positive patients for monthly assessments, including blood specimen collections to assess TFV-DP drug levels. Participants enrolled in this prospective, pilot study will be randomized to either the intervention arm in which they will receive monthly feedback on their TFV-DP drug levels (Feedback Group; N=30) or the control arm in which they will receive no feedback on TFV-DP drug levels (No Feedback Group; N=30).

The study will take place at the Gugulethu Research Offices (GRO) of the Desmond Tutu HIV Foundation (DTHF) in Gugulethu, 15km outside Cape Town, South Africa (SA). Study participants will be recruited from patients attending one of four public-sector ART clinics in the Klipfontein Health District, Western Cape, including (1) Hannan Crusaid Treatment Centre, (2) Nyanga Clinic, (3) Gugulethu Clinic (NY1), and (4) Vuyani Clinic.

Enrollment will occur over 3-4 months, during which we will recruit an average of 15-20 participants per month, for a total of 60 participants. Participants will remain in the study for 5 months, attending a baseline and 4 subsequent monthly study visits. At each monthly visit, study staff will obtain venous blood samples for dried blood spots (DBS) which will measure TFV-DP levels and a viral load (VL) assay. ART adherence will also be assessed through the Wisepill electronic monitoring device (EMD) a medication dispenser that sends an electronic medication event record to the Wisepill server when medication is taken and monthly self-reported medication adherence. Socio-demographic characteristics, medical history, mental health, substance use, and other contextual factors will be assessed at baseline and at the final study visit. In addition, at each visit, participants randomized to the intervention arm will receive feedback on their previous month's TFV-DP drug levels. Clinic providers will also receive TFV-DP drug level results for the participants in the intervention arm.

For both intervention and control groups, we will monitor any changes to ART adherence behavior on the part of patients and providers. We will do this by reviewing participants' clinic charts to determine if any changes were made to medical or adherence management of patients since the previous visit (e.g., additional VL requests beyond those prescribed for a stable patient, referral for intensive counselor-based or group adherence counselling, outreach by Health Care Workers (HCWs) for adherence monitoring and support, additional doctor-requested patient appointments). We will also conduct exit Interviews with participants and hold Provider Focus Group Discussions (FGD) to further understand whether (and if so, how) TFV-DP drug level feedback influenced medication adherence and patient management.

Schedule of Procedures/Evaluations: Participants will be seen at baseline and then monthly over 5 months for a total of 5 study visits.

Study Duration: The overall duration of the study is 8 months, with enrollment occurring over approximately 4 months. Over 4 months, participants will be enrolled at a rate of approximately 15-20 per month; each participant will be in the study for 5 months.

Study Regimen/Intervention: Participants randomized to the intervention arm will receive monthly feedback about their TFV-DP levels. Providers of participants randomized to the intervention arm will also receive monthly feedback about their patients' TFV-DP drug levels. Participants in the control group and their providers will not receive feedback about TFV-DP drug levels.

Primary Objective: The primary objective of this study is (a) to determine the feasibility of giving patients and providers monthly feedback about TFV-DP levels and (b) to examine patient and provider behaviors in response to receiving this information. This trial will assess the impact of such feedback on patient medication taking behaviors as measured with Wisepill, and clinical management of patients.

Primary Endpoint: Our primary endpoint is defined as behaviors in response to the receipt of information about TFV-DP drug levels. Behavioral responses will be assessed (and explored) by examining subsequent TFV-DP levels, subsequent VL(s), Wisepill use, self-reported medication adherence, and responses to queries in the Exit Interviews with participants, and in the provider FGDs.

5. INTRODUCTION

5.1. Background Information

5.1.1 Antiretroviral medication (ARV) non-adherence remains a critical public health problem, especially in low-resource settings. Scale-up of ART in resource-limited countries has presented huge healthcare system challenges, particularly in sub-Saharan Africa. In South Africa (SA) alone, over 7.5 million people are infected with HIV, and an estimated 3.9 million were on ART in 2017[1]. Recent ART guidlelines suggest everyone testing positive for HIV should be started on treatment, resulting in growing patient numbers[2,3]. Yet, an estimated 25%-42% of patients in care and on ART in SA have unsuppressed viral load (VL)[4,5], creating significant risks for the individual and the public health. With patient/provider ratios of 1:800-1:1000, often only obviously ill patients get adherence support[6]; and task-shifting to meet healthcare system burdens means that lay healthcare workers (HCW) with varying levels of training are typically the first resource for patients with adherence problems.

5.1.2 ART non-adherence can precede viral breakthrough by weeks or months, and routine (often annual) VL testing can miss critical points for intervention. Low levels of ART adherence can result in a detectable VL after suppression (viral rebound or breakthrough) followed by development of drug-resistant HIV (virologic failure). That said, there is not a simple relationship between level of adherence and viral breakthrough. Although it was once thought that 90-95% adherence was necessary to maintain viral suppression, with the development of new, more "forgiving" ART regimens, adherence as low as 80-85% overall may be sufficient[7]. Likewise, there are variations in time to re-emergence of detectable VL, depending on (a) stage of ART treatment (early/longer term)[8-10]; (b) type of ARV [nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), or integrase inhibitors (INSTIs)][11]; (c) duration of previous viral suppression[12,13]; and (d) non-adherence patterns (sustained gaps vs intermittent brief lapses)[14,15]. Even if VL has been suppressed in spite of sub-optimal adherence, undetected adherence problems may become habitual and worsen, and non-adherence can precede the resulting viral rebound detected by routine VL by months[16,17]. If only the current VL testing standard in SA (typically at 4 and 12 months post-ART initiation and only every 12 months thereafter)[3,4] is used as a clinical indicator of adherence, important opportunities for adherence intervention to prevent viremia are missed.

5.1.3 Assay of ARV drug levels demonstrates high reliability in monitoring pill-taking behavior and subsequent HIV viral loads and thus presents opportunities for adherence intervention. Drug concentrations in blood provide direct evidence of drug ingestion and allow for repeated sampling – especially when using dried blood spots (DBS), which are easily collected in a variety of clinical and research settings. Co-Investigator Anderson and colleagues have shown that DBS specimens are stable at room temperature for approximately 5 days and frozen at -20^{o}C or -80^{o}C for at least 2 years[18]. Anderson and colleagues[18,19] have also developed and validated an assay to quantify the active tenofovir (TFV) anabolite, tenofovir-diphosphate (TFV-DP) in DBS. They found that, once phosphorylated inside of the red blood cell, TFV-DP exhibits a long half-life of approximately 17 days, which is consistent across individuals. The inter-individual variability of steady-state concentrations is approximately 30%, and this variability is accounted for in the adherence interpretations[20]. Thus assays of TFV-DP in DBS has the potential to provide an objective, valid, and reliable measure of ARV ingestion for large numbers of people.

The assay has been characterized among HIV-negative participants in controlled settings [18,21] and more recently, among HIV-positive patients in high-resource settings in the United States (US)[22]. In persons living with HIV, TFV-DP in DBS had a strong exposure-response association with viral suppression at the time of the study visit, both in US and African patients[23]. In addition, TFV-DP in DBS has also been shown to predict the risk of future viremia, even in individuals who are virologically-suppressed at the time of their study visit[24], highlighting the potential utility of using TFV-DP in DBS to identify patients at risk of future viral breakthrough who would otherwise be missed using VL monitoring. High TFV-DP concentrations have also been associated with engagement in mental health care[25]. The table shows the relationship between TFV-DP concentration and adherence interpretation, based on a study in the United States[26].

TFV-DP (fmol/punch)	Adherence interpretation
≥1250	7 doses/week
700–1249	4–6 doses/week
350–699	2–3 doses/week
<350	<2 doses/week

Figure 1 Adherence interpretations in terms of average doses per week over prior 6–8 weeks, according to tenofovir-diphosphate concentrations in dried blood spots.

5.1.4 Aim 1 of the ADD-ART study examined the utility of using TFV-DP levels in DBS as an objective measure of adherence to ART in South Africa. In this prospective, observational cohort study, we followed 250 HIV-positive individuals on a tenofovir-containing antiretroviral therapy and virally suppressed at study enrollment. Participants provided 12 monthly blood samples which we used to measure TFV-DP levels in red blood cells, as well as VL and other measures detailed in the Aim 1 study protocol. The study took place at the Gugulethu Research Offices (GRO) of the Desmond Tutu HIV Foundation (DTHF) in Gugulethu, 15km outside Cape Town, South Africa (SA). The study began enrolling participants in November 2017 and completed data collection in December 2019. At the time of this protocol submission, we have received the DBS-TFV-DP assay results from approximately 57% of the total study samples. Preliminary analyses of this sample supports earlier findings that TFV-DP level is strongly associated with VL measured concurrently at the same study visit, and that TFV-DP levels can predict risk of future viral breakthrough. We found that after the first signal of low drug level, participants had more than 13 times the odds of viral breakthrough (VL >400 copies/ML) two months later (when adjusting for age, sex, BMI and HCT).

5.1.5 Treatment-related feedback may motivate patients' health-promoting behaviors. Providing individuals with feedback on their performance and/or adherence to a specific treatment can influence their subsequent behaviors, leading to more health-promoting behaviors (e.g., physical activity)[27-30]. In a study utilizing the Wisepill to assess adherence, participants found real-time monitoring acceptable[31] and in a separate trial using PK plasma results, patients actually recommended using real-time adherence monitoring as a preferred way to promote adherence[32]. However, it is unknown how feedback on adherence derived from drug level assays will affect patients' ART adherence behaviors and HIV providers' clinical behavior. ***Leveraging discussions from the Feedback Development Workgroups (FDWs) conducted in November 2019, we will examine the utility of giving SA patients appropriately framed feedback from the DBS TFV-DP assay in motivating them to sustain or improve adherence.***

5.1.6 The real-world success of any sophisticated technology for adherence measurement and management will depend on its actual use and, thus, its acceptability to patients and providers. The current TDF-DP assay at Anderson's laboratory has been validated under the CLIA program. In addition, technology and skills have been transferred to the University of Cape Town Clinical Pharmacology laboratory, under the guidance of Dr. Lubbe Wiesner. This laboratory is affiliated with the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT), AIDS Clinical Trials Group (ACTG), HIV PreventionTrials Network (HPTN) and HIV Vaccine Trials Network (HVTN) networks, and TDF-DP assay from DBS have been validated and approved by the DAIDS contracted Clinical Pharmacology Quality Assurance Program (CPQA). In Aim 2, we propose to use this laboratory to ensure that DBS results are available to provide timely feedback to patients and their HIV care providers. Moving laboratory procedures to the local Cape Town site will also allow the study team to analyse implementation factors that will be relevant to future scale-up this intervention. Further, the use of the local UCT laboratory can provide insights into the feasibility for migrating this model to another site and and the potential to scale up efforts globally. We have the opportunity to determine if the existing prototype for DBS-based ART adherence measurement is acceptable to patients, HCWs, and providers, and feasible and useful in resource-limited care settings. Studies have examined the utility of DBS assays in PrEP use but there are no studies, to our knowledge, that have evaluated the utility of TDF-DP in DBS to predict viral suppression or other relevant clinic outcomes, nor have examined the potential impact of providing results of DBS-based ART adherence measurement to patients and HIV providers on a monthly basis.

5.2. Rationale

We will examine the feasibility of giving patients and providers monthly feedback about TFV-DP levels and to examine patient and provider behaviors in response to receiving this information. We will leverage clinically relevant messages and modalities, developed in the FDWs, for communicating assay results to patients and providers and explore how such information influences patient and provider behavior as it relates to ART adherence.

This study will explore patients' adherence-related behaviors after they receive monthly objective feedback about their ART adherence. This study will be the first to examine how providers use feedback on TFV-DP drug levels to manage ART adherence.

5.3 Study Hypothesis

Participants who receive feedback on TFV-DP drug levels will have improved adherence, as assessed by monthly TFV-DP levels, VL, self-report; continuous Wisepill use patterns, and responses to queries in the Exit Interviews with participants, and in the provider FGDs.

6. OBJECTIVES

6.1. Primary Objectives

The primary objectives of this study are to (a) determine the feasibility of giving patients and providers monthly feedback about TFV-DP levels and (b) examine patient and provider behaviors in response to receiving this information, specifically patient medication adherence as measured with Wisepill, and clinical management of patients.

7. STUDY DESIGN

The study will take place at the Gugulethu Research Offices (GRO) of the Desmond Tutu HIV Foundation (DTHF) in Gugulethu, 15km outside Cape Town, South Africa. Study participants will be recruited from patients attending one of four public-sector ART clinics in the Klipfontein Health District, Western Cape. Recruitment clinics will include (1) Hannan Crusaid Treatment Centre, (2) Nyanga Clinic, (3) Gugulethu Clinic (NY1), and (4) Vuyani Clinic.

We will enroll a sample of (N=60) HIV-positive patients who have been on tenofovir-containing antiretroviral therapy for at least 4 months. Participants enrolled in this prospective, pilot study will be randomized to either the intervention arm and receive monthly feedback on their TFV-DP drug levels (Feedback Group; N=30) or the control group and receive no feedback (No Feedback Group; N=30). After baseline interviews and blood sample collection, all participants will begin using a Wisepill device for four months, return each month to give new blood samples and, for the Feedback Group only, receive feedback on previous month's adherence.

Providers will also be consented into this study which will allow for the review of medical notes made by the providers managing the patients who have enrolled in the trial. Providers of participants in the intervention arm will also simultaneously receive separate monthly messages on patients' TFV-DP drug levels through the clinic systems, and we will monitor subsequent clinical interactions and changes in patient management following this provider feedback. We will conduct participant Exit Interviews and provider FGDs among clinical staff to further understand how both groups did or did not use the feedback and to obtain recommendations for improvements.

8. STUDY POPULATION

The study will enroll a sample of 60 HIV-positive patients who have been on tenofovir-containing antiretroviral therapy for 4 or more months. Participants enrolled in this prospective, pilot study will be randomized to either the intervention arm and receive monthly feedback on their TFV-DP drug levels (Feedback Group; N=30) or the control group and receive no feedback (No Feedback Group; N=30).

The study will also consent ART providers, inclusive of nursing personnel (Nurse Initiated and Managed ART Therapy-NIMART providers and nursing sisters) and medical officers, at each of the four study clincs.

8.1 Inclusion/Exclusion Criteria

8.1.1. Patient Participant Inclusion Criteria

Individuals who meet all of the following criteria are eligible for inclusion in the study:

- 18 years of age or older
- HIV-positive
- Initiated ARV's containing tenofovir 4 or more months ago

- Speaks English or Xhosa
- Willing to attend 5 study visits approximately one month apart
- Willing to allow the study team to contact his/her HIV care provider about his/her monthly TFV-DP drug level
- Willing to use Wisepill to dispense ARVs for 4 months
- Willing to receive SMS and/or phone call reminders to charge the Wisepill
- Willing to allow the study team access to their medical chart/clinic folder

Participants will be recruited without regard to gender or race/ethnicity. However, based on clinic profiles, we expect the majority (about 70%) to be women and over 90% to be Black African, with the remainder, if any, of mixed race.

To generate a study sample that closely represents the clinic population, participants will be recruited regardless of VL. Based on clinic profiles, we expect the majority of participants (about 80%) to be virally suppressed based on the last standard of care (SoC) VL with the remainder being unsuppressed. The South African National Health Laboratory Service (NHLS), which assays the VL, currently uses a cut-off of less than 50 copies/mL to denote undetectable VL.

8.1.2. ART Provider Inclusion Criteria

Providers who meet the following criteria are eligible for inclusion in the study

- 18 years of age or older

- Works in a clinical setting at one of the following four HIV clinics (Hannan Crusaid Treatment Centre, Nyanga Clinic, Gugulethu Clinic/NY1, and Vuyani Clinic) and manage patients with HIV

- Providers will include physicians, nurses, nursing sisters, and medical officers

8.1.3. Patient Participant Exclusion Criteria

Individuals who do not meet inclusion criteria or who meet any of the following criteria will be excluded from the study:

- Unable to provide informed consent
- Unwilling to participate in study procedures
- Unwilling to allow the study team to contact his/her HIV care provider about his/her monthly TFV-DP drug level
- Any condition that, in the opinion of the principal investigator would make participation in the study unsafe, complicated interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

8.1.4. Provider Exlusion Criteria

- Does not manage patients with HIV

- Any condition that, in the opinion of the principal investigator would make participation in the study unsafe, or ortherwise interfere with achieving the objectives of the FGD

8.2 Recruitment Process

8.2.1 Recruitment Sites

We will recruit patient participants who are attending one of the four public-sector ART clinics in the Klipfontein Health District, Western Cape. The Hannan Crusaid Treatment Centre is one of the Western Cape's largest ART clinics with more than 15,000 patients initiating ART in the past decade, and more than 8,000 currently in care. This clinic is located within the Gugulethu Community Health Centre, and is staffed by 3 full-time doctors, 3 nurse practitioners, a pharmacist and pharmacy assistant, and 15 lay community care workers/counselors (CCWs). Each month, 40-50 non-pregnant, treatment-naïve individuals begin ART, usually a once-daily, fixed-dose tenofovir/emtricitabine/efavirenz tablet, e.g., Odimune, Atroiza, or Tribuss (Atripla® generic bioequivalents), which is first-line ART in SA. Participants will be also be recruited from Nyanga Clinic, a Provincial Department of Health (DoH) service similar in size to the Hannan Crusaid Treatment Centre, and Gugulethu Clinic (NY1) and Vuyani Clinic, which are smaller City of Cape Town clinics with a single NIMART nurse and a part time Medical Officer offering ART services. We obtained approvals from the City of Cape Town and the Provincial DoH for the Aim 1 study and will request further approvals for this protocol. These four sites will also be where the study team will recruit the providers.

8.2.2 Recruitment Methods

Patient participants will be invited to participate in the following ways:

- participants from ADD-ART Aim 1 study who provided consent to be contacted about additional research studies will be contacted and offered participation
- Participants on ART will be invited by a research assistant (RA) while in the ART pharmacy waiting room at the four eligible HIV-care facilities.
- Participants on ART will be invited by a research assistant (RA) after finishing in the blood rooms for VL monitoring at the four eligible HIV-care facilities.

Study staff will explain the study verbally in detail, including the purpose of the study, why the patient has been approached by the study staff for participation, and the study procedures (including risks and benefits) and will answer questions to ensure that the patient understands what would be expected of her/him. A patient who remains interested will be told that eligibility will depend on study staff reviewing medical records to confirm age and ART use for at least 4 months and contact her/him if eligible. Potential participants will be told that participation in this study is completely voluntary and their decision whether or not to participate in the study or provide permission for screening will not affect any medical treatment they are receiving at the clinic or their participation in any other studies being conducted by the DTHF.

PI Orrell and the study team will recruit providers to take part at the four clinics prior to patient enrollment. Providers will be reminded that participation is completely voluntary and will not affect their employment at any of the four sites. This informed consent will allow for review of their

medical notes of those participants that have enrolled in the trial, and also their participation in the FDGs.

8.3 Co-Enrollment Criteria

Participants will be excluded from study participation if they are actively enrolled in a current adherence-related interventional research study.

8.4 Screening for Eligibility

After the patient gives permission to review her/his medical/research records, the study staff member will screen for eligibility by examining the medical records to confirm that the patient initiated ART containing tenofovir within the last 4 months and record the most recent VL value and date of draw.

8.5 Study Enrollment- Patient Participants

If, after reviewing a patient's ART history, the PI/study coordinator (SCO)/MO (with input from study staff) determines that the patient meets study inclusion criteria, study staff will contact the patient by her/his preferred method (phone or in person visit) and, if the patient is still interested, will schedule the Baseline Visit at the Gugulethu Research Offices (GRO) ideally within 1 week but no more than 2 weeks after the initial date of recruitment and clinical/research record review.

If the patient does not meet the inclusion criteria, study staff will contact the patient to tell the patient that s/he is not eligible for the study.

At the Baseline Visit, the participant will provide documented (by signature or witnessed fingerprint) informed consent, be enrolled in the study, complete the baseline assessments, and provide blood samples. All activities related to screening and enrollment will be documented in a designated log.

8.6 Participant Retention

Locator information will be collected from each participant at each visit, so that s/he can be found if her/his phone number or address changes. This locator information will be collected and confirmed/updated at each monthly visit. Our study staff will track participants and maintain engagement. SoC is for study staff to send text messages, call or conduct a home visit (with advance permission only) when a patient misses clinic appointments or pharmacy refills. If the participant has given permission, study staff will send text messages reminding her/him of the monthly study appointment, and, if a participant misses an appointment, follow up via call and home visit. A participant missing a study visit will be encouraged to re-schedule the visit within 1 week of the original appointment date (and as close to the target date as possible). A visit will be considered "missed" when 2 weeks have passed since the visit target date. Use of this patient retention strategy in Aim 1 resulted in a retention above 89% across 12 months of follow up.

9. STUDY PROCEDURES/EVALUATIONS

9.1. Provider Consent and Training on Intervention

Prior to the launch of the Aim 2 study, providers will be approached about participating in this study. Consented providers will receive a didactic training from Dr. Orrell on the meaning and significance of DBS TFV-DP assay results, using protocols developed by the FDW. TFV-DP drug level feedback will then be delivered using these developed protocols.

9.2. Baseline Study Visit (Study Visit 0)

The following procedures/assessments will be performed at the baseline visit:

1. Study staff will obtain **Informed Consent** from the participant.
2. Study staff will complete the **Locator Form**.
3. Study staff will administer the **Baseline Quantitative Assessment**.
4. Study staff will assess **self-reported adherence**.
5. Staff will measure **height and weight**, and assess **pregnancy status** (by self-report, women only).
6. Study staff will obtain blood samples for the following assessments:
    - Dried Blood Spot (DBS)
    - VL (plasma will be stored and tested at patient's end of study)
    - Hematocrit (Hct)
    - Medical record abstraction of most recent Creatinine test
7. Study staff will provide the participant with a **Wisepill device**, instruct the participant on proper Wisepill use (including how to recharge the device) and conduct a Wisepill test (including confirmation that the device is properly connected to the data server).
8. Study staff will document current ARV regimen and dosing schedule(s).
9. Study staff will give the **participant compensation**.
10. Study staff will schedule the next monthly visit.

The baseline procedures/assessments may be conducted over two sessions, with the second session being no more than one week after the initial 0 session. At a minimum, informed consent and locator information will be obtained at the initial Visit 0 session.

9.3. Monthly Follow Up Visits (Study Visits 1-3)

The following procedures/assessments will be performed at every visit:

1. Study staff will verify the patient by the name on the record.
2. Study staff will obtain blood samples for the following: DBS, and 5ml venous blood for VL storage (See Standard Operating Procedure (SOP) C002 BLOOD SPECIMEN ACQUISITION, PROCESSING AND STORAGE GUGULETHU RESEARCH OFFICES (GRO) for additional details).
3. Study staff will assess **self-reported adherence**, measure weight and assess pregnancy status (women only);
4. Study staff will conduct a **Wisepill** device functionality test and will check in with the participant regarding any time(s) participant took a does without using Wisepill, and resolve any issues;
5. Study staff will update ARV regimen, dosing time(s), and HIV care provider and clinic contact information;
6. In the Feedback arm only: Study staff will use the protocols and materials developed with the FDWs to explain to the participant the results from the previous month's DBS. This will not be an intensive adherence counseling session, but an opportunity to ensure that the participant understands the feedback. If necessary, participants will be referred to an adherence counselor for further support.
7. Study staff will update the **Locator Form**;
8. Study staff will give the **participant compensation;**
9. Study staff will schedule the next month visit.
10. In the Feedback arm only: Providers will receive monthly DBS drug level results for participants randomized to the Feedback study arm, prior to the participant's monthly visit. Results will be shared according to the protocol developed by the FDW.

9.4. Final Study Visit (Visit 4)

1. Study staff will verify the patient by the name on the record;
2. Study staff will administer the **Visit 4 Quantitative Assessment.**
3. Study staff will assess **self-reported adherence**, measure weight, and assess pregnancy status (women only).

4. Study staff will obtain **blood samples for the following assessments:** DBS and VL (see Blood Specimen SOP for additional details).

5. Study staff will check in with the participant regarding any time(s) participant took a dose without using Wisepill, and collect used Wisepill.

6. Study staff will update ARV regimen and dosing time(s).

7. Study staff will give the participant **compensation**.

9.5. Clinic Chart Review (Visits 1-4 and Post Study)

Study staff will review participants' clinic charts at all visits and post-study to determine if any changes to medical or adherence management were made by providers since the previous visit. These changes could include: additional VL requests (beyond those prescribed for a stable patient), referral for intensive counsellor-based or group adherence counselling (usually only accessed if VL flagged as raised), outreach by Community Care Workers (CCWs) for adherence monitoring and support; and additional doctor-requested patient appointments. To mitigate the risk of control group participants receiving interventional DBS feedback, providers will not receive DBS results for participants in the control group.

The expected quality of the notes in the clinical charts will be variable with some clinicians making detailed notes and others making less detailed notes. The study team is reviewing FDW feedback and considering the creation of a checklist to facilitate identifying and quantifying actions that a provider may take based on DBS results .

9.6. Provider Focus Group Discussions

Once all pilot participants have completed their final visit (visit 4), study staff will hold the provider FGD to ascertain their understanding and perception of the utility of the DBS feedback and what changes they made (if any) in managing the participant's care and what additional communication (if any) they initiated with the participant. Closer to the end of the Aim 2 study, a focus group guide will be developed prompting providers to comment on whether the initial training prepared them to provide these results, whether they needed additional training, experiences they had during the study trial, and to describe any other thoughts or opinions that could inform feasibility and future scale-up of DBS feedback efforts in clinical settings. As this FGD might be scheduled out a month or two following the end of the study trial, providers will be given a window of 6-8 months for study participation.

9.7. Assessments

Detailed information about the following assessments can be found in the Assessment SOP.

9.7.1. Baseline Quantitative Assessments

At Visit 0, an RA will conduct the Baseline Quantitative Assessment, entering responses on an electronic tablet. The Baseline Quantitative Assessment will address the following domains associated with adherence and study participation with measures that have been used successfully in SA research, including our own prior studies. The Baseline Quantitative

Assessment will take approximately 1½ hours to complete. The RA conducting assessments will be blind to participant's study condition.

Socio-demographic characteristics will include gender; age; education; income and employment status; household composition; dwelling type; access to running water, electricity, and toilet; and missed meals in last month.

Medical history, assessed from the patient, will include time since HIV diagnosis, time on ART, type of ARV medication, last CD4+ cell count, last VL result, and comorbid conditions (e.g., TB, anemia), height and weight.

Social support, medication beliefs, and other contextual factors will include life events, patient-clinic relationship, medication social support, HIV stigma, HIV treatment knowledge, beliefs about medication and HIV, HIV disclosure, mental health, and substance use.

9.7.2 Visit 4 Quantitative Assessments

The Visit 4 Quantitative Assessment is a reduced version of the Baseline Quantitative Assessment. It will include a briefer battery of socio-demographic, medical history, social support or medication beliefs assessments. It will more focus on mental health, substance use, medication social support and life events. The Visit 4 Quantitiative Assessment will encompass the Exit Interivew and will take approximately 1 hour to complete.

9.7.3. Exit interview

Study staff will administer a semi-structured Exit Interview during the Visit 4 Quantitative Assessment to all study participants. Feedback arm participants will be asked about their understanding and perceptions of the meaning of the drug-level feedback, whether (and if so how) the feedback from the study staff and/or providers influence participants' behavior (e.g., medication-taking, disclosure to people in their social network, seeking adherence support, etc.). No feedback arm participants will be asked about if/how they would like to receive feedback if this was put into routine clinical practice (e.g., from a lay HCW, from a doctor, by SMS).

In both cases, the Exit Interview assessment will include closed and open-ended questions exploring the patient's thoughts about receiving DBS-based feedback.

9.7.4. Self-Reported Adherence Questionnaire.

Study staff will assess self-reported adherence in the past 30 days at every visit. The Self-Reported Adherence Questionnaire will take approximately 3 minutes to complete.

9.7.5. Pregnancy Status.

At each study visit, study staff will ask study participants (women only) whether they are currently pregnant or plan to become pregnant.

9.8. Wisepill

We will continuously monitor Wisepill (Wisepill Technologies, SA) device openings. This electronic monitoring device is a pill box that sends a signal to a secure website via cellular data

networks whenever the device is opened as a proxy for ART adherence. If connection or SIM card problems prevent real-time monitoring, records and diagnostics are stored (up to 1 year) and uploaded to the server when a connection is re-established. The device can store up to a 30-day supply of medication depending on number/size of pills. Since the majority of our participants will be on single-pill, single daily dose ARV regimens, the device will hold a 30-day supply. Wisepill-measured adherence will be operationalized as percentage of days/doses for which a device-opening signal was received in the past month.

9.8.1 Wisepill distribution and instruction.

At the baseline visit, study staff will give the participant a Wisepill device and instruct her/him on how to fill the device, open it for dosing, and re-charge the battery. Before ending this session, study staff will confirm that the Wisepill device is properly set up, that it is recognized by the Wisepill server, and that device openings are being recorded properly (date and time). Participants will be asked to bring the device with them to all study visits. Participants will also be informed that when a participants' device battery gets low, the server will automatically send an SMS to the participant reminding them to charge the device; if 7-days pass after the SMS reminder and the device still appears with a low or flat battery or is not seen at all on the server, study staff will call the participant to remind her/him to charge the battery.

At each subsequent study visit, study staff will ask if the participant is having any problems using Wisepill and will remind her/him to charge the device at least once per month and/or when the red light is blinking. If necessary, devices can be charged in the clinic or the current Wisepill battery can be replaced. Study staff will also conduct a Wisepill test to confirm that the device is properly connecting to the data server. Lastly, study staff will ask participants if her/his ARV medication or dosing schedule has changed since the previous visit and will update this information as necessary. Participants will use the Wisepill Device for four months.

Wisepill is being used in this study for measurement purposes, and not for clinical intervention purposes. As Wisepill information has not been sufficiently validated for clinical use, Wisepill information will not be shared with participants or providers involved in this study.

9.9. Blood Specimens

9.9.1. Blood specimen preparation, handling and shipping

Study staff will obtain the following blood samples: DBS, VL, and hematocrit (only at Baseline). In all cases, blood collection will be performed by trained study staff using sterile technique.

9.9.1.1. DBS samples for TFV-DP assay

DBS samples will be collected at every study visit by spotting blood directly into each of the five circles on a Whatman 903 ProteinSaver card (see Blood Specimen SOP for additional details). Study staff will take care to ensure that both hands are gloved before handling the DBS card, to not touch the areas where the blood spots will be placed with either her/his own or the participant's finger(s), to obtain spots of sufficient diameter, and to not over-run the circle markings. Study staff will ensure that DBS cards are labeled with the participant ID, visit number, and air-dried for 3 hours, individually packaged in a plastic bag with a desiccant pack and a humidity indicator card, and transferred to a -20◦C freezer for short-term storage at the GRO. DBS cards will be transferred

at least twice a week to the Groote Schuur CRS for longer term storage at -80$_0$C until transfer to the UCT Clinical Pharmacology laboratory for assay.

At the Clinical Pharmacology laboratory a 3mm disc will be punched from the DBS and extracted with 500µl of 70:30 methanol-H_2O with sonication. Supernatants will be stored at -80°C until they are assayed by LC-MS/MS using Anderson's validated assay for TFV-DP. We will use modeling to assess sources of variability in this study and will also consider other factors that could interfere with drug levels other than adherence alone, including comorbid conditions captured by the Medical History obtained at Baseline and Visit 4. We do not anticipate that the use of concomitant nephrotoxic medications will have an effect on these drug levels while the renal function is preserved.

9.9.1.2. Hematocrit

At the baseline visit, study staff will draw blood into a 2 ml EDTA tube to assess the participant's hematocrit. Study staff will then draw blood from the EDTA tube into a capillary tube, seal the capillary tube, and centrifuge it in a Gemmyco KHT-410E Micro centrifuge for five minutes at the preset fixed speed of 12,000 rpm. Hematocrit will be assessed using a measuring device that will determine the ratio of the volume of red blood cells to the total volume of blood.

9.9.1.3. HIV-1 RNA (viral load)

At all five study visits, study staff will additionally draw draw blood into a 5mL EDTA (purple top) or anticoagulated PPT (white top) tube to assess patient plasma viral load at the end of the study. After collection, the primary tubes of EDTA/PPT blood samples will be centrifuged at 3500rpm for 10 minutes to separate plasma from cells. The plasma will be removed carefully into cryovials which will be transferred to J52 Groote Schuur for storage at -80$_0$C within 24 hours of collection. HIV-1 RNA level will be determined by HIV VL assay performed at NHLS laboratories using Alinity m HIV-1 assay (Abbott Laboratories, Abbott Park, USA).

Plasma VL samples will be analyzed in a batch when the participant completes the study. Viral load information will not be shared in real-time as it would undermine the ability to evaluate the impact of DBS results feedback. This study does not affect any standard of care viral load monitoring which occurs in South Africa on an annual basis. Once all viral load data are batch analyzed, we will share any raised viral load result (VL>50 copies/ml) with a participant's provider.

9.9.1.4. Creatinine

Standard of care creatinine tests will be abstracted as part of this study. As the creatinine test is a component of the South Africa ART National programme, a value within the past 12 months should be available. Creatinine will be abstracted in order to estimate glomerular filtration rate (eGFR) which recent data has shown has implications on TDF-DP DBS drug concentrations.[24]

9.9.2. Biohazard containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention in the United States, the WHO internationally and the National Institutes of Health.

Table 1: *Schedule of events*

Visit	Pre-Study	Screening at clinic	Baseline Month 0	Month 1	Month 2	Month 3	Month 4	Post-Study
Provider Consenting	X							
Provider Training- DBS Results and Interpretation	X							
Screening permission form		X						
Eligibility determination (age, ART regimen, time on ART)		X						
Medical Chart Confirmation (age, ART regimen, time on ART)		X						
Informed consent for eligible patients			X					
Locator form		X	X	X	X	X	X	
Height			X					
Weight			X	X	X	X	X	
Pregnancy Status			X	X	X	X	X	
Blood draw for hematocrit			X					
Medical chart review for past 12 month (Creatinine)			X					
Blood draw for HIV viral load (to be assayed at study completion)			X	X	X	X	X	
Blood draw for DBS			X	X	X	X	X	
Baseline Quantitative Assessment			X					
Self-Reported ART Adherence Questionnaire			X	X	X	X	X	
Dispense Wisepill device			X					
Wisepill Functionality Test				X	X	X		
Dispense patient reimbursement			X	X	X	X	X	
FEEDBACK ARM only: drug concentration feedback to patients and providers.				X	X	X		
Clinic Chart Review				X	X	X	X	X
Return Wisepill device							X	
Visit 4 Quantitative Assessment							X	
Provider FDGs								X

10. ASSESSMENT OF SAFETY

10.1 Safety Assessment Overview

As this study involves low-risk activities and does not involve the introduction of a drug or a drug change, standard adverse event reporting will not be undertaken. While the study is providing additional VL testing, these will not be run in real-time and are collected in a research capacity. Any VL above the 50 copies/ML will be shared after a participant completes the study. The study team will collect and report all social impacts that are brought to the attention of study staff members. Study staff will be trained to recognize and report social impacts as well as provided participants with referrals for counseling and social service support, if necessary. Reports of social impacts will be reviewed quarterly or more often, if indicated, and reported to the study Medical Officers together with any actions that are taken. Social impacts will be summarized and reported to appropriate IRBs and the Performance and Safety Monitoring Board (PSMB) on an annual basis.

10.2 Adverse Event Procedures and Reporting Requirements

DAIDS policy on Critical Events will be followed in the event of an unanticipated problem/s or other Critical Events.

11. CLINICAL MANAGEMENT

11.1 Clinical Management of Study-Related Adverse Events

Adverse events related to blood draw (bleeding, bruising, dizziness) will be managed on-site by the study staff. First Aid equipment is available. See standard Operating Procedure (SOP) C002 BLOOD SPECIMEN ACQUISITION, PROCESSING AND STORAGE GUGULETHU RESEARCH OFFICES (GRO).

All patients presented with an antiretroviral therapy-related adverse event will be referred to their ART clinic for management as these will not be related to our exploratory pilot study, as we will not be altering the participants ART regimen.

11.2 Other Disease Events

Not applicable.

11.3 Pregnancy

Not applicable.

11.4 Breastfeeding/Replacement Feeding

Not applicable.

11.5 Acquisition of HIV infection while on Study

Not applicable.

11.6 Treatment Failure

Not applicable; there is no experimental treatment.

11.7 Criteria for Discontinuation

11.7.1 Criteria for permanent intervention discontinuation for an individual participant.

The criteria for permanent intervention discontinuation from the study for an individual participant are:

- Request by participant to withdraw;
- Request of the provider if s/he thinks the study is no longer in the best interest of the participant;
- Provider changes participant's ART medication to one that does not contain tenofovir or requires participant to discontinue ART medication entirely; or
- Judgment by the investigator that the participant is at sufficient risk of failing to comply with the provisions of the protocol so as to cause harm to her/himself or seriously interfere with the validity of study results.

Participants who experience viral breakthrough *will not* be discontinued from the study. We will follow all study participants for the full follow-up period of 4 months barring safety concerns (including those who experience viral breakthrough), and will continue to collect blood samples and all other study data (i.e. assessments, Wisepill).

11.7.2. Criteria for premature study discontinuation for an individual participant.

The criteria for premature discontinuation from the study for an individual participant are

- Request by participant to withdraw;
- Request of the provider if s/he thinks the study is no longer in the best interest of the participant;
- Provider changes participant's ART medication to one that does not contain tenofovir or requires participant to discontinue ART medication entirely; or

- Judgment by the investigator that the participant is at sufficient risk of failing to comply with the provisions of the protocol so as to cause harm to her/himself or seriously interfere with the validity of study results.

In addition, participants who experience viral breakthrough *will not* be discontinued from the study. We will follow all study participants for the full follow-up period of 4 months barring safety concerns (including those who experience viral breakthrough), and will continue to collect blood samples and all other study data (i.e. assessments, Wisepill).

12. STATISTICAL CONSIDERATIONS

12.1. Overview and General Design Issues

For Aim 2, we will explore whether providing adherence feedback to patients and providers results in changes to patient adherence behavior (as measured by TFV-DP levels, VL, Wisepill use patterns, and self-report) and/or provider behavior with respect to patient management (e.g., requests for additional laboratory tests, calling patient back for an additional appointment, referring patient to an adherence counselor, referring patient to the 'risk of treatment failure clinic'). Below we describe the analytical plan to assess change in patient adherence behavior using Wisepill openings as an example.

This 5-month pilot with a small sample size, will provide preliminary estimates that can be used to inform future power calculations and the design of a larger trial (e.g., estimates of effect size, interclass correlation [ICC] for within individual and within provider/clinic correlation). Using Aim 1 data on self-reported adherence, which includes about 3,000 observations, the mean adherence is 81.96% with a standard deviation of 11.42%. The current plan to recruit 60 subjects and collect their monthly adherence data over the subsequent 4-month period will result in 180 change scores (90 per group) for the Aim 2 analysis. Using the estimated standard deviation from our existing data and assuming the ICC between successive change scores is no greater than 0.20, we will be able to detect a 5.59 percentage point difference in ART adherence between the intervention and control group with 80% power. Assume the mean adherence is about 80% for the control group (very close to what we observed from our observational study in Aim 1), if in truth, the mean adherence is 85.59% (which we optimistically believe is achievable), we have 80% probability to declare the difference of adherence between intervention and control is statistically significant. Therefore, we believe that the data we will collect from 60 participants over the 4-months of follow up will provide adequate power to achieve the study goal.

To generate preliminary estimates of the effect of giving feedback on adherence behavior, we will compare change in average percentage of Wisepill openings (for example) from one month to the next between Feedback and No Feedback (Control) participants.

Because feedback begins at the first return visit at Month 1 after baseline, each Feedback Group participant will provide up to three change score outcomes (for month i–1 to month i for i=2,3,4). We will compare these to the corresponding change scores in the Control Group in a generalized linear model (GLM) using generalized estimating equations (GEE) to account for within-subject correlation (ICC) among their three change-scores. The analysis model will include a constant term and the group indicator.

With the limited pilot sample size of 60, we will be able to detect moderately large effects on average improvement in adherence. For example, if the ICC between successive change scores is no greater than 0.20, then the detectable standardized mean difference will be 2.8*[(2/30){1+0.2*(3-1)}]1/2 = 0.86, a "large" effect.

Given that this a pilot study, our ability to explore the role of the moderating variables on adherence-related behavior will be limited. However, looking at the monthly change-scores can reveal important features on which to focus. Moreover, the larger Aim 1 sample (N=250) will provide key data on individual and structural factors affecting adherence, retention, and preferences for sample collection and feedback that we will utilize in multivariable analyses as predictors of DBS TFV-DP levels and Wisepill use patterns. We will also examine these factors as potential effect modifiers in Aim 1 analyses

For providers we will examine changes in clinical management patterns, for example requests for additional tests or adherence counselling sessions usually only triggered by a raised VL.

Similar to Aim 1, the Baseline and Visit 4 (last visit) Quantitative Assessments will cover a large array of participant information and behaviors that could be potential confounders. To examine how potential confounding factors can influence our statistical analysis, we will first identify a list of variables that is possible be candidates for potential confounding factors and then test whether any of those variables is associated with our outcome (i.e., adherence) and exposure (i.e., the intervention) in our sample. If found, we will include them in the primary analysis model to obtain the adjusted intervention effect. While the official primary analysis will be the one without covariate adjustment, the adjusted analysis will help to interpret the findings from primary analysis.

An exploratory content analysis will be used to identify themes in the open-ended segments of the exit interview and the FGD discussion. These analyses will focus on themes related to training, process of providing results, and the strengths and challenges of using DBS-based feedback in the clinic setting.

12.2 Study Endpoints

12.2.1 Primary Endpoint

Our primary endpoint is defined as behaviors in response to the receipt of information about TFV-DP drug levels. Behavioral responses will be assessed (and explored) by subsequent TFV-DP levels, subsequent VL(s), Wisepill use, self-reported medication adherence, and responses to interview questions in the Exit Interviews with patient participants, and provider FGDs.

12.3. Study Objectives and Hypotheses

The primary objectives of this study are (a) to determine the feasibility of giving patients and providers monthly feedback about TFV-DP levels and (b) to examine provider and patient behaviors in response to receiving this information. This trial will assess the impact of such feedback on patient and provider medication taking behaviors, and patient management (by providers) in response to receiving this information.

The study hypothesis is that participants who receive feedback on TFV-DP drug levels will have improved adherence, as assessed by monthly TFV-DP levels, VL, self-report; continuous

Wisepill use patterns, and responses to interview questions in the Exit Interviews with participants, and provider FGDs.

12.4. Randomization/Blinding Procedures/Unblinding Procedures

Participants in the pilot study will be randomized 1:1 to either Feedback Group (N=30) or No Feedback (Control) Group (N=30) by study staff using a randomization list generated by the study Biostatistician (Leu). The study will not be blinded.

12.5. Maintenance of Trial Treatment Randomization Codes

Randomization assignment will be stored securely with all other source documents in a locked file cabinet in a locked office.

12.6. Participant Enrollment and Follow-Up

The study will recruit 60 HIV-positive patients who are taking ART containing tenofovir in the past 4 months. We expect to recruit an average of 15-20 participants/month for 4 months and suffer no more than 10% dropout.

12.7. Data and Safety Monitoring

We will work with the HIV Center's Performance and Safety Monitoring Board (PSMB) to monitor key dimensions regarding study participant recruitment, retention, and accrual of VB events.

12.7.1.1 Monitoring recruitment performance

The goal is to recruit at least 15/20 participants per month. If 10 or fewer participants are recruited for 3 consecutive months of active recruitment, the PSMB will review what recruitment problems may exist and recommend appropriate remedies. In the event that administrative or regulatory delays prevent all sites from starting recruitment concurrently, this guideline will be implemented once all recruiting sites are active.

12.7.1.2. Monitoring retention performance

For monitoring purposes, a "dropout" will be operationalized as a participant having missed two or more consecutive scheduled visits. A visit will be considered "missed" once 2 weeks have passed since the target visit date. We acknowledge that a participant who is deemed a dropout may subsequently return to the study. If at any time the percent of all enrolled participants who are current dropouts exceeds 15%, the PSMB will review and identify retention problems and recommend appropriate remedies.

12.7.2 Analysis plan.

Not applicable for this pilot trial.

13. DATA HANDLING AND RECORDKEEPING

The study will collect four distinct sources of data: (1) source documents (screening, consent, informed consent, and participant contact information); (2) assessment data; (3) blood specimen data; and (4) Wisepill data. Study participants will be identified using a confidential PID.

Data from source 1 (source documents) will contain identifiable data and will be stored separately from all other data sources, which will only contain de-identified data. Consent forms from source 1 will be stored in a locked file cabinet in a locked office, and the locator form (which contains the link between patients and their unique PIDs) will be stored in a password protected file on a shared DTHF drive folder on an encrypted study computer stored in a locked office.

All other data will be labeled only with the PID and will not contain any identifiable information. All data from source 2 (assessment data) will be collected electronically on password protected and encrypted tablets. Data on the tablets will be electronically transmitted to a secure, remote and HIPAA compliant server with partitioned and dedicated space for this study only, known as the 'study server'. Only authorized users will be able to log into the server to view and download data for analysis. The server will maintain an audit trail of all log-ins, edits, and log-outs. Data collected on the tablets can be recorded with or without an internet connection. When there is a connection, the data will be automatically uploaded to the secure study server that will require password authentication. When there is not an internet connection, the data will be cached on the tablet and automatically upload once an internet connection is established. The data will be automatically deleted from the tablet once the upload to the study server is complete and the server will send an automatic email to the US SCO indicating that new data have been uploaded. Access to the data collected on the tablets and stored on the study server will be limited to only those study personnel with data access rights. The US SCO will monitor the study server to ensure that the data collected and uploaded to the server are complete and to monitor for suspicious data activity.

Data from source 3 (blood specimens) will be documented as follows and will be identified only by the unique PID. Hematocrit results will be entered into the tablet at the time of the study visit (when the sample is processed). VL results for each patient will be processed once the patient has completed the study and will be accessible via a secure web portal managed by the NHLS. The study staff will enter these data into a study database located on the study server. DBS results processed at the UCT Clinical Pharmacology laboratory and will be entered into a database on the study server.

Data from source 4 (Wisepill data) will be stored on a separate, remote, password protected secure server.

Local IRB/Ethics Committees, Site Monitors, the NIAID, the OHRP, and other local or international regulatory authorities/entities may review study records.

13.1. Source Documents

Source documents, including screening and enrollment logs, informed consents forms, and permission forms relating to social impact events will be stored securely in a locked file cabinet in a locked office.

13.2. Assessment Data

Study staff will collect the following assessments from study participants using a secure, encrypted, password-protected tablet: (1) Baseline Assessment; (2) Self-Reported Adherence

Questionnaire; (4) Pregnancy Status, and (5) Final Assessment. To minimize data entry errors and missing data, the data collection program installed on the tablet will be programmed with automatic skip patterns, requirements that each item by answered or refused, and acceptance of only values within the appropriate range of responses for that item. To ensure that the correct assessment and procedures are completed at each study visit, the data collection program installed on the tablet will be programmed to include only the study assessments and procedures relevant to that visit. All data collected on the tablet will be time- and date-stamped, and uploaded to the study server.

13.3 Blood Speciment Data

Study staff will record the collection of specimens from the participant using a secure, encrypted, password-protected tablet for the following assessments: (1) DBS; (2) VL specimen; and (3) hematocrit test. To ensure that the correct specimens are collected at each study visit, the data collection program installed on the tablet will be programed to only include the specimen collection procedures relevant to that visit.

Study staff will identify the specimens using scannable barcodes, which will contain information on the participant ID numbers, the type of specimen, and the visit number. Study staff will store specimens according to the Blood Specimen Storage SOP.

13.3.1. Specimen transport, analysis and long-term storage.

Study staff will deliver the VL cryovials from the freezer located at the GRO to J52 Groote Schuur CRS for staroage and later to the NHLS located at the Groote Schuur Hospital campus for analysis at the end of the study. Study staff will scan the barcodes for each VL tube delivered to the NHLS using the camera function on the tablet to document which vials are being transported. Once at the NHLS, the Lab Assistant will sign the tablet to indicate that s/he has received the VL vials.

VL results will be processed by the NHLS and will be accessible via a secure web portal managed by the NHLS. Study staff will enter these data into a study database located on the study server. Once entered, the study server will automatically send an email to the US SCO indicating that test results are available.

13.4. Wisepill Data

Wisepill data will be stored on a remote, password protected secure server. Each Wisepill device will be linked to a PID. Study staff will generate user reports for each participant that include all Wisepill output from the day the device was distributed through the day it was returned. User reports will be downloaded to the secure study server. Reports will be aggregated into separate master files that will be converted into SPSS for statistical analysis. Participants will also be asked to bring their ARV pill bottle, and at the end of the Wisepill test, report any changes to their ARV regimen or dosing schedule.

13.5. Quality Control and Quality Assurance

In collecting the vast majority of the study data electronically, we will be able to closely monitor the quality and completeness of the data in near-real time and can correct any mistakes before they are propagated. To ensure that the correct assessment and procedures are completed at each study visit, the data collection program installed on the tablet will be programmed to include only the study assessments and procedures relevant to that visit. Study staff will also complete visit-specific checklists detailing all study procedures. The data collection program will also require that all questions be answered or refused, and we will build in skip patterns and logic checks for values entered to ensure data quality and completeness. We will closely monitor each step of the specimen collection, transport, storage, and analysis process to ensure that all specimens are continuously accounted for and stored and transported in conditions that will ensure their integrity. The US SCO will conduct weekly checks to confirm that the number of specimens collected match the number of assessments completed during that week, and that these specimens were transported to the correct long-term storage and analysis locations. The SA SCO will conduct weekly check to ensure that the specimen storage conditions are appropriate and will make adjustments as necessary.

Study staff will monitor Wisepill devices continuously throughout the study to identify those devices that have a low battery or that have not been detected by the server in the last 2 weeks. When a participants' device battery gets low (≤3750mv, 20-30 days of charge left), the server will automatically send an SMS to the participant asking her/ him to "charge the box" (a term used to avoid disclosure of HIV/medication status). If 7 days after sending the SMS reminder, the device still appears with a low or flat battery or is not detected at all on the server, study staff will call the participant to remind her/him to charge the battery. If contact is not able to be made and the battery remains low or flat, the participant will be reminded to charge the device while s/he is attending the study visit. If the participant does not bring the device to the study visit, s/he will be reminded to charge the device as soon as possible. Participants will be asked to bring their Wisepill device and ARV pill bottle to all study visits. Study staff will conduct a Wisepill Test at each study visit to identify and trouble-shoot any potential problems with the device, and will also update any changes to ARV regimen or dosing schedule.

14. HUMAN SUBJECTS RESEARCH

14.1 Institutional Review Board/Ethics Committee

This protocol and the permission and informed consent form(s) and any subsequent modifications, will be reviewed and approved by the DAIDS Clinical Science Review Committee with respect to scientific content and compliance with applicable research and human subjects regulations.

The protocol, informed consent form, permission forms, participant education and recruitment materials, and other requested documents, and any subsequent modifications, will also be reviewed and approved by the ethical review bodies responsible for oversight of research conducted at each study site.

Subsequent to initial review and approval, the responsible Ethics Committees/IRBs will review the protocol at least annually. The Investigators of Record will make safety and progress reports to the IRBs at least annually, and within three months of study termination or completion. These reports will include the total number of participants enrolled in the study, the number of

participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others. Continuing review documentation will be submitted to the DAIDS Protocol Registration Office, in accordance with the current DAIDS Protocol Registration Policy and Procedure Manual.

14.2 Vulnerable Participants

14.2.1 Pregnant women and fetuses

Pregnant participants will not be excluded from study participation. We will assess self-reported pregnancy and plans to become pregnant at each study visit among female participants, as this may have implications for risk of non-adherence.

14.2.2 Prisoners

Not applicable.

14.2.3 Children

Not applicable.

14.2.4 Illiterate participants.

The informed consent form will be read to all study participants regardless of their literacy, in their preferred language. However, special care will be taken with illiterate participants to ensure that they understand what they are consenting to. In addition, those who cannot write their name will be able to document their provision of informed consent and permission by providing a fingerprint on the informed consent and permission forms in place of a signature, and this process will be observed by a witness, who will also sign the informed consent form. The use of a witness will be documented in the informed consent source document.

14.3 Informed Consent

14.3.1 Informed consent process.

Informed consent will be obtained from each study participant prior to conducting study-related procedures. The informed consent process will be conducted by study staff in Xhosa or English, at the preference of the participant, and the consent form will be available in both languages. Participants will be told that participation in this study is completely voluntary and their decision whether or not to participate in the study will not affect any medical treatment they are receiving at the clinic or their participation in any other studies being conducted by the DTHF. All study procedures will be described and they will be told that all information will be kept confidential within the limits of the law.

There will also be optional activities that are not required in order to participate which include:

- The disclosure of DBS results to a patient's provider if they were in the control group
- The possibility for study staff to conduct a home visit if the patients misses a study visit.
- Participation in future study visits

Once the study has been explained in detail, time will be given for participant questions. If the participant wants to join the study, she/he will provide informed consent by signing the informed

consent form, or for those who are cannot write, by providing a fingerprint. (Further details regarding DAIDS requirements for documenting the informed consent process are provided in the DAIDS Standard Operating Procedure for Source Documentation.) A copy will be given to the participant to take home and a signed copy will be stored securely in a locked file cabinet in a locked room.

14.3.2 Assent process.

Not applicable.

14.3.3 Documentation of informed consent.

Participants will document their provision of informed consent by signing the informed consent forms. The presence of a witness, use of a translator, and which language was used to obtain the informed consent form will be documented in the informed consent source document.

14.3.4 Waiver of informed consent.

Not applicable.

14.3.5 Waiver of documentation of informed consent.

Not applicable.

14.3.6 Stored samples and associated data considerations.

All blood samples will only be labeled with the participant's study identification number and the date of collection (no identifying information will be included).

If the participant provides permission, these DBS samples may be stored for up to 50 years (until 31 December 2070) and used for future studies to find out more about HIV infection. If the participant only authorizes the use of samples for this study and not future studies, the samples will be destroyed within 10 years (no later than 31 December 2030). Any future research on stored samples will first receive approval from the appropriate Institutional Review Board and/or Research Ethics Committee.

14.4 Risks

Participants enrolled in the study may experience the following risks and discomforts. They have been informed of these potential risks prior to providing their informed consent.

The venipuncture procedures to obtain blood have some minor risks. The participant may experience a small amount of pain at the needle-prick site, but this should be minimal. A small amount of bleeding under the skin may produce a hematoma (bruising), which should dissipate in a few days. Risks will be minimized by use of sterile technique by trained, qualified study staff. The site of needle-prick will be swabbed with alcohol and protected by a band aid or cotton wool and micropore to minimize risk of infection. Care will be taken to choose a different needle entry point at subsequent visits. In an analysis carried out looking at the acceptability of venipuncture for DBS, over 85% of 67 patients in Aim 1 reported to no pain or a little pain[34].

There were also no differences in acceptability of the venipuncture method compared to finger-stick.

14.5 Social Impact Events

Participants enrolled in the study may experience personal problems resulting from the study participation. Such problems are termed social impact events and could potentially include the following:

14.5.1 Psychological distress.

Participants may experience psychological distress resulting from the assessment questions or from learning the amount of TFV-DP drug concentration in the previous month. Using strategies established in our previous SA and US studies, and in Aim 1 the following steps will be taken to minimize the risk of psychological distress resulting from assessment questions.

1. Participants will be informed that the assessments include questions about sensitive behaviors (e.g., mental health, drug use, non-adherence), and that they can decline to answer any questions with which they are uncomfortable.

2. Procedures for emergency and nonemergency situations will involve the interviewer informing the SA SCO of any such incidents of distress so that s/he can monitor compliance with distress-related protocol.

3. Participants who experience mild to moderate distress will be referred to the clinic mental health staff for counseling. Because the study will take place at the GRO based at the Hannan Crusaid Treatment Centre, we will be able to make immediate referrals as needed to health care providers.

14.5.2 Unintended disclosure.

We will take steps to minimize inadvertent disclosure of HIV status from receipt of text message reminders to charge Wisepill by keeping the text message simple and without any identifying and/or status related information; the message reads, "Please charge your ibhokisi (box)".

14.5.3 Confidentiality breach.

Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study, or information collected by the study, could become known to others, and that participants may experience stigmatization or discrimination as a result. We will take the following steps to protect against the risk of a confidentiality breach.

1. All data, including blood and DBS samples, assessment, Wisepill output, and participant files will be labeled only with study identification numbers, and no participant names will be attached to study data.

2. The participant "key" linking study identification numbers with participant names will be kept by the SCO in locked file cabinets at the DTHF. Only the SCO will have access to this “key” and file cabinets. Personal information including participant’s name, address and phone number will be stored separately from research data.

3. Electronic data files will be password protected and stored on a secure study server, which requires authentication to access.

4. All paper research data will be kept in locked file cabinets and will be available only to research staff directly involved in this project and institutional personnel for the purpose of routine audits.

5. All study staff will receive training on procedures to protect participant confidentiality and will take all required courses and certification tests. Participants will be told that all data are confidential within the limits of the law.

Social impact events will be monitored closely throughout the study. Study staff will be trained to recognize and report any social impacts as well as provide referrals for counseling and social service support, if necessary. Social impact events will be collected and reported on case report forms (CRFs) during regular visits. In the event that a participant reports a social impact event, every effort will be made by study staff to provide appropriate assistance, and/or referrals to appropriate resources. Social impact events will be documented and reviewed on a scheduled basis by the protocol team leadership with the goal of reducing their incidence and enhancing the ability of study staff to mitigate them when possible. Social impact events that are judged to be serious, unexpected, or more severe or frequent than anticipated, will be reported to the responsible site’s EC/IRB promptly, or otherwise in accordance with the EC/IRB’s requirements.

14.6 Benefits

The potential benefit to science and society is documented evidence that the DBS-derived TFV-DP assay can be used to provide an objective, clinically relevant, and actionable measure of adherence which could provide valuable information to HIV care providers and patients. This in turn can help providers and patients better manage their health and minimize the disruptions and negative health consequences caused by non-adherence to ART.

It is also possible that drug level feedback to patients and providers may result in improved ARV adherence and better HIV health outcomes. We will be testing the impact of drug level feedback on patient and provider adherence-related behaviors.

14.7 Compensation

Compensations are based on those routinely offered at the study site for this type of research. Participants completing all visits should receive a total of R860. This will be given as R250 for the Baseline and Visit 4 visits with blood sampling and comprehensive assessments; and R120 per standard visit for blood sampling and short assessments (x3).

14.8 Participant Privacy and Confidentiality

All participant-related data, including blood and DBS samples, assessment, Wisepill output, and participant files will be kept strictly confidential. All data and records will be labeled only with PIDs, and no participant names will be attached to study data. The participant "key" linking study identification numbers with participant names will be kept by the SCO in locked file cabinets at the DTHF. Only designated study staff will have access to this "key" and file cabinets. Personal information including participant's name, address and phone number will be stored separately from research data. Electronic data files will be password protected and stored on the HIV Center server, which requires authentication to access. All paper research data will be kept in locked file cabinets and will be available only to research staff directly involved in this project and institutional personnel for the purpose of routine audits. All study staff will receive training on procedures to protect participant confidentiality and will take all required courses and certification tests. Participants will be told that all data are confidential within the limits of the law.

14.9 Post-Trial Access

There is no post-trial access as ART is not sourced through this study. Participant will be asked to return their Wisepill device at the end of the study, but will be offered another (non-electronic) pillbox in exchange.

14.10 Ancillary Benefits

The use of the Wisepill device may improve adherence. However, Wisepill results will not be shared with the participant's clinic for a number of reasons: 1) Wisepill is a research tool and has not been validated for use in clinical care; 2) the Wisepill device does not measure drug ingestion, only device opening or non-opening, and therefore can over- or under-estimate adherence if a person takes a dose without opening the device or, conversely, opens the device without actually swallowing the medication; and 3) giving providers the copious amount of data generated by Wisepill would be overwhelming, and currently, no standards of clinical management have been established for Wisepill output.

14.11 Community Advisory Board

The study will be presented to the Emavundleni Community Advisory Board (part of the DTHF Emavundleni Clinical Research Site), which is regularly involved in review and comment on DTHF studies conducted in the Gugulethu area.

15. ADMINISTRATIVE PROCEDURES

15.1 Protocol Registration

Initial Registration of the protocol by the DAIDS Protocol Registration Office (PRO) is required prior to implementation of this protocol. As part of this process, each site must have the protocol and protocol informed consent form(s) approved, as appropriate, by their local institutional review

board (IRB)/ethics committee (EC) and any other applicable regulatory entity. Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS PRO at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received. Sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Following Initial Registration, any full protocol amendments require submission of a protocol registration packet to the DAIDS PRO as described above; however, the DAIDS PRO will not review and approve site-specific ICFs. Upon receiving final IRB/EC and any other applicable regulatory entity approval(s) for an amendment, sites should implement the amendment immediately. Sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files. There may be cases where a site submits as their Initial Registration a protocol amendment (Version 2.0 or higher of a protocol); in such cases, the instructions for Initial Registration will be followed.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual, which can be found at **https://www.niaid.nih.gov/sites/default/files/prmanual.pdf**.

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