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# Simplifying TREAtment and Monitoring for HIV (STREAM HIV): protocol for a randomised controlled trial of point-of-care urine tenofovir and viral load testing to improve HIV outcomes

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## ABSTRACT

**Introduction** Substantial improvements in viral suppression among people living with HIV (PLHIV) are needed to end the HIV epidemic, requiring extensive scale-up of low-cost HIV monitoring services. Point-of-care (POC) tests for monitoring antiretroviral therapy (ART) adherence and viral load (VL) may be efficient and effective tools for real-time clinical decision making. We aim to evaluate the effects of a combined intervention of POC ART adherence and VL testing compared with standard-of-care on ART adherence, viral suppression and retention at 6 and 18 months post-ART initiation among PLHIV.

**Methods and analysis** Simplifying TREAtment and Monitoring for HIV (STREAM HIV) is a two-arm, open-label, randomised controlled superiority trial of POC urine tenofovir (POC TFV) and VL monitoring in PLHIV. We aim to enrol 540 PLHIV initiating a first-line ART regimen at a public HIV clinic in South Africa. Participants will be randomised 1:1 to the intervention or control arm. Intervention arm participants will receive monthly POC TFV testing for the first 5 months and POC VL testing at months 6 and 12. Intervention arm participants will also receive reflex POC TFV testing if viraemic and reflex HIV drug resistance testing for those with viraemia and detectable TFV. Control arm participants will receive standard-of-care, including laboratory-based VL testing at months 6 and 12. Primary outcomes include ART adherence (TFV-diphosphate concentration) at 6 months and viral suppression and retention at 18 months. Secondary outcomes include viral suppression and retention at 6 months, TFV-diphosphate concentration at 18 months, cost and cost-effectiveness of the intervention and acceptability of the intervention among PLHIV and healthcare workers.

**Ethics and dissemination** STREAM HIV has received ethical approval from the University of Washington Institutional Review Board (STUDY00007544), University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC/00000833/2019) and Division of AIDS Regulatory Support Center (38509). Findings will be disseminated at international conferences and in peer-reviewed journals.

**Trial registration number** NCT04341779.

## Strengths and limitations of this study

- The Simplifying TREAtment and Monitoring for HIV study will be one of the first randomised controlled trials to assess the impact of point-of-care urine tenofovir monitoring among people living with HIV who are receiving antiretroviral therapy (ART).
- Point-of-care urine tenofovir testing is a novel method that allows real-time, objective assessment of ART adherence among persons receiving a tenofovir disoproxil fumarate (TDF)-containing ART regimen, with potentially better targeting of adherence support.
- Point-of-care urine tenofovir and HIV viral load testing may also improve monitoring for HIV drug resistance.
- The study may be limited by the point-of-care urine tenofovir test's accuracy in monitoring short-term and longer-term adherence to TDF-containing ART regimens and by the processing time (~90 min) and resource requirements needed for the point-of-care viral load test, which could impact clinic flow and visit duration.
- Results from this study may not be generalisable to other settings or populations due to potential differences in the feasibility and acceptability of the intervention.

## INTRODUCTION

The Joint United Nations Programme on HIV and AIDS (UNAIDS) set the 95-95-95 targets to drive collaborative efforts for ending the HIV epidemic by 2030.[1] These targets aim to ensure 95% of people living with HIV (PLHIV) are aware of their HIV status, 95% of diagnosed PLHIV are receiving antiretroviral therapy (ART) and 95% of PLHIV receiving ART achieve viral suppression.[1] However, a recent report by UNAIDS concludes that the current global targets of 90-90-90 were not reached by 2020, and only 59% of PLHIV globally have achieved viral suppression.[2] Barriers to achieving viral suppression for PLHIV include poor ART adherence, disengagement from care and HIV drug resistance. Sustainable and scalable interventions are necessary to help clients optimise ART adherence and retention in care, and to assist healthcare providers identify clients who experience adherence challenges or may disengage from care.

The World Health Organization (WHO) recommends that all PLHIV receive expedited ART initiation and routine HIV viral load (VL) testing.[3 4] To achieve this, cheaper and more efficient methods of decentralised VL monitoring are needed to reduce the financial burden on health systems and on patients by preventing multiple clinic visits for laboratory testing and result retrieval, ease the burden on laboratories and improve HIV care and outcomes through efficient clinical decision support and focused, timely ART adherence interventions based on real-time VL.[5] Point-of-care (POC) VL monitoring has been shown to be cost-effective and effective in improving viral suppression and retention in care among PLHIV as compared with standard-of-care laboratory-based VL monitoring and may be a scalable strategy for routine care.[6–8]

Although VL testing is considered a gold standard for monitoring ART adherence, the WHO recommends implementing other approaches to differentiate whether virologic failure is more likely resulting from non-adherence or HIV drug resistance.[4] Early identification of poor adherence, particularly before a client's first VL test when clients are most likely to be lost to follow-up, could be crucial for implementing timely adherence support interventions.[9–11] However, early identification of adherence difficulties remains a challenge for healthcare providers due to reliance on subjective and unreliable adherence metrics, such as self-reported adherence, prescription refill records and pill counts.[12–21] The recently developed and validated Abbott-manufactured POC test that objectively measures recent ART adherence via tenofovir (TFV) levels in urine shows promise as a rapid and inexpensive adherence monitoring tool to identify non-adherence when the establishment of optimal adherence patterns is critical, such before a client's first VL test.[22–26] Routine real-time ART adherence monitoring may also be beneficial in motivating subsequent good adherence among PLHIV and improving engagement in care.[27 28] However, little is known about the effects of implementing POC TFV adherence testing among PLHIV.

A package of interventions and models of care may be necessary to achieve 95% viral suppression among PLHIV on ART, particularly in settings with high HIV prevalence.[29] POC tests for routine monitoring of ART adherence and VL may be helpful in promoting good adherence practices and managing care for PLHIV in real time.[27] We seek to evaluate the effects of integrating two POC tests—a TFV adherence test and a VL test—into care for PLHIV at a large, public clinic in South Africa. Our primary objective is to determine if an integrated model for HIV monitoring, including routine POC TFV adherence testing and POC HIV VL monitoring, improves ART adherence, viral suppression and retention in care. Additionally, we aim to determine whether routine POC TFV adherence testing and POC VL monitoring will be cost-effective and acceptable to both PLHIV and healthcare providers. This study will build on the findings from the Simplifying TREAtment and Monitoring (STREAM) pilot study, which examined the impact of POC HIV VL monitoring on viral suppression and retention in care.[30 31]

## METHODS

### Study design

The STREAM HIV study is a two-arm, open-label randomised controlled superiority trial to assess the impact of routine POC TFV adherence testing and POC VL testing in comparison with standard-of-care HIV monitoring on ART adherence, VL and retention in care among PLHIV initiating ART in South Africa (figure 1). Enrolled participants will be randomised 1:1 to the intervention or standard-of-care arm. The primary outcomes will be cumulative ART adherence (assessed by TFV-diphosphate (DP) concentration in dried blood spot) at 6 months, along with viral suppression and retention in care at 18 months, all after ART initiation.

### Study setting

This study will be conducted at the Prince Cyril Zulu Communicable Disease Centre (PCZ CDC), a large, public, primary healthcare clinic in central Durban, KwaZulu-Natal, South Africa, which is directly adjacent to the Centre for the AIDS Programme of Research in South Africa (CAPRISA) eThekwini Clinical Research Site. PCZ CDC is located near the transportation hub for public commuters in central Durban and initiates approximately 2,000 PLHIV on ART each year. If necessary, participants will also be recruited from a second site, the CAPRISA Vulindlela Clinical Research Site, a large research clinic in uMgungundlovu District, KwaZulu-Natal, South Africa, which is adjacent to the Mafakathini Primary Healthcare Clinic. The clinic follows South African Department of Health guidelines, which recommend TFV disoproxil fumarate (TDF), lamivudine and dolutegravir (TLD) for most people initiating first-line ART, with TDF, emtricitabine and efavirenz (TEE) as an additional option for women who plan to conceive.[32] VL testing is routinely conducted by a centralised laboratory at 6 and 12 months

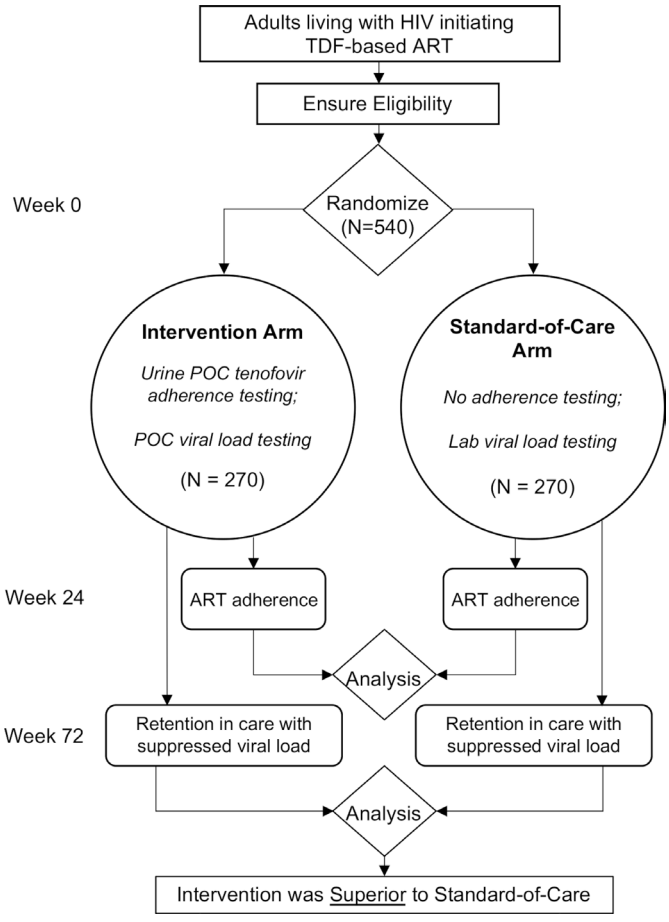


**Figure 1** CONSORT flow diagram of the STREAM HIV study. ART, antiretroviral therapy; CONSORT, Consolidated Standards of Reporting Trials; POC, point-of-care; STREAM HIV, Simplifying TREAtment and Monitoring for HIV; TDF, tenofovir disoproxil fumarate.

after ART initiation, and annually thereafter.[32] HIV drug resistance testing is not required for consideration of a regimen switch for people failing TLD or TEE treatments but may be authorised by an expert on a case-by-case basis for people failing TLD.[32] Currently, PCZ CDC is not implementing POC VL testing or testing for any antiretroviral drug concentrations as part of routine care for PLHIV.

## Study population

We aim to enrol 540 PLHIV who are initiating ART at PCZ CDC. PLHIV will be eligible to participate in the STREAM HIV study if they are ≥16 years old; initiating a TDF-containing, first-line ART regimen at PCZ CDC; do not self-report being on an ART regimen in the prior month; and are willing and able to provide written informed consent. PLHIV will be excluded from participation if they do not plan to continue receiving HIV care at PCZ CDC, or if they are deemed unsuitable for participation by the principal investigators (eg, if they have an acute medical condition that requires urgent care or in a circumstance where the safety or rights of the volunteer cannot be guaranteed).

## Recruitment, consent, screening and enrolment

PLHIV who are initiating ART at PCZ CDC will be approached by a member of the study team, provided with information about the STREAM HIV study, and asked about voluntary participation in the study. Study team members will collect socio-demographic and locator data from the volunteer and review inclusion and exclusion criteria to determine eligibility. Study team members will then provide a detailed explanation of the study to eligible volunteers in a private room of the clinic, address any questions or concerns, and ask them to provide written informed consent. Eligible volunteers will be enrolled in the study, and the enrolment evaluations will be completed (table 1).

## Randomisation

Enrolled participants will be randomised in a 1:1 ratio to either the intervention arm or the control arm using a preprogrammed randomisation tool within DFexplore (5.1.4, DF/Net Research, Seattle, Washington, USA), an electronic data collection tool. The randomisation tool will contain a preprogrammed allocation sequence with variable sized blocks of random numbers generated by the study statistician using SAS V.9.4 (SAS Institute, Cary, North Carolina, USA). The random allocation sequence will only be accessible by the study statistician and the University of Washington (UW) and CAPRISA data managers during the enrolment period to prevent any biases in study arm allocation. Participants' study arm allocation will only be revealed to the participant and other members of the study team after enrolment procedures are complete.

## Study procedures and interventions

At enrolment, a research nurse will administer a medical history questionnaire, conduct a clinical examination and tuberculosis symptom screening, and determine the WHO HIV stage.[33] The research nurse will also collect blood from all participants for standard-of-care ART initiation laboratory tests (haemoglobin, creatinine, CD4 count and hepatitis B testing) and collect samples for storage to be used for retrospective study-specific testing. Additionally, all participants will complete the following questionnaires at enrolment: the Alcohol Use Disorders Identification Test, a substance use questionnaire, a modified version of the WHO Violence Against Women Instrument (for female participants), the Patient Health Questionnaire screen for depression and an isoniazid preventive therapy assessment.[34–36]

During the study period, participants in both arms will be cared for by the study team, and the schedule of clinic visits, clinical care, and laboratory monitoring for routine care will follow South African guidelines.[32] In addition to standard-of-care procedures, intervention arm participants will receive the following interventions: POC TFV adherence testing at each of the first 5 monthly clinic visits and POC VL testing at months 6 and 12 instead of standard-of-care laboratory-based VL testing. POC TFV

**Table 1** Summary of clinic visits, intervention procedures, evaluations, study-specific testing and outcome measures for the STREAM HIV study

| | | Month | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Entry | 1 | 2 | 3 | 4 | 5 | 6 | 8 | 10 | 12 | 14 | 16 | 18 |
| Screening and enrolment procedures | | | | | | | | | | | | | |
| Informed consent | X | | | | | | | | | | | | |
| Eligibility assessment | X | | | | | | | | | | | | |
| Enrolment | X | | | | | | | | | | | | |
| Randomisation | X | | | | | | | | | | | | |
| Standard-of-care arm procedures | | | | | | | | | | | | | |
| SoC lab-based VL testing | | | | | | | X | | | X | | | |
| Intervention arm procedures | | | | | | | | | | | | | |
| POC urine TFV adherence testing | | X | X | X | X | X | | | | | | | |
| POC VL testing + reflex POC urine TFV adherence testing (when VL ≥200 copies/mL) + reflex HIV drug resistance testing (when VL ≥200 copies/mL and TFV is detectable) | | | | | | | X | | | X | | | |
| Evaluations | | | | | | | | | | | | | |
| Sociodemographics questionnaire | X | | | | | | | | | | | | |
| Medical history, WHO HIV staging, baseline HIV and ART assessment, and IPT assessment | X | | | | | | | | | | | | |
| Comprehensive physical exam | X | | | | | | | | | | | | X |
| Substance use, intimate partner violence and mental health assessments | X | | | | | | X | | | | | | X |
| TB symptom screening and vital signs assessments | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Symptom-directed physical exam | | X | X | X | X | X | X | X | X | X | X | X | |
| ART side effect and self-reported adherence assessments | | X | X | X | X | X | X | X | X | X | X | X | X |
| CCMDD eligibility assessment | | | | | | | | | | X | X | X | X |
| Study-specific testing | | | | | | | | | | | | | |
| POC HIV recency test* | X | | | | | | | | | | | | |
| POC HPV test* | X | | | | | | | | | | | | |
| Lab-based HIV drug resistance test* | X | | | | | | | | | | | | |
| Lab-based VL test | X | | | | | | X | | | | | | X |
| Lab-based urine TFV test | | | | X | | | X | | | X | | | X |
| Lab-based DBS TFV-DP test | | | | X | | | X | | | X | | | X |
| Lab-based hair TFV test* | | | | | | | X | | | | | | X |
| Primary and secondary outcome measures | | | | | | | | | | | | | |
| TFV-DP in DBS | | | | | | | X | | | | | | X |
| Combined measure of viral suppression (VL <200 copies/mL)+retention in care | | | | | | | X | | | | | | X |

Continued

**Table 1** Continued

| | Month | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Entry | 1 | 2 | 3 | 4 | 5 | 6 | 8 | 10 | 12 | 14 | 16 | 18 |
| Focus group discussions and semistructured in-depth interviews with study participants | | | | | | X | | | | | | X |
| Semistructured in-depth interviews with healthcare providers | | | | | | X | | | | | | X |
| Costing and cost-effectiveness | | | | | | X | | | | | | X |

*To be conducted for exploratory substudies.
ART, antiretroviral therapy; CCMDD, Central Chronic Medicine Dispensing and Distribution Programme; DBS, dried blood spot; HPV, human papillomavirus; IPT, isoniazid preventive therapy; POC, point-of-care; SoC, standard-of-care; STREAM HIV, Simplifying TREAtment and Monitoring for HIV; TB, tuberculosis; TFV, tenofovir; TFV-DP, tenofovir-diphosphate; VL, viral load.;

adherence testing will be conducted using the urine TFV adherence assay (Abbott Rapid Diagnostics Division, Orlando, Florida, USA) (figure 2A), a rapid, urine-based, competitive, qualitative lateral flow assay that can detect recent TFV dosing.[25] The TFV adherence assay can process test results in approximately 2 min and uses a TFV detection threshold of 1500 ng/mL, the median TFV concentration 3 days after a dose of TDF is taken.[25] It has a 99% sensitivity and 97% specificity for detecting TFV in urine 24 hours after a dose of TDF is taken.[25] POC VL testing will be performed using the GeneXpert HIV-1 VL test (Cepheid, Sunnyvale, California, USA), a validated instrument for quantitatively measuring HIV-1 VL count (figure 2B).[37–40] The GeneXpert HIV-1 VL test has a limit of quantification of 40 copies/mL and can process test results in approximately 90 min using plasma samples with a simple workflow and minimal human resources.[40] A summary of study procedures and participants' flow through the study can be found in figure 3, and the full schedule of clinic visits and evaluations is summarised in table 1.

For the first 5 months, participants in the intervention arm will provide a urine sample for the POC TFV test monthly and will receive their test result at the same visit. Participants who receive a positive test result (TFV detected) will receive standard adherence counselling at the visit, and those who receive a negative test result (TFV not detected) will receive enhanced adherence counselling at the visit, which will entail an open discussion with the research nurse about their recent ART use, the importance of taking ART every day as prescribed, barriers to adherence and strategies for improving adherence. Enhanced adherence counselling will follow the adherence guidelines and standard operating procedures set by the South African Department of Health.[41] At months 6 and 12, participants in the intervention arm will provide a whole blood sample for POC VL testing and will receive their VL test result at the same visit. Participants with a POC VL result <50 copies/mL will receive standard adherence counselling and continue with the routine VL monitoring schedule. Intervention arm participants with an elevated POC VL (50–199 copies/mL) will receive enhanced adherence counselling and continue with the routine VL monitoring schedule. Intervention arm participants with viraemia (POC VL ≥200 copies/mL) will be referred for reflex POC TFV testing at the same visit. For viraemic participants whose TFV is undetectable using the POC urine TFV test, we will conclude viraemia has occurred due to poor adherence and will provide the participant with enhanced adherence counselling at the same visit. For viraemic participants whose TFV is detectable using the POC urine TFV test, we will consider the possibility of HIV drug resistance and will request a genotypic drug resistance test to be conducted. If HIV drug resistance is detected, a clinician will consider switching the participant to a second-line ART regimen. If ART resistance is not detected, the participant will receive enhanced adherence counselling at their next clinic visit and repeat POC VL testing after 3 months. An algorithm for intervention procedures, including testing and counselling, is presented in figure 4.

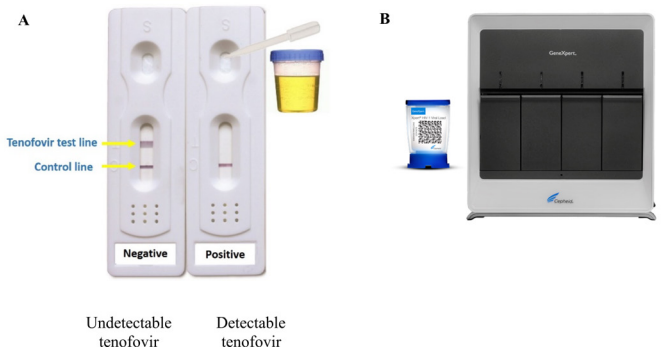


**Figure 2** (A) Urine tenofovir adherence assay (Abbott Rapid Diagnostics Division). (B) GeneXpert System and Xpert HIV viral load cartridge (Cepheid).

## Study outcomes

### Primary outcomes

This study will have two coprimary outcomes: (1) TFV-DP concentrations at 6 months in dried blood spots (DBS) after ART initiation and study enrolment as a cumulative

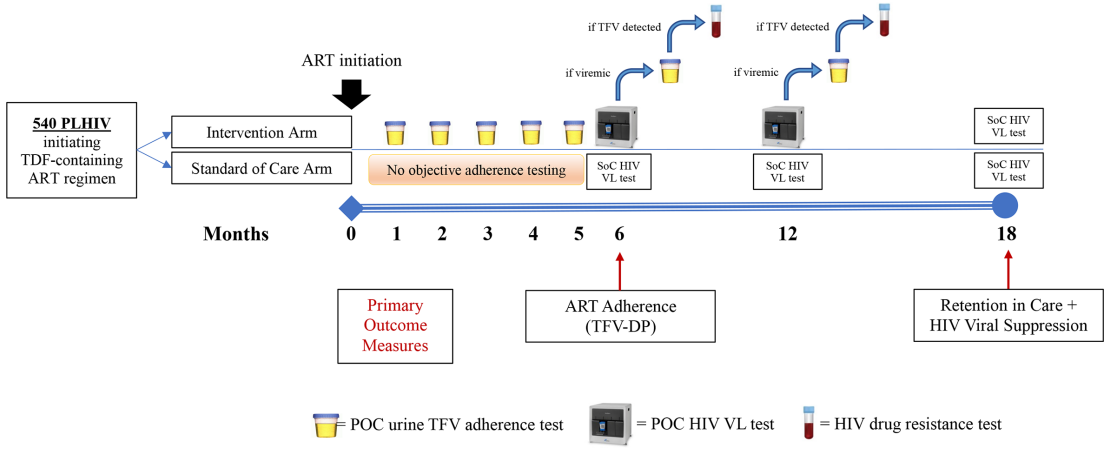


**Figure 3** Participant flow through STREAM HIV study. ART, antiretroviral therapy; POC, point-of-care; SOC, standard-of-care; STREAM, Simplifying TREAtment and Monitoring; TDF, tenofovir disoproxil fumarate; TFV-DP, tenofovir-diphosphate; VL, viral load.

long-term metric of adherence and (2) a combined measure of viral suppression and retention in care at 18 months after ART initiation and study enrolment. Conclusions will be based on findings from both of the coprimary outcomes, and we will not adjust for type I error.

For the first coprimary outcome, we will measure intracellular TFV-DP concentrations (continuous) in whole blood-based DBS using liquid chromatography/tandem mass spectrometry, which will be conducted by a laboratory approved by the National Institutes of Health (NIH)

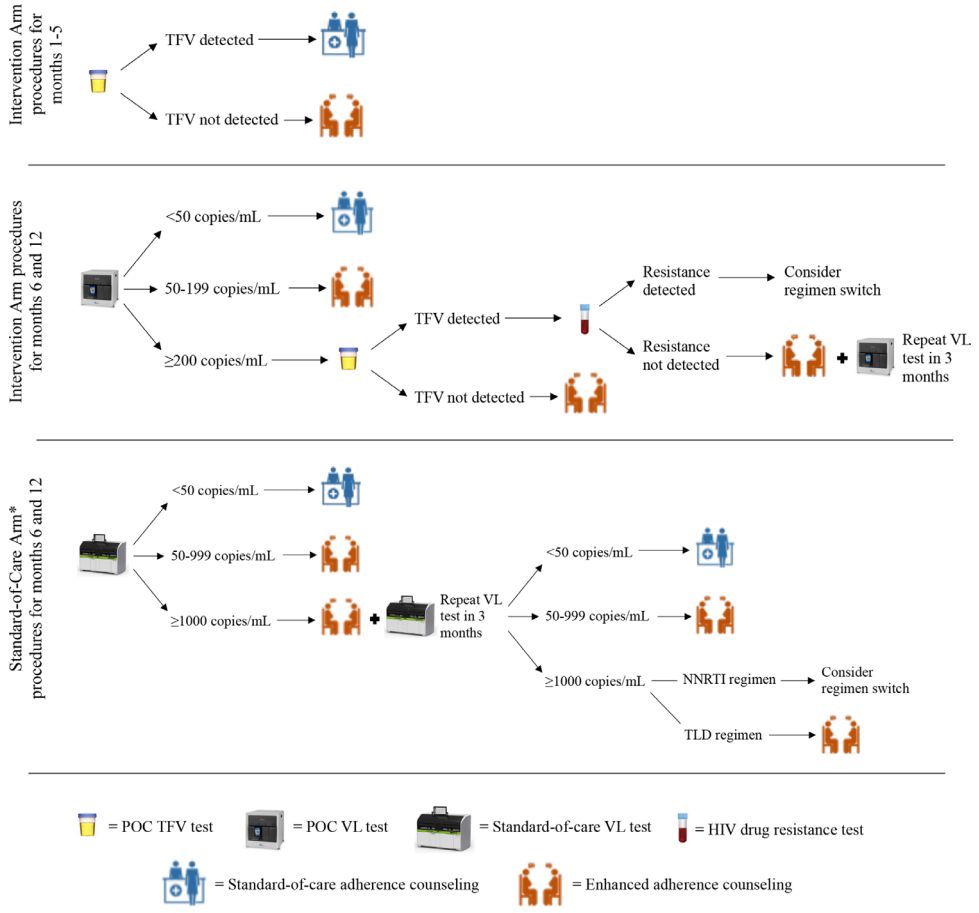


**Figure 4** Testing and counselling algorithm for participants in the STREAM HIV study. *Standard-of-care arm procedures for months 1–5 includes standard-of-care adherence counselling and no POC testing procedures. NNRTI, non-nucleoside reverse transcriptase inhibitor; POC, point-of-care; STREAM, Simplifying TREAtment and Monitoring; TFV, tenofovir; TLD, tenofovir/lamivudine/dolutegravir; VL, viral load.

Division of AIDS (DAIDS) for performing antiretroviral drug-level measurements.[42] Intracellular TFV-DP in red blood cells have a 17-day half-life and correlate with a cumulative measure of TFV dosing and average adherence in the prior 6 weeks.[43] We hypothesise that monthly POC TFV monitoring for the first 5 monthly visits will improve cumulative ART adherence at 6 months after ART initiation in comparison to standard-of-care adherence monitoring.

For the second coprimary outcome, viral suppression will be defined as achieving a VL <200 copies/mL (binary) at study exit as measured by the Roche Taqman V.2.0 (Roche Diagnostics, Basel, Switzerland). To account for potential events of transient viraemia (ie, 'viral blips'), which may not accurately reflect true cases of viraemia, we will use 200 copies/mL as the threshold for viral suppression instead of the test's lower limit of detection of 50 copies/mL. Retention in care will be defined as collecting ART from the study clinic or a community pick-up point under supervision of the study clinic within 8 weeks of study exit (binary). We hypothesise that monthly POC TFV monitoring for the first 5 monthly visits and routine POC VL monitoring will improve viral suppression and retention in care at 18 months after ART initiation in comparison to standard-of-care VL and adherence monitoring.

### Secondary outcomes

The secondary outcomes will be (1) a combined measure of viral suppression and retention in care at 6 months after ART initiation and study enrolment, (2) TFV-DP concentration in DBS at 18 months after ART initiation and study enrolment, (3) acceptability of POC TFV and VL testing among PLHIV and providers, and (4) cost-effectiveness of providing routine POC TFV and VL testing to PLHIV as compared with standard-of-care VL monitoring.

The outcomes of a combined measure of viral suppression and retention in care at 6 months after ART initiation and study enrolment, and TFV-DP concentration in DBS at 18 months after ART initiation and study enrolment, will be defined and measured for all participants (N=540) in the same manner as the corresponding coprimary outcomes.

Acceptability of POC TFV and VL testing will be assessed through focus group discussions (FGDs) and in-depth interviews (IDIs) with a small sample of intervention arm participants and healthcare workers at the study clinic. We will conduct 2 to 4 FGDs and 20 IDIs with intervention arm participants at each study endpoint (6 months and 18 months), as well as 5 to 10 IDIs with healthcare workers at each study endpoint. The FGDs and IDIs will assess participants' and providers' perspectives on their experience with POC TFV and VL testing and will cover the following domains: understanding of the POC test procedures and protocols, experiences with the POC test and test results, barriers to and facilitators of POC test implementation, impact of POC testing on the client–provider encounter and related communication about ART adherence, and impact of POC testing on participants' self-reported adherence.

We will also complete a microcosting and time-and-motion observation of the intervention to estimate programme costs and the cost-effectiveness of providing routine POC TFV and VL testing to PLHIV as compared with standard-of-care VL monitoring.

## Data collection and management

Study evaluations and data collection will be conducted electronically by study team members in DFexplore, a US Food and Drug Administration (FDA) CFR part 11 compliant and validated clinical database management system, via laptops and standardised electronic case report forms (CRFs). Electronic data will be stored on the DFdiscover server at the CAPRISA Doris Duke Medical Research Institute and backed up regularly. In the event of electronic accessibility issues, paper CRFs will be used to collect data and transferred to the electronic database. Paper CRFs and source documents will be stored in a secure, double-locked, fire-resistant unit at the CAPRISA research site with restricted access in accordance with good clinical practice requirements. Data will undergo internal quality checks, and a quality control report will be generated on a consistent basis summarising queries and reasons for data changes.

## Sample size and power

We calculated sample size and power estimates for comparison of the primary clinical outcome of viral suppression and retention in care at 18 months between the intervention and control arms using a Fisher's exact test. We estimate that 75% of control arm participants and 85% of intervention arm participants will achieve the combined outcome of viral suppression and retention in care based on a recent pilot study that evaluated the effect of POC VL monitoring and healthcare worker task shifting on viral suppression and retention in care.[6] To detect a 10% difference in achieving the primary outcome between the intervention and control arms and assuming a two-sided alpha of 0.05 and 80% power, we estimated that we would need to enrol 270 participants per study arm for a total of 540 participants. We also calculated power estimates for comparison of the primary outcome of mean TFV-DP concentration at 6 months between the intervention and control arms using a t-test. Based on a study among PLHIV in South Africa recently initiating TFV-based ART regimen, we hypothesise that the mean TFV-DP concentration for control arm participants will be approximately 1000 fmol/punch with a standard deviation (SD) of 490.[44] If our SD is similar to that found in Warne *et al* and assuming a 10% loss to follow-up, we estimate that we will have 80% power to detect a difference of 125 fmol/punch between the intervention and control arms with a sample size of 270 participants per study arm.

## Statistical analyses for primary outcomes

To assess the coprimary outcome of ART adherence at 6 months after ART initiation and study enrolment, we

will conduct a complete-case analysis to compare mean TFV-DP concentrations in whole blood-based DBS between the intervention and control arms using a two-sample t-test assuming equal variances and will present the mean concentrations and SD for each study arm. If we find that the data more closely resembles a log normal distribution than a normal distribution, we will log transform the data before making a comparison. If rates of missing TFV-DP concentrations differ between arms, we will summarise the reasons for missingness and interpret the results accordingly. Six-month outcome analyses will be conducted after all participants have passed the target visit window for the 6-month endpoint but before all participants have reached the 18-month endpoint.

To assess the coprimary outcome of a combined measure of viral suppression and retention in care at 18 months after ART initiation and study enrolment, we will conduct a complete-case analysis to estimate the relative risk of having achieved the outcome in the intervention arm relative to the control arm using Poisson regression with generalised estimating equations to adjust standard errors for a Poisson distribution and will present the relative risk, two-sided 95% confidence interval and p value. We expect very little missing data for this key clinical outcome because those not returning at 18 months by definition do not achieve the outcome and will contribute accordingly. Missing VL measurements for other reasons is expected to be rare. All analyses will be performed using the intention-to-treat method.

### Analyses for secondary outcomes

The secondary outcomes of (1) a combined measure of viral suppression and retention in care at 6 months and (2) ART adherence at 18 months, will be analysed using the same methods as the corresponding coprimary outcomes.

To assess the secondary outcome of acceptability of POC TFV and VL testing, we will conduct a content analysis, using 'Framework' and 'Interpretive description', on transcripts from FGDs and IDIs with intervention arm participants and healthcare workers.[45 46] Thematic headings will be guided by core concepts emerging from transcript data using an open coding approach and by theoretical concepts from the design.[47] We will designate specific topics as core categories, and we will explore relationships between emerging data and contextual situation using axial coding and constant comparison.[46] We will also document latent or interpreted meanings derived from the data. We will discuss preliminary findings with the research team and healthcare workers to validate our interpretations and understanding of the data.

To assess the secondary outcome of cost-effectiveness, we will conduct a model-based analysis to project the health and economic impact of implementing routine POC TFV and VL testing and standard-of-care VL monitoring in South Africa. We will use an individual-based, stochastic HIV model we developed for KwaZulu-Natal that incorporates sexual behaviour, concurrency, migration, sexually transmitted coinfections and the HIV treatment cascade.[8] Model outcomes will include HIV incidence, HIV-related deaths and disability-adjusted life-years (DALYs) in the intervention compared with standard-of-care scenario over a 20-year time horizon. We will assess the cost-effectiveness of the intervention by calculating the incremental cost-effectiveness ratios as the difference in costs (US dollars) divided by the difference in effects (DALYs) for the intervention arm compared with the control arm over 20 years.

### Patient and public involvement statement

No patients or members of the public were involved in the design of this study.

### Ethics, monitoring and dissemination

The STREAM HIV study protocol, V.2.3, 5 October 2020, has been reviewed and approved by the UW Institutional Review Board (IRB) (STUDY00007544), the University of KwaZulu-Natal (UKZN) Biomedical Research Ethics Committee (BREC) (BREC/00000833/2019), and the DAIDS Regulatory Support Center (38509). Due to the low-risk nature of this study, the establishment of a data safety monitoring board was not deemed to be necessary; however, a safety monitoring committee has been assembled in accordance with the National Institute of Allergy and Infectious Diseases (NIAID) DAIDS Safety Monitoring Committee Guidelines. Findings from this study will be disseminated in accordance with University of Washington, CAPRISA and NIH policies and will be presented at national and international conferences and published in academic, peer-reviewed journals.

### Trial status

This manuscript was developed using V.2.3, 5 October 2020, of the study protocol for the 'STREAM HIV' study. Enrolment began on 4 February 2021.

### Discussion

Monitoring the rapidly growing number of PLHIV receiving ART is challenging in sub-Saharan Africa, where many settings have inadequate infrastructure to scale up laboratory testing. POC testing strategies can increase coverage of ART adherence monitoring, identify HIV drug resistance and improve client outcomes. UNAIDS and South Africa have a goal to achieve 95% viral suppression among those on ART by 2030. To achieve this goal, novel intervention packages and adherence monitoring strategies are needed to objectively assess ART adherence, identify discrepancies in ART adherence and viral suppression, and motivate optimal adherence patterns among PLHIV.[27] Existing strategies for ART adherence monitoring may be ineffective in identifying adherence challenges or drug resistance before virological failure or disengagement from care occurs.[27] Therefore, implementing effective adherence and retention interventions, including enhanced adherence counselling for those who are at risk of developing viraemia at the point of care, is vital to extend the durability of first-line treatment.[48] To our knowledge, this will be one of the first randomised trials to assess the impact of a POC TFV adherence test among PLHIV with POC VL testing. Findings from the STREAM

HIV study will be important in understanding the impact of routine real-time adherence monitoring using a POC urine TFV assay, combined with POC VL monitoring on adherence, retention in care, and VL outcomes among PLHIV in South Africa and similar settings.

This builds on our previous work in the STREAM pilot study, which evaluated the effects of a combined intervention of POC VL monitoring and healthcare worker task shifting and found improvements in viral suppression and retention in care among those receiving the POC intervention in comparison with standard of care.[6 31] Several POC VL tests have also been validated and received FDA clearance, but little is known about their impact on care and health outcomes among PLHIV.[49] Our study design integrates POC TFV testing with POC VL testing in a novel intervention that allows concurrent and objective assessment of viraemia and ART adherence in one clinical visit. POC TFV adherence tests have been recently developed and validated, but implementation studies in clinical care settings are just starting.[25] Encouragingly, a qualitative study found that healthcare providers may be interested in implementing POC TFV testing to assess ART adherence, and PLHIV may be receptive to POC TFV testing if it were incorporated into care.[28] Other studies have found that people receiving TFV-based pre-exposure prophylaxis are interested in drug-level testing and that receiving drug-level feedback may motivate improved medication adherence.[50–53] Integrating POC VL and TFV adherence monitoring into a single client encounter may offer other benefits to clients, providers, health systems and society such as earlier identification of HIV drug resistance and prevention of unnecessary switches to second-line ART regimens, which in turn can prevent HIV transmission, reduce costs of care and improve health outcomes for PLHIV.

This trial has some limitations. Outcomes from the STREAM HIV study may be limited by the tests' characteristics. The POC urine TFV test used in this study can only detect recent dosing of TDF-containing regimens in the prior 3 days; therefore, it cannot detect long-term cumulative dosing and non-TDF-containing ART regimens.[25] Adherence assays, including POC TFV testing, may also be subject to white coat adherence bias, in which a non-adherent client improves their adherence in the days prior to testing in order to receive favourable results.[27 54] Additionally, POC VL monitoring is limited by the test's processing time of about 90 min, the need to centrifuge blood tubes to test plasma, and its reliance on a consistent power source and stable environmental conditions.[49] Reproducibility of the study outcomes will also be dependent on the intervention's implementation success in other populations and settings, in particular its feasibility and adoptability in resource-constrained settings and its acceptability by key stakeholders. Due to the combination intervention, we will not be able to determine the individual effects of POC TFV testing and POC VL testing on viral suppression and retention in care at 18 months. However, we will be able to detect the effect of POC TFV monitoring alone on the first coprimary outcome of TFV-DP concentrations, which is measured at 6 months before POC VL testing is introduced.

The STREAM HIV study will provide the first evidence regarding the clinical impact of a combined intervention of routine POC TFV adherence testing and POC VL monitoring following ART initiation in a large, public HIV clinic in South Africa. These findings can inform strategies to achieve the viral suppression targets set by UNAIDS, which may be critical to ending the HIV epidemic.

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## REFERENCES

1 Joint United Nations Programme on HIV/AIDS (UNAIDS). 90–90–90: an ambitious treatment target to help end the AIDS epidemic, 2017. Available: https://www.unaids.org/en/resources/documents/2017/90-90-90 [Accessed 17 Jul 2019].
2 Joint United Nations Programme on HIV/AIDS (UNAIDS). 2020 Global AIDS Update - Seizing the Moment - Tackling entrenched inequalities to end epidemics, 2020. Available: https://aids2020.unaids.org/report/ [Accessed 13 Nov 2020].
3 World Health Organization (WHO). Guidelines on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV, 2015. Available: http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/ [Accessed 14 Nov 2020].
4 World Health Organization (WHO). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, 2016. Available: http://www.who.int/hiv/pub/arv/arv-2016/en/
5 Carmona S, Peter T, Berrie L. HIV viral load scale-up: multiple interventions to meet the HIV treatment cascade. *Curr Opin HIV AIDS* 2017;12:157–64.
6 Drain PK, Dorward J, Violette LR, *et al*. Point-Of-Care HIV viral load testing combined with task shifting to improve treatment outcomes (STREAM): findings from an open-label, non-inferiority, randomised controlled trial. *Lancet HIV* 2020;7:e229–37.
7 Girdwood SJ, Crompton T, Sharma M, *et al*. Cost-Effectiveness of adoption strategies for point of care HIV viral load monitoring in South Africa. *EClinicalMedicine* 2020;28:100607.
8 Sharma M, Mudimu E, Simeon K, *et al*. Cost-Effectiveness of point-of-care testing with task-shifting for HIV care in South Africa: a modelling study. *Lancet HIV* 2021;8:e216–24.
9 Rosen S, Grimsrud A, Ehrenkranz P, *et al*. Models of service delivery for optimizing a patient's first six months on antiretroviral therapy for HIV: an applied research agenda. *Gates Open Res* 2020;4:116–15.
10 Lilian RR, Rees K, McIntyre JA, *et al*. Same-Day antiretroviral therapy initiation for HIV-infected adults in South Africa: analysis of routine data. *PLoS One* 2020;15:e0227572.
11 Diseko L, Overmeyer R. South Africa DSD update in CQUIN annual meeting. Johannesburg; 2019.
12 Stirratt MJ, Dunbar-Jacob J, Crane HM, *et al*. Self-Report measures of medication adherence behavior: recommendations on optimal use. *Transl Behav Med* 2015;5:470–82.
13 Simoni JM, Kurth AE, Pearson CR, *et al*. Self-Report measures of antiretroviral therapy adherence: a review with recommendations for HIV research and clinical management. *AIDS Behav* 2006;10:227–45.
14 Castillo-Mancilla JR, Haberer JE. Adherence measurements in HIV: new advancements in pharmacologic methods and real-time monitoring. *Curr HIV/AIDS Rep* 2018;15:49–59.
15 Orrell C, Cohen K, Leisegang R, *et al*. Comparison of six methods to estimate adherence in an ART-naïve cohort in a resource-poor setting: which best predicts virological and resistance outcomes? *AIDS Res Ther* 2017;14:20.
16 Agot K, Taylor D, Corneli AL, *et al*. Accuracy of self-report and Pill-Count measures of adherence in the FEM-PrEP clinical trial: implications for future HIV-Prevention trials. *AIDS Behav* 2015;19:743–51.
17 Saberi P, Chakravarty D, Ming K, *et al*. Moving antiretroviral adherence assessments to the modern era: correlations among three novel measures of adherence. *AIDS Behav* 2020;24:284–90.
18 Genn L, Chapman J, Okatch H, *et al*. Pharmacy refill data are poor predictors of virologic treatment outcomes in adolescents with HIV in Botswana. *AIDS Behav* 2019;23:2130–7.
19 Acri T, TenHave TR, Chapman JC, *et al*. Lack of association between retrospectively collected pharmacy refill data and electronic drug monitoring of antiretroviral adherence. *AIDS Behav* 2010;14:748–54.
20 Grossberg R, Gross R. Use of pharmacy refill data as a measure of antiretroviral adherence. *Curr HIV/AIDS Rep* 2007;4:187–91.
21 McMahon JH, Jordan MR, Kelley K, *et al*. Pharmacy adherence measures to assess adherence to antiretroviral therapy: review of the literature and implications for treatment monitoring. *Clin Infect Dis* 2011;52:493–506.
22 Gandhi M, Bacchetti P, Spinelli MA, *et al*. Brief report: validation of a urine tenofovir immunoassay for adherence monitoring to PreP and art and establishing the cutoff for a point-of-care test. *J Acquir Immune Defic Syndr* 2019;81:72–7.
23 Gandhi M, Bacchetti P, Rodrigues WC, *et al*. Development and validation of an immunoassay for tenofovir in urine as a real-time metric of antiretroviral adherence. *EClinicalMedicine* 2018;2-3:255–60.
24 Spinelli MA, Glidden DV, Rodrigues WC, *et al*. Low tenofovir level in urine by a novel immunoassay is associated with seroconversion in a preexposure prophylaxis demonstration project. *AIDS* 2019;33:867–72.
25 Gandhi M, Wang G, King R, *et al*. Development and validation of the first point-of-care assay to objectively monitor adherence to HIV treatment and prevention in real-time in routine settings. *AIDS* 2020;34:255–60.
26 Stalter RM, Baeten JM, Donnell D, *et al*. Urine tenofovir levels measured using a novel immunoassay predict human immunodeficiency virus protection. *Clin Infect Dis* 2021;72:486–9.
27 Drain PK, Bardon AR, Simoni JM, *et al*. Point-Of-Care and near real-time testing for antiretroviral adherence monitoring to HIV treatment and prevention. *Curr HIV/AIDS Rep* 2020;17:487–98.
28 Bardon AR, Simoni JM, Layman LM, *et al*. Perspectives on the utility and interest in a point-of-care urine tenofovir test for adherence to HIV pre-exposure prophylaxis and antiretroviral therapy: an exploratory qualitative assessment among U.S. clients and providers. *AIDS Res Ther* 2020;17:50.
29 Chaiyachati KH, Ogbuoji O, Price M, *et al*. Interventions to improve adherence to antiretroviral therapy: a rapid systematic review. *AIDS* 2014;28 Suppl 2:S187–204.
30 Drain PK, Dorward J, Violette LR. Point-Of-Care HIV viral load testing combined with task shifting to improve treatment outcomes: an open-label non-inferiority randomized controlled trial to simplify HIV treatment and monitoring (stream study). *Lancet HIV* 2019.
31 Dorward J, Garrett N, Quame-Amaglo J, *et al*. Protocol for a randomised controlled implementation trial of point-of-care viral load testing and task shifting: the simplifying HIV treatment and monitoring (stream) study. *BMJ Open* 2017;7:e017507.
32 knowledgehub. 2019 art clinical guidelines for the management of HIV in adults, pregnancy, adolescents, children, infants and neonates, 2019. Available: https://www.knowledgehub.org.za/elibrary/2019-art-clinical-guidelines-management-hiv-adults-pregnancy-adolescents-children-infants
33 World Health Organization. Interim who clinical staging of HVI/AIDS and HIV/AIDS case definitions for surveillance: African region. Geneva WHO; 2005. https://apps.who.int/iris/bitstream/handle/10665/69058/WHO_HIV_2005.02.pdf
34 World Health Organization. WHO multi-country study on women's health and domestic violence against women. Geneva WHO; 2005.
35 Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;16:606–13.
36 Bush K*et al*. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. *Arch Intern Med* 1998;158:1789–95.
37 Ceffa S, Luhanga R, Andreotti M, *et al*. Comparison of the Cepheid GeneXpert and Abbott M2000 HIV-1 real time molecular assays for monitoring HIV-1 viral load and detecting HIV-1 infection. *J Virol Methods* 2016;229:35–9.
38 Gueudin M, Baron A, Alessandri-Gradt E, *et al*. Performance evaluation of the new HIV-1 quantification assay, Xpert HIV-1 viral load, on a wide panel of HIV-1 variants. *J Acquir Immune Defic Syndr* 2016;72:521–6.
39 Kulkarni S, Jadhav S, Khopkar P, *et al*. Genexpert HIV-1 Quant assay, a new tool for scale up of viral load monitoring in the success of art programme in India. *BMC Infect Dis* 2017;17:506.
40 Jordan JA, Plantier JC, Templeton K, *et al*. Multi-site clinical evaluation of the Xpert(®) HIV-1 viral load assay. *J Clin Virol* 2016;80:27–32.
41 Department of Health, Republic of South Africa. Adherence guidelines for HIV, TB and NCDs. Pretoria; 2020.
42 Castillo-Mancilla JR, Zheng J-H, Rower JE, *et al*. Tenofovir, emtricitabine, and tenofovir diphosphate in dried blood spots for

determining recent and cumulative drug exposure. *AIDS Res Hum Retroviruses* 2013;29:384–90.
43 Castillo-Mancilla JR, Zheng J-H, Rower JE, *et al*. Tenofovir, emtricitabine, and tenofovir diphosphate in dried blood spots for determining recent and cumulative drug exposure. *AIDS Res Hum Retroviruses* 2013;29:384–90.
44 Warne P, Robbins R, Anderson P. Utility of dried blood Spot-Derived ARV biomarkers as an objective measure of treatment adherence in South Africa. *In: IAPAC Adherence. Miami, Florida* 2015.
45 Richie J, Spencer L, eds. *Analyzing Qualitative Data*. London: Routledge, 1994.
46 Thorne S. *Interpretive description*. Vol 2. Walnut Creek, CA: Left Coast Press, Inc, 2008.
47 Creswell JW, Poth CN. *Qualitative Inquiry & Research Design: Choosing Among Five Approaches*. 4th edition. Thousand Oaks: Sage Publ Inc, 2017: 1–646.
48 Fox MP, Rosen S. Retention of adult patients on antiretroviral therapy in low- and middle-income countries: systematic review and meta-analysis 2008-2013. *J Acquir Immune Defic Syndr* 2015;69:98–108.
49 Drain PK, Dorward J, Bender A, *et al*. Point-Of-Care HIV viral load testing: an essential tool for a sustainable global HIV/AIDS response. *Clin Microbiol Rev* 2019;32.
50 van der Straten A, Montgomery ET, Musara P. Disclosure of pharmacokinetic drug results to understand nonadherence: results from a qualitative study. *AIDS* 2015;29:2161–71.
51 Landovitz RJ, Beymer M, Kofron R, *et al*. Plasma tenofovir levels to support adherence to TDF/FTC preexposure prophylaxis for HIV prevention in MSM in Los Angeles, California. *J Acquir Immune Defic Syndr* 2017;76:501–11.
52 Hunt T, Lalley-Chareczko L, Daughtridge G, *et al*. Challenges to PreP use and perceptions of urine tenofovir adherence monitoring reported by individuals on PreP. *AIDS Care* 2019;31:1203–6.
53 Balán IC, Giguere R, Brown W, *et al*. Brief participant-centered convergence interviews integrate Self-Reports, product returns, and pharmacokinetic results to improve adherence measurement in MTN-017. *AIDS Behav* 2018;22:986–95.
54 Podsadecki TJ, Vrijens BC, Tousset EP, *et al*. “White Coat Compliance” Limits the Reliability of Therapeutic Drug Monitoring in HIV-1—Infected Patients. *HIV Clin Trials* 2008;9:238–46.