Point-of-care viral load testing to enable streamlined care and task shifting for chronic HIV care

The "STREAM Study"

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1. STUDY SUMMARY

Effective management of patients on antiretroviral therapy (ART) is essential to improve clinical outcomes and prevent HIV transmission, but monitoring life-long ART for over 15 million HIV-infected people has become a challenge, particularly in low- and middle-income countries (LMICs). As programs continue to focus on identifying HIV-infected people and starting ART at higher CD4 thresholds, HIV providers have been overburdened, which has resulted in falling retention rates. In addition, laboratories have been working to implement HIV viral load (VL) testing since the World Health Organization's recommendation to move away from routine CD4 count monitoring [WHO, HIV guidelines 2013]. As ART coverage scales up to include millions more people, additional strain will be placed on HIV clinicians and laboratories to manage stable patients on chronic ART. Implementing point-of-care HIV VL testing to enable task shifting to nurses for chronic HIV care may help mitigate these burdens.

Point-of-care VL testing is intended to differentiate patients who are potentially failing on their ART, so that they can be referred to the next level of care for possible ART regiment change, from patients who are virally suppressed on ART and can be managed by nurses. We have recently demonstrated the feasibility and accuracy of the rapid Xpert® HIV-1 Quant (Cepheid) VL assay in an urban South African HIV clinic. However, evidence for a combined implementation of point-of-care HIV VL testing and task shifting among healthcare workers as a novel and effective strategy for managing chronic HIV care in LMICs is needed. Our scientific objective is to test the clinical equivalence and reduced cost of implementing a model for chronic HIV care that uses a point-of-care HIV VL assay to enable streamlined care and task shifting among healthcare workers at an urban clinic in South Africa.

Our central hypothesis is that rapid HIV VL testing, implemented by nurses, is an effective and cost-efficient strategy for management of chronic HIV infection in the majority of patients, thereby allowing more resources to be directed at the minority of patients who need greater attention. We plan to objectively test our central hypothesis by pursuing the following two specific aims: (1) to test the clinical equivalence of an implementation model for chronic HIV care using point-of-care HIV VL testing to enable streamlined care and task shifting in an urban South African clinic, and (2) to assess the costs, both incurred and averted, of implementing the proposed model in Aim #1, and the cost per HIV-positive person virally suppressed on ART and retained in care.

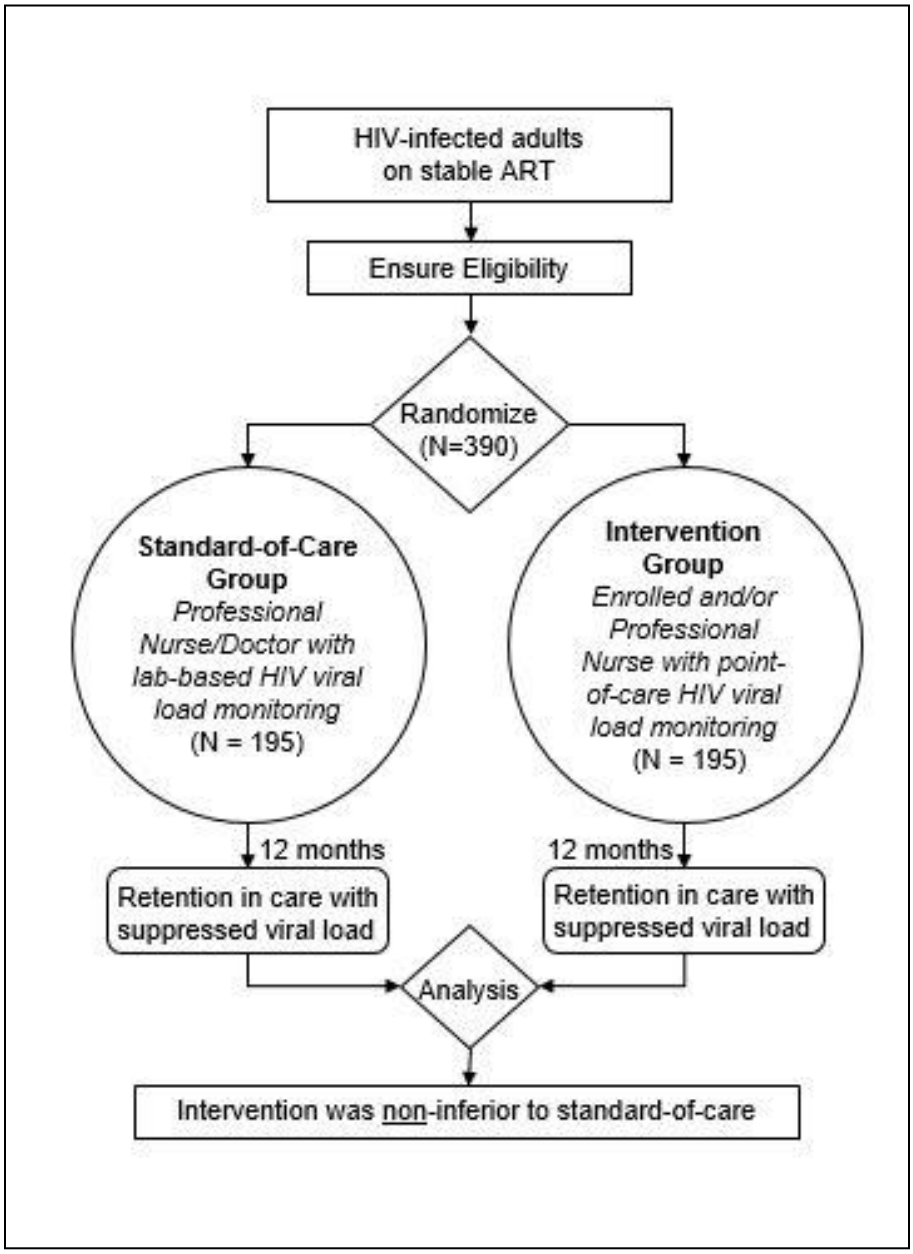
This work is innovative because it uses a randomized evaluation of an implementation model that combines a novel diagnostic point-of-care test with streamlined care and task shifting among healthcare workers compared to standard of care for chronic HIV care in a resource-limited setting. This randomized trial will then form the basis of a larger, multicountry proposal to demonstrate the clinical equivalence and cost-effectiveness of implementing an integrated point-of-care HIV VL testing and streamlined care model for chronic HIV care in LMICs. If nurses using clinic-based HIV VL testing are cost-effective for achieving both viral suppression and retention in care among patients on ART, then implementation of our chronic HIV care model would alleviate the strain on existing HIV providers and laboratories in LMICs.

POC Viral Load Study - SCHEMA

Purpose:	To test the clinical equivalence and reduced cost of implementing a model for chronic HIV care that uses a point-of-care HIV VL assay to enable streamlined care and task shifting among healthcare workers at an urban clinic in South Africa.
Design:	A Phase II randomized single-site controlled trial to assess point-of-care HIV VL assay to enable streamlined care and task shifting among healthcare workers. HIV-infected adults (≥18 years) on chronic ART will be randomized 1:1 to receive POC HIV viral load monitoring by anurse versus standard-of-care lab-based HIV viral load monitoring by a professional nurse or physician.
Population:	HIV-infected adults (≥18 years) on chronic ART regimen.
Study Size:	195 in each arm, for 390 total participants.
POC Testing:	GeneXpert® by Cepheid with the Xpert® HIV-1 VL cartridge.
Outcome Measurement:	The primary outcome for this study will be a composite measure of HIV VL suppression and retention in care at the end of a 12-month study period. Viral load suppression will be defined as HIV VL <200 copies/mL by the lab-based Roche Taqman v.2.0 assay; retention in care will be defined as collecting ART at the study exit visit.
Study Duration:	24 months, including submissions to Institutional Review Boards (IRBs), enrollment period, and 12 months of follow-up per participant.
Primary Objective:	• To test the clinical equivalence of an implementation model for chronic HIV care using point-of-care HIV VL testing to enable streamlined task shifting in an urban South African clinic
Secondary Objectives:	• To assess the costs, both incurred and averted, of implementing the proposed model in Aim #1, and the cost per HIV-positive person virally suppressed on ART and retained in care. • To determine the HIV genotype resistance pattern among HIV-infected adults who develop viremia on chronic ART. • To determine risk factors for poor retention in care or virological failure after chronic ART suppression. • To determine the incidence of virological failure among HIV-infected adults receiving antiretroviral therapy at the clinical site. • To demonstrate that a Nurse with a point-of-care HIV VL assay will minimize the costs per HIV-positive client virally suppressed and retained in care compared to the standard-of-care (Physician or Professional Nurse with a laboratory-based HIV VL assay) in this urban clinic. • To validate the GeneXpert HIV VL test against a laboratory-based HIV viral load gold standard. • To measure the time to patients receiving results among clinic-based and laboratory-based HIV viral load testing. • To compare the number of patients in the intervention versus standard of care arms who are appropriately entered into the Central Chronic Medicine Dispensing and Distribution Programme (CCMDD) at 12 months

	• To compare among patients in the intervention versus standard of care arms the time to appropriate entry into the Central Chronic Medicine Dispensing and Distribution Programme (CCMDD).
Study Site:	HIV clinic at the Prince Cyril Zulu Communicable Disease Centre, which is located adjacent to the CAPRISA eThekwini Clinical Research Site and near the transport hub for public commuters in central Durban.

POC Viral Load Study – STUDY DESIGN



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1. *To Be Determined*
2. *To Be Determined*

Research Assistants:

1. *To Be Determined*
2. *To Be Determined*

NHLS Laboratory:

Dr. Rogerio Phili
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CAPRISA Laboratory Manager (Specimen Transport):

Mrs. Natasha Samsunder

3. BACKGROUND

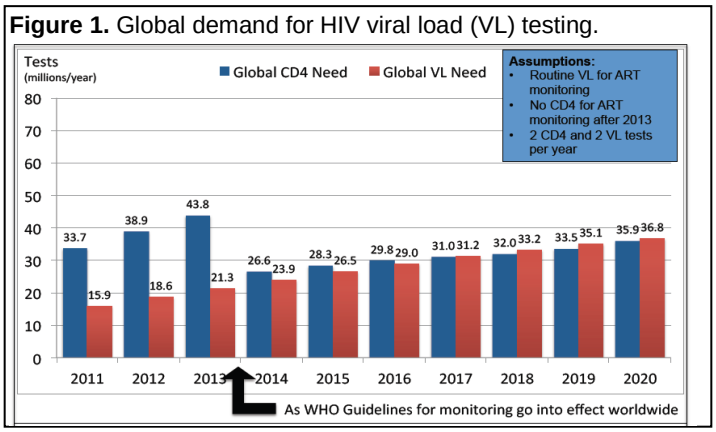
3.1. SIGNIFICANCE

Currently, 15 million people living with HIV, mostly in low- and middle-income countries (LMICs), are receiving antiretroviral therapy (ART).[1,2] The World Health Organization (WHO) recently recommended ART for all HIV-infected adults, regardless of CD4 count, which makes nearly 20 million additional people eligible to start ART.[3] As more people initiate ART, the need for an effective model of chronic HIV care will intensify. Models of care need to focus on maintaining viral suppression and improving retention in care, while not increasing the burden to HIV providers and laboratories.

The global challenge of monitoring chronic ART

Common methods of monitoring patients on chronic ART in LMICs—assessing clinical symptoms and/or CD4 count—are poor correlates of treatment failure, and have led to unnecessary switching of ART regimens.[4-6] In 2013, the WHO recommended routine HIV viral load (VL) testing, as a more effective way of monitoring patients on ART.[7] Several countries, including South Africa, have adopted HIV VL testing, which is projected to surpass CD4 testing by 2017 **(Figure 1)**. However, implementing routine HIV VL testing requires access to high-quality reference laboratories, which are not readily available throughout LMICs.

Figure 1. Global demand for HIV viral load (VL) testing.



Overburdened HIV clinicians and laboratories

South Africa has 6.4 million HIV-infected people and 2.5 million are receiving ART, making it the largest HIV program in the world.[8] Despite these efforts, only 42% of ART-eligible South African adults over 15 years of age are receiving ART.[8,9] South Africa's continuing high HIV incidence has also increased pressure to rapidly expand treatment availability.[10] Perhaps unsurprisingly, national data indicates that clinics are already overburdened, which has resulted in poor retention in care. Among those initiated on ART, >25% were lost to follow-up by 1 year, and <50% had a recorded 12-month VL.[8] In Durban, 25% of patients initiating ART were lost to follow-up, and only 39% of ART-eligible patients were started on ART within one year.[11] For the shift to HIV VL monitoring, just 5 laboratories are currently tasked with processing all VL tests for the KwaZulu-Natal province, involving over 10,000 VLs to be collected, transported, processed, and returned to various clinics each month. This strain on HIV clinicians and laboratories has detracted resources from identifying new patients, initiating more people on ART, and appropriately switching patients with treatment failure to second-line ART regimens. Aware of this problem, the WHO has called for operational research on the cost, impact, and sustainability of routine VL monitoring, with an emphasis on point-of-care testing to facilitate task shifting and decentralized care.[7]

Designing models of chronic ART management in LMICs

UNAIDS recently launched the 90-90-90 project to achieve the following goals by the year 2020: (1) identify 90% of all HIV-infected people, (2) initiate 90% of all HIV-infected people on ART, and (3) maintain viral suppression among 90% of all people receiving ART.[12] To reach these targets, coordinated efforts are required to diagnose HIV-infected people and initiate ART, but also to provide ongoing care for those already on ART and virally suppressed. Existing models of chronic HIV care were implemented when patients initiating ART had lower CD4 counts and were often symptomatic. Evidence suggests that task shifting to nurses can generate outcomes that are similar (i.e. non-inferior) to ART management by physicians or professional nurses,[13,14] and endorsed by the WHO.[15] However, a study in Cape Town showed that 'down referral' of chronic ART patients to a different site can lead to higher loss to follow-up rates.[16] Therefore, implementing a chronic HIV care model that utilizes an integrated approach of both healthcare workers and HIV VL testing efficiently, while ensuring quality care, will be essential. More recently, South Africa has begun implementing Central Chronic Medicine Dispensing and Distribution (CCMDD). In this model, patients on ART for >12 months, with a suppressed viral load are stepped down to 6 monthly clinic visits. At these visits 6 months of ART and other chronic medication is prescribed, which patients then collect in 1-2 month instalments from community pharmacies. Laboratory based VL monitoring is performed annually, which requires one clinic visit to draw blood, and another visit to collect the result. If suppressed, a further 6 months prescription is issued. POC VL monitoring has the potential to reduce the number of clinic visits and therefore streamline both the safe enrolment and effective monitoring of patients in CCMDD.

3.2. INNOVATION

Evaluating a conceptual model of task shifting for chronic ART management

Based on our clinical experience and existing literature, we have developed a conceptual model for chronic ART management in LMICs **(Figure 2)**. Our conceptual model separates 'intensive HIV care', which we define as periods when patients are symptomatic or not virally suppressed, from 'chronic HIV care' of patients who have been stable on an ART regimen for at least 6 months or had a recent (<3 month) undetectable viral load. The care model includes nurse-led POC VL monitoring to guide the enrolment and monitoring of chronic patients into the CCMDD model. The step-down into CCMDD in our model is also more gradual than in the current standard of care, with an intermediate phase of nurse led monitoring over 6 months prior to entering CCMDD. This will be performed by Registered Nurses (Enrolled Nurses in South Africa; Table 1) for the most stable patients, and Professional Nurses for all other patients. Our model maximizes the skills and training of Enrolled Nurses, who are capable of assessing symptoms/signs, obtaining blood samples, and operating a point-of-care device. Rapid VL results will ensure VL testing takes place, to allow for same-day decision-making and eliminate the need for patient recalls, all of which may improve retention in care.[17-19] Enrolled Nurses will direct patients with symptoms or a high HIV VL for more intensive ART management.

Figure 2. Conceptual model of the Chronic Care Pathway to be evaluated.

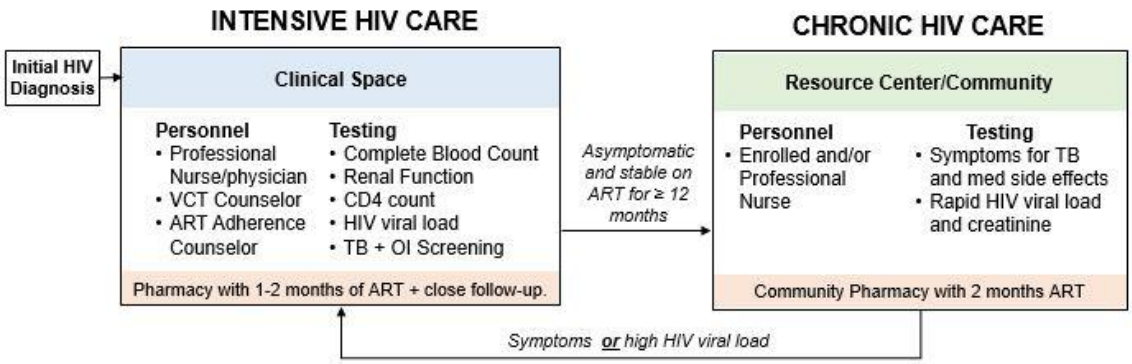


Table 1. Comparable healthcare workers (degree/title)

United States		South Africa
Physician (MD)	=	Clinician (MBChB)
Nurse Practitioner (NP)	=	Professional Nurse
Registered Nurse (RN)	=	Enrolled Nurse
Nurse Assistant (NA)	=	Enrolled Nurse Assistant

Implementing a point-of-care HIV viral load assay

Diagnostic point-of-care tests have rapidly emerged and are expanding into LMICs.[20-24] Within the last year, 3 point-of-care HIV VL products have become available, and another 9 products are expected soon.[25] The GeneXpert® by Cepheid is a fully automated molecular assay that can be used by health workers at the clinical point of care **(Figure 3)**.[26] South Africa (with support from PEPFAR and USAID) widely implemented this testing system in laboratories and health clinics for diagnosing tuberculosis. By September 2014, over 3,500 GeneXpert® instruments were in use in 110 countries.[25] In February 2015, Cepheid received European regulatory approval for the Xpert® HIV-1 VL cartridge, which uses the same system to measure HIV VL from 40-10 million copies/ml within 90 minutes.[27,28] We have conducted the first clinic-based feasibility and validation study to demonstrate good accuracy when performed in an HIV clinic. We are evaluating the RemoteXpert software, which allows for remote result monitoring and is compatible with South African National Health Laboratory Service (NHLS) monitoring systems. Our proposed project is innovative by being the first clinic-based implementation study of this novel device as a clinic-based model of chronic HIV care in LMICs. The potential impact of point-of-care testing with the GeneXpert® is depicted in **Figure 4.**

Figure 3. GeneXpert® System and Xpert® HIV-1 Viral Load cartridge.

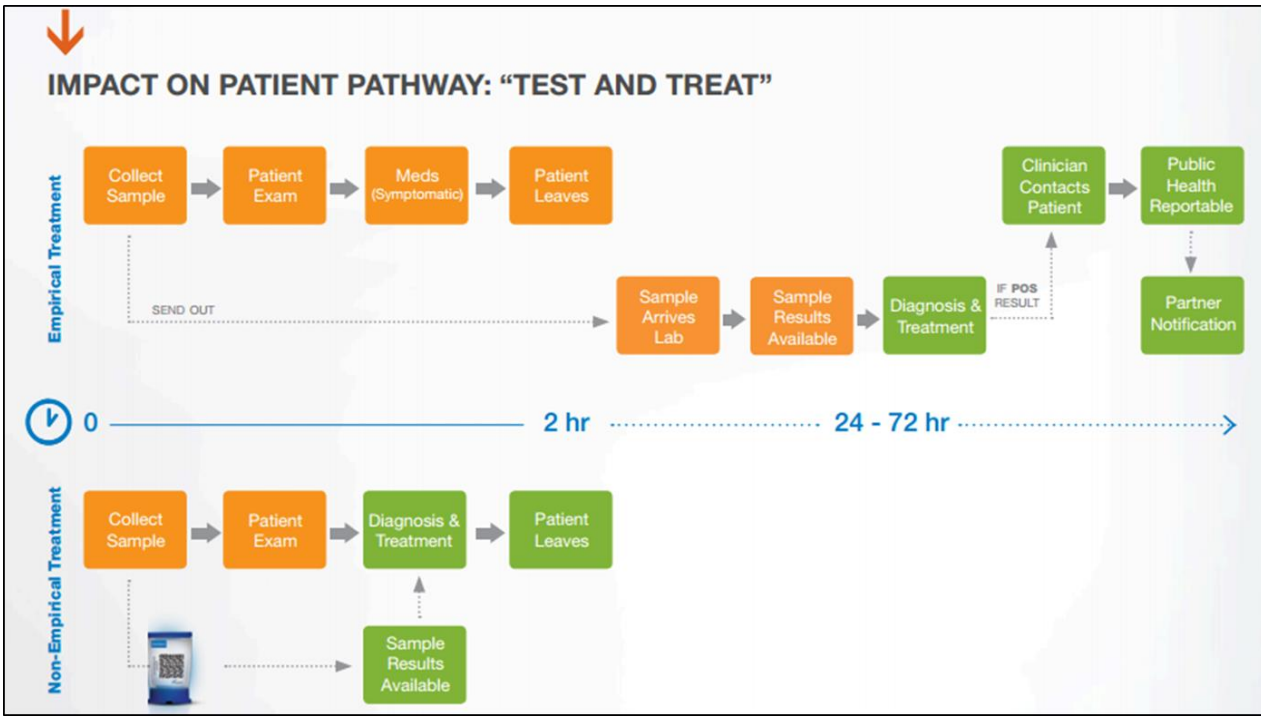


Figure 4. Potential Impact on Patient Care Pathway by providing point-of-care testing with GeneXpert®.

Cost analysis of an implementation model for chronic HIV care

This study will be innovative by conducting a cost analysis for the chronic HIV care implementation model. There are two distinct aspects that reduce costs. First, for 'super stable' patients (defined as virally suppressed, asymptomatic and with no comorbidities) we will utilize Enrolled Nurses, rather than highly trained Physicians or Professional Nurses, to perform the clinical visits and rapid HIV VL testing. We have previously demonstrated that Enrolled Nurses can perform point-of-care testing for tuberculosis diagnostics.[29,30] Second, we will utilize rapid point-of-care HIV VL testing rather than more costly laboratory-based testing. The estimated cost of the rapid HIV VL test is less than $20/cartridge, which is much lower than the estimated $60/test from a lab-based HIV VL machine. While advantages of the implementation model appear evident, our clinical trial is needed to obtain empiric data to determine the operational costs, including labor and assay costs, in order to make projections of large-scale implementation and conduct budget impact analyses.

3.3. Review of Relevant Literature.

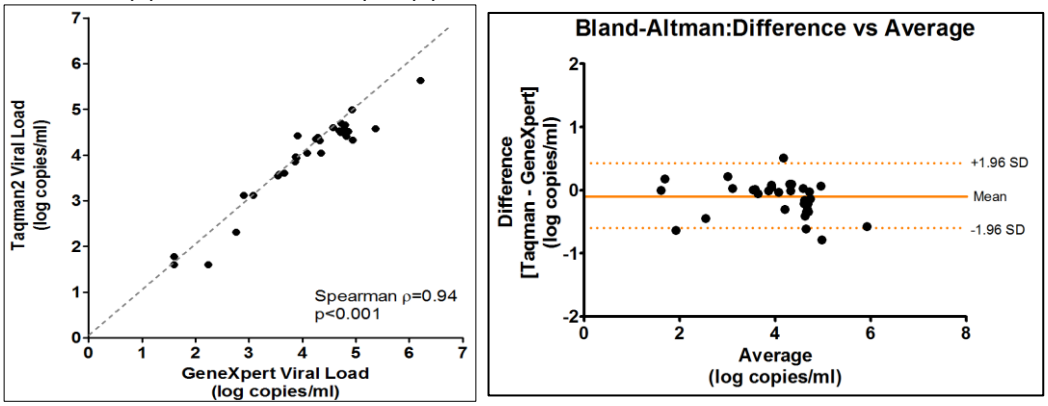
Due to the rapid expansion of ART availability, elements of task shifting and decentralized care have often been implemented in parallel to generating evidence of their effectiveness.[31] Professional nurses now initiate and manage ART in many LMICs, and the results have been favorable. In a randomized, non-inferiority trial in South Africa, professional nurse versus doctor ART management had no difference in clinical endpoints.[13] In Mozambique, the role of HIV primary care doctors has been successfully shifted to other staff members for HIV-infected patients.[14] A task-shifting program in Cape Town demonstrated that down referral to nurses made no difference to mortality or virologic failure for chronic ART management.[16] However, because patients were being down referred to a different clinical location, the nurse-managed service had

significantly higher loss to follow-up rates.[16] Currently, there are no studies evaluating the use of a rapid, point-of-care HIV VL assay for chronic HIV care. Cepheid's Xpert® HIV-1 VL test only became available for commercial use in February 2015 after receiving CE-IVD status by the European Directive on In Vitro Diagnostic Medical Devices in December 2014.[27,28] Studies evaluating point-of-care CD4 testing have reported decreased rates of pre-treatment loss to follow-up in Mozambique.[17]

3.4. Preliminary Results

We conducted a pilot study to demonstrate feasibility and accuracy of the Xpert® HIV-1 VL assay at the CAPRISA Research Clinic in Durban.[32] We performed both Xpert® and lab-based Roche Taqman v2.0 (Roche Diagnostics, Switzerland) HIV VL testing on blood samples from 42 HIV-infected women (11 were frozen samples). Among the 42 participants, 7 were within one year of HIV acquisition, 12 were chronically infected ART-naïve, 11 were virologically suppressed on ART, and 12 were not virologically suppressed. To minimize bias, different technicians conducted the assays and were blinded to results from the other test. We found a strong correlation between the Xpert® and Taqman v2.0 results across the HIV VL spectrum (Spearman ρ=0.94, p<0.001), as shown in **Figure 5 (next page)**. A Bland-Altman plot showed a mean difference between Taqman and Xpert® results of -0.10 log copies/ml (95% limits of agreement -0.59–0.39) with slightly higher values on Xpert®. All 12 observations from patients failing ART (median VL=4.37 log copies/ml, range 3.11–4.99) were detected by Xpert® (median VL=4.52 log copies/ml, range 2.90–5.36). Our results are consistent with results from European and American samples, which demonstrated excellent correlation between Xpert® and lab-based VL tests (R^2=0.97).[27,28]

Figure 5. Correlation between Xpert® HIV-1 viral load and Roche Taqman version 2 assays using a correlation curve (A) and Bland-Altman plot (B).



4. STUDY OBJECTIVES

Our central hypothesis is to prove that rapid HIV VL testing, implemented by nurses, is an effective and cost-efficient strategy for management of chronic HIV infection in the majority of patients, thereby allowing more resources to be directed at the minority of patients who need greater attention.

4.1. Primary Objective

- To evaluate a combination of streamlined task shifting to nurses and point-of-care HIV VL testing compared to the standard-of-care (Physician or Professional Nurse with a

laboratory-based HIV VL assay) on retention in care and HIV viral suppression after 12 months.

4.2 Secondary Objectives

- To determine the incidence of virological failure among HIV-infected adults receiving antiretroviral therapy at the clinical site.

- To assess the costs, both incurred and averted, of implementing the model of an Enrolled/Professional Nurse with a point-of-care HIV VL assay compared to the standard-of-care (Physician or Professional Nurse with a laboratory-based HIV VL assay), and determine the cost per HIV-positive person virally suppressed on ART and retained in care.

- To validate the POC GeneXpert HIV VL test against a laboratory-based HIV viral load gold standard.

- To measure the time to patients receiving results among clinic-based and laboratory-based HIV viral load testing.

- To determine the HIV genotype of those who have developed virological failure after initiation of ART.

- To determine risk factors for poor retention in care or virological failure after chronic ART suppression.

- To determine the incidence of virological failure among HIV-infected adults receiving antiretroviral therapy at the clinical site.

- To compare the number of patients in the intervention versus standard of care arms who are appropriately entered into the Central Chronic Medicine Dispensing and Distribution Programme (CCMDD) at 12 months

- To compare among patients in the intervention versus standard of care arms the time to appropriate entry into the Central Chronic Medicine Dispensing and Distribution Programme (CCMDD).

5. STUDY DESIGN

5.1. Study Overview

The objective of this study is to evaluate the clinical outcomes in HIV-infected patients on ART, comparing a model implementing novel point-of-care HIV VL testing with streamlined task shifting to nurses against the standard of care. This objective will be achieved through a 2-arm, randomized, non-inferiority implementation trial at a busy urban HIV clinic in Durban. The clinical outcome is a composite of retention in care with suppressed VL after 12 months from study enrollment, following South African guidelines for HIV VL testing after ART initiation.[8]

5.2. Study Design

The study design will be an open-label, randomized, non-inferiority implementation trial with 2

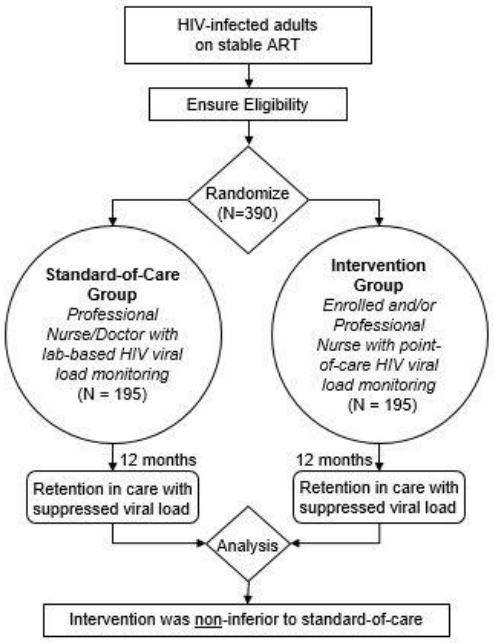
study arms **(Figure 6, next page)**. Patients will be enrolled when due their 6 month VL since initiating ART.

Participants in the Standard-of-Care control arm will receive the standard-of-care for the clinic consisting of visits with a professional clinician (Physician or Professional Nurse) and once stable, community pharmacy ART collection through CCMDD. Viral load monitoring will be lab-based. Participants will be assessed for clinical symptoms/signs of tuberculosis, other opportunistic infections, and ART side effects at each clinical encounter. Participants who have a high lab-based HIV VL (≥1,000 copies/mL) will receive intensive adherence counseling and be asked to return to the clinic in 2 months for repeat HIV VL testing. If the HIV VL remains high (≥1,000 copies/mL) after the 2 months of intensive adherence counseling, then the patient will be switched to a second-line ART regimen by a physician.

Participants in the Intervention Group will receive chronic ART management from a Professional Nurse and/or Enrolled Nurse every 2 months, and if stable after 6 months, community pharmacy ART collection through CCMDD. Viral load monitoring will be POC. Enrolled Nurse visits will consist of a clinical symptom and ART side effect checklists, and an ART adherence questionnaire, which trigger up-referral to a Professional Nurse/MO where appropriate. Point-of-care Xpert® HIV-1 VL testing will be performed while the participant is in the clinic to ensure that participants receive the VL results on the same day. Participants who have a high HIV VL (≥1,000 copies/mL) will be referred to a Professional Nurse. As with the standard-of-care arm, they will receive intensive adherence counseling and be asked to return to the clinic in 2 months for repeat point-of-care Xpert® HIV-1 VL testing.Participants who continue to have a high HIV VL (≥1,000 copies/mL) after 2 months of intensive adherence counseling will be switched to second-line ART by a physician.

Participants will also be followed for a 12-month study period to assess the study outcome measures. This study will follow all aspects of South Africa's ART guidelines, except stable patients randomized to the intervention arm will receive Nurse-based care and Xpert® VL monitoring, as a comparison to the standard of care. If funding is available, follow up may be extended to 18 months

Figure 6. Design for Implementation Study.



5.3. Study Location and Setting

- CAPRISA eThekwini Clinical Research Site, Durban, South Africa
- Prince Cyril Zulu Communicable Diseases Clinic, Durban, South Africa

We will recruit participants from the HIV clinic at the Prince Cyril Zulu Communicable Disease Centre, which is located adjacent to the CAPRISA eThekwini Clinical Research Site and near the transport hub for public commuters in central Durban. The clinic has a staff of 3 Clinicians, 14 Professional Nurses, 3 Enrolled Nurses, 2 lab technicians, and 2 radiographers to care for 10,000 HIV-infected patients, of whom over 6,000 are stable on a chronic ART regimen.

5.4. Study Inclusion Criteria

- Adult ≥18 years old
- HIV-infected and receiving antiretroviral therapy (ART)
- Receiving care at Prince Cyril Zulu Clinic in Durban
- Stable on Current ART Regimen and due the 6 month follow-up visit post ART initiation
- Willing/able to provide written informed consent to participate in the study

Eligibility criteria are meant to approximate HIV-infected persons who are best suited to receive chronic HIV care. We will enroll HIV-infected adults (≥18 years old) who are receiving ART at the Prince Cyril Zulu Clinic in Durban. We will include those who are considered to be stable on their current ART regiment. This will be defined as “Patient has been receiving the same ART regimen for the prior 6 months”. The study involves collection of clinical data and biological specimens, so

all participants will be asked to provide written informed consent to participate. Those unable or unwilling to provide written informed consent will not be able to participate in the study.

5.5. Study Exclusion Criteria

- Does not meet the study inclusion criteria above
- Have significant signs/symptoms of illness that requires active medical care by a clinic doctor.
- Does not plan to receive HIV care at the Prince Cyril Zulu Communicable Diseases Clinic for the following 12 months.
- Currently pregnant

We will include only those who appear to be stable on their current ART regimen. Therefore, we will exclude people who present to the clinic with significant signs/symptoms of illness that requires active medical care by a clinic doctor.

5.6. Study Recruitment and Enrollment

The Research Assistant dedicated to this study will approach individuals within the HIV clinic at the Prince Cyril Zulu Communicable Disease Centre. The Research Assistant will describe the study and ask for voluntary participation. The Research Assistant will explain the purpose of the study and review the study inclusion/exclusion criteria with the patient. The Research Assistant will address any questions about study participation. The eligible HIV-infected adults interested in participating in the study will be asked to sign the informed consent form to participate. Those people who decide not to participate in the study will experience no detrimental impact on their routine care at the Prince Cyril Zulu Communicable Disease Centre clinic. Those people who want to voluntarily participate will be taken to a private area of the clinic to be asked several demographic and clinical questions.
The major talking points for the Research Assistant will be the following:

- The study is for HIV-positive adults who are already receiving HIV medications.
- The purpose of the study is to investigate if an improved different approach to monitoring HIV treatment can lead to better attendance at the clinic and better treatment control of the HIV virus.
- If you agree to take part in the study, a staff member will ask you questions about your background and general health, including your HIV testing and treatment. This will be followed by a physical examination. During the examination, the study nurse will check for any signs of infection or other illnesses. If you have an active illness that requires medical attention or treatment, then you will not be able to continue with this study and will be referred to receive the care you need.
- If you are eligible to participate in the study, then the study team will randomly assign you – by chance (like a coin flip) – to either the “regular care group” or the “intervention group.” If you are in the “regular care group”, then you will receive all the same treatment that you would normally receive, including HIV medications. If you are in the “intervention group”, then you will receive all the same treatment that you would normally receive, including HIV medications but in addition, you will be seen by a nurse in the clinic without waiting in the long line, and have your HIV viral load tested and a result given to you during your clinic visit.

After enrollment, the participant will be randomized to either the control arm or the intervention arm in a 1:1 fashion. Those participants assigned to the Standard-of-Care arm will have a routine clinical visit with a clinic doctor/professional nurse and have lab-based HIV viral

load testing. Those participants assigned to the intervention arm will be seen by the Enrolled Research Nurse and have point-of-care clinic-based HIV viral load testing, with review by Professional Nurse or Physician.

5.7. Targeted/Planned Enrollment

The study design will be an open-label, randomized, non-inferiority implementation trial with 2 study arms. We will enroll healthy HIV-uninfected adults (≥18 years old) and ask participants to complete a background questionnaire and clinical examination. We will enroll a total of 390 participants: 195 participants in each study arm. Nearly all participants in this study will be Black Africans, and we anticipate a near-equal split between males and females. Based on historical performance, 80% of adults in the existing care model will meet our primary composite outcome.

	Standard of Care Arm	Intervention Arm	**Total**
Total	**195**	**195**	**390**

5.8. Baseline Assessment at Enrollment

Once written consent is obtained, a Research Assistant or Nurse will ask several demographic and health questions, related to age, birthdate, income, employment history, prior HIV testing, medical conditions, and current symptoms. The Research Assistant will also obtain each participant's phone number, address, and relevant contact information. After obtaining the baseline demographic and clinical data, the Research Assistant will determine the study group randomization of the participant.

An Enrolled Research Nurse and/or Professional Nurse will then meet the participant in the same clinical exam room. The Nurse will administer a brief clinical questionnaire, perform a clinical examination, and determine WHO HIV Stage. The nurse will coordinate the necessary blood draws for the participant, so each participant will only have one blood draw for each clinical visit. Participants in the Standard-of-Care arm will be asked to provide 25 ml (or 5 teaspoons) for complete blood count, creatinine, CD4 count, HIV viral load testing via Roche Taqman, and storage of blood in the biorepository for possible future genotype and/or tenofovir drug-level testing for ART adherence. They will also be asked to provide urine for a dipstick urinanalysis. Participants in the Intervention Group will be asked to provide a blood sample of 25 ml (or 5 teaspoons) for complete blood count, creatinine, CD4 count, HIV viral load testing via Cepheid Xpert, and storage of blood in the biorepository for possible future genotype and/or tenofovir drug-level testing for ART adherence. They may also be asked to provide a fingerprick of blood for the Quidel or other fingerprick POC HIV VL test (if available during the study period), POC creatinine test (Nova Biomedical Statsensor Express, already validated and implemented in CAPRISA site lab) and PIMA POC CD4. They will be asked to provide urine for a dipstick urinanalysis.

Those randomized to the Standard-of-Care arm will be escorted back to the clinical waiting area to be seen by a clinic physician or professional nurse..[8] All participants will be asked to return to the clinic every 2 months to be seen by a Professional Nurse who will dispense ART. All participants who are at least 1 week late for a scheduled clinical visit will be notified by the research team via an SMS or phone call about their missed appointment.

Participants in the Intervention Group will have an HIV viral load test by Cepheid's Xpert® HIV-1 VL assay performed at the beginning of the clinical encounter with the Enrolled Research Nurse, so the clinical examination can be performed during the 90 minutes required to run an Xpert HIV viral load test. The GeneXpert testing will be conducted on the GeneXpert assay located in the adjacent CAPRISA clinic site laboratory. The interventions based on the Xpert HIV

viral load are as described below in Sections 5.9 and 5.10.

When participants return to the clinic for study visits, they will be asked to present directly to the study team. The Research Assistant will be able to determine the assigned study group of the participant and direct them according to the standard-of-care arm procedures (Section 5.9) or the Intervention arm procedures (Section 5.10).

5.9. Standard-of-Care Arm Follow up Procedures

Participants in the standard-of-care arm will be directed to the regular clinical waiting area to be seen and evaluated by a clinic physician or professional nurse every 2 months. The physician or professional nurse will perform a full clinical history and examination, prescribe additional medications as appropriate, and provide adherence counseling as appropriate. The study participants in the standard-of-care arm will have lab-based HIV VL testing, creatinine and CD4 at month #6, and if eligible, will be referred by a professional nurse into CCMDD program. Eligibility criteria are:

a) Clinically stable and adherent on same first line ART regime for >6 months
b) No opportunistic infections/unstable chronic illness in previous 6 months
c) 2 x VLs < 40, at least 6 months apart, CD4 >200, normal creatinine
d) Valid South Africa ID number
e) Not on Isoniazid Prophylaxis Therapy (IPT)

A physician will sign off that these criteria have been met for each patient. In CCMDD they will be prescribed 6 months supply of ART which they collect in 2 month installments from a community pharmacy, and are seen again in the clinic after 6 months (study month #12). Those who are not in CCMDD will continue to see a professional nurse and collect ART every 2 months until study month #12. At study end (month #12) participants will also have a repeat CD4 count and lab VL performed. The lab-based HIV VL testing will be conducted in a centralized NHLS laboratory. The clinical decisions from the lab-based HIV VL testing will adhere to the South African guidelines, which are currently the following:

- HIV VL <1,000 copies/ml – Reinforce the importance of good ART adherence, provide a 2-month supply of ART, and ask participant to return for ART 2 months.
- HIV VL ≥1,000 copies/ml – Provide intensive ART adherence counseling; provide ART, and ask participant to return to the clinic in 2 months for repeat HIV VL testing. If the HIV VL remains high (≥1,000 copies/ml) upon repeat testing, then the participant should be switched to second-line ART.

5.10. Intervention Arm Follow up Procedures

Instead of being escorted to the regular clinical waiting area, participants in the Intervention arm will be seen every 2 months for the first 6 months of the study. 'Super-stable' patients with a suppressed baseline VL, no comorbidities and an ART initiation CD4 > 200 will have 6 months ART prescribed by a physician at baseline, with subsequent 2 month follow up with an enrolled nurse. As with the physician or professional nurse, these visits will consist of a full clinical history and examination, and if a patient has signs/symptoms concerning for a serious acute illness they will be evaluated by a Professional Nurse or Physician. In addition, the Enrolled Nurse can provide adherence counseling, as appropriate. All other patients (who are not 'super-stable') will see a Professional Nurse or clinician every 1-2 months depending on clinical condition. As with the standard-of-care arm, participants in the intervention arm will have CD4, creatinine and HIV VL testing at month #6, but this will be performed by POC testing during their clinical visit. The Xpert

HIV VL test will be initiated at the beginning of the clinical encounter, so the Xpert HIV VL test is run during the clinical encounter. At this visit, patients will be assessed for eligibility for CCMDD by a professional nurse as per the above criteria, and if eligible, signed off by a physician. As with the standard of care arm, those who enter CCMDD will be prescribed 6/12 of ART to be collected at 2 monthly intervals from a community pharmacy until study month #12 (study end). 'Super-stable' patients who are not in CCMDD for logistical reasons (i.e. on IPT, do not have valid SA ID) will continue to collect pre-packed ART every 2 months from an enrolled nurse as above. Patients who are not eligible for CCMDD for clinical reasons will continue to see a professional nurse and collect ART every 1-2 months until study month #12 (study end). Participants will also have a repeat lab VL, POC VL and CD4 count at study end (month #12). The interventions based on the Xpert HIV viral load are as follows:

- Xpert HIV VL <1,000 copies/ml – Reinforce the importance of good ART adherence, provide a 2-month supply of ART, and ask participant to return for ART in 2 months.
- Xpert HIV VL ≥1,000 copies/ml – Provide intensive ART adherence counseling; provide a 1-2-month supply of ART, and ask participant to return to the clinic in 2 months for repeat Xpert HIV VL testing. If the Xpert HIV VL remains high (≥1,000 copies/ml) upon repeat testing, then the participant should be switched to second-line ART.

In addition, patients in the Intervention Arm may also have a finger-prick blood obtained for HIV VL testing by the Quidel or other machine if becomes available during the study period. This is a validation sub-study only, and these results will not be used to guide the intervention. These results will be compared to the gold-standard Roche Taqman VL results.

5.11. Summary of Clinical Visits and Testing

Table 2 and Figure 7 provide a summary of clinical visits and testing in both study arms.

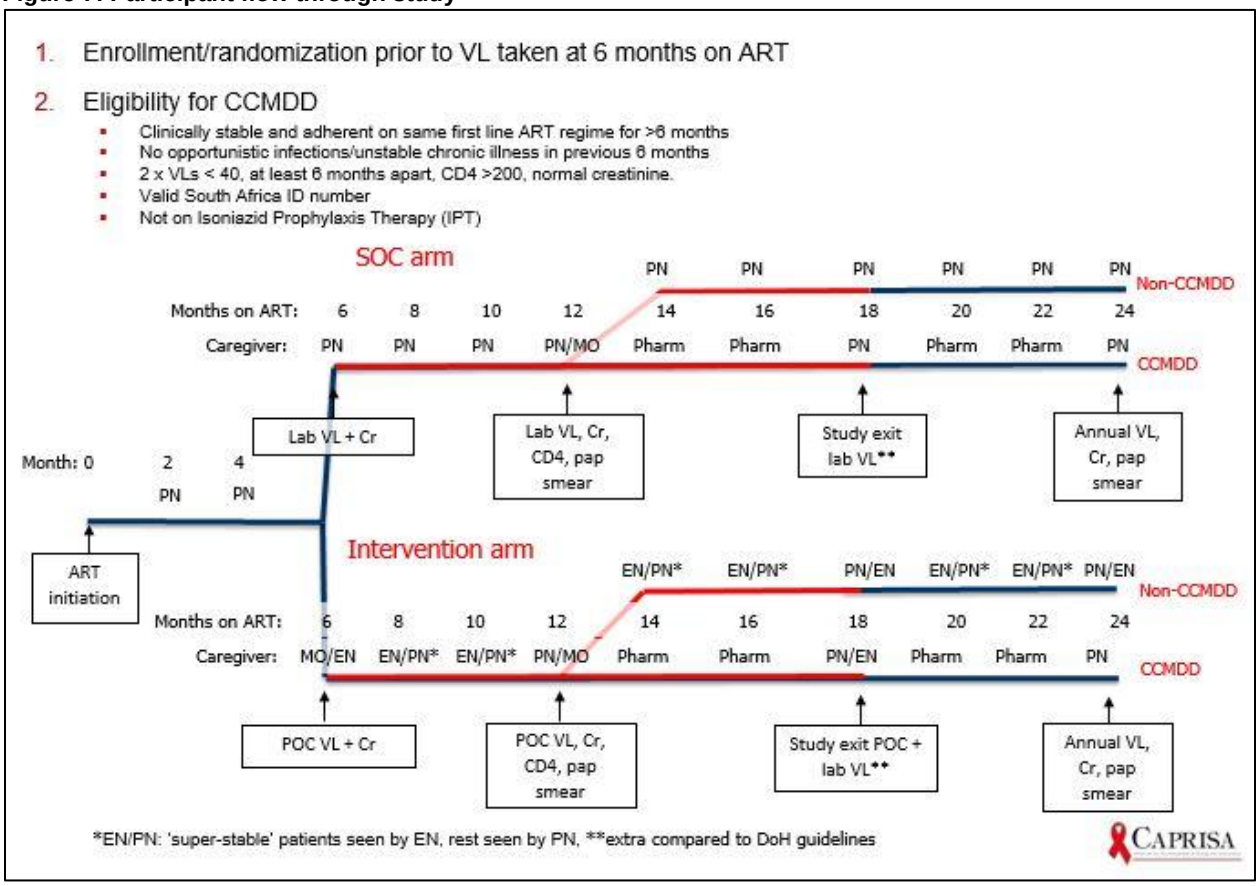
Table 2. Timeline of Clinical Visits and Testing in Intervention Arm

	Enrollment	Month 6	Month 12
Clinical Visit			
Assessment by Enrolled/Professional Nurse (Intervention arm)	x	x	x
Assessment by Professional Nurse/Physician (SoC)	x	x	X
ART side effect screen	x	x	X
TB symptom screen	x	x	X
WHO clinical staging	x		x
ART dispensing	x	x	x
Testing			
Serum creatinine (5 ml)*	x	x	x
Full blood count (5 ml)*	x		x
Urinalysis (20-30 ml of urine)	x		x
CD4 count (5 ml)*	x	x	x
Roche Taqman VL (SOC arm) (5 ml)	x	x	x
Cepheid Xpert VL (Intervention arm) (5 ml)*	x	x	x
Roche Taqman VL (Intervention arm) (5 ml)			x

Stored plasma (10 ml)	x	x	x

* Additional POC fingerprick assay in intervention arm

Figure 7: Participant flow through study



5.12. Outcome Assessments

At the end of the 12-month study period, all participants will have a repeat CD4 count and lab-based HIV VL testing by Roche Taqman v.2.0 assay. The lab-based HIV VL testing will be important to use the same HIV VL assay to compare the primary outcomes measures. In addition, the research team will evaluate the outcome of "retention in care", which will be defined as collecting ART refills at the study exit visit.

5.13. Duration of Study

All participants enrolled in this study will be followed for a total of 12 months from the date of study enrollment. If additional funding becomes available, follow up may be extended to 18 months, once BREC has been informed and approval granted.

6. STUDY OUTCOMES AND ANALYSES

6.1. Primary and Secondary Outcomes

The primary outcome for this study will be a composite measure of HIV VL suppression and

retention in care at the end of a 12-month study period. Viral load suppression will be defined as HIV VL <200 copies/mL by the lab-based Roche Taqman v.2.0 assay; retention in care will be defined as collecting ART at the study exit visit.

Primary Study Outcome:

- HIV VL <200 copies/mL and retained in care

Secondary Study Outcomes:

- HIV VL <200 copies/mL
- Retained in care
- Retention on same ART regimen
- Mean change in CD4 count
- Costs incurred and costs per HIV+ virally suppressed
- Time to detection of virological failure
- Time to initiation of appropriate alternate ART
- Time to adherence counseling if high VL
- Loss to follow-up or mortality
- Time to appropriate entry into CCMDD

6.2. Statistical Analysis

Our primary analysis will estimate the difference in proportions achieving our primary outcome between the intervention and controls groups, and will compare the lower limit of the 1-sided 95% CI for the difference (intervention-control) to the pre-specified limit for declaring non-inferiority (-10%). This is being conducted as a non-inferiority trial because the intervention is designed to shift the clinical tasks and be more efficient and cost savings at the clinic level. Therefore, if there is no difference in outcomes, then we would suggest that a nurse with less clinical training would be suitable to manage HIV-infected patients on chronic ART regimens. Our study design permits declaring superiority by ruling out a difference of 0 in the two-sided 95% CI. We will describe each secondary outcome along with differences in measures by arm, including Kaplan Meier curves to describe cumulative incidence of time to detection of virological failure, time to initiation of appropriate alternate ART, and time to adherence counseling for those with a high HIV VL. We will perform bivariate and multivariate logistic regression to identify independent risk factors for reaching the endpoints. Data will be analyzed using SAS version 9.4 (SAS Institute Inc., Cary, NC) and R.

6.3. Sample Size and Power

The sample size and power calculation are based on determining non-inferiority of the intervention arm **(Table 3)**. Based on the clinic's historical performance, 80% of adults in the existing care model are virologically suppressed and retained in care after 12 months. With a non-inferiority margin of 5% (i.e. 75% not a clinically significant worse outcome) and assuming that the intervention model is truly 5% better, a trial of 390 (195 per arm) is sufficient to be 80% sure that the lower limit of a one-sided 95% confidence interval will exclude -10% (rule out the intervention group is 10% worse than the control group). Therefore, we plan to enroll 195 participants in each study arm. If the true proportion retained and virally suppressed at 12 months is 80% and 90%, respectively, for the control and intervention, with 195 per group we will also have 80% power to declare superiority using a two-sided alpha=0.05.

Table 3. Sample Size and Power Estimates.

Non-Inferiority Design Hypothesis	Power (beta)	Est. Total Sample Size
Rule out 77.5% against true 85%	80%	663
Rule out 75% against true 85%	90%	540
Rule out 75% against true 85%	**80%**	**390**
Rule out 75% against true 87.5%	80%	326
Rule out 75% against true 90%	80%	211

7. SECONDARY COST STUDY

7.1. Introduction and Rationale

The objective of this aim is to assess whether the intervention (streamlined task shifting to nurses and and point-of-care HIV VL testing) will minimize the costs of delivering chronic HIV care per HIV-positive client virally suppressed and retained in care. If our clinical intervention proves to be non-inferior with respect to patient outcomes while reducing costs, then our conceptual model may be a more efficient method of delivering chronic HIV care in LMICs. We will also conduct a budget impact analysis of our proposed chronic care model. Cost-effectiveness analyses have been conducted for a variety of HIV interventions and management issues. However, there are no cost analyses that have assessed the combined intervention of point-of-care HIV VL testing and streamlined task shifting to nurses for chronic HIV care.

7.2. Preliminary cost-effectiveness studies

We have conducted cost-effectiveness studies on the potential impact of HIV prevention strategies in Africa, including linkage to care studies and pre-exposure prophylaxis.[33-36] Using data from our home-based HIV testing and linkage to care studies in KwaZulu-Natal,[37,38] and companion costing studies,[39] we developed an individual-based, stochastic model of HIV incidence that incorporates sexual behavior and ART use to simulate the projected intervention impact and health outcomes. Incremental cost-effectiveness ratios (ICERs) were calculated for the intervention relative to current services per HIV incident infection and disability adjusted life year (DALY) averted. Home HIV testing was very cost effective by WHO standards across all ART initiation thresholds: US$985 per DALY averted and $7,100 per infection averted with ART initiation at ≤500 cells/μL.[36] These analyses demonstrate our capacity to conduct rigorous evaluation of HIV treatment interventions, and utilize study results and mathematical models to explore the potential impact of chronic HIV care models.

7.3. Research Design

We will use an activity-based micro-costing approach, including time and motion studies, to estimate the costs incurred and averted, along with the primary study outcomes (viral suppression and retention in care) to estimate the cost per HIV-positive person virally suppressed and retained in care in the Intervention Group, as compared to the Standard-of-Care Group.

Time and motion studies will determine the nurse time necessary to conduct the point-of-care HIV VL testing and the clinical visit with a stable HIV-infected patient. Time and motion studies will be conducted during study initiation and again when the intervention is running at full capacity. An experienced research assistant will collect data on the time required to complete each step of the chronic care visit (VL testing, clinical assessment, counseling) for both study arms. Initial results will be shared with the teams to implement strategies for improved efficiency. Observing multiple visits will allow estimation of the average time taken for each step; the time taken for research

purposes (e.g. data collection) will be noted separately from the estimated time needed for monitoring. Multiple staff will be observed to capture the range of time required for a successful real-time chronic HIV care. Interviews with study staff will also quantify the effort required for each step of visit. Through time and motion studies the number of participants who could be supported by a clinic will be estimated. The staff time taken for the intervention captures the opportunity cost of the chronic care intervention, i.e. staff time that could be spent on a different program.

We will collect additional data for the incremental costs for the intervention, as well as treatment costs averted as a result of the intervention, which includes unnecessary switching to higher-cost second-line regimens, additional lab tests, and more frequent visits. We will use standardized activity-based 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,[40] 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 point-of-care VL testing saves clients, and therefore society, time and expense. Costs will be categorized as fixed or variable. Variable costs indicate which costs could change (e.g. less expensive point-of-care HIV VL assay) and influence the estimates from the study.

7.4. 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 client achieving viral suppression and retained in care in the chronic care model compared to the standard of care. These data are key for decision makers considering implementation of adherence interventions. In subsequent steps of this work we will use these cost estimates to evaluate the cost-effectiveness of the chronic-care model and conduct a budget impact analysis. A budget impact analysis assesses the overall costs incurred and averted by adding an intervention.

8. PARTICIPANT REIMBURSEMENT

Study participants will be reimbursed as per CAPRISA Policy on Study Participant Compensation guidance considering time of visits, inconvenience of study procedures, and transport expenses. It is anticipated that the reimbursement per screening or follow-up visit will be ZAR 100. The reimbursement will be collected after the participant has completed their study visit.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Risks to Human Subjects.

9.1.a. Human Involvement, Characteristics, and Design

We are proposing a research study that requires the collection of personal and clinical data, as well as biological specimens, from human participants. All participants will be ≥18 years of age and able to provide written, signed informed consent in the local language. We will have a dedicated Research Assistant at the clinical site to identify and recruit new participants at the Prince Cyril Zulu Clinic for Communicable Diseases. The Research Assistant will also be able to determine the patient's eligibility, answer any questions, enroll eligible participants, and conduct the informed consent process. All HIV-infected adults will receive the current standard of care

according to current national HIV care guidelines, and participation in this study will not impact routine medical care.

All study participants will be HIV-infected and are considered part of a vulnerable population. Maintaining the protection of the data in this vulnerable population will be paramount to this project. The HIV-infected participants may face HIV-related stigma if they are seen returning regularly to an HIV clinic. Throughout the course of the study, confidentiality will be preserved, and the data will be maintained in a secure location. We will not enroll children <18 years, prisoners, or institutionalized subjects.

9.1.b. Sources of Materials

After obtaining informed consent, data will be recorded and entered into REDCap, a secure online database designed for research trials. In addition, each participant will be assigned a study identification number, which will be maintained in a logbook. The proposed research project only involves the collection of blood samples from each participant.

An Enrolled Research nurse will collect blood samples from the anticubital vein, as is done in a routine venous blood draw. We will attempt to coordinate this with other laboratory tests, including CD4 count, in order to minimize blood draws. The venous blood sample will be collected in an appropriate laboratory vial. With each blood draw, there will be minimal risks for discomfort, bleeding, and/or infection. However, we will minimize these risks by using sterile needles and syringes, practicing good technique, and conducting procedures in a designated, controlled space. As part of routine care, participants suspected of having any medical problems will receive appropriate treatment.

9.1.c. Potential Risks

The primary risk to the participants in this study will be from the collection of blood samples. Collecting blood specimens through venipuncture have small risks of discomfort, persistent bleeding and/or bruising, and of introducing an infection. Answering demographic and health related questions have minimal risks to consenting participants. Participants in this setting are at high risk of being lost to follow-up with a known life-threatening infection. We will minimize this risk by obtaining contact information for participants and contacting them to inform them of their test results. Additional risks may include anxiety due to HIV testing and potential breach of participant confidentiality.

9.2. Adequacy of Protection Against Risks.

9.2.a. Recruitment and Informed Consent

The study protocol, consent forms, and project materials will be reviewed and approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC) in Durban and the University of Washington Institutional Review Board in Seattle prior to commencing the study or recruiting participants. All consent forms and participant education materials will be available in English and isiZulu, as appropriate. In developing the isiZulu consent form, the English document will be translated into isiZulu, and a separate person will back-translate the document into English. This process of back-translation of the isiZulu consent form will help ensure a satisfactory translation. Throughout the recruitment and informed consent process, we will adhere to ethical norms that are standard to the study setting.

During the course of the study, confidentiality will be preserved and the data will be maintained in a secure cabinet 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 a locked cabinet. The online data will be stored in REDCap, which is a password protected data management service. All computers with access to the data will be password protected. All data will be analyzed using the participants' study identification number and not their identifiable information.

9.2.b. Protection Against Risk

We will take several steps to minimize risks for participating in the proposed research project. First, the research assistant will emphasize the voluntary nature of study participation and that participants are 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 Biomedical Research Ethics Committee (BREC) 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 then back translated into English to ensure accuracy. Third, we intend to minimize any potential breach of confidentiality by conducting 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.

We will take several steps to minimize the clinical risks in the proposed research project. First, to minimize risks of discomfort, bleeding, and infection during the 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 HIV care and treatment, we will be able to refer participants to accessible counselors and social workers at Prince Cyril Zulu Clinic for Communicable Diseases in Durban.

9.3. Potential Benefits of the Proposed Research

The goal of this study is to evaluate a novel conceptual model for chronic ART management in LMICs. If our project is successful, it could be implemented to improve the care and delivery to HIV-infected people living in other resource-limited settings. 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.

9.4. Data and Safety Monitoring Plan

We will have several mechanisms in place to ensure participant confidentiality and safety. First, we will provide extensive training to the research team regarding the study protocol, consent form, the importance of maintaining participant confidentiality and safety. Second, we will be in regular communication with the HIV clinics at Prince Cyril Zulu Clinic for Communicable Diseases in Durban to ensure that we are not disrupting patient flow or treatment. Third, we will review our data on a regular basis to make certain that our proposed research projects are not causing harm or adverse events. Finally, the Principal Investigator will notify the Institutional Review Boards of any breaches in confidentiality, study protocol, or adverse events attributable to this study within ten days of the event.

10. TIMELINE

The Study Aims will be completed in two years, according to the timeline detailed in **Table 4**.

Table 4. Timeline for Research Activities and Manuscripts.

	Year 1				Year 2			
	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1
Aim #1. RCT of chronic HIV care								
IRB approval, Training & Preparation	X							
Enrollment Period		X	X	X				
Follow-up Period				X	X	X		
Manuscripts						X		X
Aim #2. Cost analysis								
Data collection				X	X	X		
Model analysis						X	X	
Manuscripts							X	X

11. POTENTIAL PROBLEMS AND ALTERNATIVE APPROACHES

Study feasibility. The clinical research team will enroll 195 patients over 9 months (~1 participant per day) in the intervention arm, which may seem ambitious. However, in our experience at this clinic, managing 2-3 stable HIV patients per day will be fully achievable with the available resources. In addition, we will conduct training sessions with nurses and research team to ensure comfort with VL testing and data collection.

Recruitment of HIV-infected participants. The Prince Cyril Zulu Clinic has over 6,000 HIV-infected people receiving a stable ART regimen and eligible for our study. If we still do not reach our full sample size, then we will recruit patients from another urban HIV clinic or the CAPRISA Vulindlela Clinical Research Site.

Burden for patients. Enrolled Nurses will draw blood for Xpert® VL testing upon participant arrival to minimize waiting times. However, if patients are still uncomfortable waiting 90 minutes for the Xpert® VL test result, then we will provide additional services, such as tea/coffee, in waiting areas.

Costing may not capture the true costs. Time and motion studies distinguish research costs from programmatic costs, but efficiencies in a research study might differ from that achieved in public programs. As part of the study, we will share target efficiencies and encourage ongoing program evaluation.

12. MULTIPLE PI LEADERSHIP PLAN

Rationale

A multiple PI leadership approach has been selected to provide for effective coordination of the diverse but complementary activities that will be performed by investigators (Dr. Drain and Dr. Garrett) who have complimentary expertise. Drs. Drain and Garrett will jointly assume responsibility for overseeing the studies in this proposal.

Dr. Paul Drain is an infectious disease physician and clinical epidemiologist with clinical research expertise in assessment of diagnostic point-of-care tests for HIV and HIV-related opportunistic infections. He has completed several clinical trials to evaluate rapid diagnostic tests for HIV, tuberculosis, and HIV-related opportunistic infections in sub-Saharan Africa.

Dr. Nigel Garrett is a specialist HIV and STI physician with extensive expertise in HIV pathogenesis and vaccine research. He has published widely on viral load dynamics, antiretroviral drug resistance and has conducted several clinical trials in South Africa.

Collaborative Organization
The team has a history of productive collaboration for this project. Drs. Drain and Garrett have recently completed a feasibility and validation study of the rapid, point-of-care HIV viral load test within the clinic in which this study is proposed.

This team, including all postdoctoral fellows, graduate students, and technicians, will hold monthly meetings for presentations of recent results, interpretation of findings, and discussion of research directions. More frequent communication between the PIs for day-to-day implementation of the studies will take place by email.

Justification for Multiple PIs
We have selected a multi-PI organization because the project features integration between clinical diagnostic research and implementation science methods developed through collaboration of the two PIs. We believe this structure is necessary in a multi-disciplinary project such as this one in order to move the project forward in a timely fashion and overcome the potential difficulties or complexities that might appear in technical or clinical arena.

By agreement, the funds will be apportioned based on the individual budgets submitted by each PI. In the case that the funded amount is less than the total requested, funds will be divided proportional to the requested budgets.

Roles, Decision Making
Dr. Drain and Dr. Garrett will discuss all major programmatic, scientific, financial, and logistic aspects of governance of this project. Any differences of opinion will be openly discussed and decisions will be made by achieving consensus.

Conflict Resolution
Finally, senior investigators Drs. Connie Celum and Salim Abdool Karim will closely mentor Drs. Drain and Garrett, both young investigators. Dr. Celum is the Director of the International Clinical Research Center at the University of Washington, and Dr. Abdool Karim is the Director of CAPRISA. Drs. Drain and Garrett's groups have not faced any major conflicts to resolve. If a disagreement on interpretation or direction arises, then Drs. Drain and Garrett will meet to resolve the dispute. Although it's not expected based on past experience, should a major disagreement between the PIs arise then the disagreement will be referred to an arbitration committee consisting of Drs. Celum and Abdool Karim.

13. RESOURCE SHARING PLAN

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

We will make quality-controlled raw data as well as processed data used in publications 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.

Drs. Drain and Garrett, as well as other personnel assigned to the project, will disseminate results from this research through presentations at public lectures, scientific institutions and meetings, and/or publication in major journals. The institutions and Principal Investigators 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 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 all 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.

14. 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 6-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 measure QC and retention rates on all studies.

15. ETHICAL CONSIDERATIONS

Ethical approval sought from the Institutional Review Boards of the University of Washington and the University of KwaZulu-Natal's Biomedical Research Ethics Committee (BREC) (FWA00000678).

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 Medicines Control Council. Informed consent will be obtained from potential participants to participate in the study and to store blood samples. 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.

16. REFERENCES

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