

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.



Signature of Investigator of Record

October 5, 2020

Date

Paul K. Drain
Investigator of Record (Print Name)



Signature of Investigator of Record

October 5, 2020

Date

Nigel J. Garrett
Investigator of Record (Print Name)

Full Protocol Title: Simplifying Treatment and Monitoring for HIV (STREAM HIV): Point-of-Care Urine Tenofovir Adherence and Viral Load Testing to Improve HIV Outcomes in South Africa

DAIDS Protocol Number: DAIDS-ES ID #38509

DAIDS Protocol Version: 2.3

Protocol Date: October 5, 2020

STUDY PROTOCOL

**Simplifying Treatment and Monitoring for HIV (*STREAM HIV*):
Point-of-Care Urine Tenofovir Adherence and Viral Load Testing to Improve HIV
Outcomes in South Africa**

“STREAM HIV Study”



DAIDS Protocol Number:

DAIDS-ES ID #38509

Trial Registration:

ClinicalTrials.gov NCT04341779

IND: Non-Investigational New Drug Study

IDE: Non-Significant Risk Medical Device

Funded by:

US National Institute of Allergy and Infectious Diseases

#A1147752

PROTOCOL VERSION 2.3

October 5, 2020

Principal Investigators:

Dr. Paul Kevin Drain

University of Washington, Seattle, USA

Ninth and Jefferson Building, 908 Jefferson St., 12th floor, Seattle, WA 98104, USA

Email: pkdrain@uw.edu Tel: 206-520-3820 Fax: 206-520-3831

Dr. Nigel Joel Garrett

CAPRISA/UKZN

2nd Floor, Doris Duke Medical Research Institute (Private Bag X7), 719 Umbilo Road, Durban 4013,
South Africa

Email: nigel.garrett@caprisa.org Tel: +27 (0)31 260 4453

CONTENTS

1. STUDY SUMMARY AND SCHEMA.....	7
1.1 Study Schema	7
1.2 Study Summary	8
1.3 Study Aims	9
2. CONSORT DIAGRAM.....	10
3. STUDY PERSONNEL	10
3.1 Leadership Team.....	10
3.2 Co-Investigators (alphabetical order)	11
4. BACKGROUND	11
4.1 Significance	11
4.2 FDA/CDRH and Nonsignificant Risk Designation for the POC Urine Tenofovir Adherence Assay	15
5. STUDY OBJECTIVES.....	16
5.1 Primary Objectives	16
5.2 Secondary Objectives.....	16
5.3 Exploratory Objectives.....	16
6. METHODS.....	17
6.1 Study Design	17
6.2 Location and Setting.....	18
6.3 Eligibility Criteria	18
6.4 Recruitment, Consent, Screening, and Enrollment	19
6.5 Randomization.....	19
6.6 Study Procedures and Interventions	20
6.6.1 Baseline.....	20
6.6.2 Follow-up.....	20
6.6.3 Standard-of-care Arm Follow-up Procedures.....	21
6.6.4 Intervention Arm Follow-up Procedures	21
6.6.5 Procedures for Participants Switched to Non-TDF-containing Regimens.....	22
6.6.6 Central Chronic Medicine Dispensing and Distribution Programme	22
6.6.7 Management of Viral Load Results – Standard of Care.....	22
6.6.8 POC Tenofovir Adherence Testing and Management of Results	23
6.7 Retention Activities	26
6.8 Targeted/Planned Enrollment.....	26
6.9 Schedule of Clinical Visits and Sample Collection	26
6.10 Additional Laboratory Testing for Aim 1 Objectives	26

6.10.1	Primary and secondary outcomes.....	27
6.10.2	Exploratory outcomes.....	27
6.11.	Participant Withdrawal	28
6.12.	Study Duration	28
7.	SAMPLE SIZE AND POWER	28
8.	ANALYSES FOR PRIMARY OUTCOMES	28
9.	SECONDARY QUALITATIVE STUDY.....	29
9.1.	Introduction and Rationale.....	29
9.2.	Justification and Feasibility.....	30
9.3.	Research Design	31
9.4.	Outcomes and Analyses.....	32
10.	SECONDARY COST-EFFECTIVENESS ANALYSIS	33
10.1.	Introduction and Rationale	33
10.2.	Preliminary Cost-effectiveness Studies	33
10.3.	Research Design	34
10.4.	Outcome Assessment and Reporting	35
11.	PARTICIPANT REIMBURSEMENT	35
12.	PROTECTION OF HUMAN SUBJECTS	36
12.1.	Risks to Human Subjects.....	36
12.2.	Adequacy of Protection Against Risks.....	37
12.3.	Potential Benefits of the Proposed Research	38
12.4.	Data Management and Safety Monitoring Plan	38
13.	TIMELINES	40
14.	POTENTIAL PROBLEMS AND ALTERNATIVE APPROACHES	40
15.	RESOURCE SHARING PLAN	41
16.	QUALITY CONTROL AND QUALITY ASSURANCE	42
17.	ETHICAL CONSIDERATIONS	42
18.	PROTOCOL REGISTRATION.....	43
19.	REFERENCES.....	44
20.	APPENDIX I: 2019 SOUTH AFRICA HIV VIRAL LOAD MONITORING GUIDELINES	56
21.	APPENDIX II: SCHEDULE OF EVALUATIONS	59

Abbreviations

AIDS	Acquired immune deficiency syndrome
AE	Adverse event
ART	Antiretroviral therapy
ARC	AIDS-related complex
CAPRISA	Centre for AIDS Programme of Research in South Africa
CCMDD	Central Chronic Medicine Dispensing and Distribution Programme
CDC	Centers for Disease Control and Prevention (US)
DAIDS	Division of AIDS (NIH)
DALY	Disability-adjusted life-year
DBS	Dried blood spots
DTG	Dolutegravir
EC	Ethics Committee
EFV/3TC/TDF	Efavirenz/emtricitabine/tenofovir diphosphate
FDA	Food and Drug Administration (US)
FDC	Fixed dose combination
FTC	Emtricitabine
FTC-TP	Emtricitabine-triphosphate
GEE	Generalized estimating equations
HAL	Hair Analytical Laboratory
HIV	Human Immunodeficiency Virus
HIVDR	HIV drug resistance
HTTP	Hypertext transfer protocol (presentation of web data)
ICRC	International Clinical Research Center
IQR	Interquartile range
IPT	Isoniazid preventive therapy
IRB	Institutional Review Board
LMIC	Low- and middle-income country
LC-MS/MS	Liquid chromatography/tandem mass spectrometry
NACOSTI	National Council of Science, Technology and Innovation
NGS	Next generation sequencing
NIH	National Institutes of Health (US)
NNRTI	Non-nucleoside reverse transcriptase inhibitor
PLHIV	People living with HIV
POC	Point-of-care
PrEP	Pre-exposure prophylaxis
RDT	Rapid diagnostic test
REDCap	Research Electronic Data Capture
SAS	Statistical Analysis Software
SoC	Standard-of-care
STI	Sexually transmitted infection

TDF	Tenofovir disoproxil fumarate
TFV	Tenofovir
TFV-DP	Tenofovir diphosphate
TLD	Tenofovir/lamivudine/dolutegravir
UCSF	University of California, San Francisco
UNAIDS	Joint United Nations Program on HIV/AIDS
US	United States
UW	University of Washington
VCT	Voluntary counseling and testing
VL	Viral load
WHO	World Health Organization

1. STUDY SUMMARY AND SCHEMA

1.1 Study Schema

Purpose:	To determine the clinical efficacy, acceptability, and cost effectiveness of implementing an integrated model for HIV monitoring using point-of-care (POC) tenofovir (TFV) adherence testing with POC HIV viral load (VL) monitoring for improving adherence and outcomes among people living with HIV (PLHIV) who initiate first-line tenofovir disoproxil fumarate (TDF)-based ART in South Africa.
Design:	A Phase IIb open-label randomized controlled trial to assess routine POC TFV adherence testing with POC VL monitoring against the standard-of-care (SoC) with no objective TFV adherence testing and SoC VL monitoring. HIV-positive individuals (≥ 16 years) will be randomized 1:1 to the intervention versus SoC.
Central Hypotheses:	Our central hypotheses are that POC TFV adherence testing combined with POC VL monitoring will improve adherence to ART, VL suppression rates, and retention in care, while being feasible, acceptable, and cost-effective.
Primary Objectives:	<ul style="list-style-type: none"> • To determine if implementing routine POC TFV adherence testing is superior to SoC (no adherence testing) in improving ART adherence at 24 weeks after ART initiation among PLHIV receiving TDF-based ART in South Africa. • To determine if implementing routine POC TFV adherence testing in combination with routine POC VL monitoring is superior to SoC VL monitoring (with no adherence testing) in improving retention in care and VL suppression (< 200 copies/mL) at 72 weeks after ART initiation among PLHIV initiated on first-line TDF-based ART in South Africa.
Secondary Objectives:	<ul style="list-style-type: none"> • To determine if implementing routine POC TFV adherence testing in combination with routine POC VL monitoring is superior to SoC VL monitoring (with no adherence testing) in improving retention in care and VL suppression (< 200 copies/mL) at 24 weeks after ART initiation among PLHIV receiving TDF-based ART in South Africa. • To determine if implementing routine POC TFV adherence testing in combination with routine POC VL monitoring is superior to SoC VL testing (with no adherence testing) in improving ART adherence at 72 weeks after ART initiation among PLHIV initiated on first-line TDF-based ART in South Africa. • To assess the acceptability of POC VL and TFV adherence testing among PLHIV and providers. • To assess the cost-effectiveness of providing POC VL and TFV adherence testing to PLHIV as compared to SoC VL monitoring.

Population:	HIV-positive individuals (≥ 16 years) initiating a first-line, TDF-based ART regimen.
Study Site:	HIV clinic at the Prince Cyril Zulu Communicable Disease Centre, which is located adjacent to the CAPRISA eThekweni Clinical Research Site and near the transport hub for public commuters in central Durban.
Study Size:	270 in each arm, for 540 total participants.
POC Testing:	GeneXpert® by Cepheid with the Xpert® HIV-1 VL cartridge. Abbott POC urine TFV adherence assay.
Primary Outcome Measurements:	<ul style="list-style-type: none"> • Tenofovir diphosphate concentrations in dried blood spots (continuous) at the 24 week visit (target visit window: weeks 22-28) after ART initiation and study enrollment. • Composite measure of requiring both HIV VL suppression and retention in care (binary) at study clinic at study exit (72 weeks after ART initiation; target visit window for retention: weeks 68-80; target visit window for VL: weeks 68-84). Participants who are either retained but not virally suppressed, or who are virally suppressed but not retained, do not achieve the endpoint. <ul style="list-style-type: none"> - Retention in care at study clinic (binary): collecting ART from the study clinic (or from community pick-up point under supervision of the study clinic) at study completion (72 weeks). - HIV VL suppression (binary): HIV VL < 200 copies/mL by a lab-based reference assay at the study exit visit (72 weeks)
Study Duration:	4 years, including enrollment period and 72 weeks of follow-up per participant.

1.2 Study Summary

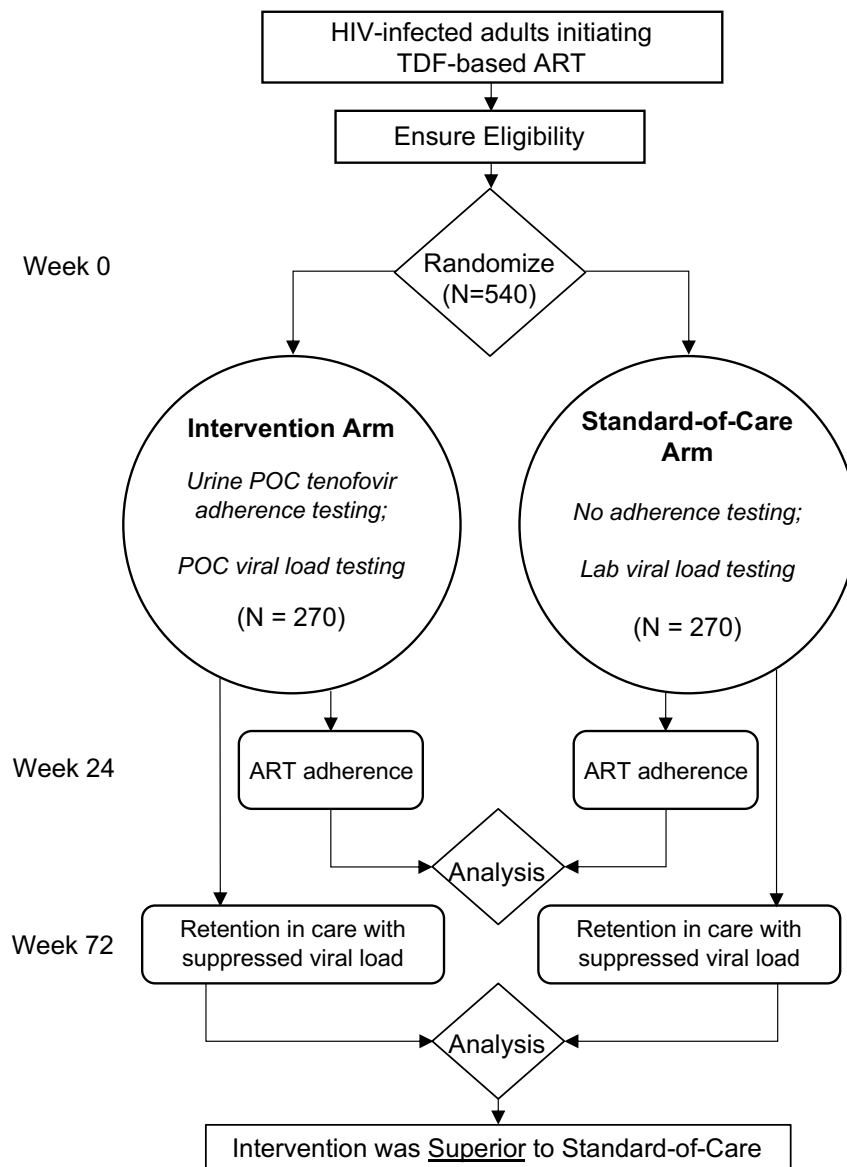
For millions of people living with HIV (PLHIV) receiving antiretroviral therapy (ART), adequate ART adherence and routine HIV viral load (VL) monitoring are critical to ensure viral suppression and good health outcomes. Initiation and management of life-long ART in low- and middle-income countries (LMICs) is challenging for both PLHIV and providers in part due to the reliance on self-reported adherence and delays with lab-based VL testing, which are part of the usual care. Drs Drain and Garrett (co-principal investigators) recently completed a pilot study in South Africa demonstrating that point-of-care (POC) VL monitoring for PLHIV receiving efavirenz-based ART increased VL suppression and retention in care by 14% (95% CI 6 - 21%) over a 12-month period compared to standard lab testing. However, the applicability of these findings to the context of newer, more robust dolutegravir-based ART regimens being introduced in several LMICs, including South Africa, is not known. To complement POC VL monitoring, we have recently completed the development and initial evaluation of a novel POC urine TFV assay which can monitor ART adherence in clinic-based settings in real-time.

Our objective in this study is to determine the clinical efficacy and cost effectiveness of implementing an integrated model for HIV monitoring using POC TFV adherence testing and POC VL monitoring in improving ART adherence, maintaining durable VL suppression, and improving retention in care among PLHIV initiating first-line tenofovir disoproxil fumarate (TDF)-based ART in South Africa. We will randomize 540 participants (1:1) at ART initiation into routine POC TFV adherence testing with POC VL monitoring (Arm 1) or standard-of-care (SoC) with no objective TFV adherence testing and SoC VL monitoring (Arm 2). Participants will be followed to compare two primary outcomes: mean plasma TFV concentrations between study arms at 24 weeks after ART initiation and a composite outcome of VL suppression and retention in care between the study arms at 72 weeks after ART initiation. We will use process evaluation data, interviews and focus groups with patients and process evaluation data and interviews with staff to assess implementation of the POC assays. We will conduct detailed micro-costing to estimate intervention costs. We will parameterize an agent-based network transmission model with costs and effectiveness data collected during the trial to project the clinical outcomes and economic impact of POC testing on HIV-related outcomes and disability-adjusted life-years (DALYs).

1.3 Study Aims

- Aim #1: To determine if an integrated model for HIV monitoring using a POC TFV adherence assay and a POC VL test will improve adherence, VL suppression, and retention in care.
- Aim #2: To monitor implementation and assess patient and provider perspectives of real-time POC TFV adherence testing and POC VL monitoring in South Africa.
- Aim #3: To estimate the costs and cost-effectiveness of implementing POC TFV adherence testing with POC VL monitoring, compared to no objective adherence testing and SoC VL monitoring.

2. CONSORT DIAGRAM



3. STUDY PERSONNEL

3.1 Leadership Team

Seattle-based Principal Investigator:

Paul Drain

USA cell phone:

1-206-306-3066

Email

pkdrain@uw.edu

Skype

pkdrain

Durban-based Principal Investigator:

Nigel Garrett

Durban Cell phone:	(076) 330-8300
Email	nigel.garrett@caprisa.org
Skype	nigegarrett

3.2 Co-Investigators (alphabetical order)

- Salim Abdool Karim, CAPRISA
- Anna Bershteyn, NYU
- Connie Celum, UW
- Tim Cressey, Chiang Mai (for TFV-DP adherence testing)
- Deborah Donnell, UW
- Jienchi Dorward, CAPRISA/U. of Oxford
- Lisa Frenkel, UW
- Geoff Gottlieb, UW
- Monica Gandhi, UCSF
- Richard Lessells, KRISP (for HIV resistance testing)
- Koleka Mlisana, NHLS
- Pravi Moodley, NHLS
- Kogie Naidoo, CAPRISA
- Hope Ngobese, eThekweni Municipality Health Unit
- Monisha Sharma, UW (for CEA aim)
- Jane Simoni, UW (for qualitative aim)

4. BACKGROUND

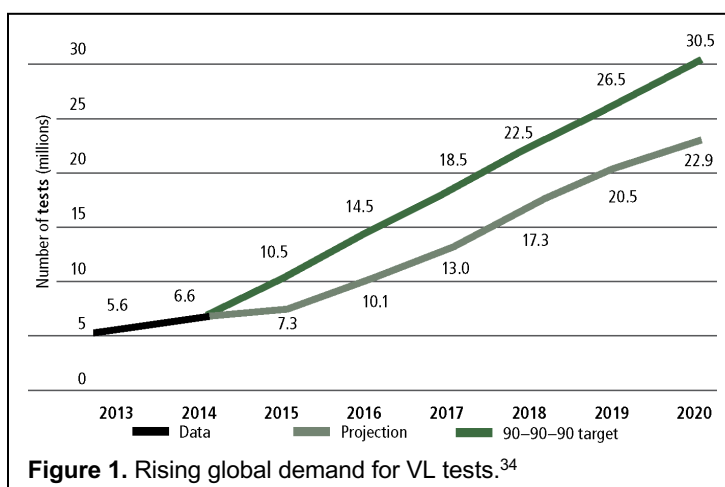
4.1 Significance

Over 20 million PLHIV, mostly in LMICs, are receiving ART.^{1,2} In South Africa, which has the world's largest HIV treatment program,^{3,4} delivery of ART has led to a 15-year increase in life expectancy and a significant reduction in HIV-associated deaths.^{5,6} Despite these gains, the requirements for PLHIV to maintain high levels of ART adherence to achieve VL suppression and prevent emergence of drug-resistant HIV remains a major challenge. ART adherence is crucial to achieving treatment success and reaching the 90-90-90 UNAIDS targets⁷ and ending the HIV/AIDS epidemic.^{8,9} With the rapid increase of PLHIV initiating ART globally, there is an urgent need to redesign models of ART monitoring and management in LMICs, while not increasing the burden to HIV providers, laboratories, and health systems.¹⁰⁻¹³

Poor HIV clinical outcomes in South Africa. Many countries, including South Africa, have adopted a universal test-and-treat policy to provide ART regardless of CD4 count.¹⁴ Despite this, South Africa is far from reaching the UNAIDS 90-90-90 goals.¹⁵ In 2017, only 52% of the 7.9 million PLHIV had achieved VL suppression.^{15,16} Global estimates are similar, with UNAIDS

reporting that in 2017, 47% of the 36.9 million PLHIV worldwide had achieved VL suppression.¹⁷ Three major contributors to this shortfall are (1) overburdened health clinics and laboratories, (2) emergence of HIV drug resistance (HIVDR), and (3) poor ART adherence. First, an overburdened health system impacts health care outcomes in South Africa - only 39% of PLHIV initiated ART within a year of diagnosis,¹⁸ 25% of PLHIV who initiated ART are lost to follow-up within one year, and <50% had a recorded VL within one year.³ This strain on HIV clinicians and laboratories has detracted resources from identifying new patients, initiating PLHIV on ART, and appropriately switching patients with treatment failure to another ART regimen. Second, to combat rising levels of HIVDR and reduce costs,¹⁹⁻²² the World Health Organization (WHO) now recommends dolutegravir (DTG), an integrase strand transfer inhibitor, in first- and second-line ART in LMICs.^{14,23-27} By the end of 2019, the South African DoH is planning to introduce tenofovir/lamivudine/DTG, known as “TLD”, in a fixed dose combination as the country’s first-line ART regimen. Since DTG-based therapy has a higher genetic barrier to resistance and a better tolerability than efavirenz-based therapy,^{14,28-32} the role of VL testing may then shift towards identifying viremia related to poor ART adherence. With the roll-out of DTG-based ART, determining the role of emerging POC technologies, including a novel TFM adherence assay for treatment monitoring, will increasingly become a priority for LMICs.

The challenge of HIV VL testing for PLHIV in LMICs. The WHO recommends routine VL testing for monitoring ART,³³ but current expansion rates of VL coverage have not met the needs of PLHIV and ART programs (Figure 1).³⁴ High quality HIV reference labs are scarce in many LMICs.³⁵ Significant challenges to scaling up capacity for VL testing include poor infrastructure, human resource shortages, delays with specimen transport, and incomplete results management - all of which impede the prompt detection and management of HIV viremia.^{35,36} In KwaZulu-Natal, the province with the highest HIV prevalence in South Africa, just five laboratories are processing and resulting over 100,000 VL tests every month (5.6 million VL tests annually in all South Africa).³⁷ With optimized systems, most PLHIV do not receive their VL result until their next clinical visit in 2-3 months.³⁸ In a cluster randomized trial evaluating the national adherence guidelines, <20% of PLHIV with a VL >1000 copies/mL received a follow-up VL test within three months (and of those who did, only 15% suppressed to <400 copies/mL).^{155,156} In a cohort study from four provinces, the median time from first VL >1000 copies/mL to confirmation of viral failure was 30 weeks (IQR 17-535,124).¹⁵⁷ To combat this challenge, the WHO has called for operational research on the cost, impact, and sustainability of models of POC VL testing for decentralized care.³³



POC HIV VL monitoring improves retention and VL suppression. Diagnostic POC tests have rapidly emerged in LMICs.³⁹⁻⁴³ Three POC HIV VL assays have recently become available, and more are in development.^{44,45} The Xpert[®] HIV-1 VL test (Cepheid, Sunnyvale, US) requires 1 mL of blood to provide a quantitative result (40-10 million copies/mL) in <2 hours (Figure 2).⁴⁶ This assay uses the fully automated molecular GeneXpert[®] platform, which is widely used in LMICs for diagnosing tuberculosis.^{47,48} In 2017, an estimated 9,449 GeneXpert[®] instruments had been procured in 130 countries.⁴⁹ We conducted the first clinic-based feasibility and validation study of the Xpert[®] HIV-1 VL test, and found a strong correlation between the Xpert[®] and Roche Taqman v2.0 (Roche Diagnostics) across the HIV VL spectrum (Spearman $\rho=0.94$, $p<0.001$)¹¹⁵ when performed in the CAPRISA eThekweni clinic.⁵⁰ A recent systematic review of subsequent studies confirmed high diagnostic accuracy when compared to laboratory reference VL assays ($R^2=0.94-0.96$).⁵¹ While other POC VL assays are available (SAMBA I/II semi-Q [Diagnostics for the Real World Ltd., Cambridge, UK];⁵² and m-PIMA, formerly Alere Q NAT [Alere, Waltham, MA, US]⁵³), the Xpert[®] HIV-1 VL has the advantage of utilizing a multiplex, multi-cartridge platform widely available in LMICs, and is the first quantitative assay to receive both European and WHO regulatory approvals.⁵⁴ We recently completed the pilot STREAM POC VL study, in which we randomized (1:1) 390 PLHIV (≥ 18 years) who were receiving ART for 6 months to receive POC HIV VL monitoring by an enrolled nurse (Arm 1) versus standard lab-based HIV VL monitoring by a professional nurse or physician (Arm 2). The primary outcome was a composite measure of HIV VL suppression (<200 copies/mL) and retention in care (collecting ART during a defined window period at study exit). After 12 months follow-up, those assigned to the POC arm had statistically significant higher VL suppression and retention by 13.9% (95% CI 6.4–21.2%), as compared to the SoC arm.³⁸ In secondary analyses, 99% of POC testing participants received their VL result nearly all on the same day, whereas only 77% of SoC participants received their VL result a median of 41 (IQR 28-69) days after blood draw. However, while VL monitoring will be critical to identify PLHIV with viremia, we do not know if these important findings will be similar for DTG-based ART, or how POC VL monitoring should be integrated with POC adherence testing.⁵⁶

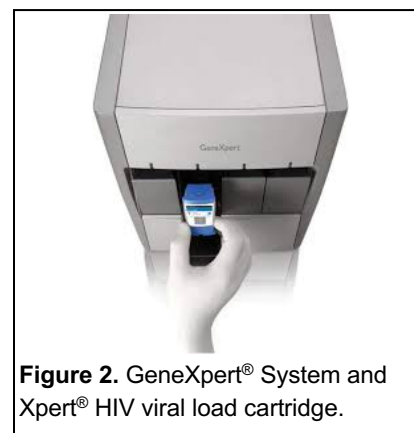
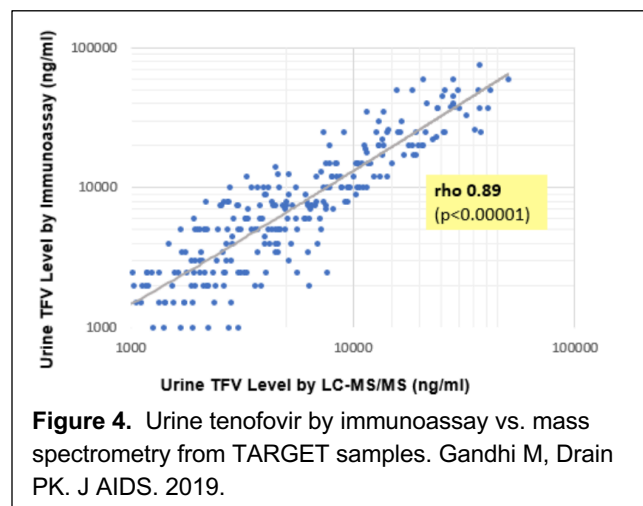
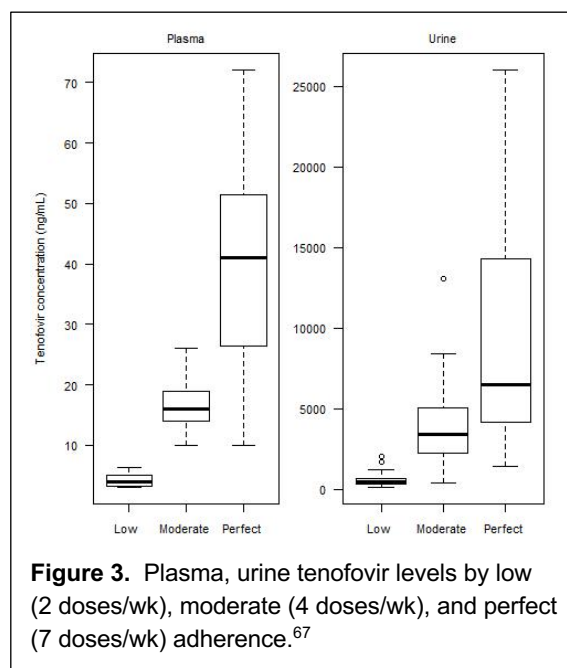


Figure 2. GeneXpert[®] System and Xpert[®] HIV viral load cartridge.

Needing better solutions to improve ART adherence. The barriers to maintaining adequate ART adherence are a complex mix of medical, behavioral, social and structural factors.^{57,58} Studies of adherence interventions, including mHealth interventions, community-based supporters, and economic assistance, have shown mixed results in improving VL suppression in LMICs. Effective interventions in high-income settings (e.g. cognitive behavioral therapy) have shown little effect in LMICs.⁵⁹⁻⁶² A primary challenge has been accurately measuring ART adherence in real-time at the clinical point-of-care. Clinicians rely on self-reported measures and

pill counts, but these are susceptible to social desirability bias and are poor measures of ART adherence.^{63,64} Clinicians in LMICs often lack access to HIVDR testing, making it difficult to distinguish whether viremia is caused by poor adherence or HIVDR.⁶⁵ The WHO recommends VL testing after 6 months on ART, so healthcare workers may not detect early problems with adherence.³³ This may be particularly problematic as adherence patterns are established early in the course of treatment and early attrition in ART programs remains high.⁶⁶ The current techniques to detect antiretrovirals, including tenofovir, in various biological matrices all require liquid chromatography/tandem mass spectrometry (LC-MS/MS) or other spectrometry machines, all of which are expensive, laborious, and require trained personnel. Therefore, a simple, inexpensive, and objective test to accurately identify poor ART adherence is a high priority for LMICs.

A POC urine tenofovir adherence test. After several years of research, we have recently developed and validated the first POC urine-based TFV adherence test as a simple antibody-based immunoassay.⁶⁸⁻⁷⁰ First, Dr. Drain et al completed a randomized controlled directly-observed pharmacokinetic study of HIV-negative participants taking TDF/emtricitabine (FTC) at 2, 4 and 7 doses per week to establish the correlation between urine and plasma tenofovir levels, and to establish a threshold for POC detection (Figure 3).⁶⁷ Subsequently, there were further collaborations with the University of California-San Francisco (UCSF) Hair Analytical Laboratory (HAL), who were working with Abbott/Alere™ Rapid Diagnostics, to develop an immunoassay to quantify urine tenofovir levels. A complex antibody selection process, involving the inoculation of rabbits, was used to isolate antibodies specific to tenofovir. These have now been purified and incorporated into an immunoassay, which has demonstrated high sensitivity (94%) and specificity (99%) for detecting tenofovir levels in urine, when compared to LC-MS/MS, from participants in the TARGET study (Figure 4).⁶⁸ The correlation between tenofovir levels was high (0.92 in all samples, $p < 0.00001$; 0.89 in samples positive for tenofovir, $p < 0.00001$).⁶⁸



The immunoassay has been translated into a corresponding lateral flow assay (LFA) for POC tenofovir-based ART adherence testing and has been validated in urine.¹⁵⁸ The threshold of the assay has been designed to distinguish between people who have taken at least one fixed dose of TDF within the prior four days (corresponding with a TFV urine concentration of ≥ 1500 ng/mL) versus those who have taken no doses of TDF within the prior four days (corresponding with a TFV urine concentration of < 1500 ng/mL).⁸⁵ The sensitivity of the LFA using the TFV urine concentration threshold of 1500 ng/mL compared to the gold standard for TFV concentration detection, LC-MS/MS, was 97% (95% CI: 95-99%). Similarly, the LFA indicated a 97% specificity (95% CI: 93-99%) when compared to LC-MS/MS.⁸⁵

The POC urine TFV adherence assay is accurate, low cost ($< \$2$ /test), enables qualitative tenofovir detection within 10 minutes, and can be easily performed by clinical personnel at the point-of-care. When combined with POC VL monitoring, the POC TFV assay directly measures the presence (or absence) of tenofovir and has the potential to shift the paradigm for monitoring ART in LMICs. Currently, there are no studies of the clinical and cost-effectiveness of utilizing a POC adherence assay with VL testing to improve VL suppression in LMICs.

Redesigning integrated models of HIV care and ART monitoring in LMICs. As the number of PLHIV receiving ART continues to rise, developing and evaluating clinic-based strategies to improve ART adherence and maintain VL suppression will be paramount to reach the ambitious UNAIDS 90-90-90 targets.⁷ Existing models of HIV monitoring were designed for CD4-guided ART initiation of efavirenz-based ART, and new models of HIV care are needed using an integrated approach with early ART adherence testing and more efficient HIV VL testing.⁷¹⁻⁷³ Combining an objective POC adherence test with efficient POC VL monitoring could enable healthcare providers to rapidly categorize patients into non-adherent viral failures versus drug-resistant viral failures, triggering expensive genotypic testing and switches to 2nd or 3rd line treatment only when appropriate (e.g., high adherence with viral failure).⁷⁴⁻⁷⁶ Furthermore, the mechanism by which a POC adherence test could improve ART monitoring for PLHIV and health care workers needs further investigation. Our proposed study will determine whether a novel POC urine TFV adherence test, combined with POC VL monitoring, could be a cost-effective intervention to support PLHIV in achieving VL suppression in LMICs.²⁹

4.2 FDA/CDRH and Nonsignificant Risk Designation for the POC Urine Tenofovir Adherence Assay

We obtained pre-trial consultation advice from the U.S. Food and Drug Administration's (FDA) Center for Devices and Radiological Health (CDRH) regarding the use of the POC urine tenofovir adherence assay that will be used in this study. The FDA verified that the POC tenofovir adherence assay is not Investigational Device Exempt (IDE) since the assay results will be returned to participants and may be used to guide clinical care decisions. Per FDA regulations

(21 CFR 812), the alternative device determinations applicable to this study are either Nonsignificant Risk (NSR) or Significant Risk (SR). The adherence assay meets the criteria for a NSR Medical Device study since the device does not pose any serious risks to the health, safety, or welfare of participants in this study. The CDRH and the University of Washington Institutional Review Board (IRB) has agreed that this device meets the criteria for a NSR Medical Device study, and we will seek approval from the relevant IRBs to conduct this study with the POC tenofovir adherence assay as a NSR Medical Device.

5. STUDY OBJECTIVES

5.1 Primary Objectives

- To determine if implementing routine POC TFV adherence testing is superior to SoC (no adherence testing) in improving ART adherence at 24 weeks after ART initiation (target visit window: weeks 22-28) among PLHIV initiated on first-line TDF-based ART in South Africa.
- To determine if implementing routine POC TFV adherence testing in combination with routine POC VL monitoring is superior to SoC VL monitoring (with no adherence testing) in improving retention in care and VL suppression (<200 copies/mL) at 72 weeks after ART initiation (target visit window for retention: weeks 68-80; target visit window for VL: weeks 68-84) among PLHIV receiving TDF-based ART in South Africa.

5.2 Secondary Objectives

- To determine if implementing routine POC TFV adherence testing in combination with routine POC VL monitoring is superior to SoC VL monitoring (with no adherence testing) in improving retention in care and VL suppression (<200 copies/mL) at 24 weeks after ART initiation (target visit window: weeks 22-28) among PLHIV receiving TDF-based ART in South Africa.
- To determine if implementing routine POC TFV adherence testing in combination with routine POC VL monitoring is superior to SoC (with no adherence testing) in improving ART adherence at 72 weeks after ART initiation (target visit window: weeks 68-84) among PLHIV receiving TDF-based ART in South African clinics.
- To assess the acceptability of POC VL and TFV adherence testing among PLHIV and providers.
- To assess the cost-effectiveness of providing POC VL and TFV adherence testing to PLHIV as compared to SoC VL monitoring.

5.3 Exploratory Objectives

Exploratory objectives may be evaluated:

- To assess the costs, both incurred and averted, of implementing the proposed model in Aim #1, and the cost per participant virally suppressed and retained in care.

- To determine the HIV genotype resistance pattern among PLHIV who develop viremia on dolutegravir-based ART.
- To determine risk factors for poor retention in care or virological failure.
- To determine the incidence of viremia and virological failure (≥ 50 copies/mL and ≥ 1000 copies/mL) among PLHIV receiving ART at the clinical site.
- To compare duration of viremia (i.e., time spent at VL ≥ 200 copies/mL) between the intervention and SoC arms.
- To compare the time to participants' receipt of VL results in the intervention versus SoC arms.
- To compare the number of participants in the intervention versus SoC arms who are appropriately entered into the Central Chronic Medicine Dispensing and Distribution Programme (CCMDD) at 12 months.
- To compare among participants in the intervention versus SoC arms the time to appropriate entry into the CCMDD.
- To compare the number of clinic visits for participants in each study arm.
- To further validate the POC TFV adherence assay against a gold-standard measure of tenofovir by tandem liquid chromatography mass spectrometry.
- To further validate novel POC VL assays against a laboratory-based gold standard.
- To compare time to appropriate ART regimen switch between the intervention and SoC arms.
- To compare the number of unnecessary ART regimen switches between the intervention and SoC arms.
- To assess TFV level in hair samples at 24 and 72 weeks after enrollment.
- To compare VL results of whole blood, plasma, and dried blood spot on the Cepheid GeneXpert machine.
- To characterize patients' HIV infection and treatment history at ART initiation using a novel HIV recency test at baseline, National Health Laboratory Service data, HIV drug resistance testing and ART blood levels.
- To assess and evaluate other relevant POC assays for PLHIV on ART, including the GeneXpert human papillomavirus (HPV) assay, if they become available.

6. METHODS

6.1 Study Design

This study will be a two-arm, open-label, randomized controlled superiority trial at an HIV clinic in Durban. HIV-positive individuals aged ≥ 16 years who are initiating a TDF-based, first-line ART will be randomized 1:1 to receive POC VL testing and POC TFV adherence testing, versus SoC viral load testing. VL testing will follow South African guidelines for HIV VL testing after ART initiation. The primary outcomes will include: (1) concentration of tenofovir diphosphate (TFV-DP) in dried blood spots (DBS) 24 weeks after ART initiation and study enrollment as a surrogate measure for adherence to first-line ART regimen and (2) a composite measure of retention in care

with suppressed VL (<200 copies/mL) 72 weeks after ART initiation and study enrollment.

6.2 Location and Setting

The study will be conducted at the Prince Cyril Zulu Communicable Disease Centre (“**CDC Clinic**”) and the adjacent CAPRISA eThekweni Clinical Research Site (ECRS). The CDC Clinic and ECRS are located near the transport hub for public commuters in central Durban. The CDC Clinic initiates approximately 2,000 PLHIV on ART annually. Current South African Guidelines recommend a fixed-dose combination (FDC) drug of tenofovir diphosphate, lamivudine, and dolutegravir (TLD) for first-line ART for adolescents and adults. For women who are pregnant or may become pregnant, efavirenz, emtricitabine, tenofovir diphosphate (EFV/3TC/TDF) is offered as an alternative to TLD due to potential risks to fetal development involved with taking TLD during pregnancy. ART initiation is recommended on the same day as a patient receives an HIV-positive test unless there are symptoms or signs of opportunistic infections such as tuberculosis or meningitis. VL testing is recommended at six and 12 months after ART initiation, and then annually thereafter. If the VL is suppressed after 12 months, patients may be referred into the CCMDD, where they collect ART every two months from community pharmacies and other community pick-up points and are seen only every six months at the clinic for clinical and laboratory monitoring.

6.3 Eligibility Criteria

Eligibility criteria are meant to be representative of PLHIV who are eligible to initiate ART in South Africa. We will enroll HIV-positive individuals (≥ 16 years old) who are initiating a TDF-based ART regimen, which is included in current and anticipated first-line ART regimens. The study involves collection of clinical data and biological specimens, so all participants must be willing and able to provide written informed consent in English or isiZulu, the local languages.

Study eligibility criteria include the following:

- HIV-positive
- ≥ 16 years old
- Initiating a TDF-based, first-line ART regimen
- Do not self-report being on an ART regimen in the prior month
- Willing/able to provide written informed consent

The exclusion criteria are the following:

- Does not meet the study inclusion criteria above
- Does not plan to continue receiving HIV care at the CDC Clinic
- Per the decision or opinion of the PI or designee (for example, a clinically significant acute or chronic medical condition or circumstances that would make the patient unsuitable for participation or jeopardize the safety or rights of the participant)

Of note, pregnancy is **not** a study exclusion criterion.

6.4 Recruitment, Consent, Screening, and Enrollment

A Research Assistant or designee dedicated to this study will approach individuals who are being initiated on ART within the HIV clinic at the CDC Clinic. The Research Assistant/designee will describe the study and ask for voluntary participation. Individuals who want to voluntarily participate will be taken to a private area of the clinic and will be provided with a detailed explanation of the purpose and procedures of the study. The Research Assistant/designee will address any questions about study participation. HIV-positive individuals (≥ 16 years) interested in participating in the study will undergo the informed consent procedure as per standard operating procedures and thereafter if they are willing to participate, will sign the informed consent form for screening and possible enrollment into the study. Those who are not willing to participate in the study will experience no detrimental impact on their routine care at the CDC Clinic. A Research Nurse/designee will review the study inclusion/exclusion criteria, assess the potential participant's eligibility, and complete the following evaluations:

- Socio-demographics questionnaire
- Locator information

If eligibility is confirmed, the participant will be enrolled, and the Research Nurse/designee will complete the following evaluations with the participant:

- HIV and ART assessment
- Medical history
- WHO staging
- TB symptom screen
- Substance use questions
- WHO intimate partner violence tool
- Mental health assessment tool (PHQ-9)
- IPT assessment
- ART adherence and counseling

6.5 Randomization

The study statistician will generate an allocation sequence with variable sized blocks of random numbers using SAS 9.4 (SAS Institute Inc., Cary, NC). Randomization will be in a 1:1 ratio to the standard of care or intervention arm. Study arm allocation for each participant will be programmed within the electronic data collection tool (iDataFax) by the Data Manager, and no other members of the research team will be able to look up the random allocation sequence throughout the enrollment period. This will prevent any biases in study arm assignment from occurring. At enrollment, the participant will be randomized to either the control arm or the intervention arm in a 1:1 fashion, using the pre-programmed randomization tool within iDataFax.

6.6 Study Procedures and Interventions

6.6.1 Baseline

Once written informed consent is obtained, but before randomization, a Research Assistant, Nurse, or designee will administer demographic, health related and locator information questionnaires. A Nurse/designee will also administer a brief clinical questionnaire, conduct a clinical examination, and determine the WHO HIV Stage. In order to minimize the number of blood draws required, if and where possible, the attending nurse will coordinate the standard ART initiation blood draws and study-specific blood draws for the participant. Blood will be drawn for haemoglobin (Hb) analysis, creatinine, CD4 count and Hepatitis B as per schedule of evaluation. Blood will also be drawn for storage of blood in the biorepository for VL testing and possible future genotype and/or tenofovir drug-level testing for ART adherence. Once all procedures are completed, participants will be randomised and assigned to a study arm via randomization procedures outlined above (Section 6.5). Participants will be provided with ART and scheduled for a follow-up visit as per South African guidelines, which typically occurs after one month.

6.6.2 Follow-up

When participants return to the clinic for routine care visits, they will be asked to present directly to the study team. The Research Assistant/designee will determine the assigned study group of the participant and direct them accordingly to either the SoC arm procedures (Section 6.6.3) or the Intervention arm procedures (Section 6.6.4). Apart from POC VL and POC TDF adherence testing in the intervention arm (as outlined in Sections 6.6.7 and 6.6.8), the schedule of follow-up visits, clinical care, and laboratory monitoring will follow standard South African guidelines. All participants will have creatinine testing at month three; VL and creatinine at month six; and VL, creatinine, and CD4 testing at month 12 as per schedule of evaluation. Participants will be scheduled for visits at an average of once a month for the first six months, then every two months between months 6-12. Participants in both arms will be assessed for CCMDD eligibility around 12 months and referred into CCMDD as appropriate. At each clinic visit, participants will see a nurse or physician, who will perform a clinical assessment, including symptoms/signs of tuberculosis, other opportunistic infections, and ART side effects. They will prescribe ART and additional medications and adherence counseling as appropriate, in accordance with South African guidelines. At each follow-up visit, all participants will complete the following evaluations with the Research Assistant, Nurse, or designee:

- Locator information
- TB symptom screen
- ART adherence and counseling
- ART side effect assessment
- Vital signs assessment
- Symptom directed physical exam (except for week 72)

In addition to those listed above, all participants will complete the following evaluations at weeks 24 and 72:

- Substance use questions
- WHO intimate partner violence tool
- Mental health assessment tool (PHQ-9)

6.6.3 Standard-of-care Arm Follow-up Procedures

In the SoC arm, routine CD4, creatinine, and VL testing will be performed according to the above schedule by the National Health Laboratory Services (NHLS) which provide all laboratory testing offsite for the CDC Clinic. The NHLS currently uses the Abbott Alinity m Analyser or Alinity m HIV-1 assays for laboratory VL testing.

6.6.4 Intervention Arm Follow-up Procedures

Participants in the intervention arm will have urine TFV measurements conducted during each clinical encounter for the first five months after ART initiation. This will be tested by utilizing a rapid urine dipstick test. As per standard operating procedures, participants will be given a urine container, shown a private place to provide a urine sample, and the testing will be conducted at the clinical point-of-care. The threshold of the assay was designed to distinguish between PLHIV who have (“adherent”) taken TDF versus those who have not (“non-adherent”) taken TDF within the prior four days. Participants who are considered “adherent” by the assay will be informed of the result and encouraged to continue with good adherence. The PLHIV who are considered “non-adherent” by the assay will also be informed of the result and receive standard enhanced adherence counseling.

Participants in the intervention arm will have all routine ART monitoring tests performed according to the schedule described in the SoC arm follow-up procedures, however the POC VL assays will be utilized instead of lab-based VL testing. POC VL testing will be performed using Cepheid’s GeneXpert® HIV-1 VL assay performed at the beginning of the clinical encounter, so the clinical examination can be performed during the 90 minutes required to run a GeneXpert HIV VL test. If the participant is not able to wait for the results, then the study team will allow the participant to leave the study clinic but will ask them to remain in the vicinity and return to the clinic for their VL results. Prior to consent and enrollment, all potential participants will be counseled on the study procedures to ensure participants are able to comply with Intervention Arm study procedures, including potentially spending more time in clinic to receive VL results than they normally would as part of SoC clinic procedures. The GeneXpert testing will be conducted in the adjacent CAPRISA clinic site laboratory. Results will be managed according to SoC South African guidelines. However, all patients with a POC VL >200 copies/mL will have reflex POC urine TFV adherence testing performed within the same clinical visit.

In addition, participants in the Intervention arm may also be asked to provide a fingerprick of blood for HIV VL testing if this assay becomes available during the study period. This would be a validation sub-study against a reference assay VL results only, and therefore, these results would not be used to guide the intervention.

6.6.5 Procedures for Participants Switched to Non-TDF-containing Regimens

Following South Africa guidelines, all participants in this study who are initiated on a TDF-containing regimen but are later found to have insufficient renal function (eGFR <50 mL/min/1.73m²) will be switched to a non-TDF based regimen. SoC arm participants who are switched to a non-TDF based regimen will continue to be followed for the duration of the study. Intervention arm participants who are switched to a non-TDF based regimen will continue to be followed for the duration of the study and will continue to receive POC VL monitoring but will not receive POC TFV adherence monitoring.

6.6.6 Central Chronic Medicine Dispensing and Distribution Programme

From 12 months after ART initiation (study enrollment), eligible participants will be referred into CCMDD. Eligibility criteria for CCMDD as per South African guidelines are the following:

- a) Clinically stable and adherent on same first-line ART regimen for ≥ 12 months
- b) No current opportunistic infections (e.g., tuberculosis) or uncontrolled chronic illness, including hypertension, in previous six months
- c) Most recent viral load results show VL <50 copies/mL
- d) Not a caregiver for a child on ART, particularly for those with scheduled pick-up points on the same schedule as the child

Eligible participants will be offered to voluntarily opt in to the program. In CCMDD, they will be prescribed a six-month supply of ART, which they collect in two-month installments from a community pick-up point including community-based organizations, churches and private pharmacies. They will be seen again in the clinic every six months. Those who are not in CCMDD will continue to see a nurse or physician in the study clinic until the end of the study.

6.6.7 Management of Viral Load Results – Standard of Care

The clinical decisions from the SoC VL testing will adhere to the South African guidelines. The algorithm for the 2019 VL monitoring guidelines can be found in Appendix I and is summarized below:

- HIV VL <50 copies/mL – Reinforce the importance of good ART adherence and continue

routine VL monitoring

- HIV VL 50-999 copies/mL – Provide enhanced ART adherence counseling, provide ART, and ask participant to return to the clinic in six months for repeat VL testing. If the VL remains high (50-999 copies/mL) upon repeat testing, then the participant should continue receiving enhanced adherence counseling and repeat VL testing every six months until viral suppression (<50 copies/mL) is achieved.
- HIV VL $\geq 1,000$ copies/mL – Provide enhanced ART adherence counseling; provide ART, and ask participant to return to the clinic in three months for repeat VL testing. If the VL remains high ($\geq 1,000$ copies/mL) after repeat testing, then participants on an NNRTI (non-nucleoside reverse transcriptase inhibitor)-based regimen will be considered for switching to a new ART regimen by a physician. Participants on a TLD regimen will only be considered for resistance testing or a regimen switch after at least three VL ≥ 1000 copies/mL over at least two years.

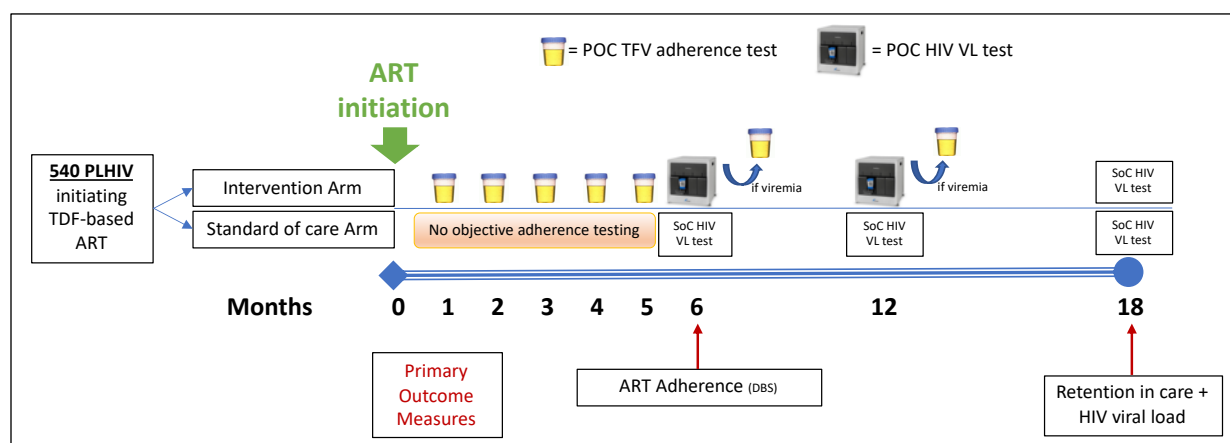


Figure 6: Participant flow through study

6.6.8 POC Tenofovir Adherence Testing and Management of Results

POC TFV adherence testing will be conducted among only Intervention arm participants using an Abbott urine TFV adherence test per the testing schedule shown in Figure 6 (above). In months 1-5, Intervention Arm participants will undergo POC TFV adherence testing at each monthly clinical check-up. Participants who are found to be “adherent” will have the importance of good adherence reinforced and will proceed with intervention monitoring procedures. Participants who are found to be “non-adherent” will be provided with enhanced adherence counseling until their next clinical check-up.

For months six and beyond, Intervention arm participants who receive a POC VL result of <50 copies/mL will proceed with routine monitoring as outlined in Section 6.6.7. Participants who receive a POC VL result of 50-199 copies/mL will proceed with enhanced adherence monitoring

and will be scheduled to receive another POC VL test in three months as described in the 2019 VL monitoring guidelines in Section 6.6.7 for those with a VL of 50-999 copies/mL. Participants who receive a POC VL result of ≥ 200 copies/mL will be asked to provide a urine sample for POC TFV adherence testing.

6.6.8.1 Adherence Testing Procedures

At scheduled and interim visits in which a POC TFV adherence test is required, the Research Assistant/designee will remind the Intervention arm participant about the purpose of adherence testing and the experimental nature of the adherence test. Participants will then be asked to provide a urine sample collected at the beginning of the participant's visit. The Research Assistant/designee will perform the test using standard operating procedures provided by Abbott. The test results will appear within approximately 3-5 minutes. As shown in Figure 7, the test results will indicate either an indeterminate result (no control line appears), a positive result (only the control line appears), or a negative result (both the control line and the tenofovir test line appear). A positive result will indicate that the assay detected tenofovir in the participant's urine and that the participant is "adherent", and a negative result will indicate that the assay was unable to detect tenofovir in the participant's urine and that the participant is "non-adherent". If an indeterminate result appears, a new test will be conducted.

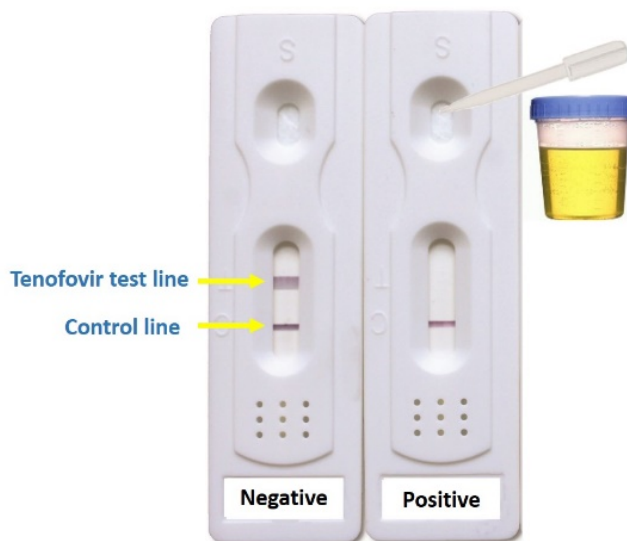


Figure 7: Abbott Urine TFV Adherence Assay

6.6.8.2 Management of Adherence Test Results and Communicating Results with Participants

If a participant is found to be "non-adherent", they will be informed of their test results and provided with enhanced adherence counseling and will be asked to return to the clinic in three months for repeat POC VL testing. More details on enhanced adherence counseling for "non-adherent" participants can be found below in Section 6.6.8.3. If a participant is found to be "adherent", they will be asked to provide a blood sample for resistance testing, the importance of good adherence all the time will be reinforced, and they will be asked to return to the clinic in three months for repeat POC VL testing. If no drug resistance is found, then participants will not be contacted about their results and will proceed with routine care. If presence of drug resistance is found, then the Research Assistant will contact the participant and ask them to return to the clinic promptly to be switched to an appropriate second-line regimen. The full algorithm for management of POC VL and tenofovir results for Intervention arm participants can be found in Figure 8.

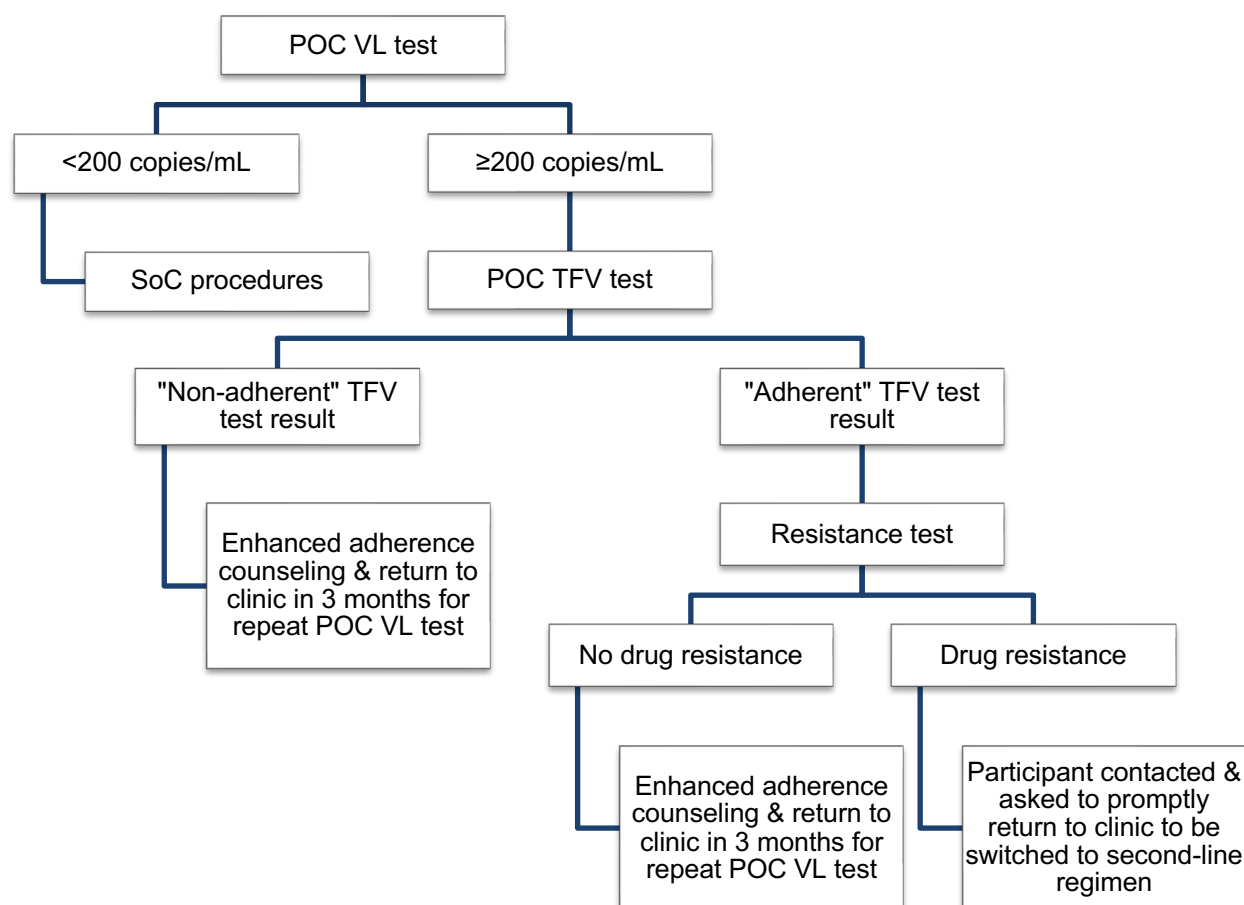


Figure 8: Algorithm for management of POC VL and TFV results after six months

6.6.8.3 Enhanced Adherence Counseling for “Non-Adherent” Participants

Intervention arm participants who are found to be “non-adherent” by the POC TFV adherence test will receive additional enhanced adherence counseling at the end of the visit in which their TFV adherence test results were received. The counseling session will begin by the Research Assistant/designee informing the participant that their test results indicated that they have not taken any of their ART pills within the prior 4 days. Participants will be reminded again of the experimental nature of the POC TFV adherence test and that diagnostic tests may sometimes, though rarely, produce inaccurate results. They will also be reminded of the importance in taking their ART every day as prescribed. The remainder of the counseling session will include a discussion with the participant about their barriers to adherence and ways to improve.

The enhanced adherence counseling for Intervention arm participants is a novel area for clinical care delivery and will be guided by a formative qualitative assessment that will be conducted

prior to commencing the study. The formative qualitative assessment will assess perspectives from providers and PLHIV on ART on the POC TFV adherence test and will help inform development of standard operating procedures for delivering POC TFV test results and subsequent adherence counseling to “non-adherent” participants in a way that will minimize any potential adverse effects such as stigmatization. After standard operating procedures for enhanced adherence counseling are developed, all research team members will be sufficiently trained to deliver POC TFV test results in a non-judgmental, supportive manner.

6.7 Retention Activities

The clinical and research teams at the CDC Clinic have long-established retention strategies to ensure high rates of retention among participants. Standard retention strategies, in line with South African guidelines, include providing clinic cards with appointment dates, and contacting participants who are at least two weeks late for a scheduled clinic visit via an SMS or phone call to remind them about their missed appointment. Towards the end of follow-up, if a participant has not attended during the retention in care window (68-80 weeks), they will be defined as not retained in care. The research team will then attempt to trace the participant within the exit VL window (up to 84 weeks). Tracing will involve contacting participants via SMS or phone call, and visiting participants in their home or place of work, when given permission, to offer them a free ride to the research clinic. Intervention and SoC arm participants will receive identical retention strategies from the CDC Clinic throughout the duration of the study.

6.8 Targeted/Planned Enrollment

We will enroll a total of 540 participants, 270 participants in each study arm. Considering the HIV epidemic is disproportionally affecting women in our setting, we expect to enroll slightly more women than men in our study. Based on historical performance, 75% of adults in the existing care model will meet our primary composite outcome.

	Standard of Care Arm	Intervention Arm	Total
Total	270	270	540

6.9 Schedule of Clinical Visits and Sample Collection

The study schedule of evaluations is outlined in Appendix II.

6.10 Additional Laboratory Testing for Aim 1 Objectives

At enrollment, weeks 24 and 72, participants will be asked to provide a blood sample for plasma storage for retrospective HIVDR testing. All participants will have urine and DBS collected at weeks 12, 24, 48, and 72 and hair collected at weeks 24 and 72 to measure long-term and short-term ART adherence.

6.10.1 Primary and secondary outcomes

Tenofovir-diphosphate levels in DBS and tenofovir levels in urine. We will measure tenofovir diphosphate (TFV-DP) in whole blood-based DBS and TFV in urine in the Program for HIV Prevention and Treatment (PHPT) laboratory at Chiang Mai University (ISO:15189 certified), led by Dr. Tim Cressey (Co-Investigator),^{67,113} which has been approved by the Division of AIDS (DAIDS) to perform antiretroviral drug level measurements by LC-MS/MS. The PHPT lab participates in the Clinical Pharmacology Quality Assurance and Quality Control Program (CPQA), which includes regular proficiency testing, external SOP review, and external audits. Dr. Drain has two NIH-supported projects with Dr. Cressey (#AI136648; #AI127200).

6.10.2 Exploratory outcomes

HIV genotypic resistance testing. Dr. Richard Lessells (Co-Investigator) and Dr. Tulio de Oliveira established KRISP as a next-generation genomics and bioinformatics laboratory at the University of KwaZulu-Natal in Durban.^{118,119} KRISP has the equipment for next-generation sequencing (NGS) using the Illumina MiSeq platform, including PCR amplification and library preparation, and *de novo* viral genome assemblage.¹²⁰ The KRISP lab will perform retrospective resistance testing for all baseline, follow-up, and exit samples from participants with a VL ≥ 200 copies/mL during the study follow-up period. For all samples with VL ≥ 200 copies/mL, they may perform next-generation sequencing (NGS) using the Illumina MiSeq platform using Primer ID. This NGS method will allow for detection of low-frequency drug resistance mutations (minority variants), which may be present at baseline and/or at time of virological failure. In addition, samples with a VL ≥ 200 copies/mL may also be tested by the PacBio method that is available either in Johannesburg or at the University of Washington. Sequences will be analyzed for HIV drug resistance mutations using the Stanford HIV drug resistance database (HIVdb) genotypic resistance interpretation system, and drug resistance mutations will be reported at detection thresholds of 1%, 2%, 5% and 20%. Genotypic resistance testing for minority variants will also be performed at the Seattle Children's Research Institute by Dr. Lisa Frenkel's laboratory.

HIV phenotypic resistance testing. Dr. Geoff Gottlieb (Co-Investigator) has agreed to perform phenotypic resistance testing in his lab at the UW. His lab requires two 2-mL cryovials of plasma, which will be collected from participants at baseline, at study exit (72 weeks), and for each participant with a VL ≥ 200 copies/mL during the study follow-up period.

Tenofovir levels in hair. Dr. Gandhi and the Hair Analytical Laboratory (HAL) lab at University of California-San Francisco (UCSF) will measure tenofovir levels in hair through independent funding. Hair collection procedures will be further described in detail in the standard operating procedures. Cumulative and recent adherence to ART will be measured by concentrations of TFV and 3TC in hair. TFV and 3TC are measured in hair samples at the

HAL at UCSF using validated methods. The trial will assess whether Tfv levels in hair increase over time when providing results of the urine Tfv assay back to participants. ART refills will be measured using routine pharmacy refill data.

6.11. Participant Withdrawal

Participants may voluntarily withdraw from the study for any reason, at any time. The site Investigator also may withdraw participants from the study as per clinical discretion, e.g. in order to protect their safety and/or if they are unwilling or unable to comply with required study procedures. Participants may also be involuntarily withdrawn from the study if the study is stopped or cancelled by the sponsor or ethics committees. Reasons for withdrawal will be recorded.

6.12. Study Duration

All participants enrolled in this study will be followed for a total of 72 weeks (18 months) from the date of study enrollment. The total study duration will be 4 years.

7. SAMPLE SIZE AND POWER

The sample size and power calculation are based on determining superiority of the intervention arm compared to the SoC arm (Table 2). Based on clinical data and our recently completed pilot study, we expect that 75% of adults will be virally suppressed and retained in care after 72 weeks. In order to detect a 10% improvement in the intervention (75% vs 85%), we need to enroll 270 people per study arm (assuming two-sided $\alpha=0.05$; $\beta=0.2$). Therefore, we plan to enroll 540 total participants over a 12-month period.

Table 2. Sample Size and Power Estimates.

Outcome for SoC arm	Outcome for Intervention arm	Power (beta)	Sample size per arm	Total sample size
75%	82.5%	80%	493	986
75%	83.0%	80%	431	862
75%	83.8%	80%	353	706
75%	85.0%	80%	270	540
75%	87.0%	80%	183	366
75%	89.0%	80%	131	262

Power calculated for Fisher's Exact test.

8. ANALYSES FOR PRIMARY OUTCOMES

Primary Outcome A: Tenofovir-diphosphate concentrations in DBS at 24 weeks (target visit window: weeks 22-28) after ART initiation and study enrollment. See also Study Schema, Primary Outcome Measures.

To assess Primary Outcome A, we will compare mean tenofovir-diphosphate concentrations measured by a lab-based assay between the Intervention and SoC study arms. We will present mean concentrations and standard deviation by study arm and compare the means using a two-sample t-test assuming equal variances.

Primary Outcome B: Composite measure of HIV VL suppression (<200 copies/mL) and retention in care at the study clinic at study exit (72 weeks from enrollment; target visit window for retention: weeks 68-80; target visit window for VL: weeks 68-84). See also Study Schema, Primary Outcome Measures. HIV VL suppression will be defined as achieving a VL <200 copies/mL, as measured by a lab-based reference assay at the study exit visit (72 weeks). The same lab-based reference assay will be used to measure HIV VL for both Intervention Arm and Control Arm participants. Retention in care will be defined as collecting ART from the study clinic (or from community pick-up point under supervision of the study clinic) at study completion (72 weeks). Participants who have met the definition for both HIV VL suppression and retention in care at the study exit visit will be classified as having met the criteria for Primary Outcome B. All others will be classified as not meeting the criteria for Primary Outcome B.

To assess Primary Outcome B, we will estimate the relative risk (RR) achieving our primary outcome in the intervention relative to standard of care study arms using Poisson regression, which provides unbiased estimates of the log relative risks, with generalized estimating equations (GEE) to adjust standard errors for the choice of Poisson distribution. RRs will be provided with two-sided 95% confidence interval (CI) and p-value.

P-values will not be adjusted for multiple testing and $p < 0.05$ will be interpreted as statistically significant. The full statistical analysis plan, including planned analyses for secondary and exploratory outcomes, is detailed in the study's Statistical Analysis Plan.

9. SECONDARY QUALITATIVE STUDY

9.1. Introduction and Rationale

The objective of this aim is to evaluate the implementation of POC TFV and viral load testing at the South African clinic and to assess the perspectives of patients and providers regarding acceptability of POC testing. This will be achieved through a mixed-methods approach: process evaluations, focus group discussions, and semi-structured interviews among the study participants as well as process evaluations and semi-structured interviews among the health care workers at the study clinic. Understanding the logistical barriers to implementation at the clinic as well as patient and provider perspectives is critical to developing feasible, acceptable, and effective clinic-based monitoring protocols. In current practice, delayed recognition of adherence challenges has compromised the ability of providers to assist patients in achieving durable VL suppression. Objective data provided at regular intervals and in real-time on recent medication adherence may open the window for more accurate and strategic provider-patient communication

about medication-taking during routine visits.

9.2. Justification and Feasibility

Poor adherence to ART has been the Achilles' heel of HIV management, in part due to the difficulties in identifying PLHIV who poorly adhere to ART. Patient reports often overestimate adherence and provider estimates are notoriously inaccurate.¹²¹ Until now, the lack of an objective assessment of adherence has hindered the ability of providers to offer, or refer patients to, supplemental adherence counseling. POC tests are minimally intrusive for patients and not time or labor intensive. They may improve clinical decision-making, patient-provider communication, and patient outcomes by the provision of real-time objective adherence data. To our knowledge, no published studies have evaluated the barriers and facilitators for POC adherence and VL testing in South Africa, particularly not with the urine-based POC TFV adherence test that we have only recently developed.

Rapid diagnostic tests (RDTs) have been widely implemented for several infectious diseases, including HIV, tuberculosis, malaria, and syphilis.⁷⁸ Feasibility studies have shown that appropriately trained nurses and/or community health workers can implement POC testing with low error rates.¹²²⁻¹²⁴ However, results from POC tests or RDTs may not necessarily change prescribing practices or improve patient outcomes, if patients are unwilling to undergo testing or if clinicians are unwilling to act upon results. One clear example has been the reluctance of clinicians to prescribe isoniazid preventive therapy (IPT) to PLHIV who do not have tuberculosis-related symptoms, even when data are rather clear that IPT is both safe and effective for preventing active tuberculosis disease.^{125,126} Similarly, we aim to change the longstanding problem of assessing and addressing non-adherence in the clinical encounter, but we first need to determine if such routine POC testing can be implemented within a busy clinic setting and if patients and providers will engage with the process.

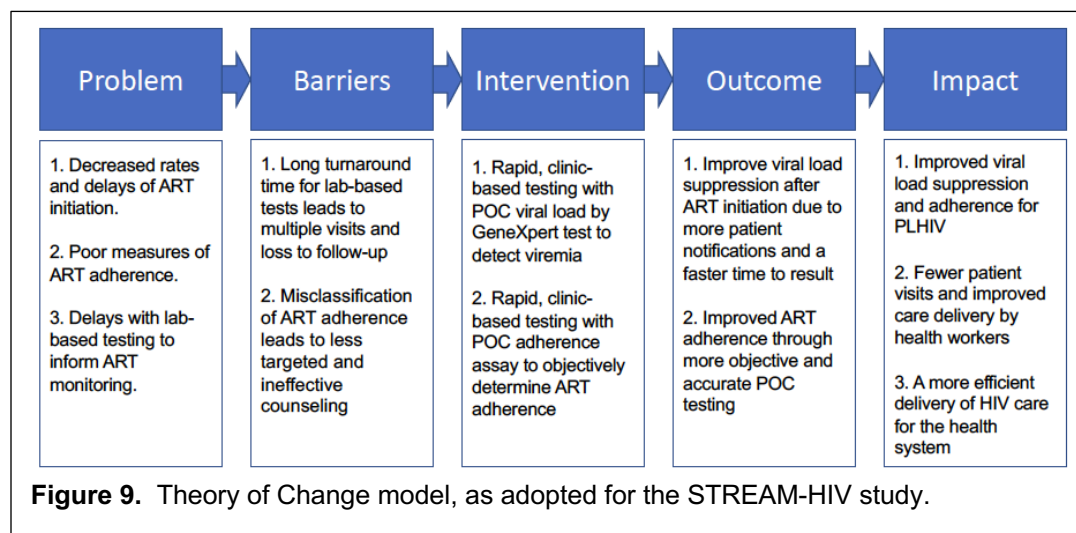
Dr. Jane M. Simoni (Co-Investigator), who will lead this study Aim, leads an acceptability research programs on new long-acting ART at UW (#AI120176)¹²⁷ and on Cell and Gene Therapy for HIV Cure (#AI126623)¹²⁸. She co-chairs the NIAID HIV/AIDS Network Coordination's Behavioral Science Consultative Group, which advises all the NIAID networks on behavioral science aspects of their research. She and Dr. Drain are colleagues at the UW Center for AIDS Research (CFAR) and have been collaborating on a pilot study of acceptability for POC adherence testing among key patient and provider populations in Seattle, US. Her ongoing work involves focus group discussions and key informant interviews for ART adherence and clinical studies to overcoming barriers to HIV care and ART initiation in several LMICs.

As part of preliminary qualitative work in the STREAM study, participants who received POC VL testing reported practical benefits of the intervention, including reducing the number of visits to the clinic and less need to take days off work. Healthcare workers also highlighted practical benefits for patients, but also expressed concerns about implementation of POC VL testing in

public sector clinics. We aim to further investigate barriers and facilitators to POC VL testing, and conduct a qualitative assessment of POC adherence testing.

9.3. Research Design

We will conduct a mixed-methods study based on the Theory of Change model (Figure 9). We will use a mix of process evaluations, semi-structured interviews and focus group discussions to collect information from PLHIV and use process evaluations and semi-structured interviews to collect information from health care workers on the implementation of a POC TFV adherence test and POC VL test and perspectives on appropriate use. At the clinic, we will collect detailed process evaluation information regarding number and timing of per-protocol POC tests requested from patients, urine samples provided, tests processed, results made available to providers, and results relayed to patients. These data will be collected by study personnel working on-site throughout the study duration. The team will scrutinize participant records and medical records and confer with providers to ensure accuracy of data. With a subset of study participants (PLHIV enrolled in Aim #1 in the intervention arm), we will complete a semi-structured interview after their six-month study visit and at/after their final (exit) visit administered by an interviewer who was not part of the clinical team. Two to four focus group discussions will also be conducted at these time points. For each healthcare worker, we will conduct two private in-depth interviews to explore key topics. These interviews will occur once all participants have completed the six-month study visit, as well as at the end of the trial, after the final results from the clinical trial are unblinded.



Study Populations: We will randomly select and recruit approximately 20 participants enrolled in the intervention arm of the main trial. The participants will be randomly selected and stratified by sex (1:1 female: male), age (1:1 ≤25 years: >25 years), and VL outcomes (1:1 suppressed: detectable) to ensure equal representation. For the healthcare workers, we will aim to enroll approximately 5-10 health care workers who provide care for participants in the main trial.

Table 3. Interview domains for PLHIV & providers.**Participant domains**

- comprehension of the clinic's routine testing and monitoring procedures
- understanding of the POC testing
- experiences with providing samples and receiving test results
- perspective of the impact of the testing on their encounters with providers—including any related communication around adherence
- impact the POC had on their self-report of adherence to their providers

Provider domains

- understanding of the POC procedures and protocols
- barriers to and facilitators of POC implementation
- approach to explaining POC and methods for requesting samples
- how results were typically relayed

Qualitative Domains and Topics: We will assess patient perspectives on their experience of POC testing with semi-structured interviews and focus group discussions at two time points (Table 3). Open-ended items will query their comprehension of the clinic's routine testing and monitoring procedures, their understanding of the POC testing specifically, their experiences with providing samples and receiving test results, their perspective of the impact of the testing on their encounters with providers - including any related communication around adherence, and what, if any, impact the POC testing had on their self-report of adherence to their providers. We will also be asking questions about whether POC results motivated increased adherence. The in-depth interviews with providers at two time points will cover the domains of understanding of the POC testing procedures and protocols, barriers to and facilitators of POC test implementation, approach to explaining POC test results and methods for requesting samples, how results were typically relayed, impact of results (if any) on timing and content of patient encounters.

Data Collection and Management: All semi-structured interviews and focus group discussions will be conducted in participants' language of choice and will be audio recorded. Each audio recording will be transcribed verbatim by a certified transcription service and will be verified by the research team to ensure accuracy. Transcripts that are completed in isiZulu will be translated to English and back-translated to isiZulu to verify accuracy of each translation. All audio recordings, original transcripts, and translated transcripts will be retained by the study team in accordance with the applicable record retention requirements.

9.4. Outcomes and Analyses

Data from the process evaluation will be summarized descriptively using counts and ranges. Notes from the semi-structured interviews as well as focus group discussion transcripts will be translated into English for analysis. The data will be analyzed with content analysis, using 'Framework'¹²⁹ and 'Interpretive description'.¹³⁰ Framework analysis involves indexing all verbatim text, charting information from each transcript onto a series of thematic matrices. Choice of thematic headings will be guided by core concepts emerging out of the data using an open coding approach and by theoretical concepts from the design.¹³¹ Specific topics will be designated as

core categories; axial coding and constant comparison will explore the relationships between emerging data and contextual situation.¹³⁰ Particular attention will be paid to documenting how latent or interpreted meanings are derived from text considering translation and context issues. Preliminary findings will be discussed with the research team, participants, and healthcare workers to validate our interpretations and enhance our understanding of the data.

10. SECONDARY COST-EFFECTIVENESS ANALYSIS

10.1. Introduction and Rationale

Our objectives are to estimate the costs of POC adherence testing and POC VL testing, and to project the budget impact and cost-effectiveness of implementing this intervention in South Africa. If our clinical intervention improves clinical outcomes at reasonable costs compared to the standard-of-care, then our conceptual model may be an efficient method of delivering HIV care in LMICs.

10.2. Preliminary Cost-effectiveness Studies

We have conducted micro-costing and cost-effectiveness analyses (CEAs) of several HIV prevention strategies in Africa, including HIV testing, linkage to ART, and PrEP.¹³³⁻¹³⁸ Using cost and clinical effectiveness data from our home-based HIV testing and linkage to care trials in KwaZulu-Natal,¹³⁹⁻¹⁴² we developed and parameterized an individual-based, stochastic HIV model that incorporates sexual behavior, concurrency, migration, sexually transmitted co-infections, and the HIV treatment cascade (including HIV testing and ART initiation/dropout). We utilized the model to simulate intervention health and economic outcomes. Incremental cost-effectiveness ratios (ICERs) were calculated by comparing the projected intervention impact relative to HIV services. Implementing home HIV testing in KwaZulu-Natal was projected to be cost effective by WHO standards across all ART initiation thresholds: US\$985 per disability adjusted life year (DALY) averted with ART initiation at CD4 count of ≤ 500 cells/ μ L.¹³⁶ Our research team has completed a preliminary micro-costing exercise as part of the pilot STREAM study and found the cost of POC VL testing was lower than centralized laboratory testing when assuming a clinic volume of at least 50 patients initiated on ART per month (Table 4).^{143,144} These collective analyses demonstrate our capacity to conduct rigorous evaluation of HIV treatment interventions, and to utilize mathematical models to calculate the economic impact for HIV programs.

Table 4. Per patient cost of VL testing in South Africa (US\$)

Test Costs	POC	Centralized Lab	
		Public	Private
HIV Viral Load			
Clinic Medical Consumables	0.41	0.48	0.48
Lab Consumables	0.11	24.72	33.41
Cartridge/Test	18.82		
Lab Staff Costs	0.33		
Equipment Costs	0.18		
Clinic Staff costs	0.44	1.55	1.55
Total Per Test	20.29	26.75	35.44

10.3. Research Design

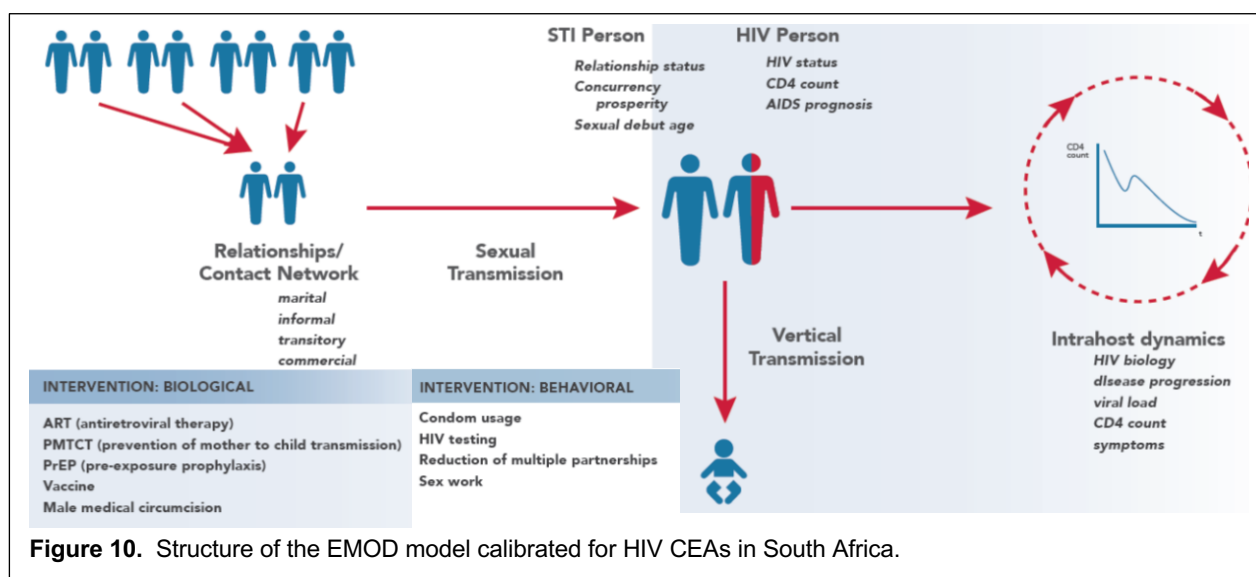
Costing: We will use activity-based micro-costing, staff interviews, and time and motion studies, to estimate the costs incurred and averted, along with the primary study outcomes to estimate the cost per PLHIV virally suppressed and retained in care in the Intervention and SoC arms. An experienced research assistant will conduct time and motion studies to estimate the nurse and clinician times necessary to complete the clinic visits for both the SoC and intervention arms, and to estimate average number of patients seen in the clinic each day. We will conduct time and motion studies during study initiation and again when the intervention is running at full capacity to explore the range of costs incurred during start up and at full efficiency. We will assess the time required to complete each step of the HIV care visit (adherence testing, VL testing, clinical assessment, counseling). Preliminary results will be shared with the teams to implement strategies for improved efficiency. Observing multiple visits by various staff members will allow estimation of the average time taken for each step; time needed for research activities (e.g. administering informed consent) will be removed from intervention time to provide an estimate of the intervention, if implemented as a government program.

We will collect intervention costs, as well as treatment costs averted as a result of the intervention. We will use standardized cost menus to collect site costs, including start-up costs, human resources, supplies, VL test costs, and other expenses. When data are not available from our cohort, we will utilize data from population-based South African studies. Additional cost data may be obtained from health facilities, published government information on labor costs, and health economics literature. Analyses will follow the guidelines for costing HIV interventions,¹⁴⁵ and will reflect the provider perspective. We will collect data on patient costs incurred in the intervention and control arms to explore the societal perspective; to demonstrate whether POC VL testing saves patients, and therefore society, time and expense.

Mathematical model: We will adapt a previously validated mathematical model of HIV transmission to project long-term intervention outcomes. We will use EMOD-HIV, an open-source agent-based network transmission model to project the cost and clinical impact of implementing this intervention in South Africa.^{146,147} We will work closely with Dr. Anna Bershteyn, who led the model's scientific development. EMOD includes geographic patterns of (1) age-specific demographics (fertility, mortality, migration); (2) a sexual network that reproduces age/sex specific patterns for different sexual relationships (marital, informal, transitory) (3) a detailed, user-configurable care continuum for HIV treatment interventions, including age, sex, heterogeneity in risky sexual behavior, and heterogeneities in access and retention in care (e.g., age and sex differences in diagnosis and linkage) (Figure 10).^{148,149} EMOD includes a detailed within-host model of HIV progression and treatment, allowing for modeling of the health and transmission benefits associated with ART.^{150,151} EMOD has been calibrated to predict health outcomes of HIV interventions in South Africa. EMOD has been shown to successfully predict HIV incidence found in the SEARCH trial and phylogenetic findings of HIV transmission in South Africa prior to availability of study results.^{152,153} The EMOD model is ideally suited to investigating the cost-

effectiveness of POC adherence and resistance testing, because of the flexible framework that allows for highly configurable interventions. We will program a novel POC testing intervention by adapting the current care cascade to allow for TFV adherence and VL testing. In addition, the EMOD model tracks costs associated with the intervention and SoC scenarios and projects HIV infections, HIV-related deaths, and DALYs. We will parameterize the model with empiric cost and effectiveness data from the proposed clinical trial.

Cost-effectiveness: We will calculate the ICERs as the ratio of the difference in mean costs divided by the difference in mean effects across simulations for the intervention compared to the standard-of-care over a 10-year time horizon. Consistent with guidelines for economic analyses, we will discount costs and health benefits at 3% annually, and consider ICERs that fall below South Africa's per capita GDP to be cost-effective, in line with WHO guidelines for CEAs.^{145,154}



10.4. Outcome Assessment and Reporting

The micro-costing data, time and motion studies, and clinical outcomes will be used to estimate the average cost per HIV-positive patient achieving VL suppression and retained in care in the integrated model for HIV monitoring, as compared to the SoC arm. Budget impact analysis will assess the overall costs incurred and averted by adding an intervention. The mathematical modeling will project clinical outcomes and estimate the cost-effectiveness of the intervention. These data are key to informing decision makers considering implementation of HIV adherence interventions.

11. PARTICIPANT REIMBURSEMENT

Study participants will be reimbursed as per CAPRISA Policy on Study Participant Compensation guidance, which adhere to the Department of Health and SAPHRA guidelines, and will consider

time of visits, inconvenience of study procedures, and transport expenses. The reimbursement will be stipulated in the consent form and will be collected after the participant has completed their study visit.

12. PROTECTION OF HUMAN SUBJECTS

12.1. Risks to Human Subjects

The proposed research project involves an intervention aimed to improve ART adherence among HIV-positive individuals. The intervention includes two POC tests that are not currently being used in South Africa as standard of care. The GeneXpert® by Cepheid HIV-1 VL test being used in this intervention was previously used in the STREAM pilot study and found no study-related adverse effects from the intervention. The Abbott POC urine TFV adherence assay has not yet been used as part of an intervention but is expected to be nonsignificant risk, as designated by the U.S. Food and Drug Administration (FDA). More details on the designation of the device's risk can be found in Section 4.2.

For the purposes of this study, only serious adverse events (SAEs), and adverse events perceived to be related to ART adherence testing will be documented. The severity of clinical symptoms will be scored using the DAIDS Table (July 2017 2.1 Version; <https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables>) for Grading the Severity of Adult and Pediatric AEs. Reporting on adverse events to the medical officer and relevant Institutional Review Boards will comply with relevant regulations.

This study also involves the collection of personal and clinical data, as well as biological specimens from human participants. The primary risk to the participants in this study will be from the collection of blood samples. Venipuncture and finger-prick have small risks of discomfort, persistent bleeding and/or bruising, and introducing an infection. Answering demographic and health-related questions have minimal risks to consenting participants. Participants in this setting have a high risk of being lost to follow-up with a known life-threatening infection. We will minimize this risk by having the research assistant contact the participants with any actionable test results. Furthermore, to assess mortality, we will obtain consent from participants to cross match the South African ID number with the South African death registry, and to search for the participants' laboratory results in the National Health Laboratory Service TrakCare system. Additional risks may be anxiety experienced due to TFV and VL testing and potential breach of participant confidentiality.

All participants will be ≥16 years of age, English or isiZulu speaking, and able to provide written, signed informed consent. Most of the participants in this study may be considered part of a vulnerable population. First, the vast majority of participants will be Zulu, which is one of 12 nationally recognized ethnic groups and an historically disadvantaged group in South Africa. Second, this project will be conducted in a low-income area of KwaZulu-Natal, where most people

live in dense, government-subsidized housing. All participants will be HIV-positive and may experience stigma if confidentiality around their HIV status is not maintained. Focus group participants may be at additional risk for a breach of confidentiality and social harm. Participation in the focus groups will be completely voluntary, and those who are asked to participate will be informed of the potential risks and counseled on these potential risks prior to enrollment in a focus group. Maintaining the protection of the data in this vulnerable population will be paramount to this project.

12.2. Adequacy of Protection Against Risks

The study related material will be approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee in Durban and University of Washington's Institutional Review Board in Seattle. All consent forms and participant education materials will be available in both English and isiZulu. To develop the isiZulu consent form, the English document was translated into isiZulu, and then back-translated by a different person. This process of back-translation of the isiZulu consent form helped ensure a satisfactory translation.

The Research Assistant/designee will approach adults and/or adolescents waiting for ART initiation in the clinics to explain the study and discuss the eligibility criteria. If the individual agrees to participate, the research assistant will read and review the consent form in English or isiZulu and ask the individual to summarize the study components. If the individual agrees to participate, he/she will be asked to sign a copy of the English or isiZulu consent form. Throughout this process, ethical norms that are standard to the study setting will be adhered to.

During the course of the study, confidentiality will be preserved, and the data will be maintained securely in the research office. The logbook containing the study identification numbers, completed consent forms, and completed data forms will remain on the premises and stored in locked cabinets. The online data will be stored in iDataFax, a password-protected data management service. All computers with access to the data will be password protected. All data will be analyzed using the participant's study identification number and not their identifiable information. The University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC), the University of Washington Institutional Review Board, study monitors, or study sponsors will retain the right to review participant records, excluding personal identifiers, to ensure the study is following the study protocol and international and local guidelines for human subjects research. Other local, U.S., and international regulatory entities may also review participants' study records.

There will be several mechanisms in place to minimize risk and ensure participant confidentiality and safety. First, research assistants will emphasize the voluntary nature of study participation and that any participant is free to withdraw from the study at any time and without impact to their routine medical care. Second, the study protocol, consent forms, and project materials will be reviewed and approved by the University of KwaZulu-Natal Medical Research Ethics Committee in Durban and the University of Washington Institutional Review Board in Seattle prior to

commencing the study or recruiting participants. Both ethics boards have a Federal-Wide Assurance number. In addition, the consent forms will be translated to isiZulu and back-translated to ensure accuracy. Third, data will be reviewed on a regular basis to make certain that the proposed research projects are not causing harm or adverse events. The Institutional Review Boards will be notified of any breaches in confidentiality, study protocol violations, or severe adverse events attributable to this study within 10 days of the event. Fourth, extensive training will be provided to both the research assistants and nurses regarding the study protocol, the consent form, the importance of maintaining participant confidentiality and safety. All study consent forms will be maintained in secure, locked cabinets at the study sites. Fifth, there will be regular communication between the study team and the clinic team in Durban, to ensure that we are not disrupting patient flow or treatment. Sixth, any potential breach of confidentiality will be minimized by conducting participant interviews in a private space, maintaining study data in a locked office, entering data onto a secure website, and ensuring that all research computers are password protected.

Several steps will be taken to minimize the clinical risks in the proposed research project. First, to minimize risks of discomfort, bleeding, and infection during blood draws, we will always use sterile needles and syringes, practicing good technique, and conducting the procedures in a designated space. Second, to mitigate the risks of anxiety related to receiving or coping with an HIV diagnosis, we have counselors at site, and are able to refer participants to social workers, if required.

12.3. Potential Benefits of the Proposed Research

This study will evaluate two novel POC tests that may improve HIV care for patients and healthcare workers in South Africa through real-time knowledge of ART adherence levels and VL. Participants in this study may benefit from learning their VL and recent ART adherence levels and receiving enhanced adherence counseling when needed during the same clinic visit in which their test is conducted. Healthcare workers may also benefit from receiving TFV and VL test results in real-time.

More broadly, the knowledge gained from the participants in this study will help inform medical practices and public health policies in other resource-limited settings. If the research findings support our hypotheses, then the relevant interventions could be a cost-effective method of monitoring HIV care and treatment.

12.4. Data Management and Safety Monitoring Plan

The data collection method that will be used is Electronic Data Capture (EDC) using DFdiscover (5.1.0, DF/Net, Seattle, USA). DFdiscover is a validated clinical database management system which is FDA CFR Part 11 compliant. Electronic Case Report Form (eCRF) data will reside on the DFdiscover server housed at CAPRISA Doris Duke Medical Research Institute and is backed

up at regular intervals by CAPRISA and securely stored at two locations, one at CAPRISA Doris Duke Medical Research Institute and the other at the UKZN Data Centre, Howard College, University of KwaZulu-Natal.

The electronic-CRF design will be guided by the study protocol with final approval by the study team. All study staff will be allocated user roles, specific to their function in the study. Database access will be restricted by passwords and validation levels. The study staff and statistician can access the database in “read-only” mode once data has been entered. The CAPRISA data management team will have write-access. All external electronic lab data must be password protected and will be imported into DFdiscover.

In the event of internet downtime, power outages, or any situation that makes the system inaccessible, one-ply paper CRFs will be used to collect the data, which will be scanned through to the CAPRISA data centre once the internet is active again. DFdiscover has optical character recognition (OCR) which will read the check boxes and numerical fields on the CRFs and store them in the study database. Any fields not recognized by the OCR system will be entered manually by data encoders. Data encoders will verify all data by cross-checking the scanned version to what is captured by OCR.

All queries and/or reasons for data changes will be generated electronically and will form part of the weekly QC Report that will be distributed to the appropriate study team members. Study staff also have the option of addressing any query at any time. Queries arising during validation of the data will be recorded in quality control (QC) reports sent to the sites on a regular basis. Any queries from scanned CRFs resulting in a change to the database must be documented on the original CRF and rescanned. QC rates will be communicated to the site on a monthly basis. Scheduled monthly downloads will be sent to the University of Washington study data manager in the SAS format. These downloads will also be made available on request.

Study staff who have access to the data on their computer systems will be trained on how to use the system and the importance of system security. Support will always be available from the data manager and IT department at CAPRISA, if any issues arise.

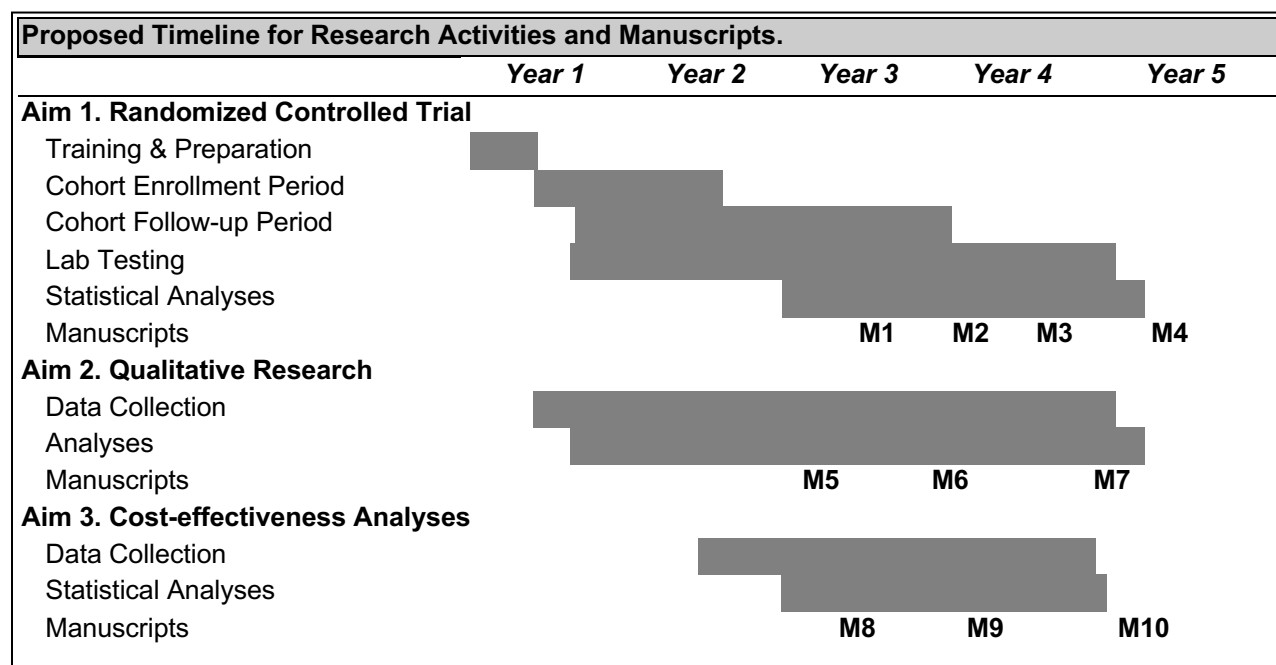
All CRFs and source documents are to be securely stored in the participant study file in a secure double-locked, fire resistant unit with restricted access in accordance with GCP requirements. Upon completion of the study, the close-out site monitoring visit and finalization of the database for analysis, any original forms will be bound and kept for long term storage. Study documentation and CRFs will not be destroyed without written permission from the sponsor.

Please note that after discussions with the NIH Program Officers, the establishment of a Data Safety Monitoring Board (DSMB) was not considered to be necessary for this proposed study; however, a Safety Monitoring Committee (SMC) will be established to monitor the study's

progress and participants' safety. The full Safety Monitoring Plan (SMP) is detailed elsewhere and will follow the guidelines established by the NIAID Division of AIDS (DAIDS) Safety Monitoring Committee Guidelines. NIAID will be responsible for the formation of the SMC, unless otherwise specified by the NIAID Program Officer, and the SMP will be approved by NIAID in writing before the study may be initiated.

13. TIMELINES

The proposed timeline for study-related activities and manuscripts can be found below. Of note, the actual timeline for research activities may deviate from the proposed timeline.



14. POTENTIAL PROBLEMS AND ALTERNATIVE APPROACHES

Study feasibility. In the pilot STREAM study, participants were recruited six months after ART initiation, and ~20 PLHIV were enrolled per week. In this proposed study, the aim is to enroll an average of 10.4 participants per week (10.4 PLHIV x 52 weeks = 540 participants), which may seem ambitious. However, from past experience at this high-volume clinic, enrolling and managing 2-3 PLHIV/day will be fully achievable with the requested resources.

Recruitment of HIV-infected participants. The CDC Clinic initiates around 2000 PLHIV on ART each year. However, if necessary, participants can be recruited from another HIV clinic or from CAPRISA's clinical research site in Vulindlela.

Burden for patients. POC Xpert® VL testing will be expedited upon participant arrival. If

participants are unable to wait two hours for their VL result, their permission will be sought to disclose the result over the phone.

Costing may not capture the true costs. Time and motion studies may distinguish research costs from programmatic costs, but efficiencies in a research study might differ from that achieved in public programs.

Mathematical modelling is subject to uncertainty. A well-calibrated and validated model will be utilized, and extensive uncertainty analyses will be performed to identify influential parameters.

15. RESOURCE SHARING PLAN

For all data generated during the course of this project, the prevailing standards and guidelines in documenting and depositing data sets will be followed.

Quality-controlled raw data, as well as processed data used in publications will be made available. As described in the grant application, protocols and workflows will be implemented exactly as described and documented such that other groups will be able to precisely reproduce results from the raw data.

The PIs, as well as other personnel assigned to the study, will disseminate results from this research through presentations at public lectures, scientific institutions and meetings, and/or publication in major journals. The institutions and PIs will adhere to the NIH Grants Policy on Sharing of Unique Research Resources including the Sharing of Biomedical Research Resources: Guidelines for Recipients of NIH Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources.

Data Sharing Plan

Intellectual property and data generated under this project will be administered in accordance with University of Washington, CAPRISA, and NIH policies, including the NIH Data Sharing Policy and Implementation Guidance of March 5, 2003. Materials generated under the project will be disseminated in accordance with University of Washington, CAPRISA and NIH policies. Depending on such policies, materials may be transferred to others under the terms of a material transfer agreement. Access to databases and associated software tools generated under the project will be available for educational, research, and non-profit purposes. Such access will be provided using web-based applications, as appropriate. Publication of data shall occur during the project, if appropriate, or at the end of the project, consistent with normal scientific practices. Research data that documents, supports, and validates research findings will be made available after the main findings from the final research data set have been accepted for publication. Such research data will be modified to prevent the disclosure of personal identifiers to remain in compliance with the Protection of Human Subjects guidelines.

Publications

We will disseminate the results from this research as broadly as possible. First, we will publish our results in Open Access journals, if appropriate. Second, we will post author PDFs of our manuscripts on our respective websites in accordance with the copyright rules of the journals. Third, we will practice posting our manuscripts on Internet archives (such as arxiv.org) when possible.

Presentations

We expect that the research personnel will attend national conferences periodically and present the results from this research to the scientific community. Because of the multidisciplinary nature of the work, different group members will present at various conferences, such as the Conference on Retrovirus and Opportunistic Infections, International AIDS Society, and South African HIV Clinicians conferences, which focus on the appropriate aspects of our research.

16. QUALITY CONTROL AND QUALITY ASSURANCE

The University of Washington's International Clinical Research Center and CAPRISA have a long track record of conducting quality research. This study will be monitored by the CAPRISA Quality Assurance Team, which will include six-monthly reports on study conduct findings. Particular attention will be placed on consent forms, adherence to the protocol, completion of source documents and CRFs, and appropriate and timely communication with the ethics committee, especially in the case of any protocol deviation. In addition, the study team will have weekly meetings to monitor study progress. CAPRISA routinely measures QC and retention rates on all studies.

17. ETHICAL CONSIDERATIONS

The study has been approved (IRB# STUDY00007544) by the University of Washington Institutional Review Board (FWA00006878). Ethical approval will also be sought from the University of KwaZulu-Natal's Biomedical Research Ethics Committee (BREC).

Collection and analyses of socio-demographic information and biological samples taken for clinical purposes will be covered by ethics approval. No investigational products will be utilized in this study and hence there is no requirement for regulatory approval from the South African Health Products Regulatory Authority. Informed consent will be obtained from potential participants to participate in the study and to store blood samples. A waiver for requiring parental consent for potential participants under age 18 was approved by the University of Washington Institutional Review Board and will be sought from University of KwaZulu-Natal's Biomedical Research Ethics Committee. Thus, potential participants aged 16-17 years will provide independent informed consent, and we will not require these participants to re-consent to the study at age 18. These

biological specimens will be handled by trained staff and labeled with a unique identifier for each participant. The results will be transmitted to the clinics in an electronic format but only accessed by authorized and trained clinic staff. Only key members of the data team will have access to the electronic data, which will be password protected. Once enrolled into the study, participants will be able to withdraw at any point.

18. PROTOCOL REGISTRATION

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol informed consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (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.

Site-specific informed consent forms (ICFs) WILL NOT be reviewed or approved by the DAIDS PRO, and sites will receive an Initial Registration Notification when the DAIDS PRO receives a complete registration packet. Receipt of an Initial Registration Notification indicates successful completion of the protocol registration process. Sites will not receive any additional notifications from the DAIDS PRO for the initial protocol registration. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) WILL NOT be reviewed and approved by the DAIDS PRO and 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.

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.

19. REFERENCES

1. World Health Organization. Antiretroviral therapy (ART) coverage among all age groups [Global Health Observatory (GHO) data]; Geneva, Switzerland: World Health Organization, 2015. Accessed at: https://www.who.int/gho/hiv/epidemic_response/ART_text/en/#.
2. UNAIDS. How AIDS changed everything. Geneva, UNAIDS, 2015. Accessed at: http://www.unaids.org/sites/default/files/media_asset/MDG6Report_en.pdf.
3. South African National AIDS Council (SANAC). The people living with HIV stigma index: South Africa 2014 - summary report; 2015 May.
4. Shisana O, Rehle T, Simbayi L, Zuma K, Jooste S, Zungu N, Labadarios D, Onoya D. South African national HIV prevalence, incidence and behaviour survey, 2012. Cape Town, South Africa: HSRC Press; 2014.
5. Reniers G, Blom S, Calvert C. Trends in the burden of HIV mortality after roll-out of antiretroviral therapy in KwaZulu-Natal, South Africa: an observational community cohort study. *Lancet HIV*. 2017;4(3):e113-e121. doi:10.1016/S2352-3018(16)30225-9.
6. Bor J, Herbst AJ, Newell M-L, Barnighausen T. Increases in adult life expectancy in rural South Africa: valuing the scale-up of HIV treatment. *Science*. 2013;339(6122):961-965. doi:10.1126/science.1230413.
7. UNAIDS. 90-90-90: An Ambitious Treatment Target to Help End the AIDS Epidemic; 2014. http://www.unaids.org/sites/default/files/media_asset/90-90-90_en.pdf.
8. World Health Organization. HIV drug resistance report 2017. Geneva, Switzerland: World Health Organization, 2017. Accessed at: <http://www.who.int/hiv/pub/drugresistance/hivdr-report-2017/en/>.
9. Beyrer C, Pozniak A. HIV Drug Resistance – an emerging threat to epidemic control. *N Engl J Med*. 2017; 377(17): 1605-7.
10. World Health Organization. Task shifting : Rational redistribution of tasks among health workforce teams : global recommendations and guidelines. Geneva, Switzerland: World Health Organization; 2008.
11. Grimsrud A, Kaplan R, Bekker LG, Myer L. Outcomes of a nurse-managed service for stable HIV-positive patients in a large South African public sector antiretroviral therapy programme. *Trop Med Int Health*. 2014;19(9):1029-39.
12. Sanne I, Orrell C, Fox MP, Conradie F, Ive P, Zeinecker J, Cornell M, Heiberg C, Ingram C, Panchia R, Rassool M, Gonin R, Stevens W, Truter H, Dehlinger M, van der Horst C, McIntyre J, Wood R. Nurse versus doctor management of HIV-infected patients receiving antiretroviral therapy (CIPRA-SA): a randomised non-inferiority trial. *Lancet*. 2010;376(9734):33-40. PMID: 3145152.
13. Sherr K, Pfeiffer J, Mussa A, Vio F, Gimbel S, Micek M, Gloyd S. The role of nonphysician clinicians in the rapid expansion of HIV care in Mozambique. *J Acquir Immune Defic Syndr*. 2009;52 Suppl 1:S20-3.
14. World Health Organization: Transition to new antiretrovirals in HIV programmes: Policy brief. Geneva, Switzerland: World Health Organization, 2016. Accessed at: <http://apps.who.int/iris/bitstream/10665/255888/1/WHO-HIV-2017.20-eng.pdf?ua=1>.
15. Human Sciences Research Council (HSRC). The Fifth South African National HIV Prevalence, Incidence, Behaviour and Communication Survey, 2017: HIV Impact Assessment Summary Report. Cape Town, 2018.

16. MacLeod W, Fraser N, Bor J. Analysis of age- and sex-specific HIV care cascades in South Africa suggests unequal progress towards UNAIDS 90-90-90 treatment targets. *J Int AIDS Soc.* 2016.
17. Joint United Programme on HIV/AIDS (UNAIDS). Miles to Go: Global AIDS Update 2018. Geneva, 2018. Accessed at: <http://www.unaids.org/en/resources/documents/2018/global-aids-update>.
18. Losina E, Bassett IV, Giddy J, Chetty S, Regan S, Walensky RP, Ross D, Scott CA, Uhler LM, Katz JN, Holst H, Freedberg KA. The "ART" of linkage: pre-treatment loss to care after HIV diagnosis at two PEPFAR sites in Durban, South Africa. *PLoS One.* 2010;5(3):e9538. PMID: 2832018.
19. Hamers RL, Schuurman R, Sigaloff KCE, Wallis CL, Kityo C, Siwale M. Effect of pretreatment HIV-1 drug resistance on immunological, viral, and drug-resistance outcomes of first-line antiretroviral treatment in sub-Saharan Africa: a multicentre cohort study. *Lancet Infect Dis* 2012; 12:307–17.
20. Manasa J, Lessells R, Rossouw T, Naidu K, van Vuuren C, Goedhals D, van Zyl G, Bester A, Skingsley A, Stott K, Danaviah S, Chetty T, Singh L, Moodley P, Iwuji C, McGrath N, Seebregts CJ, de Oliveira T. Southern African Treatment Resistance Network (SATuRN) RegaDB HIV Drug Resistance and Clinical Management Database: supporting patient management, surveillance and research in Africa. *Database (Oxford)* 2014; bat082. doi:10.1093/database/bat082. PMID: 5630899.
21. Manasa J, Lessells RJ, Skingsley A, Naidu KK, Newell ML, McGrath N, de Oliveira T. High levels of acquired drug resistance in adult patients failing first-line antiretroviral therapy in a rural HIV treatment programme in KwaZulu-Natal, South Africa. *PLoS One* 2013; 8(8): e72152. doi: 10.1371/journal.pone.0072152. PMID: 3749184.
22. Pillay S, Bland RM, Lessells RJ, Manasa J, de Oliveira T, Danaviah S. Drug resistance in children at viral failure in a rural KwaZulu-Natal, South Africa, cohort. *AIDS Res Ther* 2014; 11: 3. doi: 10.1186/1742-6405-11-3. PMID: 3922737.
23. Steegen K, Carmona S, Bronze M, Papathanasopoulos MA, van Zyl G, Goedhals D. Moderate levels of pretreatment HIV-1 antiretroviral drug resistance detected in the first South African National survey. *PLoS One* 2016; 11:e0166305
24. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd ed, 2016. Geneva, Switzerland: World Health Organization, 2016. Accessed at: <http://www.who.int/hiv/pub/arv/arv-2016/en/>.
25. PEPFAR. Botswana Country Operational Plan 2017: Strategic Direction Summary. March 2017. <https://www.pepfar.gov/documents/organization/272002.pdf>.
26. Venter WDF, Kaiser B, Pillay Y, Conradie F, Gomez GB, Clayden P. Cutting the cost of South African antiretroviral therapy using newer, safer drugs. *S Afr Med J* 2017; 107(1): 28-30.
27. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. 2017. Accessed at: <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>.
28. TIVICAY (dolutegravir) tablets, for oral use. Package Insert. ViiV Healthcare group of companies. Revised: June 2016.
29. Dorward J, Lessells R, Drain PK, Naidoo K, de Oliveira T, Pillay Y, Abdool Karim SS, Garrett N.

- Dolutegravir for first-line antiretroviral therapy in low-income and middle-income countries: uncertainties and opportunities for implementation and research. *Lancet HIV* 2018; 5: e400-e404.
30. Cavanaugh J. PEPFAR transition to tenofovir disoproxil fumarate/lamivudine/dolutegravir (TLD). Scientific Advisory Board presentation. November 2017.
 31. Walmsley SL, Antela A, Clumeck N, Duiculescu D, Eberhard A, Gutierrez F, Hocqueloux L, Maggiolo F, Sandkovsky U, Granier C, Pappa K, Wynne B, Min S, Nichols G and SINGLE Investigators. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N Engl J Med*. 2013; 369(19): 1807-18.
 32. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Accessed at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>.
 33. World Health Organization. Interim technical update: technical and operational considerations for implementing HIV viral load testing. Geneva, Switzerland: World Health Organization. July 2014.
 34. World Health Organization. Combined global demand forecasts for antiretroviral medicines and HIV diagnostics in low- and middle-income countries from 2015 to 2020. Geneva, Switzerland: World Health Organization. 2016.
 35. Peter T, Zeh C, Katz Z, et al. Scaling up HIV viral load - Lessons from the large-scale implementation of HIV early infant diagnosis and CD4 testing: *J Int AIDS Soc* 2017; 20: 9–15.
 36. Lecher S, Ellenberger D, Kim AA, et al. Scale-up of HIV Viral Load Monitoring — Seven Sub-Saharan African Countries. *MMWR Morb Mortal Wkly Rep* 2015; 64: 1287–90.
 37. Personal communication with Dr. Pravi Moodley, Director of Virology, National Health Laboratory Service, Albert Luthuli Memorial Hospital, Durban, South Africa.
 38. Drain PK, Violette L, Dorward J, Celum C, Garrett N. Point-of-care HIV viral load monitoring improved viral suppression and retention in South Africa: Results of a randomized controlled trial. Accepted to the Conference for Retroviruses and Opportunistic Infections, Seattle, 2019.
 39. Boyle DS, Hawkins KR, Steele MS, Singhal M, Cheng X. Emerging technologies for point-of-care CD4 T-lymphocyte counting. *Trends Biotechnol*. 2012;30(1):45-54. PMID: 3386801.
 40. Drain P, Hyle E, Noubary F, Freedberg K, Wilson D, Bishai W, Rodriguez W, Bassett I. Evaluating diagnostic point-of-care tests in resource-limited settings. *Lancet Infect Dis*. 2014;14(3):239-49.
 41. Peeling RW, Mabey D. Point-of-care tests for diagnosing infections in the developing world. *Clin Microbiol Infect*. 2010;16(8):1062-9.
 42. Schito M, Peter TF, Cavanaugh S, Piatek AS, Young GJ, Alexander H, Coggin W, Domingo GJ, Ellenberger D, Ermantraut E, Jani IV, Katamba A, Palamounain KM, Essajee S, Dowdy DW. Opportunities and challenges for cost-efficient implementation of new point-of-care diagnostics for HIV and tuberculosis. *J Infect Dis*. 2012;205 Suppl 2:S169-80. PMID: 3334507.
 43. Jani IV, Peter TF. How point-of-care testing could drive innovation in global health. *N Engl J Med*. 2013;368(24):2319-24.
 44. UNITAID. HIV/AIDS diagnostics technology landscape; semi-annual update 2015. Geneva, Switzerland: UNITAID; 2015.
 45. Drain PK, Dorward J, Garrett N. Point-of-care HIV viral load testing: An essential tool for a sustainable global HIV/AIDS response. *Clin Micro Reviews* (in press).
 46. Cepheid. Cepheid and FIND announce European approval of Xpert HIV-1 Viral Load. Quantitative test for rapid measurement of the HIV-1 viral load in plasma delivers individual results in about 90 minutes. Press release; 2014 [updated 2014; cited 2015 May 26]; Available

- from: <http://ir.cepheid.com/releasedetail.cfm?releaseid=888964>.
47. Boehme CC, Nabeta P, Hillemann D, Nicol MP, Shenai S, Krapp F, Allen J, Tahirli R, Blakemore R, Rustomjee R, Milovic A, Jones M, O'Brien SM, Persing DH, Ruesch-Gerdes S, Gotuzzo E, Rodrigues C, Alland D, Perkins MD. Rapid molecular detection of tuberculosis and rifampin resistance. *N Engl J Med*. 2010;363(11):1005-15. PMID: 2947799.
 48. Cepheid. Monitoring for quality of life, Xpert HIV-1 viral load [Product brochure]; 2015 [updated 2015; cited]; Available from: http://www.cepheid.com/administrator/components/com_productcatalog/library-files/fadd5b909331644ab1415fe39ec94dd5-Xpert-HIV-1-Viral-Load-Brochure-CEIVD-3039-03.pdf.
 49. World Health Organization. Global Tuberculosis Report. Geneva, Switzerland: World Health Organization, 2018. Accessed at: https://www.who.int/tb/publications/global_report/en/.
 50. Garrett NJ, Drain PK, Werner L, Samsunder N, Abdool Karim SS. Diagnostic accuracy of the point-of-care xpert HIV-1 viral load assay in a south african HIV clinic. *J Acquir Immune Defic Syndr* 2016; 72: e45–8.
 51. Nash M, Huddart S, Badar S, Baliga S, Saravu K, Pai M. Performance of the Xpert HIV-1 viral load assay: A systematic review and meta-analysis. *J Clin Microbiol* 2018; 56: 1–8.
 52. Goel N, Ritchie A V., Mtapuri-Zinyowera S, et al. Performance of the SAMBA I and II HIV-1 Semi-Q Tests for viral load monitoring at the point-of-care. *J Virol Methods* 2017; 244: 39–45.
 53. Jani I V., Meggi B, Vubil A, et al. Evaluation of the whole-blood alere q nat point-of-care RNA assay for HIV-1 viral load monitoring in a primary health care setting in Mozambique. *J Clin Microbiol* 2016; 54: 2104–8.
 54. World Health Organization. WHO prequalification of in vitro diagnostics. Product: Xpert® HIV-1 Viral Load with GeneXpert® Dx, GeneXpert® Infinity- 48, GeneXpert® Infinity-48s and GeneXpert® Infinity-80. Geneva, Switzerland: World Health Organization, 2017. Accessed at: http://www.who.int/diagnostics_laboratory/evaluations/pq-list/hiv-vrl/170720_final_pq_report_pqdx_0192_0193_0194_0195_070-00.pdf?ua=1.
 55. Dorward J, Garrett N, Quame-Amaglo J, Samsunder N, Ngobese H, Ngomane N, Moodley P, Mlisana K, Schaafsma T, Donnell D, Barnabas R, Naidoo K, Abdool Karim S, Celum C, Drain PK. 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 [original work]. doi: 10.1136/bmjopen-2017-017507. PMID: 5623564.
 56. Dorward J, Drain PK, Garrett N. Point-of-care viral load testing and differentiated HIV care. *Lancet HIV*. 2018;5:e8-9. doi: 10.1016/S2352-3018(17)30211-4.
 57. Heestermaans T, Browne JL, Aitken SC, Vervoort SC, Klipstein-Grobusch K. Determinants of adherence to antiretroviral therapy among HIV-positive adults in sub-Saharan Africa: a systematic review. *BMJ Glob Heal* 2016; 1: e000125.
 58. Shubber Z, Mills EJ, Nachega JB, et al. Patient-Reported Barriers to Adherence to Antiretroviral Therapy: A Systematic Review and Meta-Analysis. *PLoS Med* 2016; 13: e1002183.
 59. Lester RT, Ritvo P, Mills EJ, et al. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): A randomised trial. *Lancet* 2010; 376: 1838–45.
 60. Ferrand RA, Simms V, Dauya E, et al. The effect of community-based support for caregivers on the risk of virological failure in children and adolescents with HIV in Harare, Zimbabwe (ZENITH): an open-label, randomised controlled trial. *Lancet Child Adolesc Heal* 2017; 1: 175–83.

61. Bermudez LG, Ssewamala FM, Neilands TB, et al. Does Economic Strengthening Improve Viral Suppression Among Adolescents Living with HIV? Results From a Cluster Randomized Trial in Uganda. *AIDS Behav* 2018; 22: 3763–72.
62. KanTERS S, Park JJH, Chan K, et al. Interventions to improve adherence to antiretroviral therapy: a systematic review and network meta-analysis. *Lancet HIV* 2017; 4: e31–40.
63. Haberer JE. Actionable adherence monitoring to optimise intervention. *Lancet HIV* 2017; 4: e5–6.
64. Orrell C, 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. doi: 10.1186/s12981-017-0138-y.
65. Murphy RA, Court R, Maartens G, Sunpath H. Second-line antiretroviral therapy in sub-Saharan Africa: It's time to mind the gaps. *AIDS Res Hum Retroviruses* 2017; 00: AID.2017.0134.
66. 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.
67. Cressey TR, Siriprakaisil O, Klinbuayaem V, Quame-Amaglo J, Kubiak RW, Suktrakanchana P, Than-in-at K, Baeten J, Sirirungsi W, Cressey R, Drain PK. A randomized clinical pharmacokinetic trial of tenofovir in blood, plasma and urine in adults with perfect, moderate and low PrEP adherence: The TARGET Study. *BMC Infect Dis*. 2017;17:496. doi: 10.1186/s12879-017-2593-4.
68. Gandhi M, Bacchetti P, Spinelli MA, Okochi H, Baeten JM, Siriprakaisil O, Klinbuayaem V, Rodrigues WC, Wang W, Vincent M, Cressey TR, Drain PK. Validation of a Urine Tenofovir Immunoassay for Adherence Monitoring to PrEP and ART and Establishing the Cut-Off for a Point-of-Care Test. *J AIDS* 2019 (in press).
69. Gandhi M, Bacchetti P, Rodrigues WC, Spinelli M, Koss CA, Drain PK, Baeten JM, Mugo NR, Ngure K, Benet LZ, Okochi H, Wang G, Vincent M. Development and Validation of an Immunoassay for Tenofovir in Urine as a Real-Time Metric of Antiretroviral Adherence. *EClinical Medicine*. 2018.
70. Spinelli MA, Glidden DV, Rodrigues W, Wang G, Vincent M, Okochi H, Kuncze K, Mehrotra M, Defechereux P, Buchbinder SP, Grant RM, Gandhi M. Low tenofovir level in urine by a novel immunoassay is associated with seroconversion in a PrEP demonstration project. *AIDS* 2019 (in press).
71. Ford N, Mills EJ. Simplified ART delivery models are needed for the next phase of scale up. *PLoS Med*. 2011;8(7):e1001060.
72. Faal M, Naidoo N, Glencross DK, Venter WD, Osih R. Providing immediate CD4 count results at HIV testing improves ART initiation. *J Acquir Immune Defic Syndr*. 2011;58(3):e54-9.
73. Jani IV, Siteo NE, Alfai ER, Chongo PL, Quevedo JI, Rocha BM, Lehe JD, Peter TF. Effect of point-of-care CD4 cell count tests on retention of patients and rates of antiretroviral therapy initiation in primary health clinics: an observational cohort study. *Lancet*. 2011;378(9802):1572-9.
74. Sigaloff KC, Hamers RL, Wallis CL, Kityo C, Siwale M, Ive P, Botes ME, Mandaliya K, Wellington M, Osibogun A, Stevens WS, van Vugt M, de Wit TF. Unnecessary antiretroviral treatment switches and accumulation of HIV resistance mutations; two arguments for viral load monitoring in Africa. *J Acquir Immune Defic Syndr*. 2011;58(1):23-31.
75. Lessells RJ, Avalos A, de Oliveira T. Implementing HIV-1 genotypic resistance testing in antiretroviral therapy programs in Africa: needs, opportunities, and challenges. *AIDS Rev* 2013; 15: 221-9.

76. Lessells RJ, Stott KE, Manasa J, Naidu KK, Skingsley A, Rossouw T, de Oliveira T. Implementing antiretroviral resistance testing in a primary health care HIV treatment programme in rural KwaZulu-Natal, South Africa: early experiences, achievements and challenges. *BMC Health Serv Res* 2014; 14: 116.
77. Drain PK, Garrett NJ. The arrival of a true point-of-care molecular assay—ready for global implementation? *Lancet Glob Heal*. 2015;3(11):e663-e664. doi:10.1016/S2214-109X(15)00186-2.
78. Drain PK, Hyle EP, Noubary F, Freedberg KA, Wilson D, Bishai WR, et al. Diagnostic point-of-care tests in resource-limited settings. *Lancet Infect Dis*. 2014;14(3):239-49.
79. Drain PK, Losina E, Coleman SM, Giddy J, Ross D, Katz JN, Bassett IV. Value of urine lipoarabinomannan grade and second test for optimizing clinic-based screening for HIV-associated pulmonary tuberculosis. *J Acquir Immun Defic Syndr*. 2015;68:274-80. doi: 10.1097/QAI.0000000000000436. PMID: 4326555.
80. Drain PK, Mayeza L, Bartman P, Hurtado R, Moodley P, Varghese S, Maartens G, Alvarez GG, Wilson D. Diagnostic accuracy and clinical role of rapid C-reactive protein testing in HIV-infected individuals with presumed tuberculosis in South Africa. *Int J Tuber Lung Dis*. 2014;18:20-27.
81. Drain PK, Kleene JM, Coleman SM, Losina E, Katz JN, Giddy J, Ross D, Freedberg KA, Bassett IV. Prevalence of cryptococcal antigenuria at initial HIV diagnosis in KwaZulu-Natal. *HIV Med*. 2015;16: 640-4.
82. Drain PK, Losina E, Coleman SM, Giddy J, Ross D, Katz JN, Walensky RP, Freedberg KA, Bassett IV. Diagnostic accuracy of a point-of-care urine test for tuberculosis screening among newly-diagnosed HIV-infected adults: a prospective, clinic-based study. *BMC Infect Dis*. 2014;14:110.
83. Drain PK, Gounder L, Grobler A, Sahid F, Bassett IV, Moosa MYS. Urine lipoarabinomannan to monitor antituberculosis therapy response and predict mortality in an HIV-endemic region: a prospective cohort study. *BMJ Open*. 2015;5:e006833.
84. Cohen GM, Drain PK, Noubary F, Cloete C, Bassett IV. Diagnostic delays and clinical decision making with centralized Xpert MTB/RIF testing in Durban, South Africa. *J Acquir Immun Defic Syndr*. 2014;67:e88-93.
85. Gandhi M, Bacchetti P, Rodrigues WC, Spinelli M, Koss CA, Drain PK, Baeten JM, Mugo NR, Ngure K, Benet LZ, Okochi H, Wang G, Vincent M. Development and validation of an immunoassay for tenofovir in urine as a real-time metric of antiretroviral adherence. *Lancet E Clin Med*. 2019 (in press).
86. Gandhi M, Ofokotun O, Bacchetti P, Jin C, Ribaudo H, Haas DW, Sheth AN, Horng H, Phung N, Kuncze K, Okochi R, Landovitz RJ, Lennox J, Currier JS; AIDS Clinical Trials Group (ACTG) 5257 Study Team. Antiretroviral concentrations in hair strongly predict virologic response in a large HIV treatment-naïve clinical trial. *Clinical Infectious Diseases* 2018 Sept 3 doi: 10.1093/cid/ciy764 [Epub ahead of print].
87. Koss CA, Natureeba P, Mwesigwa J, Cohan D, Nzarubara B, Bacchetti P, Horng H, Clark TD, Plenty A, Ruel TD, Achan J, Charlebois ED, Kamya MR, Havlir DV, Gandhi M. Hair Concentrations of Antiretrovirals Predict Viral Suppression in HIV-Infected Pregnant and Breastfeeding Ugandan Women. *AIDS* 2015 Apr 29(7): 825-830 PMID: PMC4438773
88. Gandhi M, Ameli N, Bacchetti P, et al. Atazanavir Concentrations in Hair Samples are the Strongest Predictor of Outcomes in HIV Infection. *Clinical Infectious Diseases* 2011 May 15; 52(10): 1267-1275.
89. Koss CA, Hosek SG, Bacchetti P, Anderson PL, Liu AY, Horng H, Benet LZ, Kuncze K, Saberi P,

- Wilson CM, Gandhi M. Comparison of measures of adherence to HIV preexposure prophylaxis among adolescent and young men who have sex with men in the United States. *Clinical Infectious Diseases* 2017 Aug 24.
90. Koss CA, Bacchetti P, Hillier SL, Livant E, Horng H, Mgodini N, Mirembe BG, Gomez Feliciano K, Horn S, Liu AY, Glidden DV, Grant RM, Benet LZ, Louie A, van der Straten A, Chirenje MZ, Marrazzo JM, Gandhi M. Differences in Cumulative Exposure and Adherence to Tenofovir in the VOICE, iPrEx OLE, and PrEP Demo Studies as Determined via Hair Concentrations. *AIDS Research and Human Retroviruses*. 2017 March 2. doi: 10.1089/aid.2016.0202.
 91. Gandhi M, Murnane PM, Bacchetti, Elion R, Kolber MA, Cohen SE, Horng H, Louie A, Kuncze K, Koss CA, Anderson PL, Buchbinder S, Liu A. Hair Levels of PrEP Drugs Measure Adherence and are Associated with Renal Decline Among Men/Transwomen in an Open Label PrEP Study. *AIDS* 2017 Oct 23;31(16):2245-2251. PMCID: PMC5633521
 92. Gandhi M, Glidden V, Mayer K, Schechter M, Buchbinder S, Grinsztejn B, Hosek S, Casapia M, Guanira J, Bekker L-G, Louie A, Horng H, Benet LZ, Liu A, Grant RM. Age, baseline kidney function, and medication exposure are associated with declines in creatinine clearance on PrEP: an observational cohort study. *Lancet HIV*. 2016 Nov;3(11):e521-e528. PMCID: PMC5085869
 93. Marquard, JL, Saver B, Kandaswamy S, Martinez VI, Simoni JM, Stekler JD, Ganesan D, Scanlan J. Designing a wrist-worn sensor to improve medication adherence: accommodating diverse user behaviors and technology preferences. *JAMA Open*, 1(2), 2018, 153-8.
 94. Simoni JM, Huh D, Frick PA, Pearson CR, Andrasik MP, Dunbar PJ, Hooton T. A randomized controlled trial of peer support and pager messaging to promote antiretroviral therapy adherence and clinical outcomes. *Journal of Acquired Immune Deficiency Syndromes* 2009; 52, 465-473. PMCID: PMC2795576.
 95. Odeny TA, Bailey RC, Bukusi EA, Simoni JM, Tapia KA, Yuhas K, Holmes KK, McClelland RS. Text messaging to improve attendance at post-operative clinic visits after adult male circumcision for HIV prevention: a randomized controlled trial. *PLoS One*. 2012;7(9):e43832. PMCID: PMC3434192.
 96. Horvath KJ, Danilenko GP, Williams ML, Simoni J, Amico KR, Oakes JM, Rosser BRS. Technology use and reasons to participate in social networking health websites among people living with HIV in the US. *AIDS and Behavior*, 2012; 16(4), 900–910. PMCID: PMC3454490.
 97. Simoni JM, Huh D, Frick PA, Pearson CR, Andrasik MP, Dunbar PJ, Hooton T. Peer support and pager messaging to promote antiretroviral modifying therapy in Seattle: A randomized controlled trial. *Journal of Acquired Immune Deficiency Syndromes*, 2009; 52(4), 465-473. PMCID: PMC2795576
 98. Simoni JM, Wiebe JS, Saucedo JA, Huh D, Sanchez G, Longoria V. A preliminary RCT of CBT-AD for adherence and depression among HIV-positive Latinos on the U.S.-Mexico border: The Nuevo Día study. *AIDS and Behavior*, 2013; 17(8), 2816–2829. PMCID: PMC3788062
 99. Simoni JM, Chen WT, Huh D, Fredriksen-Goldsen KI, Pearson C, Zhao H, Shiu CS, Wang X, Zhang F. A preliminary randomized controlled trial of a nurse-delivered medication adherence intervention among antiretroviral therapy-naïve outpatients in Beijing, China. *AIDS Behavior*, 2011; 15(5), 919-29. PMCID: PMC3583199
 100. Simoni JM, Pantalone DW, Plummer MD, Huang B. A randomized controlled trial of a peer support intervention targeting antiretroviral adherence and depressive symptomatology among HIV-positive men and women. *Health Psychology*, 2007; 26(4), 488-495. PMCID: PMC4044097
 101. Simoni JM, Pearson CR, Pantalone DW, Marks G, Crepaz N. Efficacy of interventions in

- improving highly active antiretroviral therapy adherence and HIV-1 RNA viral load: A meta-analytic review of randomized controlled trials. *Journal of Acquired Immuno-Deficiency Syndrome* 2006; 43, S23-S35. PMID: PMC4044045
102. Simoni JM, Kurth AE, Pearson CR, Pantalone DW, Frick PA, Merrill JO. Self-report measures of antiretroviral therapy adherence: A review with recommendations for HIV clinical management. *AIDS and Behavior*, 2006; 10(3), 227-45. PMID: PMC16783535
 103. Simoni JS, Amico KR, Pearson, CR, Malow RM. Strategies for promoting adherence to antiretroviral therapy: A Review of the literature. *Current Infectious Disease Reports*, 2008; 10, 515-521. PMID: PMC18945394
 104. Thompson MA, Mugavero MJ, Amico KR, Cargill VA, Chang LW, Gross R, Orrell C, Altice FL, Bangsberg DR, Bartlett JG, Beckwith CG, Dowshen N, Gordon CM, Horn T, Kumar P, Scott JD, Stirratt MJ, Remien RH, Simoni JM, & Nachega JB. (2012). Guidelines for improving entry into and retention in care and antiretroviral adherence for persons with HIV: evidence-based recommendations from an International Association of Physicians in AIDS Care panel. *Annals of Internal Medicine*, 156(11), 817–33. PMID: PMC4044043
 105. Barnabas RV, van Rooyen H, Tumwesigye E. Uptake of antiretroviral therapy and male circumcision after community-based HIV testing and strategies for linkage to care versus standard clinic referral: a multisite, open-label, randomised controlled trial in South Africa and Uganda. *Lancet HIV*. 2016;3:e212-20. doi: 10.1016/S2352-3018(16)00020-5. PMID: 4852382.
 106. Barnabas RV, van Rooyen H, Tumwesigye E. Initiation of antiretroviral therapy and viral suppression after home HIV testing and counselling in KwaZulu-Natal, South Africa, and Mbarara district, Uganda: a prospective, observational intervention study. *Lancet HIV*. 2014;1:e68-e76. doi: 10.1016/S2352-3018(14)70024-4. PMID: 4292844.
 107. Ying R, Sharma M, Celum C, Baeten JM, van Rooyen H, Hughes JP, Garnett G, Barnabas RV. Home HIV testing and counselling to reduce HIV incidence in a generalised epidemic setting: a mathematical modeling analysis. *Lancet HIV*. 2016;3:e275-82 [original work]. doi: 10.1016/S2352-3018(16)30009-1. PMID: 4927306.
 108. van Rooyen H, Barnabas RV, Baeten JM, et al. High HIV testing uptake and linkage to care in a novel program of home-based HIV counseling and testing with facilitated referral in KwaZulu-Natal, South Africa. *J Acquir Immune Defic Syndr*. 2013;64:e1-e8. doi: 10.1097/QAI.0b013e31829b567d. PMID: 3744613.
 109. Ying R, Sharma M, Heffron R, Celum C, Baeten JM, Katabira E, Bulya N, Barnabas RV. Cost-effectiveness of pre-exposure prophylaxis targeted to high-risk serodiscordant couples as a bridge to sustained ART use in Kampala, Uganda. *J Int AIDS Soc*. 2015;18:20013. doi: 10.7448/IAS.18.4.20013. PCMID: 4509901.
 110. Celum C, Baeten JM, Hughes JP, Barnabas R, et al. Integrated strategies for combination HIV prevention: principles and examples for men who have sex with men in the Americas and heterosexual African populations. *J Acquir Immune Defic Syndr*. 2013;63:S213-20 [review]. PMID: 3708491.
 111. Hallett TB, Baeten JM, Heffron R, Barnabas R, et al. Optimal uses of antiretrovirals for prevention in hiv-1 serodiscordant heterosexual couples in South Africa: a modelling study. *PLoS Med*. 2011; 8:e1001123. doi: 10.1371/journal.pmed.1001123. PMID: 3217021.
 112. Barnabas RV, Revill P, Tan N, Phillips A. Cost-effectiveness of routine viral load monitoring in low- and middle-income countries: A systematic review. *J Int AIDS Soc*. 2017;20:50-61 [original work]. doi: 10.1002/jia2.25006.

113. Cressey TR, Avihingsanon A, Halue G, Leenasirimakul P, Sukrakanchana PO, Tawon Y, Jaisieng N, Jourdain G, Podany AT, Fletcher CV, Klinbuayaem V, Bowonwatanuwong C. Plasma and Intracellular Pharmacokinetics of Tenofovir Disoproxil Fumarate 300 mg Every 48 Hours vs 150 mg Once Daily in HIV-Infected Adults With Moderate Renal Function Impairment. *Clin Infect Dis* 2015;15;61(4):633-9.
114. Carballo-Diéguez A, Balán IC, Brown W III, Giguere R, Dolezal C, Leu C-S, et al. (2017) High levels of adherence to a rectal microbicide gel and to oral Pre-Exposure Prophylaxis (PrEP) achieved in MTN-017 among men who have sex with men (MSM) and transgender women. *PLoS ONE* 12(7): e0181607.
115. Garrett N. Assessment of the Xpert® HIV-1 point-of-care viral load assay in an HIV care setting. South African AIDS Conference; June 11; Durban, South Africa: 2015. Oral Presentation.
116. Nash M, Huddart S, Badar S, Baliga S, Saravu K, Paia M. Performance of the xpert HIV-1 viral load assay: A systematic review and meta-analysis. *J Clin Microbiol* 2018; 56: 1–8.
117. South African HIV guidelines. South African Department of Health, Pretoria, 2018.
118. de Oliveira T, Kharsany ABM, Graf T, Cawood C, Khanyile D, Grobler A, Puren A, Madurai S, Baxter C, Abdool Karim Q, Abdool Karim SS. Transmission networks and risk of HIV infection in KwaZulu-Natal, South Africa: a community-wide phylogenetic study. *Lancet HIV* 2017; 4(1): e41-e50.
119. Pillay D, Herbeck J, Cohen MS, de Oliveira T, Fraser C, Ratmann O, Brown AL, Kellam P, PANGAEA-HIV Consortium. PANGAEA-HIV: phylogenetics for generalized epidemics in Africa. *Lancet Infect Dis* 2015; 15(3): 259-261.
120. Vilsker M, Moosa Y , Nooij S, Fonseca V , Gheysens Y , Dumon K, Pauwels R, Alcantara LC, Eynden EW, Vandamme A-M, Deforche K, de Oliveira T. Genome Detective: An Accurate, Fast and Automated System for Virus Identification from High-throughput next generation sequencing (NGS) data. *Bioinformatics* 2018; bty695.
121. Barnighausen T, Chaiyachati K, Chimbindi N, Peoples A, Haberer J, Newell ML. Interventions to increase antiretroviral adherence in sub-Saharan Africa: a systematic review of evaluation studies. *Lancet Infect Dis*. 2011;11(12):942-51.
122. Mwai GW, Mburu G, Torpey K, Frost P, Ford N, Seeley J. Role and outcomes of community health workers in HIV care in sub-Saharan Africa: a systematic review. *Journal of the International AIDS Society*. 2013;16(1).
123. Theron G, Zijenah L, Chanda D, Clowes P, Rachow A, Lesosky M, Bara W, Mungofa S, Pai M, Hoelscher M, Dowdy D, Pym A, Mwaba P, Mason P, Peter J, Dheda K. Feasibility, accuracy, and clinical effect of point-of-care Xpert MTB/RIF testing for tuberculosis in primary-care settings in Africa: a multicentre, randomised, controlled trial. *Lancet*. 2014;383(9915):424-35. Epub 2013/11/02.
124. Gous N, Scott L, Potgieter J, Ntabeni L, Enslin S, Newman R, Stevens W. Feasibility of performing multiple point of care testing for HIV anti-retroviral treatment initiation and monitoring from multiple or single fingersticks. *PloS one*. 2013;8(12):e85265. Epub 2014/01/01.
125. World Health Organization. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva: World Health Organization, 2011.
126. The TEMPRANO ANRS 12136 Study Group; A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. *The New England Journal of Medicine* 2015.
127. Simoni JM, Beima-Sofie K, Mohamed ZH, Christodoulou J, Tapia K, Graham SM, Ho R, Collier

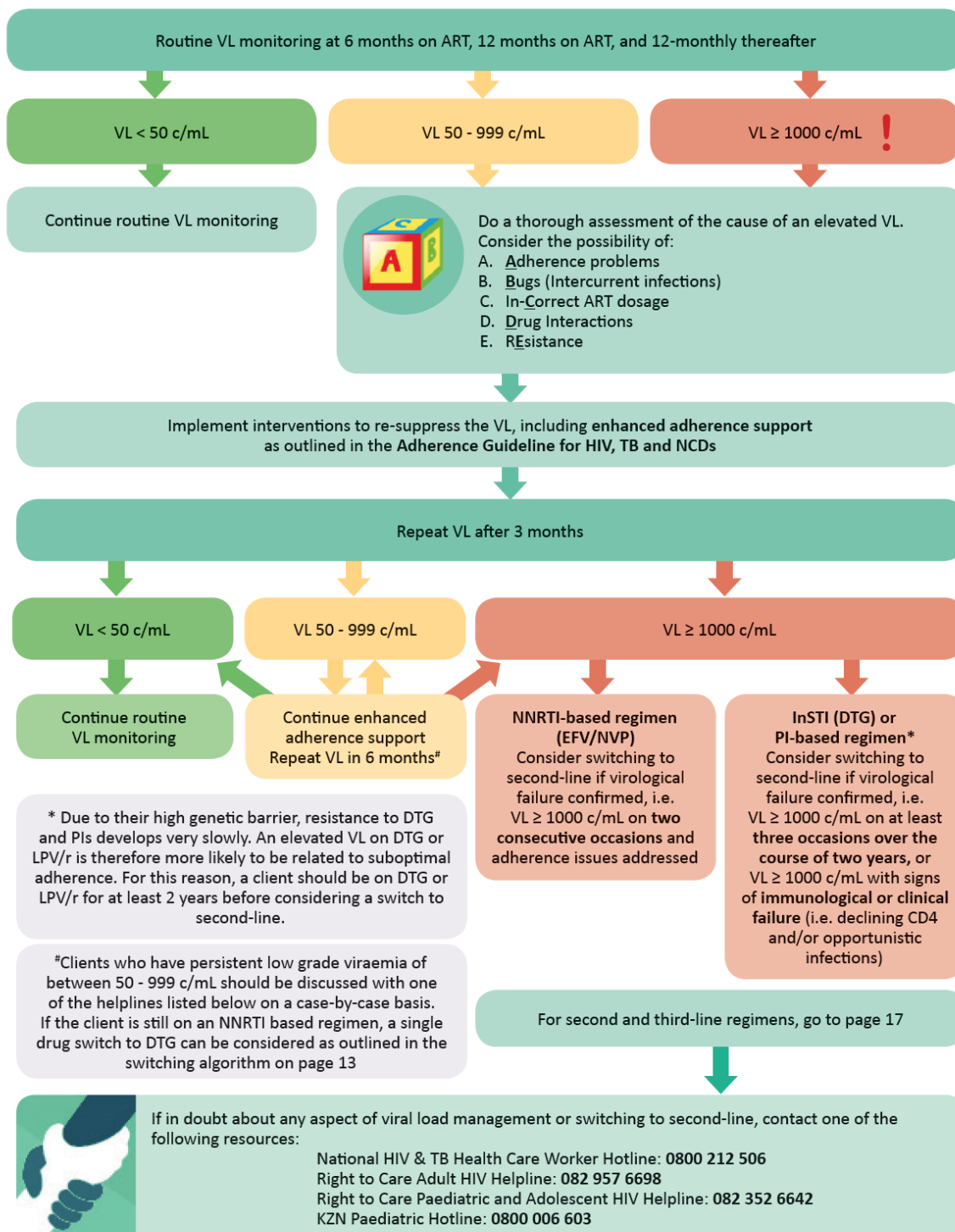
- AC. Long-acting injectable ART acceptability and preferences: A qualitative study among U.S. providers, adults living with HIV, and parents of youth living with HIV. *AIDS Patient Care and STDs*, 2018 (in press).
128. Simoni JM, Sylla L, Louella M, Patel H, Luter S, Collier AC, Dubé K. Acceptability of Cell and Gene Therapies for Curing HIV: A Qualitative Investigation among Persons Living with HIV (PLWH) in the Northwestern United States. Poster presentation at 2018 NIH-sponsored workshop on HIV Cure, October 2018, Washington, D.C., USA.
 129. Richie J, Spencer L, eds. *Analyzing Qualitative Data*. London: Routledge; 1994.
 130. Thorne S. *Interpretive Description*. Vol 2. Walnut Creek, Ca: Left Coast Press, Inc.; 2008.
 131. Creswell J. *Qualitative Inquiry & Research Design: Choosing Among Five Approaches*. Second Edition ed. Thousand Oaks: Sage Publications; 2007.
 132. Barnabas RV, Revill P, Tan N, Phillips A. Cost-effectiveness of routine viral load monitoring in low- and middle-income countries: A systematic review. *J Int AIDS Soc* 2017; 20: 50–61.
 133. Hallett TB, Baeten JM, Heffron R, Barnabas R, de Bruyn G, Cremin I, et al. Optimal uses of antiretrovirals for prevention in HIV-1 serodiscordant heterosexual couples in South Africa: a modelling study. *PLoS Medicine* 2011; 8(11):e1001123.
 134. Abu-Raddad LJ, Barnabas RV, Janes H, Weiss HA, Kublin JG, Longini IM, Jr., et al. Have the explosive HIV epidemics in sub-Saharan Africa been driven by higher community viral load? *Aids* 2013; 27(6):981-989
 135. Barnabas R, Ying R, van Rooyen H, Murnane P, Hughes J, Baeten J. Use of HIV viral-load suppression to estimate the effect of community-wide home-based HIV counselling and testing and linkage to antiretroviral therapy on HIV incidence in South Africa: a mathematical modelling analysis. *Lancet* 2013; 382:S6
 136. Smith JA, Sharma M, Levin C, Baeten JM, van Rooyen H, Celum C, et al. Cost-effectiveness of community-based strategies to strengthen the continuum of HIV care in rural South Africa: a health economic modelling analysis. *The Lancet HIV* 2015; 2(4):e159-e168.
 137. Sharma M, Smith JA, Farquhar C, Ying R, Cherutich P, Golden M, Wamuti B, Bukusi D, Spiegel H, Barnabas RV. Assisted partner notification services are cost-effective for decreasing HIV burden in western Kenya. *AIDS*. 2018 Jan 14;32(2):233-241.
 138. Sharma M, Ying R, Farquhar C, Krakowiak D, Kinuthia J, Osoti A, Asila V, Gone A, Mark J, Barnabas R. Modeling the Cost-Effectiveness of Home-Based HIV Testing and Education (HOPE) for Pregnant Women and Their Male Partners in Nyanza Province, Kenya. *J Acquir Immune Defic Syndr*. 2016 Aug 1;72 Suppl 2:S174-80
 139. Barnabas RV, van Rooyen H, Tumwesigye E, Murnane PM, Baeten JM, Humphries H, et al. Initiation of antiretroviral therapy and viral suppression after home HIV testing and counselling in KwaZulu-Natal, South Africa, and Mbarara district, Uganda: a prospective, observational intervention study. *The lancet HIV* 2014; 1(2):e68-e76.
 140. van Rooyen H, Barnabas RV, Baeten JM, Phakathi Z, Joseph P, Krows M, et al. High HIV testing uptake and linkage to care in a novel program of home-based HIV counseling and testing with facilitated referral in KwaZulu-Natal, South Africa. *Journal of acquired immune deficiency syndromes* 2013; 64(1):e1-8.
 141. Sharma M, van Rooyen H, Celum C, Baeten J, Levin C, Barnabas R. The cost of community based HIV counseling and testing and linkage to care in rural South Africa: Estimates from the Linkages randomized control trial. In: *HIV Research for Prevention (HIV R4P) Meeting*. Cape Town, South Africa; 2014. pp. Abstract P09.17 LB.

142. Golovaty I, Sharma M, Van Heerden A, van Rooyen H, Baeten JM, Celum C, Barnabas RV. Cost of integrating non-communicable disease screening into home-based HIV testing and counseling in South Africa. *JAIDS*. 2018 May 10.
143. Simeon K, Dorward J, Garrett N, Barbabas R, Drain P. Cost of point-of-care test monitoring for HIV positive patients on antiretroviral therapy. 9th Annual CUGH Global Health Conference, New York, New York, USA, March 15-18, 2018. Abstract Fri_01.12.
144. Stime, KJ, Garrett N, Yuktेशwar S., Dorward J, Dlamini N, Olowolagba A, Sharma M, Barnabas R, Drain P. Clinic flow for STI, HIV, and TB patients in an urban infectious disease clinic offering point-of-care testing services in Durban, South Africa. *BMC Health Serv Res*. 2018 May 11;18(1):363.
145. UNAIDS. Costing Guidelines for HIV Prevention Strategies. . In. Geneva: UNAIDS; 2000 World Health Organization. HIV drug resistance report 2017. Accessed from: http://data.unaids.org/publications/irc-pub05/jc412-costguidel_en.pdf.
146. Bershteyn A, Gerardin J, Bridenbecker D, Lorton CW, Bloedow J, Baker RS, Chabot-Couture G, Chen Y, Fischle T, Frey K, Gauld JS, Hu H, Izzo AS, Klein DJ, Lukacevic D, McCarthy KA, Miller JC, Ouedraogo AL, Perkins TA, Steinkraus J, ten Bosch QA, Ting H-F, Titova S, Wagner BG, Welkhoff PA, Wenger EA, Wiswell CN. Implementation and applications of EMOD, an individual-based multi-disease modeling platform. *Pathog Dis* [Internet]. 2018 Jul 1 [cited 2018 Nov 30];76(5).
147. Bershteyn A, Klein DJ, Wenger E, Eckhoff PA. Description of the EMOD-HIV Model v0. 7. *ArXiv Prepr ArXiv12063720*. 2012.
148. Bershteyn A, Mutai KK, Akullian AN, Klein DJ, Jewell BL, Mwalili SM. The influence of mobility among high-risk populations on HIV transmission in Western Kenya. *Infect Dis Model*. 2018 Jan 1;3:97–106.
149. Klein DJ, Bershteyn A, Eckhoff PA. Dropout and re-enrollment: implications for epidemiological projections of treatment programs. *AIDS*. 2014;28:S47–S59.
150. Eaton JW, Menzies NA, Stover J, Cambiano V, Chindelevitch L, Cori A, Hontelez JA, Humair S, Kerr CC, Klein DJ. Health benefits, costs, and cost-effectiveness of earlier eligibility for adult antiretroviral therapy and expanded treatment coverage: a combined analysis of 12 mathematical models. *Lancet Glob Health*. 2014;2(1):e23–e34.
151. Bershteyn A, Klein D, Oishi K, Eckhoff P. Where to strengthen care: model-based triangulation of trends in the HIV care cascade [Internet]. Oral Presentation presented at: 8th IAS Conference on HIV Pathogenesis; 2015 Jul 21; Vancouver, BC. Available from: <http://www.ias2015.org/>
152. Jewell BL, Bershteyn A. Predicting HIV Incidence in the SEARCH Trial: A Mathematical Modelling Study. *bioRxiv*. 2018 Jul 25;376244.
153. de Oliveira T, Kharsany ABM, Gräf T, Cawood C, Khanyile D, Grobler A, Puren A, Madurai S, Baxter C, Karim QA, Karim SSA. Transmission networks and risk of HIV infection in KwaZulu-Natal, South Africa: a community-wide phylogenetic study. *Lancet HIV*. 2017 Jan 1;4(1):e41–e50
154. World Health Organization. WHO Guide to Cost-Effectiveness Analysis. Geneva, Switzerland, World Health Organization, 2018. Accessed from: https://www.who.int/choice/publications/p_2003_generalised_cea.pdf on 12/9/2018.
155. Fox MP, Pascoe SJ, Huber A, et al. Assessing the impact of the National Department of Health's National Adherence Guidelines for Chronic Diseases in South Africa using routinely collected data: a cluster-randomised evaluation. *BMJ Open* 2018; 8: e019680.
156. Fox MP, Pascoe SJS, Huber AN, et al. Effectiveness of interventions for unstable patients on

- antiretroviral therapy in South Africa: results of a cluster-randomised evaluation. *Trop Med Int Health* 2018; 23(12): 1314-1325.
157. Hermans LE, Tempelman HA, Carmona S, et al. High rates of viral resuppression on first-line ART after initial virological failure. CROI 2018 [abstract 1118].

20. APPENDIX I: 2019 SOUTH AFRICA HIV VIRAL LOAD MONITORING GUIDELINES


Management of Viral Load Results in Infants, Children, Adolescents and Adults




Second-Line (2L) and Third-Line (3L) ART Regimens

If in doubt about any aspect of switching to second-line, contact one of the helplines provided on page 16

Second-line ART Regimens for Adults with Confirmed Virological Failure

	First-Line Regimens				Second-Line Regimens	
	NNRTI-based Regimen		InSTI-based Regimen for > 2 years		PI-based Regimen for > 2 years	
Regimen	TDF + 3TC/FTC + EFV/NVP		TDF + 3TC/FTC + DTG		AZT/TDF + 3TC/FTC + LPV/r or ATV/r	
Resistance Testing	Resistance test <u>not</u> required		Resistance testing may be required under expert consultation ⁵		Resistance test required	
Resistance Test results	Not applicable		Not applicable		No PI resistance	PI resistance
HBV Co-infection Status ¹	HBV-negative	HBV-positive	HBV-negative	HBV-positive	HBV-positive or -negative	
New Regimen	AZT + 3TC/FTC + DTG ²	TDF ¹ + AZT + 3TC/FTC + DTG ²	AZT + 3TC/FTC + LPV/r	TDF + 3TC/FTC + LPV/r ⁴	Continue current regimen and address adherence. If intolerance to LPV/r is affecting adherence, discuss possible substitutions with an expert	Refer to Third-Line Committee. Regimen will be determined by results of resistance test
	If DTG not suitable ² , AZT + 3TC/FTC + LPV/r	If DTG not suitable ² , TDF + 3TC + LPV/r ⁴				

Second and Third-line ART Regimens for Children and Adolescents with Confirmed Virological Failure

	NNRTI-based Regimen		PI-based Regimen for > 2 years		InSTI-based Regimen for > 2 years	
	ABC/AZT/TDF + 3TC/FTC + EFV/NVP		ABC/AZT/TDF + 3TC/FTC + LPV/r or ATV/r		ABC/AZT/TDF + 3TC/FTC + DTG	
Resistance Testing	Resistance test not required		Resistance test required		Resistance test required	
Resistance Test Results	Not applicable		No PI resistance	PI resistance (or genotype unsuccessful)	No InSTI resistance	InSTI resistance
Weight	< 20 kg	≥ 20 kg	< 20 kg	≥ 20 kg	All	All children/adolescents on DTG will be ≥ 20 kg
New Regimen or Other Action Required	ABC/AZT + 3TC + LPV/r ⁴	2 NRTIs + DTG ² In consultation with an expert, ensure that at least 1 NRTI is active ³	Continue current regimen and address adherence	2 NRTIs + DTG ² In consultation with an expert, ensure that at least 1 NRTI is active ³	Refer to Third-line committee	2 NRTIs + DTG ² In consultation with an expert, ensure that at least 1 NRTI is active ³
		If NRTI activity cannot be confirmed, expert will recommend 2 NRTIs + PI/r		If NRTI activity cannot be confirmed, expert will recommend 2 NRTIs + PI/r. Adherence must be addressed		If NRTI activity cannot be confirmed, refer to Third-line committee

¹ Always check hepatitis B status before stopping TDF. If client has chronic hepatitis B, stopping TDF may lead to a severe hepatitis flare. If hepatitis B-positive, TDF should be continued in the second-line regimen.

² Prior to DTG initiation, all women and adolescent girls of childbearing potential must be appropriately counseled on the potential risk of NTDs with DTG use around conception time and provided with contraceptives as desired (see "Dolutegravir" on page 8).

³ From the DAWNING study, DTG was shown to achieve viral suppression when used in combination with two NRTIs, at least one of which was fully active (Aboud M et al., IAS Oral abstract, 2017). It is as yet unknown if DTG will work if combined with two NRTIs, neither of which are fully active.

⁴ In the EARNST study, LPV/r was shown to be effective even if combined with two NRTIs that are known to have genotypic resistance (Paton, et al., N Engl J Med, 2014). For this reason, AZT is omitted from LPV/r-containing regimens when TDF is continued due to HBV co-infection. Resistant NRTIs may be recycled with an active PI if no other feasible options are available.

⁵ Resistance testing in clients failing DTG may be authorised by an expert on a case-by-case basis.

21. APPENDIX II: SCHEDULE OF EVALUATIONS

STREAM HIV Schedule of Evaluations (Version 2.3 14 September 2020)																
Evaluations	Sample	Visit														
		1	2	3	4	5	6	7	8	9	10	11	12	13		
		Screening	Enrollment	W4	W8	W12	W16	W20	W24	W32	W40	W48	W56	W64	W72	
		Target Visit Window														
		0	W3-6	W7-10	W11-14	W15-18	W19-22	W22-28	W30-34	W38-42	W46-50	W54-58	W62-66	W68-84		
Informed consent		x														
Locator information		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Socio-demographics questionnaire		x														x
Eligibility assessment		x														
Baseline HIV and ART assessment			x													
Medical history			x													
WHO Staging			x													
TB symptom screen			x	x	x	x	x	x	x	x	x	x	x	x	x	
Substance use questions			x					x								x
WHO Intimate partner violence tool [§]			x					x								x
Mental health assessment tool (PHQ-9)			x					x								x
IPT assessment			x													
ART adherence and counselling			x	x	x	x	x	x	x	x	x	x	x	x	x	
ART side effect assessment				x	x	x	x	x	x	x	x	x	x	x	x	
CCMDD assessment											x	x	x	x		
Semi-structured interview~								x								x
Focus group discussion~								x								x
Clinical																
Vital signs assessment			x	x	x	x	x	x	x	x	x	x	x	x	x	
Comprehensive physical exam			x													x
Symptom directed physical exam				x	x	x	x	x	x	x	x	x	x	x		
Department of Health Routine Testing																
Haemoglobin	EDTA (4mls)		x													
Creatinine	SST (5mls)		x			x			x			x				
CD4 count [#]	EDTA (4mls)		x									x				
Hep B surface antigen	SST (5mls)		x													
Pregnancy Test [§]	Urine		x													
Cervical smear [§]	Cytobrush/smear		x													
Laboratory Viral load (SOC arm)	EDTA (4mls)							x			x					
Study specific Testing																
POC Viral load (intervention arm)	EDTA (4mls)							x			x					
Tenofovir Adherence Test (Intervention arm)	Urine			x	x	x	x	x	x*			x*				
HIV Incidence Test (Sedia) [§]	Whole blood		x													
Genexpert HPV testing [§]	Vaginal swab		x													
ART resistance testing (intervention arm)	EDTA (4mls)							x^			x^					
Storage																
VL and resistance testing* &	EDTA (10mls)		x					x								x
Plasma HIV incidence test (plasma)			x													
Tenofovir diphosphate levels (dry blood spots)	EDTA (4mls)					x		x			x					x
Short-term tenofovir adherence testing	Urine					x		x			x					x
Longterm tenofovir adherence testing	Hair							x								x
Total blood volume (mls)			28			9		27			21					14
Key:																
[§] female participants only																
[#] can be POC in intervention arm																
[*] only if viraemic >200 copies/ml																
[§] test not used for clinical management, and not provided to participant																
[^] only if viraemic >200 copies/ml and detectable tenofovir levels																
~ only for subset of participants																
^{&} VL will be retrospectively tested on stored specimens for primary outcome measure for all participants																