Point-of-care testing, new antiretroviral regimens and community-based treatment to enhance primary care HIV services in South Africa

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ABSTRACT

Background: The global rollout of antiretroviral therapy has significantly reduced HIV/AIDS related morbidity and mortality. However, there are new challenges in a) providing HIV viral load testing to monitor the effectiveness of ART, b) combating HIV drug resistance, and c) efficiently providing treatment to the 39 million people living with HIV globally. In low- and middle-income countries such as South Africa, most ART is provided in primary care, where there is limited laboratory capacity and where available, viral load testing typically takes several days to turn around, resulting in additional clinic visits for review of results and treatment adjustment. New point-of-care assays have been developed which could be used in primary care clinics to provide same-day viral load results. Patients with viraemia and uncontrolled HIV infection could receive immediate adherence counselling, and ART optimization for those likely to have HIV drug resistance. However, we do not know the clinical effectiveness of these point-of-care assays HIV in primary care settings. Furthermore, the new antiretroviral dolutegravir, which has a higher genetic barrier to HIV drug resistance, has been introduced and will require new monitoring strategies. Lastly, the impacts of dolutegravir, and new models of efficient community ART provision, are not known.

Aims: To determine whether point-of-care viral load testing is a promising strategy to improve management of viraemia in primary care in South Africa, and whether its clinical effectiveness can be tested in a large, randomised trial. To assess changes in the ART programme, including the introduction of dolutegravir and community ART delivery programmes, which may necessitate new monitoring strategies.

Methods: First, I evaluated the diagnostic accuracy of three point-of-care viral load assays, and conducted the Point-Of-care HIV viral load testing to Enhance Re-suppression (POwER) trial, a randomised pilot/feasibility study. I assessed trial feasibility outcomes (enrolment and retention), 12-week point-of care viral load process outcomes,

and the future trial primary outcome of viral suppression at <50 copies/mL after 24 weeks, in the point-of-care and laboratory viral load arms.

Second, to explore the impact of a new, likely more effective antiretroviral, dolutegravir, I conducted a post-hoc analysis within POwER, evaluating viral load outcomes and HIV drug resistance by baseline ART regimen. I then evaluated the analytic performance of a novel point-of-care test that measures urine concentrations of tenofovir, a key component of most ART regimens.

Third, I evaluated the healthcare context in which these assays may be implemented. I assessed the rollout of dolutegravir, and its impact on viral load outcomes, in a retrospective cohort study using data from 59 South African primary care clinics. Then, using interviews and focus group discussions with patients and healthcare workers, I explored the impact of a community ART programme, that includes over 1 million patients, on the 'social practice' of engagement in HIV care. Lastly, I used interrupted time series analysis of routine data from 60 clinics to quantify the impact of COVID-19 on primary care HIV services in South Africa.

Results: First, in 189 paired samples, sensitivity and specificity of three different point-of-care viral load assays to detect viraemia was >90%. Enrolment into POwER was disrupted by the COVID-19 pandemic, with 80 eligible participants enrolled between August 2020 to March 2022, versus an initial target of 100 in six months. The 12-week point-of-care viral load result was delivered to participants a median of 3.1 hours (IQR 2.6-3.8) after blood draw, versus 7 days (IQR 6-8, p<0.001) for standard laboratory viral load results. Point-of-care participants had median 3 (IQR 3-4) clinic visits versus 4 (IQR 4-5) in the standard-of-care arm (p<0.001). Retention was high at 95.0% at 24 weeks, and the exploratory primary outcome of 24-week viral suppression was achieved by 27/39 (69.2% [95%CI 53.4-81.4]) point-of-care participants versus 29/40 (72.5% [57.0-83.9]) standard-of-care participants (p=0.808).

Second, at enrolment into POwER, 43 participants were receiving dolutegravir, and 37 were receiving the older drug efavirenz as part of their ART regimen. People receiving dolutegravir had no major HIV drug resistance, and therefore achieved rapid viral resuppression after enhanced adherence counselling, meaning there was little opportunity for the point-of-care viral load to exert an effect. The point-of-care urine test had good analytic performance, with >90% sensitivity and specificity to detect tenofovir.

Third, in over 220,000 people in 59 South African primary care clinics, over 75% of people were receiving dolutegravir by February 2022. Viral suppression was slightly higher in people receiving dolutegravir compared to those receiving efavirenz (adjusted risk ratio 1·04 [1·01,1·06], adjusted risk difference 3·1% [1·2,5·1]). In a qualitative study, the South African community-based ART programme was found to be acceptable to both patients and healthcare workers and was perceived to overcome several barriers to clinic-based ART collection, resulting in quicker and more convenient care for people living with HIV. Lastly, the COVID-19 lockdown led to a 47.6% drop in HIV testing (incidence rate ratio [IRR] 0.52, 95% CI 0.45-0.62) and a 46.2% decrease in ART initiations (IRR 0.54, 95% CI 0.46-0.63), while there was no marked change in ART collection visits (IRR 0.93, 95% CI 0.79-1.09).

Conclusion: Point-of-care viral load assays have acceptable clinical performance in primary care, and it would be feasible to assess their clinical effectiveness in a larger randomised trial. However, the widespread rollout of dolutegravir means that there may be less HIV drug resistance and a potential smaller role for point-of-care viral load tests to improve HIV viraemia. Instead, combination interventions including novel point-of-care adherence assays should be investigated to manage viraemia. Whether point-of-care viral load tests may have more of a role in improving efficiency of community ART delivery programmes should also be evaluated.

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LIST OF ABBREVIATIONS

ART	Antiretroviral therapy
aRD	Adjusted Risk Difference
aRR	Adjusted Risk Ratio
aHR	Adjusted Hazard Ratio
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CCMDD	Centralise Chronic Medication Dispensing and Distribution
CI	Confidence Interval
COVID-19	Coronavirus disease 2019
CRF	Case Report Form
DBS	Dried Blood Spot
DHIS	District Health Information System
EAC	Enhance Adherence Counselling
GP	General Practitioner
HIV	Human Immunodeficiency Virus
HIVDR	HIV Drug Resistance
INSTI	Integrase Strand Transferase Inhibitor
IQR	Interquartile Range
IRR	Incidence Rate Ratio
LC-MS/MS	Liquid chromatography - tandem mass spectrometry
LMIC	Low- and middle-income countries
m-PIMA	m-PIMA HIV-1/2 VL
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NPV	Negative Predictive Value
NRTI	Nucleoside reverse transcriptase inhibitor
OxTREC	University of Oxford Tropical Research Ethics Committee
PCR	Polymerase Chain Reaction

PEPFAR	President's Emergency Plan for AIDS Relief
PLHIV	People living with HIV
POC	Point
PrEP	Pre-exposure prophylaxis
SOC	Standard-of-care
TDF	Tenofovir Disoproxil Fumarate
TLD	Tenofovir Lamivudine Dolutegravir
UKZN BREC	University of KwaZulu-Natal Biomedical Research Ethics Committee
UNAIDS	Joint United Nations Programme on HIV/AIDS
VL	Viral Load
WHO	World Health Organization
Xpert XC	Xpert HIV-1 VL XC
Xpert VL	Xpert HIV-1 Viral Load

STATEMENT OF CONTRIBUTIONS

I confirm that this thesis contains my own work. I conducted all statistical analyses in the thesis, with support and advice from Ms Lara Lewis (CAPRISA) in Chapters 4, 5, 8 and 10, Dr Thomas Fanshawe (Nuffield Department of Primary Care Health Sciences, University of Oxford) for Chapter 3 and Dr Christian Bottomley (London School of Hygiene & Tropical Medicine) for Chapters 8 and 10. Mr Lindani Msimango and Ms Hlengiwe Shozi conducted interviews and focus group discussions in isiZulu and English for Chapter 9, and Mr Lindani Msimango translated and transcribed these, and checked my coding of transcripts.

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DECLARATION OF INTERESTS

Cepheid (Sunnyvale, California, USA) and Abbott (Chicago, Illinois, USA) provided point-of-care viral load assays at no cost. Abbott also provided point-of-care urine tenofovir tests at no cost. I have no other competing interests to declare.

Chapter 1

1. OVERVIEW AND STRUCTURE OF THESIS

1.1. Rationale of thesis

My rationale for this thesis was to explore whether point-of-care viral load testing can improve management of HIV viraemia in primary care. I also wanted to assess major changes in the ART programme in primary care, to inform future post-doctoral work of other tests and strategies to improve HIV primary care services.

1.1.1. Overarching hypothesis

Point-of-care viral load testing will improve the management of HIV viraemia. Improved ART and community ART programmes will allow more streamlined HIV services and may provide other opportunities for point-of-care testing to improve HIV services.

1.1.2. Overall aim

Firstly, to determine whether point-of-care viral load testing is a promising strategy to improve management of viraemia in primary care in South Africa. Secondly, to determine how HIV treatment in primary care in South Africa changed over the course of the DPhil, and what implications does this have for ART monitoring strategies

1.2. Thesis structure

1.2.1. Chapter 2: Background

I present background information regarding the global HIV epidemic, and the importance of ART in maintaining viral suppression. I explore problems with HIV viral load testing to monitor ART, and describe the WHO guidelines for management of HIV viraemia. I then discuss new point-of-care viral load assays, and review the evidence to support the use of these assays in primary care clinics. I also discuss how new ART regimens and community

ART delivery programmes change the context in which point-of-care viral load testing may be used. I conclude the chapter by identifying the gaps in the evidence, and by outlining the aims of my thesis.

1.2.2. Chapter 3: Diagnostic accuracy of point-of-care HIV viral load tests

I present the results of a diagnostic accuracy study of three point-of-care viral load tests. I showed that the novel Xpert HIV-1 VL XC (Xpert XC), and the more established Xpert HIV-1 VL (Xpert VL) and m-PIMA HIV-1/2 VL (m-PIMA) had acceptable performance when testing was conducted by laboratory staff or by nurses in the study clinic. This was the first diagnostic accuracy study of the clinical performance of the Xpert HIV-1 VL XC assay.

1.2.3. Chapter 4: The POwER trial protocol

I outline the protocol of the *Point-Of-care HIV viral load testing to Enhance Re-suppression (POwER)* trial; the main study which underpins the bulk of the work in this thesis. I designed POwER as an open label, randomised feasibility trial of point-of-care viral load testing, in order to provide preliminary data for the development of a larger future trial to improve the management of HIV viraemia in primary care in South Africa.

1.2.4. Chapter 5: The POwER trial: Feasibility study results

I present the main findings from the POwER trial. COVID-19 severely disrupted and slowed enrolment, but overall retention in care was good, and point-of-care testing was conducted well, leading to viral load results being available seven days earlier, and with fewer clinical visits compared to standard laboratory-based viral load testing. Therefore, conducting a larger trial of point-of-care viral load testing is potentially feasible. However, at 24 weeks after enrolment, the primary outcome of viral suppression was similar in the point-of-care arm and the standard laboratory testing arm. This may have been due to a higher quality of care in the standard of care arm than is typically seen in South African clinics, and the introduction of a new antiretroviral medication, called dolutegravir, into the South African ART programme, which I explore in Chapter 6.

1.2.5. Chapter 6: High levels of viral re-suppression among people receiving dolutegravir-based first-line ART

I present further data from the POwER study, exploring viral re-suppression by baseline ART regimen. Among people receiving the older antiretroviral, efavirenz, there was a high prevalence of HIV drug resistance, and so the majority needed a switch to second-line ART to achieve viral re-suppression. In contrast, among people receiving, dolutegravir, there was little drug resistance, meaning viraemia was likely caused by poor ART adherence. In this group, viral re-suppression occurred very quickly, without the need for a change in ART regimen, and often before the point-of-care testing intervention was administered. This may partly explain the lack of a signal of benefit with point-of-care viral load testing. New diagnostic interventions may therefore be needed to improve management of viraemia for people receiving dolutegravir.

1.2.6. Chapter 7: Evaluation of a novel point-of-care urine tenofovir adherence assay in the POwER trial

I present findings from a sub-study within POwER to assess the analytic performance of a novel point-of-care urine test which measures drug levels of the antiretroviral medication, tenofovir, which is a component of most ART regimens. I showed that the point-of-care urine tenofovir test is accurate at detecting tenofovir at the manufacturer specified threshold. I also found that there is an association between self-reported adherence and urine tenofovir levels, but some people who reported perfect recent adherence had undetectable tenofovir, meaning the point-of-care test may be an additional tool to identify people with inconsistent adherence in primary care. This could be of particular use among people receiving dolutegravir.

1.2.7. Chapter 8: Implementation and outcomes of dolutegravir-based first-line antiretroviral therapy for people with HIV in South Africa: a retrospective cohort study

I present results of a retrospective cohort study evaluating the rollout of dolutegravir in 59 primary care clinics in South Africa. I showed that women were less likely to receive dolutegravir than men, likely because of initial safety concerns among women of child-bearing potential. By early 2022, over 75% of people were using dolutegravir. People receiving dolutegravir had only slightly better viral suppression compared to those receiving efavirenz, meaning strategies to detect viraemia remain important.

1.2.8. Chapter 9: Qualitative assessment of a community-based HIV treatment programme

I present results from a qualitative study evaluating a community ART delivery programme that has been rolled out in South Africa. The Centralised Chronic Medication Dispensing and Distribution system (CCMDD) allows people with viral suppression to collect their ART from community pick-up points and private pharmacies, which are closer to home or more convenient than collecting in clinics. Using interviews and focus group discussions with clients and healthcare workers, I found that CCMDD overcame material barriers to attending clinics, changed the meanings associated with collecting ART and was less disruptive to other social practices in clients' lives. Clients and healthcare workers had to negotiate problems with CCMDD implementation, including some pharmacies reaching capacity or only allowing ART collection at restricted times.

1.2.9. Chapter 10: Impact of COVID-19 on HIV primary care services in South Africa

The POWER trial was conducted during the COVID-19 epidemic in South Africa. I outline results of a separate study assessing the impact of the COVID-19 lockdown on HIV testing, ART initiation and ART collection visits in 65 South African primary care clinics. I used interrupted time series analyses of a large routine dataset to demonstrate almost 50%

decreases in HIV testing and ART initiations when the national lockdown started, with a subsequent gradual increase towards pre-lockdown levels. Of note, I did not find evidence of a decrease in treatment collection visits during lockdown, which suggested that worst-case scenarios from previous modelling studies were unlikely to materialise, and allowed policy makers to prioritise HIV testing and treatment initiation as part of the response to COVID-19.

1.2.10. Chapter 11: Discussion and conclusions

I summarise my findings in previous chapters, with respect to the overall aims of the thesis, and then discuss the contributions of this thesis to the existing evidence base. I critically appraise my work, and explore the implications for policy and research, including my post-doctoral research plans. I then reflect on what I have learnt, before concluding.

1.2.11. Note on published chapters

Chapters three to ten are based on manuscripts that have been published in, or are submitted or being prepared for submission to, peer-reviewed journals. I have made minimal changes to the text in the chapters, and I have included any published papers in their journal formatting in the relevant chapter appendix.

1.3. Personal motivation for conducting thesis on point-of-care testing in South African primary care clinics

In 2012 I took two years out from my UK General Practice (Family Medicine) training to work as a medical officer in Bethesda Hospital, a rural, public-sector district hospital in KwaZulu-Natal, South Africa (Figure 1.1). This was the most rewarding job of my career so far. It was fascinating to work on the front-line of the largest ART programme globally as it developed and responded to the changing nature of the HIV epidemic. I became the medical lead for the primary care HIV programme that was providing ART to 7000 people at community clinics, and also managed inpatient HIV and TB care. One of the most frustrating challenges was seeing people in the primary care clinics who had been failing their ART for several

months or sometimes even years, with repeated HIV viraemia that had not been managed correctly. Tragically, we would sometimes admit these people to hospital (Figure 1.2) with life-threatening opportunistic infections, resulting from immunocompromise caused by their ongoing viraemia.

Figure 1.1: View from Bethesda Hospital over the Makhathini flats



I conducted an audit at three of the clinics which identified that approximately 10% of patients on ART had viraemia. I then lead the development of a multidisciplinary programme of adherence support and clinical management for these patients, involving counsellors, social workers, dieticians and the hospital psychologist. We piloted this at the hospital primary care clinic and then rolled it out across the eight community primary care clinics. Some of the challenges that we identified were the difficulty in obtaining timely viral load results to guide management on the days that the medical officer visited the clinic. Without

recent viral load results, clinicians were often reluctant to follow guidelines to switch people to second-line ART.

Figure 1.2: Bethesda Hospital Resuscitation Unit



New point-of-care viral load tests were becoming available, and after I completed my General Practice specialty training, and an MSc in Public Health in Developing Countries, I moved back to South Africa. I worked at the Centre for the AIDS Programme of Research in South Africa (CAPRISA) as a research clinician and project manager on the Simplifying TREAtment and Monitoring of HIV (STREAM) trial of point-of-care viral load testing. This study was the first trial of point-of-care viral load testing, and the results were incorporated into WHO guidelines recommending that point-of-care viral load testing may be used to monitor patients on ART. However, STREAM did not specifically focus on people with viraemia, who I felt could gain the most from this intervention. Hence, I built on the experience of working on STREAM, to develop a proposal for a study among people with

viraemia, which became the backbone of this DPhil. I also continued to maintain my connections with front-line healthcare workers and programme managers in rural Bethesda and Durban, and used my developing research skills to evaluate new changes and challenges that these colleagues reported in the ART programme.

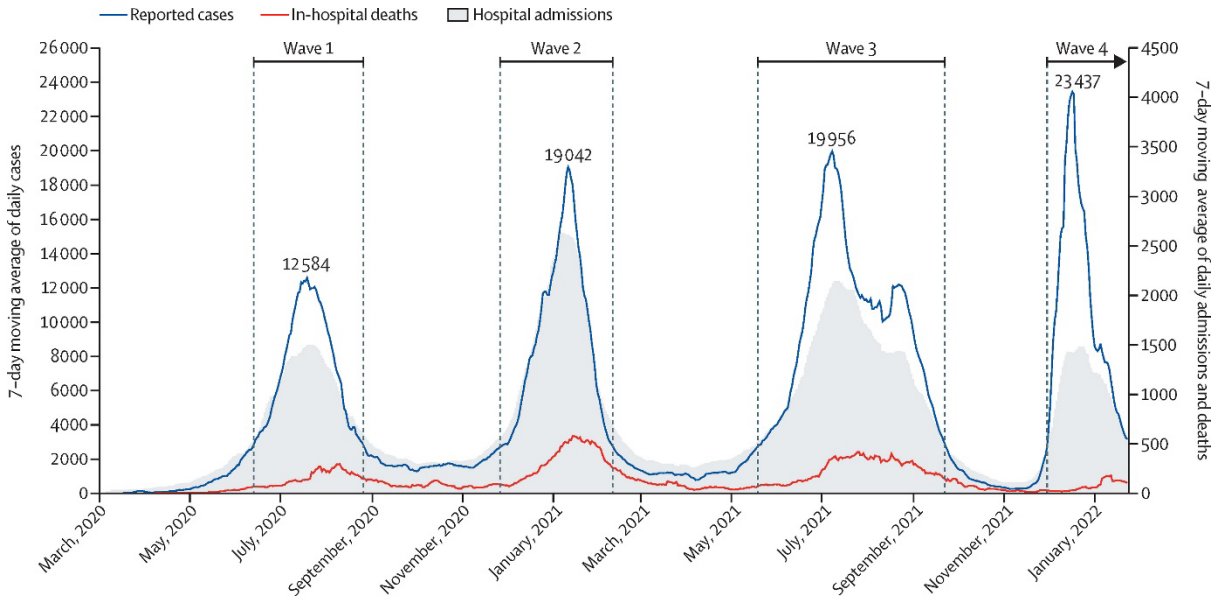
1.4. Impact of COVID-19 on my DPhil

I successfully applied for funding to conduct two studies of point-of-care viral load testing in my DPhil; the POwER study among people with viraemia, and the PHILA study in a community-based ART programme. We planned to complete POwER enrolment over about six months, with follow up finishing six months later, and then to conduct PHILA over about 6-9 months. By late February 2020, we had received provisional ethics approval for both studies, with full approval expected a month later, so I travelled to South Africa to prepare to start the POwER study. I had a week in Durban, at the CAPRISA study site, in which we conducted protocol training for the research team. I then travelled to India for a family wedding, with flights booked back to South Africa for mid-March, to start the study. Of course, this never happened, as COVID-19 led to travel bans and global lockdowns. I got the last flight from Mumbai to London, and while stuck in the UK I joined in COVID-19 research efforts by becoming part of the PRINCIPLE and PANORAMIC trial teams, the UK government platform trials for COVID-19 treatments in the community. I became a co-investigator and member of both Trial Management Groups, and drafted intervention specific appendices for the protocols, and several of the manuscripts from PRINCIPLE which were published in *The Lancet* and *British Journal of General Practice*.[1-5]

Despite this, and the severity of the COVID-19 pandemic in South Africa, we managed to start POwER in August 2020, as the first COVID-19 wave in South Africa was subsiding (Figure 1.3). Enrolment proved challenging, not least because of difficulties with laboratory viral load testing with the National Health Laboratory Service, who conducted pre-enrolment viral load tests, and were under immense strain with SARS-CoV-2 PCR testing. With me

working remotely, it was hard to resolve problems with enrolment and to build relationships with the public sector clinic team to implement point-of-care testing; no one had capacity to take on any new projects or challenges. We resorted to the research team conducting point-of-care testing, and we also had supply chain issues for point-of-care test cartridges. We had to stop enrolment in December 2020 until Feb 2021, due to the Beta variant wave in South Africa, at which point South Africa was also put on the UK travel 'Red List', which meant I had to cancel plans to travel early in 2021. The Delta variant wave in June-August 2021 meant I had to push back travel again. We asked the PHILA study funder for permission to repurpose the funds to increase enrolment in POwER instead, but they requested that we complete PHILA, with a no-cost extension, instead.

Figure 1.3: Seven day moving average of SARS-CoV-2 cases, COVID-19 hospital admissions, and in-hospital deaths in South Africa



Reproduced under terms of CC BY license from Jassat et al 2022, Lancet Global Health[6]

Finally, in October 2021, with cases low and South Africa off the UK travel 'Red List', I was able to make it back to Durban for two months, with the aim of enrolling the remaining 30 participants that we needed to enrol into POWER, and making preparations to start the PHILA study. We managed to ramp up enrolment, before, out of the blue, and with no other

known cases in the clinic, I tested positive for COVID-19 in mid-November. Richard Lessells, whose team at the University of KwaZulu-Natal have done the sequencing for HIV drug resistance mutations in POwER, kept messaging me, surprisingly frequently, to check how I was. Two days later, he and his colleague Prof Tulio de Oliveira were alongside the South African Minister for Health, at the press conference announcing that they had sequenced a new SARS-CoV-2 variant in South Africa, the Omicron variant. Everything stopped again, and we did not manage to enrol another POwER participant until the end of Jan 2022, with the last participant enrolled on 25th March 2022. This left very little time to complete enrolment, six months of follow up and analysis of data by the end of the academic year in October 2022. Thankfully, I was given a three months COVID-19 extension by the Wellcome Trust, giving me more time to submit by December 2022. We were only able to start PHILA in August 2022, meaning this project will be part of my post-doctoral work.

Alongside my DPhil study and work on PRINCIPLE and PANORAMIC, I have tried to engage with the research questions regarding COVID-19 and my field of interest, HIV in primary care. Early in the pandemic, the antiretroviral medication, lopinavir, was suggested as a potential treatment for COVID-19. I led a rapid review, published in *Antiviral Therapy*, which found no evidence to support lopinavir use among people hospitalised with COVID-19, and a lack of studies in primary care, where earlier treatment may have a better chance of preventing severe disease.[7] I also supervised two medical students in conducting a rapid review of whether COVID-19 differentially affected people living with HIV. We found accumulating evidence of worse outcomes among people living with HIV, and this review, on which I was last author, has now been cited over 30 times, including in WHO guidelines.[8] Lastly, I used existing collaborations with the eThekwini (Durban) Municipality Health Unit and Bethesda Hospital (where I used to work) to assess the impact of COVID-19 on HIV services in South Africa. This paper was published in *The Lancet HIV* and has been cited over 120 times; I have included it as the final results chapters of this thesis.

1.5. Key accomplishments

1.5.1. Publications

During my DPhil I have been first-author on ten peer-reviewed papers, last-author on three, and co-author on 20 (Chapter 1 Appendix), with an additional six papers currently submitted or under review.

1.5.2. Conference presentations

I have presented seven oral abstracts and seven poster presentations at international and national conferences (Chapter 1 Appendix).

1.5.3. Teaching and supervision

I lecture on the University of Kwazulu-Natal MSc. in Public Health, Health Measure Descriptive (Epi 1/Biostats 1) module, giving lectures in 2021 and 2022. I currently supervise one MSc Fellow at CAPRISA, and after my DPhil I should be eligible to formally supervise a PhD candidate at the University of Cape Town who I have been informally advising/supervising. I supervised two University of Oxford medical students to publish a rapid review of COVID-19 and HIV.[8]

1.5.4. Formal training

I audited the Centre for Evidence Based Medicine (CEBM) Stata/R for data analysis course in 2019. I formally attended the CEBM course on Knowledge into Action/Implementation Science in May 2019, and the Oxford NIHR Community Healthcare MIC Diagnostic Evidence Workshop in October 2019.

1.5.5. Funding and grants

My DPhil is funded by a Wellcome Trust PhD Program for Primary Care Clinicians Fellowship (203921/Z/16/Z, PI Dorward, £256,000). The POwER study was funded by grants from the

University of Oxford's Research England QR Global Challenges Research Fund (0007365, co-PIs Dorward & Butler, £50,000), the Africa-Oxford Initiative (AfiOx-119, co-PIs Dorward & Garrett, £5000) and the Tropical Health Education Trust (PI Dorward, £3000). HIV drug resistance testing and drug concentration testing was funded by the National Institute for Health and Care Research (NIHR) Community Healthcare MedTech and In Vitro Diagnostics Co-operative at Oxford Health NHS Foundation Trust (MIC-2016-018). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. During my DPhil I also lead or contributed to several successful grant applications for additional work on COVID-19 and HIV primary care services in South Africa (Chapter 1 Appendix).

Chapter 2

2. BACKGROUND

2.1. Introduction

Antiretroviral therapy (ART) to treat human immunodeficiency virus (HIV) has drastically changed the global HIV epidemic. Of the estimated 38.4 million people living with HIV globally in 2021, approximately 28.7 million (75%) are now receiving ART, up from 1.3 million in 2005.[9,10] This rapid scale up has led to large decreases in annual HIV/AIDS related deaths, from 2.8 million in 2005, to 650,000 in 2021.[9,10] Consistent adherence with effective ART suppresses HIV viral load to undetectable levels in the blood, which prevents further depletion of CD4+ T cells and allows immune reconstitution. People living with HIV who are taking ART and have viral suppression have been found to have similar life expectancy to the general population, while those who did not have viral suppression in the first year on ART had lower life expectancy.[11] Viral suppression also prevents the development of HIV drug resistance, which occurs when viral replication occurs in the presence of sub-optimal plasma drug levels (often due to inconsistent adherence), leading to selective drug pressure.[12]

Increasing evidence has emerged demonstrating that viral suppression also prevents onward HIV transmission. The landmark HPTN 052 randomised trial assessed the rate of new HIV infections among sero-discordant couples, where the partner living with HIV was randomised to receive early versus delayed ART.[13] There was a 96% reduction in new HIV infections among the early ART group, and no transmissions among people with a suppressed viral load. More recently, the PARTNER1[14] and PARTNER2[15] studies assessed new HIV infections in sero-discordant couples. Among couples where the partner with HIV had a viral load <200 copies/mL, there were no HIV transmissions after 135,000 occurrences of condomless sexual intercourse. This, along with other evidence, has led the World Health Organization (WHO) to endorse the Undetectable = Untransmittable (U = U)

campaign, which states that "*A person living with HIV who is on treatment and has an undetectable viral load cannot sexually transmit HIV*".[16]

Detecting and managing viraemia is therefore crucial to prevent HIV related morbidity and mortality, the development of drug resistance, and onwards HIV transmission. The WHO recommends viral load testing at six and 12 months after ART initiation, and annually thereafter.[17] As ART has been rolled out, viral load testing capacity has had to rapidly scale up across low- and middle-income countries (LMICs), often in settings with weak laboratory capacity.[18] By 2021, an estimated 20.3 million viral load tests were conducted globally, representing approximately 75% coverage,[19] with wide variation in coverage across countries. In most LMICs, as part of the WHO public health approach to ART rollout and monitoring, the majority of viral load testing takes place in centralized specialist laboratories with very high throughput. However, the majority of HIV care is provided in primary care settings which are often geographically distant, leading to difficulties getting samples to laboratories, and returning results back to clinicians to manage viraemia.

Viraemia can be caused either by inconsistent adherence to effective ART, or HIV drug resistance rendering ART ineffective. In high income settings, genotypic drug resistance is normally conducted for people with viraemia, but in LMICs the costs are often prohibitive.[20] In these settings, it can be difficult for clinicians to determine whether viraemia is caused by inconsistent adherence, or drug resistance. In particular, non-nucleoside reverse transcriptase inhibitor (NNRTI) antiretrovirals, which until recently were a key component of global ART regimens, have a low genetic barrier to resistance. Therefore, WHO recommends that people with viraemia ≥1000 copies/mL should receive enhanced adherence counselling and adherence support, with a repeat viral load after three months. A consecutive high viral load of ≥1000 copies/mL is defined as viral failure. Clients experiencing viral failure, in the presence of presumed good adherence, are assumed to have drug resistance, and a switch to second-line ART is recommended.

In the absence of diagnostic tests for drug resistance or objective measures of adherence, the WHO approach is supported by data showing that among people with viral failure on first-line NNRTI-based ART, approximately 70% will have HIV drug resistance,[21,22] and specifically in South African primary care, approximately 75% have HIV drug resistance.[23] However, several studies have demonstrated that the WHO clinical pathway is not well conducted, with multiple delays in this algorithm. Annual viral load testing is often not conducted when recommended,[24] viraemic results are not acted on and repeat viral loads are not done or delayed,[25] resulting in ongoing viraemia and delayed switching to second-line ART.[26-28] Furthermore, poor adherence can be due to complex social and psychological issues (e.g. gender-based violence, alcohol use, migrant labour and long distances to clinics).[29] Therefore, multiple visits for blood draws and result review confers an additional burden for these vulnerable populations.

New point-of-care viral load testing may overcome some of the challenges of managing viraemia in primary care settings. The WHO define point-of-care viral load testing as being "*conducted at the site at which clinical care is being provided, with results being returned to the patient or caregiver on the same day as sample collection and test to allow for clinical decisions to be made in a timely manner*".[30] While several assays have been developed,[31] only two have been approved through the WHO pre-qualification process for point-of-care viral load testing in LMICs. Both require separation of plasma from whole blood, to remove cell-associated proviral DNA and RNA which can result in over-quantification of viral load.[32]

The Xpert HIV-1 viral load is a fully automated molecular polymerase chain reaction (PCR) assay which received WHO pre-qualification in 2017.[33] It runs on the GeneXpert platform (Cepheid, Sunnyvale, USA), which is widely used for tuberculosis diagnostics in LMICs, and can also test for other infectious diseases including sexually transmitted infections and SARS-CoV-2. GeneXpert units come in modules with different sizes, with capacity to test one, two, four, 16 or 84 cartridges simultaneously, allowing for testing for different infections with different cartridges. The Xpert HIV-1 VL cartridge provides a quantitative viral load

between 40 - 10,000,000 copies using 1mL of plasma, within 90 minutes. The m-PIMA HIV-1/2 Viral Load (formerly known as the Alere Q) (Abbott, Chicago, USA) is another fully automated molecular PCR assay, which received WHO pre-qualification in 2019.[34] Each m-PIMA unit can test one cartridge at a time, and takes approximately 70 minutes to provide a quantitative viral load result between 800 to 1,000,000 copies/mL, using 50 µL of plasma. Below, I review the evidence that was available at the start of my DPhil to support the use of point-of-care viral load assays in primary care.

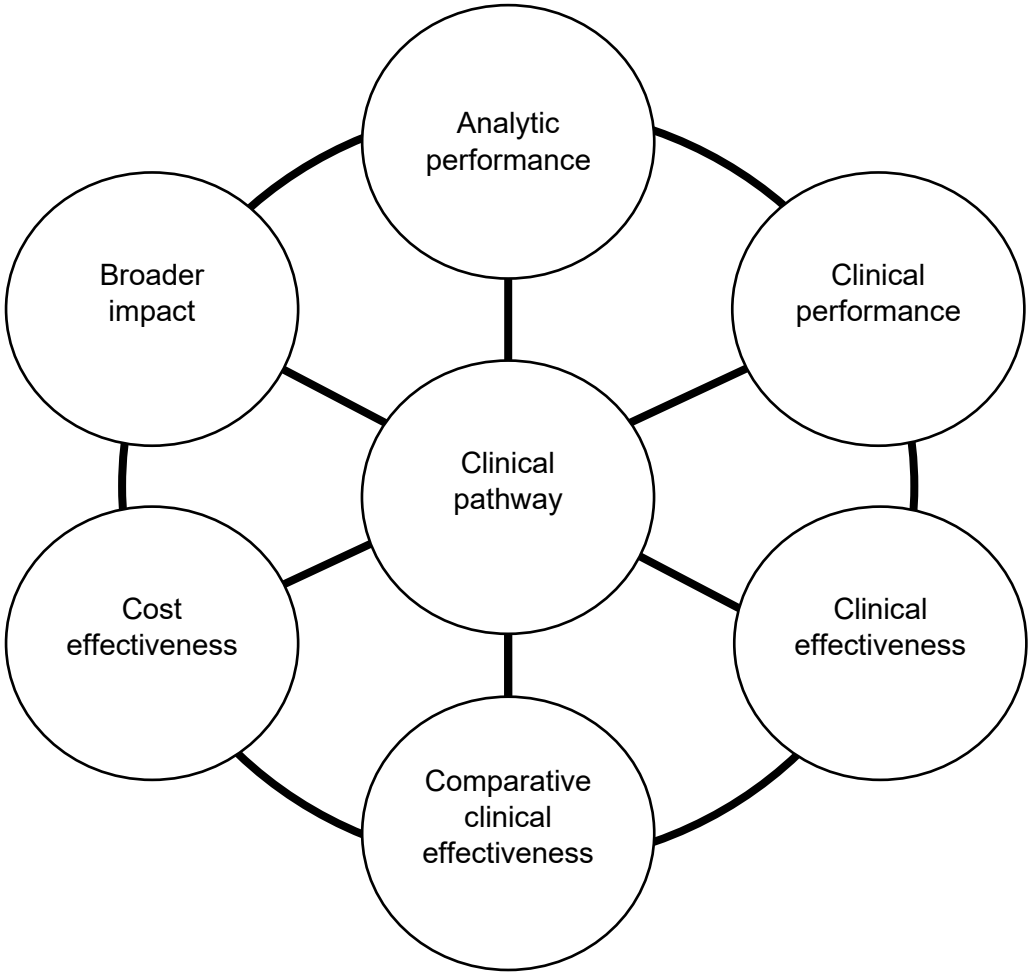
2.2. Review of evidence to support point-of-care viral load testing in primary care

2.2.1. Rationale

The type of evidence that is used to support the use of diagnostic tests has been classified in a cyclical framework by Horvath et al. (Figure 2.1),[35] consisting of five key components. They defined analytical performance as the ability of a test to meet pre-specified technical specifications, clinical performance as the ability to accurately detect 'clinical conditions or physiological states' in patients, clinical effectiveness as the impact of the test on health outcomes, and cost-effectiveness as the economic cost of achieving these health impacts. The fifth component, which they term 'broader impacts', rather loosely encompasses all other consequences of testing, such as psychological impacts, acceptability, and organisational considerations. Therefore, while not explicitly stated, considerations around implementing tests in routine clinical settings can be considered under broader impacts.

A comprehensive review, based on the above framework, found that the evidence to support the use of a variety of point-of-care diagnostic tests largely consists of studies of analytic performance, with less evidence available regarding clinical effectiveness, implementation or cost effectiveness.[36] Evidence was generated in a non-linear, non-cyclical process, with some tests being introduced into clinical practice without any evidence of clinical effectiveness. I used these frameworks to identify evidence supporting the clinical impact of point-of-care viral load testing.

Figure 2.1: Cyclical framework for the evaluation of medical tests



Adapted from Horvath et al 2014[35]

2.2.2. Aim

I aimed to identify the state of the clinical evidence to support the use of point-of-care viral load testing in primary care services at the beginning of my DPhil.

2.2.3. Methods

I conducted a systematic search to identify relevant studies, and did a narrative account of the evidence which I identified, as it was not suitable for meta-analysis. I excluded studies focussed solely on analytic performance, and focussed on studies in primary care (i.e. testing was conducted in community settings, and not in hospitals or centralised

laboratories) of a) clinical performance b) clinical effectiveness c) comparative clinical effectiveness, d) cost-effectiveness and e) implementation, including service delivery outcomes (as part of Horvath's 'broader impact'). I excluded studies which focussed solely on the use of point-of-care viral load testing for HIV diagnosis.

I searched PubMed using the following terms, (("point-of-care" OR "POC" OR "point of care" OR "POCT") AND (HIV)) AND (viral load), from inception until October 11, 2019, the date of submission of my DPhil study protocol. I searched the reference lists of identified articles to find further relevant articles. I also included data from studies which I was involved in (the STREAM trial), which had not yet been published but for which results were available. After removing duplicates, I screened titles and abstracts, before doing a full text review of remaining articles to assess whether they met inclusion criteria.

2.2.4. Results

I identified 188 records through PubMed, of which 16 were retained after title and abstract screening, and six were retained after full text screening. I identified one other study from reference and citation lists, and included two additional papers from studies that I was involved with that were under review but had not yet been published. Three of the studies were systematic reviews which mainly focused on analytic performance or clinical performance in non-community settings, but did include some community-based studies.[37-39] Three studies evaluated clinical performance in community settings;[40-42] none of these studies used point-of-care viral load results for clinical management. One study assessed clinical effectiveness and feasibility,[43] and one study assessed comparative clinical effectiveness.[44] One study assessed acceptability of point-of-care viral load testing.[45]

2.2.4.1. Systematic reviews of analytic and clinical performance

Two systematic reviews by Nash et al.[38] (n = 13 studies, of 2,011 quantifiable samples) and Sacks et al.[39] (n = 13 studies [not all the same studies as Nash et al], of 3790 paired plasma

and viral load results) assessed the analytic and clinical performance of the Xpert HIV-1 Viral Load assay (Cepheid, Sunnyvale USA). Nash et al. found strong correlation (pooled Spearman corelation co-efficient 0.96, 95% CI 0.86-0.99) and good agreement (there was too much heterogeneity for pooling, but all mean bias were <0.35 $\log_{10}$ copies/mL) between the Xpert HIV-1 VL and reference viral load assays, but did not assess diagnostic accuracy to detect viraemia. Sacks et al. found good agreement (mean bias 0.04 $\log_{10}$ copies/mL, 95% CI 0.02, 0.07) and high sensitivity (96.5, 95% CI 95.1, 97.5) and specificity (96.6, 95% CI 92.9, 98.4) to detect viraemia at ≥1000 copies/mL.

Another systematic review by Agutu et al.[46] assessed analytic and clinical performance, as well as broader aspects such as useability and result turn-around time, of four assays marketed as potential point-of-care viral load assays for monitoring of HIV. Out of 18 studies, 13 evaluated the Xpert HIV-1 Viral Load, with results similar to the above two systematic reviews. Studies of the SAMBA I/II HIV Semi-Quantitative (Diagnostics for the Real World, Cambridge, UK) (n = 3 studies), which reports a binary result of ≥1000 copies/mL versus < 1000 copies/mL, only reported sensitivity of 100%, but did not report specificity to detect viraemia. The Liat HIV Quant (IQuum, Marlborough, USA) (n = 1 study) had good correlation (Pearson correlation co-efficient 0.96) when using plasma samples, and sensitivity of 100% to detect viraemia ≥1000 copies/mL, but specificity was lower at 88.2%. One study of the Alere q HIV-1/2 Detect (now known as the Abbott m-PIMA HIV-1/2 Viral Load, n = 1 study) is discussed below.

2.2.4.2. Clinical performance in community settings

Of all the studies in the above reviews, the majority placed the point-of-care viral load assay in hospital or centralised laboratories. From my PubMed search, and from the above reviews, I identified three studies evaluating clinical performance of the point-of-care assay in community settings; all three were contained in the above reviews.[40-42] Two were studies of the Xpert HIV-1 VL. A study of testing conducted by research laboratory technicians in a

clinic site laboratory in South Africa found good correlation (n= 62, Spearman coefficient = 0.94, p<0.001) and agreement (mean bias between laboratory reference and Xpert results of −0.10 log_{10} copies/mL, −0.59, 0.39).[42] A study of Xpert HIV-1 VL testing conducted in a mobile clinic in Botswana among 277 individuals found good correlation (r^2 = 0.92, p<0.001) and mean bias of 0.34 log_{10} copies/ml (0.26, 0.40). Sensitivity to detect viraemia ≥1000 copies/mL was low at 0.66 (0.54, 0.77), specificity was high at 0.99 (0.97, 1.00).[41] One study evaluated the Alere q HIV-1/2 Detect in a primary care clinic in Mozambique, with testing of finger-prick whole blood samples by laboratory technicians among 443 individuals. Results showed poor correlation with the laboratory reference viral load assay with an r^2 of 0.36. Sensitivity to detect viraemia at ≥1000 copies/mL was good at 96.8%, but specificity was lower at 84.0%. Results were not given to patients or used for clinical management in any of these studies.

2.2.4.3. Clinical effectiveness

One study assessed clinical effectiveness and feasibility of using the Xpert HIV-1 VL in two district hospital laboratories and one primary care clinic in rural Zimbabwe.[43] Testing was conducted by laboratory technicians in a dedicated, specially adapted site laboratory in the clinic, with the GeneXpert platform also used for tuberculosis testing and early infant diagnosis of HIV, and results used for clinical management. At the primary care clinic 245 Xpert HIV-1 VL tests were conducted with a median turnaround time of 1 day (IQR 0, 1) to get results to the clinician. There was an error rate of 3.7%, and overall laboratory technicians found the test straightforward to use. At a threshold of ≥1000 copies/mL, the Xpert HIV-1 VL was concordant with the centralised laboratory test result in 96.8% of samples. 23/245 (9.3%) were viraemic, and the median time from testing to receiving enhanced adherence counselling was 23 days. Eleven had a documented outcome after enhanced adherence counselling; four re-suppressed < 1000 copies/mL, four were switched to second-line ART, and three remained unsuppressed and not switched.

2.2.4.4. Comparative clinical effectiveness

There was only one study which assessed the comparative clinical effectiveness of point-of-care viral load testing; the STREAM study which I project managed as a research clinician.[44] This was the first randomised trial of point-of-care viral load testing, using the Xpert HIV-1 VL in a research clinic laboratory, adjacent to a public sector primary care clinic . We randomised 390 people living with HIV who were stable and receiving ART to either point-of-care viral load testing and task shifting of care to an enrolled research nurse, versus standard laboratory based viral load testing and care provided by public sector professional nurses. At enrolment, only 18/390 (4.6%) had viraemia ≥1000 copies/mL. After 12 months, the primary outcome of viral suppression and retention in care was higher in the intervention arm (175/195, 90%) compared to the standard of care arm (148/195, 76%, risk difference 13.9%, 95% CI 6.1, 21.2, p <0.001). 397/398 (99%) of point-of-care results were given to participants on the same day. However, because clinical care in the intervention arm was provided by research staff, the extent to which the improved outcome can be attributed to point-of-care testing cannot be determined.

2.2.4.5. Broader impacts

We also conducted a sub-study within STREAM to assess the acceptability of point-of-care viral load testing using in-depth interviews and focus group discussions with 55 trial participants and eight healthcare workers.[47] Point-of-care viral load testing was generally acceptable, with the benefits of same day results including fewer clinic visits (less days off work and lower transport costs), less anxiety waiting for results, better motivation for good adherence, and quicker referrals into a community ART programme for people with viral suppression. As the intervention was provided by research staff, there was concern that point-of-care testing may not be feasible to implement in busy public sector clinics, due to problems with clinic flow for the large numbers of patients, and the need for trained staff and good quality control procedures.

2.2.5. Discussion

The majority of evidence which I identified in this review assessed the analytic and clinical performance of point-of-care viral load assays used in centralised laboratories and hospitals. The assay with the most evidence of good clinical performance was the Xpert HIV-1 VL, with high sensitivity and specificity to detect viraemia at ≥1000 copies/mL. In the few studies of other assays, sensitivity and specificity were poorer (Liat and Alere q), or not fully reported (SAMBA Semi-Quantitative).

In non-hospital, community settings, two studies demonstrated reasonable clinical performance of the Xpert HIV-1 VL, although sensitivity to detect viraemia was low in the study using a mobile clinic in Botswana. The reason for lower sensitivity is not clear, but this appears to be an isolated issue within this study as it was not seen in hospital or laboratory-based studies. There were only two studies assessing clinical effectiveness in community care settings, and both had few participants with viraemia (9.3% and 4.6% respectively). In the study from Zimbabwe, very few patients received their Xpert HIV-1 viral load results on the same day, and very few of the patients with viraemia were appropriately managed. In the STREAM trial, using the Xpert to deliver point-of-care results was far more successful, when delivered by a research team, and patients and staff found point-of-care testing to be acceptable.

Therefore, this literature review supports the use of the Xpert HIV-1 VL due to its acceptable clinical performance, but I did not find evidence demonstrating that the Xpert HIV-1 VL can be used effectively in public sector, primary care settings and whether testing can be conducted by nurses. Furthermore, I found no evidence to support its use to manage people with viraemia, who may stand the most to benefit from more readily available viral load results and quicker clinical management. Therefore, new studies are needed to evaluate whether point-of-care viral load testing can be used to improve the management of viraemia in primary care clinics.

2.3. The changing context of HIV services in primary care in South Africa

As well as a need for new data on the use of point-of-care viral load to manage viraemia, there is a need to better understand the context within which these tests may be implemented, in order to guide their most efficient use. This is particularly important as public sector ART programmes continue to evolve rapidly to incorporate new ART regimens[48] and innovations in service delivery,[49] both globally and in South Africa. Understanding the impact of these changes is crucial to ensure the development of appropriate and relevant strategies for monitoring ART. Two major changes that have happened during the course of my DPhil, which have a direct impact on how point-of-care viral load testing could be used, are the rollout of a new antiretroviral, dolutegravir, and the implementation of new models of community-based HIV care.

2.3.1. Dolutegravir rollout

Since the beginning of the ART rollout in LMICs, a key component of WHO recommended regimens have been NNRTIs such as nevirapine and efavirenz.[17] While relatively safe and tolerable, NNRTIs have a low genetic barrier to drug resistance, and their continued use has led to rising levels of drug resistance. By 2017, surveillance data suggested that in many settings, including Eastern and Southern Africa, over 10% of people newly starting ART had resistance to NNRTI's, making NNRTI-based first-line regimens ineffective.[22] Therefore, since 2018, the WHO has recommended dolutegravir in first-line regimens.[50] Dolutegravir has a higher genetic barrier to drug resistance, is more efficacious in achieving viral load suppression and is more tolerable than NNRTI regimens.[48] This has implications for viral load monitoring and management of viraemia, as it is not clear whether the WHO viral failure algorithm should be continued. With drug resistance expected to be less frequent, viraemia may be more likely to be caused by inconsistent adherence alone, and so switching to second-line ART may not be appropriate. Dolutegravir has now been introduced into over 100 countries, including South Africa,[51] but there is very little robust data from non-trial,

routine settings assessing the impact of the dolutegravir rollout on the frequency of viraemia, and the proportion of people with viraemia who have drug resistance. If drug resistance to dolutegravir is rare, then tests that objectively measure adherence may be important additions to algorithms to monitor and manage viraemia.

2.3.2. Novel point-of-care urine drug level tests to measure adherence

Tenofovir disoproxil fumarate is a key component of ART regimens, and is used by over 95% of people receiving ART in LMICs.[19] The most common formulation is in fixed dose combination tablets, either combined with emtricitabine and efavirenz, or more recently, with lamivudine and dolutegravir. Once ingested, it is metabolised to tenofovir and excreted in urine.[52] New lateral flow, point-of-care tests to rapidly measure levels of urine tenofovir have recently been developed.[52,53] These could provide an alternative method to objectively measure ART adherence in primary care settings, and may be of particular value in the context of the dolutegravir rollout, where viraemia is most likely to be caused by poor adherence. However, there is little data evaluating the analytic performance of these new assays, and so they have yet to be approved for use in routine settings.

2.3.3. Community ART delivery programmes

As numbers of people receiving ART have grown, new, more efficient ways of providing ART have been developed that focus on meeting clients' needs in a 'people first' manner.[54] These 'differentiated ART delivery' models have moved away from a one-size fits all approach, to providing tailored services depending on the needs of the client. For people with viral suppression who are stable on lifelong ART, the need for clinical oversight is often minimal, and so strategies have focussed on streamlining services through increasing the interval between clinic visits, multi-month dispensing of ART, and community delivery of ART.[55,56] In South Africa, many of these services have been delivered through the Chronic Centralised Medication Dispensing and Distribution programme (CCMDD), which allows people with viral suppression to collect their treatment at community pick-up points, including private

pharmacies and community centres, rather than having to attend clinic.[57] Point-of-care viral load testing, could fit well into CCMDD by allowing viral loads to be reviewed in one annual clinic visit, with people with viral suppression then being referred directly back to the community to collect ART. However, at the beginning of my DPhil there was no published data evaluating CCMDD and its impact on engagement in HIV care.

2.4. Aims of the thesis

From my review of the literature and appraisal of the evidence, the research questions that I aim to answer in this thesis are:

- Is point-of-care viral load testing a promising strategy to improve management of viraemia in primary care in South Africa?
    - I will evaluate the clinical performance of a novel point-of-care HIV viral load assay, as well as two existing assays, when testing is conducted by laboratory technicians or nurses.
    - I will conduct a randomised feasibility/pilot study to assess whether it is feasible to conduct a larger randomised trial of point-of-care viral load testing in South African primary care clinics.
    - Within the above study, I will assess whether viraemia in people taking dolutegravir is caused predominantly by HIV drug resistance or inconsistent adherence, and how this impacts on the role of point-of-care viral load testing in managing viraemia.
    - I will evaluate the analytic performance of a novel point-of-care urine tenofovir test.
- How has HIV treatment in primary care in South Africa changed over the course of the DPhil, and what implications does this have for ART monitoring strategies?

- I will evaluate the extent to which dolutegravir has been rolled out in primary care clinics in South Africa and what impact it has had on the frequency of viraemia.
- I will evaluate client and healthcare worker perspective on the impact of a community ART delivery programme on clients' engagement in primary care HIV services.
- I will evaluate the impact of the first COVID-19 lockdown in South Africa on HIV care in South African primary care clinics.

Chapter 3

Based on a paper for which I am first author, entitled “Diagnostic Accuracy of the Rapid Xpert HIV-1 Viral Load XC, Xpert HIV-1 Viral Load, & m-PIMA HIV-1/2 Viral Load in South African Clinics”, peer-reviewed and published in the *Journal of Acquired Immune Deficiency Syndromes (JAIDS)*.[58]

3. DIAGNOSTIC ACCURACY OF POINT-OF-CARE HIV VIRAL LOAD TESTS

3.1. Chapter rationale

In Chapter 2 I highlighted a lack of evidence regarding the clinical performance of point-of-care viral load assays when testing is conducted in primary care. In this Chapter, I present results demonstrating the clinical performance of three different point-of-care viral load assays, when testing was conducted by laboratory technicians in a primary care site laboratory, and by nurses in the clinic.

3.2. Introduction

The World Health Organization (WHO) recommends antiretroviral therapy (ART) for all people living with HIV, to suppress the HIV viral load.[17] This prevents immunosuppression and related morbidity and mortality,[59,60] as well as onward HIV transmission. Regular HIV viral load testing is a key component for monitoring the effectiveness of ART in current WHO guidelines, which recently endorsed the use of point-of-care viral load assays, where testing is conducted at the clinical site by laboratory professionals or specifically-trained healthcare workers.[61] These assays can reduce the time from blood draw to results being available, allowing clinicians to take decisions on the same day in one clinic visit, rather than having to schedule follow up appointments to discuss the results.[31,62] A randomised trial conducted by our team in South Africa, using the Xpert HIV-1 VL assay(Cepheid, Sunnyvale, USA), found that point-of-care testing improved the primary outcome of HIV viral suppression and retention in care by 13.7%.[44]

Currently, there are two point-of-care HIV viral load assays that are approved by the WHO for use in low and middle-income countries. The m-PIMA HIV 1/2 VL (Abbott, Chicago, USA) received WHO pre-qualification in 2019,[34] and has been found to perform well in one laboratory-based[63] and two clinic-based evaluation studies.[64,65] The Xpert HIV-1 VL received WHO pre-qualification in 2017,[33] and has also been found to perform well in 19 studies, which have been summarised in two systematic reviews.[38,39] Only three of these studies reported conducting Xpert HIV-1 VL testing in clinics, as opposed to centralised laboratories. Because the assay was not able to detect certain recombinant HIV-1 sub-types,[66] Cepheid have recently released a next generation dual target assay, the Xpert HIV-1 Viral Load XC (HIV VL XC).[67] This assay was developed to improve accuracy in specific HIV recombinant sub-types (namely CRF02_AG), which were not detected in one study of the Xpert HIV-1 VL assay.[66] CRF02_AG is more common in West and Central Africa than in South Africa. This assay recently received CE-IVD clearance,[68] but has not yet been evaluated in any published studies that we are aware of.

3.2.1. Objectives

In this study, we aimed to assess the analytic performance of the novel, dual target Xpert HIV-1 VL XC, the existing Xpert HIV-1 VL and the m-PIMA HIV 1/2 VL, when used in South African clinics, compared to an established laboratory reference assay.

3.3. Methods

3.3.1. Study design and participants

We conducted a prospective diagnostic accuracy evaluation as a sub-study within the Point-Of-care HIV viral load testing to Enhance Re-suppression (POwER) study, and the Centre for the AIDS Program of Research in South Africa (CAPRISA) 002 Acute Infection study. POwER is a randomised feasibility study in one urban and one rural public sector, primary care clinic in KwaZulu-Natal, South Africa, and the study protocol has been published

elsewhere.[69] In summary, approximately 100 non-pregnant adults aged 18 and over, receiving first-line ART and with HIV viraemia >1000 copies/mL in the past 6 weeks, are randomised to receive a second viral load test after 12 weeks by point-of-care test, or by standard laboratory based viral load testing. The primary outcome of viral suppression <50 copies/mL is assessed after 24 weeks. The CAPRISA 002 study is taking place in the same two clinics, and is a long-term cohort study of women living with HIV who are on ART.[70] For this sub-study, POwER and CAPRISA 002 participants who provided written informed consent, had additional 4 to 8mLs of venous blood drawn for point-of-care assay evaluation, taken alongside the main study blood draws at enrolment or during follow up. We initially planned to use consecutive participants enrolling in POwER and attending follow up in CAPRISA 002, but disruptions in test cartridge supply chains, assay training and staffing due to the COVID-19 pandemic meant that there were periods where various assay cartridges were not available or rarely nurses did not have time to conduct testing. We therefore used a convenience sampling strategy instead, where consenting patients enrolling or attending follow up in either study had samples tested on whichever assays were available at that time in the respective clinic. This meant that some participants in POwER had multiple samples taken for this evaluation at up to three different visits.

3.3.2. Test methods

Assay manufacturers provided point-of-care training to both research laboratory technicians and research nurses, as well as ongoing testing support. Initially, laboratory technicians conducted testing in a dedicated on-site point-of-care laboratory in the clinics. Once laboratory technician testing was established, research nurses conducted testing in a dedicated space in the clinic, with ongoing troubleshooting support from the manufacturer and on-site laboratory staff. For point-of-care viral load testing, 4 to 8mLs whole blood was obtained by venepuncture into an EDTA tube and centrifuged (by laboratory technicians or nurses respectively) to obtain plasma, which was transferred into the test cartridge and loaded into the respective assay platform. The m-PIMA HIV 1/2 platform is a single module

instrument which requires 50 µL of plasma, and provides a quantitative viral load result between 800 to 1,000,000 copies/mL in approximately 70 minutes. The manufacturer states that the m-PIMA HIV 1/2 has a lower limit of detection of 342 (95% confidence interval [CI] 279 - 451) copies/mL for HIV-1 group M, and 228 (95% CI 187-295) copies/mL for HIV-1 group O.[71] The new Xpert HIV 1 VL XC and existing Xpert HIV 1 VL use the same GeneXpert platform (Cepheid, Sunnyvale, USA) and both require 1 mL of plasma to provide a quantitative viral load result between 40 - 10,000,000 copies/mL in approximately 90 minutes. The lower limit of detection as stated by the manufacturer is 13.6 (95% CI 11.1-15.6) copies/mL for the Xpert HIV-1 VL XC,[67] and 15.3 (95% CI 13.5-17.0) copies/mL for the Xpert HIV-1 VL.[72] We used research use only cartridges of the same version as the now commercially released Xpert XC, and single module GXP I and four module GXP IV instruments. If a point-of-care assay resulted in an error or an invalid result, the test was repeated using remaining plasma, if available. Point-of-care viral load results from this evaluation were not provided to patients and were not used for clinical decision making.

For reference laboratory testing, a nurse drew whole blood in an EDTA tube at the same timepoint, which was centrifuged to plasma and stored at -80°C in the CAPRISA bio-repository. These samples were then defrosted and tested in two batches (study mid-point and study end) on the cobas® HIV-1 reference assay using the cobas 6800 platform (Roche, Basel, Switzerland) at the Inkosi Albert Luthuli Hospital National Health Laboratory Service in Durban, KwaZulu-Natal. We chose this assay because it is one of the standard viral load assays which has been widely validated and used in the South African National Health Laboratory Service. Staff performing laboratory reference testing were blinded to results of the point-of-care testing and vice versa.

3.3.3. Analysis

For the Xpert assays, we evaluated sensitivity and specificity to detect viraemia at thresholds of 50 copies/mL, 200 copies/mL and 1000 copies/mL. Because the m-PIMA HIV 1/2 VL does

not provide a quantitative viral load below 800 copies/mL, we only evaluated the 1000 copies/mL threshold. We evaluated accuracy at these thresholds as they are used in national and international guidelines to define viraemia and treatment failure.[61,73-75] We assessed agreement with the laboratory reference assay using Bland-Altman plots, and association using Pearson correlation coefficients, restricted to paired samples with a quantifiable viral load on both the point of care and reference laboratory assay. Although there are well known limitations with using correlations in diagnostic evaluations,[76] they are commonly reported in other studies of viral load assays, and so we report them here alongside Bland-Altman plots.

We conducted sensitivity analyses using bootstrap methods to account for repeat testing in the same participants at different time points, which could introduce clustering of errors. For example, if a participant had a viral sub-type that was not detected by a particular assay, inaccurate results would be more common among repeat tests in that participant, compared to tests in the general sample. In the bootstrap models we randomly selected samples from one timepoint per participant, and calculated the sensitivity, specificity, mean bias and correlation from this population. We then repeated this 1000 times, and calculated the mean sensitivity, mean specificity, mean mean bias and mean correlation from the 1000 bootstrap samples.

We estimated that with the resources and time available, we could test approximately 150 samples on each assay. However, the COVID-19 pandemic interrupted cartridge supply chains for the m-PIMA HIV 1/2 VL, meaning fewer tests were possible for this assay. Because not all samples were tested on all point-of-care assays, we did not directly compare the performance of the point-of-care assays against each other.

3.3.4. Ethical approval

The POwER and CAPRISA 002 protocols, including use of samples for point-of-care viral load assay evaluation, were approved by the University of KwaZulu-Natal Biomedical

Research Ethics Committee (BREC/00000836/2019 and E013/04 respectively), and POwER has also been approved by the University of Oxford Tropical Research Ethics Committee (OxTREC 66-19) and is registered with the Pan-African Clinical Trials Registry (PACTR202001785886049).

3.4. Results

3.4.1. Participants

Between June 26, 2020 and September 15, 2021, 140 participants provided paired samples, at one or more timepoints, for testing in this evaluation. Testing was conducted in the rural clinic for 25 participants, and at the urban clinic for 115 participants. 98 (70%) were women, median age was 37 years (interquartile range [IQR] 33-43), median time on ART was 4.6 years (IQR 2.9-6.0) and median CD4 count was 569 cells/μL (IQR 356-792).

3.4.2. Test results

Overall, 189 samples were tested on at least one point-of-care viral load assay. 174 samples were tested using the Xpert HIV-1 VL XC, 188 samples using the Xpert HIV-1 VL, and 128 samples using the m-PIMA HIV 1/2 VL (Table 3.1). Nurses conducted testing for 54/174 (31%) of Xpert HIV-1 VL XC samples, 26/188 (14%) Xpert HIV-1 VL samples, and 23/128 (18%) m-PIMA HIV 1/2 VL samples. Initial errors were produced for eight (4.6%) Xpert HIV-1 VL XC samples, two (1.1%) Xpert HIV-1 VL samples, and three (2.5%) m-PIMA HIV 1/2 VL samples. In some cases, tests were successfully repeated, meaning that final results were not available due to assay errors for eight (4.6%) Xpert HIV-1 VL XC samples, one (0.5%) Xpert HIV-1 VL sample, and two (1.7%) m-PIMA HIV 1/2 VL samples (see Table 3.1 for total number of errors and Table 13.1 for error codes). Four of the Xpert HIV-1 VL XC errors occurred at the beginning of the nurse testing process; this was the first assay that the nurses were trained to use.

Table 3.1 Samples tested on point-of-care viral load assays

	Xpert HIV-1 VL XC	Xpert HIV-1 VL	m-PIMA HIV 1/2 VL
Samples from one timepoint per participant	84 (48.3)	97 (51.6)	67 (56.8)
Samples from two timepoints per participant	70 (40.2)	78 (41.5)	46 (39.0)
Samples from 3 timepoints per participant	12 (6.9)	12 (6.4)	3 (2.5)
No result due to assay errors [a]	8 (4.6) [b]	1 (0.5) [c]	2 (1.7) [d]
Total	174	188	118

[a] See Table 13.1 in chapter appendix for error codes

[b] Eight samples (4.6%) produced an error. Four were retested, with the repeat test also producing an error meaning no result was available. Four were not retested meaning no result was available

[c] Two samples (1.1%) produced an error, and both were retested. One repeat test also produced an error meaning no result was available, the other produced a valid result.

[d] Three samples (2.5%) produced an error, and all were retested. Two repeat tests also produced an error meaning no result was available, the other produced a valid result.

3.4.2.1. Sensitivity and specificity

Sensitivity and specificity at 1000 copies/mL, compared to the Cobas 6800, were 97% and 98% (Xpert XC), 100% and 96% (Xpert VL), and 92% and 99% (m-PIMA) respectively. For the Xpert assays, sensitivity and specificity at 50 copies/mL were 93% and 96% (Xpert XC), and 95% and 95% (Xpert VL) respectively (Table 3.2). The m-PIMA was not assessed at 50 and 200 copies/mL because the lower limit of quantitation is 800 copies/mL.

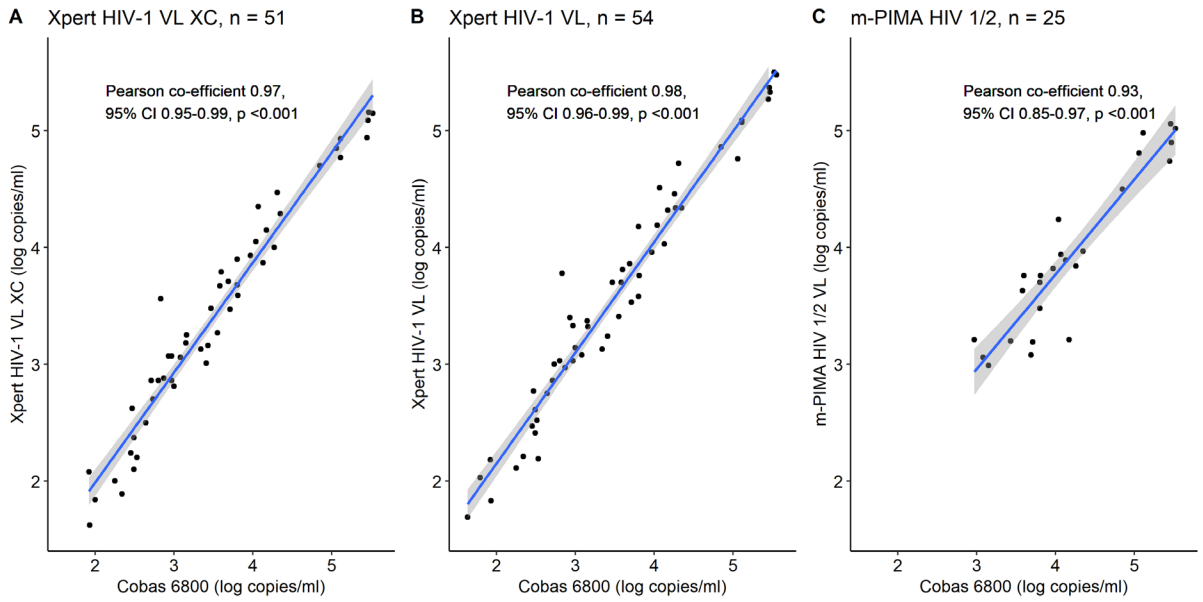
Table 3.2 Raw numbers, sensitivity, and specificity (95% confidence intervals) of three point-of-care viral load assays at different viral load thresholds

		Roche Cobas 6800					Roche Cobas 6800					Roche Cobas 6800		
		<50	*≥50*	*Total*			*<50*	*≥50*	*Total*			*<50*	*≥50*	*Total*
Xpert HIV-1 VL XC	*<50*	108	4	112	**Xpert HIV-1 VL**	*<50*	125	3	128	**m-PIMA HIV 1/2 VL**	*<50*	-	-	-
	≥50	4	50	54		*≥50*	6	53	59		*≥50*	-	-	-
	Total	112	54	166		*Total*	131	56	187		*Total*	-	-	-
	Sensitivity: 0.93 (0.81, 0.98) Specificity: 0.96 (0.91, 0.99)					Sensitivity: 0.95 (0.84, 0.99) Specificity: 0.95 (0.90, 0.98)					Sensitivity: NA Specificity: NA			
		<200	*≥200*	*Total*			*<200*	*≥200*	*Total*			*<200*	*≥200*	*Total*
Xpert HIV-1 VL XC	*<200*	116	4	120	**Xpert HIV-1 VL**	*<200*	137	2	139	**m-PIMA HIV 1/2 VL**	*<200*	-	-	-
	≥200	3	43	46		*≥200*	1	47	48		*≥200*	-	-	-
	Total	119	47	166		*Total*	138	49	187		*Total*	-	-	-
	Sensitivity: 0.91 (0.79, 0.97) Specificity: 0.97 (0.92, 0.99)					Sensitivity: 0.96 (0.85, 0.99) Specificity: 0.99 (0.95, 1.00)					Sensitivity: NA Specificity: NA			
		<1000	*≥1000*	*Total*			*<1000*	*≥1000*	*Total*			*<1000*	*≥1000*	*Total*
Xpert HIV-1 VL XC	*<1000*	131	1	132	**Xpert HIV-1 VL**	*<1000*	148	0	148	**m-PIMA HIV 1/2 VL**	*<1000*	90	2	92
	≥1000	3	31	34		*≥1000*	6	33	39		*≥1000*	1	23	24
	Total	134	32	166		*Total*	154	33	187		*Total*	91	25	116
	Sensitivity: 0.97 (0.82, 1.00) Specificity: 0.98 (0.93, 0.99)					Sensitivity: 1.00 (0.87, 1.00) Specificity: 0.96 (0.91, 0.98)					Sensitivity: 0.92 (0.72-0.99) Specificity: 0.99 (0.93-1.00)			

3.4.2.2. Correlation and agreement

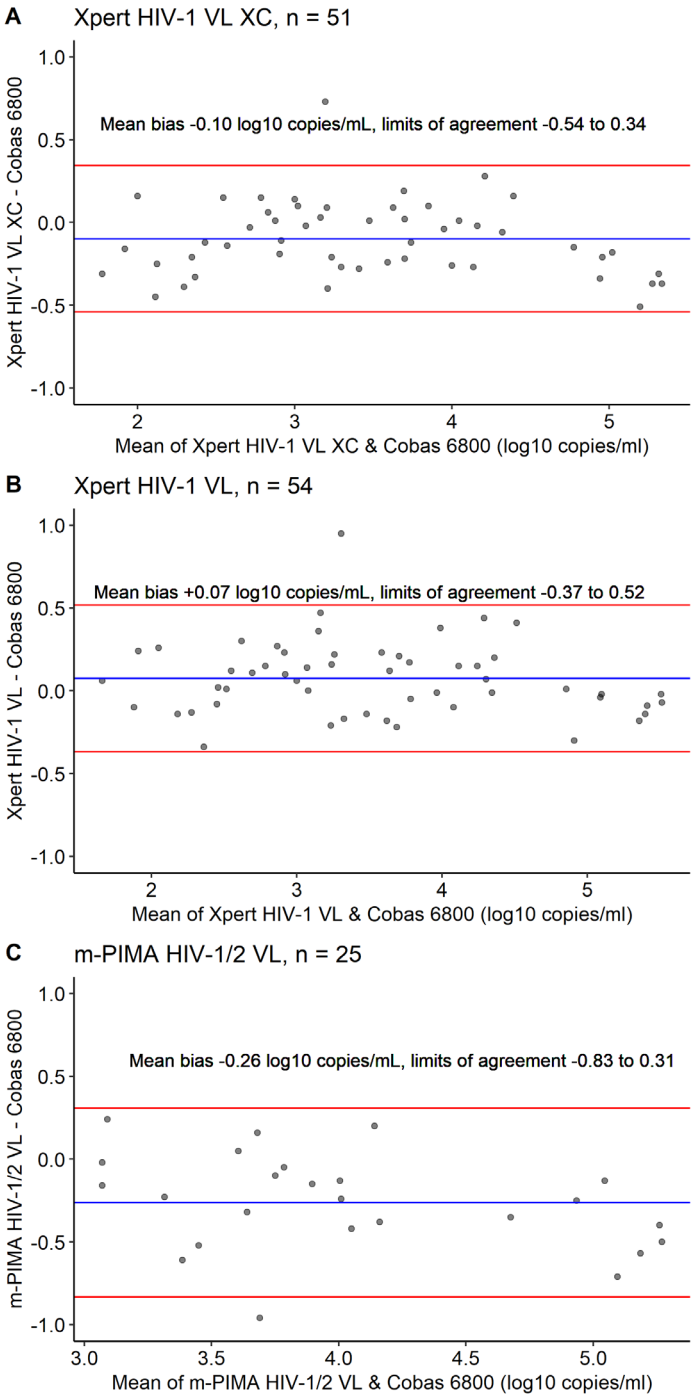
When restricted to paired samples quantifiable at ≥40 copies/mL, the Xpert HIV-1 VL XC had a Pearson correlation co-efficient of 0.97 (95% CI 0.95 to 0.99, p < 0.001, r^2 = 0.95, Figure 3.1) and a mean bias of -0.10 log_{10} copies/mL (95% limits of agreement -0.54 to 0.34, Figure 3.2), while the Xpert HIV-1 VL had a Pearson correlation co-efficient of 0.98 (95% CI 0.96-0.99, p <0.001, r^2 = 0.95, Figure 3.1), and a mean bias of +0.07 log_{10} copies/mL (95% limits of agreement -0.37 to 0.52, Figure 3.2). For the m-PIMA HIV 1/2 VL, when restricted to paired samples quantifiable at ≥800 copies/mL, the Pearson correlation co-efficient was 0.93 (95% CI 0.85-0.97, p <0.001, r^2 = 0.87, Figure 3.1) and the mean bias was -0.26 log_{10} copies/mL (95% limits of agreement -0.83 to 0.31, Figure 3.2).

Figure 3.1 Correlation of Xpert HIV-1 VL XC, Xpert HIV-1 VL & m-PIMA HIV 1/2 VL vs Cobas 6800



Restricted to paired samples quantifiable on both the point-of-care and laboratory reference assay

Figure 3.2 Bland Altman plots of Xpert HIV-1 VL XC, Xpert HIV-1 VL & m-PIMA HIV 1/2 vs Cobas 6800



Restricted to paired samples quantifiable on both the point-of-care and laboratory reference assay. The point estimate of the mean difference (bias) between the point-of-care and laboratory reference assay was within +/- 0.3 log_{10} copies/mL for all three assays.

3.4.2.3. Nurse-led testing

Accuracy, correlation and agreement of the assays were comparable when conducted by nurses and laboratory technicians, but numbers of nurse tested samples were small, particularly for the Xpert HIV-1 VL and the m-PIMA HIV-1/2 VL (Table 3.3 and Table 3.4).

Table 3.3: Sensitivity and specificity of three point-of-care viral load assays when used by laboratory technicians and nurses

Assay	Threshold (copies/mL)	Laboratory technician testing		Nurse testing	
		Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Xpert HIV-1 VL XC	N	116		50	
	<50	0.90 (0.73-0.97)	0.98 (0.91-1.00)	0.96 (0.76-1.00)	0.93 (0.74-0.99)
	<200	0.93 (0.74-0.99)	0.99 (0.93-1.00)	0.90 (0.67-0.98)	0.93 (0.76-0.99)
	<1000	0.95 (0.72-1.00)	0.98 (0.92-1.00)	1.00 (0.72-1.00)	0.97 (0.84-1.00)
Xpert HIV-1 VL	N	162		25	
	<50	0.95 (0.82-0.99)	0.95 (0.89-0.98)	0.94 (0.68-1.00)	1.00 (0.63-1.00)
	<200	0.97 (0.84-1.00)	0.99 (0.95-1.00)	0.92 (0.62-1.00)	1.00 (0.70-1.00)
	<1000	1.00 (0.83-1.00)	0.97 (0.92-0.99)	1.00 (0.60-1.00)	0.88 (0.62-0.98)
m-PIMA HIV-1/2 VL	N	93		23	
	<1000	0.94 (0.71-1.00)	0.99 (0.92-1.00)	0.86 (0.42-0.99)	1.00 (0.76-1.00)

Table 3.4: Mean log_{10} bias and correlation coefficients of three point-of-care viral load assays when used by laboratory technicians and nurses

Assay	Laboratory technician testing		Nurse testing	
	Mean bias, log_{10} copies/mL (95% CI)	Correlation co-efficient (95% CI)	Mean bias, log_{10} copies/mL (95% CI)	Correlation co-efficient (95% CI)
N	28		23	
Xpert HIV-1 VL XC (n = 123)	-0.12 (-0.49-0.24)	0.98 (0.95-0.99)	-0.07 (-0.59-0.45)	0.97 (0.93-0.99)
N	38		16	
Xpert HIV-1 VL (n = 140)	0.04 (-0.34-0.41)	0.98 (0.96-1.00)	0.16 (-0.39-0.71)	0.98 (0.94-0.99)
N	18		7	
m-PIMA HIV-1/2 VL (n = 91)	-0.21 (-0.74-0.33)	0.94 (0.80-0.97)	-0.40 (-1.01-0.21)	0.93 (0.61-0.99)

3.4.2.4. Sensitivity analyses

In sensitivity analyses using bootstrap methods to account for some participants having samples drawn for evaluation at repeated timepoints, results were relatively similar (Table 3.5).

Table 3.5: Bootstrap estimates of sensitivity, specificity, bias and correlation of three point-of-care viral load assays at different viral load thresholds, taking into account repeat testing

Assay	Threshold (copies/mL)	Sensitivity (95% CI)	Specificity (95% CI)	Mean bias, log_{10} copies/mL (95% CI)	Correlation co-efficient (95% CI)
Xpert HIV-1 VL XC (n = 123)	50	0.95 (0.81-0.99)	0.98 (0.92-1.00)	-0.10 (-0.57-0.38)	0.97 (0.94-0.99)
	200	0.89 (0.73-0.97)	0.99 (0.93-1.00)		
	1000	0.98 (0.79-1.00)	0.98 (0.92-0.99)		
Xpert HIV-1 VL (n = 140)	50	0.95 (0.81-0.99)	0.96 (0.90-0.99)	0.07 (-0.37-0.52)	0.97 (0.95-0.99)
	200	0.96 (0.81-0.99)	0.99 (0.95-1.00)		
	1000	1.00 (0.82-1.00)	0.97 (0.91-0.99)		
m-PIMA HIV-1/2 VL (n = 91)	1000	0.89 (0.63-0.98)	0.99 (0.93-1.00)	-0.30 (-0.89-0.30)	0.93 (0.80-0.97)

3.5. Discussion

3.5.1. Summary

We found that the novel Xpert HIV-1 VL XC, the Xpert HIV-1 VL and the m-PIMA HIV-1/2 VL had clinically acceptable performance when used in a South African clinic. At the WHO threshold for treatment failure of 1000 copies/mL, both the Xpert HIV-1 VL XC and Xpert HIV-1 VL had >95% sensitivity and specificity, while the m-PIMA HIV-1/2 VL had sensitivity of 92% and specificity of 99%. Both Xpert assays were also accurate at detecting low level viraemia.

3.5.2. Related literature

Our findings are similar to other studies of these three point-of-care assays, the majority of which have been conducted in centralised laboratory settings.

3.5.2.1. Xpert HIV-1 VL XC

Our study is the first to evaluate the Xpert HIV-1 VL XC in a clinical setting. In a centralised laboratory-based study, 513 fresh, frozen and diluted samples, were tested on the Xpert HIV-1 VL XC and compared with the Alinity m HIV-1 reference assay (Abbott, Chicago, USA).[77] The Xpert HIV-1 VL XC had a mean bias of +0.003 $\log_{10}$ copies/mL (95% CI -0.38 to +0.37), compared to the reference assay, and r^2 was 0.9788. Taken together, these results suggest that the Xpert HIV-1 VL XC performs well when used in centralised laboratory and clinic-based settings.

3.5.2.2. Xpert HIV-1 VL

For the Xpert HIV-1 VL, our findings were similar to a meta-analysis of 13 studies including 3790 patients,[39] which found a mean bias of 0.04 (95% CI: 0.02-0.07) copies/mL, and r^2 of 0.941 (P<0.001). Sensitivity and specificity were >95% at 200 and 1000 copies/mL, but was not evaluated at 50 copies/mL. Instead, a threshold of 'detectable' was used (40 copies/mL on the Xpert HIV-1 VL assay versus 20, 25 and 40 copies/mL in the different comparator assays used in the studies), with sensitivity of 93.3% (88.2–96.3), and much lower specificity at 80.6% (64.6–90.4). Specificity was particularly poor (69.3%) when compared to the Abbott RealTime HIV-1 VL assay. We used the 50 copies/mL threshold as this is used in South African guidelines.[73] Our finding that both the Xpert HIV-1 VL XC and Xpert HIV-1 VL performed well at this threshold contrasts slightly with the systematic review findings, but suggests that these assays are appropriate for use in the South African setting.

3.5.2.3. m-PIMA HIV-1/2 VL

Three published studies have evaluated the m-PIMA HIV-1/2 VL assay. Two of these were clinic-based; one multi-site study in Mozambique compared 686 samples tested by nurses with the m-PIMA HIV-1/2 VL versus the Cobas AmpliPrep/Cobas TaqMan 96 HIV-1 v2 (Roche) assay,[64] while another multi-site study from Kenya compared 555 samples tested by laboratory technicians on the m-PIMA HIV-1/2 VL in clinics, with the RealTime HIV-1 assay (Abbott).[65] The final study was a centralised laboratory evaluation comparing 413 frozen samples tested on the m-PIMA HIV -1/2 VL with results from fresh samples tested on the RealTime HIV-1 assay. At 1000 copies/mL, sensitivity and specificity were above 95% in all studies, except for the laboratory evaluation where specificity was 76.9 % (95% CI: 69.8–83.1). The correlation coefficients were 0.92, 0.92 and 0.93 respectively, with mean bias of -0.20, +0.16 and +0.26 $\log_{10}$ copies/mL respectively versus the laboratory reference assay. The WHO prequalification report found a bias of -0.21 $\log_{10}$ copies/mL versus the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test, v2.0, with sensitivity of 95.1% and specificity of 99% at 1000 copies/mL[34]. Overall, these findings, particularly when using Roche reference laboratory assays, are similar to our results, although reasons for the low specificity in the laboratory study are not clear, but could be related to the use of frozen samples for m-PIMA testing.

3.5.2.4. *Nurse testing*

There is only one published study which has evaluated nurse-led quantitative point-of-care viral load testing, with good results using the m-PIMA HIV1/2 viral load in Mozambique, as described above.[64] Our data suggest that the Xpert HIV-1 VL XC performs well when used by nurses, and results with the Xpert HIV-1 VL and m-PIMA HIV-1/2 VL were relatively similar, although numbers were small. However, our study was not explicitly designed to compare nurse versus laboratory testing, and research nurses had support available to them from on-site laboratory technicians, which does not reflect conditions across South African

primary care. Nurses and/or midwives have accurately used qualitative viral load assays (that use the GeneXpert and m-PIMA platforms) for early infant diagnosis of HIV,[78,79] and there is increasing interest in task-shifting point-of-care HIV diagnostics to non-laboratory staff in low and middle income countries.[80-82] As these assays require plasma, venous blood samples had to be centrifuged by nurses in the study clinic. This required specific training and may not be feasible for nurses in many settings, which could limit use at the clinical point-of-care. A whole blood fingerstick assay would circumvent this problem, and point-of-care early infant diagnosis assays, which also use whole blood, have demonstrated clear benefits in clinical outcomes.[79,83] This highlights the potential benefits of providing same day results using point-of-care technologies.

3.5.3. Strengths and limitations

Strengths of our study include the assessment of clinic-based testing in a setting with high HIV prevalence, and the inclusion of multiple point-of-care assays. As well as assessing correlation and mean bias, we focussed our analysis on sensitivity and specificity to detect viraemia at viral load thresholds that are directly relevant for patient management in South Africa and internationally. Most viral load testing was conducted by laboratory technicians, but we included some nurse led viral load testing, which has not been widely evaluated previously. Supply chain and operational disruptions due to the COVID-19 pandemic meant that our sample size was smaller than anticipated for some assays, and we were unable to test samples on all three assays concurrently. Instead, we allowed paired samples from repeat timepoints in the same participant, and conducted sensitivity analyses to account for potential clustering, with similar results. Nevertheless, the sample size of this study is relatively small, meaning confidence intervals for sensitivity estimates are wide for all assays at all viraemia thresholds, and for sensitivity and specificity estimates for nurse testing. Reference laboratory testing was conducted retrospectively using frozen plasma samples, in accordance with manufacturer's instructions, which should not have affected results.[84]

3.5.4. Implications

A previous cost-effectiveness modelling study found that a sensitivity and specificity of 90% or more at a threshold of 1000 copies/mL would be acceptable for a point-of-care viral load assay in Southern Africa,[85] while mean bias should ideally be within 0.3 $\log_{10}$ copies/mL of reference laboratory assays.[31,86] In our evaluation, all three evaluated assays fell within these criteria.

Balancing assay analytic performance and other characteristics that influence clinical outcomes, such as ease of use, turn-around time and result availability will depend on the context of where the assay is being implemented. We found that the Xpert HIV-1 VL XC performed well at both the 50 copies/mL and 1000 copies/mL thresholds, which are the two key thresholds for ART management in South Africa, suggesting that the clinical performance is appropriate for this setting. The m-PIMA HIV-1/2 VL is not able to quantitate viral loads <800 copies/mL, making it less suited to assessment of low level viraemia. More recent evidence has found that low level viraemia among people receiving efavirenz-based ART regimens predicts subsequent treatment failure,[87] although whether this remains true on dolutegravir based regimens is not yet known.[48] South African guidelines currently use 50 copies/mL to define viraemia, and determine whether a patient is eligible for down-referral into streamlined ART delivery programmes,[88,89] or whether they need enhanced adherence counselling to encourage re-suppression,[88] meaning the m-PIMA is less suited for use in these situations. However, the m-PIMA has a simple interface, shorter run time, and may be more suited to implementation in clinic-based settings, particularly in settings where access to viral load testing is poor. Further work is needed to confirm the performance of these assays when used by nurses, and we are conducting qualitative work with nurses and other healthcare workers, to explore feasibility and acceptability of implementing nurse testing in clinical settings. Using these assays to provide same-day, point-of-care results is crucial to achieving the reported benefits of expedited clinical decision-making, and reduced clinic visits and patient travel costs.[45]

3.5.5. Conclusions

The diagnostic accuracy of the Xpert HIV-1 VL XC, Xpert HIV-1 VL and m-PIMA HIV-1/2 VL assays was clinically acceptable when testing was conducted in these South African clinics. The Xpert assays have the added benefit of accurately detecting low level viraemia. However, further clinical studies are needed to determine if these assays can be implemented in routine primary healthcare settings, and whether there are operational and clinical benefits to patients and providers when used at the clinical point-of-care.

CHAPTER 4

Based on a paper for which I am first author, entitled “Protocol for a randomised feasibility study of Point-Of-care HIV viral load testing to Enhance Re-suppression in South Africa: the POwER study”, peer-reviewed and published in *BMJ Open*.[69]

4. POWER TRIAL PROTOCOL

4.1. Chapter rationale

In Chapter 2 I discussed how point-of-care viral load assays could be a tool to improve management of viraemia, but there is a lack of evidence regarding their clinical performance and effectiveness in primary care clinics in LMICs. In Chapter 4, I outline the protocol of a randomised feasibility study to generate preliminary evidence that could inform the design of a larger trial to test the clinical effectiveness of a point-of-care viral load intervention.

4.2. Introduction

Initiating ART to achieve viral load suppression amongst all people with HIV is crucial to achieve the UNAIDS target of ending AIDS by 2030. However, poor adherence to ART and/or HIV drug resistance can lead to HIV viraemia, with associated increases in morbidity, mortality, onward HIV transmission and the development and spread of HIV drug resistance.[26] Viral load testing can identify viraemia and guide adherence counselling, and/or switching to second-line ART regimens if HIV drug resistance is suspected. However, in low- and middle-income countries (LMICs), the majority of ART is provided in primary care, where there is limited laboratory viral load capacity, weak clinic systems to act on viral load results and a paucity of evidence based interventions to improve adherence.[26,90-93] Laboratory viral load results are often not reviewed until the next routine clinic visit after several months, by which time adherence problems may have worsened.[26,90-92]

Point-of-care viral load testing could allow same-day adherence counselling and switching to second-line ART, and more efficient, person-centred care by reducing the burden of clinic visits for review of blood results; thereby leading to faster viral load re-suppression. The World Health Organization (WHO) has approved the Xpert HIV-1 VL (Cepheid, Sunnyvale, USA)[33] and the m-PIMA HIV-1/2 VL (Abbott, Chicago, USA)[94] as accurate, quantitative point-of-care HIV viral load assays for use in LMICs. However, these assays have not yet been rolled out for ART monitoring in low- and middle-income countries, due to concerns around implementation, and with limited randomised trial evidence to support clinical effectiveness.

4.2.1. Objectives

The overall aim of this pilot/feasibility study[95] is to provide exploratory estimates to guide the development of a future larger trial of point-of-care testing to manage HIV viraemia. Our specific objectives are to:

1. Broadly estimate the effect size of point-of-care viral load testing compared to standard laboratory viral load testing on viral re-suppression <50 copies/ml after 24 weeks.
2. Determine the feasibility of recruiting, randomising and following up patients in a randomised trial of point-of-care viral load testing to manage HIV viraemia.
3. Assess the perceptions of staff and the practical changes in clinic systems that are required to implement point-of-care viral load testing for a subset of patients in a primary care clinic in South Africa.

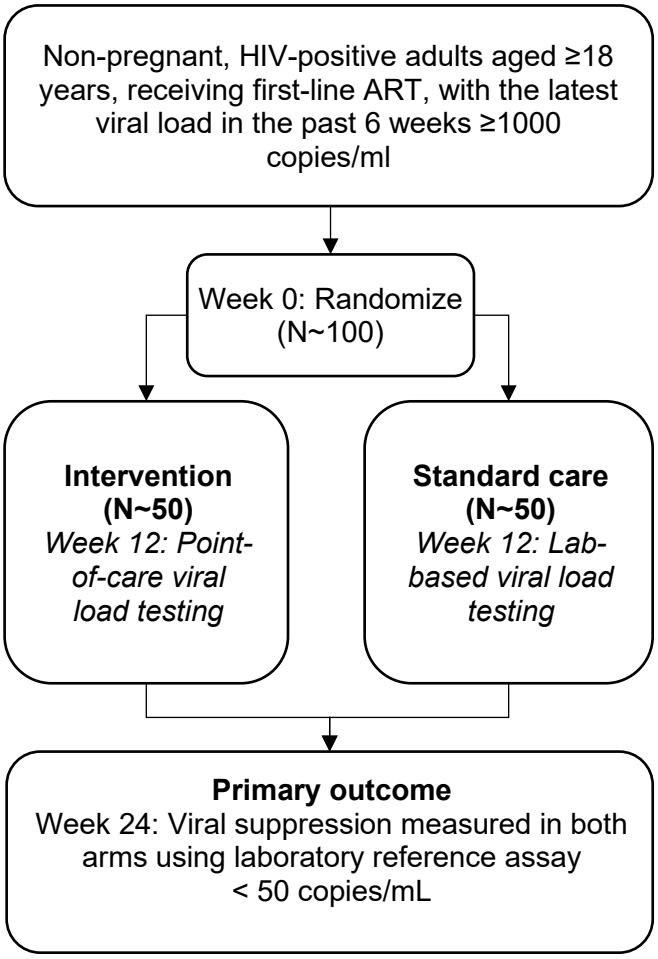
4.3. Methods and analysis

4.3.1. Trial design

This will be a an open-label, single site, individually randomised, feasibility study of point-of-care viral load testing for the management of HIV viraemia (Figure 4.1). We aim to enrol

approximately 100 adults receiving first-line ART and who have viraemia, and randomise them in a 1:1 ratio to receive point-of-care versus standard laboratory-based viral load testing. We will assess viral suppression after 24 weeks in each arm, and estimate recruitment, fidelity of the intervention and retention in care. We will also assess the implementation of point-of-care viral load testing using process evaluation data, in-depth interviews and focus group discussions. We describe POwER as a feasibility study according to the framework outlined by Eldridge et al..[95] Within this framework, the terms "*randomised pilot study"* and "*randomised feasibility study*" can be used interchangeably, with both meaning a study to determine the feasibility of a future definite randomised trial. Hence, POwER could also be defined as a randomised pilot study.

Figure 4.1 CONSORT diagram of the POwER study



ART = antiretroviral therapy, VL = viral load

4.3.2. Study setting

The study will take place at the Prince Cyril Zulu Clinic; a large public sector clinic run by the eThekwini Municipality Health Unit in central Durban, South Africa. The clinic manages approximately 11,000 people receiving ART and follows South African National Department of Health guidelines.[96] Since December 2019, South Africa has started replacing current non-nucleoside reverse transcriptase inhibitors (NNRTIs), with the new drug dolutegravir for first-line ART.[48,97] Dolutegravir is an integrase strand transfer inhibitor that, in high-income settings, has been found to have better tolerability, efficacy, and durability than regimens based on NNRTIs such as efavirenz.[20,48] Current first-line ART regimens at Prince Cyril Zulu Clinic are therefore tenofovir disoproxil fumarate, emtricitabine and efavirenz, or tenofovir disoproxil fumarate, lamivudine and dolutegravir.[48,96] Viral load testing is performed at six and twelve months after ART initiation, and annually thereafter. Similar to WHO guidelines, patients with viraemia are given enhanced adherence counselling, with a repeat viral load within three months. If viraemia persists on NNRTI-based regimens, then HIV drug resistance is more likely, and so a switch to second-line ART should be considered.[96,98] For dolutegravir-based regimens, HIV drug resistance is less likely, and so a switch to second-line ART is only recommended if there are signs of clinical or immunological failure, or after two years of persistent viraemia.[96]

4.3.3. Eligibility criteria

Eligible patients will be HIV-positive adults aged ≥18 years, receiving first-line NNRTI- or dolutegravir-based ART, with the latest viral load in the past 6 weeks ≥1000 copies/ml, and with no previous enhanced adherence counselling for this episode of viraemia. Pregnant women will not be eligible as they are routinely referred out of the Prince Cyril Zulu Clinic for antenatal care.

4.3.4. Study procedures

4.3.4.1. Recruitment

Potential participants will be identified by clinic staff using laboratory reports, electronic clinic information systems and clinic notes.

4.3.4.2. Informed consent, screening and enrolment

A research assistant or nurse will describe the study to potential participants, address any questions and seek written informed consent for participation. A research nurse will then assess eligibility using the patient's demographics, and a brief medical history and examination, including pregnancy testing for all women.

4.3.4.3. Randomisation and blinding

A statistician will generate the allocation sequence using random numbers generated in SAS 9.4 (SAS Institute Inc., Cary, USA). We will stratify randomisation by first-line ART regimen at enrolment (NNRTI-based or dolutegravir-based). The allocation sequence will contain variable block sizes, with participants randomised in a 1:1 ratio to the intervention or standard of care arm. All study staff apart from the statistician and data manager will be blinded to the allocation sequence. The allocation sequence will be programmed into the REDCap version 8.7.1 (Vanderbilt University, Nashville, USA)[99] enrolment electronic case report form (eCRF). At enrolment, the research assistant or research nurse will complete the enrolment eCRF, which will automatically assign the intervention allocation. As this is an open label study, study staff, clinic staff and participants will not be blinded to intervention allocation.

4.3.4.4. Baseline assessments

At enrolment, a nurse will administer a baseline sociodemographic questionnaire, and take a clinical history and examination, including an ART history. Throughout the study, South African Department of Health guidelines for managing viraemia will be used.[96] This includes enhanced

adherence counselling, which will be performed by clinic staff with participants in both arms using the pre-enrolment viral load result. Techniques used during the counselling include ART education, evaluation of social support, mental health screening and the use of treatment supporters where appropriate.[100] A nurse will also draw blood for routine tests for investigation of viraemia, which currently include CD4 count testing, hepatitis B surface antigen, creatinine and haemoglobin (Table 4.1).[96]

4.3.4.5. Follow-up

Participants in both arms will have routine clinic visits scheduled at the healthcare worker and participant's discretion, which is typically every 28 days to coincide with ART collection. At these visits, clinic staff will provide ongoing enhanced adherence guidelines, clinical support and ART when necessary. South African guidelines recommend a repeat viral load three months after the first high result ≥1000 copies/mL. As this study is taking place within a routine care setting, we anticipate that not all participants will attend within the three month visit window. In these cases we will allow repeat viral load to be done at another time, at the attending clinician's discretion.

4.3.4.6. Viral load testing interventions

For participants in the point-of-care arm, the repeat viral load test will be performed by a nurse, phlebotomist or laboratory technician in the clinic, using a WHO-approved, fully automated point-of-care viral load assay (such as the Xpert HIV-1 VL). Assay run times are ≤90 minutes. Clinic staff will be encouraged to provide results in the same clinic visit to inform ongoing management. If the participant cannot wait, or results are not available in the same visit, they will be available at the next clinic visit scheduled at staff and participant's discretion.

In the standard of care arm, samples for viral load testing will be transported on the same day to the National Health Laboratory Service (NHLS) for testing using their routine laboratory assays (e.g. Alinity m HIV-1 assay [Abbott, Chicago, USA]). Results are normally available

after 7 days and will be provided to the participant at the next clinic visit, arranged at the participants and healthcare worker's discretion (typically after 7-28 days for results, depending on the participant's availability, ART supply and clinic schedules).

Table 4.1 Schedule of evaluation in the POwER study

	Enrol	Routine clinic visit follow-up[a]					Study exit
Weeks in study	**0**	**4**	**8**	**12**	**16**	**20**	**24[b]**
Informed consent	X						
Locator information	X						
Demographics	X						
Medical history	X						
Vital signs	X	X	X	X	X	X	X
Physical examination	X						
Urine pregnancy test	X						
Eligibility screen	X						
Enhanced adherence counselling	X	X	X	X	X[c]	X[c]	X[c]
Randomization	X						
Routine Department of Health testing [d]	X						
POC viral load (intervention arm)				X[e]			
Laboratory viral load (standard of care arm)				X[e]			
Reference viral load outcome measure							X
Evaluation of new POC assays[f]	X			X			X
Stored blood & HIV drug resistance testing[g]	X			X			X
Stored urine for ART drug level testing	X						

[a] Scheduled at participants and healthcare worker's discretion but typically every 28 days
[b] Study exit visit window 22-30 weeks
[c] Ongoing enhanced adherence counselling for participants with viral load ≥50 copies/mL
[d] CD4 count testing (4 mL EDTA), hepatitis B surface antigen (5 mL SST), creatinine (5 mL SST) and haemoglobin (4 mL EDTA)
[e] Repeat viral load testing recommended at 12 weeks but may be done any time during follow up at the attending clinician's discretion

[f] *Maximum of 8 mL venous blood and/or a finger-prick capillary blood sample*
[g] *Retrospective drug resistance testing for viraemic participants at enrolment, follow up or study exit (10 mL EDTA)*
ART = antiretroviral therapy, POC = point-of-care

4.3.4.7. Management of viral load results at routine follow-up clinic visits

Viral load results will be managed by clinic staff in accordance with South African guidelines, which include guidance for management of both efavirenz and dolutegravir-based regimens, and do not advise routine HIV drug resistance testing.[73] Participants with a viral load ≥1000 copies/ml may meet criteria for viral failure (two consecutive viral loads ≥1000 copies/mL over 3 months apart) and will be considered for a switch to second-line ART. Switching to second-line ART and the choice of regimen will be at the clinician's discretion and will depend on the participant's first-line ART regimen, previous ART history, participant's preferences, perceived adherence and current guidelines.[73] Participants with a second viral load <1000 copies/mL will remain on first-line ART. In accordance with guidelines for the transition to dolutegravir, those receiving an NNRTI may have this switched to a dolutegravir-based first-line regimen.[96]

4.3.4.8. Data capture during routine clinic visits

Research staff will monitor participants' clinical records to capture visit dates, whether enhanced adherence counselling was conducted by a counsellor, nurse or doctor, medication prescriptions including ART, and laboratory results.

4.3.4.9. Study Exit Visit

The study exit visit will occur at 24 weeks (visit window 22-30 weeks), after which participants will continue receiving standard care at the Prince Cyril Zulu Clinic. At 24 weeks, any participant who has not attended the study exit visit will be called by the research team and asked to attend, irrespective of whether they have a routine clinic visit scheduled in the exit visit window.

4.3.4.10. Participant Reimbursement

We will reimburse study participants ZAR 150 (approximately GBP 8.00) after the enrolment visit and ZAR 100 (GBP 5.50) after the 24 week visit, to cover any additional time spent at the clinic and any inconvenience due to study participation.[101]

4.3.4.11. Extended follow up of routine data

For participants who provide additional consent, research staff may access routine medical records for up to five years after the study exit visit, in order to determine longer term retention in care, ART adherence and viral load results. For participants who are lost to follow up, and who provided consent at enrolment, the participants mortality status may be checked on the South African National Population Register.

4.3.4.12. Additional laboratory specimens

Participants who provide additional consent will also have 10 mL of venous blood taken for storage and retrospective ART drug level and HIV drug resistance testing. Plasma will be stored at enrolment, during follow up alongside the repeat viral load test, and at study exit. In addition, at enrolment, 5 mL of urine will be taken for storage and ART drug level testing. We may use study samples to validate new point-of-care viral load, HIV drug resistance, or ART drug level assays. These results would not be used to guide clinical management.

4.3.5. Study outcomes

We aim to broadly estimate the effect of point-of-care viral load testing using the primary outcome of viral suppression < 50 copies/mL at 24 weeks after enrolment, measured on a laboratory reference assay (e.g. Alinity m HIV-1) in both arms. Feasibility outcomes include proportions of participants enrolled, followed-up and who had same-day viral load testing in the point-of-care arm (Table 4.2).

Table 4.2 Study objectives and outcomes in the POwER study

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective To estimate the effect of implementing point-of-care viral load testing versus standard laboratory viral load testing on the proportion of HIV positive participants with viraemia who subsequently achieve viral re-suppression	The proportion of participants in each arm with viral load <50 copies/mL measured on laboratory reference assay	24 weeks after enrolment
Secondary Objectives To assess whether it is feasible to perform a randomised implementation trial of point-of-care viral load testing to manage viraemia in a routine South African clinic, by determining:		
a) What proportion of people with HIV viraemia is feasible to enrol?	a) Proportion of patients with viraemia at the study clinic who are successfully enrolled in the study	a) During study enrolment period
b) What proportion of those enrolled is feasible to follow up?	b) Proportion of enrolled participants who attend the study exit visit overall and in each arm	b) 24 weeks after enrolment
c) What proportion of point-of-care viral load results are received and acted on in the same day?	c1) The proportion of point-of-care viral load tests that are communicated to participants on the same day AND c2) The proportion of point-of-care viral load tests ≥1000 copies/mL that result in same day enhanced adherence counselling AND c3) The proportion of point-of-care viral load tests ≥1000 copies/mL that result in same day switch to second-line ART	c) 12 weeks after enrolment when point-of-care testing is performed
Tertiary Objectives To estimate the effect of point-of-care viral load testing versus standard laboratory viral load testing on:		
a) Time to detection of viral failure (consecutive viral loads ≥1000 copies/mL) in each arm	a) Days from enrolment to availability of viral load result ≥1000 copies/mL	a) By 24 weeks after enrolment
b) Time to switch to second-line ART in each arm	b) Days from enrolment to appropriate switching to second-line ART, amongst participants with viral failure	b) By 24 weeks after enrolment
c) Appropriate switching to dolutegravir in each arm	c) Time to appropriate switching to dolutegravir in each arm	c) By 24 weeks after enrolment

d) HIV drug resistance in each arm	d) The proportion of participants in each arm with HIV drug resistance	d) 24 weeks after enrolment
Qualitative Study Objectives: What changes in clinic systems are required and what are the views and experiences of staff in implementing point-of-care viral load testing to manage viraemia?	Staff perspectives regarding implementation of point-of-care viral load testing in a routine clinic	During enrolment when point-of-care testing is being implemented, and after study conclusion

4.3.6. Data collection and management

The research team will capture study data using standardised electronic CRFs in REDCap, which is a password protected data management service stored on a secure server.[99] All data entry will undergo three stages of quality control including pre-programmed data validity checks in electronic CRFs, immediate source document review, and weekly quality reports generated using REDCap. To protect confidentiality, all study-specific documents, other than the signed consent, will refer to the participant using their study participant number rather than their name. All documents will be stored in a secure cabinet in the locked research office and will only be accessible by study staff and authorised personnel.

4.3.7. Statistical methods

At the conclusion of the study, we will assess the proportion of participants achieving study outcomes in each arm, with 95% confidence intervals calculated using the Wilson method. We will conduct exploratory analyses using Fisher's exact test to compare the proportions achieving binary study outcome measures in each arm, using an intention to treat analysis. As this is a feasibility study, these exploratory analyses will likely not be powered to test the hypotheses that there is a difference between the two arms for most outcome measures.

4.3.7.1. Primary outcome

We will calculate the proportion of participants in each arm achieving the binary primary outcome of viral suppression <50 copies/mL at 24 weeks (Table 4.2). Participants who are

lost to follow up with no viral load result will be included in the analysis as not having achieved the primary outcome.

4.3.7.2. Secondary outcomes

We will calculate the proportion of potentially eligible patients with viraemia at the Prince Cyril Zulu clinic who are enrolled in the study (Table 4.3). The denominator will be the number of patients with viraemia during the study enrolment period, which will be calculated by clinic staff using NHLS high viral load reports. These reports are routinely used for monitoring and evaluation of clinic performance and include the number of first high viral loads ≥1000 copies/mL taken from the Prince Cyril Zulu Clinic each week. To assess study follow-up, we will calculate the proportion of participants who attend the study exit visit at 24 weeks after enrolment, overall and in each arm in case point-of-care testing influences retention. To assess implementation of point-of-care viral load testing, we will calculate the proportion of point-of-care viral load tests which are provided to participants on the same day, the proportion of viral loads ≥1000 copies/mL which resulted in same day enhanced adherence counselling, and the proportion of viral loads ≥1000 copies/mL resulting in appropriate same-day switch to second-line ART.

Table 4.3 Study & process evaluation outcomes with precision estimates

Outcome	Estimated n/N, %	95% CI (Wilson)
Percentage with viral load <50 copies/ml at 24 weeks in POC arm	35/50, 70.0	56.2-80.9
Percentage with viral load <50 copies/ml at 24 weeks in SOC arm	25/50, 50.0	36.6-63.4
Percentage of viraemic patients successfully enrolled in study	100/240*, 41.7	35.6-48.0
Percentage of those enrolled who are retained at 24 weeks	90/100, 90.0	82.6-94.5
Percentage in POC arm with same-day viral load testing	40/50, 79.5	70.0-88.8

**Assuming 240 viraemic patients during enrolment period, many of whom will not be eligible due to being on second-line ART, having had previous high viral loads, already having received enhanced adherence counselling or pregnancy. POC = point-of-care, SOC = standard-of-care*

4.3.7.3. Tertiary Outcomes

In each arm we will assess the median number of days (and interquartile range) from enrolment to detection of viral failure, and from enrolment to appropriate switch to second-line ART (among participants with viral failure), and from enrolment to appropriate switching to dolutegravir (among participants on an NNRTI-based regimen). We will compare time to event outcomes using Cox proportional hazards. We will also calculate the proportion of participants with HIV drug resistance detected at 24 weeks after enrolment.

4.3.7.4. Sample size considerations

We conservatively estimate (based on our previous study)[102,103] that we could enrol approximately 100 participants in 6 months. If enrolment proceeds better than anticipated, and resources allow us to enrol more, this will provide more precise estimates of the study outcomes. If enrolment proceeds slower than expected, we will consider expanding to another clinic site to achieve a minimum of 80 participants. Therefore, while we anticipate 100 participants, the final number may be between approximately 80-180 participants, and will be determined by the time and resources available. We will use NHLS, Prince Cyril Zulu Clinic and study data to assess outcomes, with estimated precision, in . Although not the primary aim of this feasibility study, assuming 50% of SOC participants achieve the main outcome of viral load suppression <50 copies/ml at 24 weeks, a sample size of 100 participants (50 per study arm) would provide 91% power to detect a +30% difference in the point-of-care testing arm, using a 2-sided alpha of 0.05.

4.3.8. Quality assurance procedures

Study documentation will be subject to internal quality audits by the Centre for the AIDS Programme of Research (CAPRISA) Quality Assurance team, in accordance with CAPRISA standard operating procedures.

4.3.9. Qualitative sub-study

We will undertake a qualitative sub-study within POwER to assess what changes in clinic systems are required and what the views of staff are in implementing point-of-care viral load testing, its potential impact on adherence and adherence counselling, and managing viraemia. We will conduct semi-structured interviews and a focus group discussion with approximately 8-10 staff during, and then again after, implementation of point-of-care viral load testing in the study. Staff will include counsellors, phlebotomists, nurses, pharmacy staff, laboratory staff, doctors and health service managers. Topic guides will be informed by Normalisation Process Theory which aims to identify what is needed to 'normalise' use of a technology in a healthcare system.[104,105] Discussions will be transcribed and thematically analysed using NVIVO software (QSR International, Melbourne, Australia).

4.4. Ethics and dissemination

We will conduct the trial in accordance with the principles of the Declaration of Helsinki. The eThekwini Municipality Health Unit Research Committee, the KwaZulu-Natal Provincial Health Research Ethics Committee (KZ_202002_005), the University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC/00000836/2019) and the University of Oxford Tropical Research Ethics Committee (OxTREC 66-19) have approved the study. We will present study results to front-line clinical workers and programme managers in eThekwini Municipality and KwaZulu-Natal Provincial Department of Health. We will also submit our findings to academic conferences and open-access, peer-reviewed journals.

4.4.1. Trial status

We registered POwER on the Pan African Clinical Trials Registry (PACTR202001785886049) on the 21st January 2020 and on the South African Clinical Trials (DOH-27-072020-6890) on the 17th July 2020. Enrolment started on 20th August 2020, under protocol version 2.0 dated 24th June 2020 (supplementary file).

4.5. Discussion

Evidence-based interventions to improve the management of viraemia are needed to achieve global HIV treatment targets, prevent the development and spread of HIV drug resistance, and improve patient outcomes. In this paper, we outline a feasibility trial of point-of-care viral load testing among people with viraemia who are receiving first-line ART in South Africa. Results from this study will inform the design of future trials to assess the clinical effectiveness of point-of-care testing to manage viraemia.

4.5.1. Problems with management of viraemia

Several studies highlight gaps in the management of viraemia in LMICs, and the resulting negative impacts on treatment outcomes. First, addressing potential poor adherence, which may have caused viraemia, is challenging. A meta-analysis of interventions to improve adherence did not find any strategies that resulted in better viral suppression in LMICs,[106] while a more recent cluster-randomised trial of the South African National Adherence Guidelines found no difference in long-term viral re-suppression among patients with viraemia.[93] Second, follow up viral load testing is often poorly performed. In the South African trial, less than 20% of patients had a repeat viral load within the recommended 3 months to confirm viral failure.[93] Similar delays have been reported in a large analysis of South African laboratory data; among 260,323 patients with viraemia, the median time to a repeat viral load was 6.2 months, (interquartile range [IQR] 4.0-11.1).[107] Third, among people with confirmed viral failure, a systematic review,[108] and more recent individual studies,[92,109-111] have found that only 30-60% are switched to second-line ART. Even among patients who are switched, this can take a further 3 to 12 months,[109-111] with delays of even a few months being associated with increased risk of opportunistic infections and mortality, particularly among people with low CD4 counts.[26,92,109-111] Taken together, these data highlight the need for interventions to reduce delays and improve the management of viraemia.

4.5.2. Existing research regarding clinical effectiveness of point-of-care viral load testing

We conducted the STREAM trial, which was the first randomised trial of point-of-care HIV viral load testing for monitoring ART.[102,103] Overall, the STREAM intervention improved retention in care and viral suppression by 14.3% compared to the standard-of-care laboratory viral load arm. However, STREAM was designed to enrol stable patients; less than 5% of participants had viraemia at enrolment, and only 16 participants developed viral failure (seven in the point-of-care arm, nine in the standard care arm). Time to detection of viral failure was faster in the intervention arm (55 days [IQR 55–57] vs 123 days [IQR 98–162]) but numbers with viraemia were too small to determine whether point-of-care testing was effective at improving switching to second line ART, or subsequent viral load outcomes. In STREAM, the research team provided point-of-care testing and clinical care, so the observed benefits may also not be applicable to routine public sector settings.

Several more trials of point-of-care viral load testing are in progress, but none focus on management of viraemia. Studies in Zimbabwe[112,113], Kenya[114] and Haiti[115], are assessing point-of-care viral load for monitoring ART amongst pregnant women, children and/or adolescents. A study in Nigeria is enrolling adults at ART initiation and will report on the effect of point-of-care viral load testing after 12 months[116], while a trial in South Africa[117] is enrolling adults on ART who are due for their annual viral load test. One trial in Uganda is assessing a viral load intervention package that includes ‘near point-of-care testing’ (at the clinic or a nearby clinic and therefore results may not be provided on the same day), and is enrolling ‘high-risk groups’ including patients with previous viraemia or no viral load in the past year[118].

4.5.3. Implementation of point-of-care viral load testing

Point-of-care diagnostics have been used widely in healthcare systems in many LMICs.[119] In HIV programmes, some tests such as rapid, lateral flow assays for diagnosis of HIV, have been evaluated, endorsed and incorporated into WHO guidelines and successfully adopted in

many settings.[120] However, other assays, such as more complex molecular polymerase chain reaction technologies for tuberculosis, have remained as laboratory tests despite being marketed as point-of-care assays.[119] Given that the Xpert HIV-1 VL and m-PIMA assays use similar platforms and take over 1 hour for results to be available, they have also been criticized as not being implementable as true point-of-care tests. A large systematic review of barriers to point-of-care HIV diagnostic implementation in LMICs found that in 132 studies, integration of the point-of-care test into clinical work flows was the most commonly identified challenge to test utilization.[121] More recently, studies have reported implementation of qualitative point-of-care viral load assays for early infant diagnosis of HIV[78], and monitoring of ART in maternity wards in South Africa[122], and de-centralised ART clinics in Malawi[123]. While these studies have reported quantitative outcomes related to point-of-care viral load use, there is little qualitative work using theory-based approaches to evaluate what is required for successful implementation.

4.5.4. Strengths and limitations

A major strength of this study is the focus on patients with viraemia, who are a priority population at high risk of increased morbidity and mortality, onwards HIV transmission, and development of HIV drug resistance.[26] Interventions to improve viral suppression amongst this group have been prioritized by the WHO and align with several objectives in the Global Action Plan on HIV Drug Resistance[124]. While our study may be under-powered to detect a significant effect of point-of-care viral load testing on viral re-suppression, we will determine the feasibility of conducting larger studies to answer this question in this setting. Our use of Normalisation Process Theory will allow a rigorous assessment of what is needed to 'normalise' point-of-care testing in the South African healthcare system.

A limitation of this study is the focus on 'supply side' implementation of point-of-care viral load testing. Receiving results on the same day could also increase patient understanding and motivate adherence, but evaluating this from the patient perspective is beyond the

scope of the study. Furthermore, findings from this large urban, clinic may not be applicable to other settings, including smaller clinics in rural settings where advantages of point-of-care testing over laboratory-based testing may differ. Our future trial may be best designed as a cluster-randomised trial, with individual clinics randomised to receive the point-of-care testing intervention. While POwER is an individually randomised study, estimates of the effect of point-of-care testing will remain valuable for design of potential cluster randomised or individually randomised future studies.

Coinciding with the rollout of dolutegravir is both a strength and a weakness of our study. We will enrol patients on either NNRTI- or dolutegravir-based ART, therefore allowing estimates of the effect of point-of-care testing in either group. For patients enrolled on NNRTIs, this also presents an opportunity to assess whether point-of-care viral load testing can assist the transition to dolutegravir-based regimens. For patients enrolled on dolutegravir, a potential limitation is that point-of-care viral load testing will not be used to expedite a switch to second line, although it may still improve enhanced adherence counselling and allow more efficient care that can help ensure retention and virological suppression. Lastly, we will be able to assess early viral suppression outcomes and the frequency of HIV drug resistance among people with viraemia on dolutegravir. This is a pressing research question for global policy makers, because it determines the need for HIV drug resistance testing and second-line ART after introduction of a dolutegravir-based first-line in LMICs.

In summary, we aim to provide evidence as to whether a trial of point-of-care viral load testing to manage viraemia is feasible, and how testing may be implemented in South African clinics. This work will contribute to the development of interventions to improve the management of viraemia amongst people receiving ART, thereby improving health and leading to longer and better lives, as well as reducing the spread of HIV and preventing drug resistance.

Chapter 5

5. POWER TRIAL: FEASIBILITY STUDY RESULTS

This chapter is based on a paper for which I am first author, entitled “Point-of-care viral load testing to manage HIV viraemia during the rollout of dolutegravir-based ART in South Africa: a randomised feasibility study (POwER)”, currently under review with the *Journal of Acquired Immune Deficiency Syndromes (JAIDS)*.

5.1. Chapter rationale

In Chapter 4, I described the protocol for the POwER study. In Chapter 5, I now present the main findings from the POwER study, which aimed to determine if it is feasible to conduct a randomised trial of point-of-care viral load testing to manage viraemia in primary care.

5.2. Introduction

The World Health Organization (WHO) recommends annual viral load (VL) testing to monitor antiretroviral therapy (ART) for people living with HIV (PLHIV).[30] Identifying people with viraemia is important because they are at risk of immunocompromise, morbidity and mortality, onward HIV transmission and the potential development and transmission of HIV drug resistance.[26] Viraemia may be caused by inconsistent adherence to effective ART, which can be managed with adherence counselling, and/or HIV drug resistance, which requires a change to second-line ART. Although the importance of achieving rapid viral re-suppression is clear, several studies in low- and middle-income countries (LMICs) have documented long periods of sustained viraemia due to poor clinical management, with associated increased morbidity and mortality.[26,28,92,125-129]

In these settings, HIV services are predominantly provided in primary care, where delays in receiving VL results from centralised laboratories[130] can further impede management of viraemia. New diagnostic strategies to improve the detection of viraemia and achieve rapid

viral re-suppression are needed. Point-of-care VL testing, where testing is conducted in the clinic and results are provided to clinicians for management on the same day,[31,62] may lead to faster VL re-suppression, by allowing immediate enhanced adherence counselling and rapid switching to second-line ART. Furthermore, point-of-care testing may reduce the burden of clinic visits for review of test results. To date, two point-of-care assays have been approved as accurate by the WHO for use in LMICs.[33,34] Clinical trials of these assays among children,[131] adolescents[132] and adults,[102,133,134] have demonstrated shorter turnaround times, but effects on clinical outcomes have been mixed.

None of these trials focussed on point-of-care testing among people with viraemia, who may benefit the most from quicker access to VL results. We plan a future efficacy trial of a diagnostic intervention to improve re-suppression among people with viraemia, and require further data to aid design of this trial. First, the global rollout of dolutegravir, which has a higher genetic barrier to resistance,[48] means we require more data on the proportion of people likely to achieve viral re-suppression with this new drug. We also require estimates of the potential effect size of point-of-care VL on viral re-suppression, to guide power calculations for the planned trial. Second, poor adherence is often associated with social and psychological issues, such as financial problems, unstable employment, migrant labour, alcohol abuse and stigma,[29] meaning people with viraemia may be more likely to be from marginalised and/or disadvantaged groups. Therefore, we do not know whether it is feasible to rapidly enrol people with viraemia in clinical trials in our setting, and to follow them up to successfully assess outcomes. Third, we do not know whether routine healthcare staff will successfully use point-of-care VL results in clinical management.

We therefore aimed to conduct a feasibility study of a randomised trial of point-of-care VL testing to improve management viraemia, in the context of the dolutegravir-based ART rollout in South Africa.

5.3. Methods

5.3.1. Trial design

We conducted the POwER study, an open-label, individually randomised, feasibility study of point-of-care HIV VL testing among people with HIV viraemia while receiving first-line ART. The full protocol has been previously published[69].

5.3.2. Setting and participants

The study opened at the Prince Cyril Zulu Communicable Disease Centre (PCZ CDC), a large, public clinic next to the central Durban transport hub, with support from the adjacent Centre for the AIDS Programme of Research in South Africa (CAPRISA) eThekwini Clinical Research Site. In January 2021 we expanded the study to a rural, medium-sized primary care clinic in the uMgungundlovu District, Mafakathini Clinic, with support from the adjacent CAPRISA Vulindlela Clinical Research Site. The is located in a rural part of the uMgungudlovu District. Both sites provide HIV, tuberculosis and other primary care services and are in the province of KwaZulu-Natal, which has an estimated HIV prevalence of 27% among adults aged 15-49[135].

HIV treatment is provided free at the point of service, according to South African Department of Health guidelines,[73] which recommend HIV VL testing at six months after ART initiation, and then annually. Before December 2019, the standard first-line ART regimen was tenofovir disoproxil fumarate, emtricitabine and efavirenz (TEE). From December 2019 onwards, a new regimen was introduced, containing tenofovir disoproxil fumarate, lamivudine and dolutegravir (TLD). During the trial, people already receiving TEE with VL <50 copies/mL were recommended to switch to TLD.

People were eligible for enrolment into POwER if they were living with HIV, aged ≥18 years, receiving first-line efavirenz- or dolutegravir-based ART, had their latest VL ≥1000 copies/ml within the past six weeks, and had not received enhanced adherence counselling for this

episode of viraemia. Pregnant women were not eligible, as guidelines for VL monitoring and management of viraemia differ in pregnancy.[73]

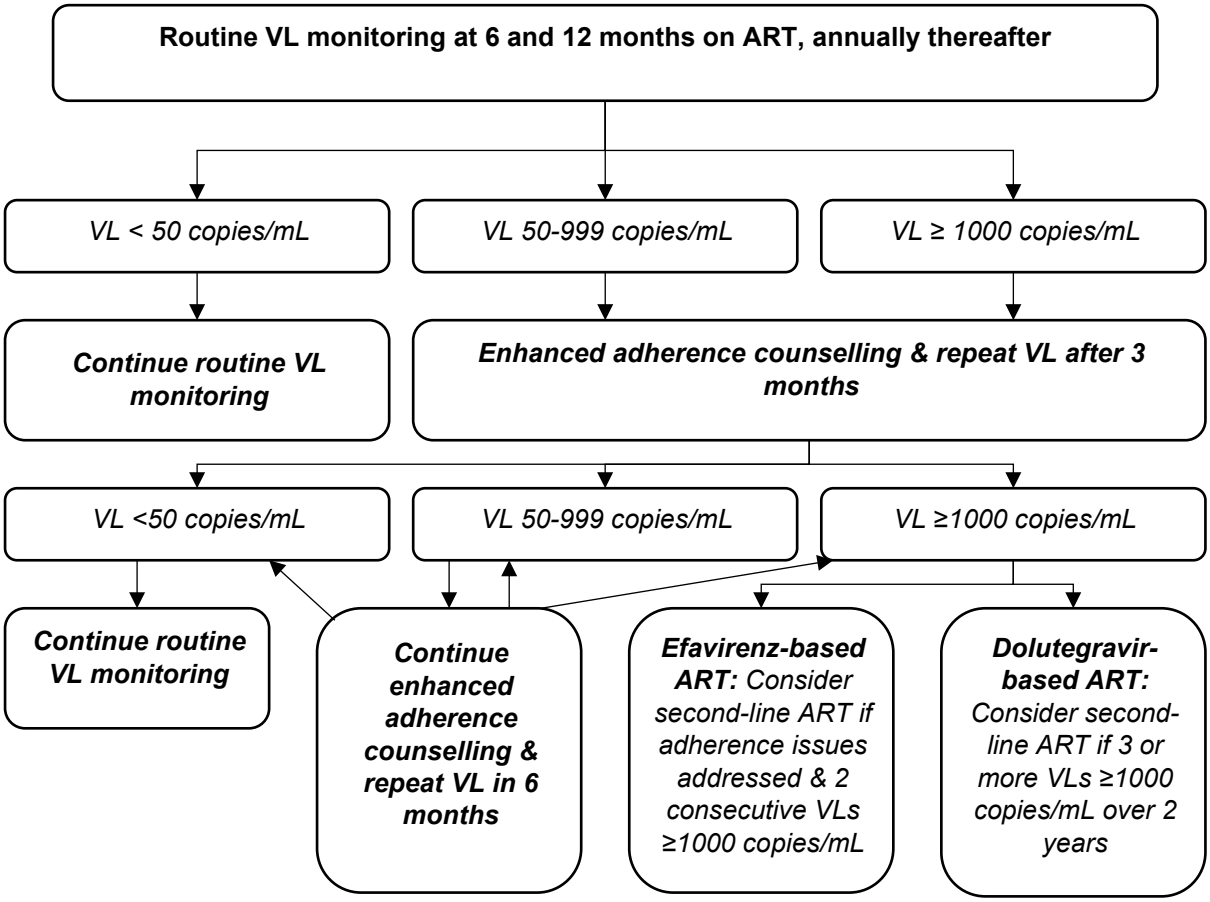
5.3.3. Randomisation

After providing informed consent, eligible participants were randomised by a study nurse, using a pre-programmed electronic case report form, in a 1:1 ratio to the point-of-care arm or the standard-of-care arm. A statistician generated the allocation sequence using random numbers with variable block sizes. Randomisation was stratified by ART regimen at enrolment (efavirenz or dolutegravir-based). All study staff except the statistician were blinded to the allocation sequence. Clinic staff and participants were told the participant's allocation at enrolment.

5.3.4. Interventions

During follow up, clinical management was provided by public-sector clinic counsellors, HIV nurses or clinicians, according to South African Department of Health guidelines, which specify that people with a VL >1000 copies/mL should receive enhanced adherence counselling and a repeat VL after three months (Figure 5.1).[73] The recommended enhanced adherence counselling package includes discussing VL results and treatment strategies, and jointly identifying barriers and facilitators to adherence.[88] After three months, if the repeat VL remains >1000 copies/mL, guidelines recommend that people receiving efavirenz-based ART are switched to a second-line ART regimen, as they are presumed to have HIV drug resistance (Figure 5.1). If the repeat VL is <1000 copies/mL, then people receiving efavirenz-based regimens are recommended to transition to a dolutegravir-based first-line regimen. People receiving dolutegravir-based first-line regimens with a repeat VL of >1000 copies/mL are presumed to be more likely to experience viraemia due to poor adherence, as dolutegravir has a higher genetic barrier to resistance.[48] They are therefore recommended to receive ongoing adherence support, and only to consider switching to second-line ART after two years of ongoing viraemia.

Figure 5.1: Management of viraemia according to South African National Department of Health Guidelines



ART = antiretroviral therapy, VL = viral load. Adapted from South African National Department of Health, 2019 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy, Adolescents, Children, Infants and Neonates. Pretoria, South Africa, 2019.

In both arms, stored plasma samples were taken at the enrolment, follow-up VL and exit visits, for retrospective VL and HIV drug resistance testing. Participants who were late for visits were tracked by clinic staff according to routine clinic procedures, which generally involve telephone follow up if the participant is more than 14 days late.

5.3.4.1. Point-of-care VL testing

For participants randomised to the point-of-care VL intervention arm, all VLs during follow-up were conducted using the Xpert HIV-1 VL assay (Cepheid, Sunnyvale, USA). Initially, we

planned for nurses to do the Xpert HIV-1 VL testing in the study clinic, but staff shortages and COVID-19 related disruption meant that it was conducted by a research laboratory technician in a clinic site laboratory, in accordance with manufacturer instructions. Briefly, a venous blood sample was centrifuged to provide 1ml of plasma, which was tested using the Xpert HIV-1 VL cartridge. Participants were encouraged to wait for the result, which was provided to routine clinic staff to inform clinical management. If participants were not willing/able to wait, results were provided at their next clinic appointment, scheduled by study staff in consultation with participants at the soonest possible date. In the case of invalid results, leftover plasma was used for retesting, or a repeat sample was taken.

5.3.4.2. Laboratory-based VL testing

For participants randomised to the standard-of-care arm, all VL testing during follow up was done off-site by the National Health Laboratory Service, usually using the Alinity m HIV-1 VL analyser (Abbott, Chicago, USA). Participants would receive the VL result at their next clinical appointment, typically scheduled as soon as possible after 1 week, to allow for laboratory VL turnaround time.

5.3.5. Outcomes

To assess trial feasibility, we evaluated the proportion of potentially eligible participants who were enrolled, who completed follow-up, and who had same-day VL testing (point-of-care arm only). We obtained approvals to retrospectively assess routine, de-identified laboratory and clinic data from PCZ CDC, to determine the total number of potentially eligible participants during the study period, allowing us to calculate the proportion we managed to enrol. To provide estimates of the potential effect of point-of-care VL testing, we assessed the primary outcome of viral suppression <50 copies/mL at 24 weeks after enrolment in each arm, according to intention-to treat. Outcome VLs were measured retrospectively testing stored samples with the cobas® HIV-1 assay on the cobas 6800 platform (Roche, Basel, Switzerland). Additional pre-specified exploratory outcomes were HIV drug resistance in

each arm at study exit, and time to detection of viral failure (consecutive VLs ≥1000 copies/mL), switch to second-line ART, and appropriate switch/transition to dolutegravir-based ART.

5.3.6. Sample Size and Statistical methods

We estimated enrolling at least 100 participants in 6 months, but allowed for flexibility to enrol 80-180 participants based on available time and resources. We calculated the proportions of participants achieving study outcomes and compared proportions in each arm using Fisher's exact test. For the primary outcome, participants who were lost-to-follow-up were included as not virally suppressed. For time to event outcomes, we assessed the median number of days from enrolment to each outcome and compared outcomes using Cox proportional hazards.

5.3.7. Ethical approvals

The University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC 00000836/2019) and the University of Oxford Tropical Research Ethics Committee (OxTREC 66-19) approved the study. POwER is registered on the Pan African Clinical Trials Registry (PACTR202001785886049) and the South African Clinical Trials Registry (DOH-27-072020-6890).

5.4. Results

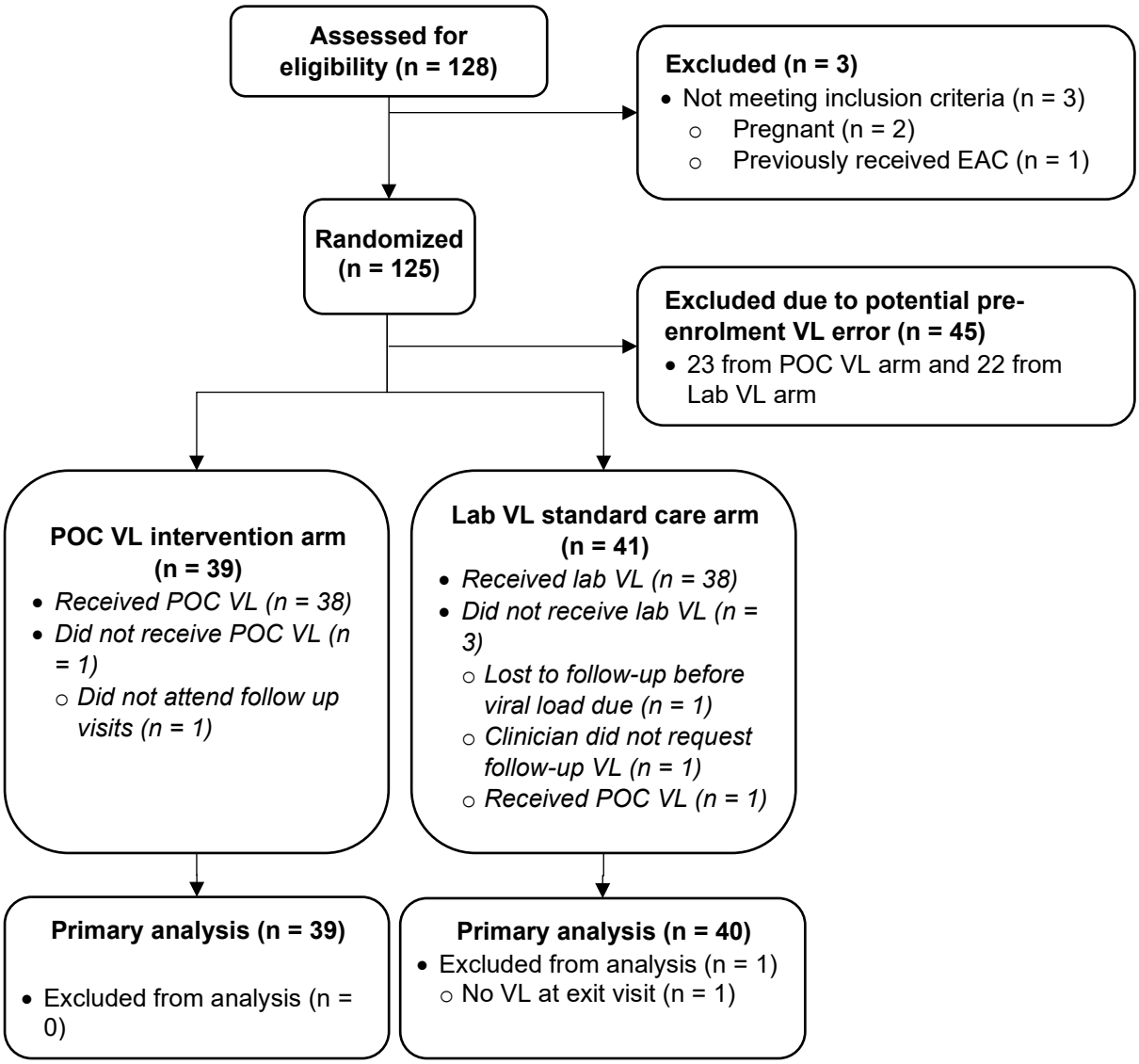
5.4.1. Study population

We enrolled the first participant on August 20th, 2020. In December 2020 we were informed that before mid-October, 45/63 (71.4%) POwER participants had their routine pre-enrolment VLs measured on a defective Alinity m HIV-1 VL analyser that overestimated some VL results. Therefore, the viraemic sample used to determine eligibility may have been falsely high. After discussion with the ethics committees, we informed affected participants immediately, and offered them to continue or terminate from the study; all opted to continue.

We determined to exclude these participants from the primary analysis, and to enrol a total of 125 participants (Figure 5.2). There were no enrolments between December 2020-February 2021, and November 2021-January 2022, due to SARS-CoV-2 waves affecting South Africa. The last participant was enrolled on March 25th, 2022 and completed follow-up on September 7th, 2022.

After excluding the stated 45 participants, we enrolled 80 participants who met the eligibility criteria. Median age was 38.5 years (interquartile range [IQR] 33-45), 58.8% were female, 78/80 (97.5%) were enrolled at the PCZ CDC, and median time on ART was 3.1 years (IQR 1.0-5.7) (Table 5.1). At enrolment, 37/80 (46.2%) were receiving efavirenz, and 43/80 (53.8%) were receiving dolutegravir-based ART. 16/43 (37.2%) had been initiated on dolutegravir, while the other 27/43 (62.8%) had been initiated on an efavirenz-based regimen and were subsequently transitioned to first-line dolutegravir. Median time on the dolutegravir-based regimen was 8.2 months (6.4-12.6). Median time since the viraemic pre-enrolment VL was 15 days (range 6-36), with 95% receiving enhanced adherence counselling at enrolment. On retrospective testing of enrolment samples, 45 participants remained viraemic ≥1000 copies/mL.

Figure 5.2: POwER study CONSORT diagram



POC = point-of-care, VL = viral load, EAC = enhanced adherence counselling

There was a slightly higher proportion of women (27/41, 65.9% versus 20/39, 51.3%), people who reported never missing a dose of ART (21/41, 51.2% versus 14/39, 35.9%), unemployed people (18/41, 43.9% versus 10/39, 25.6%) and people with ≤30 minutes travel time to clinic (24/41, 58.5% versus 18/39, 46.2%) in the standard-of-care arm versus the intervention arm. Other demographics and clinic variables were well balanced between the two groups.

Table 5.1: Baseline characteristics of eligible participants enrolled in the POwER study, n = 80

Variable	Levels	Intervention arm*	Standard of care arm*	Total*
Age, years	Median (IQR)	38.0 (33.0-45.5)	39.0 (33.0-43.0)	38.5 (33.0-45.0)
Gender	Female	20 (51.3)	27 (65.9)	47 (58.8)
	Male	19 (48.7)	14 (34.1)	33 (41.2)
Time since ART initiation, years	Median (IQR)	4.1 (1.0-5.1)	3.1 (1.0-7.0)	3.1 (1.0-5.7)
Current ART regimen at enrolment	TDF/3TC/DTG	22 (56.4)	20 (48.8)	42 (52.5)
	TDF/FTC/EFV	17 (43.6)	20 (48.8)	37 (46.2)
	ABC/3TC/DTG		1 (2.4)	1 (1.3)
Time on current regimen, years	Median (IQR)	1.1 (0.6-4.1)	1.0 (0.6-2.8)	1.1 (0.6-3.1)
Time on dolutegravir-based regimen, years	Median (IQR)	0.8 (0.5-1.2)	0.7 (0.5-1.0)	0.7 (0.5-1.1)
Co-morbidities at enrolment?	Yes	5 (12.8)	4 (9.8)	9 (11.2)
ART side effects?	Yes	0 (0.0%)	2 (4.9)	2 (2.5)
Last time participant missed a dose of ART	Within past week	10 (25.6)	7 (17.1)	17 (21.2)
	1-2 weeks ago	1 (2.6)	3 (7.3)	4 (5.0)
	2-4 weeks ago	9 (23.1)	3 (7.3)	12 (15.0)
	1-3 months ago	5 (12.8)	5 (12.2)	10 (12.5)
	>3 months ago	0 (0.0)	2 (4.9)	2 (2.5)
	Never	14 (35.9)	21 (51.2)	35 (43.8)
Hazardous drinking (AUDIT-C)	Yes	12 (30.8)	14 (34.1)	26 (32.5)
Ethnicity	Black African	39 (100.0)	40 (97.6)	79 (98.8)
Highest level of education completed	Lower secondary	20 (51.3)	20 (48.8)	40 (50.0)
	Upper secondary (matriculation)	16 (41.0)	16 (39.0)	32 (40.0)
	Tertiary	3 (7.7)	5 (12.2)	8 (10.0)
Employment status	Unemployed	10 (25.6)	18 (43.9)	28 (35.0)
	Informal	4 (10.3)	2 (4.9)	6 (7.5)
	Part time	5 (12.8)	4 (9.8)	9 (11.2)
	Full-time	16 (41.0)	11 (26.8)	27 (33.8)
	Student	3 (7.7)	2 (4.9)	5 (6.2)
	Self-employed	1 (2.6)	4 (9.8)	5 (6.2)
Monthly personal income, ZAR	<1000	16 (41.0)	20 (48.8)	36 (45.0)
	1000-4000	12 (30.8)	11 (26.8)	23 (28.8)
	4001-8000	8 (20.5)	8 (19.5)	16 (20.0)
	>8000	3 (7.7)	2 (4.9)	5 (6.2)
Travel time to clinic	≤30 min	18 (46.2)	24 (58.5)	42 (52.5)
	31-59 min	18 (46.2)	15 (36.6)	33 (41.2)
	1-2 hours	3 (7.7)	2 (4.9)	5 (6.2)
Cost of travel to clinic and back (round trip)	R0-25	13 (33.4)	17 (41.5)	30 (37.4)
	R26-50	23 (59.0)	22 (53.7)	45 (56.2)
	R>50	3 (7.7)	2 (4.9)	5 (6.3)
Enrolment CD4 count, cells/μL	<200	10 (25.6)	11 (26.8)	21 (26.2)
	200-349	12 (30.8)	9 (22.0)	21 (26.2)

Variable	Levels	Intervention arm*	Standard of care arm*	Total*
	350-499	8 (20.5)	10 (24.4)	18 (22.5)
	>=500	9 (23.1)	11 (26.8)	20 (25.0)
Time since viraemic sample taken **before** enrolment, days	Median (IQR)	15.0 (14.0-20.5)	15.0 (13.0-21.0)	15.0 (13.0-21.0)
EAC at enrolment visit?	Yes	38 (97.4)	38 (92.7)	76 (95.0)
Enrolment viral load, copies/ml	<50	6 (15.4)	8 (19.5)	14 (17.5)
	50-999	11 (28.2)	10 (24.4)	21 (26.2)
	≥1000	22 (56.4)	23 (56.1)	45 (56.2)

* N, (%) unless stated otherwise. EAC = enhanced adherence counselling

5.4.2. Study feasibility outcomes

We retrospectively identified 262 non-pregnant adults with a VL ≥1000 copies/mL who were receiving first-line ART between October 2020 and March 2022 and may have been eligible for enrolment. During the same period, we were able to screen 65 and enrol 62/262 participants (23.7%), approximately 3.6 per month. The other 18 enrolments occurred before mid-October 2020 and were known to not have been affected by the laboratory error. Overall, 76/80 (95.0%, 95%CI 87.0-98.4%) participants attended the study exit visit; 38/39 (97.4%, 95%CI 84.9-99.9%) in the intervention arm and 38/41 (92%, 95%CI 79.0-98.1%) in the standard-of-care arm (Table 5.2). Two participants relocated, and two were lost to follow up and not contactable.

5.4.3. 24-week viral suppression outcome

After excluding one standard-of-care participant with no VL at their 24-week exit visit, 27/39, 69.2% (53.6-81.4) participants in the intervention arm and 29/40 72.5% (57.2-83.9) in the standard-of-care arm achieved the primary outcome of VL <50 copies/mL at 24 weeks (p=0.808). Point estimates were similar when stratified by dolutegravir and efavirenz-based regimens at enrolment (Table 5.2).

Table 5.2: POwER study outcomes, n = 80

Outcome	POC VL intervention arm n/N, % (95% CI)	Lab VL standard care arm n/N, % (95% CI)	P value
Primary outcome			
VL at 24 weeks (copies/mL)			
<50	27/39, 69.2% (53.4-81.4)	29/40*, 72.5% (57.0-83.9)	0.808†
50-999	6/39, 15.4% (7.0-30.2)	5/40, 12.5% (5.1-26.7)	-
≥1000	5/39, 12.8% (5.2-27.3)	3/40, 7.5% (2.0-20.7)	-
Lost to follow up	1/39, 2.6% (0.0-14.6)	3/40, 7.5% (2.0-20.7)	-
Receiving efavirenz at enrolment			
<50	12/17, 70.6% (46.5-86.8)	13/19, 68.4% (45.8-84.7)	-
50-999	3/17, 17.6% (5.6-42.0)	4/19, 21.1 (8.1-44.0)	-
≥1000	1/17, 5.9 (0.0-29.2)	1/19, 5.3 (0.0-26.8)	-
Lost to follow up	1/17, 5.9 (0.0-29.2)	1/19, 5.3 (0.0-26.8)	-
Receiving dolutegravir at enrolment			
<50	15/22, 68.2% (47.1-83.7)	16/21, 76.2% (54.4-89.6)	-
50-999	3/22, 13.6 (4.1-34.4)	1/21, 4.8% (0.0-24.7)	-
≥1000	4/22, 18.2 (6.9-39.3)	2/21, 9.5% (1.6-30.4)	-
Lost to follow up	0/22, 0.0% (0.0-17.9)	2/21, 9.5% (1.6-30.4)	-
Secondary study feasibility outcomes			
Proportion of potentially eligible participants in PCZ CDC who were enrolled‡	62/262, 23.7% (18.9-29.2)		
Proportion of enrolled participants who attended study exit visit	38/39, 97.4% (85.4-100)	38/41, 92.7%, (79.7-98.1)	0.616
Secondary VL process outcomes			
Median days from enrolment to follow up VL	84 (IQR 84-96)	85 (IQR 78-91)	0.562
Time from follow up VL blood draw to result with patient	3.1 hours (IQR 2.6-3.8)	7 days 0 hours (IQR 6 days 18 hours – 8 days 0 hours)	<0.001
Proportion of VL results communicated to participant on the same day	33/38§, 86.8% (72.1-94.6)	1/39‖, 2.6% (0.0-14.6)	<0.001
Median number of visits during follow up	3 (IQR 3-4)	4 (IQR 4-5)	<0.001
Mean number of EAC sessions during follow-up	1.51 (95% CI 1.29-1.73)	1.49 (95% CI 1.25-1.72)	
Follow up VL (copies/mL)			
<50	22/39, 56.4% (41.0-70.7)	9/41, 22.0% (11.9-37.0)	0.003†
50-999	3/39, 7.7% (2.0-21.2)	14/41, 34.1% (21.6-49.5)	-
≥1000	13/39, 33.3% (20.6-49.1)	16/41, 39.0% (25.7-54.3)	-
Missing	1/39, 2.6% (0.0-14.6)	2/41, 4.9% (0.6-17.2%)	-
Viral failure outcomes			
Proportion of those with viral failure (repeat VL ≥1000 copies/mL) receiving same day EAC	11/13, 84.6% (56.3-96.6)	0/16, 0.0% (0.0-23.1)	<0.001

Outcome	POC VL intervention arm n/N, % (95% CI)	Lab VL standard care arm n/N, % (95% CI)	P value
Median days from enrolment to viral failure ≥1000 copies/mL result being given to participant	85 (IQR 84-96)	95 (IQR 88.5-115)	0.038
Proportion of those with viral failure switched to second-line ART¶	11/13, 84.6% (56.3-96.6)	12/16, 75.0% (0.50-0.90)	0.663
Proportion of those with viral failure with same day switch to second-line ART	8/11, 72.7% (42.8-90.5)	0/12, 0.0% (0.0-28.7)	<0.001
Median days from enrolment to switching to second-line ART	86 (IQR 84-92.5)	98 (IQR 87-106)	0.056
Participants receiving efavirenz at enrolment who were changed to dolutegravir-based ART			
Primary analysis population (n=37)	15/17, 88.2% (64.2-97.7)	12/20, 60.0% (38.6-78.1)	0.073
All enrolled participants (n=75)	31/37, 83.8% (68.4-92.6)	21/38, 55.3% (39.7-69.8)	0.012

**Excluding one participant who did not have a VL sample taken at the study exit visit*

† Comparing proportion with viral suppression <50 copies/mL in each arm

‡After excluding potentially falsely high VLs from before mid-October 2013, we retrospectively identified 262 participants who were potentially eligible for enrolment between October 13th, 2020 to March 11th, 2022. 62 were enrolled in POwER

§ Of the five not communicated on the same day, results were communicated on day 1, 2, 2, 5 and 7 respectively, due to sample being drawn too late in the day for result to be ready during opening hours (n=1), participant not being able to wait for result (n=4).

‖ *Viral load tested using point-of-care assay in error*

¶11/13 (84.6%) with viral failure in point of care arm and 12/16 (68.8%) in standard care arm were receiving efavirenz based first-line ART at time of failure, all of those receiving efavirenz were switched to second-line ART

PCZ CDC = Prince Cyril Zulu Communicable Disease Centre, VL = viral load

5.4.4. Viral load process outcomes

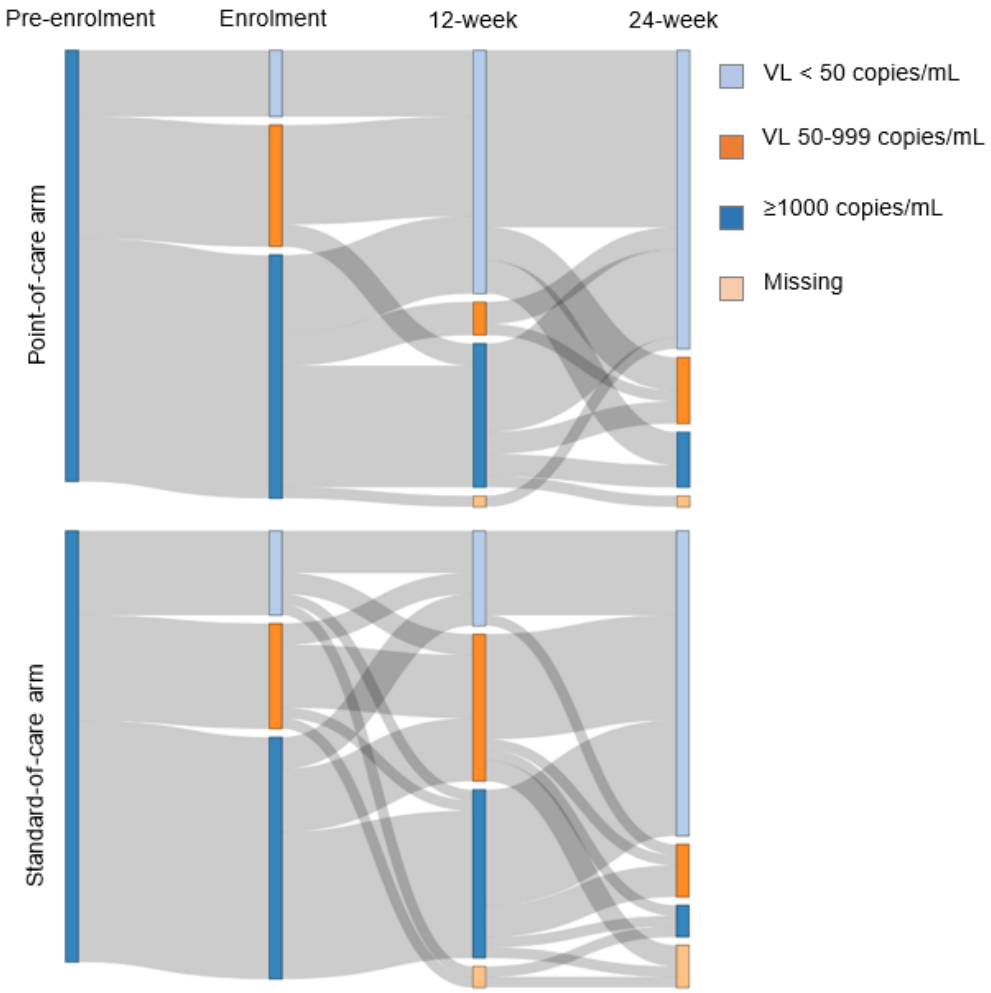
The proportion with 12-week follow-up VLs was high (intervention arm 97.4%, standard-of-care arm 95.1%), taken a median of 84 and 85 days from enrolment respectively. 33/38 (86.8%) point-of-care participants received 12-week VL results on the same day, at a median time of 3.1 hours from blood draw, versus 7 days in the standard-of-care arm. One

standard-of-care participant had their 12-week VL using the point-of-care assay in error. The proportion of patients with a 12-week VL <50 copies/mL was higher in the intervention (22/39, 56.4% [41.0-70.7]) versus the standard-of-care arm (9/41, 22.0% [12.0-36.7], p=0.003), although proportions with viral failure (12-week VL >1000 copies/mL) were similar (Table 5.2, Figure 5.3). 12-week viral failure was also much lower among participants receiving dolutegravir (7/43, 16.3%), compared to efavirenz (22/37, 59.5%). Among those with viral failure, time to the participant receiving VL result was a median 10 days shorter in the intervention arm (Table 5.2). Of the 13 with viral failure in the intervention arm, 11/13, 84.6% (56.3-96.6) received same-day enhanced adherence counselling, and 8/11, 72.7% (43.4-90.3) had same-day switch to second-line ART. Time from enrolment to second-line ART was 12 days shorter in the intervention arm (p=0.056). Overall, there was a median of three (IQR 3-4) follow-up visits in the intervention arm versus four (IQR 4-5) in the standard-of-care arm (p<0.001).

5.4.5. Transition/switch to dolutegravir

Among the 37 participants in the primary analysis population who were on an efavirenz-based regimen at enrolment, 15/17 (88.2%, 95%CI 65.7-96.7) in the intervention arm transitioned/switched to dolutegravir by 24 weeks versus 12/20 (60.0%, 95%CI 38.7-78.1, p=0.073) in the standard-of-care arm. Transition to first-line dolutegravir is particularly recommended for people with viral suppression, and therefore we also assessed transition among all participants enrolled, including those who likely had a falsely high pre-enrolment VL. Transition remained higher in the intervention arm (31/37, 83.8% [95%CI 68.4-92.6] versus 21/38, 55.3% [95%CI 39.7-69.8], p=0.012).

Figure 5.3: Changes in viral loads from pre-enrolment to study exit



5.5. Discussion

5.5.1. Summary

In this feasibility study for a randomised trial of point-of-care VL testing to manage viraemia, enrolment was challenging in the context of the COVID pandemic, but once enrolled, follow-up was high. There was good fidelity to the point-of-care intervention, with faster time to results, quicker switching to second-line ART, and fewer clinic visits in the point-of-care arm. However, point estimates of viral suppression at 24 weeks were similar in the point-of-care and standard-of-care arms.

5.5.2. Interpretation

The major feasibility challenge was enrolment, with an estimated 23.7% of potentially eligible patients enrolled. Disruptions during COVID-19 waves, with staff shortages due to illness/self-isolation, sometimes halted recruitment efforts and hampered clinic processes to track and call back patients with viraemia for referral to study staff. Among participants who were enrolled, retention was good. It may be that these participants were more engaged in the clinic, and therefore more likely to be retained in care, than the average person with viraemia.

While this study was not powered to detect an improvement in the primary outcome of viral suppression between the point-of-care and standard laboratory testing arms, the point estimates were similar. Point-of-care testing was generally conducted well, but there are several reasons which could explain why this did not translate into better viral re-suppression. First, viraemia was managed well in the standard-of-care arm. Results were provided to participants after a median 7 days, and those requiring second-line ART were switched after a median 10 days. These results contrast sharply with other South African studies which found long delays of 14-68 weeks until switching to second-line ART.[92,109,128,129] While we attempted to avoid influencing clinical management in this study, it is likely that being included in POwER increased focus on these patients, thereby improving the standard-of-care. We have previously observed this same phenomenon in an evaluation of a point-of-care versus laboratory testing tuberculosis diagnostic strategy.[136] Second, the small sample size may have exaggerated imbalances in the baseline characteristics between the two arms, which may have favoured the standard-of-care arm. Third, viral failure at 12-weeks (i.e., at the time of the point-of-care intervention) was already low (36.3%), particularly among people receiving dolutegravir (16.3%), meaning there was less potential for the intervention to improve outcomes. A systematic review of people with viraemia on first-line non-nucleoside reverse transcriptase inhibitors (like efavirenz), found that just over 50% developed viral failure,[108] with the remainder re-suppressing after

adherence counselling alone. Our findings suggest that much lower viral failure on dolutegravir means there is less of a role for interventions that improve switching to second-line ART.

Among participants who were receiving efavirenz-based regimens at enrolment, a higher proportion were transitioned/switched to dolutegravir in the intervention arm. This was likely because of the higher proportion of participants with 12-week VL <50 copies/mL in this arm, making clinicians more comfortable to transition to dolutegravir. Reasons for the difference in 12-week VL suppression between the point-of-care and laboratory assay are not clear, as we have found the Xpert HIV-1 VL to be sensitive and specific at a VL threshold of 50 copies/mL.[58]

5.5.3. Comparison with other studies

Several trials of point-of-care VL testing have been published with mixed results. Our previous trial of point-of-care VL testing combined with task-shifting found an improvement of 13.9% in the combined outcome of 12 month viral suppression and retention in care, as well as increased availability and quicker turnaround time of VL results.[102] However, all participants were on first-line efavirenz-based regimens, there were few participants with viral failure (16/390, 4.1%), and the research team conducted clinical management in the intervention arm, meaning it is difficult to determine the contribution of point-of-care testing within the overall implementation strategy. Trials among children in Kenya,[131] adolescents in Haiti,[132] and adults in Nigeria,[133,134] found that point-of-care VL testing improved time to receipt of VL results by 2, 4 and 20 weeks respectively, with improved switching to second-line ART. However, none of these trials found a clear impact on viral suppression.

5.5.4. Strengths and limitations

Strengths of our study include the high fidelity to the point-of-care VL intervention and the use of routine healthcare staff and settings, with management following South African and

WHO guidelines. Our study was severely impacted by the COVID-19 pandemic, which delayed study start and made it harder to consistently enrol participants. Although we were able to demonstrate the accuracy of nurse-led point-of-care testing in a sub-study,[58] we were not able to implement nurse-led testing in POwER as planned, and conducted testing in a site laboratory instead. These difficulties may not be generalisable once the COVID-19 pandemic subsides. While the dolutegravir rollout may have impacted the potential for point-of-care VL testing to influence outcomes, we provide early data on viral re-suppression among people with viraemia who are receiving dolutegravir, which will help to guide the development of interventions. Lastly, we targeted people who had already been identified as viraemic using a laboratory-based assay, meaning point-of-care VL was only used for the 12-week VL, with participants already having received enhanced adherence counselling at enrolment. Identifying people at risk of viraemia using other methods, and then conducting the initial and 12-week VL using point-of-care assays, may provide more opportunities for point-of-care testing to influence outcomes.

5.5.5. Implications for research and policy

Our findings suggest that a larger randomised trial of point-of-care VL testing to manage viraemia may be feasible, but would likely need to be conducted at multiple sites to ensure adequate enrolment. Furthermore, our findings highlight the difficulty in evaluating diagnostic interventions that require changes in clinic flow, without inadvertently improving standard-of-care. Cluster randomised trials may be more appropriate for evaluating this kind of intervention, although it is harder to generate small scale preliminary data. In the context of the ongoing dolutegravir-based ART rollout, the opportunity for point-of-care testing to influence management[137] (e.g. switching to second-line ART) is likely less, and therefore combining point-of-care VL with other interventions that improve the detection and management of adherence, may be more promising.[138] The reduced number of visits with point-of-care testing also suggests that further work should explore healthcare utilization outcomes from the healthcare service and service user perspectives.

5.5.6. Conclusion

Apart from COVID-19 related challenges, it was feasible to conduct a trial of point-of-care VL testing to manage viraemia. Point-of-care testing reduced time to results and clinical visits, but we did not find evidence of improved re-suppression. Further work is needed to identify potential interventions for people with viraemia in the context of the ongoing dolutegravir rollout.

Chapter 6

Based on a manuscript being prepared for submission to a peer-review journal, and on which I am first author.

6. VIRAL RE-SUPPRESSION AMONG PEOPLE WITH VIRAEMIA WHILE RECEIVING DOLUTEGRAVIR-BASED FIRST-LINE ART

6.1. Chapter rationale

In Chapter 5, I discussed how the number of POwER participants who had re-suppression by 12 weeks was greater than expected. In particular, people receiving dolutegravir were more likely to re-suppress. In Chapter 6, I explore reasons for this using HIV drug resistance results taken from stored samples in POwER, and discuss what implications these findings have for management of viraemia in people receiving dolutegravir.

6.2. Introduction

Dolutegravir is an integrase strand transfer inhibitor (INSTI) which is currently being rolled out across low and middle income countries (LMICs).[48,97] Compared to previous non-nucleoside reverse transcriptase (NNRTI) based regimens, dolutegravir has been found to be more effective, tolerable and to have an increased genetic barrier to drug resistance.[139] People receiving dolutegravir who become viraemic may therefore be more likely to have inconsistent adherence, rather than HIV drug resistance. However, in many LMIC settings, HIV drug resistance and drug level testing are not widely available,[20] making it difficult for clinicians to determine the cause of viraemia and therefore manage it appropriately.

Among people receiving NNRTIs, current World Health Organization (WHO) guidelines recommend that those with viraemia ≥1000 copies/mL should receive enhanced adherence counselling, and a repeat viral load after three months. Persistent viraemia after three months, with presumed good adherence, is defined as virological failure. Approximately 70%

of people with viral failure while receiving NNRTIs have been found to have drug resistance,[21,23] and therefore WHO guidelines recommend switching to second-line ART. Current World Health Organization guidelines now recommend dolutegravir instead of NNRTIs for first-line ART, but are not clear as to how subsequent viraemia should be managed. This is because there is little data from LMICs regarding the prevalence of HIV drug resistance among people with viraemia who are receiving dolutegravir-based ART.

Therefore, among people with viraemia in the POwER study, we aimed to compare viral re-suppression and the prevalence of drug resistance between those receiving dolutegravir and those receiving efavirenz-based first-line ART.

6.3. Methods

6.3.1. Study design

We conducted a sub-study within the POwER study, an open-label, individually randomised, feasibility study of point-of-care HIV viral load testing among people with HIV viraemia while receiving first-line ART. The full protocol has been previously published.[69]

6.3.2. Setting and participants

POwER was conducted at two sites in the province of KwaZulu-Natal, South Africa; the Prince Cyril Zulu Communicable Disease Centre in central Durban, with support from the adjacent CAPRISA eThekwini Clinical Research Site, and the Mafakathini Clinic in rural uMgungundlovu District, with support from the adjacent CAPRISA Vulindlela Clinical Research Site. Prince Cyril Zulu and Mafakathini clinics provide care in accordance with South African guidelines, which started recommending dolutegravir in both first- and second-line ART regimens from December 2019.[73] People with viraemia ≥1000 copies/mL are recommended to receive enhanced adherence counselling and then a repeat viral load in three months. If this remains high, those receiving efavirenz are recommended to switch to

second line ART, while those receiving dolutegravir are recommended to continue enhanced adherence counselling and repeat viral load testing.

People receiving care at these clinics were eligible for enrolment into POwER if they were living with HIV, aged ≥18 years and receiving first-line dolutegravir or efavirenz based ART, with recent viraemia ≥1000 copies/mL in the past six weeks. We excluded people who had already received enhanced adherence counselling, and who were pregnant.

6.3.3. Recruitment, enrolment and study procedures

Potentially eligible participants were identified in the study clinics from recent routine viral load tests with viraemic results, and referred to study team for screening and enrolment. A research nurse recorded clinical and demographic details at enrolment, and randomised participants to receive point-of-care or standard laboratory based viral load testing after 12 weeks. Participants received enhanced adherence counselling at the enrolment visit, and all clinical care during the 24 weeks of follow up was provided by routine clinic nurses, counsellors and doctors. Plasma samples were stored at enrolment, 12-week viral load and 24-week study exit visits, for retrospective viral load and drug resistance testing. Any samples with viral load ≥1000 copies/mL were retrospectively sequenced using next-generation sequencing with the Illumina MiSeq platform. We determined HIVDR mutations in protease, integrase and reverse transcriptase regions using the Stanford HIVDR database. Results were not available for clinical management during the study period.

6.3.4. Variables

6.3.4.1. Exposures

The main exposure of interest was whether the participant was receiving dolutegravir- or efavirenz-based ART at enrolment.

6.3.4.2. Outcomes

We assessed the proportion of participants in each group who had viral re-suppression <1000 copies/mL at enrolment, 12 weeks and 24 weeks after enrolment. Enrolment and 24-week viral loads were measured retrospectively using stored samples on the Cobas® HIV-1 reference assay using the cobas 6800 platform (Roche, Basel, Switzerland). 12-week viral loads were measured either using point-of-care or standard laboratory viral load assays, depending on study arm. In each ART group, we also described the proportion with HIV drug resistance at each timepoint, and the proportion switched to second-line ART.

6.3.5. Statistical methods

We conducted descriptive analyses of the proportions in the dolutegravir and efavirenz group achieving each of the study outcomes. We used Fisher's exact test to compare proportions achieving viral re-suppression between the two groups.

6.3.6. Ethical approvals

The eThekwini Municipality Health Unit Research Committee, the KwaZulu-Natal Provincial Health Research Ethics Committee (KZ_202002_005), the University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC 00000836/2019) and the University of Oxford Tropical Research Ethics Committee (OxTREC 66-19) approved the study. POwER is registered on the Pan African Clinical Trials Registry (PACTR202001785886049) and the South African Clinical Trials Registry (DOH-27-072020-6890).

6.4. Results

6.4.1. Participants

We enrolled 80 eligible participants with viraemia between August 20th, 2020 and March 25th, 2022. Median age was 38.5 years (interquartile range [IQR] 33-45), 58.8% were female,

78/80 (97.5%) were enrolled at the Prince Cyril Zulu clinic, and median time on ART was 3.1 years (IQR 1.0-5.7) (Table 6.1).

At enrolment, 37 (46.3%) had been receiving efavirenz-based first-line regimens for a median of 3.2 years (1.1-5.0), and 43 (53.7%) participants had been receiving dolutegravir for a median of 0.7 years (IQR 0.5-1.1). 16/43 (37.2%) had been initiated on dolutegravir, while the other 27/43 (62.8%) had been initiated on an efavirenz-based regimen and were subsequently transitioned to first-line dolutegravir. Participants receiving dolutegravir had less time on ART overall (2.5 years [IQR 0.6-6.0] versus 3.8 years [1.4 to 5.1]). The dolutegravir group also had slightly higher incomes, and higher CD4 counts, compared to those receiving efavirenz (Table 6.1), but otherwise the two groups were very similar. All participants were receiving tenofovir disoproxil fumarate as part of their ART regimen, apart from one in the dolutegravir group who was receiving abacavir.

6.4.2. Analysis of outcomes among patients with viraemia on dolutegravir and efavirenz-based first-line ART

6.4.2.1. Outcomes at enrolment

The median time since the pre-enrolment viral load of ≥1000 copies/mL to enrolment was around two weeks in both groups. At enrolment, the numbers who had re-suppressed <1000 copies/mL was 60.5% of the dolutegravir group, compared to 24.3% (p = 0.002) in the efavirenz group (Table 6.2). Of the 45 with viraemia ≥1000 copies/mL at enrolment, HIV drug resistance testing was successful in 44 (97.8%). The proportion with any nucleoside reverse transcriptase inhibitor (NRTI) mutations was lower in the dolutegravir group (2/15,13.3%, 95% CI 2.7, 39.4) compared to the efavirenz group (21/37, 56.8%, 95% CI 40.9, 71.3) (Table 6.2). In the efavirenz group, 24/37 (64.9%, 95% CI 48.7, 78.2) had NNRTI mutations which conferred efavirenz resistance, while in the dolutegravir group there were no INSTI mutations against dolutegravir.

Table 6.1 Baseline characteristics in the POwER study by ART regimen at enrolment

Variable	Levels	Dolutegravir, n = 43	Efavirenz, n = 37	Total
Age, years	Median (IQR)	40.0 (34.0 to 47.5)	38.0 (33.0 to 41.0)	38.5 (33.0 to 45.0)
Gender	Female	25 (58.1)	22 (59.5)	47 (58.8)
	Male	18 (41.9)	15 (40.5)	33 (41.2)
Time since ART initiation, years	Median (IQR)	2.5 (0.6 to 6.0)	3.8 (1.4 to 5.1)	3.1 (1.0 to 5.7)
NRTI backbone	ABC	1 (2.3)		1 (1.2)
	TDF	42 (97.7)	37 (100.0)	79 (98.8)
Time on current regimen, years	Median (IQR)	0.7 (0.5 to 1.1)	3.2 (1.1 to 5.0)	1.1 (0.6 to 3.1)
History other medical conditions	No	37 (86.0)	34 (91.9)	71 (88.8)
	Yes	6 (14.0)	3 (8.1)	9 (11.2)
ART side effects	No	41 (95.3)	37 (100.0)	78 (97.5)
	Yes	2 (4.7)		2 (2.5)
Last time participant missed a dose of ART	Within past the week	9 (20.9)	8 (21.6)	17 (21.2)
	1-2 weeks ago	3 (7.0)	1 (2.7)	4 (5.0)
	2-4 weeks ago	7 (16.3)	5 (13.5)	12 (15.0)
	1-3 months ago	5 (11.6)	5 (13.5)	10 (12.5)
	>3 months ago	2 (4.7)	0 (0.0)	2 (2.5)
	Never	17 (39.5)	18 (48.6)	35 (43.8)
Hazardous drinking (AUDIT-C)	No	31 (72.1)	23 (62.2)	54 (67.5)
	Yes	12 (27.9)	14 (37.8)	26 (32.5)
Body mass index, kg/m^2	Median (IQR)	28.8 (24.7 to 32.9)	24.8 (22.2 to 30.9)	27.3 (22.9 to 31.7)
Ethnicity	Black African	43 (100.0)	36 (97.3)	79 (98.8)
	Other		1 (2.7)	1 (1.2)
Highest level of education completed	Primary school only	1 (2.3)	0 (0.0)	1 (1.2)
	Secondary school	22 (51.2)	17 (45.9)	39 (48.8)
	Matriculation	16 (37.2)	16 (43.2)	32 (40.0)
	Tertiary	4 (9.3)	4 (10.8)	8 (10.0)
Employment status	Unemployed	14 (32.6)	14 (37.8)	28 (35.0)
	Informal employment	5 (11.6)	1 (2.7)	6 (7.5)
	Part time employment	6 (14.0)	3 (8.1)	9 (11.2)
	Full-time employment	15 (34.9)	12 (32.4)	27 (33.8)
	Student	1 (2.3)	4 (10.8)	5 (6.2)
	Self-employed	2 (4.7)	3 (8.1)	5 (6.2)
Monthly personal income, ZAR	<1000	17 (39.5)	19 (51.4)	36 (45.0)
	1000-4000	13 (30.2)	10 (27.0)	23 (28.8)
	4001-8000	8 (18.6)	8 (21.6)	16 (20.0)
	>8000	5 (11.6)	0 (0.0)	5 (6.2)
Days since pre-enrolment viral load	Median (IQR)	16.0 (14.0 to 20.0)	14.0 (12.0 to 21.0)	15.0 (13.0 to 21.0)
Enrolment CD4 count category, cells/μL	<200	6 (14.0)	15 (40.5)	21 (26.2)
	200-349	12 (27.9)	9 (24.3)	21 (26.2)
	350-499	13 (30.2)	5 (13.5)	18 (22.5)
	>=500	12 (27.9)	8 (21.6)	20 (25.0)

Table 6.2 Outcomes among patients with viraemia on dolutegravir and efavirenz based first-line ART

Variable	Levels	Dolutegravir, n = 43	Efavirenz, n = 37	p
Enrolment viral load, copies/mL	<1000 copies/mL	26 (60.5)	9 (24.3)	0.002
	≥1000 copies/mL	17 (39.5)	28 (75.7)	
NRTI mutations	No	14 (32.6)	7 (18.9)	-
	Yes	2 (4.7)	21 (56.8)	
	HIVDR testing unsuccessful	1 (2.3)	0 (0.0)	
	VL < 1000 copies/mL	26 (60.5)	9 (24.3)	
NNRTI mutations	No	7 (16.3)	4 (10.8)	-
	Yes	9 (20.9)	24 (64.9)	
	HIVDR testing unsuccessful	1 (2.3)	0 (0.0)	
	VL < 1000 copies/mL	26 (60.5)	9 (24.3)	
INSTI mutations	No	16 (37.2)	28 (75.7)	-
	Yes	0 (0.0)	0 (0.0)	
	HIVDR testing unsuccessful	1 (2.3)	0 (0.0)	
	VL < 1000 copies/mL	26 (60.5)	9 (24.3)	
Time to follow-up viral load, days	Median (IQR)	91.0 (84.0 to 98.0)	90.5 (84.0 to 98.2)	-
Follow-up viral load, copies/mL	<1000 cps/ml	33 (76.7)	15 (40.5)	<0.001
	≥1000 cps/ml	7 (16.3)	22 (59.5)	
	(Missing)	3 (7.0)	0 (0.0)	
ART regimen change during follow up?	No	42 (97.7)	10 (27.0)	-
	Yes	1 (2.3)	27 (73.0)	
Reason for ART regimen change	Virological failure	1 (100.0)	23 (85.2)	-
	ART policy change		4 (14.8)	
New ART regimen	AZT / 3TC / LPVr	1 (100.0)	1 (3.7)	-
	AZT / 3TC / DTG		18 (66.7)	
	TDF / 3TC / DTG		4 (14.8)	
	TDF / AZT / 3TC / DTG		3 (11.1)	
	TDF / FTC / LPVr		1 (3.7)	
Exit viral load, copies/mL	<1000	35 (81.4)	32 (86.5)	0.280
	≥1000	6 (14.0)	2 (5.4)	
	Lost to follow up	2 (4.7)	2 (5.4)	
	(Missing)	0 (0.0)	1 (2.7)	

6.4.2.2. Outcomes at 12 and 24 weeks

After enhanced adherence counselling and by the time of the viral load at 12 weeks, 76.7% of participants on dolutegravir had re-suppressed <1000 copies/mL, compared to 40.5% of those on efavirenz ($p < 0.001$). All 22 participants who remained unsuppressed and had viral

failure in the efavirenz group, and one other with a repeat viral load of 937 copies/mL, were switched to a second-line regimen (Table 6.2 and Supplementary Table 15.1). At the 24-week exit visit, the proportion achieving a suppressed viral load <1000 copies/ml was similar in the two groups.

6.5. Discussion

6.5.1. Summary

At enrolment, people receiving efavirenz based ART had high levels of HIV drug resistance against their first-line regimen, while there was no resistance against dolutegravir. This was reflected in higher levels of re-suppression by three months in the dolutegravir group compared to the efavirenz group. After switching to second-line ART, 24-week viral re-suppression in the efavirenz group became similar to the dolutegravir group.

6.5.2. Interpretation and comparison with other literature

Among participants receiving dolutegravir-based ART at baseline, there were no INSTI mutations, meaning that poor adherence was likely the cause of viraemia. Our study is one of the first to provide data on re-suppression among people who experience viraemia while receiving first-line dolutegravir, with 76.7% and 58.1% reaching a viral load of <1000 copies/mL and < 50 copies/mL after three months. In contrast, a high proportion of participants receiving efavirenz-based ART had baseline NNRTI resistance, meaning resistance was contributing to viraemia. After three months, 40.5% of those receiving efavirenz had re-suppressed to <1000 copies/mL. This is similar to findings from a large systematic review of outcomes among people with viraemia while receiving NNRTI-based ART, which found that 46.4% had viral resuppression.[108] The remaining participants only re-suppressed after switching to second-line ART.

There is one other study that we are aware of which compares re-suppression among people with viraemia who are receiving dolutegravir with those receiving efavirenz.[140] This is

a sub-study of the ADVANCE trial, a large randomised trial comparing tenofovir alafenamide, emtricitabine, dolutegravir with tenofovir disoproxil fumarate, emtricitabine, dolutegravir, and tenofovir disoproxil fumarate, emtricitabine, efavirenz, taking place in South Africa.[141] Among people with viraemia in ADVANCE, re-suppression was more frequent among people receiving dolutegravir based regimens (155/247, 62.8%) compared to efavirenz (44/138, 32%, p <0.001). There was one case of emergent resistance to dolutegravir, versus six cases in the efavirenz group.

6.5.3. Strengths and limitations

Strengths of our study include the focus on people with viraemia while receiving dolutegravir, the high proportion with viraemia who we were able to successfully test for drug resistance, and the regular frequency of tests to determine viral load trajectories. Our sample size was small, meaning we were unable to adjust for potential confounding factors that could also contribute to the difference in HIV drug resistance and resuppression between the dolutegravir and efavirenz groups. For example, people who were transitioned to dolutegravir may been better engaged in care or motivated to adhere to treatment, and therefore also more likely to resuppress. Follow up time was short, and the median time on dolutegravir was less than a year, which may not be sufficient time for resistance to dolutegravir to develop.

6.5.4. Implications for research and policy

Nevertheless, our findings, alongside those of the ADVANCE study, demonstrate that viraemia among people receiving dolutegravir is largely due to poor adherence, rather than drug resistance. This supports the current South African guidelines, which do not recommend early switching to second-line ART among people with viraemia who are receiving dolutegravir. Currently, drug resistance testing is not recommended until after two years of viraemia, which seems reasonable given the high cost of the test and low prevalence of drug resistance. Instead, managing viraemia should have a renewed focus on

interventions to support adherence. New tests have been developed which can be used to measure antiretroviral drug levels at the point-of-care, and these may facilitate assessment of adherence and provision of adherence support. Further work is needed to evaluate the analytic and clinical performance of these assays, and whether they can be integrated into algorithms to improve adherence support.

6.5.5. Conclusion

In conclusion, we demonstrated high levels of re-suppression, and low prevalence of HIV drug resistance, in people with viraemia who are receiving first-line dolutegravir. Interventions to support adherence, rather than dealing with HIV drug resistance, should be prioritised for people with viraemia who are receiving dolutegravir.

Chapter 7

Based on a manuscript being prepared for submission to a peer-review journal, and on which I am first author.

7. DIAGNOSTIC ACCURACY OF A NOVEL POINT-OF-CARE TEST TO MEASURE URINE TENOFOVIR DRUG LEVELS

7.1. Chapter rationale

In Chapter 6 I showed that HIV drug resistance was very uncommon among participants in POwER who were receiving dolutegravir at baseline, meaning viraemia was likely caused by inconsistent adherence. In Chapter 7, I evaluate the diagnostic accuracy of a novel point-of-care test that measures concentrations of urine tenofovir. Tenofovir disoproxil fumarate (TDF) is included in single tablet, fixed-dose ART combinations of TDF, emtricitabine and efavirenz, and more recently, TDF, lamivudine and dolutegravir, which are used by over 95% of people receiving ART in LMICs.[19,30] Therefore, a test which accurately measures tenofovir levels in urine could be used to detect inconsistent adherence to ART, which may be even more important after the rollout of dolutegravir.

7.2. Introduction

Early identification and management of HIV viraemia among people living with HIV (PLHIV) receiving antiretroviral treatment (ART) is important to ensure rapid viral re-suppression, which in turn prevents HIV transmission, the development of HIV drug resistance (HIVDR), and morbidity and mortality.[26] Viraemia may be caused by inconsistent adherence to effective ART and/or HIVDR, but in low- and middle-income countries (LMICs), resistance and drug level testing are prohibitively expensive and inaccessible,[20] meaning it is difficult for clinicians to determine the cause of viraemia.

TDF is a key component of World Health Organization recommended ART. After ingestion, it is metabolised to tenofovir, which is converted intracellularly to tenofovir-diphosphate. Tenofovir has a short plasma half-life[142] and is excreted renally, meaning it is readily measured in urine, and is therefore a potential target for objective adherence monitoring. Urine tenofovir concentrations have mainly been evaluated among people without HIV, who are using TDF as part of pre-exposure prophylaxis,[52] showing an association with HIV seroconversion.[143] However, measurement currently requires liquid chromatography tandem mass spectrometry (LC-MS/MS), which is not feasible in many clinical settings. More recently, point-of-care urine tenofovir assays using antibody-based technology have been developed which can be readily used in clinical settings to accurately detect TDF adherence within the past 2-5 days.[53]

While several clinical trials are planned or underway to evaluate the clinical impact of point-of-care urine tenofovir assays on HIV treatment outcomes,[138,144,145] there are no studies assessing their diagnostic accuracy in people living with HIV. Therefore, we aimed to evaluate the diagnostic accuracy of the Abbot point-of-care test to detect urine tenofovir, compared to the gold standard LC-MS/MS. We also aimed to evaluate the association between point-of-care urine tenofovir results, and self-reported adherence.

7.3. Methods

7.3.1. Study design

We conducted a cross-sectional sub-study within the POwER study. POwER is an open-label, individually randomised, feasibility study of point-of-care HIV viral load (VL) testing to enhance re-suppression among people with HIV viraemia while receiving first-line ART. The POwER protocol has been previously published[69].

7.3.2. Participants

We included all participants enrolled into POwER who were taking tenofovir disoproxil fumarate. People were eligible for enrolment into POwER if they were living with HIV, receiving first-line ART and with recent viraemia >1000 copies/mL in the past 6 weeks, for which they had not yet received adherence counselling. At enrolment, participants provided sociodemographic and clinical details, including self-reported adherence using previously validated questions,[146,147] and had urine samples taken and stored at -80°C, for retrospective testing in this sub-study.

7.3.3. Test Methods

We thawed the frozen urine samples and tested them according to manufacturer's instructions using the Abbott (Abbott, Chicago, USA) lateral flow point-of-care urine tenofovir assay. 3-4 drops of urine were added to the test well, and the result was read by two independent laboratory technicians after 3-5 minutes. Photos of discrepant results were adjudicated by a third investigator. We used LC-MS/MS at the Africa Health Research Institute in Durban, to measure quantitative tenofovir levels in thawed urine samples. For all the above testing methods, the person conducting the test was not aware of the results from other methods.

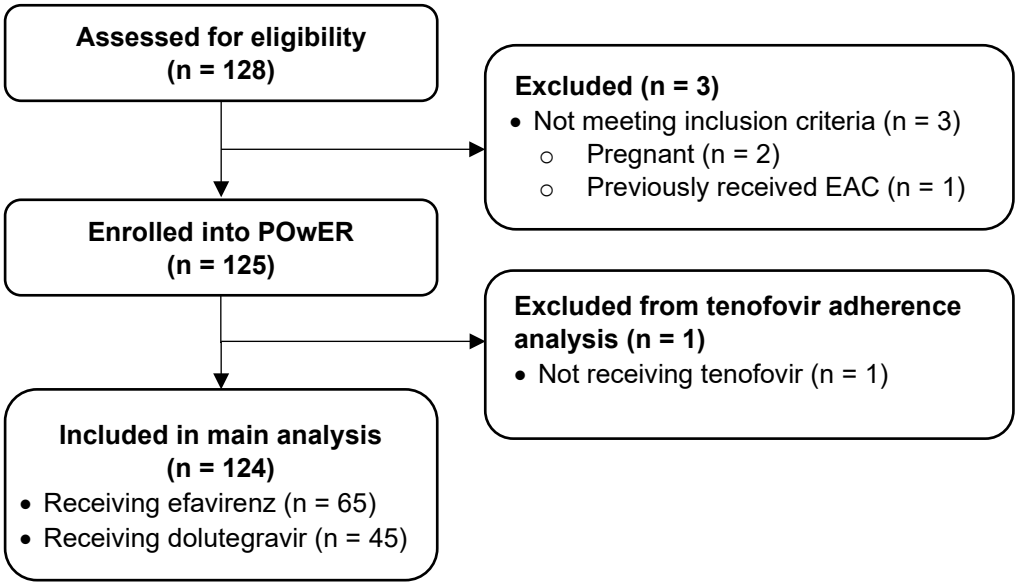
7.3.4. Statistical analysis

We assessed the diagnostic accuracy (sensitivity, specificity and positive and negative predictive values), of the point-of-care tenofovir test to detect urine tenofovir at the manufacturer stated threshold of 1500ng/mL. We also compared self-reported adherence with point-of-care urine tenofovir results using logistic regression models. Sample size was determined by the number of participants enrolled into POwER and receiving TDF.

7.3.5. Ethical approvals

The eThekwini Municipality Health Unit Research Committee, the KwaZulu-Natal Provincial Health Research Ethics Committee (KZ_202002_005), the University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC 00000836/2019) and the University of Oxford Tropical Research Ethics Committee (OxTREC 66-19) approved the study. POwER is registered on the Pan African Clinical Trials Registry (PACTR202001785886049) and the South African Clinical Trials Registry (DOH-27-072020-6890).

Figure 7.1 Flow diagram of POwER participants included in point-of-care urine tenofovir evaluation



7.4. Results

7.4.1. Summary data

Between August 20th, 2020 and March 25th, 2022, we enrolled 125 participants into POwER, of whom 124 were receiving TDF and were included in this analysis (Figure 7.1). The median age was 39 years (IQR 34-45) and 68 (54.8%) were women (Table 7.1). In December 2020, we were informed that 45 participants had their pre-enrolment VLs measured on a defective VL analyser which had been overestimating some VL results.

Therefore, the viraemic sample used to determine eligibility may have been falsely high. After discussion with the ethics committees, we continued to include these participants in POwER, and included them in this sub-study in order to have a larger number of participants. At enrolment, 101 (81.5%) had urine tenofovir detected with the point-of-care test. Median urine tenofovir concentration was 20000 ng/mL (IQR 7280 to 33625). 23.4% reported missing a dose in the past 4 days, and 62.9% reported last missing a dose over four weeks ago (Table 7.1).

Table 7.1 Baseline characteristics of participants in POwER who were receiving tenofovir disoproxil fumarate at enrolment, n = 124

Variable	Levels	Total
Age, years	Median (IQR)	39.0 (34.0 to 45.0)
Gender	Female	68 (54.8)
	Male	56 (45.2)
Time since ART initiation, years	Median (IQR)	4.1 (1.5 to 6.1)
Time on current regimen, years	Median (IQR)	1.6 (0.7 to 5.0)
Current ART regimen	TDF / FTC / EFV	75 (60.5)
	TDF / 3TC / DTG	49 (39.5)
ART side effects	No	120 (96.8)
	Yes	4 (3.2)
Ethnicity	Black African	121 (97.6)
	Coloured	1 (0.8)
	Other	2 (1.6)
Enrolment CD4 count category, cells/μL	<200	21 (16.9)
	200-349	25 (20.2)
	350-499	29 (23.4)
	>=500	49 (39.5)
POC urine tenofovir test	Not Present	23 (18.5)
	Present	101 (81.5)
Urine tenofovir concentration, ng/mL	Median (IQR)	20000.0 (7280.0 to 33625.0)
Last time participant missed a dose of ART	<2 weeks	30 (24.2)
	2-4 weeks	16 (12.9)
	1-3 months	16 (12.9)
	>3 months	8 (6.5)
	Never	54 (43.5)
Number of ART doses missed in past 4 days	0	95 (76.6)
	1	14 (11.3)
	2	9 (7.3)
	3	2 (1.6)
	4	4 (3.2)

7.4.2. Diagnostic accuracy

Compared to quantitative urine tenofovir concentrations, the point-of-care tenofovir test was accurate at detecting tenofovir at the manufacturer stated threshold of 1500 ng/mL, with a sensitivity of 96.1% (95% confidence interval [CI] 90.0-98.8), specificity of 90.5% (69.6-98.4), positive predictive value of 98.0 (92.5-99.9) and negative predictive value of 82.6 (62.1-93.5, Table 7.2). All six discrepant results occurred in samples with LC-MS/MS tenofovir between 500 and 3000ng/mL (Table 7.3).

Table 7.2 Analytic performance of the point-of-care test to detect urine tenofovir at the manufacturer threshold of 1500ng/mL

		LC-MS/MS urine TFV (ng/mL)		
		<1500	*≥1500*	*Total*
POC TFV	TFV not detected	19	4	23
	TFV detected	2	99	101
	Total	21	103	124
Sensitivity		96.1% (90.0-98.8), p<0.001		
Specificity		90.5% (69.6-98.4), p<0.001		
PPV		98.0% (92.5-99.9), p<0.001		
NPV		82.6% (62.1-93.5), p=0.003		

TFV = tenofovir, LC-MS/MS = liquid chromatography – tandem mass spectrometry

Table 7.3 Point-of-care urine tenofovir results for samples measured between 500-3000ng/mL with LC-MS/MS

Participant	LC-MS/MS Urine TFV concentration (ng/mL)	Point-of-care urine TFV result	Discrepant result?
A	613	Present	Discrepant
B	687	Present	Discrepant
C	697	Not Present	Not Discrepant
D	944	Not Present	Not Discrepant
E	1030	Not Present	Not Discrepant
F	1150	Not Present	Not Discrepant
G	1620	Not Present	Discrepant
H	2090	Not Present	Discrepant
I	2430	Not Present	Discrepant
J	2790	Not Present	Discrepant

TFV = tenofovir, LC-MS/MS = liquid chromatography – tandem mass spectrometry

7.4.3. Self-reported adherence

Self-reported missed doses in the past four days, and more recently self-reported missed doses were both associated with undetectable point-of-care urine tenofovir (Table 7.4). However, 11/95 (11.6%) people who reported missing no doses in the past four days had undetectable urine tenofovir. Two of these were false negatives, with LC-MS/MS concentrations >1500 ng/mL.

Table 7.4 Self-reported adherence compared to point-of-care urine tenofovir results

Adherence variable		POC TFV assay		
		Not Present	Present	Odds ratio* (95% CI), P
Number of ART doses missed in past 4 days	0	11 (11.6)	84 (88.4)	0.42 (0.25-0.65) P = <0.001
	1	3 (21.4)	11 (78.6)	
	2	5 (55.6)	4 (44.4)	
	3	1 (50.0)	1 (50.0)	
	4	3 (75.0)	1 (25.0)	
Last time participant missed a dose of ART (weeks)	Never	4 (7.4)	50 (92.6)	0.63 (0.46-0.84) P = 0.002
	>12	1 (12.5)	7 (87.5)	
	4-12	4 (25.0)	12 (75.0)	
	2-4	3 (18.8)	13 (81.2)	
	<2	11 (36.7)	19 (63.3)	

TFV = tenofovir

7.5. Discussion

7.5.1. Summary

In this diagnostic accuracy study we demonstrate that a novel point-of-care test is accurate at detecting urine tenofovir, and that there was an association between urine tenofovir results and self-reported adherence.

7.5.2. Comparison with other studies

There is one other published study assessing the analytic performance of this assay. The TARGET study was a dosing trial in Thailand among 30 adults without HIV, who were randomised to take TDF 300mg and emtricitabine 200mg on 7, 4 or 2 days a week, as HIV

pre-exposure prophylaxis.[148] As part of the development and validation of the point-of-care tenofovir assay, 300 randomly selected stored urine samples from TARGET were tested using the point-of-care assay and on LC-MS/MS. The point-of-care urine tenofovir assay had sensitivity of 97% (95-99) and specificity of 99% (94-100) at a cut-off of 1500ng/mL.[53] These results are slightly higher than the point estimates in our study, but are within the 95% confidence intervals of our estimates. Of note, all the discrepant results in our analysis were close to the cut-off of 1500ng/mL.

The cut-off of 1500ng/mL was selected using modelled data from the TARGET study, as it would correctly classify 98% of people who took a TDF dose 24 hours ago as adherent, and 86% of those who last took a dose 96 hours ago as non-adherent.[149] Several other studies have also demonstrated a relationship between quantitative urine tenofovir levels and time since the last dose of TDF.[150,151] In our study, we did not have objective data on timing of recent ART doses, and instead used self-reported measures. However, multiple studies have demonstrated the limitations of self-reported adherence.[152-154] While we demonstrated an association between self-reported adherence and urine tenofovir levels, we also found that around 10% of people who reported missing no doses in the past four days had undetectable urine tenofovir using the point-of-care test. Therefore, additional people with adherence problems could be identified quickly and easily for targeted enhanced adherence counselling using point-of-care urine tenofovir testing.

7.5.3. Strengths and limitations

This is one of the first evaluations of the analytic performance of the Abbot point-of-care urine tenofovir assay, beyond the validation conducted as part of the assay's development.[53] Point-of-care urine tenofovir testing was conducted by laboratory staff, and so results may not be generalisable to use in clinic settings. However, the assay is a simple lateral flow device, similar to other assays which front-line healthcare workers are familiar with using in LMIC primary care settings. The sample size in our study was limited by the number of

participants enrolled into POwER, and meant that confidence intervals of our estimates were wide.

7.5.4. Implications for future research

Further work is needed to determine the association between urine tenofovir levels and clinical outcomes in people living with HIV who are taking ART. Among people who are taking dolutegravir, in whom HIV drug resistance is rare, viraemia is likely to be caused by poor adherence. Furthermore, among people receiving efavirenz who have viraemia, a detectable urine tenofovir result may indicate good adherence, and therefore that HIV drug resistance is the likely cause. We therefore plan to assess the association between urine tenofovir results, and viraemia and HIV drug resistance, using samples from POwER. Studies to determine the feasibility and acceptability of point-of-care tenofovir testing in primary care settings, for healthcare workers and people receiving ART, should be conducted,[155] as well as to establish the clinical performance in these settings. We are currently running the STREAM-HIV trial, which will assess whether using this assay to guide enhanced adherence counselling will improve adherence during the first six months after initiation ART.[138]

7.5.5. Conclusion

We have demonstrated that a novel point-of-care assay is accurate at detecting urine tenofovir, and could help to identify people with inconsistent ART adherence and allow better targeted adherence support.

Chapter 8

Based on a paper for which I am first author, entitled “Implementation and outcomes of dolutegravir-based first-line antiretroviral therapy for people with HIV in South Africa: a retrospective cohort study”, currently under review at *The Lancet HIV.*

8. IMPLEMENTATION AND OUTCOMES OF DOLUTEGRAVIR-BASED FIRST-LINE ANTIRETROVIRAL THERAPY FOR PEOPLE WITH HIV IN SOUTH AFRICA: A RETROSPECTIVE COHORT STUDY

8.1. Chapter rationale

In Chapter 6 I found that HIV drug resistance is very uncommon among people receiving dolutegravir, and that this has implications for the management of viraemia, which will likely require new diagnostic strategies. In Chapter 7 I evaluated a novel point-of-care test that could help to detect inconsistent adherence and has potential to be included in new algorithms to manage viraemia among people receiving dolutegravir. How important these findings are will depend on how widely dolutegravir is used. Therefore, in this chapter I evaluate the extent of the dolutegravir rollout in South African primary care clinics, and the impact of dolutegravir use on viral suppression, in order to guide future directions of diagnostic monitoring strategies.

8.2. Introduction

Since 2018 the World Health Organization (WHO) has recommended dolutegravir-based first-line antiretroviral therapy (ART),[156] due to clinical trial evidence of increased efficacy compared to non-nucleoside reverse transcriptase inhibitors (NNRTIs). This is largely driven by better tolerability and less discontinuations, and dolutegravir is also more robust against the development of HIV drug resistance.[48,139] Initially, safety concerns regarding a potential increased risk of neural tube defects if dolutegravir was taken at conception, led the WHO to recommend restricted use among women of child-bearing potential.[156] However, new data

suggesting a lower risk of neural tube defects, risk-benefit analyses from modelling studies,[157] and community advocacy[158] led WHO to remove these restrictions in July 2019.[156] By mid-2022 dolutegravir had been introduced into the preferred first-line ART regimen in approximately 108 countries.[51]

To date, there are few published studies examining the impact of the above restrictions on dolutegravir uptake over time,[159-161] and little data comparing effectiveness of dolutegravir with alternative first-line regimens in non-trial settings in Africa.[162] In regions with high prevalence of tuberculosis co-infection, there are also important concerns regarding the use of dolutegravir with rifampicin-containing tuberculosis treatment, which reduces dolutegravir drug levels. This can be overcome by doubling the dolutegravir dose,[163] which may not always be feasible in large-scale ART programmes. Dolutegravir use is particularly pertinent in South Africa, where there are over 7·5 million PLHIV, the majority of whom are women of child-bearing potential, and tuberculosis incidence is high.

We aimed to assess the impact of the first-line dolutegravir rollout on HIV treatment outcomes in South Africa. We determined a) the extent to which women were less likely to receive dolutegravir over time, b) the relationship between dolutegravir use, and retention-in-care and viral suppression, and c) the effect of dolutegravir use on HIV treatment outcomes among people receiving concurrent tuberculosis treatment.

8.3. Methods

8.3.1. Study design and setting

We conducted a retrospective cohort study using de-identified, routinely collected data from 59 public sector, primary care clinics run by the eThekwini Municipality Health Unit, in the province of KwaZulu-Natal, South Africa. These clinics represent approximately 60% of all public clinics in the eThekwini Metro, which includes the city of Durban. ART is provided free of charge in accordance with South African National Department of Health guidelines,[73]

which recommended dolutegravir from December 1, 2019. Initially, ART initiations were prioritised, and women of child-bearing potential required to sign an 'acknowledgement of risk' form. On February 24, 2020, eligibility was expanded to include people already receiving first-line ART, with a risk-benefit discussion replacing the signed risk form for women of child-bearing potential.[164] In June 2021, the risk-benefit discussion for women was removed, and dolutegravir became the preferred first-line ART regimen.[165] For PLHIV with tuberculosis co-infection, dolutegravir was only recommended after completing tuberculosis treatment. Viral load testing was recommended annually, and transition to first-line dolutegravir was only recommended if people had a suppressed viral load of <50 copies/mL in the previous six months, or consecutive viral loads between 50-999 copies/mL.[73]

8.3.2. Participants

We analysed two mutually exclusive groups; the 'initiator cohort', and the 'transition cohort'. For the initiator cohort, we evaluated dolutegravir use by gender among all PLHIV aged ≥15 years and newly initiating first-line ART (irrespective of NRTI backbone) at participating clinics, between December 1, 2019 and February 28, 2022. We excluded people with known previous ART exposure, as South African guidelines recommend re-initiating the previous regimen, which would often not be dolutegravir-based. We then analysed outcomes among those who initiated ART before December 1, 2020 and therefore had at least 12 months of follow-up time plus 90 days to assess retention-in-care before the data cut on February 28th, 2022. We assessed viral load outcomes only among those who were retained-in-care at 12 months.

For the transition cohort, we assessed transition to first-line dolutegravir by gender among PLHIV aged ≥15 years who were in care and receiving non-dolutegravir first-line ART at participating clinics on December 1st, 2019. We excluded those with viral load ≥1000 copies/mL in the previous 12-months, as they would not have been eligible for transition to first-line dolutegravir. We then analysed outcomes among a subset who had initiated

dolutegravir before December 1, 2020, compared to people who had not initiated dolutegravir at the same timepoint, matched 1:1 using propensity score matching (see below).

8.3.3. Data sources and data management

For people initiating and receiving ART in the South African public sector, data on demographics, clinical status, ART and clinic visits are routinely recorded in the TIER.net[166] electronic register. TIER.net data from participating clinics was collated and de-identified by the South African National Department of Health's TB/HIV Information Systems (THIS - www.tbhivinfosys.org.za/) before being extracted for analysis.

8.3.4. Variables

We used demographic and clinical variables recorded at ART initiation or during follow-up.

8.3.4.1. Outcomes

We defined first-line dolutegravir use from the ART initiation regimen (initiator cohort) or the date of first use of dolutegravir in a first-line regimen (transition cohort, see Chapter 8 Appendix for full definition). We defined retention-in-care as not being recorded in TIER.net as deceased, lost-to-follow-up (defined as 90 days late for a visit by the South African ART programme, with date of last visit used as date of loss-to-follow-up) or 'transferred out' to another clinic (as we could not access or link to data at other clinics to establish retention-in-care). We used viral suppression <50 copies/ml, as per clinical trials[141,167,168] and South African guidelines. In this programmatic setting, not all patients had annual viral loads. Therefore, in both cohorts we included viral loads five to 18 months after baseline, and used the result closest to 12 months.

8.3.5. Statistical analysis

Among the initiator cohort, we first used univariable Poisson regression models with robust standard errors to assess the association between gender, and the outcome of dolutegravir initiation. We also conducted sensitivity analyses, defined a priori, to assess whether the effect of gender on dolutegravir use was modified by age at ART initiation, and by time. We then used univariable and multivariable Poisson regression models with robust standard errors to assess the association between being initiated on dolutegravir, and 12-month retention-in-care, and viral suppression. To assess whether tuberculosis treatment impacted on viral suppression with dolutegravir, we did a sensitivity analyses, defined a priori, with an interaction term between initiation ART regimen and tuberculosis status.

Among the transition cohort, we used univariable Cox proportional hazards models to assess the association between gender and time to transition to a dolutegravir-based first-line regimen. We started follow-up time from December 1, 2019, and censored people at date of loss-to-follow-up, death, transfer to another clinic, or switch to second-line ART. We also censored people with a viral load of >1000 copies/mL during follow-up, as they would not have been eligible for immediate transition to first-line dolutegravir.

Comparing outcomes between people transitioned and not transitioned to dolutegravir is complicated by potential underlying differences between the two groups, and the lack of a clear baseline time in those whose treatment remains unchanged. We addressed these issues by emulating a ‘target trial’, in which each person transitioned to dolutegravir was matched to a control who had not yet been transitioned at the same timepoint.[169] To increase comparability between the two groups, we matched participants 1:1 using a time-dependent propensity score of the log-hazard of transition to dolutegravir,[170,171] with direct matching by time since most recent viral load, and whether the participant was in a differentiated ART delivery programme. Individuals could only be matched once, and we only matched participants transitioned to dolutegravir before December 1st, 2020, to allow 12

months of follow-up time. Further details are provided in Chapter 8 Appendix. We then used multivariable Poisson regression models to compare the outcomes of 12-month retention-in-care and viral suppression between people transitioned to dolutegravir, and their matched controls.

In both the initiation and transition cohort, the primary viral load analysis was an intention-to-treat analysis, with a secondary 'as-treated' analysis that excluded people who changed ART regimen after baseline. We hypothesised, a priori, that dolutegravir rollout and clinical outcomes would vary by clinic, and accounted for this using robust standard errors. We analysed data using R 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria) and STATA 14.0 (StataCorp, Texas, USA).

8.3.6. Ethical approval

This work was approved by the University of Kwazulu-Natal Biomedical Research Ethics Committee (BE646/17), the KwaZulu-Natal Provincial Health Research Ethics Committee (KZ_201807_021), the THIS Data Request Committee, and the eThekwini Municipality Health Unit, with a waiver for informed consent for analysis of de-identified, routinely collected data.

8.3.7. Role of the funding source

The funders had no role in the study design, data collection, analysis, interpretation, writing of the paper, or the decision to submit for publication.

8.4. Results

8.4.1. Initiation cohort

8.4.1.1. Summary data

Between December 1st, 2019 and February 28th, 2022, 45,392 people were initiated on ART (Figure 8.1). 23,945 (52·8%) were non-pregnant women, 4,780 (10·5%) were pregnant women, and 16,667 (36·7%) were men (Table 8.1). Median age was 31·0 years (IQR 26·0, 38·0) and 2401 (5·3%) were receiving TB treatment at time of ART initiation.

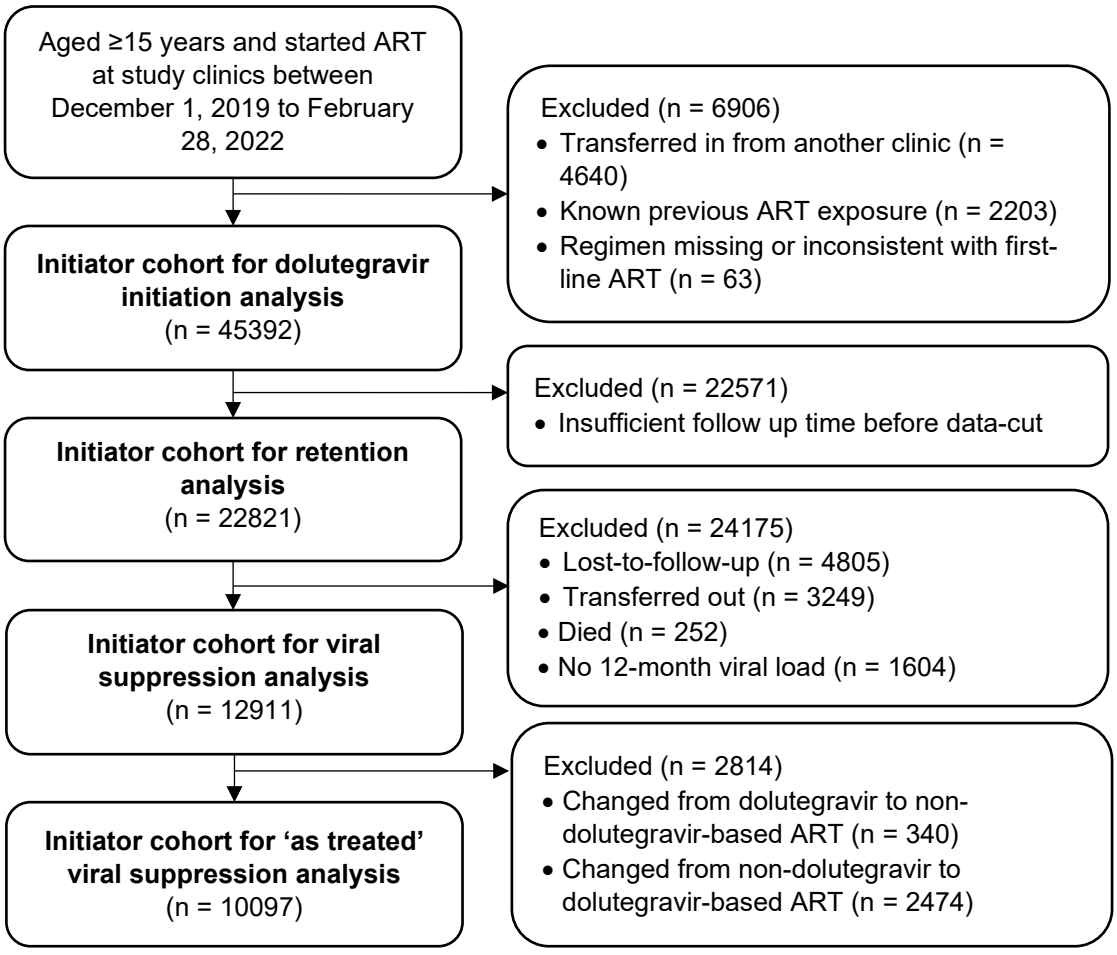
Table 8.1 Univariable Poisson regression models of baseline characteristics associated with being initiated on dolutegravir-based first line ART versus non-dolutegravir ART, n = 45,392

Variable	Level	Total (column %)	Non-dolutegravir regimen, n (row %)	Dolutegravir regimen, n (row %)	RR	P value
Gender	Male	16667 (36·7)	2948 (17·7)	13719 (82·3)	1	<0·001
	Female, not pregnant	23956 (52·8)	8650 (36·1)	15306 (63·9)	0·78 (0·74-0·82)	
	Female, pregnant	4769 (10·5)	2530 (53·1)	2239 (46·9)	0·57 (0·49-0·66)	
Age (years)	55+	1170 (2·6)	277 (23·7)	893 (76·3)	1	<0·001
	45-54	3823 (8·4)	862 (22·5)	2961 (77·5)	1·01 (0·98-1·05)	
	35-44	11833 (26·1)	3127 (26·4)	8706 (73·6)	0·96 (0·93-1·00)	
	25-34	20274 (44·7)	6690 (33·0)	13584 (67·0)	0·88 (0·84-0·92)	
	15-24	8292 (18·3)	3172 (38·3)	5120 (61·7)	0·81 (0·76-0·86)	
Initiation time period	Dec 19 - Feb 20	7174 (15·8)	5797 (80·8)	1377 (19·2)	1	<0·001
	Mar 20 - May 20	5582 (12·3)	2953 (52·9)	2629 (47·1)	2·45 (2·03-2·96)	
	Jun 20 - Aug 20	4940 (10·9)	1730 (35·0)	3210 (65·0)	3·39 (2·74-4·19)	
	Sep 20 - Nov 20	5125 (11·3)	1473 (28·7)	3652 (71·3)	3·71 (2·99-4·60)	
	Dec 20 - Feb 21	4663 (10·3)	936 (20·1)	3727 (79·9)	4·16 (3·34-5·20)	
	Mar 21 - May 21	5668 (12·5)	602 (10·6)	5066 (89·4)	4·66 (3·72-5·83)	
	Jun 21 - Aug 21	4216 (9·3)	321 (7·6)	3895 (92·4)	4·81 (3·85-6·02)	
	Sep 21 - Nov 21	4063 (9·0)	180 (4·4)	3883 (95·6)	4·98 (3·97-6·24)	
	Dec 21 - Feb 22	3961 (8·7)	136 (3·4)	3825 (96·6)	5·03 (4·03-6·28)	
TB at ART initiation	No TB	42991 (94·7)	13032 (30·3)	29959 (69·7)	1	<0·001
	Known TB	2401 (5·3)	1096 (45·6)	1305 (54·4)	0·78 (0·70-0·87)	
Initiation CD4 count (cells/μL)	<200	7038 (15·5)	2090 (29·7)	4948 (70·3)	1	<0·001
	200-349	7543 (16·6)	2381 (31·6)	5162 (68·4)	0·97 (0·95-1·00)	
	350-499	6704 (14·8)	2187 (32·6)	4517 (67·4)	0·96 (0·93-0·98)	
	>=500	11020 (24·3)	3670 (33·3)	7350 (66·7)	0·95 (0·92-0·98)	
	Missing	13087 (28·8)	3800 (29·0)	9287 (71·0)	1·01 (0·94-1·09)	

8.4.1.2. Dolutegravir use

31,264 (69·9%) people were initiated on dolutegravir, 14,102 (31·1%) on efavirenz, and 26 (0·1%) on nevirapine. Dolutegravir use increased over time; between December 1, 2019 to February 29, 2020, 19·2% were initiated on dolutegravir-based ART, compared to 96·6% between December 1, 2021 and February 28, 2022 (Table 8.1). Over the study period, 46·9% of pregnant women, 63·9% of non-pregnant women and 82·3% of men were initiated on dolutegravir. In a univariable Poisson regression model, pregnant women (risk ratio [RR] 0·57 [95% confidence interval 0·49, 0·66], risk difference [RD] -35·4% [-42·3, -28·5]) non-pregnant women (RR 0·78 [0·74, 0·82], RD -18·4% [-21·6, -15·2]) were less likely to be initiated on dolutegravir than men (Table 8.1).

Figure 8.1 Flow diagram of initiation cohort at 59 primary care clinics in South Africa



The effect of gender was strongest among people aged 15-24 years (non-pregnant women versus men RR 0·73 [0·69, 0·77]), and decreased with older age, with no difference between men and women in the ≥55 year-old group (RR 0·97 [0·90, 1·03], Wald test for interaction p <0·001, Table 8.2). Early in the rollout women were much less likely to receive dolutegravir than men (December 1, 2019 to February 29, 2020: non-pregnant women RR 0·29 [0·23, 0·38], pregnant women 0·25 [0·12, 0·53], compared to men, Table 8.2), but this difference declined and disappeared by September 1, 2021 to November 30, 2021 for both non-pregnant (RR 1·00 [0·98, 1·03]) and pregnant women (RR 0·98 [0·94, 1·02], Wald test for interaction p <0·001).

Table 8.2 Likelihood of being initiated on dolutegravir based first line ART among women compared to men, stratified by A) age and B) time period

	Men	Women, non-pregnant		Women, pregnant	
	(n/N)	(n/N)	RR (95% CI)	(n/N)	RR (95% CI)
A) Age (years)*					
≥55	431/555 (77·7%)	462/615 (75·1%)	0·97 (0·90-1·03)	-	-
45-54	1620/2005 (80·8%)	1321/1789 (73·8%)	0·91 (0·87-0·96)	-	-
35-44	5091/6185 (82·3%)	3308/5040 (65·6%)	0·80 (0·76-0·83)	-	-
25-34	5642/6805 (82·9%)	6747/10832 (59·0%)	0·75 (0·71-0·80)	-	-
15-24	935/1117 (83·7%)	3468/5680 (61·1%)	0·73 (0·69-0·77)	-	-
B) Time period					
Dec 19 - Feb 20	926/2660 (34·8%)	390/3808 (10·2%)	0·29 (0·23-0·38)	61/706 (8·6%)	0·25 (0·12-0·53)
Mar 20 - May 20	1647/2104 (78·3%)	906/2875 (31·5%)	0·40 (0·33-0·49)	76/603 (12·6%)	0·16 (0·08-0·32)
Jun 20 - Aug 20	1529/1714 (89·2%)	1553/2653 (58·5%)	0·66 (0·58-0·74)	128/573 (22·5%)	0·25 (0·16-0·40)
Sep 20 - Nov 20	1690/1859 (90·9%)	1753/2657 (66·0%)	0·73 (0·66-0·80)	209/609 (34·3%)	0·38 (0·27-0·52)
Dec 20 - Feb 21	1590/1725 (92·2%)	1853/2413 (76·8%)	0·83 (0·78-0·90)	284/525 (54·1%)	0·59 (0·49-0·70)
Mar 21 - May 21	2020/2105 (96·0%)	2716/3076 (88·3%)	0·92 (0·88-0·96)	330/487 (67·8%)	0·71 (0·63-0·79)
Jun 21 - Aug 21	1427/1485 (96·1%)	2088/2273 (91·9%)	0·96 (0·92-0·99)	380/458 (83·0%)	0·86 (0·80-0·94)
Sep 21 - Nov 21	1441/1509 (95·5%)	2040/2125 (96·0%)	1·00 (0·98-1·03)	402/429 (93·7%)	0·98 (0·94-1·02)
Dec 21 - Feb 22	1449/1506 (96·2%)	2007/2076 (96·7%)	1·00 (0·99-1·02)	369/379 (97·4%)	1·01 (0·99-1·04)

Pregnant women excluded as there were too few pregnant women in older age groups

Wald test for age-gender interaction, p < 0.001, and time period-gender interaction, p <0.001

8.4.1.3. Loss-to-follow-up and viraemia

22,821 people initiated ART before December 1, 2020, and had the opportunity to complete 12 months of follow-up, plus 90 days to assess retention, before the data cut. Of those who were initiated on a dolutegravir-based regimen, 476/10868 (4·4%) were changed to efavirenz (n=462) or another non-dolutegravir based regimen (n = 14), after a median 120 days (66, 201) from ART initiation. Of those initiated on a non-dolutegravir regimen, 2944/11953 (24·6%) were changed to dolutegravir, after a median of 191 days (98, 252).

Table 8.3 Univariable and multivariable Poisson regression models of factors associated with retention-in-care in people initiating dolutegravir and non-dolutegravir-based first line ART, n = 22,8210

Variable	Levels	Retained-in-care	RR	P-value	aRR*	P-value
ART regimen	Non-DTG regimen	7407 (62·0)	1	0·005	1	<0·001
	DTG regimen	7108 (65·4)	1·06 (1·02-1·10)		1·09 (1·04-1·14)†	
Gender	Male	5432 (65·2)	1	0·004	1	0·005
	Female, not pregnant	7518 (62·7)	0·96 (0·94-0·99)		1·04 (1·02-1·07)	
	Female, pregnant	1565 (62·6)	0·96 (0·91-1·02)		1·10 (1·02-1·18)	
Age (years)	55+	415 (69·3)	1	<0·001	1	<0·001
	45-54	1368 (73·1)	1·05 (1·00-1·11)		1·05 (0·99-1·11)	
	35-44	3945 (68·4)	0·99 (0·94-1·04)		0·99 (0·94-1·04)	
	25-34	6461 (62·3)	0·90 (0·86-0·94)		0·91 (0·86-0·95)	
	15-24	2326 (55·3)	0·80 (0·75-0·85)		0·81 (0·76-0·86)	
Initiation time period	Dec 19 - Feb 20	4624 (64·5)	1	0·019	1	0·043
	Mar 20 - May 20	3637 (65·2)	1·01 (0·98-1·05)		0·98 (0·95-1·02)	
	Jun 20 - Aug 20	3083 (62·4)	0·97 (0·93-1·00)		0·94 (0·89-0·99)	
	Sep 20 - Nov 20	3171 (61·9)	0·96 (0·92-1·00)		0·93 (0·88-0·98)	
TB at ART initiation	No TB	13646 (63·0)	1	<0·001	1	<0·001
	Known TB	869 (74·8)	1·19 (1·14-1·23)		1·17 (1·13-1·22)	
Initiation CD4 count (cells/μL)	<200	2645 (71·3)	1	<0·001	1	<0·001
	200-349	2724 (68·5)	0·96 (0·93-0·99)		0·99 (0·96-1·03)	
	350-499	2291 (66·2)	0·93 (0·90-0·96)		0·98 (0·94-1·01)	
	>=500	3539 (64·1)	0·90 (0·87-0·93)		0·95 (0·91-0·98)	
	Missing	3316 (53·9)	0·76 (0·69-0·83)		0·78 (0·72-0·86)	

By 12 months, in the dolutegravir group 7108 (65·4%) were retained-in-care, 1391 (12·8%) had transferred to another clinic, 2233 (20·5%) were lost-to-follow-up, and 136 (12·8%) were

known to have died, compared to 7407 (62·0%) retained-in-care, 1858 (15·5%) transferred, 2572 (21·5%) lost-to-follow-up and 116 (9·7%) died in the non-dolutegravir group. Overall median time to loss-to-follow-up was 35 days (0-156); 1895 (39·4%) were not seen again after ART initiation. In a Poisson model adjusted for age, gender, time, tuberculosis status and initiation CD4 count, people initiated on dolutegravir were more likely to be retained-in-care compared to those initiated on non-dolutegravir based regimens (adjusted risk ratio [aRR] 1·09 [1·04, 1·14], aRD 5·2% [2·2, 8·4], Table 8.3). In post-hoc sensitivity analysis including transfers to another clinic as retained-in-care, the association between dolutegravir and retention was attenuated (aRR 1·03 [0·99, 1·08], aRD 2·4% [-0·9, 5·7]).

Table 8.4 Univariable and multivariable Poisson regression models of factors associated with viral suppression in people initiating dolutegravir and non-dolutegravir-based first line ART, n = 12,911

Variable	Levels	Viral suppression	RR	P-value	aRR*	P-value
ART regimen	Non-DTG regimen	5327 (81·4)	1	0·055	1	0·002
	DTG regimen	5289 (83·0)	1·02 (1·00-1·04)		1·04 (1·01-1·06)‡	
Gender	Male	3808 (79·4)	1	<0·001	1	<0·001
	Female, not pregnant	5685 (84·0)	1·06 (1·04-1·07)		1·06 (1·04-1·07)	
	Female, pregnant	1123 (83·6)	1·05 (1·02-1·08)		1·06 (1·02-1·09)	
Age (years)	55+	319 (84·2)	1	0·492	1	0·023
	45-54	1036 (83·0)	0·99 (0·94-1·04)		0·99 (0·94-1·04)	
	35-44	2902 (81·6)	0·97 (0·93-1·01)		0·98 (0·93-1·02)	
	25-34	4707 (82·5)	0·98 (0·93-1·03)		0·97 (0·92-1·02)	
	15-24	1652 (81·8)	0·97 (0·93-1·02)		0·94 (0·90-0·99)	
Initiation time period	Dec 19 - Feb 20	3324 (80·7)	1	<0·001	1	<0·001
	Mar 20 - May 20	2746 (83·5)	1·03 (1·01-1·06)		1·03 (1·00-1·05)	
	Jun 20 - Aug 20	2325 (84·9)	1·05 (1·03-1·08)		1·03 (1·00-1·06)	
	Sep 20 - Nov 20	2221 (80·3)	0·99 (0·97-1·02)		0·98 (0·95-1·00)	
TB at ART initiation	No TB	10032 (82·7)	1	<0·001	1	0·063
	Known TB	584 (75·5)	0·91 (0·88-0·95)		0·96 (0·93-1·00)	
Initiation CD4 count (cells/μL)	<200	1786 (73·6)	1	<0·001	1	<0·001
	200-349	2011 (81·3)	1·10 (1·07-1·14)		1·10 (1·07-1·14)	
	350-499	1734 (84·5)	1·15 (1·11-1·19)		1·14 (1·11-1·18)	
	>=500	2798 (88·1)	1·20 (1·17-1·23)		1·19 (1·15-1·22)	
	Missing	2287 (82·2)	1·12 (1·08-1·15)		1·11 (1·08-1·15)	

Of those retained-in-care at 12 months, 12,911/14,515 (88·9%) had a documented viral load result after a median 365 (347, 380) days from initiation. Of these, 10,616 (82·2%) were supressed <50 copies/mL. In a multivariable model adjusted for the same variables as the retention model, people initiated on dolutegravir had better viral suppression compared to non-dolutegravir regimens (aRR 1·04 [1·01, 1·06], aRD 3·1% [1·2, 5·1], Table 8.4). In 'as treated' analyses, excluding people who had a change in ART from or to dolutegravir after ART initiation, the association between dolutegravir and viral suppression was stronger (aRR 1·09 [1·05, 1·12], aRD 6·8% [4·3, 9·4]), Supplementary Table 16.2).

Among people with tuberculosis, 316/774 (40·8%) were initiated on dolutegravir. In this group, the association between dolutegravir and viral suppression was stronger (aRR 1·14 [1·07, 1·22]) than among those without tuberculosis (aRR 1·03 [1·01, 1·06], Wald test for interaction p = 0·006, Table 8.5).

Table 8.5 Viral suppression among people initiated on dolutegravir versus non-dolutegravir ART, by tuberculosis status*, n = 12, 911

	Proportion with viral suppression <50 copies/mL		
TB status at ART initiation	**Non-dolutegravir regimen (n/N)**	**Dolutegravir regimen (n/N)**	**aRR (95% CI)**
No TB	5000/6083 (82·2%)	5032/6054 (83·1%)	1·03 (1·01-1·06)
Known TB	327/458 (71·4%)	257/316 (81·3%)	1·14 (1·07-1·22)

Wald test for interaction, p = 0.006

**Multivariable Poisson regression model adjusted for age, gender, time, initiation time period and initiation CD4 count*

8.4.2. Transition cohort

8.4.2.1. Summary data

On December 1st, 2019, 180,956 people were receiving non-dolutegravir based first-line ART at the study clinics (Figure 8.2), of whom 124,168 (68·6%) were women (Table 8.6). Median age was 38 (32, 45) years, and median time on ART was 3·9 (2·0, 6·4) years, with the majority receiving efavirenz (98·7%) and tenofovir (98·4%).

Figure 8.2 Flow diagram of transition cohort at 59 primary care clinics in South Africa

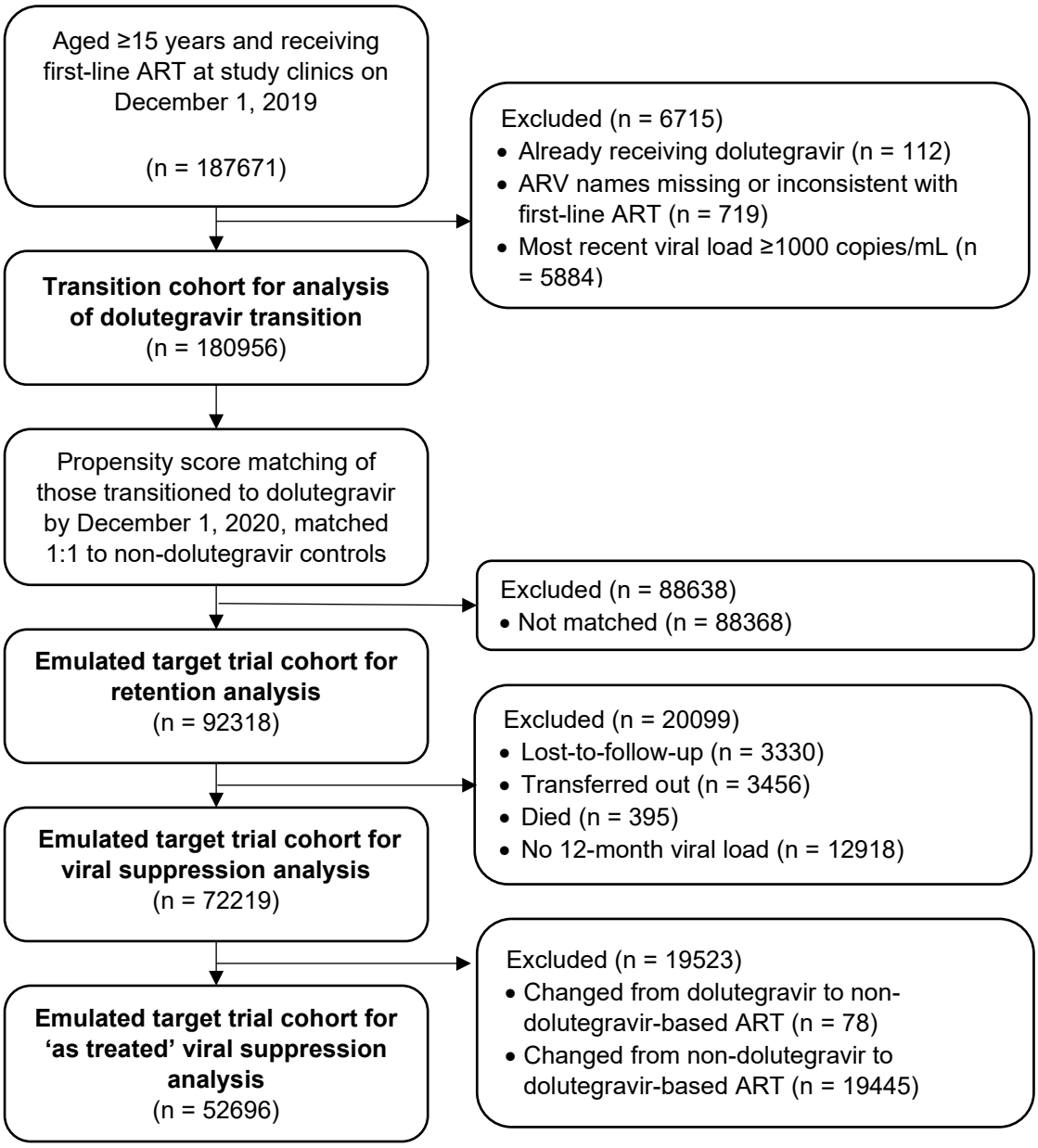


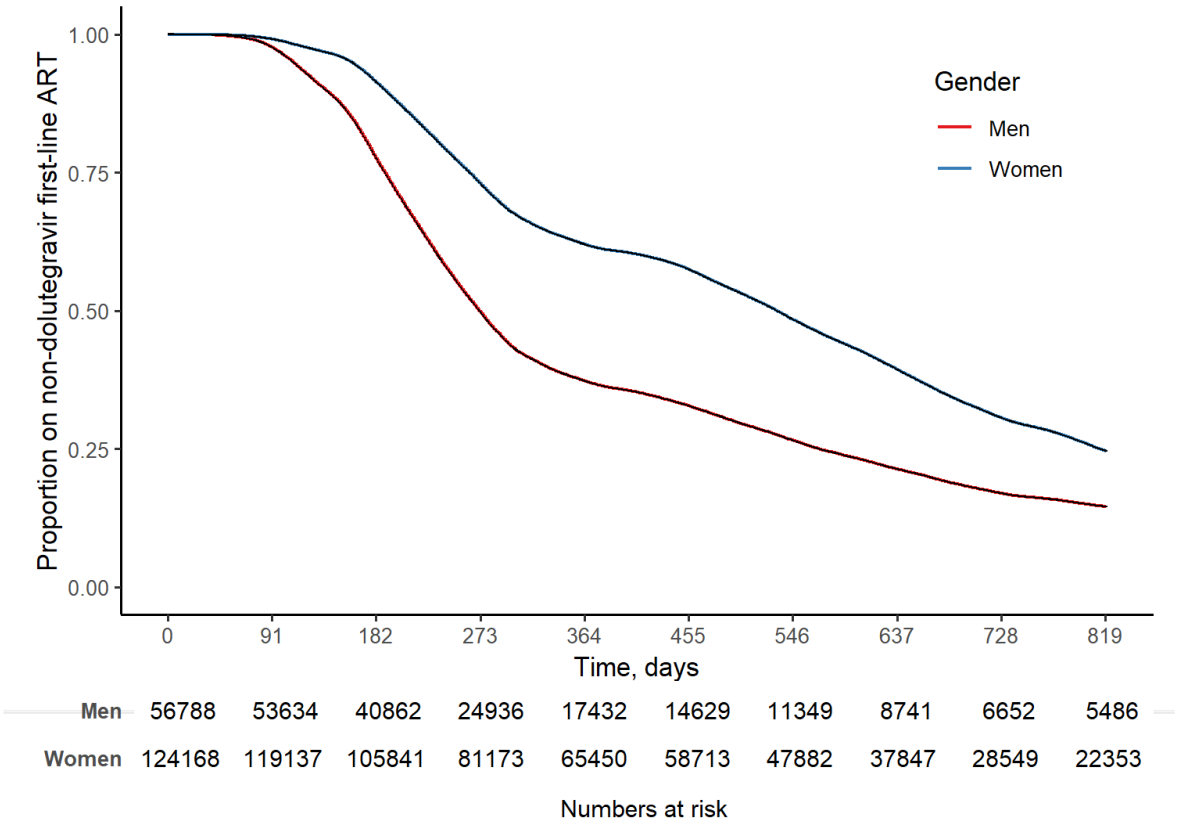
Table 8.6 Univariable Cox regression models of baseline characteristics associated with transitioning to dolutegravir-based first line ART, N = 180,956

Variable	Levels	Total, n (column %)	Transition to dolutegravir events	Time, person-years	Rate per 100 person-years (95% CI)	HR	P value
Gender	Male	56788 (31·4)	41967	52094	805·6 (797·9-813·3)	1	<0·001
	Female	124168 (68·6)	79207	153937	514·5 (511·0-518·1)	0·56 (0·56-0·57)	
Baseline age (cat.), years	55+	14010 (7·7)	10075	14302	704·4 (690·7-718·3)	1	<0·001
	45-54	34223 (18·9)	25720	35322	728·2 (719·3-737·1)	1·04 (1·01-1·06)	
	35-44	67118 (37·1)	46514	77154	602·9 (597·4-608·4)	0·82 (0·80-0·84)	
	25-34	55944 (30·9)	33822	67823	498·7 (493·4-504·0)	0·66 (0·64-0·67)	
	15-24	9661 (5·3)	5043	11431	441·2 (429·1-453·5)	0·56 (0·54-0·58)	
Baseline time on ART, years	Median (IQR)	3·9 (2·0 to 6·4)	-	-	-	1·01 (1·01-1·01)	<0·001
Baseline most recent CD4 count (cat.), cells/μL	>=500	70180 (38·8)	47141	83106	567·2 (562·1-572·4)	1	<0·001
	350-499	39875 (22·0)	27399	45353	604·1 (597·0-611·3)	1·10 (1·08-1·11)	
	200-349	34093 (18·8)	23200	37544	617·9 (610·0-625·9)	1·14 (1·12-1·15)	
	<200	21477 (11·9)	14139	22859	618·5 (608·4-628·8)	1·17 (1·14-1·19)	
	Missing	15331 (8·5)	9295	17170	541·3 (530·4-552·5)	0·98 (0·96-1.00)	
TB during follow-up	No	178426 (98·6)	121008	205179	589·8 (586·4-593·1)	1	<0·001
	Yes	2530 (1·4)	166	853	194·7 (166·2-226·7)	0·41 (0·35-0·48)	
Pregnancy during follow-up	No	116628 (64·5)	120826	204581	590·6 (587·3-593·9)	1	<0·001
	Yes	7540 (4·2)	348	1450	239·9 (215·4-266·5)	0·40 (0·36-0·44)	
In CCMDD during follow-up?	No	85523 (47·3)	79942	122844	650·8 (646·3-655·3)	1	<0·001
	Yes	95433 (52·7)	41232	83187	495·7 (490·9-500·5)	0·68 (0·67-0·69)	

8.4.2.2. Dolutegravir transition

Participants were followed up to endpoint or censoring date for a median 319 days (IQR 205, 646), totalling 206,050 person-years at risk. By February 28, 2022, 121,174 (67·0%) had transitioned to first-line dolutegravir at a median of 283 (IQR 203, 526) days. 27,702 (15·3%) remained in care and continued receiving non-dolutegravir-based first-line ART. 9404 (5·2%) had a viral load ≥ 1000 copies/mL, 657 (0·4%) had been switched to second-line ART, 12,074 (6·7%) transferred care to another clinic, 9,127 (5·0%) were lost-to-follow-up and 818 (0·5%) were known to have died. The rate of dolutegravir transition peaked between June 1, 2020 and August 31, 2020 (1118·6 [1107·0 to 1130.4] per 1000 person-years), and was lowest between December 1, 2020 and February 28, 2021 (345·3 [337·1 to 353·7] per 1000 person-years (Supplementary Table 16.3, Figure 8.3).

Figure 8.3 Kaplan Meier curve of transition to dolutegravir among people already receiving non-dolutegravir based first-line ART in December 2019



In a univariable Cox regression model the hazard of being transitioned to dolutegravir was lower in women than in men (hazard ratio [HR] 0·56 [0·56, 0·57], Table 8.6). The effect of gender on dolutegravir transition was largest among younger age groups (15, 24 years, HR 0·50 [0·46, 0·53], ≥55 years, HR 0·93 [0·90, 0·97], Table 8.7, likelihood ratio test for interaction p <0·001). When including an interaction term between gender and time, the hazard of initiating dolutegravir was lower in women compared to men earlier in the rollout (December 1, 2019 to February 29, 2020, HR 0·37 [0·34, 0·40]), but converged as the rollout progressed, and became higher in women than men by September 1, 2021 to November 30, 2021 (HR 1·09 [1·04, 1·15], likelihood ratio test for interaction p < 0·001, Table 8.7).

Table 8.7 Cox regression models of hazard of transition to dolutegravir among women versus men, stratified by A) age group and B) time period

	Proportion transitioned to dolutegravir		
	Women (n/N)	**Men (n/N)**	**aHR (95% CI)**
A) Age group (years)*			
≥55	6423/8886 (72·3%)	3652/5124 (71·3%)	0·93 (0·90-0·97)
45-54	15371/20707 (74·2%)	10349/13516 (76·6%)	0·76 (0·74-0·78)
35-44	28460/43198 (65·9%)	18063/23920 (75·5%)	0·54 (0·53-0·55)
25-34	24970/43351 (57·6%)	8874/12593 (70·5%)	0·48 (0·47-0·49)
15-24	4007/8026 (49·9%)	1041/1635 (63·7%)	0·50 (0·46-0·53)
B) Time period†			
Dec 19 - Feb 20	1056/124168	1305/56788	0·37 (0·34-0·40)
Mar 20 - May 20	9096/119157	10696/53646	0·35 (0·34-0·36)
Jun 20 - Aug 20	20813/105885	14286/40886	0·50 (0·49-0·51)
Sep 20 - Nov 20	11929/81235	6049/24966	0·57 (0·55-0·58)
Dec 20 - Feb 21	4697/65529	2049/17469	0·59 (0·56-0·62)
Mar 21 - May 21	9100/58794	2727/14666	0·81 (0·78-0·84)
Jun 21 - Aug 21	8778/47947	2172/11380	0·94 (0·90-0·99)
Sep 21 - Nov 21	8259/37886	1755/8758	1·09 (1·04-1·15)
Dec 21 - Feb 22	5503/28568	940/6661	1·39 (1·30-1·49)

**Likelihood ratio test for interaction p < 0·001, †Likelihood ratio test for interaction p < 0·001*

8.4.2.3. Loss-to-follow-up and viraemia

75,223 had been transitioned to dolutegravir before December 1, 2020. After propensity score matching, 46,159 people who transitioned to dolutegravir were matched with 46,159 controls who had not yet been transitioned at the same timepoint, and were included in the target trial. Baseline characteristics were well balanced between the two groups (Table

16.4). In the dolutegravir group, 88/46,159 (0·2%) people subsequently changed back to a non-dolutegravir first-line regimen, at a median of 211 days (IQR 116, 308) from baseline. In the matched controls, 23,620/46,159 (51·2%) subsequently transitioned to dolutegravir at a median of 154 days (73, 253) from baseline. By 12 months, in the dolutegravir group 43,178 (93·5%) were retained-in-care, 1388 (3·0%) had transferred out, 1460 (3·2%) were lost-to-follow-up and 133 (0·3%) were known to have died, compared to 41,959 (90·1%) retained-in-care, 2068 (4·5%) transferred, 1870 (4·1%) lost-to-follow-up and 262 (0·6%) died in the non-dolutegravir group. The likelihood of retention in care was higher among the dolutegravir group versus matched controls (aRR 1·03 [1·02, 1·03], RD 2·5%, 2·1, 2·9), but was partially attenuated in post-hoc sensitivity analysis where transfers out were included as retained in care (aRR 1·01 [1·00, 1·01], RD 1·1% [0·7, 1·5]).

Table 8.8 Poisson regression models of viral suppression among people transitioned to dolutegravir versus those not transitioned, by baseline viral load

	Proportion with viral suppression		
Baseline viral load (copies/ml)	**Dolutegravir (n/N)**	**Non-dolutegravir (n/N)**	**aHR (95% CI)**
Intention-to-treat analysis*			
<50	31414/34477 (91·1%)	29843/32921 (90·7%)	1·01 (1·00-1·01)
50-199	1082/1301 (83·2%)	997/1239 (80.5%)	1·03 (1·00-1·07)
200-399	265/329 (80·5%)	275/394 (69·8%)	1·15 (1·05-1·26)
400-999	255/309 (82·5%)	221/335 (66·0%)	1·25 (1·13-1·38)
Missing	407/504 (80·8%)	312/410 (76·1%)	1·06 (0·97-1·16)
As-treated analysis			
<50	31351/34408 (91·1%)	13275/14766 (89·9%)	1·02 (1·01-1·02)
50-199	1080/1299 (83·1%)	417/543 (76.8%)	1·08 (1·02-1·15)
200-399	263/327 (80·4%)	108/187 (57·8%)	1·39 (1·22-1·58)
400-999	254/308 (82·5%)	81/162 (50·0%)	1·65 (1·40-1·95)
Missing	403/500 (80·6%)	134/196 (68·4%)	1·18 (1·04-1·32)

**Wald test for interaction p<0.001, †Wald test for interaction p<0.001*

Among those retained-in-care, 72,219 (84·8%) had a viral load result after median 336 days (266, 422) from baseline. In the dolutegravir group, 33,423 (90·5%) were suppressed at <50 copies/mL, compared to 31,648 (89·7%) in matched controls (aRR 1·01 [1·00, 1·02], RD 0·8% [0·3, 1·4]). In sensitivity analysis with an interaction term between dolutegravir use and

baseline viral load, dolutegravir was only associated with improved viral suppression among people with baseline viral load ≥200 copies/mL (e.g. 200-399 copies/mL, aRR 1.15 [1.05, 1.26], 400-999 copies/mL, aRR 1.25 [1.13, 1.38], Table 8.8). In 'as treated' analysis, the association between dolutegravir and viral suppression was slightly stronger (aRR 1·03 [1·02, 1·04], RD 2·3% [1·4, 3·2], Table 8.8).

8.5. Discussion

8.5.1. Summary

In this large retrospective cohort study from 59 South African clinics, women were less likely than men to receive dolutegravir, with the difference strongest early in the rollout and among younger women. In both people initiating and already receiving first-line ART, dolutegravir use was associated with better 12-month retention-in-care and viral suppression. The association between dolutegravir use and viral suppression was stronger among people receiving concurrent tuberculosis treatment when initiating ART, and among people transitioned to dolutegravir with most recent viral load at baseline ≥200 copies/mL.

8.5.2. Comparison to existing evidence

8.5.2.1. Dolutegravir rollout

We provide longer term data compared to studies from earlier in the dolutegravir rollout, which showed that initially younger women were less likely to receive dolutegravir.[159-161] A multi-site study of 134,672 PLHIV from 11 countries up to March 2020 (eight months after the WHO recommended dolutegravir for all PLHIV), found that in people aged 16-49, dolutegravir use was lower among women compared to men, but longer term trends were not assessed.[159] In our South African study, younger women were less likely to receive dolutegravir up to two years after WHO recommended dolutegravir for all. This difference decreased over time and disappeared shortly after South African guidelines recommended dolutegravir for all in June 2021, with the hazard of transition to dolutegravir becoming higher

among women compared to men in the subsequent months; a likely 'catch-up' effect. However, by the end of the follow-up period, women remained overall less likely to be on dolutegravir than men, and a high proportion of people remained on non-dolutegravir first-line ART.

8.5.2.2. Treatment outcomes

Retention-in-care at 12-months was low at 63·6% among people newly initiating ART in our cohort, with a higher proportion (14·2%) transferring to other clinics than seen in a previous study (6·1%),[172] which may reflect mobility due to COVID-19. Our finding that first-line dolutegravir was associated with better retention-in-care may be due to increased tolerability, and is similar to findings from clinical trials, in which the superior efficacy of dolutegravir has largely been driven by reduced discontinuations from adverse events.[141,167,168] However, better retention was partly driven by less clinic transfers among people receiving dolutegravir, reasons for which are not clear, but could represent people seeking better treatment at another clinic. We also found better 12-month viral suppression with dolutegravir, particularly in people initiating ART, with the risk difference within the range seen in two clinical trials in Africa.[141,168] Among those transitioning from other first-line ART regimens (a group in which no clinical trials have been conducted), we only found improved viral suppression with dolutegravir among those with most recent viral loads ≥200 copies/mL. This could be due to HIV drug resistance against efavirenz among people with low level viraemia, or improved adherence due to better tolerability of dolutegravir.

There is little data from non-trial settings directly comparing outcomes between dolutegravir and other regimens, particularly in Africa. Public health data from Brazil showed good safety outcomes,[173] and better 12-month viral suppression among people initiated on dolutegravir compared to efavirenz,[174] but the proportion on dolutegravir was low (10·5%), and there was no assessment of retention-in-care. Studies from Malawi, Lesotho, and Uganda suggest low levels of dolutegravir HIV drug resistance mutations, and high levels of viral suppression,

among people transitioned to dolutegravir, but do not compare results with people remaining on non-dolutegravir regimens.[175-177] A retrospective cohort study of 3,108 people from four African countries found that people transitioned to dolutegravir had better viral suppression compared to those who remained on the same first or second-line regimen.[162] However, analyses such as this are susceptible to bias because it is difficult to choose an appropriate baseline time zero in the control group whose treatment remains unchanged,[178] resulting in baseline timepoints and viral load schedules differing between the two groups, and potential for immortal time bias. We emulated a target trial to overcome this, and present the largest analysis comparing outcomes after transition to dolutegravir among people on first-line ART, who are the largest group of people who will use dolutegravir globally.

8.5.2.3. Tuberculosis

South African guidelines recommend efavirenz rather than dolutegravir among people initiating ART who are receiving rifampicin containing tuberculosis treatment. However, we found that over 50% (n=1305) nevertheless received dolutegravir, and among this group, the beneficial effect of dolutegravir on viral suppression was even greater. The INSPIRING trial demonstrated good tolerability and acceptable viral suppression among people receiving tuberculosis treatment who were given double dose dolutegravir. While the extent of dolutegravir double dosing is not recorded in our data, our findings provide re-assurance that co-treating TB-HIV co-infection did not compromise HIV outcomes in a high TB burden programmatic setting. Our findings are supported by evidence from a smaller cohort study including 465 people receiving dolutegravir co-treatment alongside tuberculosis treatment, which found better viral suppression compared to people receiving co-treatment with efavirenz.[179]

8.5.3. Strengths and limitations

Our study is the largest thus far to evaluate dolutegravir uptake and compare subsequent treatment outcomes against non-dolutegravir based regimens in a public health programme.

We used data from routine public sector clinics, which provide care according to South African Department of Health guidelines, and used programmatic outcome definitions,[73] making our findings more generalisable to other public sector settings (although our clinics were limited to one urban district). We directly compared both retention-in-care and viral suppression between dolutegravir and non-dolutegravir regimens, with precise estimates due to the large sample size. Our use of an emulated target trial in the transition cohort, with propensity score matching to balance the dolutegravir and non-dolutegravir groups, should increase comparability, although we cannot rule out residual unmeasured confounding. We are likely to have overestimated loss-to-follow-up as mortality and 'silent transfers' to other clinics are underestimated in TIER.net.[180] As we used routinely collected data, we were unable to search for silent transfers to other clinics, and did not have consent to search for deaths on the national registry. We assessed 12-month treatment outcomes, and further work will be required to assess if outcomes remain similar after longer follow-up. We were unable to assess the dose of dolutegravir used in people with tuberculosis, and adverse events such as weight gain, as these are not recorded in TIER.net.

8.5.4. Implications for policy and research

Our findings demonstrate the extent to which women were excluded from the early dolutegravir rollout. They also provide reassurance that in programmatic settings, dolutegravir is associated with similar or better outcomes than efavirenz, consistent with findings from clinical trials. While improvements in retention-in-care and viral suppression with dolutegravir were modest, incremental gains are important in reaching the 95-95-95 targets. However, overall loss-to-follow-up of 20% by 12 months among people newly initiating ART demonstrates that early retention-in-care remains a key challenge for HIV programmes, and this could limit the potential benefit of improved ART regimens. Our findings support ongoing efforts to continue the transition to dolutegravir, and to remove restrictions on dolutegravir use among people being treated for tuberculosis. Efforts should

particularly focus on ensuring that women receive updated safety information and are provided the opportunity to use dolutegravir without restrictions. More broadly, strategies to introduce newer antiretrovirals at scale should ensure that the necessary safety evidence is been generated as quickly as possible prior to rollout.[181] Further research is needed in non-trial settings to assess reasons for not transitioning to dolutegravir,[182] adverse events such as weight gain,[183] the impact of transition to dolutegravir among people with viraemia ≥1000 copies/mL,[184] and the use of dolutegravir in second-line regimens.[185]

8.6. Conclusions

In this large South African cohort, we found that young women were less likely to receive dolutegravir until September 2021, and that people receiving dolutegravir had better retention-in-care and viral suppression compared to those receiving efavirenz. Efforts to transition to dolutegravir should continue.

Chapter 9

Based on a peer-reviewed paper for which I am first author, entitled “Understanding how community antiretroviral delivery influences engagement in HIV care: a qualitative assessment of the Centralised Chronic Medication Dispensing and Distribution programme in South Africa”, published in *BMJ Open.*[89]

9. QUALITATIVE ASSESSMENT OF A COMMUNITY-BASED HIV TREATMENT PROGRAMME

9.1. Chapter rationale

In Chapters 6-8 I showed that point-of-care viral load testing may have less of a role in management of viraemia due to the dolutegravir rollout. However, in Chapter 5 I did find that point-of-care viral load testing reduced the number of clinic visits for participants, and delivered results more quickly, which may still help to improve efficiency of primary care services. Another major change in the South African ART programme has been the introduction of the Chronic Centralised Medication Dispensing and Distribution (CCMDD) programme, which aims to provide a more efficient, client centred service by allowing people to collect their ART at community pick-up points, like community pharmacies, rather than having to attend clinics. In this chapter, I explore the CCMDD programme to better understand its impact on clients’ engagement in HIV care. If CCMDD can improve engagement in HIV care, then integrating point-of-care viral load testing into the CCMDD programme could have additional benefits for clients and the healthcare system.

9.2. Background

Expanding access to life-saving antiretroviral therapy (ART) for people with HIV has been one of the biggest global health successes of the 21st century. Since 2004, the number of people on ART globally has increased more than ten-fold to 23.3 million, while HIV related

mortality has dropped from 1.7 million annual deaths to 0.8 million.[1] ART is now recommended for all people living with HIV, meaning that a further 14.6 million people still require treatment, mainly in low- and middle-income countries.[1] Therefore, ART programmes in these settings will need to continue expanding, while also providing treatment through efficient, convenient services that encourage life-long engagement in HIV care.

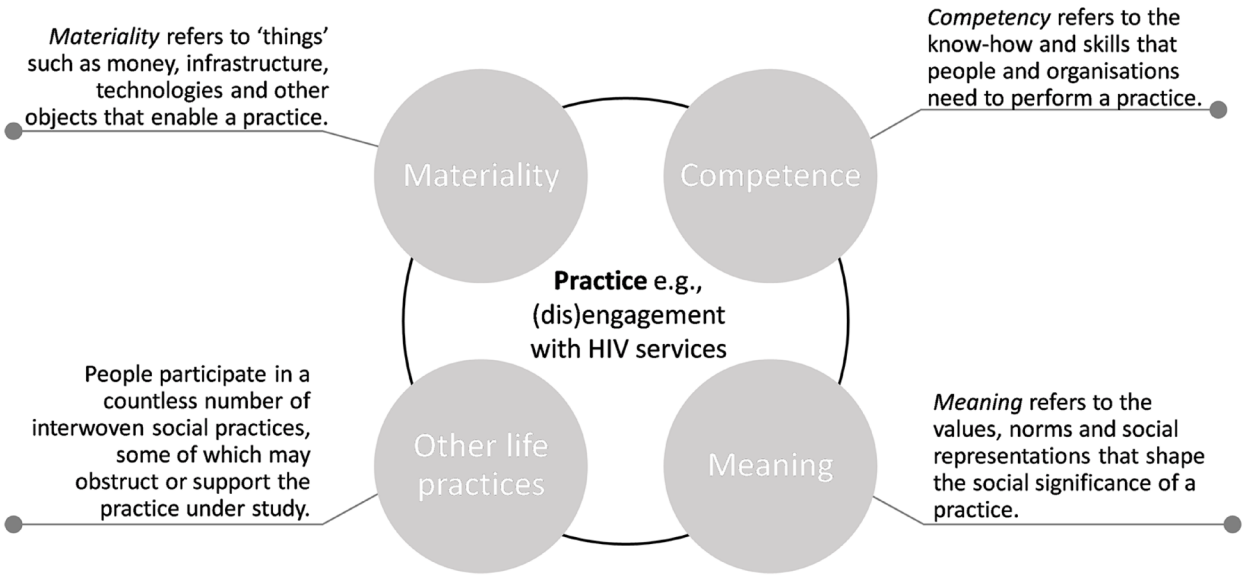
Several new models of 'differentiated ART delivery' have been developed, including providing ART through community adherence clubs (where clients meet in a community group to collect ART), delivering ART to decentralized pick-up points, and increasing the intervals between ART collection dates using multi-month prescribing.[2] These services aim to provide streamlined, efficient treatment in a client-centred manner for people who are doing well on ART, thereby allowing more resources to be directed towards initiating people on treatment and to managing those who are less well.[3,4]

South Africa currently runs the largest differentiated ART delivery programme in the world as part of the Centralized Chronic Medication Dispensing and Distribution Programme (CCMDD).[5] The CCMDD programme allows people with and without HIV to collect pre-packed chronic medications (e.g. ART, antihypertensives, diabetes treatment, lipid-lowering medication,) in the community, instead of having treatment dispensed at clinics. People living with HIV can be referred into CCMDD by their ART clinic if they are non-pregnant, stable on ART and have had two consecutive suppressed HIV viral loads, at least six months apart. In CCMDD, clients collect their treatment every 2 months at local pick-up points, including private pharmacies and community-based organizations.[6] Every six months, they return to the clinic for review and re-referral into CCMDD. An annual viral load is also performed at the clinic assessing whether they remain virally suppressed. If clients in CCMDD are unwell, they can return to their clinic at any time for medical attention. CCMDD is a public-private partnership; patients are referred by healthcare workers in government sector clinics, while a private company is responsible for centrally dispensing medication and

delivering it to community pick-up points.[5,7] CCMDD was started in 2014 and provides treatment to over 1.7 million people[8]. However, despite its size, there is little published data evaluating how this programme influences engagement in HIV care.

Several different frameworks and theories have been proposed to evaluate factors influencing engagement in HIV care. Skovdal et al [9] propose a theoretical framework around engagement in HIV care as a social practice (Figure 9.1). 'Theories of practice' conceptualise patterns of behaviour as social practices which depend on *materialities* (e.g. clinic accessibility), *competencies* (e.g. knowing how to access services and/or maintain healthy lifestyle), *meanings* (e.g. HIV-associated stigma, the normalisation of HIV as a common experience), and *other life practices* (e.g. employment).[9] These different components dynamically interact to influence the 'practice' of engagement in HIV care. Here, we aim to use this framework to explore engagement in clinic-based HIV services, and to analyse how CCMDD may influence the social practice of engagement in HIV care.

Figure 9.1 Summary of Theories of Practice Framework



Reproduced with permission from Skovdal et al., 2017[7]

9.3. Methods

9.3.1. Study design and setting

We undertook semi-structured in-depth interviews and focus group discussions with clients, and interviews with healthcare workers, who were part of the Simplified TREAtment and Monitoring (STREAM) study, a clinical trial of point-of-care HIV viral load testing and task shifting to enrolled nurses.[10,11] We previously reported qualitative findings from this study regarding the acceptability of point-of-care viral load testing and enrolled nurse care[12]. Here, we focus on findings related to CCMDD.

Eligible participants in STREAM were adults aged ≥18 years who were stable on first-line ART for 6 months after initiation. At enrolment, participants were randomised 1:1 to receive point-of-care viral load testing and potential task shifting to enrolled nurses, versus standard laboratory viral load testing and professional nurse care. After six months in the study (one year on ART) participants in both arms who had a suppressed viral load and met other eligibility criteria (clinically stable, non-pregnant, CD4 count >200 cells/mm^3)[6] were offered referral into CCMDD.

Once accepted into CCMDD, participants were able to collect treatment every two months at private pharmacies and community-based organisations. The CCMDD system would automatically send SMS-texts to clients' mobile phones to remind them of their ART collection dates. After six months they were reviewed at the clinic by a nurse. The STREAM study took place at the Prince Cyril Zulu Clinic and the adjacent CAPRISA eThekwini Clinical Research Site, which are situated next to the main transport hub in central Durban, South Africa. Prince Cyril Zulu Clinic serves a large, urban population and was one of the first clinics to implement CCMDD in Durban, as part of a pilot implementation programme.

9.3.2. Participants

We used a purposive sampling frame to select a range of patients including those who received care in CCMDD, who had suppressed and unsuppressed viral loads at any point in the study, and who received point-of-care testing versus standard laboratory testing in the STREAM trial (Table 9.1). We approached potential participants in person or by telephone after they had exited the STREAM study, explained reasons for performing the research and obtained written informed consent for their participation.

Table 9.1: Client in-depth interview sampling frame

		Point-of-care arm	**Standard-of-care arm**	**Total target**
		Target	Target	
Viral load result	**Care provider**			
< 1000 copies/ml	CCMDD and/or enrolled nurse	5	5	10
	Professional nurse	5	5	10
> 1000 copies/ml	Professional nurse	5	5	10
Total target		15	15	30

CCMDD, Centralised Chronic Medication Dispensing and Distribution programme

9.3.3. Data collection

Trained research assistants (one male, one female) conducted interviews and focus groups in IsiZulu or English in a private room in the clinic, using semi-structured topic guides. One research assistant was not previously known to participants, the other was known to patients as she was involved in recruitment and scheduling in STREAM. Neither research assistant had any involvement in CCMDD or clinical patient care. Focus groups were broadly organised by STREAM study arm, and by attendance in CCMDD. The research assistants audio recorded interviews and focus groups, and took accompanying field notes where

appropriate. Recordings and notes were anonymised, transcribed and translated from isiZulu to English where necessary. Participants did not review transcripts or the analysis.

9.3.4. Data analysis and theoretical framework

We initially performed a deductive thematic analysis[13] using a framework based on predefined themes informed by 'theories of practice' (Figure 9.1).[9] Through detailed reading of transcripts, we coded meaningful segments of data into lower order codes that we grouped into the four overarching themes of materialities, competencies, meanings and other life practices. Data could be assigned to multiple codes. Within these overarching themes, we grouped similar codes into relevant sub-themes. During analysis, we also inductively identified new themes and codes that were derived from the data and integrated them into the pre-defined themes in the coding frame (Table 17.1). While we list the complete coding frame in Table 17.1, in the results section we present sub-themes that were either commonly mentioned, or of specific relevance and importance to the research questions. We used quotes to provide examples to illustrate the sub-themes. Data for this analysis was coded by JD, with assistance and checking by one of the research assistants, using NVivo 12.0 (QSR International, Melbourne, Australia).

9.3.5. Ethics

Ethical approval for the STREAM study and this qualitative sub-study was provided by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal and the Institutional Review Board of the University of Washington. The Oxford Tropical Research Ethics Committee (OxTREC) did not formally review the study because the data collection was completed before JD joined the University of Oxford, but OxTREC were sent the protocol and ethical approvals and approved publication of the findings with University of Oxford affiliation.

9.3.6. Patient and public involvement

Patients and the public were not involved in the design, recruitment or conduct of the study, beyond being enrolled as participants. Results have been shared with the CAPRISA Community Advisory Board as part of dissemination activities.

9.4. Results

Between March and August 2018 we undertook 25 interviews and four focus groups (five to ten participants each) with a total of 55 clients, and eight interviews with healthcare workers. One client was both interviewed individually and also participated in a focus group. The median age of clients was 31 years, 56.4% were female, 52.7% were employed and 58.2% had collected ART in CCMDD (Table 9.2). The median age of healthcare workers was 39 years, 75.0% were women, and all were nurses (Table 9.2). Interviews lasted 30-60 minutes and focus groups 60-80 minutes. Below, we present our findings, with supporting quotes, regarding the challenges to engagement in clinic-based services, and the influence of CCMDD on the social practice of engagement in HIV care. We use themes based on the four constructs of *materialities*, *competencies*, *meanings* and *other life practices* from theories of practice,[9] as well as the theme of problems with CCMDD implementation which we identified in the analysis (Table 9.3).

Table 9.2: Participants demographic and clinical characteristics

Clients			
		Frequency (N=55)	%
Age (years)	Median (IQR)	31 (27 - 37)	
Gender	Male	24	43.6
	Female	31	56.4
Ethnicity	Black African	55	100.0
Educational level	None or primary school	2	3.6
	Did not pass secondary school	14	25.5
	Passed secondary school	27	49.1
	Some tertiary education	12	21.8
Employed	Yes	29	52.7

	No	26	47.3
Income in ZAR per month (approximate USD)	<1000 (70)	23	41.8
	1000-4000 (70-280)	20	36.4
	> 4000 (280)	12	21.8
Has a regular/stable partner	Yes	42	76.4
	No	13	23.6
Number of children	None	10	18.1
	1 or more	45	81.8
Disclosed HIV status to anyone	Yes	52	94.6
	No	3	5.5
Travel time to clinic > 1 hour	Yes	7	12.7
	No	48	87.2
Distance travelled to clinic ≤ 5 kilometres	Yes	44	80.0
	No	11	20.0
Primary method of travel to clinic	Walking	3	5.5
	Public transport	49	89.1
	Private transport	3	5.5
VL <1000 copies/ml	Yes	49	10.9
	No	6	89.1
Collected ART in CCMDD	Yes	32	58.2
	No	23	41.8
Healthcare Providers			
Age (years)	Median (IQR)	39 (36 - 42)	
Gender	Male	2	25.0
	Female	6	75.0
Profession	Professional nurse	4	50.0
	Enrolled nurse	4	50.0

IQR, interquartile range

9.4.1. Materialities

Clients and healthcare workers described several ways in which the *materialities* of clinic-based HIV services presented challenges to ART provision, with overcrowded primary care clinics and long waiting times deterring people from collecting treatment.

> "*Sometimes I would end up not even collecting them [ART], because of the thought of the queue.*" Focus group 2, Participant 9, Female

> *"The clinic gets very full, you will wait there the whole day."* Focus group 3, Participant 3, Male

> *"When you are coming to the clinic, you must cancel all the plans you have and tell yourself that you will spend the rest of the day there. Because chances are you will finish late in the afternoon."* Focus group 2, Participant 1, Male

In contrast, many clients and healthcare workers described how CCMDD introduced changes in the *materialities* of ART delivery, with faster ART collection and more convenient opening hours.

> *"I think collecting at [the private pharmacy] is quicker than here. When I came back here at the clinic, I waited for a good two hours."* Focus group 1, Participant 7, Male

> *"They [patients] like CCMDD, [because] when they go to the pick-up points there's no queues like here in the clinic. They come in, they go straight to the pharmacies then they get their pack."* Staff interview 4

> *"Collecting… [at the community-based organization] saves a lot of time, you don't spend 5 minutes. It doesn't get full, you can come anytime if it's still open. You just get in there, take your medication and leave."* Focus group 3, Participant 5, Female

These material differences between clinic-based ART provision and CCMDD, impacted and interacted with the other components of the social practice of engagement in HIV care.

9.4.2. Competencies

Clients described how time pressures and rushed appointments in clinics prevented communication with healthcare workers, which stopped them from gaining *competency* in understanding and managing their health and HIV treatment.

> *"They would just tell you your bloods are fine and you leave…We don't ask questions, we want to finish and allow other people to come in… there are a lot of patients [waiting] outside who also want to come in and be assisted.*" Client interview 3, Male

"Maybe you weren't feeling well two days ago and you want to tell the nurse about it, sometimes you can't… because you are looking at the situation the nurse is under. You see that she has no time for you and she will not tolerate you telling her other things." Focus group 3, Participant 4, Female

Some clients also described being treated badly by clinic staff, further limiting their ability to become *competent* at taking medication.

"Sometimes you speak with [the nurse], and she gives you medication, [but] at the same time she's shouting at you. You can't do anything as a patient, you end up not knowing how you should take the medication." Focus group 3, Participant 4, Female

Two healthcare workers expressed concerns that clients who become unwell in CCMDD could then have difficulty accessing clinical care. This could be overcome by communicating well to ensure that clients understood that they could return to the clinic at any time.

"*What I don't like about CCMDD is that... you can say the patient is stable, but tomorrow is another story. So if such patients go to CCMDD… and something new develops… they [CCMDD staff] tell you that you must go back to your facility [by which time] … it will be late and the damage is done.*" Staff interview 7

"*I don't think there's anything bad [about CCMDD] as such. But the thing is, if a patient becomes unstable, then there's nobody to care for them because at [the pick-up point] they just issue the medication... the patient must be educated to return to us if they are not feeling well.*" Staff interview 5

Most clients seemed to understand that quicker ART collection through CCMDD came at the cost of receiving less clinical oversight, but understood that they could return to the clinic if they were unwell or needed additional care.

"It's quicker to just collect [at the community-based organisation], because you know how you are taking your treatment… because when all these things [measuring vital signs, seeing a nurse] are done, you will be delayed." Focus group 2, Participant 8, Female

"…but at [the private pharmacy] you take your medication and leave, and it's good. When you have a problem, you come to the clinic." Focus group 2, Participant 9, Female

However, one client refused referral into CCMDD because she liked having vital signs monitored and the opportunity to talk to nurses in clinic, while another client in CCMDD felt that it could be improved by a quick physical check-up in the community.

"They once said we can now get them [ART] outside... I don't want that, I am fine here [at the clinic]… You weigh, check blood pressure and then go to the nurse to collect medication and she will look at your results and tell you everything is going well, or you are lacking here and you are lacking here." Client interview 16, Female

"I was relieved [that I was in CCMDD] because things were going to be quicker now, because this thing of staying all day at the clinic is not nice. But then the fact that you don't get checked up is not good. Otherwise, it's fine because it [the community-based organization] is quick. If your vital signs were done as well, it would have been better." Client interview 5, Female

Clients not in CCMDD developed other *competencies* to overcome the multiple challenges to engagement in clinic-based care. These included sending relatives or friends to collect treatment, sharing ART, arriving at clinic very early in the morning to miss queues, and extreme patience because of the life-saving benefits and positive *meanings* associated with receiving ART.

> *"When it's my appointment date I wake up very early to get to the clinic… I will be here for the whole day… because there are a lot of people… You must wait that long and sometimes you get so tired and you wish you can just leave. What can we say? We must wait because it's our lives."* Client interview 12, Female

While successfully collecting ART in CCMDD required development of new *competencies*, some clients' previous experiences of buying from pharmacies was helpful.

> *"Ok, so [the first time I collected from the private pharmacy] I got in there and looked around to see where I'm supposed to go, because I'm used to just buying and then leaving. Ok, I saw that I need to go [to] the dispensary because I am coming to collect and I didn't have a problem I did everything well and I found a good person who was full of jokes."* Client interview 18, Female

9.4.3. Meanings

The physical organization of clinic services sometimes threatened clients' confidentiality, potentially revealing their HIV status, which for them *meant* potential exposure to HIV-related stigma.

> *"There are two polyclinics, there's an old one and the new one… [HIV] positive people go to the 'old poly', so when a person says, "He is an old poly" [it means] they saw you at the 'old poly'. They know when you go to the 'old poly' that you are coming for ART."* Focus group 1, Participant 1, Male

In order to manage the risk of HIV-related stigma in clinics, clients developed *competencies* to avoid disclosing their HIV status to people that they knew. Some reported pretending to collect treatment for someone else, or choosing to collect their treatment at a clinic far from home.

> "[There is] *another thing that makes us collect medication in other areas. We do have clinics in our local communities, [but] we are afraid to collect medication in those clinics because it is not safe… we are in one room with other patients and maybe we are only separated by a wall, so when I enter that door, people will see that I am going to collect my "qo" [ART]."* Focus group 3, Participant 7, Male

In contrast, several staff felt that CCMDD helped to change the *meanings* associated with HIV treatment by normalizing HIV services.

> *"Being on ART, it disrupted their [clients] normal lives, so with CCMDD people go back to their normal life routine. You don't have to feel that 'I am sick'… you don't have to be burdened with getting treatment.*" Staff interview 1

Specifically, collecting ART in private pharmacies, where clients could be getting non-HIV related medication, helped with maintaining confidentiality.

> *"[In the private pharmacy] they wrap the medication well and pack it well. They don't just give you un-wrapped medication where everyone can see. They wrap them and put them in a plastic bag…it looks like any medication you buy from [the pharmacy]."* Client interview 12, Female

However, as we found in clinics, stigma still affected the *meanings* of engagement with CCMDD. Some clients who collected from private pharmacies felt that they were treated differently, because they were not paying customers.

> *"They [the private pharmacy staff] were paying attention to the customers who were coming to buy. Because we don't come with money, we only come with our [CCMDD] cards, they weren't paying attention to us."* Client interview 8, Female

In some pharmacies there was a separate queue for CCMDD clients, which they felt could expose their HIV-positive status to others, despite people without HIV also collecting other chronic medication through CCMDD.

> *"Where I collect, there is our [CCMDD] queue and then there is a queue for everyone else. That is why I say sometimes they would say "these people are coming to collect their thing [ART]".* Focus group 1, Participant 1, Male

Furthermore, integrating HIV treatment with everyday life felt threatening to some clients. One declined referral to CCMDD because he was worried about revealing his HIV status and experiencing stigma.

> "Interviewer: *Okay, why don't you like going there [private pharmacy in CCMDD]?*
>
> Participant: *"Uhm… because this thing [collecting ART] is confidential. Imagine, since I'm working at the mall, how many people who live by my house come there? … Imagine a lady who stays by my place and sees me when I go to this. This is a secret... So, I would prefer to collect them here [at the clinic], because I don't want to feel embarrassed*." Client interview 3, Male

In general, clients understood that CCMDD was for stable patients, and associated being referred into CCMDD as *meaning* that they had been taking ART well. Some used this to motivate their own adherence.

> "*No one wants to go back to the clinic anymore, and I think that is why we are taking our medication so well... When the nurse showed me my results, I was relieved that I will be going back [to CCMDD]."* Focus group 2, Participant 9, Female

9.4.4. Other life practices

Many clients found that long waiting times in clinics and inflexible clinic opening hours (weekdays between 0700 to 1600 hours) clashed with employment opportunities and family responsibilities:

> "*Yes, but if I could be able to collect it on weekends… During the week I sometimes have temporary jobs somewhere, so I wish I could collect on weekends.*" Client interview 18, Female

> "*I did go to the clinic and the line was massive. So, I couldn't collect [ART], because I had to go back to work.*" Focus group 2, Participant 4, Male

> "…*because the time here [at clinic] clashes with my work time… When you come here [to the clinic] you do it for yourself and when you are at work you do it for the family, you see. You must choose sometimes*." Client interview 24, Male

Quicker services in CCMDD and more flexible opening times meant that collecting ART was less disruptive for *other life practices*.

> "*Everything [at the community-based organisation] is perfect and fast. If… I'm supposed to start work at half past eight I can make it, because at eight o'clock I will be there and by ten past or quarter past I'm done*." Client interview 14, Male

> "*[In CCMDD] the patients… are independent, they can go on a Saturday or after hours to pick up their medication, they don't have to take time off work to come to us [at the clinic].*" Staff interview 5

However, some pharmacies seemed to be placing restrictions on when ART could be collected, despite being open for other services. This inflexibility meant that some employed clients still had difficulties collecting their ART in CCMDD.

"The problem with [this private pharmacy] is that they don't issue treatment on weekends. So, since we are working, we don't have time because if I didn't come to work they will deduct a certain amount from my salary. When you go there in the afternoon, they tell you that they don't issue medication at the certain times. Which means I will not be getting my treatment whereas it is very important to me." Focus group 1 Participant 9, Female

9.4.5. Challenges with implementation of CCMDD

Despite the general benefits of CCMDD, a few staff and clients also reported occasional problems with the implementation of the programme (Table 9.3). These included delays in receiving reminder SMS, the client's ART not being found at the pick-up point and inflexible pick-up dates at some pharmacies, with pick-up points sending ART back to the central depot, if clients were a few days late (Table 9.3). At the time of the interviews, several pick-up points had reached capacity and were no longer accepting referrals, meaning that some clients had no pick-up points near to their homes. Staff also reported some barriers to registering people into CCMDD. Referral criteria require a valid identification card or passport, which excluded some clients. Furthermore, isoniazid prophylaxis therapy, a daily tablet to prevent tuberculosis, is not available in CCMDD, meaning clients could not be referred until they had completed the recommended twelve-month prophylactic course. Lastly, the electronic prescription system for CCMDD was occasionally offline, which could make CCMDD registration more time consuming (Table 9.3).

Table 9.3: Challenges with implementation of CCMDD

Issue	Quotes
Barriers to registering patients in CCMDD	
Need for ID card	*"If a patient wants to be registered on CCMDD, strictly that patient must have a South African ID [or foreign passport] and every time the patient is going to collect the medication, they have to positively identify themselves using their ID. Something that we are not doing in the clinics. Some patients are not happy with that, ID's do get lost from time to time and then once the ID is not there, then they cannot give you that package at the pick-up point, then the*

	patient would be forced to come back to the clinic… [and] then they get de-registered in the process." Staff interview 4*
Problems with electronic prescription system	*"The online registration system crashes quite often so there's days where the nurses can't get online, they just have to register manually. It creates a problem because online registration is a lot quicker, so on the days when they have to do manual then they are backed up for quite a while, and then it just makes the work a lot more."* Staff interview 6
TB prophylaxis	*"There's a category of patients that can be stable on ARV's but still don't qualify for CCMDD. A typical point in example, if at any given point you decide to put this patient on IPT, which is Isoniazid Preventive Therapy for TB, they don't take that patient. You see, for the patient to qualify for CCMDD they must be stable, but now CCMDD will not take a patient that is on IPT. So we have to keep that patient up until they finish the course of IPT before you can enrol them on CCMDD."* Staff interview 4 *"They said because I am still taking the ones for protecting me against TB and I will finish them in August… after that I will hear from them [about referral to CCMDD]"* Client interview 21, Male.
Problems with CCMDD implementation	
SMS	*"I will receive the text message the following day in the afternoon, after I collected today. I never receive the text message [on time]. I receive it after."* Focus group 1 Participant 3, Female
ART not being found at the pick-up point	*"I once received an SMS and I went there [to the private pharmacy] the very same day I received the SMS, and I got there and they said my name is not there [on the list of people with ART to collect]. I then came here [to the clinic], and I got my treatment here. Fortunately, I had time on that day to end up coming here."* Focus group 2 Participant 4, Male
Inflexible pick-up dates	*The service providers are very strict when it comes to appointment dates, very strict. You get given a date and then you are expected to collect your parcel within 48 hours. After those two days then the medication will be sent back… and they get de-registered as a result. But here in the clinic they can miss the date by a day or 2 or 3 or 4 or 5, it's not that much of an issue.* Staff interview 4 *"It was my fault because I came after two days and I found that my treatment has been sent back [to the depot]."* Focus group 1 Participant 6, Male
Restricted ART pick-up times	*"They [private pharmacy staff] don't even take into consideration that I am coming from work… They are still at work and their job is to give me what I came here for [ART], but they tell me that they have closed and there is a queue."* Focus group 1, Participant 1, Male
Pick-up points reaching capacity	*"Most of the pick-up points were full, you know. They were full and some of the participants collect their medication far from where they stay, far from where they work you know. Jah, I think those were the disadvantages."* Staff interview 2

9.5. Discussion

In this qualitative study, clients and healthcare workers identified several problems with collecting ART from clinics in Durban, South Africa. Using the themes of materialities, competencies, meanings and other life practices based on 'theories of practice',[9] we showed how these problems interact with, and impact on, engagement in HIV care. We present one of the first qualitative assessments of the largest differentiated ART delivery programme in the world and show how it overcame some of these problems, helped to normalise HIV treatment and reduced the impact of collecting ART on other social practices in the clients' lives. However, several challenges and inconsistencies remain in the implementation of CCMDD.

9.5.1. Materialities

We found several material barriers to engagement in clinic-based services, which are similar to findings from other studies. In a qualitative systematic review of 59 studies regarding long-term ART adherence and engagement in care in Africa, poor clinic services were identified as a major theme, with long waiting times, inflexible services and rigid and demanding policies all leading clients to disengage from care.[14] In our study, CCMDD changed some of the 'materialities' of ART provision, leading to clear practical benefits for clients. Similar findings have been reported in qualitative assessments of community adherence clubs in Mozambique, Kenya, Malawi, Zimbabwe and South Africa, which found reductions in clinic visits, waiting times, and transport costs for clients.[15–19]

9.5.2. Competencies

The material challenges to attending clinics interacted with other components of the social practice of engagement in HIV services. For example, in our study and in another study from South Africa, [20] rushed clinic appointments impeded communication with nurses, meaning there was no time for healthcare workers to equip patients with the competencies required to engage with HIV services and learn about taking ART. Accessing ART through the CCMDD

programme also required clients to develop new skills and competencies. When the CCMDD system worked well, clients generally found it easy to navigate, and understood that they could return to their normal clinic if they needed additional care. However, a few healthcare workers expressed concerns that CCMDD could delay clients from accessing appropriate medical attention if they became unwell, and highlighted the need for adequate counselling of clients to ensure appropriate healthcare seeking. These findings are similar to a study of community adherence groups in Zimbabwe, where healthcare workers were worried about delayed access to care, while clients were happy to spend less time in clinics, and felt "empowered to visit the clinic whenever they needed".[19]

9.5.3. Meanings

We found that healthcare workers in clinics were often overburdened, sometimes disrespectful, and did not always maintain confidentiality, as has been seen in many other studies.[14] Clinics that separated HIV services from other care also threatened clients' confidentiality, therefore exposing clients to stigma, which has been widely reported as impacting negatively on engagement in HIV care.[21,22] CCMDD also impacted on the meanings of engagement in HIV care. Attending private pharmacies was less burdensome, less obviously associated with being HIV positive, and more easily integrated with everyday life, thereby helping to normalise ART collection. In Kenya, integrated adherence clubs for non-communicable diseases and HIV were reported to reduce stigma, by normalising HIV to be like other chronic conditions.[16] However, we found multiple reports of preferential treatment by private pharmacy staff towards paying customers, suggesting some ongoing discrimination towards public sector CCMDD clients. Some clients also remained concerned that their HIV status could be revealed when collecting at community pick-up points, where they could be more likely to see neighbours or people they knew. In studies of community adherence clubs, clients were mainly concerned about revealing their HIV status to other group members, and therefore created strict rules around maintaining group confidentiality.[15–18] The risk of other adherence club members breaching confidentiality

was offset by increased peer support from within the group.[15,17,19,20] In contrast, clients in CCMDD did not report benefits of peer support, but also did not have to negotiate group dynamics when collecting ART, as they tended to collect individually at pick-up points. Lastly, referral into CCMDD provided a new positive meaning to ART collection, and was seen as a reward and incentive to take ART well. Similarly, adherence clubs clients felt like staff were trusting them to manage their own HIV, and saw being sent back to the clinic as a punishment or failure to adhere to treatment.[20]

9.5.4. Other life practices

Several studies have described how the time spent travelling to clinics and waiting for ART can impact on clients' ability to seek or attend employment, and meet family responsibilities.[15,17,19] We found that a major benefit of CCMDD was reduced disruption to employment, although some working clients encountered problems with restricted collection times in a few private pharmacies. Similarly, in differentiated care programs in Malawi, Kenya and Zimbabwe, clients had more time to attend their businesses and farming,[17,19] and avoided taking days off work.[15,18]

9.5.5. Challenges with CCMDD implementation

As with other differentiated ART delivery programmes,[14–17] there were several reports of implementation problems that clients had to negotiate, such as delayed SMS reminders, ART not being available at the pick-up point, and a few pharmacies placing restrictions on ART pick-up times. Furthermore, some of the eligibility criteria for CCMDD seemed to contradict other stated aims of the healthcare system. For example, the need for an identification card could exclude the most vulnerable clients, while not providing tuberculosis prophylaxis within CCMDD could hamper tuberculosis control measures.[22]

9.5.6. Strengths and limitations

This is one of the first qualitative studies to assess differentiated ART delivery within the CCMDD programme. Qualitative research methods are suited to achieving a deeper understanding of the issues that are important to clients and clinical staff. While surveys quantify responses to pre-selected questions, interviews and focus group discussions give respondents the opportunity to raise topics which they themselves identify as being relevant, and which those constructing quantitative survey tools may not have yet considered. While we conducted a deductive analysis based on a framework of 'theories of practice', we also inductively data presented by participants which did not fit this framework. The use of theories of practice also highlighted the relationship between the materialities of ART provision, and how changes in these impacted on engagement in HIV care as well as clients' broader lives. Our interviewers were not involved in CCMDD or clinical patient care, which reduces the potential for social desirability bias. Limitations of our study include the use of a single urban clinic, and the use of clinical trial participants, meaning our findings may not be generalisable to other settings, such as rural areas. While our purposive sampling aimed to include a range of clients, clients who felt more positive towards CCMDD may have been more likely to participate. Lastly, the CCMDD programme is adapting quickly, and some of the early implementation problems that we report (e.g. pick-up points reaching capacity) may now have been resolved.

9.5.7. Implications

Our findings support the ongoing rollout of CCMDD, while highlighting areas where improvements are needed. Better regulation of private pharmacies could ensure consistent implementation of less restrictive ART collection times, and allow development of strategies to better protect confidentiality and prevent CCMDD clients from receiving inferior care. Increasing the flexibility of the ART collection date window could also increase clients' autonomy to collect on a day that suits them in CCMDD. Steps to reduce HIV-related stigma

at a broader societal level are needed, as fear of disclosure remained a barrier to engagement in both clinic-based services and CCMDD. Further research is needed to establish the impact of CCMDD on clinical outcomes such as viral suppression and retention in care, and whether it is cost-effective. Of note, cost-effectiveness studies should attempt to capture the wider non-healthcare system costs and benefits for employed people, given that CCMDD may be particularly beneficial to them. Lastly, we also identify several areas that could be improved in clinic-based HIV services, including less restrictive opening times, more respectful treatment of clients, and better confidentiality.

9.5.8. Conclusion

In conclusion, we highlight how the material changes to ART provision in CCMDD facilitated engagement with HIV services, reduced disruption in clients' everyday lives, and helped to normalise HIV care. Improvements to the implementation of CCMDD could allow even greater benefits, and contribute towards achieving universal ART through more client-centred healthcare services.

Chapter 10

I am first author on a peer-reviewed paper which this chapter is based on, entitled “The impact of the COVID-19 lockdown on HIV care in 65 South African primary care clinics: an interrupted time series analysis”, and which was published in *The Lancet HIV*.[186]

10. THE IMPACT OF THE CORONAVIRUS DISEASE 2019 LOCKDOWN ON HIV CARE IN 65 SOUTH AFRICAN PRIMARY CARE CLINICS: AN INTERRUPTED TIME SERIES ANALYSIS

10.1. Chapter rationale

In Chapters 2 and 5 I outlined how the COVID-19 pandemic impacted on my DPhil and the conduct of the POwER study. In this chapter, I explore how the first COVID-19 lockdown impacted on primary care HIV services in South Africa.

10.2. Introduction

While the number of deaths from coronavirus disease 2019 (COVID-19) continues to rise globally, there are few empirical data quantifying the impacts of the pandemic on other health conditions, especially in low- and middle-income countries. In these settings, there has been concern that interruption of supply chains, diversion of resources and overwhelmed health systems could have had severe collateral effects on existing public health programmes.[187-190] Furthermore, COVID-19 control measures, such as stay-at-home orders or ‘lockdowns’, might limit access to healthcare services, further jeopardising broader public health goals.[189,191,192]

In Africa, the impact on HIV services is of particular concern. Despite recent gains in prevention, testing and treatment, HIV/AIDS remains one of the leading causes of mortality, with over 400,000 deaths on the continent in 2019.[193] Out of the estimated 25.8 million people living with HIV in Africa, 4.3 million had not been diagnosed with HIV, and a further

3.4 million were not receiving antiretroviral therapy (ART).[193] Modelling studies of COVID-19 disruptions to HIV programmes have estimated that interruptions in ART would have the largest impact on HIV-related mortality.[194,195] In a 'worst case' scenario, a 6 month ART interruption for 50% of people receiving ART is predicted to result in 296,000 excess HIV-related deaths.[194]

Whether such large-scale disruptions to HIV services have occurred in Africa is not clear. An interrupted time series analysis of data from 11 rural clinics in South Africa found an unexpected 20% increase in HIV related primary care visits after lockdown implementation.[196] In contrast, two small studies in Kenya[197,198] described 16-30% decreases in HIV testing after lockdown. However, these analyses were from relatively few sites and may be biased by longer term trends in outcomes that were not accounted for. We therefore aimed to quantify the impact of COVID-19 lockdown on key components of HIV care: HIV testing, ART initiation and retention in HIV care.

10.3. Methods

10.3.1. Study design and setting

We conducted an interrupted time series analysis of routinely collected data from 65 public sector, primary care clinics run by eThekwini Municipality and Bethesda Hospital in KwaZulu-Natal, South Africa. South Africa is the most heavily affected country by both COVID-19 and HIV in Africa. By 31st July 2020 (the last day of data collection for the present study), there were 493,183 confirmed COVID-19 cases,[199] while in 2019 there were an estimated 7.5 million people living with HIV. The province of KwaZulu-Natal has an estimated 1.7 million people living with HIV, and an HIV prevalence of 27% amongst adults aged 15-49.[200] Regarding COVID-19, there were 76,706 confirmed cases by 31st July 2020, making it the third most COVID-19 affected province in South Africa.[199] Within KwaZulu-Natal, the largest urban area is the eThekwini Metropolitan Municipality which has a population of approximately 3.7 million and includes the city of Durban.[201] We used data

from 56 urban primary care clinics run by the eThekwini Municipality Health Unit, which represents approximately 60% of all public clinics in the Metro. We also used data from all nine fixed and mobile primary care clinics which are overseen by Bethesda Hospital, a district hospital in the rural uMkhanyakude District, in northern KwaZulu-Natal.

ART is provided free of charge at all these clinics, and they remained open during the South African national lockdown which was announced on the 23rd March 2020 and implemented on the 27th March 2020.[192] Starting at 'level 5', the lockdown was one of the most severe globally, with restrictions on movement and cancellation of public transport, although travel to receive healthcare was allowed.[192] The lockdown was eased to level 4 on 1st May 2020, when public transport was allowed,[192] and to level 3 on 1st June 2020, which allowed limited economic activity to resume. Before and throughout the lockdown, there were no reports of ART stockouts in the study clinics, and public health messaging highlighted the importance of ART for all people living with HIV.[202]

10.3.2. Participants

We included data from people testing for HIV, initiating ART, and collecting ART at participating clinics during the study period, with no age restrictions. For counts of ART initiations, we excluded patients who were already receiving ART and were transferring in care from another clinic. For HIV testing, data were available from the 1st January 2018 to 31st August 2020, for all other outcome variables data were available until 15th June 2020. We chose, a priori, not to use data before January 2018, as trends before this time may have been influenced by changes in ART initiation criteria and the implementation of 'universal test and treat' in South Africa at the end of 2016.

10.3.3. Data sources and data management

In the South African public sector, data on the number of HIV tests performed per month at each clinic are routinely recorded in the District Health Information System (DHIS),[201] and

reported by gender and age group. For patients initiating and receiving ART, data on demographics, clinical status and clinic visits are routinely recorded in an electronic register (TIER.net),[166] which is compared monthly against clinic registers and a subset of clinical charts. For this analysis, anonymised patient level data from TIER.net were analysed, and aggregated into weekly counts of ART initiations and ART collection visits. During the COVID-19 lockdown, clinical staff, data capturers and health information system managers were classed as essential workers. This meant that transport arrangements were made to enable attendance at work, ensuring that disruptions to data entry and data capture were minimised.

10.3.4. Variables

The primary outcomes of interest were monthly counts of HIV tests, and weekly counts of ART initiations and ART collection visits, at participating clinics during the study period. The number of weekly ART collection visits is a function of when visits are scheduled, and whether patients attend these scheduled visits. Because visit scheduling may also have changed during lockdown, we assessed a secondary outcome of weekly counts of missed ART collection visits. For the missed visits variable, we used the date of next scheduled ART collection visit to calculate visits that were missed by more than two weeks, as defined by South African guidelines.[73] Patients who attended earlier than their next scheduled visit were not defined as missing a visit. For this outcome, we restricted the time period of interest to end two weeks before the last day of data collection, because by definition a missed visit requires no visit to occur in the following two weeks. We also assessed counts stratified by gender and by rural or urban district (according to clinic location).

10.3.5. Statistical analysis

We used descriptive statistics to summarise demographic and clinical data, and present crude summaries of outcomes before and after lockdown. We did not summarise HIV testing data by age, because different age categories were used for recording during the study

period. We conducted interrupted time series segmented regression analyses by fitting a Poisson regression model, with Newey West standard errors[203,204] to account for autocorrelation and heteroskedasticity. The model included a time variable, a dummy lockdown variable indicating pre-lockdown and post-lockdown, and an interaction term between time and the lockdown variable. This approach takes account of pre-lockdown trends and allows estimation of the effect of lockdown at different timepoints, by centring time at that timepoint. We used the model to estimate the immediate impact of lockdown, as well as the effect of the lockdown by the end of the study period. We also estimated the post-lockdown trend by summing the coefficients associated with time, and the time-lockdown interaction. While we conducted analyses for most outcomes using weekly counts, we present trends using monthly time periods to facilitate comparisons. We built separate models for each gender, age, and rural and urban group. To account for seasonal changes in clinic activity (for example, holiday periods where clinics remain open but visits are typically fewer), we performed a sensitivity analysis with two pairs of sine and cosine terms (Fourier terms) included in the model. We also conducted a sensitivity analysis of trends in positive HIV tests. We analysed data using R 4.0 (R Foundation for Statistical Computing, Vienna, Austria); code is available in the supplementary material.

10.3.6. Ethical approval

This work was approved by University of Kwazulu-Natal Biomedical Research Ethics Committee (BE646/17), the KwaZulu-Natal Department of Health's Provincial Health Research Ethics Committee (KZ_201807_021), the eThekwini Municipality Health Unit, and the Bethesda Hospital Ethics Committee, with a waiver for informed consent for analysis of anonymised, routinely collected data.

10.3.7. Role of the funding source

The funders had no role in the study design, data collection, analysis, interpretation or writing of the paper.

10.4. Results

10.4.1. Summary data

Between 1st January 2018 and 31st July 2020 there were a total of 1,315,439 HIV tests conducted at all participating clinics. Regarding ART, between 1st January 2018 and 15th June 2020, there were a total of 71,142 individuals initiated on ART, and 2,319,992 ART collection visits by 235,719 individuals (median 9 visits per person [IQR 5-14]). Between 1st January 2018 and 1st June 2020, there were a total of 339,474 missed ART collection visits. Demographic details are presented in Table 10.1. The majority of people were women, and came from urban clinics. Pre-lockdown, the periods around Christmas and New Year 2018 and 2019 had the lowest counts of HIV tests, ART initiations, ART collection visits, and missed visits (Figure 1.1).

Table 10.1 Demographics of people who had HIV tests, initiated ART and collected ART between January 2018 and July 2020 at 65 clinics in KwaZulu-Natal, South Africa

		HIV tests[a], N =1,315,439	ART initiations[b], N = 71,142	ART collection visits[b], N = 2,319,992	Missed ART collection visits[c], N = 339,474
Age[d] (years)	All, median (IQR)	NA	32(27-39)	37 (31-45)	36 (30-43)
	0-14, N (%)	NA	891 (1.2)	48,440 (2.1)	7,112 (2.1)
	15-24, N (%)	NA	9,734 (13.7)	135,649 (5.9)	26,249 (7.7)
	25-49, N (%)	NA	55,840 (78.5)	1,785,187 (76.9)	265,408 (78.2)
	50+, N (%)	NA	4,741 (6.7)	457,647 (15.1)	40,705 (12.0)
Sex	Female, N (%)	861,265 (65.5)	46,520 (65.4)	1,580,202 (68.1)	224,799 (66.2)
	Male, N (%)	454,174 (34.5)	24,622 (34.6)	739,790 (31.9)	114,675 (33.8)
District of clinic	Urban, N (%)	1,269,811 (96.5)	68,821 (96.7)	2,216,761 (95.6)	311,746 (91.8)
	Rural, N (%)	45,628 (3.5)	2,321 (3.3)	103,231 (4.4)	27,728 (8.2)

[a] HIV testing data from 1st January 2018 to 31st July 2020. [b] ART data from 1st January 2018 to 14th June 2020. [c] Missed visit data from 1st January 2018 to 1st June 2020. [d] Age in routine HIV testing data was recorded using different age categories during the study period and therefore is not available

10.4.2. Interrupted time series analysis

In the 27 months before the lockdown on the 27th March 2020, there were a median 41,926 (interquartile range [IQR] 37,838-51,069) HIV tests per month, compared to 38,911 (IQR 32,699-42,756) tests per month in the four months after lockdown. Before lockdown, a median of 2691 (IQR 2425-2906) of these HIV tests were positive per month, compared to 1638 (IQR 1568-1662) after lockdown. In the Poisson segmented regression analysis, there was a 47.6% drop in HIV testing in the first month of lockdown (April 2020) (incidence rate ratio [IRR] 0.524, 95% confidence interval (CI) 0.446-0.615) (Figure 10.1A; Table 10.2). After April 2020, HIV testing increased by 18.3% per month (IRR 1.183, 95% CI 1.113-1.256), reaching 0.827 (95% CI 0.704-0.972) of pre-lockdown levels by July 2020. Findings were similar in separate models for both women and men, and in a sensitivity analysis of positive HIV tests (Supplementary Table 18.1). In the urban clinics, the decrease in HIV testing at lockdown (IRR 0.515, 95% CI 0.436-0.610) was larger than in the rural clinics (IRR 0.823, 95% CI 0.681-0.994) (Table 10.2).

Regarding ART initiations, in the 117 weeks before lockdown, there were a median 571 (IQR 498-678) ART initiations per week, compared to 375 (IQR 331-399) per week in the 11 weeks after implementation of lockdown. The segmented regression analysis demonstrated a 46% drop in ART initiations at lockdown (IRR 0.538, 95% CI 0.459-0.630) (Figure 10.1B; Table 10.2), with a subsequent gradual recovery of 15.6% per month after the start of lockdown (IRR 1.156 per month, 95% CI 1.085-1.230), reaching 0.753 (95% CI 0.637-0.890) of pre-lockdown levels by mid-June 2020. In separate analysis by gender, this recovery in ART initiations occurred mainly in women (IRR 1.225 per month, 95% CI 1.118-1.341), whereas amongst men, ART initiations remained low (IRR per month 1.040, 95% CI 0.957-1.132). The effect of lockdown on ART initiations was similar in different age groups, and rural and urban clinics (Table 10.2).

For ART collection visits, there were a median of 18,519 (IQR 17,074-19,922) visits per week before lockdown, and 17,863 (IQR 17,509-18,995) after implementation of lockdown (Figure 10.1C; Table 10.2). In the segmented regression analysis, there was very weak evidence of a small decrease in the number of ART collection visits at lockdown (IRR 0.932, 95% CI 0.794-1.093). After lockdown, the number of ART collections per month remained broadly constant (IRR 0.974, 95% CI 0.900-1.053), but by the end of data collection in mid-June, there was some evidence that ART collections visits were lower than pre-lockdown (IRR 0.859, 95% CI 0.747-0.989). Results were similar between separate models for men and women, age groups, and for rural and urban clinics (Table 10.2). In post-hoc analyses, we added an indicator term for the four weeks between the date of the first confirmed South African SARS-CoV-2 case and the start of the South African lockdown. The number of ART collection visits were increased throughout this period (IRR 1.233, 95% CI 1.113-1.366), even when taking seasonality into account (IRR 1.165, 95% CI 1.042-1.303). We also found that the number of early visits, where people attended more than seven days before their scheduled visit date, increased in this pre-lock down period (IRR 1.271, 95% CI 1.110-1.456).

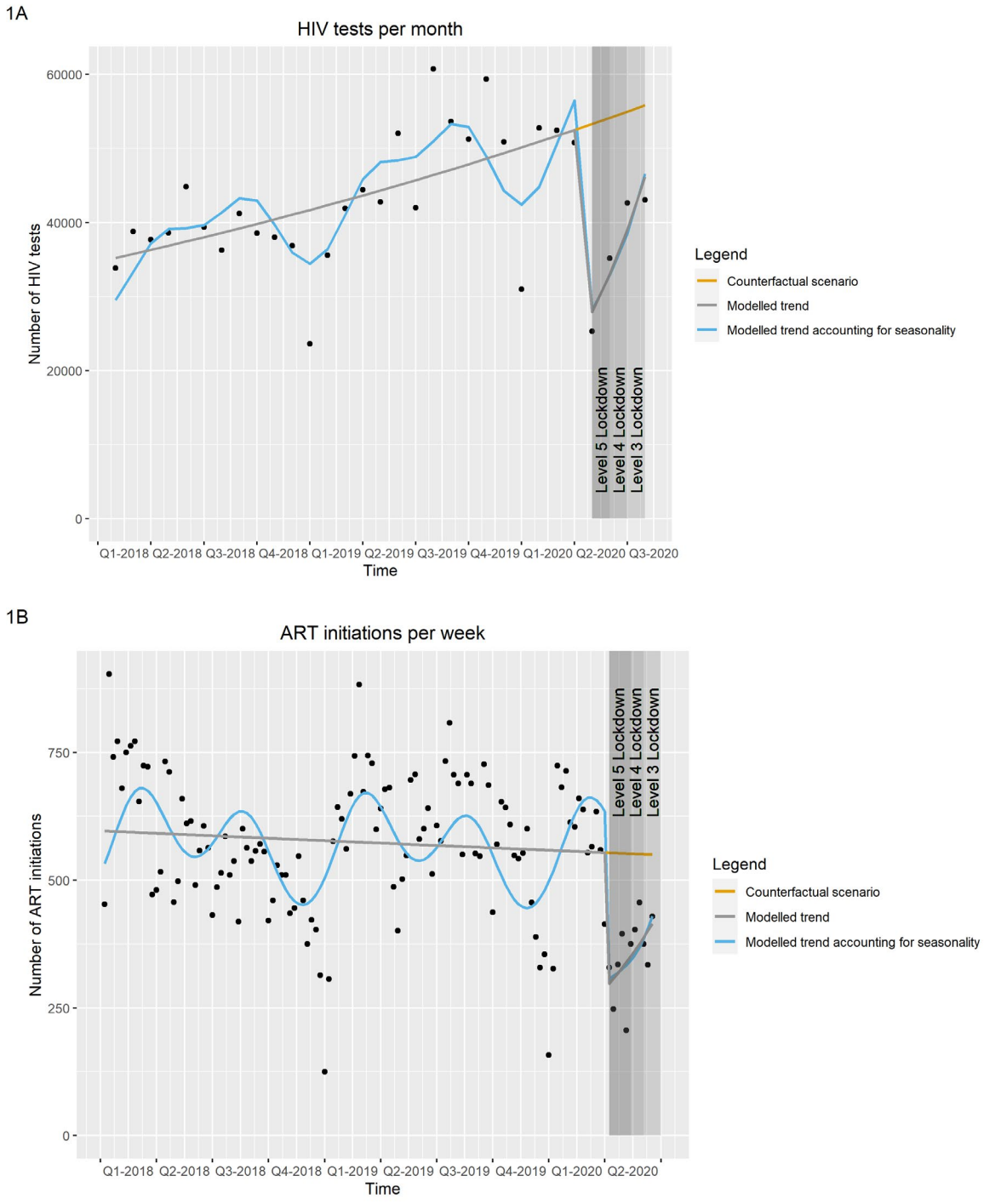
Table 10.2: Poisson segmented regression models of the impact of COVID-19 lock-down on HIV services at 65 clinics in KwaZulu-Natal, South Africa

		Incidence rate ratio at lock-down (95% CI)	Incidence rate ratio at study end (95% CI)	Pre-lockdown trend[a] (95% CI)	Post-lockdown trend[b] (95% CI)
HIV testing[c]	Overall	0.524 (0.446-0.615)	0.827 (0.704-0.972)	1.015 (1.009-1.022)	1.183 (1.113-1.256)
Gender	Women	0.563 (0.480-0.661)	0.865 (0.741-1.010)	1.013 (1.007-1.019)	1.169 (1.100-1.247)
	Men	0.456 (0.387-0.537)	0.761 (0.638-0.907)	1.020 (1.013-1.028)	1.210 (1.147-1.277)
District	Urban	0.515 (0.436-0.610)	0.827 (0.700-0.978)	1.016 (1.010-1.023)	1.190 (1.115-1.270)
	Rural	0.823 (0.681-0.994)	0.785 (0.639-0.965)	0.996 (0.985-1.006)	0.980 (0.922-1.042)
ART initiation[d]	Overall	0.538 (0.459-0.630)	0.753 (0.637-0.890)	0.996 (0.991-1.004)	1.156 (1.085-1.230)
Gender	Women	0.495 (0.417-0.588)	0.801 (0.651-0.985)	0.996 (0.987-1.004)	1.225 (1.118-1.341)
	Men	0.616 (0.513-0.740)	0.675 (0.571-0.797)	1.000 (0.996-1.009)	1.040 (0.957-1.132)
Age (years)	0-14	0.370 (0.153-0.896)	0.544 (0.270-1.096)	0.996 (0.987-1.004)	1.175 (0.640-2.164)
	15-24	0.400 (0.334-0.479)	0.772 (0.640-0.932)	1.022 (1.013-1.031)	1.363 (1.256-1.476)
	25-49	0.577 (0.492-0.676)	0.739 (0.624-0.876)	0.991 (0.987-1.000)	1.108 (1.040-1.180)
	50+	0.481 (0.399-0.579)	0.796 (0.664-0.953)	0.991 (0.983-1.000)	1.230 (1.161-1.335)
District	Urban	0.536 (0.458-0.628)	0.750 (0.631-0.892)	0.996 (0.991-1.004)	1.156 (1.080-1.230)
	Rural	0.588 (0.365-0.947)	0.863 (0.625-1.191)	0.987 (0.983-0.996)	1.166 (0.869-1.560)
ART collection visits[d]	Overall	0.932 (0.794-1.093)	0.859 (0.747-0.989)	1.009 (1.000-1.013)	0.974 (0.900-1.053)
Gender	Women	0.916 (0.780-1.075)	0.865 (0.753-0.994)	1.009 (1.000-1.013)	0.983 (0.908-1.062)
	Men	0.965 (0.823-1.131)	0.847 (0.733-0.978)	1.009 (1.004-1.013)	0.953 (0.880-1.031)
Age (years)	0-14	0.908 (0.790-1.043)	0.780 (0.703-0.866)	1.013 (1.009-1.017)	0.949 (0.888-1.017)
	15-24	0.875 (0.766-1.001)	0.851 (0.753-0.960)	1.026 (1.017-1.031)	1.013 (0.957-1.071)
	25-49	0.933 (0.796-1.094)	0.865 (0.751-0.995)	1.009 (1.000-1.013)	0.974 (0.900-1.053)
	50+	0.946 (0.787-1.137)	0.836 (0.710-0.984)	1.004 (1.000-1.009)	0.949 (0.861-1.049)
District	Urban	0.926 (0.786-1.090)	0.850 (0.736-0.982)	1.009 (1.004-1.013)	0.970 (0.896-1.053)
	Rural	1.065 (0.969-1.171)	1.080 (0.985-1.185)	0.996 (0.991-1.000)	1.000 (0.957-1.044)

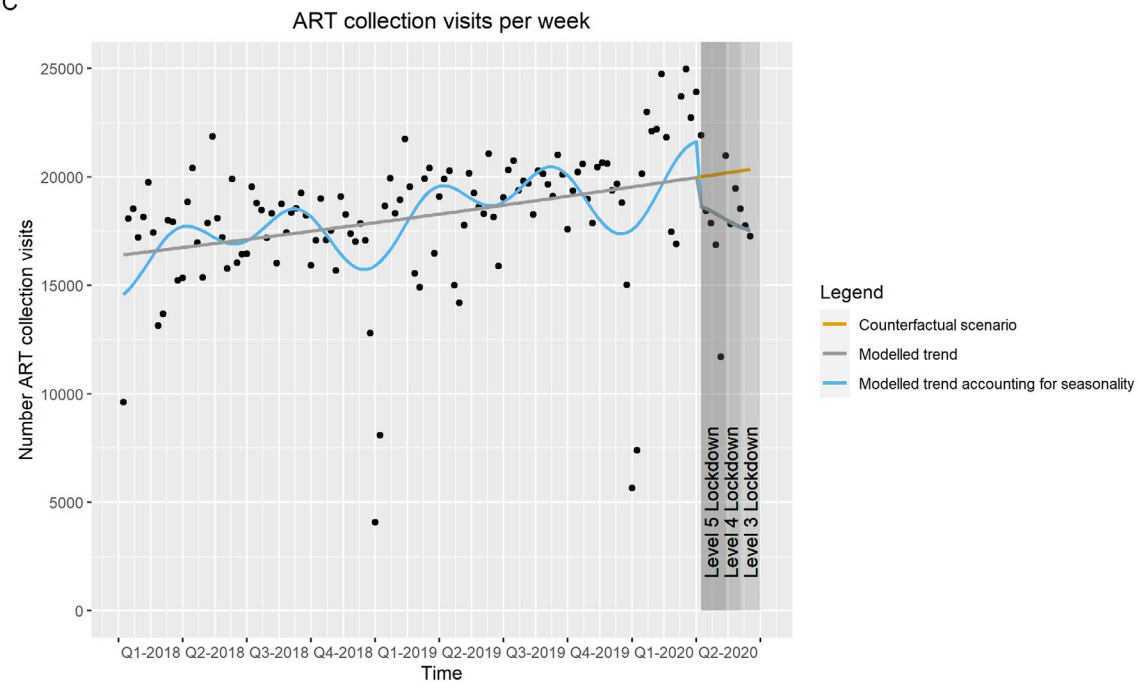
Table 10.2 cont. Poisson segmented regression models of the impact of COVID-19 lock-down on HIV services at 65 clinics in KwaZulu-Natal, South Africa

		Incidence rate ratio at lock-down (95% CI)	Incidence rate ratio at study end (95% CI)	Pre-lockdown trend[a] (95% CI)	Post-lockdown trend[b] (95% CI)
Missed ART collection visits[d]	Overall	1.926 (1.585-2.341)	0.682 (0.455-1.021)	1.000 (0.996-1.004)	0.569 (0.432-0.747)
Gender	Women	2.045 (1.686-2.481)	0.691 (0.454-1.052)	0.996 (0.991-1.000)	0.555 (0.419-0.734)
	Men	1.710 (1.399-2.090)	0.664 (0.457-0.965)	1.000 (0.996-1.004)	0.601 (0.463-0.779)
Age (years)	0-14	1.568 (1.325-1.856)	0.555 (0.429-0.717)	1.004 (1.000-1.009)	0.572 (0.472-0.690)
	15-24	1.682 (1.413-2.001)	0.554 (0.374-0.820)	1.022 (1.017-1.026)	0.561 (0.430-0.727)
	25-49	1.947 (1.594-2.378)	0.685 (0.451-1.042)	1.000 (0.996-1.000)	0.566 (0.428-0.751)
	50+	2.030 (1.665-2.474)	0.782 (0.552-1.109)	0.987 (0.983-0.991)	0.589 (0.463-0.751)
District	Urban	1.991 (1.621-2.446)	0.677 (0.433-1.057)	1.000 (0.996-1.004)	0.555 (0.412-0.751)
	Rural	1.274 (1.111-1.460)	0.745 (0.636-0.872)	1.004 (0.996-1.009)	0.751 (0.674-0.834)

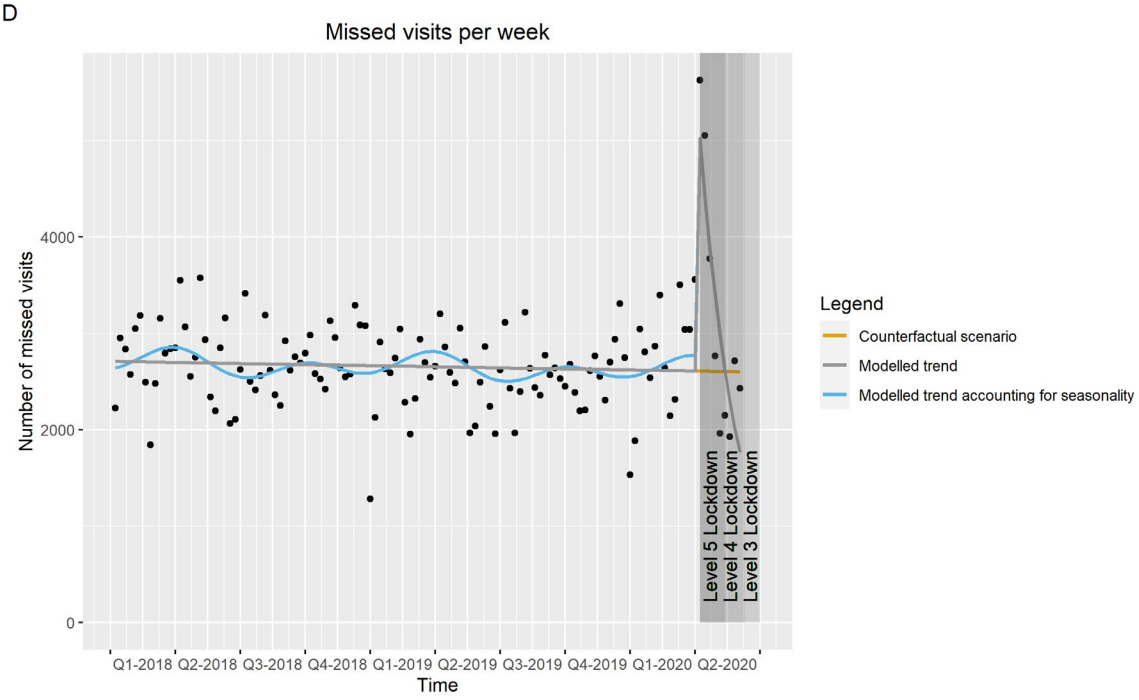
Figure 10.1: Quasi-Poisson segmented regression analyses of HIV testing, ART initiations, ART collection visits, and missed visits, before and after the COVID-19 lock-down in 65 clinics in KwaZulu-Natal, South Africa



1C


ART collection visits per week
Number ART collection visits
25000
20000
15000
10000
5000
0
Q1-2018 Q2-2018 Q3-2018 Q4-2018 Q1-2019 Q2-2019 Q3-2019 Q4-2019 Q1-2020 Q2-2020
Time
Level 5 Lockdown
Level 4 Lockdown
Level 3 Lockdown
Legend
Counterfactual scenario
Modelled trend
Modelled trend accounting for seasonality

1D


Missed visits per week
Number of missed visits
4000
2000
0
Q1-2018 Q2-2018 Q3-2018 Q4-2018 Q1-2019 Q2-2019 Q3-2019 Q4-2019 Q1-2020 Q2-2020
Time
Level 5 Lockdown
Level 4 Lockdown
Level 3 Lockdown
Legend
Counterfactual scenario
Modelled trend
Modelled trend accounting for seasonality

We then assessed counts of ART collection visits that were missed by more than two weeks. There were a median of 2637 (IQR 2420-2938) missed visits per week before lockdown, and a median of 2714 (IQR 2151-3777) per week after lockdown (Figure 10.1D). Missed visits nearly doubled in the first week of lockdown (IRR 1.926, 95% CI 1.550-2.394), but rapidly decreased by 43% per month as lockdown continued (IRR 0.569, 95% CI 0.432-0.747), and returned to pre-lockdown levels by the end of May, when the lockdown moved from level 5 to level 4 (IRR 1.006, 95% CI 0.794-1.276) (Figure 10.1D). Of the 19,183 people who missed a visit by two weeks during the level 5 lockdown period, 11,259 (58.7%, 95% CI 58.0-59.4) subsequently collected within the following month (i.e. 42 days after their scheduled visit). In separate models for men and women, and by age group, we did not observe any marked differences in results. In the rural clinics, the increase in missed visits in the first week of lockdown was much less marked (IRR 1.274, 95% CI 1.076-1.509) than in the urban clinics (IRR 1.991, 95% CI 1.584-2.503) (Table 10.2).

10.4.3. Sensitivity analysis

After adding two Fourier terms to account for seasonality, our findings were broadly similar to those when seasonality was not included in the model (Table 10.3, Figure 10.1). We also performed a post-hoc analysis among people referred into a community ART delivery programme.[89] Community ART collections are not recorded as clinic visits, and so difficulties in collecting treatment from community pick-up points during lockdown could have led to an increase in ART collection visits at study clinics. We found no evidence of this; the number of unscheduled clinic visits from people referred into the community ART delivery programme was lower in the first week of lockdown (IRR 0.732, 95% CI 0.551-0.974), and was similar to pre-lockdown levels by the end of the study period (IRR 1.163, 95% CI 0.973-1.391).

Table 10.3: Sensitivity analyses taking account of seasonality using two Fourier pairs in Poisson segmented regression models of the impact of COVID-19 lockdown on HIV services in KwaZulu-Natal, South Africa

	Incidence rate ratio at lock-down (95% CI)	Incidence rate ratio at study end (95% CI)	Pre-lockdown trend[a] (95% CI)	Post-lockdown trend[b] (95% CI)
HIV testing[c]	0.475 (0.404-0.559)	0.741 (0.631-0.872)	1.018 (1.012-1.023)	1.180 (1.090-1.279)
ART initiation[d]	0.496 (0.411-0.598)	0.798 (0.645-0.987)	1.000 (0.991-1.004)	1.225 (1.113-1.352)
ART collection visits[d]	0.859 (0.733-1.007)	0.852 (0.745-0.975)	1.009 (1.004-1.013)	1.004 (0.924-1.090)
Missed ART collection visits[d]	1.812 (1.494-2.197)	0.693 (0.459-1.048)	1.000 (0.996-1.004)	0.595 (0.451-0.783)

[a] Relative change in the outcome of interest per month during the pre-lockdown period [b] Relative change in the outcome of interest per month during the post-lockdown period [c] Autocorrelation addressed using Newey-West standard errors to calculate confidence interval, with lag up to 2. [d] Autocorrelation addressed using Newey-West standard errors to calculate confidence interval, with lag up to 3

10.5. Discussion

10.5.1. Summary

We present data from a large clinic population in KwaZulu-Natal, South Africa that demonstrate an almost 50% decrease in HIV testing and ART initiations at the beginning of the COVID-19 lockdown, with a gradual improvement over the following three months towards pre-lockdown levels. While there was a short increase in missed ART collection visits, these were a small proportion of overall ART collection visits, which decreased very slightly. These trends did not differ markedly by age or gender, apart from ART initiations, where numbers among men remained low, in contrast to a gradual improvement in the number of initiations among women. Overall, the impacts of the lockdown tended to be less marked in the rural clinics. Taken together, these findings suggest that HIV services were generally maintained for people already receiving ART. However, engaging new people into care through HIV testing, and subsequent treatment initiation, was impeded by the lockdown, particularly in urban clinics.

10.5.2. Comparison to existing literature

To date, there are few published data from low- and middle-income countries that quantify the effect of COVID-19 lockdowns on HIV services and patient-related outcomes along the HIV care cascade. The studies that have been published are limited in size, and unlike our analysis, they do not account for longer term trends, or seasonal variations, which may have influenced outcomes. A single-site, pre-exposure prophylaxis study of 455 pregnant women in South Africa found that 34% missed visits before lockdown, increasing to 57% after lockdown (odds ratio 2·36, 95% CI 1·73–3·16).[205] In keeping with our findings, two descriptive analyses from small studies in Kenya (two sites[197] and three sites[198] each) found that 15-30% less HIV tests were conducted in April 2020 compared to the months of January-March 2020.[197,198] National laboratory data from South Africa comparing the two months pre-lockdown to the first month of lockdown demonstrated decreases of 33% in CD4+ T-cell count testing (usually done at HIV diagnosis and/or ART initiation) and 22% in viral load testing (usually done for ART monitoring).[206] However, decreased HIV viral load PCR testing could reflect changes in laboratory system capacity due to increased SARS-CoV-2 PCR testing, rather than changes in patient clinic attendance and ART provision.

An interrupted time series analysis in 11 primary care clinics in rural KwaZulu-Natal found no difference in the number of overall clinic visits, but paradoxically did show a 20% increase in HIV-related visits immediately after lockdown implementation.[196] The study did not distinguish between HIV testing, ART initiation or ART collection visits, although the authors hypothesise that the increase in use of HIV services reflected a rush to collect ART in anticipation of further restrictions or drug stock-outs. In our study, we also found that the COVID-19 lockdown impacted the rural clinics less than clinics in urban areas, where lockdown restrictions may have been more heavily enforced. Furthermore, some people who had migrated to urban areas for work may have moved back to rural areas during the lockdown.

Why were HIV testing and ART initiation most affected? A qualitative study in rural Uganda,[207] and anecdotal reports from studies in Kenya,[197,198] suggest that drops in testing could be due to a lack of personal protective equipment and space for social distancing in clinics, as well as reduced clinic opening times and staff being redeployed from HIV testing to COVID-19 response activities.[197,207] In South Africa, 28,000 HIV community healthcare workers were diverted from HIV outreach to instead conduct COVID-19 symptom screening,[208] which may have led to fewer referrals to clinics for HIV testing, as seen in our data. People without established patterns of engagement in care and regular clinic attendance to collect treatment may also have been less likely to overcome the multiple challenges involved in attending clinics during lockdown. These include increased costs, transport difficulties, the potential need to provide proof of the reason for travel, lack of resources and fear of contracting SARS-CoV-2 infection at clinics.[197,198,207] The drops in HIV testing, positive HIV tests, and ART initiations were broadly similar. This suggests that the decrease in ART initiations was largely due to decreased testing, which resulted in less new HIV diagnoses, rather than additional attrition in the cascade between testing HIV positive and initiating ART.

The lockdown did cause some disruption to ART collections, with a short increase in missed ART collection visits in the first month of lockdown. However, these rapidly returned to pre-lockdown levels, and the majority of people who missed a visit did manage to attend in the following month, meaning that overall ART collection visits did not decrease drastically in the study clinics. This is similar to findings from a survey of 301 patients using a community ART delivery programme in urban KwaZulu-Natal, where only 8% reported recently delaying ART collection during the lockdown.[209] This was despite 34% reporting increased travel times or costs to collect ART, and 51% reporting longer waiting times to collect treatment.[209] ART collection may have been prioritised by patients who are already engaged in HIV care and are aware of the importance of maintaining high levels of adherence. Similar to the study from rural KwaZulu-Natal,[196] we found a pre-lockdown increase in ART collection visits,

suggesting that people were ‘stocking up’ in preparation for potential disruptions. Clinics were also able to facilitate ART provision, through strategies such as multi-month prescribing and differentiated service delivery programmes.[202,210,211] We plan further analyses to quantify how these strategies were implemented, as they may account for the slight decrease in ART collection visits post-lockdown. For the present analysis, any unmeasured increase in multi-month prescribing or community ART delivery would bias our results towards larger decreases in clinic-based ART collection visits after lockdown, rather than masking a significant drop in visits. We also found no evidence of an increase in people returning early to study clinics, instead of collecting in the community ART delivery programme during lockdown.

10.5.3. Strengths and limitations

Strengths of our study include the large number of routine public sector clinics from both urban and rural settings that are likely to reflect aspects of HIV programmes across Southern and Eastern Africa; although South Africa’s large ART programme may be better resourced and hence more resilient to COVID-19 impacts.[212] Our use of longer term routine data takes into account underlying trends in HIV testing and ART use, and allows more accurate quantification of the effect of the COVID-19 lockdown. However, due to the format of HIV testing data, we were not able to assess HIV testing by weekly counts, which would have allowed a more detailed assessment of shorter-term trends. We were also unable to assess HIV viral load outcomes due to the time taken for these results to be entered into the TIER.net system.

10.5.4. Implications for policy

Our findings suggest that to date, in one of the regions most affected by both HIV and COVID-19, the worst modelled predictions of the impact of COVID-19 on HIV are unlikely to play out. We did not find evidence of large disruptions to ART provision, which is the main driver of morbidity and mortality in published models.[194] Instead, efforts to continue providing

treatment to people in the ART programme appear to have been largely successful. While this is reassuring, COVID-19 related disruptions to ART supply chains, and future COVID-19 outbreaks and lockdowns, still pose a threat to HIV programmes.[213] Furthermore, our findings suggest that people who are not yet in HIV care were most affected by the lockdown. As countries in Africa consolidate health systems after the first wave of COVID-19, and prepare for potential second waves, efforts to 'catch-up' with HIV testing and initiation of ART should be prioritised. Integrating HIV and SARS-CoV-2 testing programs may be beneficial,[214] while the WHO and other international organisations are now advocating for an increased focus on HIV self-testing.[211] Innovative strategies to facilitate access to treatment are also required, such as home and community-based ART initiation.[215] Research into HIV service provision in other settings, and the factors that impeded HIV testing and treatment initiation during the COVID-19 lockdown is needed to inform public health responses to future COVID-19 outbreaks.

10.6. Conclusions

In primary care clinics in KwaZulu-Natal in South Africa, engaging people in HIV care through HIV testing and treatment initiation were severely impacted by the COVID-19 lockdown, with a gradual recovery towards pre-lockdown levels as restrictions eased. There were no large changes in ART collection visits. Strategies to increase HIV testing and treatment initiation should be implemented.

Chapter 11

11. DISCUSSION

11.1. Summary

In this thesis, I aimed to determine whether point-of-care viral load testing has potential to improve the management of HIV viraemia in primary care clinics in KwaZulu-Natal, South Africa, and whether it is feasible to test this hypothesis in a larger, definitive trial. I also aimed to evaluate changes in the South African ART programme, to inform the design of potential future diagnostic interventions, that could improve primary care HIV services. Here, I summarise my findings with respect to these aims. I discuss how my work contributes to the field, and critically appraise my studies. I then explore what implications my work has for policy and research (including my post-doctoral research plans) and reflect on what I have learnt, before concluding.

11.2. Summary of key findings

11.2.1. To determine whether point-of-care viral load testing is a promising strategy to improve management of viraemia in primary care in South Africa

In my introduction and literature review in Chapter 2, I showed that there was a paucity of evidence regarding the clinical performance and effectiveness of point-of-care viral load testing in primary care to manage viraemia. Therefore, in Chapter 3 I evaluated the clinical performance of a novel point-of-care viral load assay, the Xpert HIV-1 VL XC, as well as two existing assays; the Xpert HIV-1 VL and the m-PIMA HIV-1/2 VL. I found that all three assays had acceptable performance, when used by laboratory technicians or by nurses in primary care. I also conducted the POwER trial, a randomised feasibility study of point-of-care viral load testing to manage viraemia, which was outlined in Chapter 4.

In Chapter 5 I presented the main outcomes of the POwER study. COVID-19 impacted enrolment, and also meant we could not implement nurse-led testing in the clinic as we had planned. Despite this, it was feasible to retain participants in care and for point-of-care viral load results to be used by routine clinic staff to effectively manage viraemia, with the majority of results provided to participants on the day, a median of 7 days before laboratory viral load tests. However, earlier provision of results did not materially impact on viral re-suppression after 24 weeks, with very similar point-estimates of re-suppression in the point-of-care arm and standard laboratory viral load testing arm. One possible reason for this could be the already high standard of care that the clinic provided in the standard-of-care arm; a potential unintended effect implementing the trial. Another potential reason is that participants who were receiving dolutegravir tended to re-suppress their viral load very rapidly, such that many were already virally suppressed by the time of the point-of-care viral load intervention, meaning there was less potential for point-of-care testing to exert an effect. Therefore, although it may be feasible to conduct a larger, multi-site randomised trial of point-of-care viral load testing, it may not be the most appropriate strategy for managing viraemia in the context of the ongoing dolutegravir rollout. This demonstrates the value of doing feasibility studies ahead of moving straight to large scale, fully powered trials based on limited preliminary experience and evidence.

I further explore the implications of the dolutegravir rollout in Chapter 6, where I demonstrate that participants receiving dolutegravir had very low levels of drug resistance, meaning they were able to re-suppress after receiving enhanced adherence counselling. In contrast, those receiving efavirenz had high levels of drug resistance, and therefore remained viraemic until they were switched to second-line ART. This finding suggests that new strategies are needed to manage viraemia among people receiving dolutegravir. Therefore, in Chapter 7, I evaluated the analytic performance of a novel point-of-care urine test which measures the antiretroviral tenofovir, a key component of global ART regimens. I found that the test accurately detects urine tenofovir at the manufacturer threshold of 1500ng/mL, and that it

identified additional people with adherence problems compared to self-reported measures of adherence.

11.2.2. To determine how HIV treatment in primary care in South Africa changed over the course of the DPhil, and what implications does this have for ART monitoring strategies

In Chapter 8 I evaluated the extent to which dolutegravir had been rolled out in South African primary care clinics, and its impact on retention-in-care and viral suppression. I showed that initial safety concerns led to young women being disadvantaged in receiving dolutegravir early in the rollout, but that by early 2022 over 75% of people on first-line ART were receiving dolutegravir. Therefore, new diagnostic strategies will need to be adapted to be clinically effective and applicable in the context of this new regimen. Furthermore, I showed that people who were receiving dolutegravir had only slightly better retention-in-care and viral suppression than those receiving efavirenz. This means that strategies to detect and manage viraemia remain important, and until HIV drug resistance to dolutegravir emerges, these strategies will need to focus more on strategies to improve adherence.

In Chapter 9, I used qualitative research methods to evaluate a new community-based ART delivery programme which aims to provide more efficient services for clients who are stable on ART, by allowing them to collect their treatment at community pick-up points rather than at the clinic. I found that this overcame some of the barriers that clients faced when attending clinics, and helped to normalise taking ART. Point-of-care testing has the potential to further improve efficiencies in this programme, by reducing the number of clinic visits required to draw blood and review results. COVID-19 had a dramatic impact on the research activities in my DPhil. In Chapter 10, I demonstrated that it also heavily impacted on primary care HIV services in South Africa, in particular HIV testing and ART initiations. However, I did not find a drastic change in ART collection visits, meaning there was likely less of a disruption for people already taking ART.

11.3. Contribution to and comparison with existing evidence base

The WHO provides influential global HIV guidelines which are generally followed in many LMICs, including South Africa. To inform the guideline development process, the WHO team conduct systematic reviews to summarise the evidence regarding key treatment and service delivery questions. Summaries of these reviews are included in the guidelines, where the WHO also highlight evidence gaps and priority areas for future research.[30] Some of these priority research areas have also been highlighted in a recent paper from the WHO team.[49] In the section below, I discuss areas where my DPhil makes novel contributions to the field of HIV research in LMIC primary care settings, and highlight where this research meets priority areas identified by WHO.

11.3.1. Clinical performance of point-of-care viral load assays

Chapter 3 is the first evaluation of the clinical performance of the Xpert HIV-1 VL XC when conducted in a primary care clinic, and the first to explore clinical performance when used by nurses. The only other evaluation of the Xpert XC that I am aware of was conducted in a centralised, specialist laboratory,[77] and results were similar to my study. I also evaluated the slightly older Xpert HIV-1 VL and the m-PIMA HIV-1/2 VL, neither of which have been extensively evaluated in primary care settings, or when testing is conducted by non-laboratory personnel. Again, my results were broadly similar to existing evidence.[34,39,63-65] Evidence to support the clinical performance of point-of-care tests conducted by non-laboratory personnel is lacking, as identified in this WHO systematic review,[82] which has resulted in calls for more studies directly comparing performance of the same test when used by different cadres of healthcare worker.[49]

11.3.2. Clinical effectiveness of point-of-care viral load testing

In March 2021, while the POwER study was ongoing, new WHO HIV guidelines recommended that point-of-care viral load testing "*may be used to monitor treatment among*

people living with HIV".[61] This recommendation was based on results from the two studies included in my earlier literature review (Chapter 2),[43,44] and one more recent study,[216] assessing the clinical effectiveness of point-of-care viral load testing. The STREAM HIV trial, which I had worked on, found that participants randomised to receive point-of-care viral load testing and task-shifting to a less highly qualified enrolled nurse, had 13.9% higher retention-in-care and viral suppression compared to those receiving standard-of-care laboratory viral load testing and clinical care by a professional nurse.[44] However, use of a research team to provide testing and care in the intervention arm meant that the contribution of point-of-care viral load testing to the improvement in the intervention arm cannot be determined. The other study identified in my literature review showed that point-of-care viral load testing could be conducted by laboratory technicians in a primary care clinic in Zimbabwe, but viraemic results were not acted on quickly and were only used for clinical management a median of 23 days after blood was taken.[43]

The more recent study included in the WHO guidelines was an evaluation of the implementation of point-of-care viral load testing in 57 health facilities with on-site laboratories in seven African countries.[216] The types of health facility were not specified, but each facility received a single GeneXpert or m-PIMA device for point-of-care testing, which was conducted by existing site-laboratory staff. When comparing 6795 point-of-care viral load results with 17614 centralised laboratory viral loads taken from the same facilities, time to result availability was a median 1 day (IQR 0, 1) using point-of-care versus 35 days (IQR 20, 48) using centralised laboratory testing, and time to patient receipt of results was a median 6 days (IQR 1, 33) versus 68 days (54, 87) respectively. Among patients with viraemia >1000 copies/mL, 37% in the point-of-care group had documented clinical action within 30 days, compared to 7% in the centralised laboratory viral load group. Therefore, although point-of-care results were available quicker, there remained significant gaps in translating this into clinical action that could improve patient outcomes.

Based on these data, and recognising that capacity for point-of-care testing remains far below the required 30 million annual viral load tests globally, the WHO recommended that point-of-care viral load testing should be integrated into monitoring guidelines alongside existing centralised laboratory-based strategies.[30,61] The WHO particularly highlighted specific groups where viraemia is more common and so rapid point-of-care results may be of most benefit, including children and adolescents, pregnant and breast-feeding women, people with advanced HIV disease, and people having a repeat viral load to follow up on previous viraemia. As part of the guidelines, the WHO also called for more studies assessing the clinical effectiveness of point-of-care viral load testing in these groups, as well as how to best optimise implementation.

The work described in this thesis therefore provides timely results regarding the use of point-of-care viral load testing among people with known viraemia. I showed that point-of-care viral load testing can be used to manage viraemia, with 86.8% of point-of-care results delivered to patients on the same day as blood draw, a median of 7 days earlier than standard laboratory viral loads, with one clinic visit less in the point-of-care arm. People with viral failure were also switched to second-line a median of 12 days earlier in the point-of-care arm. Despite these improvements in result delivery and clinical action, point estimates of viral re-suppression were similar in the point-of-care and standard laboratory viral load arm. One other study, from two HIV clinics in Malawi, assessed process outcomes of point-of-care viral load testing for people with advanced HIV or previous viraemia, in an observational study with no comparator group.[217] Similar to my findings, of 926 people with viraemia, 719 (78%) had a documented clinical action (77% switched to second-line ART, 15% receiving enhanced adherence counselling), and 567 (78%) of these occurred on the same day as the blood draw. Levels of re-suppression and comparison with laboratory based viral load testing were not presented, meaning POwER is the only published evidence including comparative clinical effectiveness outcomes of point-of-care viral load testing in people with viraemia.

Several other studies have recently been published assessing the comparable clinical effectiveness of point-of-care viral load testing among other specific groups recommended for targeted testing by the WHO. Point-of-care viral load results were available two, three and four weeks earlier than laboratory viral loads in a multicentre randomised trial among 704 children in Kenya[131], an observational study of 1782 pregnant women in Zimbabwe at 20 public sector clinics,[218] and a randomised trial of 150 adolescents/young adults in Haiti[132] respectively. However, there was no improvement in the primary outcomes of viral suppression in any of these studies. Similarly, in a randomised trial among 496 adults and 45 children in Nigeria, point-of-care results were received by participants a median of 143 days earlier (IQR 56, 177).[133] Eight of the nine in the point-of-care arm with virological failure were switched to second-line ART after a median of 0 days (IQR 0, 18) from blood draw, versus five of eight in the laboratory viral load arm after a median 66 days (IQR 63, 123, p=0.007). Again, there was no difference in viral suppression at 12 months between the two arms.[134]

Why is it that improvements in timeliness of viral load results in POwER, and the other studies mentioned above, do not seem to have affected clinical outcomes? To answer this question, it is worth reconsidering specific issues with trials of diagnostic interventions. First, Bossuyt et al. and Ferrante di Ruffano et al. highlight the importance of very clearly delineating how a diagnostic test influences the clinical management that then affects the outcome of interest; the 'test-treatment' pathway'.[137,219] Point-of-care viral load testing could lead to viraemia being detected earlier, and in more people (if more point-of-care results are returned to patients than laboratory results). This could allow quicker/more enhanced adherence counselling, and switching to second-line ART. However, in most of the comparative studies of point-of-care viral load testing, point-of-care results were only available a few weeks earlier than laboratory results, which may not affect outcomes such as viral suppression measured after three or more months of follow up. Secondly, there is evidence that enhanced adherence counselling is often not conducted well, with a

randomised trial in South Africa finding no evidence of an impact on viral suppression.[93] Furthermore, even when viral load results are available, clinicians may not be available to do the switching to second-line regimens, or may be reluctant to switch in the absence of a clear diagnostic test to inform them whether drug resistance or adherence is the cause for viraemia. Therefore, if enhanced adherence counselling and switching to second-line regimens are not well conducted, there is no clear pathway for point-of-care viral load to improve viral suppression.

This highlights a need to strengthen the clinical pathways downstream of the viral load test, to ensure that results are acted on effectively. In the context of a clinical trial, it can be hard to justify doing this in the intervention arm only, meaning that clinical management may also be improved in the standard of care arm. This is what was seen in POwER, with people in the standard care arm being switched to second line after a median of 10 days, compared to 14-68 weeks seen in observational studies in routine care in South Africa.[92,109,128,129] In the STREAM study, where both point-of-care testing and clinical management were conducted by the research team, there was an improvement in viral suppression and retention in care in the intervention arm compared to the standard of care, which was provided by routine public sector staff.[44] This begs the question, what is the additional benefit of point-of-care viral load testing beyond what can be gained by improving the use of laboratory viral load testing and the clinical management of results? And do these benefits outweigh the work required to implement currently available point-of-care assays, which require a dedicated space, centrifuge, quality assurance procedures and supply chain management of cartridges?

Further studies of implementation strategies for both point-of-care and laboratory based viral load testing in different settings, and cost-effectiveness of these different strategies, are required to answer these questions, as set out by the WHO.[30] However, there are other potential benefits from point-of-care viral load testing beyond viral suppression. In POwER, and in the STREAM study, there were fewer clinic visits among people in the point-of-care arm, likely because one less visit is needed for the review of blood results. Participants in

STREAM also reported less anxiety waiting for results, and that same day results helped to encourage adherence.[45] Findings from the Nigerian trial were similar, where 90% of point-of-care participants said they preferred point-of-care testing, and 96% reported that same-day results motivated ART adherence.[134] Therefore, there may be a role for point-of-care viral load testing to increase efficiencies within clinical pathways for people who are stable on ART, by reducing the number of clinic visits and allowing faster referral into more streamlined care pathways for people with confirmed viral suppression, such as CCMDD.

11.3.3. *Viral re-suppression and HIV drug resistance in people receiving dolutegravir and efavirenz*

With the rollout of dolutegravir-based first-line ART, WHO recognised in the latest 2021 guidelines that the previous treatment monitoring algorithm, with switching to second line ART after two consecutive viral loads ≥1000 copies/mL for people receiving NNRTIs, would need to be modified.[30] However, the guidelines are notably silent on how viraemia should be managed for people receiving dolutegravir, and call for further evidence regarding the role of drug resistance to guide the development of an appropriate clinical algorithm. One other study that I am aware of assesses outcomes among people with viraemia while receiving first-line dolutegravir in LMICs.[140] In this sub-study of the ADVANCE clinical trial,[141] there were 247 episodes of viraemia among 144 people receiving first-line dolutegravir, and 138 among 52 people receiving efavirenz. 65.6% of viraemic episodes resulted in re-suppression <50 copies/mL in the dolutegravir group, versus 32% in the efavirenz groups. There was one regimen change due to emergent dolutegravir resistance in the dolutegravir group, and seven regimen changes due to emergent efavirenz resistance in the efavirenz group. These results are similar to my findings in POwER, where viral re-suppression was much higher in people receiving dolutegravir (58.2% <50 copies/mL by 12 weeks) versus efavirenz (16.2%). I found no dolutegravir drug resistance, and higher prevalence of efavirenz drug resistance than in ADVANCE, which is likely explained by longer exposure to efavirenz, and shorter exposure to dolutegravir in POwER. The high levels of re-suppression and lack of drug

resistance among people receiving dolutegravir emphasises the need for interventions to improve adherence to manage viraemia.

11.3.4. Measures of adherence using urine and dried blood spot tenofovir levels

The WHO "strongly recommends that adherence support interventions should be provided to people on ART",[30] but recognises that existing measures (e.g. self-report, pill counts, pharmacy refill data) to identify inconsistent adherence and viraemia are often not accurate. Therefore, WHO specifically identifies developing more accurate and feasible adherence measures as a key research priority.[49] I directly contribute to this by showing that a new point-of-care test is accurate at detecting urine tenofovir levels, at a previously validated threshold which is strongly associated with recent adherence. Apart from the original study describing the development and validation of this assay,[53] there are no other papers evaluating its analytic performance. I also demonstrate that some people who reported perfect recent adherence to ART had undetectable tenofovir levels, meaning this assay could be used to better identify people with inconsistent adherence in primary care settings. While other studies have assessed the relationship between urine tenofovir levels and self-reported adherence,[154,220] none have done so using this point-of-care assay. As dolutegravir is rolled out, a role for these tests in assessing adherence seems more likely.

11.3.5. Dolutegravir rollout and outcomes

Since recommending dolutegravir for first line ART in 2018, the WHO has monitored uptake at a country level,[51] but has little data on individual risk factors for being excluded from receiving dolutegravir. In particular, concerns were raised in 2018 regarding a potential association between dolutegravir use at conception and neural tube defects, leading to WHO to caution against use in women of child-bearing potential. Since then, there have been three observational studies comparing the uptake of dolutegravir between women and men in Africa. Early in the rollout, a cross-sectional study of 5,500 people on first-line ART at one facility in Kenya found that by February 2019, 57% of men versus 28% of women had been

transitioned to dolutegravir. A multi-site retrospective cohort study, from 11 LMICs, used data up to March 2020 from 134,672 participants, and found that cumulative incidence of transition to dolutegravir among 16-49 years old was 29·4% (95% CI, 29·0, 29·7) in women and 57·7% (57·2, 58·3) in men. In a retrospective cohort study from four African countries of 2,476 people in care by September 2021, 68% of women had been transitioned to dolutegravir, compared to 80% of men (p<0·001).

Regarding clinical outcomes on dolutegravir, a large network meta-analysis of 68 randomised controlled trials (four of which directly compared dolutegravir 50mg daily with efavirenz among people newly initiating first-line ART) found that dolutegravir had better viral suppression (odds ratio [OR] 1·94, 95% credible interval [CrI] 1·48, 2·56 at 96 weeks), less HIV drug resistance (OR 0·13, 95%CrI 0·04, 0·48) and fewer discontinuations (OR 0·58, 95%CrI 0·48, 0·70) compared to first-line efavirenz. One trial from predominantly higher income settings (SINGLE, n = 833) found better viral suppression by 48 weeks among those receiving dolutegravir compared to those receiving efavirenz (88% versus 81%, p = 0·003), with the difference in efficacy mainly due to fewer deaths and discontinuations due to adverse events in the dolutegravir arm. The NAMSAL trial in Cameroon compared dolutegravir with lower dose efavirenz (400mg) among 613 people and found similar 48-week viral suppression (74·5% versus 69·0%, p=0·66). The ADVANCE trial in South Africa found no difference in 48-week viral suppression between dolutegravir combined with tenofovir disoproxil fumarate (85%), dolutegravir with tenofovir alafenamide (84%), and efavirenz with tenofovir disoproxil fumarate (79%). There are no trials assessing transition to dolutegravir among people already receiving efavirenz.

Despite the large scale dolutegravir rollout in LMICs, there have been few assessments of the effectiveness of dolutegravir compared to other first-line regimens in non-trial settings. Among people initiating first-line ART in Brazil between 2014-2017 (before concerns regarding safety in pregnancy were raised), 12-month viral suppression <50 copies/mL was higher among 11,262 people initiated on dolutegravir versus 76,986 initiated on efavirenz

(90·5% versus 84·0%, adjusted odds ratio 1·56, 95% CI 1·40–1·75), but people with no 12-month viral load were excluded and loss-to-follow-up was not assessed. A retrospective cohort study among 3,108 people in care in September 2021 in four African countries found higher hazard of viraemia >1000 copies/mL (aHR 4·26, 95% CI 2·72, 6·68) among people who remained on non-dolutegravir regimens compared to those transitioned to dolutegravir. However, this analysis is susceptible to multiple biases, including systematic differences in viral load schedules and the start of follow-up time between the two groups, and the use of events after baseline to determine inclusion in the time-to-event analysis.

Regarding use of dolutegravir among people with tuberculosis, rifampicin has been found to reduce dolutegravir levels. This may be overcome by doubling the dose of dolutegravir to 50mg twice daily, an approach that was found to be well tolerated in the INSPIRING trial, with 52/69 (75%, 95% CI 65, 86%) of dolutegravir and 36/44 (82% 95% CI 70, 93%) of efavirenz participants having viral suppression after 48 weeks. In non-trial settings, a cohort study among 3563 people with HIV receiving rifampicin-containing tuberculosis treatment found that those on dolutegravir-based regimens had better viral suppression compared to those who received efavirenz in contemporaneous (adjusted sub-distribution hazard ratio [aSHR] 1·28, 95% CI 1·08–1·51) and historical cohorts (aSHR: 1·47, 95% CI 1·28–1·68).

In Chapter 8, I present the largest study to date to assess dolutegravir uptake in women versus men, and to compare outcomes with non-dolutegravir first-line regimens in routine care settings. I showed that younger women were less likely to be initiated or transitioned to dolutegravir early in the rollout, but this difference resolved once South African guidelines recommended dolutegravir for all people living with HIV, irrespective of child-bearing potential. Among both people initiating first-line ART, or already receiving first-line ART, dolutegravir use was associated with slightly better 12-month retention and viral suppression. The association between dolutegravir and better viral suppression was even higher among people being treated for tuberculosis.

11.3.6. CCMDD

Much new data has been published in recent years regarding new, more efficient 'differentiated care services' which include community ART delivery programmes and other more efficient ways to provide ART to people living with HIV.[54-56] The CCMDD programme in South Africa is one of the largest such programmes, but has not been extensively studied, with my qualitative study being one of the first evaluations. Since then, a more recent qualitative evaluation also found that CCMDD was highly acceptable to clients and healthcare providers.[221] Similar to my findings, CCMDD was popular due to being quicker and more convenient, particularly for employed clients. The authors also identified rigid CCMDD policies and inflexible pick-up point opening hours as a barrier to implementation. In addition, this study further explored implementation issues, and identified poor communication between the central dispensing service provider, clinics and community pick-up points as a key implementation barrier. Despite these issues, CCMDD has continued to expand, with just over two million actively collecting patients by the end of 2019.[57] However, another one million patients were registered in CCMDD, but did not have an active prescription. Reasons for this are not known, but one hypothesis is that inefficiencies in reviewing annual viral load results at the clinic lead to delays in renewals of CCMDD prescriptions.

11.3.7. Impact of COVID-19 on primary care HIV services

My interrupted time series analysis was one of the first studies to robustly assess the impact of COVID-19 on HIV services. The finding that ART collection visits were not dramatically affected was important, as it demonstrated that the worst-case scenarios from modelling studies[194,195] were unlikely to play out. However, I did find a significant decrease in HIV testing and ART initiations early in the lockdown. Our findings were influential with policy-makers, and were discussed by Prof Salim Abdool Karim, Chair of the South African COVID-19 Ministerial Advisory Committee[222] & Dr John Nkengasong, previous director of Africa

CDC & now head of PEPFAR (U.S. President's Emergency Plan for AIDS Relief).[223] Subsequent data from multiple sources confirmed our findings, with decreases in ART initiations seen nationally across South Africa,[224] and decreases in HIV diagnoses seen across multiple PEPFAR supported countries.[225] Similar to our findings, there was no decrease in the number of people receiving ART in PEPFAR programmes during COVID-19, and there was an overall increase in viral suppression of 2%, again suggesting that ART collection and retention-in-care was not greatly impacted. While I was unable to analyse the impact of COVID-19 on viral load testing and results in my analysis, I collaborated with paediatric colleagues and did another interrupted time series analysis to show that there was no change in the numbers of viral loads taken, or the proportion with viral suppression, during successive COVID-19 waves.[226]

11.4. Strengths and limitations

In each individual results chapter I have discussed the strengths and limitations of that particular analysis. Here, I assess the strengths and limitations of the thesis as a whole. An overall strength is that the findings included in my thesis contribute to answering several WHO-defined priority research questions, as highlighted in the previous section. I was able to conduct novel fieldwork in a setting of high HIV prevalence, with some findings potentially applicable to many LMIC contexts. The COVID-19 pandemic meant that I was not able to complete certain planned aspects of the DPhil, but by being flexible during the different phases of the pandemic, and by using different methods (e.g. analysis of de-identified routine data alongside clinical trial work), I was able to tackle broader questions, such as the dolutegravir rollout, which have important implications for HIV services in primary care. POwER is the first randomised study of point-of-care viral load testing focussing on people with viraemia, who are a priority group. However, there are several limitations which I discuss below.

First, COVID-19 severely disrupted and slowed enrolment into POwER, meaning the sample size was smaller than hoped, which affected the precision of outcome estimates, and the evaluation of point-of-care viral load and urine tenofovir assays. This meant that I was unable to formally compare clinical performance between different point-of-care assays, and between nurse-led versus laboratory technician testing. Second, COVID-19 pressures on routine laboratories contributed to an error in the viral load tests conducted by the National Health Laboratory Service and used to define eligibility, meaning we enrolled 45 people who likely did not have viraemia; a potential waste of time and resources in enrolling these ineligible participants. However, I was able to turn this into a strength, as these participants were included in the evaluation of point-of-care viral load assays and the urine tenofovir assay, meaning there was a broader range of viral load results.

Third, although I was able to validate the accuracy of nurse-led point-of-care viral load testing, staffing disruptions and the lack of capacity to implement new projects during COVID-19 meant that we have not yet been able to fully implement nurse-led point-of-care viral load testing in the clinic, as had been originally planned. I therefore also did not complete the qualitative evaluation of implementation of point-of-care testing, which would have provided further insights into the POwER trial results, and whether these results are generalisable to other settings. COVID-19 also meant that I was unable to complete the PHILA study during the DPhil, to evaluate point-of-care viral load testing within the CCMDD programme. Instead, we recently started this study and plan to use it to fully implement nurse led point-of-care testing, which will then allow me to complete the qualitative assessment as part of post-doctoral work. This will also allow me to elicit opinions on the relative merits of implementing point-of-care viral load testing versus improved laboratory result management and communication.

Fourth, the introduction of dolutegravir during POwER was both a limitation and a strength. As I have shown, dolutegravir likely reduces the potential for point-of-care viral load testing to have an impact on managing viraemia, as less switching to second line ART is required.

However, the inclusion of participants receiving either dolutegravir or efavirenz allowed me to compare outcomes between the two, and clearly demonstrate that a change in the WHO algorithm for managing viraemia is needed. Given the extent of the dolutegravir rollout in South Africa, generating evidence that is only generalisable to people receiving efavirenz would have been less impactful.

11.5. Implications for policy and research, including my post-doctoral plans

The findings of my thesis have several implications for policy and future research directions. My findings of acceptable clinical performance of the novel Xpert HIV-1 VL XC suggest that this assay may also be used for clinical management, although larger studies are likely needed to determine more precise estimates of its clinical performance, and the assay has not yet received WHO prequalification status. Nurses were able to conduct point-of-care viral load testing with acceptable clinical performance, but further work, which I plan to do as part of my post-doctoral work, is needed to determine whether nurse testing can be integrated into clinical flows and implemented effectively.

I showed that it is likely feasible, in the absence of COVID-19 disruptions, to conduct a trial of point-of-care viral load testing to improve the management viraemia. In the POwER study, point-of-care viral load test were available more quickly, were acted on by routine clinicians, and led to less clinic visits for participants. However, these findings are tempered by exploratory analyses of 24-week viral re-suppression, where point estimates were similar in each arm. Several other recent studies in people at high risk of viraemia did not find evidence that point-of-care viral load testing improved viral suppression. Furthermore, the widespread rollout of dolutegravir appears to reduce the need for switching to second-line ART, a key part of the hypothesised pathway through which point-of-care viral load testing could exert an effect on viral re-suppression. Therefore, point-of-care viral load testing on its own, without improvements in clinical management and enhanced adherence counselling, may not be the most appropriate stand-alone intervention to improve viral re-suppression.

Instead, any intervention to manage viraemia in the context of the widespread dolutegravir rollout should focus on monitoring and improving adherence. A simple, low-cost point-of-care urine tenofovir test, which detects whether someone has taken ART in the last four days, may therefore be a useful tool for detecting and monitoring poor adherence. I demonstrated that this assay is accurate at detecting urine tenofovir. Further research is required to determine the clinical performance of this assay and the best strategy for integrating it into algorithms for detecting and managing viraemia. I am a co-investigator on the United States National Institutes of Health funded STREAM-HIV trial, a randomised controlled trial of a combined intervention of point-of-care viral load and urine tenofovir testing, which aims to enrol 540 participants.[138]

Point-of-care viral load testing, and point-of-care adherence measures, may also be beneficial in clinical scenarios other than managing viraemia, as more rapid results and reduced clinical visits may have health system and patient benefits, irrespective of whether they are associated with viral suppression. These health system benefits may be particularly useful in community ART programmes, which aim to decongest clinics and provide ART in more convenient community pick-up points that are closer to home and more convenient for clients. Point-of-care viral load testing could allow clients to have viral suppression confirmed in one visit, and be referred directly into the community ART programme.[62] I am conducting the PHILA trial, [227] a randomised trial which will evaluate whether point-of-care viral load testing can increase renewals of community ART prescriptions and reduce the number of clinic visits for participants (see Chapter 11 Appendix for the protocol). We will use stored urine to evaluate the association between urine tenofovir and viraemia in these participants, as the urine tenofovir assay could again be useful to quickly monitor adherence in community settings.

My findings of no resistance against dolutegravir among people with viraemia support the South African guidelines, which no longer recommend switching to second line ART if viraemia persists for three months. Coupled with similar findings from the ADVANCE

trial,[140,228] these findings suggest that the WHO guidelines should also be clearer, to ensure that people with viraemia on dolutegravir are not needlessly switched to second-line ART when they do not have drug resistance. Further research is required to determine the optimum strategy to manage viraemia, in particular using drug resistance surveillance data to determine whether dolutegravir resistance will become more common, and routine data to determine the longer-term trajectory of viraemia and re-suppression in people receiving dolutegravir. As part of my post-doctoral work, I plan to build on my collaboration with the eThekwini Municipality and South African National Department of Health to use large de-identified routine datasets to answer some of these questions. With colleagues, we plan to assess longer term viral load outcomes with dolutegravir, and have already been in discussion with South African clinical guideline developers who have been interested in using our data to feed into the guideline development process. We also plan to assess the role of laboratory viral load testing in gatekeeping the CCMDD programme, and to answer other questions regarding whether the South African Department of Health should continue adaptations to the community ART programme that were implemented during COVID-19.

11.6. Reflections on the skills I have gained

This program of work has given me the opportunity to develop a wide range of skills. Under my supervisors Prof Chris Butler, Prof Nigel Garrett and Prof Gail Hayward, I have been part of several trial management groups covering a range of clinical trial designs both in the UK and in South Africa (PRINCIPLE and PANORAMIC adaptive platform trials, STREAM-HIV multi-site diagnostic intervention trial, and my smaller POwER and PHILA trials), through which I have learnt a range of trial management skills. Under my supervisor Dr Sarah Tonkin-Crine, I have learnt qualitative methods including conducting interviews and thematic analyses of qualitative data using NVIVO software (Chapter 9). I taught myself different statistical methods in R through various online resources, with supervision from Dr Tom Fanshawe in my department at the Nuffield Department of Primary Care Health Sciences (measures of diagnostic accuracy, bootstrap sampling [Chapter 3], and receiver operating

characteristic curves and area under the curve analyses), and Dr Christian Bottomley at the London School of Hygiene and Tropical Medicine (Poisson regression models with robust standard errors, survival analyses with time varying covariates, propensity score matching, target trial emulation [all in Chapter 8], and interrupted time series analyses [Chapter 10]). Research resources were limited, and so I had to much of the data management myself. Using online resources, and with support from CAPRISA and Oxford data management teams, I have learnt data management skills including teaching myself REDCap case report form (CRF) design. I generated all the CRFs and REDCap databases for my DPhil, as well as automated weekly data management reports. I have also learnt information governance skills, data curation, diplomacy when working with different institutions (including non-research institutions with different aims and objectives), obtaining ethics and other approvals, financial management, people management, issues around conducting international research (e.g. data curation and financial transfers), leading a team, time management, minute taking, record keeping, working to deadlines and being flexible and adaptive in the light of unexpected events.

11.7. Conclusion

In conclusion, in this thesis I have shown that three point-of-care viral load assays have acceptable clinical performance to detect viraemia when used in primary care clinics, including when testing is conducted by nurses. I also found that without COVID-19 disruptions, it is likely feasible to conduct a larger trial of point-of-care viral load testing to improve re-suppression. However, preliminary results from POwER, coupled with findings from other clinical effectiveness studies, suggest that point-of-care viral load testing on its own may not be the best intervention to improve re-suppression rates among people with viraemia. Furthermore, I have shown that while viraemia is only slightly less common in people receiving dolutegravir, it is mainly due to poor adherence, rather than drug resistance. Therefore, in the context of the widespread dolutegravir rollout, strategies to manage viraemia should focus on the detection and management of inconsistent adherence.

I found that a novel point-of-care urine tenofovir assay has good analytic performance, and may therefore have a role to play, independently or combined with point-of-care viral load testing, in improving re-suppression. In POwER, point-of-care viral load testing led to quicker results and fewer clinic visits. Therefore, these assays may have other benefits, including in clinical scenarios where people are not virally suppressed. I showed that a community ART delivery programme, for people with viral suppression, helped to overcome barriers to engagement in HIV care. In my post-doctoral work, I will conduct a follow up study to evaluate whether point-of-care viral load and adherence assays could be used to increase efficiencies in the community ART delivery programme. Lastly, COVID-19 severely disrupted my DPhil work, but also meant that I became involved in other COVID-19 research. As part of this, I demonstrated that COVID-19 had a severe impact on HIV testing and ART initiations in South African primary care clinics, but that ART collection visits were not drastically affected.

Appendices

12. CHAPTER 1 APPENDIX

12.1. List of papers published during my DPhil programme

I have published 33 peer-reviewed papers and had 14 oral or poster presentations at conferences during my DPhil.

12.1.1. DPhil related

1. **Dorward J**, Khubone T, Gate K, Ngobese H, Sookrajh Y, Mkhize S, et al. The impact of the COVID-19 lockdown on HIV care in 65 South African primary care clinics: an interrupted time series analysis. Lancet HIV. 2021;8(3):e158-e65. Epub 2021/02/08. doi: 10.1016/S2352-3018(20)30359-3. PubMed PMID: 33549166.
2. **Dorward J**, Sookrajh Y, Ngobese H, et al. Protocol for a randomised feasibility study of Point-Of-care HIV viral load testing to Enhance Re-suppression in South Africa: the POwER study. *BMJ Open* 2021;11:e045373.
3. **Dorward J**, Naidoo J, Moodley P, et al. Diagnostic Accuracy of the Rapid Xpert HIV-1 Viral Load XC, Xpert HIV-1 Viral Load, & m-PIMA HIV-1/2 Viral Load in South African Clinics. J Acquir Immune Defic Syndr **2022**; 91(2): 189-96
4. **Dorward J**, Msimango L, Gibbs A, *et al*. Understanding how community antiretroviral delivery influences engagement in HIV are: a qualitative assessment of the Centralised Chronic Medication Dispensing and Distribution programme in South Africa. *BMJ Open* 2020;10:e035412. doi:10.1136/bmjopen-2019-035412

12.1.2. COVID-19 in UK primary care

5. Yu L-M*, Bafadhel M*, **Dorward J*** (*joint first authors), Hayward G, Saville BR, Gbinigie O, et al. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. The Lancet. 2021. doi: 10.1016/S0140-6736(21)01744-X
6. **Dorward J***, Yu L-M* (*joint first authors), Hayward G, et al. Colchicine for COVID-19 in the community (PRINCIPLE): a randomised, controlled, adaptive platform trial. *British Journal of General Practice* 2022: BJGP.2022.0083.
7. Butler C, Yu L-M, **Dorward J**, et al. Doxycycline for community treatment of suspected COVID-19 in people at high risk of adverse outcomes in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial *The Lancet Respiratory Medicine.* 2021. doi: 10.1016/S2213-2600(21)00310-6
8. Patel MG, **Dorward J**, Yu L-M, et al. Inclusion and diversity in the PRINCIPLE trial. The Lancet 2021;397(10291):2251-52. doi: 10.1016/S0140-6736(21)00945-4
9. Butler CC, **Dorward J**, Yu L-M, et al. Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *The Lancet.* 2021;397(10279):1063-1074. doi: 10.1016/s0140-6736(21)00461-x

10. Hayward G., … **Dorward J** (middle),… et al., Platform Randomised trial of INterventions against COVID-19 In older peoPLE (PRINCIPLE): Protocol for a randomised, controlled, open-label, adaptive platform, trial of community treatment of COVID-19 syndromic illness in people at higher risk. *BMJ Open.* 2021. doi: 10.1136/bmjopen-2020-046799
11. Joy M., … **Dorward J** (middle),… et al. Excess mortality in the first COVID pandemic peak: cross-sectional analyses of the impact of age, sex, ethnicity, household size, and long-term conditions in people of known SARS-Cov-2 status in England. *Br J Gen Pract* 2020; DOI: https://doi.org/10.3399/bjgp20X713393
12. de Lusignan S, Jones N, **Dorward J**, et al. Oxford Royal College of General Practitioners Clinical Informatics Digital Hub: Rapid innovation to deliver extended COVID-19 surveillance and trial platforms. *JMIR Public Health Surveill* 2020;6(3):e19773. doi:10.2196/19773
13. de Lusignan S, **Dorward J**, Correa A, et al. Risk factors for SARS-CoV-2 among patients in the Oxford Royal College of General Practitioners Research and Surveillance Centre primary care network: a cross-sectional study. *The Lancet Infectious Diseases.* 2020;20(9) :1034-1042. doi: 10.1016/s1473-3099(20)30371-6

12.1.3. COVID-19 and HIV

14. **Dorward J**, Gbinigie O, Cai T, Roberts NW, Garrett N, Hayward G, et al. The protease inhibitor lopinavir, boosted with ritonavir, as treatment for COVID-19: a rapid review. *Antiviral Therapy*. 2021. doi: 10.3851/imp3385.
15. Mathamo A, Naidoo K, **Dorward J**, et al. COVID-19 and HIV viral load suppression in children and adolescents in Durban, South Africa. Southern African Journal of HIV Medicine 2022
16. Mellor, M. M., Bast, A. C., Jones, N. R., Roberts, N. W., Ordonez-Mena, J. M., Reith, A. J. M., . . . **Dorward, J**. (2021). Risk of adverse coronavirus disease 2019 outcomes for people living with HIV. AIDS, 35(4), F1-F10. doi:10.1097/QAD.0000000000002836

12.1.4. Papers from additional projects

17. **Dorward J,** Hamers RL. Dolutegravir in Sub-Saharan Africa: context is crucial. *The Lancet HIV* 2019;6:e72–3. doi:10.1016/S2352-3018(18)30331-X
18. **Dorward J**, Sookrajh Y, Gate K, et al. HIV treatment outcomes among people with initiation CD4 counts >500 cells/microL after implementation of Treat All in South African public clinics: a retrospective cohort study. *J Int AIDS Soc* 2020; **23**(4): e25479
19. **Dorward J**, Drain PK, Osman F, et al. Early antiretroviral therapy is associated with better viral suppression and less HIV drug resistance after implementation of universal treatment in South Africa. AIDS Res Hum Retroviruses 2020; 36(4):297-299. doi:10.1089/AID.2019.0206
20. Asare K, Andine T, Naicker N, **Dorward J**, et al. Impact of point-of-care testing on the management of sexually transmitted infections in South Africa: Evidence from the HVTN702 HIV vaccine trial. Clin Infect Dis 2022.
21. Bodley N, **Dorward J**, Naidoo J, et al. Diagnostic accuracy of the Alere Afinion AS100 point-of-care assay to screen for non-communicable diseases amongst people living with HIV. J Acquir Immune Defic Syndr 2022

22. van der Westhuizen H-M, **Dorward J**, Roberts N, et al. Health worker experiences of implementing TB infection prevention and control: A qualitative evidence synthesis to inform implementation recommendations. *PLOS Global Public Health* 2022; **2**(7): e0000292.
23. Lewis L, Sookrajh Y, Gate K. **Dorward J**. Differentiated service delivery for people using second-line antiretroviral therapy: clinical outcomes from a retrospective cohort study in KwaZulu-Natal, South Africa. *Journal of the International AIDS Society* 2021; **24**(S6): e25802.
24. Bardon AR, **Dorward J**, Sookrajh Y, et al. Simplifying TREAtment and Monitoring for HIV (STREAM HIV): protocol for a randomised controlled trial of point-of-care urine tenofovir and viral load testing to improve HIV outcomes. *BMJ Open* 2021; **11**(10): e050116.
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12.2. Conference presentations

12.2.1. Oral presentations

1. **Dorward J**. et al. Rapid HIV viral load testing at the clinical point-of-care to improve treatment outcomes in South Africa. Main plenary presentation. 13th National Conference of AIDS Society of India (ASICON) 2022, Hyderabad. Invited speaker.
2. **Dorward J.** et al. Evaluation of site-laboratory & nurse-led testing using the novel, dual target Xpert HIV-1 VL XC assay in a South African clinic. 21st Edition of the International Conference on AIDS & STIs in Africa (ICASA) 2021. Oral presentation in satellite session.
3. **Dorward J.** et al. Women are less likely to receive dolutegravir-based first-line ART in South Africa. Mini oral presentation. Conference on Retroviruses and Opportunistic Infection (CROI) 2021, virtual.
4. **Dorward J**. et al. The impact of the coronavirus disease 2019 lockdown on HIV care in 65 South African primary care clinics: an interrupted time series analysis. IAS COVID-19 Conference: Prevention, 2021, virtual.
5. **Dorward J,** Ngobese H, Khubone T, et al. Marked increase in antiretroviral therapy initiation after implementation of universal test and treat in Durban, South Africa. Fast Track Cities Conference, 2019, London, UK.
6. **Dorward J**. Universal test and treat: challenges and opportunities for healthcare systems. CISM HIV Research Symposium and Palestra Annual 2019, Maputo, Mozambique.
7. **Dorward J**, Sookrajh Y, Gate K, Garrett N. Successful viral outcomes after implementation of Treat All in South African clinics. Crossing Boundaries Conference on Global Health Systems Research, 2018, Oxford UK.

12.2.2. Poster presentations

1. **Dorward J**. et al. Uptake and outcomes of first-line dolutegravir in a large South African cohort. 2023 Conference on Retroviruses and Opportunistic Infections (CROI 2023), Seattle. (accepted)
2. **Dorward J**. et al. Performance evaluation of the point-of-care m-PIMA HIV-1/2 Viral Load assay in two South African clinics. 24th International AIDS Conference 2022, Montreal.
3. **Dorward J**. et al. Evaluation of the Xpert ® HIV 1 Viral Load XC RUO: a novel point of care HIV viral load assay. 31st European Congress of Clinical Microbiology & Infectious Diseases (ECCMID) 2021
4. **Dorward J**. et al. Understanding how community-based ART delivery influences engagement in HIV services: a qualitative assessment of South Africa's differentiated care CCMDD programme. 23rd International AIDS Conference, 2020, virtual.
5. **Dorward J**, Drain P, Osman F et al. High Levels of Dual Class HIV Drug Resistance Amongst People Initiated at Low CD4 Counts after Implementation of Universal Treatment in a South African Public Clinic. 18th International Workshop on HIV Drug Resistance and Treatment Strategies, 2019, Johannesburg, South Africa.
6. Msimango L, Gibbs A, Shozi H, Ngobese N, Humphries H, Drain P, Garrett N, **Dorward J**. Acceptability of point-of-care viral load testing to facilitate differentiated HIV care: a qualitative study amongst people living with HIV and healthcare workers in South Africa. 10th International AIDS Society Conference on HIV Science, 2019, Mexico City, Mexico.

7. **Dorward J**, Sookrajh Y, Gate K, Garrett N. Successful viral outcomes after implementation of Treat All in South African clinics. Conference on Retroviruses and Opportunistic Infections, 2019, Seattle, Washington.

12.3. Grants and funding won during my DPhil research program

During my DPhil I have led or been part of the following successful grant applications, in addition to the direct funding for my DPhil:

1. Bill & Melinda Gates Foundation (INV-051067, USD450,000), co-PIs Dorward & Garrett. Two year grant to evaluate the South African HIV programme using routine de-identified data from primary care clinics.
2. Countess Dowager Eleanor Peel Trust (280, £20,000), co-PIs Dorward & Garrett. Two year grant to conduct a randomised trial of point-of-care viral load testing in a community ART programme.
3. The International Association of Providers of AIDS Care (Fast Track Cities Implementation Science Grant, USD 50,000) co-PIs Dorward & Garrett. One year grant to evaluate how the South African HIV programme adapted to COVID-19, using quantitative and qualitative data.
4. National Institute of Health and Social Care Research (NIHR) – Platform Adaptive Trial of Novel Antivirals for Early Treatment of COVID-19 in the Community (PANORAMIC) and Platform Randomised Trial of Treatments in the Community for Epidemic and Pandemic Illnesses (PRINCIPLE). PI – Butler. I am a co-investigator and Trial Management Group member of these two UK Government National Platform Trials for novel antivirals and repurposed medications to treat COVID-19 in the community, with over 37,000 participants enrolled across the UK (www.panoramictrial.org and www.principletrial.org).
5. National Institute of Health (R01 AI147752, USD 2.5 million). Simplifying Treatment and Monitoring for HIV (STREAM HIV): A randomised controlled trial of Point-of-Care Urine Tenofovir Adherence and Viral Load Testing to Improve HIV Outcomes in South Africa. Co-PIs Drain and Garrett. I am a co-investigator.

13. CHAPTER 3 APPENDIX

Table 13.1 Error codes for invalid point-of-care viral load assay results

ID	Tester	Error code	Potential causes	Comment
XPERT HIV-1 VL XC				
8	Lab technician	5007	Sample related: PCR inhibitors in sample Instrument related: Sub-optimal optical channels	First test error
8	Lab technician	5007	Sample related: PCR inhibitors in sample Instrument related: Sub-optimal optical channels	Repeat test error: no valid result
9	Lab technician	5007	Sample related: PCR inhibitors in sample Instrument related: Sub-optimal optical channels	First test error
9	Lab technician	5007	Sample related: PCR inhibitors in sample Instrument related: Sub-optimal optical channels	Repeat test error: no valid result
33	Lab technician	2126	Instrument related: Communication error, e.g. cables not properly connected	First test error
33	Lab technician	2126	Instrument related: Communication error, e.g. cables not properly connected	Repeat test error: no valid result
34	Lab technician	2126	Instrument related: Communication error, e.g. cables not properly connected	First test error
34	Lab technician	2126	Instrument related: Communication error, e.g. cables not properly connected	Repeat test error: no valid result
79	Nurse	2126	Instrument related: Communication error, e.g. cables not properly connected	First test error, no repeat so no valid result
81	Nurse	2008	Sample related: Pressure error most often due to viscosity or particulate matter	First test error, no repeat so no valid result
54	Nurse	2097	User related: Insufficient plasma volume	First test error, no repeat so no valid result
89	Nurse	2096	User related: Insufficient plasma volume	First test error, no repeat so no valid result
XPERT HIV-1 VL				
58	Lab technician	5007	Sample related: PCR inhibitors in sample Instrument related: Sub-optimal optical channels	Test repeated and valid result obtained
85	Nurse	2037	Cartridge-related: Pressure error	First test error
85	Nurse	2097	User related (insufficient plasma volume)	Repeat test error: no valid result
MPIMA HIV-1/2 VL				
437	Lab technician	23215	Instrument related: lint / particle on optic	Result obtained on repeat
402	Lab technician	23020	Sample related: Interfering substances or coagulated Cartridge related (seldom): Cartridge defect Instrument related: Lysis heater or mixer module failure	First test error
402	Lab technician	23020	Sample related: Interfering substances or coagulated Cartridge related (seldom): Cartridge defect	Repeat test error: no valid result

ID	Tester	Error code	Potential causes	Comment
			Instrument related: Lysis heater or mixer module failure	
92	Lab technician	23210	User related: Incorrect cartridge insertion Cartridge related: Microarray dislocated Instrument related: Cartridge lock issue	First test error
92	Lab technician	23210	User related: Incorrect cartridge insertion Cartridge related: Microarray dislocated Instrument related: Cartridge lock issue	Repeat test error: no valid result

13.1. Published manuscript

The following pages contain the published manuscript on which Chapter 3 was based.

Dorward J, Naidoo J, Moodley P, et al. Diagnostic Accuracy of the Rapid Xpert HIV-1 Viral Load XC, Xpert HIV-1 Viral Load, & m-PIMA HIV-1/2 Viral Load in South African Clinics. J Acquir Immune Defic Syndr 2022; 91(2): 189-96.

OPEN

Diagnostic Accuracy of the Rapid Xpert HIV-1 Viral Load XC, Xpert HIV-1 Viral Load, & m-PIMA HIV-1/2 Viral Load in South African Clinics

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Background: We aimed to evaluate the analytic performance of 3 rapid HIV viral load assays: the novel Xpert HIV-1 VL XC (Xpert XC), Xpert HIV-1 VL (Xpert VL), and m-PIMA HIV-1/2 VL (m-PIMA).

Setting: Two South African clinics.

Methods: We conducted a prospective diagnostic accuracy study. Site-laboratory technicians and nurses used the Xpert XC, Xpert VL, and m-PIMA to test plasma samples from people with HIV receiving antiretroviral therapy. We compared results with the Roche cobas HIV-1 reference assay. We determined accuracy to detect viraemia at the World Health Organization (WHO) failure threshold of 1000 copies/mL on all 3 assays, and 50 and 200 copies/mL on the Xpert assays. We assessed the agreement using Bland–Altman plots.

Results: We enrolled 140 participants (98 [70%] women, median age 37 years), who provided 189 paired samples at one or more timepoints. We tested 174 samples with the Xpert XC, 188 with the Xpert VL, and 128 with the m-PIMA. At 1000 copies/mL, sensitivity and specificity (95% confidence intervals) were 97% (82 to 100) and 98% (93 to 99) (Xpert XC), 100% (87 to 100) and 96% (91 to 98) (Xpert VL), and 92% (72 to 99) and 99% (93 to 100) (m-PIMA) respectively. At 50 copies/mL, sensitivity and specificity were 93% (81 to 98) and 96% (91 to 99) (Xpert XC), and 95% (84 to 99) and 95% (90 to 98) (Xpert VL) respectively. Mean bias was −0.10 (−0.54 to 0.34) $\log_{10}$ copies/mL (Xpert XC), 0.07 (−0.37 to 0.52) $\log_{10}$ copies/mL (Xpert VL), and −0.26 (−0.83 to 0.31) $\log_{10}$ copies/mL (m-PIMA).

Conclusions: In these South African clinics, the accuracy of all 3 assays was clinically acceptable to detect viraemia at the WHO failure threshold, whereas both Xpert assays were also accurate at detecting low-level viraemia.

Key Words: HIV, point-of-care, viral load testing

(*J Acquir Immune Defic Syndr* 2022;91:189–196)

INTRODUCTION

The World Health Organization (WHO) recommends antiretroviral therapy (ART) for all people living with HIV, to suppress the HIV viral load.[1] This prevents immunosuppression and related morbidity and mortality,[2,3] and onward HIV transmission. Regular HIV viral load testing is a key component for monitoring the effectiveness of ART in current WHO guidelines, which recently endorsed the use of

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point-of-care viral load assays, where testing is conducted at the clinical site by laboratory professionals or specifically-trained health care workers.[4] These assays can reduce the time from blood draw to results being available, allowing clinicians to take decisions on the same day in one clinic visit, rather than having to schedule follow-up appointments to discuss the results.[5,6] A randomized trial conducted by our team in South Africa, using the Xpert HIV-1 Viral Load (Xpert HIV-1 VL) assay (Cepheid, Sunnyvale), found that point-of-care testing improved the primary outcome of HIV viral suppression and retention in care by 13.7%.[7]

Currently, there are 2 point-of-care HIV viral load assays that are approved by the WHO for use in low- and middle-income countries. The m-PIMA HIV 1/2 VL (Abbott, Chicago) received WHO prequalification in 2019,[8] and has been found to perform well in one laboratory-based[9] and 2 clinic-based evaluation studies.[10,11] The Xpert HIV-1 VL received WHO prequalification in 2017,[12] and has also been found to perform well in 19 studies, which have been summarized in 2 systematic reviews.[13,14] Only 3 of these studies reported conducting Xpert HIV-1 VL testing in clinics, as opposed to centralized laboratories. Because the assay was not able to detect certain recombinant HIV-1 sub-types,[15] Cepheid have recently released a next generation dual target assay, the Xpert HIV-1 Viral Load XC (HIV-1 VL XC), that detects a wider range of HIV subtypes.[16] This assay recently received CE-IVD clearance,[17] but has not yet been evaluated in any published studies that we are aware of.

Objectives

In this study, we aimed to assess the analytic performance of the novel, dual target Xpert HIV-1 VL XC, the existing Xpert HIV-1 VL, and the m-PIMA HIV 1/2 VL, when used in South African clinics, compared with an established laboratory reference assay.

METHODS

Study Design and Participants

We conducted a prospective diagnostic accuracy evaluation as a substudy within the Point-Of-care HIV viral load testing to Enhance Resuppression (POwER) study, and the Centre for the AIDS Program of Research in South Africa (CAPRISA) 002 Acute Infection study. POwER is a randomized feasibility study in one urban and one rural public sector, primary care clinic in KwaZulu-Natal, South Africa, and the study protocol has been published elsewhere.[18] In summary, approximately 100 nonpregnant adults aged 18 and above, receiving first-line ART and with HIV viraemia >1000 copies/mL in the past 6 weeks, are randomized to receive a second viral load test after 12 weeks by point-of-care test, or by standard laboratory-based viral load testing. The primary outcome of viral suppression <50 copies/mL is assessed after 24 weeks. The CAPRISA 002 study is taking place in the same 2 clinics, and is a long-term cohort study of women living with HIV who are on ART.[19] For this substudy, POwER and CAPRISA 002 participants who provided written informed consent, had additional 4–8 mL of venous blood drawn for point-of-care assay evaluation, taken alongside the main study blood draws at enrolment or during follow-up. We initially planned to use consecutive participants enrolling in POwER and attending follow-up in CAPRISA 002, but disruptions in test cartridge supply chains, assay training, and staffing because of the COVID-19 pandemic meant that there were periods where various assay cartridges were not available or rarely nurses did not have time to conduct testing. We therefore used a convenience sampling strategy instead, where consenting patients enrolling or attending follow-up in either study had samples tested on whichever assays were available at that time in the respective clinic. This meant that some participants in POwER had multiple samples taken for this evaluation at up to 3 different visits.

Test Methods

Assay manufacturers provided point-of-care training to research laboratory technicians and research nurses, and ongoing testing support. Initially, laboratory technicians conducted testing in a dedicated on-site point-of-care laboratory in the clinics. Once laboratory technician testing was established, research nurses conducted testing in a dedicated space in the clinic, with ongoing troubleshooting support from the manufacturer and on-site laboratory staff. For point-of-care viral load testing, 4–8 mL whole blood was obtained by venipuncture into an EDTA tube and centrifuged (by laboratory technicians or nurses respectively) to obtain plasma, which was transferred into the test cartridge and loaded into the respective assay platform. The m-PIMA HIV 1/2 platform is a single module instrument which requires 50 μL of plasma, and provides a quantitative viral load result between 800 and 1,000,000 copies/mL in approximately 70 minutes. The manufacturer states that the m-PIMA HIV 1/2 has a lower limit of detection of 342 (95% confidence interval [CI] 279 to 451) copies/mL for HIV-1 group M, and 228 (95% CI: 187 to 295) copies/mL for HIV-1 group O.[20] The new Xpert HIV-1 VL XC and existing Xpert HIV-1 VL use the same GeneXpert platform (Cepheid, Sunnyvale) and both require 1 mL of plasma to provide a quantitative viral load result between 40 and 10,000,000 copies/mL in approximately 90 minutes. The lower limit of detection as stated by the manufacturer is 13.6 (95% CI: 11.1 to 15.6) copies/mL for the Xpert HIV-1 VL XC,[16] and 15.3 (95% CI: 13.5 to 17.0) copies/mL for the Xpert HIV-1 VL.[21] We used research-use-only cartridges of the same version as the now commercially released Xpert HIV-1 VL XC, and single module GXP I and 4 module GXP IV instruments. If a point-of-care assay resulted in an error or an invalid result, the test was repeated using remaining plasma, if available. Point-of-care viral load results from this evaluation were not provided to patients and were not used for clinical decision making.

For reference laboratory testing, a nurse drew whole blood in an EDTA tube at the same timepoint, which was centrifuged to plasma and stored at −80°C in the CAPRISA biorepository. These samples were then defrosted and

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tested in 2 batches (study midpoint and study end) on the cobas HIV-1 reference assay using the cobas 6800 platform (Roche, Basel, Switzerland) at the Inkosi Albert Luthuli Hospital National Health Laboratory Service in Durban, KwaZulu-Natal. We chose this assay because it is one of the standard viral load assays which has been widely validated and used in the South African National Health Laboratory Service. Staff performing laboratory reference testing were blinded to results of the point-of-care testing and vice versa.

Analysis

For the Xpert assays, we evaluated sensitivity and specificity to detect viraemia at thresholds of 50 copies/mL, 200 copies/mL, and 1000 copies/mL. Because the m-PIMA HIV 1/2 VL does not provide a quantitative viral load below 800 copies/mL, we only evaluated the 1000 copies/mL threshold. We evaluated accuracy at these thresholds because they are used in national and international guidelines to define viraemia and treatment failure.[4,22–24] We assessed agreement with the laboratory reference assay using Bland–Altman plots, and association using Pearson correlation coefficients, restricted to paired samples with a quantifiable viral load on the point-of-care and reference laboratory assay.

We conducted sensitivity analyses using bootstrap methods (see Supplementary Material for Methods, Supplemental Digital Content, http://links.lww.com/QAI/B921) to account for repeat testing in the same participants at different time points, which could introduce clustering of errors. For example, if a participant had a viral subtype that was not detected by a particular assay, inaccurate results would be more common among repeat tests in that participant, compared with tests in the general sample.

We estimated that with the resources and time available, we could test approximately 150 samples on each assay. However, the COVID-19 pandemic interrupted cartridge supply chains for the m-PIMA HIV 1/2 VL, meaning fewer tests were possible for this assay. Because not all samples were tested on all point-of-care assays, we did not directly compare the performance of the point-of-care assays against each other.

Ethical Approval

The POwER and CAPRISA 002 protocols, including use of samples for point-of-care viral load assay evaluation, were approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC/00000836/2019 and E013/04 respectively), and POwER has also been approved by the University of Oxford Tropical Research Ethics Committee (OxTREC 66-19) and is registered with the Pan-African Clinical Trials Registry (PACTR202001785886049).

RESULTS

Participants

Between June 26, 2020 and September 15, 2021, 140 participants provided paired samples, at one or more time-points, for testing in this evaluation. Testing was conducted in the rural clinic for 25 participants, and at the urban clinic for 115 participants. 98 (70%) were women, median age was 37 years (interquartile range [IQR] 33–43), median time on ART was 4.6 years (IQR 2.9–6.0), and median CD4 count was 569 cells/μL (IQR 356–792).

Test Results

Overall, 189 samples were tested on at least one point-of-care viral load assay. One hundred seventy-four samples were tested using the Xpert HIV-1 VL XC, 188 samples using the Xpert HIV-1 VL, and 128 samples using the m-PIMA HIV 1/2 VL (Table 1). Nurses conducted testing for 54/174 (31%) of Xpert HIV-1 VL XC samples, 26/188 (14%) Xpert HIV-1 VL samples, and 23/128 (18%) m-PIMA HIV 1/2 VL samples. Initial errors were produced for 8 (4.6%) Xpert HIV-1 VL XC samples, 2 (1.1%) Xpert HIV-1 VL samples, and 3 (2.5%) m-PIMA HIV 1/2 VL samples. In some cases, tests were successfully repeated, meaning that final results were not available because of assay errors for 8 (4.6%) Xpert HIV-1 VL XC samples, 1 (0.5%) Xpert HIV-1 VL sample, and 2 (1.7%) m-PIMA HIV 1/2 VL samples (see Table 1 for total number of errors and see Table S1, Supplemental Digital Content, http://links.lww.com/QAI/B921 for error codes). Four of the Xpert HIV-1 VL XC errors occurred at the beginning of the nurse testing process; this was the first assay that the nurses were trained to use.

Sensitivity and Specificity

Sensitivity and specificity at 1000 copies/mL, compared with the Cobas 6800, were 97% and 98% (Xpert HIV-1 XC), 100% and 96% (Xpert HIV-1 VL), and 92% and 99% (m-PIMA) respectively. For the Xpert assays, sensitivity and specificity at 50 copies/mL were 93% and 96% (Xpert HIV-1 XC), and 95% and 95% (Xpert HIV-1 VL) respectively

TABLE 1. Samples Tested on Point-of-Care Viral Load Assays

	Xpert HIV-1 VL XC	Xpert HIV-1 VL	m-PIMA HIV 1/2 VL
Samples from one timepoint per participant	84 (48.3)	97 (51.6)	67 (56.8)
Samples from 2 timepoints per participant	70 (40.2)	78 (41.5)	46 (39.0)
Samples from 3 timepoints per participant	12 (6.9)	12 (6.4)	3 (2.5)
No result because of assay errors*	8 (4.6)†	1 (0.5)‡	2 (1.7)§
Total	174	188	118

*See Table S1, Supplemental Digital Content, http://links.lww.com/QAI/B921 for error codes.

†Eight samples (4.6%) produced an error. Four were retested, with the repeat test also producing an error meaning no result was available. Four were not retested meaning no result was available.

‡Two samples (1.1%) produced an error, and both were retested. One repeat test also produced an error meaning no result was available, the other produced a valid result.

§Three samples (2.5%) produced an error, and all were retested. Two repeat tests also produced an error meaning no result was available, the other produced a valid result.

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TABLE 2. Raw Numbers, Sensitivity, and Specificity (95% Confidence Intervals) of Three Point-of-Care Viral Load Assays at Different Viral Load Thresholds

		Roche Cobas 6800					Roche Cobas 6800					Roche Cobas 6800		
		<50	≥50	Total			<50	≥50	Total			<50	≥50	Total
Xpert HIV-1 VL XC	<50	108	4	112	Xpert HIV-1 VL	<50	125	3	128	m-PIMA HIV 1/2 VL	<50	—	—	—
	≥50	4	50	54		≥50	6	53	59		≥50	—	—	—
	Total	112	54	166		Total	131	56	187		Total	—	—	—
	Sensitivity: 0.93 (0.81, 0.98)					Sensitivity: 0.95 (0.84, 0.99)					Sensitivity: NA			
	Specificity: 0.96 (0.91, 0.99)					Specificity: 0.95 (0.90, 0.98)					Specificity: NA			
		<200	≥200	Total			<200	≥200	Total			<200	≥200	Total
Xpert HIV-1 VL XC	<200	116	4	120	Xpert HIV-1 VL	<200	137	2	139	m-PIMA HIV 1/2 VL	<200	—	—	—
	≥200	3	43	46		≥200	1	47	48		≥200	—	—	—
	Total	119	47	166		Total	138	49	187		Total	—	—	—
	Sensitivity: 0.91 (0.79, 0.97)					Sensitivity: 0.96 (0.85, 0.99)					Sensitivity: NA			
	Specificity: 0.97 (0.92, 0.99)					Specificity: 0.99 (0.95, 1.00)					Specificity: NA			
		<1000	≥1000	Total			<1000	≥1000	Total			<1000	≥1000	Total
Xpert HIV-1 VL XC	<1000	131	1	132	Xpert HIV-1 VL	<1000	148	0	148	m-PIMA HIV 1/2 VL	<1000	90	2	92
	≥1000	3	31	34		≥1000	6	33	39		≥1000	1	23	24
	Total	134	32	166		Total	154	33	187		Total	91	25	116
	Sensitivity: 0.97 (0.82, 1.00)					Sensitivity: 1.00 (0.87, 1.00)					Sensitivity: 0.92 (0.72, 0.99)			
	Specificity: 0.98 (0.93, 0.99)					Specificity: 0.96 (0.91, 0.98)					Specificity: 0.99 (0.93, 1.00)			

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(Table 2). The m-PIMA was not assessed at 50 and 200 copies/mL because the lower limit of quantitation is 800 copies/mL.

Correlation and Agreement

When restricted to paired samples quantifiable at ≥40 copies/mL, the Xpert HIV-1 VL XC had a mean bias of −0.10 $\log_{10}$ copies/mL (95% limits of agreement −0.54 to 0.34, Fig. 1A) and a Pearson correlation coefficient of 0.97 (95% CI: 0.95 to 0.99, $P < 0.001$, $r^2 = 0.95$, Fig. 2A), whereas the Xpert HIV-1 VL had a mean bias of +0.07 $\log_{10}$ copies/mL (95% limits of agreement −0.37 to 0.52, Fig. 1B) and Pearson correlation coefficient of 0.98 (95% CI: 0.96–0.99, $P < 0.001$, $r^2 = 0.95$, Fig. 2B). For the m-PIMA HIV 1/2 VL, when restricted to paired samples quantifiable at ≥800 copies/mL, the mean bias was −0.26 $\log_{10}$ copies/mL (95% limits of agreement −0.83 to 0.31, Fig. 1C) and the Pearson correlation coefficient was 0.93 (95% CI: 0.85–0.97, $P < 0.001$, $r^2 = 0.87$, Fig. 2C).

Nurse-Led Testing

Accuracy, correlation, and agreement of the assays were comparable when conducted by nurses and laboratory technicians, but numbers of nurse-tested samples were small, particularly for the Xpert HIV-1 VL and the m-PIMA HIV-1/2 VL (see Tables S2 and S3, Supplemental Digital Content, http://links.lww.com/QAI/B921).

Sensitivity Analyses

In sensitivity analyses using bootstrap methods to account for some participants having samples drawn for evaluation at repeated timepoints, results were relatively similar (see Table S4, Supplemental Digital Content, http://links.lww.com/QAI/B921).

DISCUSSION

Summary

We found that the novel Xpert HIV-1 VL XC, Xpert HIV-1 VL, and m-PIMA HIV-1/2 VL had clinically acceptable performance when used in a South African clinic. At the WHO threshold for treatment failure of 1000 copies/mL, the Xpert HIV-1 VL XC and Xpert HIV-1 VL had >95% sensitivity and specificity, whereas the m-PIMA HIV-1/2 VL had sensitivity of 92% and specificity of 99%. Both Xpert assays were also accurate at detecting low-level viraemia.

Related Literature

Our findings are similar to other studies of these 3 point-of-care assays, most of which have been conducted in centralized laboratory settings.

Xpert HIV-1 VL XC

Our study is the first to evaluate the Xpert HIV-1 VL XC in a clinical setting. In a centralized laboratory-based study, 513 fresh, frozen and diluted samples, were tested on the Xpert HIV-1 VL XC and compared with the Alinity m HIV-1 reference assay (Abbott, Chicago).[25] The Xpert HIV-1 VL XC had a mean bias of +0.10 $\log_{10}$ copies/mL (95% CI −0.54 to 0.35), compared with the reference assay, and r^2 was 0.9788. Taken together, these results suggest that the Xpert HIV-1 VL XC performs well when used in centralized laboratory and clinic-based settings.

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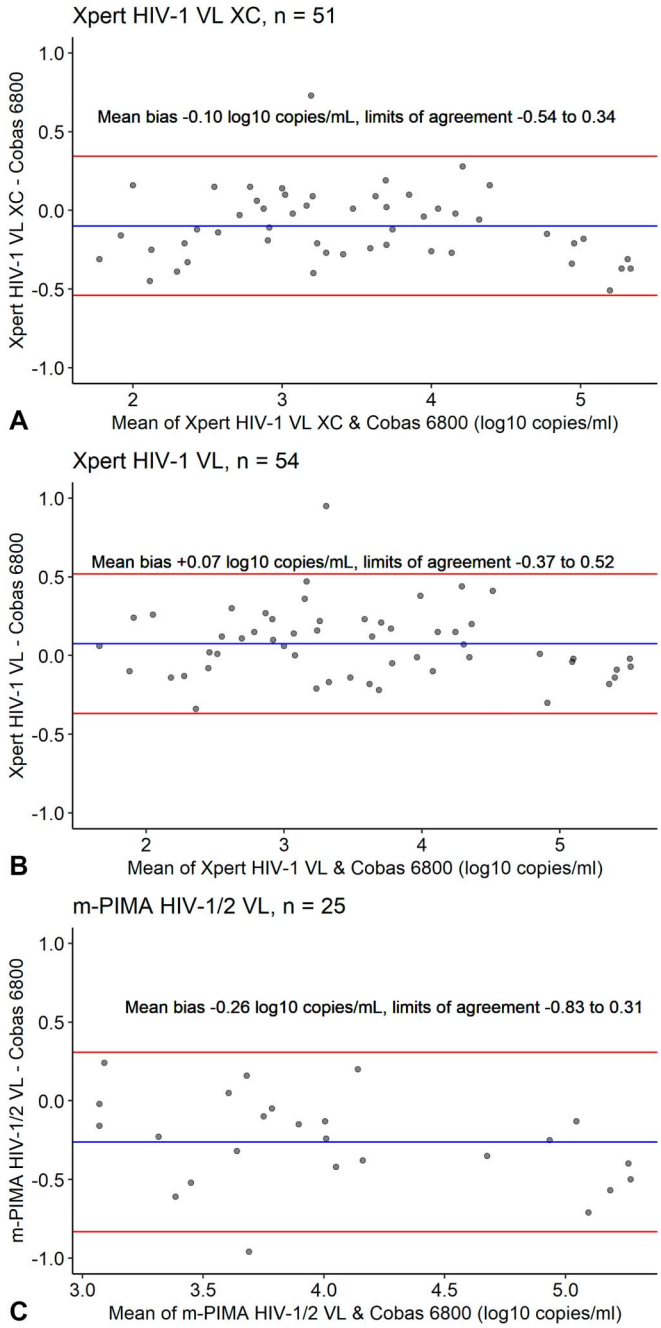


FIGURE 1. Bland–Altman plots of Xpert HIV-1 VL XC, Xpert HIV-1 VL, & m-PIMA HIV 1/2 vs Cobas 6800. Restricted to paired samples quantifiable on the point-of-care and laboratory reference assay. The point estimate of the mean difference (bias) between the point-of-care and laboratory reference assay was within ±0.3 $\log_{10}$ copies/mL for all 3 assays. full color online

Xpert HIV-1 VL

For the Xpert HIV-1 VL, our findings were similar to a meta-analysis of 13 studies including 3790 patients,[14] which found a mean bias of 0.04 (95% CI: 0.02 to 0.07) copies/mL, and r^2 of 0.941 ($P < 0.001$). Sensitivity and specificity were >95% at 200 and 1000 copies/mL, but were not evaluated at 50 copies/mL. Instead, a threshold of "detectable" was used (40 copies/mL on the Xpert HIV-1 VL assay versus 20, 25 and 40 copies/mL in the different comparator assays used in the studies), with sensitivity of 93.3% (88.2–96.3), and much lower specificity at 80.6% (64.6–90.4). Specificity was particularly poor (69.3%) when compared with the Abbott RealTime HIV-1 VL assay. We used the 50 copies/mL threshold because this is used in South African guidelines.[22] Our finding that the Xpert HIV-1 VL XC and Xpert HIV-1 VL performed well at this threshold contrasts slightly with the systematic review findings, but suggests that these assays are appropriate for use in the South African setting.

m-PIMA HIV-1/2 VL

Three published studies have evaluated the m-PIMA HIV-1/2 VL assay. Two of these were clinic-based; one multisite study in Mozambique compared 686 samples tested by nurses with the m-PIMA HIV-1/2 VL versus the Cobas AmpliPrep/Cobas TaqMan 96 HIV-1 v2 (Roche) assay,[10] whereas another multisite study from Kenya compared 555 samples tested by laboratory technicians on the m-PIMA HIV-1/2 VL in clinics, with the RealTime HIV-1 assay (Abbott).[11] The final study was a centralized laboratory evaluation comparing 413 frozen samples tested on the m-PIMA HIV -1/2 VL with results from fresh samples tested on the RealTime HIV-1 assay. At 1000 copies/mL, sensitivity and specificity were above 95% in all studies, except for the laboratory evaluation where specificity was 76.9% (95% CI: 69.8 to 83.1). The correlation coefficients were 0.92, 0.92, and 0.93 respectively, with mean bias of −0.20, +0.16 and +0.26 $\log_{10}$ copies/mL respectively versus the laboratory reference assay. The WHO prequalification report found a bias of −0.21 $\log_{10}$ copies/mL versus the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test, v2.0, with a sensitivity of 95.1% and specificity of 99% at 1000 copies/mL.[8] Overall, these findings, particularly when using Roche reference laboratory assays, are similar to our results, although reasons for the low specificity in the laboratory study are not clear, but could be related to the use of frozen samples for m-PIMA testing.

Nurse Testing

There is only one published study that has evaluated nurse-led quantitative point-of-care viral load testing, with good results using the m-PIMA HIV1/2 viral load in Mozambique, as described above.[10] Our data suggest that the Xpert HIV-1 VL XC performs well when used by nurses, and results with the Xpert HIV-1 VL and m-PIMA HIV-1/2 VL were relatively similar, although numbers were small. However, our study was not explicitly designed to compare nurse versus laboratory testing, and research nurses had support available to them from on-site laboratory technicians, which does not reflect conditions across South African primary care. Nurses and/or midwives have accurately used qualitative viral load assays (that use the GeneXpert and m-PIMA platforms) for early infant diagnosis of HIV,[26,27] and there is increasing interest in task-shifting point-of-care HIV diagnostics to nonlaboratory staff in low- and middle-

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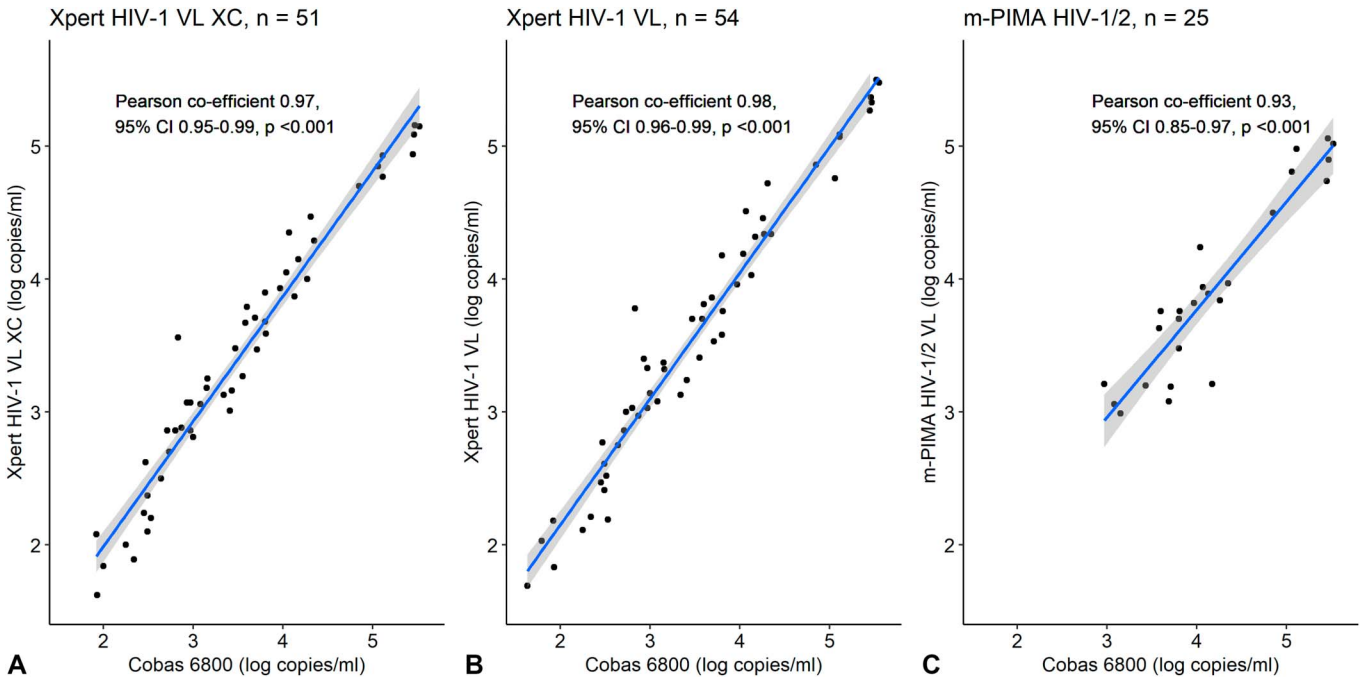


FIGURE 2. Correlation of Xpert HIV-1 VL XC, Xpert HIV-1 VL, & m-PIMA HIV 1/2 VL vs Cobas 6800. Restricted to paired samples quantifiable on the point-of-care and laboratory reference assay. full color online

income countries.[28–30] As these assays require plasma, venous blood samples had to be centrifuged by nurses in the study clinic. This required specific training and may not be feasible for nurses in many settings, which could limit use at the clinical point-of-care. A whole blood fingerstick assay would circumvent this problem, and point-of-care early infant diagnosis assays, which also use whole blood, have demonstrated clear benefits in clinical outcomes.[26,31] This highlights the potential benefits of providing same day results using point-of-care technologies.

Strengths and Limitations

Strengths of our study include the assessment of clinic-based testing in a setting with high HIV prevalence, and the inclusion of multiple point-of-care assays. Apart from assessing correlation and mean bias, we focused our analysis on sensitivity and specificity to detect viraemia at viral load thresholds that are directly relevant for patient management in South Africa and internationally. Most viral load testing was conducted by laboratory technicians, but we included some nurse-led viral load testing, which has not been widely evaluated previously. Supply chain and operational disruptions because of the COVID-19 pandemic meant that our sample size was smaller than anticipated for some assays, and we were unable to test samples on all 3 assays concurrently. Instead, we allowed paired samples from repeat timepoints in the same participant, and conducted sensitivity analyses to account for potential clustering, with similar results. Nevertheless, the sample size of this study is relatively small, meaning confidence intervals for sensitivity estimates are wide for all assays at all viraemia thresholds, and for sensitivity and specificity estimates for nurse testing. Reference laboratory testing was conducted retrospectively using frozen plasma samples, in accordance with manufacturer's instructions, which should not have affected results.[32]

Implications

A previous cost-effectiveness modelling study found that a sensitivity and specificity of 90% or more at a threshold of 1000 copies/mL would be acceptable for a point-of-care viral load assay in Southern Africa,[33] whereas mean bias should ideally be within 0.3 $\log_{10}$ copies/mL of reference laboratory assays.[6,34] In our evaluation, all 3 evaluated assays fell within these criteria.

Balancing assay analytic performance and other characteristics that influence clinical outcomes, such as ease of use, turn-around time, and result availability will depend on the context of where the assay is being implemented. We found that the Xpert HIV-1 VL XC performed well at the 50 copies/mL and 1000 copies/mL thresholds, which are the 2 key thresholds for ART management in South Africa, suggesting that the clinical performance is appropriate for this setting. The m-PIMA HIV-1/2 VL is not able to quantitate viral loads <800 copies/mL, making it less suited to assessment of low-level viraemia. More recent evidence has found that low-level viraemia among people receiving efavirenz-based ART regimens predicts subsequent treatment failure,[35] although whether this remains true on dolutegravir-based regimens is not yet known.[36] South African guidelines currently use 50 copies/mL to define viraemia, and determine whether a patient is eligible for down-referral into streamlined ART delivery programmes,[37,38] or whether they need

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enhanced adherence counselling to encourage resuppression,[37] meaning the m-PIMA is less suited for use in these situations. However, the m-PIMA has a simple interface, shorter run time, and may be more suited to implementation in clinic-based settings, particularly in settings where access to viral load testing is poor. Further work is needed to confirm the performance of these assays when used by nurses, and we are conducting qualitative work with nurses and other health care workers, to explore feasibility and acceptability of implementing nurse testing in clinical settings. Using these assays to provide same-day, point-of-care results is crucial to achieving the reported benefits of expedited clinical decision-making, and reduced clinic visits and patient travel costs.[39]

CONCLUSIONS

The diagnostic accuracy of the Xpert HIV-1 VL XC, Xpert HIV-1 VL and m-PIMA HIV-1/2 VL assays was clinically acceptable when testing was conducted in these South African clinics. The Xpert assays have the added benefit of accurately detecting low-level viraemia. However, further clinical studies are needed to determine whether these assays can be implemented in routine primary health care settings, and whether there are operational and clinical benefits to patients and providers when used at the clinical point-of-care.

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14. CHAPTER 4 APPENDIX

14.1. Published manuscript

The following pages contain the published manuscript on which Chapter 4 was based.

Dorward J, Sookrajh Y, Ngobese H, et al. Protocol for a randomised feasibility study of Point-Of-care HIV viral load testing to Enhance Re-suppression in South Africa: the POwER study. *BMJ Open* 2021;11:e045373.

BMJ Open

Protocol for a randomised feasibility study of Point-Of-care HIV viral load testing to Enhance Re-suppression in South Africa: the POwER study

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ABSTRACT

Introduction Access to HIV viral load testing remains difficult for many people on antiretroviral therapy (ART) in low-income and middle-income countries. Weak laboratory and clinic systems often delay the detection and management of viraemia, which can lead to morbidity, drug resistance and HIV transmission. Point-of-care testing could overcome these challenges. We aim to assess whether it is feasible to conduct a randomised trial of point-of-care viral load testing to manage viraemia.

Methods and analysis We will conduct an open-label, single-site, individually randomised, feasibility study of Point-Of-care HIV viral load testing to Enhance Re-suppression, in Durban, South Africa. We will enrol approximately 100 people living with HIV who are aged ≥18 years, receiving first-line ART but with recent viraemia ≥1000 copies/mL, and randomise them 1:1 to receive point-of-care viral load or standard laboratory viral load monitoring, after 12 weeks. All participants will continue to receive care from public sector healthcare workers following South African HIV management guidelines. Participants with persistent viraemia ≥1000 copies/mL will be considered for switching to second-line ART. We will compare the proportion in each study arm who achieve the primary outcome of viral suppression <50 copies/mL at 24 weeks after enrolment. Additional outcomes include proportions retained in the study, proportions with HIV drug resistance, time to viral load results and time to switching to second-line ART. We will assess implementation of point-of-care viral load testing using process evaluation data, and through interviews and focus groups with healthcare workers.

Ethics and dissemination University of Oxford Tropical Research Ethics Committee and the Biomedical Research Ethics Committee of the University of KwaZulu-Natal have approved the study. We will present results to stakeholders, and through conferences and open-access, peer-reviewed journals.

Trial registration number PACTR202001785886049.

Strengths and limitations of this study

- The Point-Of-care HIV viral load testing to Enhance Re-suppression (POwER) study will provide new evidence to guide the development of interventions using point-of-care HIV viral load testing to improve the management of viraemia in low-income and middle-income countries.
- The study will be conducted in a public health facility and will inform the utility and ease of implementation of point-of-care viral load testing in a routine clinical setting.
- The study is limited by a moderate sample size and limited power to detect an effect of point-of-care viral load testing on viral resuppression.

INTRODUCTION

Initiating antiretroviral therapy (ART) to achieve viral load suppression among all people with HIV is crucial to achieve the Joint United Nations Programme on HIV/AIDS target of ending AIDS by 2030. However, poor adherence to ART and/or HIV drug resistance can lead to HIV viraemia, with associated increases in morbidity, mortality, onward HIV transmission and the development and spread of HIV drug resistance.[1] Viral load testing can identify viraemia and guide adherence counselling, and/or switching to second-line ART regimens if HIV drug resistance is suspected. However, in low-income and middle-income countries (LMICs), the majority of ART is provided in primary care, where there is limited laboratory viral load capacity, weak clinic systems to act on viral load results and a paucity of evidence-based interventions to improve adherence.[1–5] Poor adherence can be due to complex social and psychological issues (eg, gender-based violence, alcohol use, migrant labour and long distances to clinics).[6] Therefore, multiple visits for blood draws and result review confers an additional burden for these

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vulnerable populations. Laboratory viral load results are often not reviewed until the next routine clinic visit after several months, by which time adherence problems may have worsened.[1–4]

Point-of-care viral load testing could allow same-day adherence counselling and switching to second-line ART, and more efficient, person-centred care by reducing the burden of clinic visits for review of blood results; thereby leading to faster viral load resuppression. WHO has approved the Xpert HIV-1 VL (Cepheid, Sunnyvale, USA)[7] and the m-PIMA HIV-1/2 VL (Abbott, Chicago, USA)[8] as accurate, quantitative point-of-care HIV viral load assays for use in LMICs. However, these assays have not yet been rolled out for ART monitoring in LMICs, due to concerns around implementation, and with limited randomised trial evidence to support clinical effectiveness. To date there is only one, single-site, randomised trial that has evaluated the clinical effectiveness of these assays. This was the (Simplifying HIV Treatment and Monitoring) STREAM point-of-care viral load trial, conducted by our team, in which 390 adults stable on ART for 6 months were randomised to receive either usual care with laboratory viral load testing, or care by an enrolled nurse and point-of-care viral load testing.[9] After 12 months, people in the intervention arm were more likely to have been referred into a community ART delivery programme, and had 14% higher retention in care and viral suppression.[10] However, the combined intervention was provided by research staff, meaning we do not know if point-of-care viral load assays can be implemented effectively in public sector clinics in LMICs.[11] Furthermore, STREAM only enrolled clinically stable patients (5% had viraemia at enrolment), and so there is inadequate data on the effect of point-of-care viral load testing among people with viraemia who are a vulnerable, priority population.

OBJECTIVES

The overall aim of this feasibility study[12] is to provide exploratory estimates to guide the development of a future larger trial of point-of-care testing to manage HIV viraemia. Our specific objectives are to:

1. Broadly estimate the effect size of point-of-care viral load testing compared with standard laboratory viral load testing on viral resuppression <50 copies/mL after 24 weeks.
2. Determine the feasibility of recruiting, randomising and following up patients in a randomised trial of point-of-care viral load testing to manage HIV viraemia.
3. Assess the perceptions of staff and the practical changes in clinic systems that are required to implement point-of-care viral load testing for a subset of patients in a primary care clinic in South Africa.

METHODS AND ANALYSIS

Trial design

This will be a an open-label, single-site, individually randomised, feasibility study of point-of-care viral load testing for the management of HIV viraemia (figure 1). We aim to enrol approximately 100 adults receiving first-line ART and who have viraemia, and randomise them in a 1:1 ratio to receive point of care versus standard laboratory-based viral load testing. We will assess viral suppression after 24 weeks in each arm, and estimate recruitment, fidelity of the intervention and retention in care. We will also assess the implementation of point-of-care viral load testing using process evaluation data, in-depth interviews and focus group discussions.

Study setting

The study will take place at the Prince Cyril Zulu Clinic; a large public sector clinic run by the eThekwini Municipality Health Unit in central Durban, South Africa. The clinic manages approximately 11 000 people receiving ART and follows South African National Department of Health guidelines.[13] Since December 2019, South Africa has started replacing current non-nucleoside reverse transcriptase inhibitors (NNRTIs), with the new drug dolutegravir for first-line ART.[14 15] Dolutegravir is an integrase strand transfer inhibitor that, in high-income settings, has been found to have better tolerability, efficacy and durability than regimens based on NNRTIs such as efavirenz.[14 16] Current first-line ART regimens at Prince Cyril Zulu Clinic are therefore tenofovir disoproxil fumarate, emtricitabine and efavirenz, or tenofovir disoproxil fumarate, lamivudine and dolutegravir.[13 14] Viral load

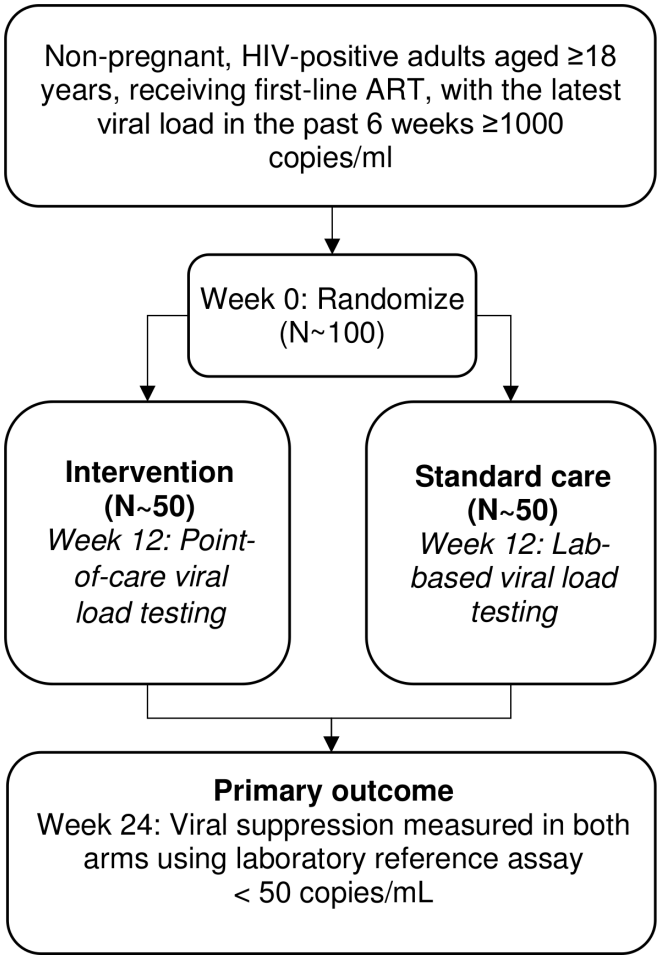


Figure 1 Consort diagram of the POwER study. ART, antiretroviral therapy.

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testing is performed at six and twelve months after ART initiation and annually thereafter. Similar to the WHO guidelines, patients with viraemia are given enhanced adherence counselling, with a repeat viral load within 3 months. If viraemia persists on NNRTI-based regimens, then HIV drug resistance is more likely, and so a switch to second-line ART should be considered.[13 17] For dolutegravir-based regimens, HIV drug resistance is less likely, and so a switch to second-line ART is only recommended if there are signs of clinical or immunological failure, or after 2 years of persistent viraemia.[13]

Eligibility criteria

Eligible patients will be HIV-positive adults aged ≥18 years, receiving first-line NNRTI-based or dolutegravir-based ART, with the latest viral load in the past 6 weeks ≥1000 copies/mL, and with no previous enhanced adherence counselling for this episode of viraemia. Pregnant women will not be eligible as they are routinely referred out of the Prince Cyril Zulu Clinic for antenatal care.

Study procedures

Recruitment

Potential participants will be identified by clinic staff using laboratory reports, electronic clinic information systems and clinic notes.

Informed consent, screening and enrolment

A research assistant or nurse will describe the study to potential participants, address any questions and seek written informed consent for participation. A research nurse will then assess eligibility using the patient's demographics, and a brief medical history and examination, including pregnancy testing for all women.

Randomisation and blinding

A statistician will generate the allocation sequence using random numbers generated in SAS V.9.4 (SAS Institute). We will stratify randomisation by first-line ART regimen at enrolment (NNRTI-based or dolutegravir based). The allocation sequence will contain variable block sizes, with participants randomised in a 1:1 ratio to the intervention or standard of care arm. All study staff apart from the statistician and data manager will be blinded to the allocation sequence. The allocation sequence will be programmed into the REDCap V.8.7.1 (Vanderbilt University, Nashville, USA)[18] enrolment electronic case report form (eCRF). At enrolment, the research assistant or research nurse will complete the enrolment eCRF, which will automatically assign the intervention allocation. As this is an open label study, study staff, clinic staff and participants will not be blinded to intervention allocation.

Baseline assessments

At enrolment, a nurse will administer a baseline sociodemographic questionnaire, and take a clinical history and examination, including an ART history. Throughout the study, South African Department of Health guidelines for managing viraemia will be used.[13] This includes enhanced adherence counselling, which will be performed by clinic staff with participants in both arms using the pre-enrolment viral load result. Techniques used during the counselling include ART education, evaluation of social support, mental health screening and the use of treatment supporters where appropriate.[19] A nurse will also draw blood for routine tests for investigation of viraemia, which currently include CD4 count testing, hepatitis B surface antigen, creatinine and haemoglobin (table 1).[13]

Follow-Up

Participants in both arms will have routine clinic visits scheduled at the healthcare worker and participant's discretion, which is typically every 28 days to coincide with ART collection. At these visits, clinic staff will provide ongoing enhanced adherence guidelines, clinical support and ART when necessary. South African guidelines recommend a repeat viral load 3 months after the first high result ≥1000 copies/mL. As this study is taking place within a routine care setting, we anticipate that not all participants will attend within the 3-month visit window. In these cases, we will allow repeat viral load to be done at another time, at the attending clinician's discretion.

Viral load testing interventions

For participants in the point-of-care arm, the repeat viral load test will be performed by a nurse, phlebotomist or laboratory technician in the clinic, using a WHO approved, fully automated point-of-care viral load assay (such as the Xpert HIV-1 VL). Assay run times are ≤90 min. Clinic staff will be encouraged to provide results in the same clinic visit to inform ongoing management. If the participant cannot wait, or results are not available in the same visit, they will be available at the next clinic visit scheduled at staff and participant's discretion.

In the standard of care arm, samples for viral load testing will be transported on the same day to the National Health Laboratory Service (NHLS) for testing using their routine laboratory assays (eg, Alinity m HIV-1 assay (Abbott, Chicago, USA)). Results are normally available after 7 days and will be provided to the participant at the next clinic visit, arranged at the participants and healthcare worker's discretion (typically after 7–28 days for results, depending on the participant's availability, ART supply and clinic schedules).

Management of viral load results at routine follow-up clinic visits

Viral load results will be managed by clinic staff in accordance with South African guidelines, which include guidance for management of both efavirenz and dolutegravir-based regimens, and do not advise routine HIV drug resistance testing.[20] Participants with a viral load ≥1000 copies/mL may meet criteria for viral failure (two consecutive viral loads ≥1000 copies/mL over 3 months apart) and will be considered for a switch to second-line ART. Switching to second-line ART and the choice of regimen will be at the clinician's discretion and will depend on the participant's first-line ART regimen, previous ART history, participant's preferences, perceived

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Table 1 Schedule of evaluation in the POwER study

	Enrol	Routine clinic visit follow-up*					Study exit
Weeks in study	0	4	8	12	16	20	24†
Informed consent	X						
Locator information	X						
Demographics	X						
Medical history	X						
Vital signs	X	X	X	X	X	X	X
Physical examination	X						
Urine pregnancy test	X						
Eligibility screen	X						
Enhanced adherence counselling	X	X	X	X	X‡	X‡	X‡
Randomisation	X						
Routine Department of Health testing§	X						
POC viral load (intervention arm)				X¶			
Laboratory viral load (standard of care arm)				X¶			
Reference viral load outcome measure							X
Evaluation of new POC assays**	X			X			X
Stored blood and HIV drug resistance testing††	X			X			X
Stored urine for ART drug level testing	X						

*Scheduled at participants and healthcare worker's discretion but typically every 28 days.
†Study exit visit window 22–30 weeks.
‡Ongoing enhanced adherence counselling for participants with viral load ≥50 copies/mL.
§CD4 count testing, hepatitis B surface antigen, creatinine and haemoglobin.
¶Repeat viral load testing recommended at 12 weeks but may be done any time during follow-up at the attending clinician's discretion.
**Maximum of 8 mL venous blood and/or a finger-prick capillary blood sample.
††Retrospective drug resistance testing for viraemic participants at enrolment, follow-up or study exit (10 mL EDTA).
ART, antiretroviral therapy; POC, point-of-care; POwER, Point-Of-care HIV viral load testing to Enhance Re-suppression.

adherence and current guidelines.[20] Participants with a second viral load <1000 copies/mL will remain on first-line ART. In accordance with guidelines for the transition to dolutegravir, those receiving an NNRTI may have this switched to a dolutegravir-based first-line regimen.[13]

Data capture during routine clinic visits

Research staff will monitor participants' clinical records to capture visit dates, whether enhanced adherence counselling was conducted by a counsellor, nurse or doctor, medication prescriptions including ART and laboratory results.

Study exit visit

The study exit visit will occur at 24 weeks (visit window 22–30 weeks), after which participants will continue receiving standard care at the Prince Cyril Zulu Clinic. At 24 weeks, any participant who has not attended the study exit visit will be called by the research team and asked to attend, irrespective of whether they have a routine clinic visit scheduled in the exit visit window.

Participant reimbursement

We will reimburse study participants ZAR150 (approximately £8.00) after the enrolment visit and ZAR100 (£5.50) after the 24-week visit, to cover any additional time spent at the clinic and any inconvenience due to study participation.[21]

Extended follow-up of routine data

For participants who provide additional consent, research staff may access routine medical records for up to 5 years after the study exit visit, in order to determine longer term retention in care, ART adherence and viral load results. For participants who are lost to follow-up, and who provided consent at enrolment, the participants mortality status may be checked on the South African National Population Register.

Additional laboratory specimens

Participants who provide additional consent will also have 10 mL of venous blood taken for storage and retrospective ART drug level and HIV drug resistance testing. Plasma will be stored at enrolment, during follow-up alongside the repeat viral load test, and at study exit. In addition, at enrolment, 5 mL of urine will be taken for storage and ART drug-level testing. We may use study samples to validate new point-of-care viral load, HIV drug resistance or

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Table 2 Study objectives and outcomes in the power study

Objectives	Outcome measures	Time point(s) of evaluation of this outcome measure (if applicable)
Primary objective To estimate the effect of implementing point-of-care viral load testing versus standard laboratory viral load testing on the proportion of HIV positive participants with viraemia who subsequently achieve viral resuppression	The proportion of participants in each arm with viral load <50 copies/mL measured on laboratory reference assay	24 weeks after enrolment
Secondary objectives To assess whether it is feasible to perform a randomised implementation trial of point-of-care viral load testing to manage viraemia in a routine South African clinic, by determining:		
(A) What proportion of people with HIV viraemia is feasible to enrol?	(A) Proportion of patients with viraemia at the study clinic who are successfully enrolled in the study	(A) During study enrolment period
(B) What proportion of those enrolled is feasible to follow-up?	(B) Proportion of enrolled participants who attend the study exit visit overall and in each arm	(B) 24 weeks after enrolment
(C) What proportion of point-of-care viral load results are received and acted on in the same day?	(C1) The proportion of point-of-care viral load tests that are communicated to participants on the same day and (C2) The proportion of point-of-care viral load tests ≥1000 copies/mL that result in same day enhanced adherence counselling and (C3) The proportion of point-of-care viral load tests ≥1000 copies/mL that result in same day switch to second-line ART	(C) 12 weeks after enrolment when point-of-care testing is performed
Tertiary Objectives To estimate the effect of point-of-care viral load testing versus standard laboratory viral load testing on:		
(A) Time to detection of viral failure (consecutive viral loads ≥1000 copies/mL) in each arm	(A) Days from enrolment to availability of viral load result ≥1000 copies/mL	(A) By 24 weeks after enrolment
(B) Time to switch to second-line ART in each arm	(B) Days from enrolment to appropriate switching to second-line ART, among participants with viral failure	(B2) By 24 weeks after enrolment
(C) Appropriate switching to dolutegravir in each arm	(C) Time to appropriate switching to dolutegravir in each arm	(C3) By 24 weeks after enrolment
(D) HIV drug resistance in each arm	(D) The proportion of participants in each arm with HIV drug resistance	(D4) 24 weeks after enrolment
Qualitative study objectives: What changes in clinic systems are required and what are the views and experiences of staff in implementing point-of-care viral load testing to manage viraemia?	Staff perspectives regarding implementation of point-of-care viral load testing in a routine clinic	During enrolment when point-of-care testing is being implemented, and after study conclusion

ART, antiretroviral therapy.

ART drug level assays. These results would not be used to guide clinical management.

Study outcomes

We aim to broadly estimate the effect of point-of-care viral load testing using the primary outcome of viral suppression <50 copies/mL at 24 weeks after enrolment, measured on a laboratory reference assay (eg, Alinity m HIV-1) in both arms. Feasibility outcomes include proportions of participants enrolled, followed up and who had same-day viral load testing in the point-of-care arm (table 2).

Data collection and management

The research team will capture study data using standardised electronic CRFs in REDCap, which is a password protected data management service stored on a secure server.[18] All data entry will undergo three stages of quality control including preprogrammed data validity checks in electronic CRFs, immediate source document review

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and weekly quality reports generated using REDCap. To protect confidentiality, all study-specific documents, other than the signed consent, will refer to the participant using their study participant number rather than their name. All documents will be stored in a secure cabinet in the locked research office and will only be accessible by study staff and authorised personnel.

Statistical methods

At the conclusion of the study, we will assess the proportion of participants achieving study outcomes in each arm, with 95% CIs calculated using the Wilson method. We will conduct exploratory analyses using Fisher's exact test to compare the proportions achieving binary study outcome measures in each arm, using an intention to treat analysis. As this is a feasibility study, these exploratory analyses will likely not be powered to test the hypotheses that there is a difference between the two arms for most outcome measures.

Primary outcome

We will calculate the proportion of participants in each arm achieving the binary primary outcome of viral suppression <50 copies/mL at 24 weeks (table 2). Participants who are lost to follow-up with no viral load result will be included in the analysis as not having achieved the primary outcome.

Secondary outcomes

We will calculate the proportion of potentially eligible patients with viraemia at the Prince Cyril Zulu clinic who are enrolled in the study (table 3). The denominator will be the number of patients with viraemia during the study enrolment period, which will be calculated by clinic staff using NHLS high viral load reports. These reports are routinely used for monitoring and evaluation of clinic performance and include the number of first high viral loads ≥1000 copies/mL taken from the Prince Cyril Zulu Clinic each week. To assess study follow-up, we will calculate the proportion of participants who attend the study exit visit at 24 weeks after enrolment, overall and in each arm in case point-of-care testing influences retention. To assess implementation of point-of-care viral load testing, we will calculate the proportion of point-of-care viral load tests which are provided to participants on the same day, the proportion of viral loads ≥1000 copies/mL which resulted in same day enhanced adherence counselling, and the proportion of viral loads ≥1000 copies/mL resulting in appropriate same-day switch to second-line ART.

Tertiary outcomes

In each arm, we will assess the median number of days (and IQR) from enrolment to detection of viral failure, and from enrolment to appropriate switch to second-line ART (among participants with viral failure), and from enrolment to appropriate switching to dolutegravir (among participants on an NNRTI-based regimen). We will compare time to event outcomes using Cox proportional hazards. We will also calculate the proportion of participants with HIV drug resistance detected at 24 weeks after enrolment.

Sample size considerations

We conservatively estimate (based on our previous study)[9 10] that we could enrol approximately 100 participants in 6 months. If enrolment proceeds better than anticipated, and resources allow us to enrol more, this will provide more precise estimates of the study outcomes. If enrolment proceeds slower than expected, we will consider expanding to another clinic site to achieve a minimum of 80 participants. Therefore, while we anticipate 100 participants, the final number may be between approximately 80–180 participants, and will be determined by the time and resources available. We will use NHLS, Prince Cyril Zulu Clinic and study data to assess outcomes, with estimated precision, in table 3. Although not the primary aim of this feasibility study, assuming 50% of standard care participants achieve the main outcome of viral load suppression <50 copies/mL at 24 weeks, a sample size of 100 participants (50 per study arm) would provide 91% power to detect a +30% difference in the point-of-care testing arm, using a two-sided alpha of 0.05.

Quality assurance procedures

Study documentation will be subject to internal quality audits by the Centre for the AIDS Programme of Research in South Africa (CAPRISA) Quality Assurance team, in accordance with CAPRISA standard operating procedures.

Table 3 Study and process evaluation outcomes with precision estimates

Outcome	Estimated n/N, %	95% CI (Wilson)
Percentage with viral load <50 copies/mL at 24 weeks in POC arm	35/50, 70.0	56.2 to 80.9
Percentage with viral load <50 copies/mL at 24 weeks in SOC arm	25/50, 50.0	36.6 to 63.4
Percentage of viraemic patients successfully enrolled in study	100/240*, 41.7	35.6 to 48.0
Percentage of those enrolled who are retained at 24 weeks	90/100, 90.0	82.6 to 94.5
Percentage in POC arm with same-day viral load testing	40/50, 79.5	70.0 to 88.8

*Assuming 240 viraemic patients during enrolment period, many of whom will not be eligible due to being on second-line ART, having had previous high viral loads, already having received enhanced adherence counselling or pregnancy.
ART, antiretroviral therapy; POC, point-of-care; SOC, standard-of-care.

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Qualitative substudy

We will undertake a qualitative substudy within Point-Of-care HIV viral load testing to Enhance Re-suppression (POwER) to assess what changes in clinic systems are required and what the views of staff are in implementing point-of-care viral load testing, its potential impact on adherence and adherence counselling and managing viraemia. We will conduct semistructured interviews and a focus group discussion with approximately 8–10 staff during, and then again after, implementation of point-of-care viral load testing in the study. Staff will include counsellors, phlebotomists, nurses, pharmacy staff, laboratory staff, doctors and health service managers. Topic guides will be informed by normalisation process theory which aims to identify what is needed to 'normalise' use of a technology in a healthcare system.[22 23] Discussions will be transcribed and thematically analysed using NVIVO software (QSR International, Melbourne, Australia).

Patient and public involvement

Patients were not involved in the design of this study.

Ethics and dissemination

We will conduct the trial in accordance with the principles of the Declaration of Helsinki. The eThekwini Municipality Health Unit Research Committee, the KwaZulu-Natal Provincial Health Research Ethics Committee (KZ_202002_005), the University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC/00000836/2019) and the University of Oxford Tropical Research Ethics Committee (OxTREC 66–19) have approved the study. We will present study results to front-line clinical workers and programme managers in eThekwini Municipality and KwaZulu-Natal Provincial Department of Health. We will also submit our findings to academic conferences and open-access, peer-reviewed journals.

DISCUSSION

Evidence-based interventions to improve the management of viraemia are needed to achieve global HIV treatment targets, prevent the development and spread of HIV drug resistance, and improve patient outcomes. In this paper, we outline a feasibility trial of point-of-care viral load testing among people with viraemia who are receiving first-line ART in South Africa. Results from this study will inform the design of future trials to assess the clinical effectiveness of point-of-care testing to manage viraemia.

Problems with management of viraemia

Several studies highlight gaps in the management of viraemia in LMICs, and the resulting negative impacts on treatment outcomes. First, addressing potential poor adherence, which may have caused viraemia, is challenging. A meta-analysis of interventions to improve adherence did not find any strategies that resulted in better viral suppression in LMICs,[24] while a more recent cluster randomised trial of the South African National Adherence Guidelines found no difference in long-term viral resuppression among patients with viraemia.[5] Second, follow-up viral load testing is often poorly performed. In the South African trial, less than 20% of patients had a repeat viral load within the recommended 3 months to confirm viral failure.[5] Similar delays have been reported in a large analysis of South African laboratory data; among 260 323 patients with viraemia, the median time to a repeat viral load was 6.2 months, (IQR 4.0–11.1)[25]. Third, among people with confirmed viral failure, a systematic review,[26] and more recent individual studies,[4 27–29] have found that only 30%–60% are switched to second-line ART. Even among patients who are switched, this can take a further 3–12 months,[27–29] with delays of even a few months being associated with increased risk of opportunistic infections and mortality, particularly among people with low CD4 counts.[1 4 27–29] Taken together, these data highlight the need for interventions to reduce delays and improve the management of viraemia.

Existing research regarding clinical effectiveness of point-of-care viral load testing

We conducted the STREAM trial, which was the first randomised trial of point-of-care HIV viral load testing for monitoring ART.[9 10] Overall, the STREAM intervention improved retention in care and viral suppression by 14.3% compared with the standard-of-care laboratory viral load arm. However, STREAM was designed to enrol stable patients; less than 5% of participants had viraemia at enrolment, and only 16 participants developed viral failure (seven in the point-of-care arm, nine in the standard care arm). Time to detection of viral failure was faster in the intervention arm (55 days (IQR 55–57) vs 123 days (IQR 98–162)) but numbers with viraemia were too small to determine whether point-of-care testing was effective at improving switching to second line ART, or subsequent viral load outcomes. In STREAM, the research team provided point-of-care testing and clinical care, so the observed benefits may also not be applicable to routine public sector settings.

Several more trials of point-of-care viral load testing are in progress, but none focus on management of viraemia. Studies in Zimbabwe,[30 31] Kenya[32] and Haiti,[33] are assessing point-of-care viral load for monitoring ART among pregnant women, children and/or adolescents. A study in Nigeria is enrolling adults at ART initiation and will report on the effect of point-of-care viral load testing after 12 months,[34] while a trial in South Africa[35] is enrolling adults on ART who are due for their annual viral load test. One trial in Uganda is assessing a viral load intervention package that includes 'near point-of-care testing' (at the clinic or a nearby clinic and therefore results may not be

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provided on the same day), and is enrolling 'high-risk groups' including patients with previous viraemia or no viral load in the past year.[36]

Implementation of point-of-care viral load testing

Point-of-care diagnostics have been used widely in healthcare systems in many LMICs.[37] In HIV programmes, some tests such as rapid, lateral flow assays for diagnosis of HIV, have been evaluated, endorsed and incorporated into WHO guidelines and successfully adopted in many settings.[38] However, other assays, such as more complex molecular PCR technologies for tuberculosis, have remained as laboratory tests despite being marketed as point-of-care assays.[37] Given that the Xpert HIV-1 VL and m-PIMA assays use similar platforms and take over 1 hour for results to be available, they have also been criticised as not being implementable as true point-of-care tests. A large systematic review of barriers to point-of-care HIV diagnostic implementation in LMICs found that in 132 studies, integration of the point-of-care test into clinical work flows was the most commonly identified challenge to test utilisation.[39] More recently, studies have reported implementation of qualitative point-of-care viral load assays for early infant diagnosis of HIV,[40] and monitoring of ART in maternity wards in South Africa,[41] and decentralised ART clinics in Malawi.[42] While these studies have reported quantitative outcomes related to point-of-care viral load use, there is little qualitative work using theory-based approaches to evaluate what is required for successful implementation.

Strengths and limitations

A major strength of this study is the focus on patients with viraemia, who are a priority population at high risk of increased morbidity and mortality, onwards HIV transmission and development of HIV drug resistance.[1] Interventions to improve viral suppression among this group have been prioritised by the WHO and align with several objectives in the Global Action Plan on HIV drug resistance.[43] While our study may be underpowered to detect a significant effect of point-of-care viral load testing on viral resuppression, we will determine the feasibility of conducting larger studies to answer this question in this setting. Our use of normalisation process theory will allow a rigorous assessment of what is needed to 'normalise' point-of-care testing in the South African healthcare system.

A limitation of this study is the focus on 'supply-side' implementation of point-of-care viral load testing. Receiving results on the same day could also increase patient understanding and motivate adherence, but evaluating this from the patient perspective is beyond the scope of the study. Furthermore, findings from this large urban, clinic may not be applicable to other settings, including smaller clinics in rural settings where advantages of point-of-care testing over laboratory-based testing may differ. Our future trial may be best designed as a cluster randomised trial, with individual clinics randomised to receive the point-of-care testing intervention. While POwER is an individually randomised study, estimates of the effect of point-of-care testing will remain valuable for design of potential cluster randomised or individually randomised future studies.

Coinciding with the rollout of dolutegravir is both a strength and a weakness of our study. We will enrol patients on either NNRTI- or dolutegravir-based ART, therefore, allowing estimates of the effect of point-of-care testing in either group. For patients enrolled on NNRTIs, this also presents an opportunity to assess whether point-of-care viral load testing can assist the transition to dolutegravir-based regimens. For patients enrolled on dolutegravir, a potential limitation is that point-of-care viral load testing will not be used to expedite a switch to second line, although it may still improve enhanced adherence counselling and allow more efficient care that can help ensure retention and virological suppression. Lastly, we will be able to assess early viral suppression outcomes and the frequency of HIV drug resistance among people with viraemia on dolutegravir. This is a pressing research question for global policy makers, because it determines the need for HIV drug-resistance testing and second-line ART after introduction of a dolutegravir-based first-line in LMICs.

In summary, we aim to provide evidence as to whether a trial of point-of-care viral load testing to manage viraemia is feasible, and how testing may be implemented in South African clinics. This work will contribute to the development of interventions to improve the management of viraemia among people receiving ART, thereby improving health and leading to longer and better lives, as well as reducing the spread of HIV and preventing drug resistance.

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15. CHAPTER 6 APPENDIX

Table 15.1 HIV drug resistance mutations among POwER participant who were viraemic at enrolment*

PID	Enrolment regimen	Enrolment VL (log_{10} cps/mL)	NRTI mutations	NNRTI mutations	Second-line regimen
1	TDF / FTC / EFV	3.55	None	V108I	TDF / 3TC / DTG
2	TDF / FTC / EFV	3.41	None	None	Not switched
3	TDF / FTC / EFV	5.11	A62V,K65R,M184V	L100I,K103N,Y188L	AZT / 3TC / DTG
4	TDF / FTC / EFV	3.16	K219E	None	AZT / 3TC / DTG
5	TDF / FTC / EFV	4.13	D67N,K70E,M184V	K101E,V106M,G190A,F227L	AZT / 3TC / DTG
6	TDF / FTC / EFV	5.06	D67N,M184V,K219R	A98G,K103N,P225H	AZT / 3TC / DTG
7	TDF / FTC / EFV	3.80	K65R,D67G	V106M,G190A	AZT / 3TC / DTG
8	TDF / FTC / EFV	4.04	M184V	K101P,K103N	AZT / 3TC / DTG
9	TDF / FTC / EFV	3.81	K70R,M184V,K219Q	K103N,P225H,K238T	AZT / 3TC / LPVr
10	TDF / FTC / EFV	3.94	D67N,K70E,L74I,M184V	K103N,V106M,V179T	AZT / 3TC / DTG
11	TDF / FTC / EFV	4.77	K65R,D67N,M184I	A98G,K103N,L234I	AZT / 3TC / DTG
12	TDF / FTC / EFV	4.97	L74I,M184V	K103N,G190S	TDF / AZT / 3TC / DTG
13	TDF / FTC / EFV	5.45	K70E,L74I,M184V,K219R	A98G,K103N,P225H,F227L	TDF / AZT / 3TC / DTG
14	TDF / FTC / EFV	3.08	K219R	K103N	TDF / 3TC / DTG
15	TDF / FTC / EFV	3.71	A62V,K65R,K70Q,M184V	K101P,Y181C,G190A	AZT / 3TC / DTG
16	TDF / FTC / EFV	5.55	T69D,M184V	V179D,Y188L	AZT / 3TC / DTG
17	TDF / FTC / EFV	3.15	D67N,M184V,K219R	K103N,V108I	Not switched
18	TDF / FTC / EFV	3.80	D67T,K70R,M184V,T215V,K219E	A98G,K103N,V108I,P225H	TDF / AZT / 3TC / DTG
19	TDF / FTC / EFV	4.35	K65R	V106M,V179D	AZT / 3TC / DTG
20	TDF / FTC / EFV	4.37	None	None	Not switched
21	TDF / FTC / EFV	4.28	A62V,K65R,K70T,M184V	V106M,V179D,Y181C,H221Y,F227I	AZT / 3TC / DTG
22	TDF / FTC / EFV	3.07	None	K103N,V106M,G190A	AZT / 3TC / DTG
23	TDF / FTC / EFV	3.34	D67N,M184V,K219E	K103N,V108I	AZT / 3TC / DTG
24	TDF / FTC / EFV	5.43	None	V106M	Not switched
25	TDF / FTC / EFV	4.34	None	None	TDF / 3TC / DTG
26	TDF / FTC / EFV	3.13	K70R,M184V,K219Q	K103N,P225H,K238T	Not switched
27	TDF / FTC / EFV	3.78	K70Q,L74I,M184V	K103S,V106M	AZT / 3TC / DTG
28	TDF / FTC / EFV	4.30	None	K103N	AZT / 3TC / DTG
29	TDF / 3TC / DTG	5.25	HIVDR testing unsuccessful	HIVDR testing unsuccessful	Not switched

PID	Enrolment regimen	Enrolment VL (log_{10} cps/mL)	NRTI mutations	NNRTI mutations	Second-line regimen
30	TDF / 3TC / DTG	4.27	None	K103N	Not switched
31	TDF / 3TC / DTG	3.34	None	None	Not switched
32	TDF / 3TC / DTG	3.60	M184V	K103N,V106M	Not switched
33	TDF / 3TC / DTG	4.13	None	None	Not switched
34	TDF / 3TC / DTG	4.26	HIVDR testing unsuccessful	HIVDR testing unsuccessful	Not switched
35	TDF / 3TC / DTG	3.69	None	None	Not switched
36	TDF / 3TC / DTG	3.47	None	Y188L	Not switched
37	TDF / 3TC / DTG	5.52	None	None	Not switched
38	TDF / 3TC / DTG	5.47	None	None	Not switched
39	TDF / 3TC / DTG	4.07	None	None	Not switched
40	TDF / 3TC / DTG	4.17	None	K103N,E138A	Not switched
41	TDF / 3TC / DTG	3.51	None	Y188L	Not switched
42	TDF / 3TC / DTG	5.33	None	A98G	Not switched
43	TDF / 3TC / DTG	4.55	None	A98G	Not switched
44	TDF / 3TC / DTG	3.56	None	V106M,Y188C	Not switched
45	ABC / 3TC / DTG	4.98	L74I,M184V	K103N,G190S	Not switched

**There were no INSTI mutations detected in this cohort*

16. CHAPTER 8 APPENDIX

16.1. Definition of first-line dolutegravir based-ART in transition cohort

Dolutegravir can be used in both first and second-line ART regimens. The standard second-line regimens in South Africa are zidovudine, lamivudine, dolutegravir, and prior to this, zidovudine, lamivudine, lopinavir/ritonavir. Therefore, in the transition cohort we classified all people changed to these regimens as being on second-line ART. The only exception was for people who were previously receiving zidovudine, lamivudine, efavirenz/nevirapine as part of their first-line regimen, and who were changed to zidovudine, lamivudine, dolutegravir; we defined this as transition to a first-line dolutegravir regimen. We also censored anyone with a viral load ≥1000 copies/mL, as they would not have been eligible for dolutegravir in a first-line regimen until they re-suppressed, and may have been put on tenofovir, lamivudine, dolutegravir as part of a second-line regimen, as is advised by some clinicians.

16.2. Emulated target trial methods

We emulated a 'target trial' within the transition cohort[169] (Table 16.1). We fitted a Cox proportional hazards model, to estimate the log hazard of transition to dolutegravir during follow-up,[170,171] which we then used as a time dependent propensity score. The model adjusted for gender, age, time on ART, facility, and most recent CD4 count, with interaction terms between gender and time, and gender and age. Tuberculosis, pregnancy, viral load and time in a differentiated ART program (CCMDD) were included as time dependent covariates. We included participation in a differentiated ART delivery programme[57,89] as a time dependent co-variate, as we hypothesised that people who receive ART in the differentiated ART delivery programme may have been less likely to be transitioned to dolutegravir, as clinicians may have worried about less clinical oversight. We included viral load as a time dependent co-variate as people with low-level

viraemia may have been less likely to be transitioned to dolutegravir. Individuals were censored at loss-to-follow-up, death, transfer out or if they had a viral load ≥1000 copies/mL (as they would not have been eligible at that time for transition to first-line dolutegravir). We matched people transitioned to dolutegravir with a corresponding control who had a clinic visit in the same week, but was not transitioned to dolutegravir,. We used a calliper width of 0·2 times the standard deviation of the log hazard and nearest neighbour matching, and also matched directly on time since most recent viral load, and whether the participant was in a differentiated ART delivery programme. Individuals could only be matched once, and we only matched participants transitioned to dolutegravir before December 1st, 2020, to allow 12 months of follow-up time, plus 90 days to assess retention-in-care. This method allows definition of time zero in both the dolutegravir cohort (i.e. date of transition to dolutegravir) and their matched controls who were not transitioned to dolutegravir in the same week. Among the matched cohort, we then used multivariable Poisson regression models with robust standard errors to compare the outcomes of 12-month retention and viral suppression between the dolutegravir group and matched controls. We adjusted for gender, age, time on ART, baseline time period, most recent CD4 count, baseline viral load, and community ART delivery programme (CCMDD) use at baseline. We did not use methods that consider the data to be paired for the final analysis of outcomes.[229]

16.3. Supplementary Tables

Table 16.1 Specifications of emulated target trial

Emulated Protocol Component	Description
Eligibility criteria	Adults >15 with HIV on first line, non-dolutegravir based antiretroviral therapy on 01 Dec 2019 at 59 clinics in eThekwini Municipality. Those with most recent viral load ≥1000 copies/mL were excluded.
Treatment strategies	Transitioned to dolutegravir based first line ART versus remain on non-dolutegravir based first-line ART
Assignment procedures	Matching 1:1 of people transitioned to dolutegravir before 01 Dec 2020, with controls selected if not transitioned to dolutegravir by the same week. Nearest neighbour matching with calliper width of 0.2 standard deviations of the log hazard, and additional matching by CCMDD use, clinic visit in same week, and time since previous viral load.
Follow-up period	Starts at baseline timepoint (week of matching) and ends at 15 months after baseline date (to allow assessment of 12-month outcomes, with an extra 90 days to assess retention)
Outcome	1. Retention in care at 12 months 2. Viral suppression < 50 copies/mL at 12 months
Causal contrasts of interest	Intention-to-treat effect, with sensitivity analysis assessing per-protocol effect (excluding people who changed from or to dolutegravir-based ART during follow-up)
Analysis plan	Multivariable Poisson regression model with robust standard errors to account for clustering by clinic.

CCMDD = Centralised Chronic Medicines Dispensing and Distribution programme

Table 16.2 'As treated' analysis using univariable and multivariable Poisson regression models of the association between initiation on dolutegravir and 12-month viral suppression, n = 10,097

Variable	Levels	Viral suppression	RR	P-value	aRR*	P-value
ART regimen	Non-DTG regimen	3187 (78·7)	1	<0·001	1	<0·001
	DTG regimen	5029 (83·2)	1·06 (1·03-1·09)		1·09 (1·05-1·12†	
Gender	Male	2998 (78·9)	1	<0·001	1	<0·001
	Female, not pregnant	4439 (83·0)	1·05 (1·04-1·07)		1·07 (1·05-1·09)	
	Female, pregnant	779 (82·4)	1·05 (1·01-1·08)		1·08 (1·04-1·13)	
Age (years)	55+	230 (82·4)	1	0·616	1	0·203
	45-54	799 (82·7)	1·00 (0·94-1·07)		1·01 (0·95-1·08)	
	35-44	2238 (80·8)	0·98 (0·93-1·04)		1·00 (0·94-1·06)	
	25-34	3654 (81·5)	0·99 (0·93-1·05)		0·99 (0·93-1·05)	
	15-24	1295 (81·0)	0·98 (0·93-1·04)		0·97 (0·91-1·03)	
Initiation time period	Dec 19 - Feb 20	2167 (78·1)	1	<0·001	1	<0·001
	Mar 20 - May 20	2172 (82·9)	1·06 (1·03-1·09)		1·04 (1·01-1·07)	
	Jun 20 - Aug 20	1988 (84·8)	1·09 (1·05-1·12)		1·04 (1·01-1·08)	
	Sep 20 - Nov 20	1889 (80·0)	1·02 (0·99-1·06)		0·98 (0·95-1·02)	
TB at ART initiation	No TB	7770 (81·7)	1	0·003	1	0·899
	Known TB	446 (76·1)	0·93 (0·89-0·98)		1·00 (0·95-1·04)	
Initiation CD4 count (cells/μL)	<200	1394 (72·7)	1	<0·001	1	<0·001
	200-349	1542 (80·0)	1·10 (1·06-1·14)		1·10 (1·06-1·14)	
	350-499	1320 (83·2)	1·14 (1·10-1·19)		1·14 (1·10-1·19)	
	>=500	2204 (87·9)	1·21 (1·17-1·24)		1·20 (1·17-1·24)	
	Missing	1756 (81·4)	1·12 (1·08-1·16)		1·11 (1·08-1·15)	

**The primary exposure effect (dolutegravir use) is adjusted for all other variables in the model as potential confounders. Unlike the primary exposure effect, the presented adjusted risk ratios for potential confounding variables should not be interpreted as causal. †Estimated risk difference 6.8%, 95% CI 4.3-9.4.*

Table 16.3 Rates of transition to dolutegravir by time period among people receiving non-dolutegravir based ART

Time period	Events	Time (person-years)	Event rate per 1000 person-years (95% CI)
Dec 19 - Feb 20	2361	44300	53.3 (51.2-55.5)
Mar 20 - May 20	19791	40254	491.6 (484.8-498.5)
Jun 20 - Aug 20	35094	31371	1118.6 (1107.0-1130.4)
Sep 20 - Nov 20	17977	22870	786.0 (774.6-797.6)
Dec 20 - Feb 21	6746	19534	345.3 (337.1-353.7)
Mar 21 - May 21	11820	16507	716.0 (703.2-729.0)
Jun 21 - Aug 21	10936	13150	831.6 (816.1-847.3)
Sep 21 - Nov 21	10009	10080	993.0 (973.6-1012.6)
Dec 21 - Feb 22	6440	7960	809.0 (789.4-829.0)

Table 16.4 Baseline characteristics of participants included in the emulated target trial, N = 92318

Variable	Levels	No DTG	DTG	Total
Gender	Male	17860 (38.7)	17626 (38.2)	35486 (38.4)
	Female	28299 (61.3)	28533 (61.8)	56832 (61.6)
Baseline age (cont.), years	Median (IQR)	39.0 (33.0 to 46.0)	40.0 (34.0 to 47.0)	39.0 (33.0 to 47.0)
Baseline age (cat.), years	55+	4250 (9.2)	4657 (10.1)	8907 (9.6)
	45-54	10378 (22.5)	10795 (23.4)	21173 (22.9)
	35-44	17518 (38.0)	17656 (38.3)	35174 (38.1)
	25-34	12093 (26.2)	11470 (24.8)	23563 (25.5)
	15-24	1920 (4.2)	1581 (3.4)	3501 (3.8)
Baseline time on ART, years	Median (IQR)	4.0 (1.9 to 6.6)	4.2 (2.3 to 6.7)	4.1 (2.1 to 6.7)
Most recent CD4 count (cont.), cells/μL	Median (IQR)	443.0 (290.0 to 627.0)	445.0 (292.0 to 627.0)	444.0 (291.0 to 627.0)
Most recent CD4 count (cat.), cells/μL	>=500	17397 (37.7)	17639 (38.2)	35036 (38.0)
	350-499	10505 (22.8)	10458 (22.7)	20963 (22.7)
	200-349	8951 (19.4)	9125 (19.8)	18076 (19.6)
	<200	5704 (12.4)	5512 (11.9)	11216 (12.1)
	Missing	3602 (7.8)	3425 (7.4)	7027 (7.6)
Baseline time period	Dec 19 - Feb 20	1439 (3.1)	1439 (3.1)	2878 (3.1)
	Mar 20 - May 20	13607 (29.5)	13607 (29.5)	27214 (29.5)
	Jun 20 - Aug 20	21503 (46.6)	21503 (46.6)	43006 (46.6)
	Sep 20 - Nov 20	9610 (20.8)	9610 (20.8)	19220 (20.8)
TB at baseline?	No	46063 (99.8)	46085 (99.8)	92148 (99.8)
	Yes	96 (0.2)	74 (0.2)	170 (0.2)
Pregnant at baseline?	No	46059 (99.8)	46042 (99.7)	92101 (99.8)
	Yes	100 (0.2)	117 (0.3)	217 (0.2)
Most recent viral load at baseline (copies/mL)	<50	42614 (92.3)	42782 (92.7)	85396 (92.5)
	50-199	1665 (3.6)	1651 (3.6)	3316 (3.6)
	200-399	505 (1.1)	423 (0.9)	928 (1.0)
	400-999	464 (1.0)	392 (0.8)	856 (0.9)
	Missing	911 (2.0)	911 (2.0)	1822 (2.0)
In CCMDD at baseline	No	32224 (69.8)	32224 (69.8)	64448 (69.8)

17. CHAPTER 9 APPENDIX

Table 17.1: Coding frame based on Framework of Theories of Practice

Code	Description	Quote
MATERIALITIES: Physical 'things' that impact on engagement in HIV services		
Characteristics of HIV services	The physical aspects of HIV services that determine access	
Waiting times	Descriptions of waiting times in HIV services	*"When you are coming to the clinic, you must cancel all the plans you have and tell yourself that you will spend the rest of the day there. Because chances are you will finish late in the afternoon."* Focus group 2, Participant 1 *"The clinic gets very full, you will wait there the whole day."* Focus group 3, Participant 3 *"I think collecting at [the private pharmacy] is quicker than here, when I came back here at the clinic I waited for a good two hours."* Focus group 1, Participant 7 *"They [patients] like CCMDD, [because] when they go to the pick-up points there's no queues like here in the clinic. They come in, they go straight to the pharmacies then they get their pack."* Staff interview 4
Numbers of patients	Descriptions of the number of patients receiving treatment	*"They [nurses] are always in a rush and there are a lot of us. Maybe we are more than 100 and there's a queue."* Focus group 1, Participant 4 Interviewer: *"Ok, so the first time you went to the hall [CCMDD community pick-up point], how was it?"* Participant: *"It was nice because there was not a lot of us, I would just take my ID out and then take my treatment and leave."* Focus group 2, Participant 2.

Code	Description	Quote
Staffing levels	Descriptions of staffing levels in HIV services	*"There is not enough staff [in the clinic], everyone is rushing to finish... Maybe only three nurses are working, and they are seeing all these people. You are also rushing and she is also rushing and you are thinking as a patient that you left a lot of people outside [waiting to be seen after you]. So adding more staff would help."* Client interview 3
Flexibility of HIV services	Descriptions of (in)flexibility of HIV services with regard opening hours and ability to change appointment days	*"Collecting on weekends would be a great idea, because you will not have an excuse especially if you are not working. Even at work they will have a problem if you have a specific day where you don't come to work or leave early [to collect ART]."* Focus group 2, Participant 1 *"Collecting… [in CCMDD] saves a lot of time, you don't spend 5 minutes. It doesn't get full, you can come anytime if it's still open. You just get in there take your medication and leave."* Focus group 3, Participant 5
Accessing other medical care apart from ART	Descriptions of how the ability to access other, non-ART related care influenced engagement with HIV services	*"It's quicker to just collect [ART] because you know how you are taking your treatment… When all these things [measuring vitals] are done you will be delayed."* Focus group 2, Participant 8 *"The problem with it [CCMDD] is that you only come to collect your medication and then leave, they don't do other things as well. Like checking your blood pressure and other things to know how your health is."* Client interview 5
Maintaining confidentiality	Descriptions of how the design of the service impacts on confidentiality	*"But at the nearby clinics, most of the nurses just display everything [ART] in front of everyone… there is no privacy in these clinics."* Focus group 1, Participant 8 *"When your neighbours see you sitting there they will start to ask you questions. Even when they don't know*

Code	Description	Quote
		why you are there, but they will know at the end why." Focus group 1, Participant 6
ART not being available in facility or pick-up point	Descriptions of attending services but ART not being available	*"Sometimes you find that there is no treatment [in the clinic] and people would be scheduled for another date when the treatment is available."* Client interview 21
Distance to HIV services	Descriptions of the distance and travel to HIV services affecting engagement in care	*"There are people who live far [from the clinic]… you find that they don't even have money for transport."* Client interview 6
Barriers to engagement with CCMDD	Descriptions of factors that stop people from being referred into CCMDD or continuing to collect there (see Table 9.3)	See Table 9.3 for specific quotes
Poverty	The dynamics of lacking financial and material resources (e.g. food, other medication to manage side effects) that would support engagement with HIV services.	*"Fetching medication is problematic. You find that you don't have money, you need to fetch your medication and you don't have it [money]."* Client interview 1
COMPETENCIES: Knowledge and skills that impact on engagement in HIV services		
Communication between healthcare workers and patients	The role of healthcare workers in communicating competencies and also clinical information about HIV and treatment to patients	*"Patient education… should be constant, it should be regular, regular talking with the patients, teaching patients how to live positively, considering things like the use of condoms, proper dieting and… the function of adherence."* Staff interview 4 Interviewer: *"When you ask the nurse about your results, what do they say?"* Participant: *"You even get afraid to ask, because they don't have time, they are always rushing to see the next person."* Focus group 3, Participant 4
Healthcare worker attitude	Descriptions of the importance of healthcare worker attitude in imparting these competencies towards patients	*"They [healthcare workers] must not judge us, they must do their job and what they were employed to do. Also, they need to learn to communicate, nurses can't*

Code	Description	Quote
		communicate with people. You make one small mistake [and] they shout at you and talk to you the way they like." Client interview 19
To manage stigma	Knowledge and skills needed to manage the (non)disclosure of one's HIV status to others, and to deal with stigma from others including partners, family members and the wider community.	*"I didn't want to go to the clinic by where I live because I was afraid of people's eyes. Because when you start this [ART] people look at you in different way."* Client interview 20
To negotiate problems with HIV services	Descriptions of strategies and skills that people have developed to mitigate problems with HIV services	*"You see, I make it a point that when it's my appointment date I wake up very early to get to the clinic… I will be here for the whole day… because there are a lot of people… You must wait that long and sometimes you get so tired and you wish you can just leave. What can we say? We must wait because it's our lives."* Client interview 12 *"If you don't have a day-off on that day you can send someone to collect the medication for you."* Client interview 1
Social support	The use of family and or the wider community as a source of knowledge to help maintain engagement with HIV services	"*[After starting ART] I did have a bad dream on the first day... But after that there were no problems. I asked other people, and they told me that they did have side-effects on the first day, you will have bad dreams and I didn't have a problem with that, it passed. Because when I asked other people they said, yes, it happens. But the ARVs are no longer the same as the previous ones, these ones are better because you only take one pill at night. Yes, I continued I took the medication."* Client interview 1.
Maintaining a healthy lifestyle	Knowledge and skills needed to maintain recommended lifestyle changes for people living with HIV	*"They were advising us that we shouldn't tell ourselves that we are going to die you see… that if you are person living with HIV you practice safe sex and not sleep around and try to eat healthy things in life. If you smoke*

Code	Description	Quote
		reduce a bit and [reduce] drinking. General things were being spoken that we need to deal with." Client interview 10
MEANINGS: The meanings that are attached to HIV and engagement with HIV services		
Stigma	Prejudice and discrimination experienced by people living with HIV. Can be internal ('self-stigma') or external (enacted by others) and both perceived or actual.	*"[if there is a separate queue for ART] it's easier to be discriminated against, because they know what you are here for, so it's better for a person not to know what you are queuing for."* Focus group 1, Participant 4 *"I wish they could make this disease [HIV] like flu, and not something scary. That is the reason why people don't even want to come close to you."* Focus group 1, Participant 7 *"My concern is the stigma we have as infected people, we get treated as people who don't live in this world. So, we try to hide ourselves."* Focus group 2, Participant 4.
Normalisation of HIV	The portrayal of HIV as a common and normal experience share with many others, that does not have to affect health if ART is taken.	Interviewer: *"When you found out [that you were HIV-positive] … how did you feel about that?"* Participant: *"I didn't feel like a different person, I didn't see any difference, I saw myself as a normal person who needs to take care of herself and take her medication properly so life can go on. I didn't feel any change and I wasn't sick at all."* Client interview 5
Meanings of CCMDD	Descriptions of the meaning associated with being referred to CCMDD including reasons for being referred	*"They transferred me to CCMDD because I was taking my treatment properly and I also know that I was taking my treatment well."* Focus group 2, Participant 7
Public and private treatment	The meanings associated with receiving government funded versus private care	*"Sometimes you wait for other [customers] to buy and they [private pharmacy staff] will serve the other people before you. Even if you are in the queue, it's like they are sifting us [public CCMDD clients] from the crowd."* Focus group 1, Participant 5

Code	Description	Quote
		"They [private pharmacy staff] were paying attention to the customers who were coming to buy. Because we don't come with money, we only come with our [CCMDD] cards and ID's [so] they were not paying attention to us." Client interview 8
Experience of HIV and treatment	Having had personal experience, or having witnessed in others, the effects of HIV and life-saving treatment. Having faith in treatment and HIV services in restoring health and life	*"As for me, even when I walk on the streets I feel healthy and confident because I know I am taking my medication properly."* Focus group 2, Participant 9
OTHER LIFE PRACTICES: Other repeated activities of daily life that clients engage in that impact on engagement in HIV services		
Employment	The duties and daily activities of employment and formal and informal work	*"I even go after work, I knock off at 4 and go there [CCMDD pick-up point] and take my medication. Even during my break time, I go, or when I am swamped I ask [my supervisor] and quickly rush there take my medication and come back… What I love [about CCMDD] is that I don't need to take a day off at work to collect medication at the clinic and wait for the whole day. Now at work I ask for that 20 minutes and go there [to CCMDD]. It's fine. I don't skip work, and there is no one that sees me."* Client interview 12 *"I think it [CCMDD] is good, because clinics get full. It's better because if you work you can quickly go there [the community pick-up point], collect and come back. I think it's a good method."* Client interview 4
Family life	Activities of daily life that revolve around family	*"Last time [I had to collect ART from the clinic] you know what happened? I had to send my wife. I'd got a part time job, so I couldn't manage to come. [So I asked her], 'Please just go with my card to collect my medication'. She doesn't want to come back here [to the clinic] ever again. Because of the time that she spent [waiting for treatment]."* Client interview 14

17.1. Published manuscript

The following pages contain the published manuscript on which Chapter 9 was based.

Dorward J, Msimango L, Gibbs A, *et al*. Understanding how community antiretroviral delivery influences engagement in HIV are: a qualitative assessment of the Centralised Chronic Medication Dispensing and Distribution programme in South Africa. *BMJ Open* 2020;10:e035412. doi:10.1136/bmjopen-2019-035412

BMJ Open

Understanding how community antiretroviral delivery influences engagement in HIV care: a qualitative assessment of the Centralised Chronic Medication Dispensing and Distribution programme in South Africa

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ABSTRACT

Introduction Providing antiretroviral therapy (ART) for millions of people living with HIV requires efficient, client-centred models of differentiated ART delivery. In South Africa, the Centralised Chronic Medication Dispensing and Distribution (CCMDD) programme allows over 1 million people to collect chronic medication, including ART, from community pick-up points. We aimed to explore how CCMDD influences engagement in HIV care.

Methods We performed in-depth interviews and focus group discussions with clients receiving ART and healthcare workers in Durban, South Africa. We analysed transcripts using deductive thematic analysis, with a framework informed by 'theories of practice', which highlights the *materialities*, *competencies*, *meanings* and *other life practices* that underpin clients' engagement in HIV care.

Results Between March 2018 to August 2018 we undertook 25 interviews and four focus groups with a total of 55 clients, and interviewed eight healthcare workers. The material challenges of standard clinic-based ART provision included long waiting times, poor confidentiality and restricted opening hours, which discouraged clients from engagement. In contrast, CCMDD allowed quicker and more convenient ART collection in the community. This required the development of new competencies around accessing care, and helped change the meanings associated with HIV, by normalising treatment collection. CCMDD was seen as a reward by clients for taking ART well, and helped reduce disruption to other life practices such as employment. At private pharmacies, some clients reported receiving inferior care compared with paying customers, and some worried about inadvertently revealing their HIV status. Clients and healthcare workers had to negotiate problems with CCMDD implementation, including some pharmacies reaching capacity or only allowing ART collection at restricted times.

Conclusions In South Africa, CCMDD overcame material barriers to attending clinics, changed the meanings associated with collecting ART and was less disruptive to other social practices in clients' lives. Expansion of community-based ART delivery programmes may help to facilitate engagement in HIV care.

Trial registration number STREAM study clinical trial registration: NCT03066128, registered February 2017.

Strengths and limitations of this study

- This is one of the first qualitative assessments of the Centralised Chronic Medication Dispensing and Distribution (CCMDD) programme, which provides chronic medication, including ART, to over 1 million people in South African communities.
- Our analysis is strengthened by the use of 'theories of practice', which highlights the different components of the social practice of engagement in HIV care, and how these interact and may be influenced by CCMDD.
- Participants in our study were part of a clinical trial at a large urban clinic, meaning our findings may not be generalisable to other settings, such as rural areas.
- Lastly, the CCMDD programme is adapting quickly, and some of the early implementation problems that we report may now have been resolved.

BACKGROUND

Expanding access to life-saving antiretroviral therapy (ART) for people with HIV has been one of the biggest global health successes of the 21st century. Since 2004, the number of people on ART globally has increased more than 10-fold to 23.3 million, while HIV related mortality has dropped from 1.7 million annual deaths to 0.8 million.[1] ART is now recommended for all people living with HIV, meaning that a further 14.6 million people

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still require treatment, mainly in low- and middle-income countries.[1] Therefore, ART programmes in these settings will need to continue expanding, while also providing treatment through efficient, convenient services that encourage life-long engagement in HIV care.

Several new models of 'differentiated ART delivery' have been developed, including providing ART through community adherence clubs (where clients meet in a community group to collect ART), delivering ART to decentralised pickup points and increasing the intervals between ART collection dates using multi-month prescribing.[2] These services aim to provide streamlined, efficient treatment in a client-centred manner for people who are doing well on ART, thereby allowing more resources to be directed towards initiating people on treatment and to managing those who are less well.[3 4]

South Africa currently runs the largest differentiated ART delivery programme in the world as part of the Centralised Chronic Medication Dispensing and Distribution (CCMDD) programme.[5] The CCMDD programme allows people with and without HIV to collect prepacked chronic medications (eg, ART, antihypertensives, diabetes treatment, lipid-lowering medication,) in the community, instead of having treatment dispensed at clinics. People living with HIV can be referred into CCMDD by their ART clinic if they are non-pregnant, stable on ART and have had two consecutive suppressed HIV viral loads, at least 6 months apart. In CCMDD, clients collect their treatment every 2 months at local pickup points, including private pharmacies and community-based organisations.[6] Every 6 months, they return to the clinic for review and re-referral into CCMDD. An annual viral load is also performed at the clinic assessing whether they remain virally suppressed. If clients in CCMDD are unwell, they can return to their clinic at any time for medical attention. CCMDD is a public-private partnership; patients are referred by healthcare workers in government sector clinics, while a private company is responsible for centrally dispensing medication and delivering it to community pickup points.[5 7] CCMDD was started in 2014 and provides treatment to over 1.7 million people.[8] However, despite its size, there is little published data evaluating how this programme influences engagement in HIV care.

Several different frameworks and theories have been proposed to evaluate factors influencing engagement in HIV care. Skovdal *et al*[9] propose a theoretical framework around engagement in HIV care as a social practice (figure 1). 'Theories of practice' conceptualise patterns of behaviour as social practices which depend on *materialities* (eg, clinical accessibility), *competencies* (eg, knowing how to access services and/or maintain healthy lifestyle), *meanings* (eg, HIV-associated stigma, the normalisation of HIV as a common experience) and *other life practices* (eg, employment).[9] These different components dynamically interact to influence the 'practice' of engagement in HIV care. Here, we aim to use this framework to explore engagement in clinic-based HIV services, and to analyse how CCMDD may influence the social practice of engagement in HIV care.

METHODS

Study design and setting

We undertook semi-structured in-depth interviews and focus group discussions with clients, and interviews with healthcare workers, who were part of the Simplified TREAtment and Monitoring (STREAM) study, a clinical trial of point-of-care HIV viral load testing and task shifting to enrolled nurses.[10 11] We previously reported qualitative findings from this study regarding the acceptability of point-of-care viral load testing and enrolled nurse care.[12] Here, we focus on findings related to CCMDD.

Eligible participants in STREAM were adults aged ≥18 years who were stable on first-line ART for 6 months after initiation. At enrolment, participants were randomised 1:1 to receive point-of-care viral load testing and potential task shifting to enrolled nurses, versus standard laboratory viral load testing and professional nurse care. After 6 months in the study (1 year on ART) participants in both arms who had a suppressed viral load and met other eligibility criteria (clinically stable, non-pregnant, CD4 count >200 cells/mm^3)[6] were offered referral into CCMDD.

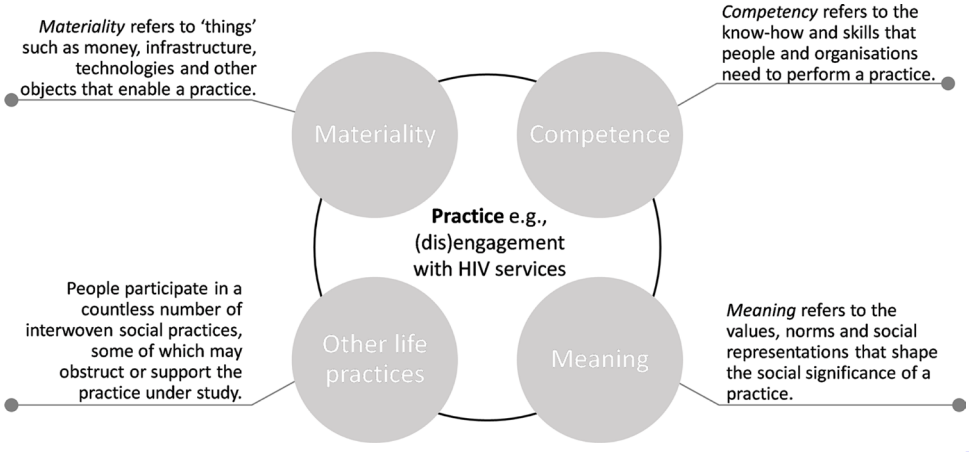


Figure 1 Summary of theories of practice framework, reproduced with permission from Skovdal *et al*, 2017.[7 9]

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Table 1 Client in-depth interview sampling frame

		Point-of-care arm	Standard-of-care arm	
		Target	Target	Total target
Viral load result	**Care provider**			
<1000 copies/ml	CCMDD and/or enrolled nurse	5	5	10
	Professional nurse	5	5	10
>1000 copies/ml	Professional nurse	5	5	10
Total target		15	15	30

CCMDD, Centralised Chronic Medication Dispensing and Distribution programme.

Once accepted into CCMDD, participants were able to collect treatment every 2 months at private pharmacies and community-based organisations. The CCMDD system would automatically send SMS texts to clients' mobile phones to remind them of their ART collection dates. After 6 months they were reviewed at the clinic by a nurse. The STREAM study took place at the Prince Cyril Zulu Clinic and the adjacent Centre for the AIDS Programme of Research in South Africa (CAPRISA) eThekwini Clinical Research Site, which are situated next to the main transport hub in central Durban, South Africa. Prince Cyril Zulu Clinic serves a large, urban population and was one of the first clinics to implement CCMDD in Durban, as part of a pilot implementation programme.

Participants

We used a purposive sampling frame to select a range of patients including those who received care in CCMDD, who had suppressed and unsuppressed viral loads at any point in the study and who received point-of-care testing versus standard laboratory testing in the STREAM trial (table 1). We approached potential participants in person or by telephone after they had exited the STREAM study, explained reasons for performing the research and obtained written informed consent for their participation.

Data collection

Trained research assistants (LM (male), HS (female)) performed interviews and focus groups in isiZulu or English in a private room in the clinic, using semi-structured topic guides (online supplementary material). LM was not previously known to participants. HS was known to patients as she was involved in recruitment and scheduling in STREAM. Neither LM or HS had any involvement in CCMDD or clinical patient care. Focus groups were broadly organised by STREAM study arm, and by attendance in CCMDD. We audio recorded interviews and focus groups, and took accompanying field notes where appropriate. Recordings and notes were anonymised, transcribed and translated from isiZulu to English where necessary. Participants did not review transcripts or the analysis.

Data analysis and theoretical framework

We initially performed a deductive thematic analysis[13] using a framework based on predefined themes informed by theories of practice.[9] During analysis, we inductively identified new themes and codes that were derived from the data and integrated them into the predefined themes in the coding frame (online supplementary table S1). Data for this analysis was predominantly coded by JD, with assistance by LM, using NVivo 12.0 (QSR International, Melbourne, Australia).

Patient and public involvement

Patients and the public were not involved in the design, recruitment or conduct of the study, beyond being enrolled as participants. Results will be shared with the CAPRISA Community Advisory Board as part of dissemination activities.

RESULTS

Between March 2018 and August 2018 we undertook 25 interviews and four focus groups (5 to 10 participants) with a total of 55 clients, and eight interviews with healthcare workers. One client was both interviewed and also in a focus group. Among clients, median age was 31 years, 56.4% were female, 52.7% were employed and 58.2% had collected ART in CCMDD (table 2). Among healthcare workers the median age was 39, 75.0% were women, and all were nurses (table 2). Interviews lasted 30 to 60 min and focus groups 60 to 80 min. Below, we present our findings, with supporting quotes, regarding the challenges to engagement in clinic-based services, and the influence of CCMDD on the social practice of engagement in HIV care. We use themes based on the four constructs of *materialities*, *competencies*, *meanings* and *other life practices* from theories of practice,[9] as well as the theme of problems with CCMDD implementation which we identified in the analysis (online supplementary table S1).

Materialities

Clients and healthcare workers described several ways in which the *materialities* of clinic-based HIV services presented challenges to ART provision, with overcrowded

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Table 2 Participants demographic and clinical characteristics

Clients			
		Frequency (n=55)	**%**
Age (years)	Median (IQR)	31 (27 to 37)	
Gender	Male	24	43.6
	Female	31	56.4
Ethnicity	Black African	55	100.0
Educational level	None or primary school	2	3.6
	Did not pass secondary school	14	25.5
	Passed secondary school	27	49.1
	Some tertiary education	12	21.8
Employed	Yes	29	52.7
	No	26	47.3
Income in ZAR per month (approximate USD)	<1000 (70)	23	41.8
	1000 to 4000 (70 to 280)	20	36.4
	>4000 (280)	12	21.8
Has a regular/stable partner	Yes	42	76.4
	No	13	23.6
Number of children	None	10	18.1
	One or more	45	81.8
Disclosed HIV status to anyone	Yes	52	94.6
	No	3	5.5
Travel time to clinic >1 hour	Yes	7	12.7
	No	48	87.2
Distance travelled to clinic ≤5 kilometres	Yes	44	80.0
	No	11	20.0
Primary method of travel to clinic	Walking	3	5.5
	Public transport	49	89.1
	Private transport	3	5.5
VL <1000 copies/ml	Yes	49	10.9
	No	6	89.1
Collected ART in CCMDD	Yes	32	58.2
	No	23	41.8
Healthcare providers			
Age (years)	Median (IQR)	39 (36 to 42)	
Gender	Male	2	25.0
	Female	6	75.0
Profession	Professional nurse	4	50.0
	Enrolled nurse	4	50.0

.ART, antiretroviral therapy; CCMDD, Centralised Chronic Medication Dispensing and Distribution; USD, United Stated Dollar; VL, viral load; ZAR, South African Rand.

primary care clinics and long waiting times deterring people from collecting treatment.

> "Sometimes I would end up not even collecting them (ART), because of the thought of the queue." Focus group 2, Participant 9, Female

> "The clinic gets very full, you will wait there the whole day." Focus group 3, Participant 3, Male

> "When you are coming to the clinic, you must cancel all the plans you have and tell yourself that you will spend the rest of the day there. Because chances are you will finish late in the afternoon." Focus group 2, Participant 1, Male

In contrast, many clients and healthcare workers described how CCMDD introduced changes in the *material circumstances* of ART delivery, with faster ART collection and more convenient opening hours.

> "I think collecting at (the private pharmacy) is quicker than here. When I came back here at the clinic, I

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waited for a good 2 hours." Focus group 1, Participant 7, Male

"They (patients) like CCMDD, (because) when they go to the pickup points there's no queues like here in the clinic. They come in, they go straight to the pharmacies then they get their pack." Staff interview 4

"Collecting… (at the community-based organisation) saves a lot of time, you don't spend 5 minutes. It doesn't get full, you can come anytime if it's still open. You just get in there, take your medication and leave." Focus group 3, Participant 5, Female

These material differences between clinic-based ART provision and CCMDD, impacted and interacted with the other components of the social practice of engagement in HIV care.

Competencies

Clients described how time pressures and rushed appointments in clinics prevented communication with healthcare workers, which stopped them from gaining *competency* in understanding and managing their health and HIV treatment.

"They would just tell you your bloods are fine and you leave… We don't ask questions, we want to finish and allow other people to come in… there are a lot of patients (waiting) outside who also want to come in and be assisted." Client interview 3, Male

"Maybe you weren't feeling well 2 days ago and you want to tell the nurse about it, sometimes you can't… because you are looking at the situation the nurse is under. You see that she has no time for you and she will not tolerate you telling her other things." Focus group 3, Participant 4, Female

Some clients also described being treated badly by clinical staff, further limiting their ability to become *competent* at taking medication.

"Sometimes you speak with (the nurse), and she gives you medication, (but) at the same time she's shouting at you. You can't do anything as a patient, you end up not knowing how you should take the medication." Focus group 3, Participant 4, Female

Two healthcare workers expressed concerns that clients who become unwell in CCMDD could then have difficulty accessing clinical care. This could be overcome by communicating well to ensure that clients understood that they could return to the clinic at any time.

"What I don't like about CCMDD is that… you can say the patient is stable, but tomorrow is another story. So if such patients go to CCMDD… and something new develops… they (CCMDD staff) tell you that you must go back to your facility (by which time) … it will be late and the damage is done." Staff interview 7

"I don't think there's anything bad (about CCMDD) as such. But the thing is, if a patient becomes unstable, then there's nobody to care for them because at (the pickup point) they just issue the medication… the patient must be educated to return to us if they are not feeling well." Staff interview 5

Most clients seemed to understand that quicker ART collection through CCMDD came at the cost of receiving less clinical oversight, but understood that they could return to the clinic if they were unwell or needed additional care.

"It's quicker to just collect (at the community-based organisation), because you know how you are taking your treatment… because when all these things (measuring vital signs, seeing a nurse) are done, you will be delayed." Focus group 2, Participant 8, Female

"…but at (the private pharmacy) you take your medication and leave, and it's good. When you have a problem, you come to the clinic." Focus group 2, Participant 9, Female

However, one client refused referral into CCMDD because she liked having vital signs monitored and the opportunity to talk to nurses in clinic, while another client in CCMDD felt that it could be improved by a quick physical check-up in the community.

"They once said we can now get them (ART) outside… I don't want that, I am fine here (at the clinic)… You weigh, check blood pressure and then go to the nurse to collect medication and she will look at your results and tell you everything is going well, or you are lacking here and you are lacking here." Client interview 16, Female

"I was relieved (that I was in CCMDD) because things were going to be quicker now, because this thing of staying all day at the clinic is not nice. But then the fact that you don't get checked up is not good. Otherwise, it's fine because it (the community-based organisation) is quick. If your vital signs were done as well, it would have been better." Client interview 5, Female

Clients not in CCMDD developed other *competencies* to overcome the multiple challenges to engagement in clinic-based care. These included sending relatives or friends to collect treatment, sharing ART, arriving at clinic very early in the morning to miss queues and extreme patience because of the life-saving benefits and positive *meanings* associated with receiving ART.

"When it's my appointment date I wake up very early to get to the clinic… I will be here for the whole day… because there are a lot of people… You must wait that long and sometimes you get so tired and you wish you can just leave. What can we say? We must wait because it's our lives." Client interview 12, Female

While successfully collecting ART in CCMDD required development of new *competencies*, some clients' previous experiences of buying from pharmacies was helpful.

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"Ok, so (the first time I collected from the private pharmacy) I got in there and looked around to see where I'm supposed to go, because I'm used to just buying and then leaving. Ok, I saw that I need to go (to) the dispensary because I am coming to collect and I didn't have a problem I did everything well and I found a good person who was full of jokes." Client interview 18, Female

Meanings

The physical organisation of clinical services sometimes threatened clients' confidentiality, potentially revealing their HIV status, which for them *meant* potential exposure to HIV-related stigma.

"There are two polyclinics, there's an old one and the new one… (HIV) positive people go to the 'old poly', so when a person says, "He is an old poly" (it means) they saw you at the 'old poly'. They know when you go to the 'old poly' that you are coming for ART." Focus group 1, Participant 1, Male

In order to manage the risk of HIV-related stigma in clinics, clients developed *competencies* to avoid disclosing their HIV status to people that they knew. Some reported pretending to collect treatment for someone else, or choosing to collect their treatment at a clinic far from home.

"(There is) another thing that makes us collect medication in other areas. We do have clinics in our local communities, (but) we are afraid to collect medication in those clinics because it is not safe… we are in one room with other patients and maybe we are only separated by a wall, so when I enter that door, people will see that I am going to collect my 'qo' (ART)." Focus group 3, Participant 7, Male

In contrast, several staff felt that CCMDD helped to change the *meanings* associated with HIV treatment by normalising HIV services.

"Being on ART, it disrupted their (clients) normal lives, so with CCMDD people go back to their normal life routine. You don't have to feel that 'I am sick'… you don't have to be burdened with getting treatment." Staff interview 1

Specifically, collecting ART in private pharmacies, where clients could be getting non-HIV related medication, helped with maintaining confidentiality.

"(In the private pharmacy) they wrap the medication well and pack it well. They don't just give you unwrapped medication where everyone can see. They wrap them and put them in a plastic bag… it looks like any medication you buy from (the pharmacy)." Client interview 12, Female

However, as we found in clinics, stigma still affected the *meanings* of engagement with CCMDD. Some clients who collected from private pharmacies felt that they were treated differently, because they were not paying customers.

"They (the private pharmacy staff) were paying attention to the customers who were coming to buy. Because we don't come with money, we only come with our (CCMDD) cards, they weren't paying attention to us." Client interview 8, Female

In some pharmacies there was a separate queue for CCMDD clients, which they felt could expose their HIV-positive status to others, despite people without HIV also collecting other chronic medication through CCMDD.

"Where I collect, there is our (CCMDD) queue and then there is a queue for everyone else. That is why I say sometimes they would say 'these people are coming to collect their thing (ART)'." Focus group 1, Participant 1, Male

Furthermore, integrating HIV treatment with everyday life felt threatening to some clients. One declined referral to CCMDD because he was worried about revealing his HIV status and experiencing stigma.

Interviewer: "Okay, why don't you like going there (private pharmacy in CCMDD)?"

Participant: "Uhm… because this thing (collecting ART) is confidential. Imagine, since I'm working at the mall, how many people who live by my house come there?… Imagine a female who stays by my place and sees me when I go to this. This is a secret… So, I would prefer to collect them here (at the clinic), because I don't want to feel embarrassed." Client interview 3, Male

In general, clients understood that CCMDD was for stable patients, and associated being referred into CCMDD as *meaning* that they had been taking ART well. Some used this to motivate their own adherence.

"No one wants to go back to the clinic anymore, and I think that is why we are taking our medication so well… When the nurse showed me my results, I was relieved that I will be going back (to CCMDD)." Focus group 2, Participant 9, Female

Other life practices

Many clients found that long waiting times in clinics and inflexible clinic opening hours (weekdays between 0700 to 1600 hours) clashed with employment opportunities and family responsibilities:

"Yes, but if I could be able to collect it on weekends… During the week I sometimes have temporary jobs somewhere, so I wish I could collect on weekends." Client interview 18, Female

"I did go to the clinic and the line was massive. So, I couldn't collect (ART), because I had to go back to work." Focus group 2, Participant 4, Male

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"…because the time here (at clinic) clashes with my work time… When you come here (to the clinic) you do it for yourself and when you are at work you do it for the family, you see. You must choose sometimes." Client interview 24, Male

Quicker services in CCMDD and more flexible opening times meant that collecting ART was less disruptive for *other life practices*.

"Everything (at the community-based organisation) is perfect and fast. If… I'm supposed to start work at half past 8 I can make it, because at 8 o'clock I will be there and by 10 past or quarter past I'm done." Client interview 14, Male

"(In CCMDD) the patients… are independent, they can go on a Saturday or after hours to pick up their medication, they don't have to take time off work to come to us (at the clinic)." Staff interview 5

However, some pharmacies seemed to be placing restrictions on when ART could be collected, despite being open for other services. This inflexibility meant that some employed clients still had difficulties collecting their ART in CCMDD.

"The problem with (this private pharmacy) is that they don't issue treatment on weekends. So, since we are working, we don't have time because if I didn't come to work they will deduct a certain amount from my salary. When you go there in the afternoon, they tell you that they don't issue medication at the certain times. Which means I will not be getting my treatment whereas it is very important to me." Focus group 1 Participant 9, Female

Challenges with implementation of CCMDD: Despite the general benefits of CCMDD, a few staff and clients also reported occasional problems with the implementation of the programme (table 3). These included delays in receiving reminder SMS, the client's ART not being found at the pickup point and inflexible pickup dates at some pharmacies, with pickup points sending ART back to

Table 3 Challenges with implementation of CCMDD

Issue	Quotes
Barriers to registering patients in CCMDD	
Need for ID card	"If a patient wants to be registered on CCMDD, strictly that patient must have a South African ID (or foreign passport) and every time the patient is going to collect the medication, they have to positively identify themselves using their ID. Something that we are not doing in the clinics. Some patients are not happy with that, ID's do get lost from time to time and then once the ID is not there, then they cannot give you that package at the pickup point, then the patient would be forced to come back to the clinic… (and) then they get de-registered in the process." Staff interview 4*
Problems with electronic prescription system	"The online registration system crashes quite often so there's days where the nurses can't get online, they just have to register manually. It creates a problem because online registration is a lot quicker, so on the days when they have to do manual then they are backed up for quite a while, and then it just makes the work a lot more." Staff interview 6
TB prophylaxis	"There's a category of patients that can be stable on ARV's but still don't qualify for CCMDD. A typical point in example, if at any given point you decide to put this patient on IPT, which is Isoniazid Preventive Therapy for TB, they don't take that patient. You see, for the patient to qualify for CCMDD they must be stable, but now CCMDD will not take a patient that is on IPT. So we have to keep that patient up until they finish the course of IPT before you can enrol them on CCMDD." Staff interview 4 "They said because I am still taking the ones for protecting me against TB and I will finish them in August… after that I will hear from them (about referral to CCMDD)" Client interview 21, Male.
Problems with CCMDD implementation	
SMS	"I will receive the text message the following day in the afternoon, after I collected today. I never receive the text message (on time). I receive it after." Focus group 1 Participant 3, Female
ART not being found at the pickup point	"I once received an SMS and I went there (to the private pharmacy) the very same day I received the SMS, and I got there and they said my name is not there (on the list of people with ART to collect). I then came here (to the clinic), and I got my treatment here. Fortunately, I had time on that day to end up coming here." Focus group 2 Participant 4, Male
Inflexible pickup dates	"The service providers are very strict when it comes to appointment dates, very strict. You get given a date and then you are expected to collect your parcel within 48 hours. After those 2 days then the medication will be sent back… and they get de-registered as a result. But here in the clinic they can miss the date by a day or two or three or four or five, it's not that much of an issue." Staff interview 4 "It was my fault because I came after 2 days and I found that my treatment has been sent back (to the depot)." Focus group 1 Participant 6, Male
Restricted ART pickup times	"They (private pharmacy staff) don't even take into consideration that I am coming from work… They are still at work and their job is to give me what I came here for (ART), but they tell me that they have closed and there is a queue." Focus group 1, Participant 1, Male
Pickup points reaching capacity	"Most of the pickup points were full, you know. They were full and some of the participants collect their medication far from where they stay, far from where they work you know. Jah, I think those were the disadvantages." Staff interview 2

ART, antiretroviral therapy; CCMDD, Centralised Chronic Medication Dispensing and Distribution programme; TB, tuberculosis.

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the central depot, if clients were a few days late (table 3). At the time of the interviews, several pickup points had reached capacity and were no longer accepting referrals, meaning that some clients had no pickup points near to their homes. Staff also reported some barriers to registering people into CCMDD. Referral criteria require a valid identification card or passport, which excluded some clients. Furthermore, isoniazid prophylaxis therapy, a daily tablet to prevent tuberculosis, is not available in CCMDD, meaning clients could not be referred until they had completed the recommended 12-month prophylactic course. Lastly, the electronic prescription system for CCMDD was occasionally offline, which could make CCMDD registration more time consuming (table 3).

DISCUSSION

In this study, clients and healthcare workers identified several problems with collecting ART from clinics in Durban, South Africa. Using the themes of materialities, competencies, meanings and other life practices based on 'theories of practice',[9] we showed how these problems interact with, and impact on, engagement in HIV care. We present one of the first qualitative assessments of the largest differentiated ART delivery programme in the world and show how it overcame some of these problems, helped to normalise HIV treatment and reduced the impact of collecting ART on other social practices in the clients lives. However, several challenges and inconsistencies remain in the implementation of CCMDD.

Materialities

We found several material barriers to engagement in clinic-based services, which are similar to findings from other studies. In a qualitative systematic review of 59 studies regarding long-term ART adherence and engagement in care in Africa, poor clinical services were identified as a major theme, with long waiting times, inflexible services and rigid and demanding policies all leading clients to disengage from care.[14] In our study, CCMDD changed some of the 'materialities' of ART provision, leading to clear practical benefits for clients. Similar findings have been reported in qualitative assessments of community adherence clubs in Mozambique, Kenya, Malawi, Zimbabwe and South Africa, which found reductions in clinical visits, waiting times and transport costs for clients.[15–19]

Competencies

The material challenges to attending clinics interacted with other components of the social practice of engagement in HIV services. For example, in our study and in another study from South Africa,[20] rushed clinical appointments impeded communication with nurses, meaning there was no time for healthcare workers to equip patients with the competencies required to engage with HIV services and learn about taking ART. Accessing ART through the CCMDD programme also required clients to develop new skills and competencies. When the CCMDD system worked well, clients generally found it easy to navigate, and understood that they could return to their normal clinic if they needed additional care. However, a few healthcare workers expressed concerns that CCMDD could delay clients from accessing appropriate medical attention if they became unwell, and highlighted the need for adequate counselling of clients to ensure appropriate healthcare seeking. These findings are similar to a study of community adherence groups in Zimbabwe, where healthcare workers were worried about delayed access to care, while clients were happy to spend less time in clinics, and felt 'empowered to visit the clinic whenever they needed'.[19]

Meanings

We found that healthcare workers in clinics were often overburdened, sometimes disrespectful, and did not always maintain confidentiality, as has been seen in many other studies.[14] Clinics that separated HIV services from other care also threatened clients' confidentiality, therefore exposing clients to stigma, which has been widely reported as impacting negatively on engagement in HIV care.[21 22] CCMDD also impacted on the meanings of engagement in HIV care. Attending private pharmacies was less burdensome, less obviously associated with being HIV positive, and more easily integrated with everyday life, thereby helping to normalise ART collection. In Kenya, integrated adherence clubs for non-communicable diseases and HIV were reported to reduce stigma, by normalising HIV to be like other chronic conditions.[16] However, we found multiple reports of preferential treatment by private pharmacy staff towards paying customers, suggesting some ongoing discrimination towards public sector CCMDD clients. Some clients also remained concerned that their HIV status could be revealed when collecting at community pickup points, where they could be more likely to see neighbours or people they knew. In studies of community adherence clubs, clients were mainly concerned about revealing their HIV status to other group members, and therefore created strict rules around maintaining group confidentiality.[15–18] The risk of other adherence club members breaching confidentiality was offset by increased peer support from within the group.[15 17 19 20] In contrast, clients in CCMDD did not report benefits of peer support, but also did not have to negotiate group dynamics when collecting ART, as they tended to collect individually at pickup points. Lastly, referral into CCMDD provided a new positive meaning to ART collection, and was seen as a reward and incentive to take ART well. Similarly, adherence clubs clients felt like staff were trusting them to manage their own HIV, and saw being sent back to the clinic as a punishment or failure to adhere to treatment.[20]

Other life practices

Several studies have described how the time spent travelling to clinics and waiting for ART can impact on clients'

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ability to seek or attend employment, and meet family responsibilities.[15 17 19] We found that a major benefit of CCMDD was reduced disruption to employment, although some working clients encountered problems with restricted collection times in a few private pharmacies. Similarly, in differentiated care programmes in Malawi, Kenya and Zimbabwe, clients had more time to attend their businesses and farming,[17 19] and avoided taking days off work.[16 19]

Challenges with CCMDD implementation

As with other differentiated ART delivery programmes,[15–18] there were several reports of implementation problems that clients had to negotiate, such as delayed SMS reminders, ART not being available at the pickup point and a few pharmacies placing restrictions on ART pickup times. Furthermore, some of the eligibility criteria for CCMDD seemed to contradict other stated aims of the healthcare system. For example, the need for an identification card could exclude the most vulnerable clients, while not providing tuberculosis prophylaxis within CCMDD could hamper tuberculosis control measures.[23]

Strengths and limitations

This is one of the first qualitative studies to assess differentiated ART delivery within the CCMDD programme. Our analysis is strengthened by the use of 'theories of practice' which highlighted the relationship between the materialities of ART provision, and how changes in these impacted on engagement in HIV care as well as clients' broader lives. Our interviewers were not involved in CCMDD or clinical patient care, which reduces the potential for social desirability bias. Limitations of our study include the use of a single urban clinic, and the use of clinical trial participants, meaning our findings may not be generalisable to other settings, such as rural areas. While our purposive sampling aimed to include a range of clients, clients who felt more positive towards CCMDD may have been more likely to participate. Lastly, the CCMDD programme is adapting quickly, and some of the early implementation problems that we report (eg, pickup points reaching capacity) may now have been resolved.

Implications

Our findings support the ongoing roll-out of CCMDD, while highlighting areas where improvements are needed. Better regulation of private pharmacies could ensure consistent implementation of less restrictive ART collection times, and allow development of strategies to better protect confidentiality and prevent CCMDD clients from receiving inferior care. Increasing the flexibility of the ART collection date window could also increase clients' autonomy to collect on a day that suits them in CCMDD. Steps to reduce HIV-related stigma at a broader societal level are needed, as fear of disclosure remained a barrier to engagement in both clinic-based services and CCMDD. Further research is needed to establish the impact of CCMDD on clinical outcomes such as viral suppression and retention in care, and whether it is cost-effective. Of note, cost-effectiveness studies should attempt to capture the wider non-healthcare system costs and benefits for employed people, given that CCMDD may be particularly beneficial to them. Lastly, we also identify several areas that could be improved in clinic-based HIV services, including less restrictive opening times, more respectful treatment of clients and better confidentiality.

CONCLUSION

In conclusion, we highlight how the material changes to ART provision in CCMDD facilitated engagement with HIV services, reduced disruption in clients' everyday lives and helped to normalise HIV care. Improvements to the implementation of CCMDD could allow even greater benefits, and contribute towards achieving universal ART through more client-centred healthcare services.

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18. CHAPTER 10 APPENDIX

18.1. Formula for Poisson regression models

Calculating the change in outcome at lockdown, no seasonality

$$\log(\mathrm{y}) = b_0 + b_1 t + b_2 x + b_3 xt$$

where y = mean outcome of interest, x = lockdown indicator and t = time in weeks since the start of the study.

Calculating the change in outcome at time T

To estimate the intervention at this timepoint, we centre t about T

$$\log(\mathrm{y}) = b_0 + b_1 (t - T) + b_2 x + b_3 x (t - T)$$

Model including seasonality

$$\log(\text{mean inititiations}) = b_0 + b_1 t + b_2 x + b_3 xt + b_4 \sin\left(\frac{2\pi \mathrm{t}}{52}\right) + b_5 \cos\left(\frac{2\pi \mathrm{t}}{52}\right) + b_6 \sin\left(\frac{4\pi \mathrm{t}}{52}\right) + b_7 \cos\left(\frac{4\pi \mathrm{t}}{52}\right)$$

18.2. Sample R code for Poisson regression models

```
###############
## Install and load packages
###############
# install.packages("sandwich"); install.packages("tidyverse"); install.packages("tsModel")
library(sandwich); library(tidyverse); library(tsModel)

###############
```

```
### Centre time
###############
data$time_c <- data$time - 118  # Time centred at lockdown
data$time_e <- data$time - 128 # Time centred at end of the study period
###############
### Poisson regression model of ART initiations pre and post lockdown
###############
model_init <- glm(init_n ~ lock_d + time + lock_d:time_c, family = poisson, data)
summary(model_init)
## Look at residuals for autocorrelation
data$res1 <- residuals(model_init, type = "deviance")
ggplot(data = data, mapping = aes(x = time, y = res1,)) +
  geom_point(aes(colour = lock_d))
acf(data$res1)
pacf(data$res1)
## Calculate Newey-West standard errors using lag 3
est <- exp(c(coef(model_init)["lock_d:time_c"], coef(model_init)["lock_d"],
coef(model_init)["time"]))
se1 <- sqrt(diag(NeweyWest(model_init, prewhite = F, lag = 3)))["lock_d:time_c"]
se2 <- sqrt(diag(NeweyWest(model_init, prewhite = F, lag = 3)))["lock_d"]
se3 <- sqrt(diag(NeweyWest(model_init, prewhite = F, lag = 3)))["time"]
lb <- est * exp(-1.96 * c(se1, se2, se3))
ub <- est * exp(1.96 * c(se1, se2, se3))
table <- cbind(round(est, digits = 3), round(lb, digits = 3), round(ub, digits = 3))
table
## Calculate post-lockdown trend and confidence intervals
V <- NeweyWest(model_init, prewhite = F, lag = 3)
se <- sqrt(V["time", "time"] + V["lock_d:time_c", "lock_d:time_c"]
```

```
        + 2 * V["time", "lock_d:time_c"])
slope_post <- sum(coef(model_init)[c("time", "lock_d:time_c")])
lower <- slope_post - 1.96 * se
upper <- slope_post + 1.96 * se
exp(cbind(slope_post, lower, upper))
## Estimate the impact of lockdown at the end of the study period
model_init_end <- glm(init_n ~ lock_d + time + lock_d:time_e, family = poisson, data)
summary(model_init_end)
###############
### Poisson regression model of ART initiations adjusting for seasonality
###############
# Specifying the number of sin and cosine pairs to include (2) and the interval (52 weeks)
model_seas <- glm(init_n ~ lock_d + time + lock_d:time_c + harmonic(wk, 2, 52),
            family = poisson, data)
summary(model_seas)
```

Table 18.1 Segmented Poisson regression models of the impact of COVID-19 lock-down on positive HIV tests at 65 clinics in KwaZulu-Natal, South Africa

	Incidence rate ratio at lock-down (95% CI)	**Incidence rate ratio at study end (95% CI)**	**Pre-lockdown trend[a] (95% CI)**	**Post-lockdown trend[a] (95% CI)**
Positive HIV test results [b]	0.611 (0.532-0.702)	0.739 (0.634-0.861)	0.993 (0.986-1.000)	1.057 (1.017-1.100)
Positive HIV test results, accounting for seasonality [b]	0.602 (0.511-0.710)	0.696 (0.571-0.848)	0.994 (0.988-1.001)	1.044(0.964-1.130)

[a] Slope change per month [b] Autocorrelation addressed using Newey-West standard errors to calculate confidence interval, with lag up to 2.

18.3. Published manuscript

The following pages contain the published manuscript on which Chapter 10 was based.

Dorward J, Khubone T, Gate K, Ngobese H, Sookrajh Y, Mkhize S, et al. The impact of the COVID-19 lockdown on HIV care in 65 South African primary care clinics: an interrupted time series analysis. Lancet HIV. 2021;8(3):e158-e65. Epub 2021/02/08. doi: 10.1016/S2352-3018(20)30359-3. PubMed PMID: 33549166.

The impact of the COVID-19 lockdown on HIV care in 65 South African primary care clinics: an interrupted time series analysis

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Summary

Background The effect of the COVID-19 pandemic on HIV outcomes in low-income and middle-income countries is poorly described. We aimed to measure the impact of the 2020 national COVID-19 lockdown on HIV testing and treatment in KwaZulu-Natal, South Africa, where 1·7 million people are living with HIV.

Methods In this interrupted time series analysis, we analysed anonymised programmatic data from 65 primary care clinics in KwaZulu-Natal province, South Africa. We included data from people testing for HIV, initiating antiretroviral therapy (ART), and collecting ART at participating clinics during the study period, with no age restrictions. We used descriptive statistics to summarise demographic and clinical data, and present crude summaries of the main outcomes of numbers of HIV tests per month, ART initiations per week, and ART collection visits per week, before and after the national lockdown that began on March 27, 2020. We used Poisson segmented regression models to estimate the immediate impact of the lockdown on these outcomes, as well as post-lockdown trends.

Findings Between Jan 1, 2018, and July 31, 2020, we recorded 1 315 439 HIV tests. Between Jan 1, 2018, and June 15, 2020, we recorded 71 142 ART initiations and 2 319 992 ART collection visits. We recorded a median of 41 926 HIV tests per month before lockdown (January, 2018, to March, 2020; IQR 37 838–51 069) and a median of 38 911 HIV tests per month after lockdown (April, 2020, to July, 2020; IQR 32 699–42 756). In the Poisson regression model, taking into account long-term trends, lockdown was associated with an estimated 47·6% decrease in HIV testing in April, 2020 (incidence rate ratio [IRR] 0·524, 95% CI 0·446–0·615). ART initiations decreased from a median of 571 per week before lockdown (IQR 498–678), to 375 per week after lockdown (331–399), with an estimated 46·2% decrease in the Poisson regression model in the first week of lockdown (March 30, 2020, to April 5, 2020; IRR 0·538, 0·459–0·630). There was no marked change in the number of ART collection visits (median 18 519 visits per week before lockdown [IQR 17 074–19 922] *vs* 17 863 visits per week after lockdown [17 509–18 995]; estimated effect in the first week of lockdown IRR 0·932, 95% CI 0·794–1·093). As restrictions eased, HIV testing and ART initiations gradually improved towards pre-lockdown levels (slope change 1·183/month, 95% CI 1·113–1·256 for HIV testing; 1·156/month, 1·085–1·230 for ART initiations).

Interpretation ART provision was generally maintained during the 2020 COVID-19 lockdown, but HIV testing and ART initiations were heavily impacted. Strategies to increase testing and treatment initiation should be implemented.

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Introduction

The number of deaths from COVID-19 continues to rise globally, but data quantifying the effect of the pandemic on other health conditions are scarce, especially in low-income and middle-income countries. Interruption of supply chains, diversion of resources, and overwhelmed health systems could have severe collateral effects on existing public health programmes.[1–4] Furthermore, COVID-19 control measures, such as stay-at-home orders, or lockdowns, might limit access to health-care services, further jeopardising broader public health goals.[3,5,6]

In Africa, the impact on HIV services is of particular concern. Despite improvement in HIV prevention, testing, and treatment, HIV/AIDS remains one of the leading causes of mortality, with more than 400 000 deaths on the continent in 2019.[7] Of the estimated 25·8 million people in Africa living with HIV in 2019, 4·3 million were not diagnosed, and a further 3·4 million were not receiving antiretroviral therapy (ART).[7] Modelling studies of disruptions to HIV programmes by the COVID-19 pandemic estimate that interruptions in ART would have the largest effect on HIV-related mortality.[8,9] In a worst case scenario, interruption of ART for 6 months for 50% of patients would result in 296 000 excess HIV-related deaths.[8]

Such scenarios are of particular concern in the province of KwaZulu-Natal, in South Africa, which is

Research in context

Evidence before this study

The COVID-19 pandemic could greatly affect HIV programmes in low-income and middle-income countries. Modelling studies have suggested that disruptions to antiretroviral therapy (ART) provision would have the worst consequences, with a 6-month interruption in treatment for half of people who receive ART, leading to nearly 300 000 excess HIV deaths in sub-Saharan Africa. However, whether such high levels of disruption have occurred is not clear. We searched PubMed for the terms (COVID-19 OR SARS-CoV-2) AND (HIV OR AIDS) AND (LMIC OR low income country OR middle income country OR Asia OR Africa OR Latin America) AND (lockdown OR lock-down OR curfew OR impact OR shelter OR restriction) from inception until Oct 16, 2020. We found four small studies that provided quantitative data comparing HIV care outcomes before and after COVID-19 lockdowns. A single site cohort study of pre-exposure prophylaxis in 455 pregnant women in South Africa found an increase in missed visits after lockdown. An interrupted time series analysis from 11 clinics in rural South Africa found a 20% increase in HIV-related primary care visits after lockdown implementation, and two studies from Kenya described a decrease in numbers of HIV tests in the first month of lockdown, compared with the previous 3 months.

Added value of this study

We contribute new evidence of the impact of the COVID-19 lockdown on HIV care in KwaZulu-Natal, South Africa, which has the largest ART programme in the world, and had one of the strictest lockdowns in Africa. We analysed a large dataset from urban and rural primary care clinics between Jan 1, 2018, and July 31, 2020, and used interrupted time series analysis to account for longer-term trends. HIV testing and ART initiations decreased substantially when lockdown was implemented, but ART collection visits decreased only slightly.

Implications of all the available evidence

ART provision was largely maintained during the South African lockdown, while HIV testing and ART initiations were more heavily affected. After lockdown, and in any future COVID-19 restrictions, strategies to catch up with HIV testing and increase ART initiation should be implemented, alongside efforts to maintain treatment provision.

the country most heavily affected by both COVID-19 and HIV in Africa. 493 183 cases of COVID-19 had been confirmed in South Africa by July 31, 2020,[10] and in 2019 an estimated 7·5 million people were living with HIV in the country. An estimated 1·7 million people are living with HIV in KwaZulu-Natal, a prevalence of 27% in adults aged 15–49 years.[11] 76 706 cases of COVID-19 had been confirmed in KwaZulu-Natal by July 31, 2020, making it the third most COVID-19 affected province in South Africa.[10] The largest urban area in KwaZulu-Natal is the eThekwini Metropolitan Municipality, which has a population of approximately 3·7 million and includes the city of Durban.[12] South Africa announced a national lockdown on March 23, 2020, which was implemented on March 27.[6] Starting at level 5, the lockdown was one of the most severe globally, with restrictions on movement and cancellation of public transport, although travel to receive health care was allowed.[6] The lockdown was eased to level 4 on May 1, 2020, when public transport was allowed,[6] and to level 3 on June 1, 2020, which allowed some economic activity to resume.

The impact of lockdown measures in South Africa and other African countries on HIV programmes is not clear. An interrupted time series analysis[13] of data from 11 rural clinics in South Africa found a 20% increase in HIV-related primary care visits after lockdown implementation. By contrast, two small studies in Kenya[14,15] described 16–30% decreases in HIV testing after lockdown. However, these analyses were from few sites and might be biased by long-term trends that were not accounted for.

We aimed to quantify the impact of COVID-19 lockdown in South Africa on key components of HIV care, namely HIV testing, ART initiation, and retention in HIV care, which was measured using ART collection visits and missed visits.

Methods

Study design

We did an interrupted time series analysis of routinely collected data from 65 public sector, primary care clinics in KwaZulu-Natal, South Africa. We used data from 56 urban clinics run by the eThekwini Municipality Health Unit, which represents approximately 60% of all public clinics in the Metro. We also used data from all nine fixed and mobile primary care clinics overseen by Bethesda Hospital, a district hospital in the rural uMkhanyakude District in northern KwaZulu-Natal. ART is provided free of charge at all these clinics, and they remained open during the South African national lockdown. Before and throughout the lockdown, there were no reports of ART stockouts in the study clinics, and public health messaging highlighted the importance of ART for all people living with HIV.[16]

Participants

We included data from people testing for HIV, initiating ART, and collecting ART at participating clinics during the study period, with no age restrictions. For ART initiations, we excluded patients who were already receiving ART and were transferring into care from another clinic. For HIV testing, data were available from Jan 1, 2018, to July 31, 2020, for all other outcome variables data were

available until June 15, 2020. We chose not to use data before January, 2018, as earlier trends might have been influenced by changes in ART initiation criteria and the implementation of universal test and treat in South Africa at the end of 2016.

Data sources and data management

In the South African public sector, data on the number of HIV tests done per month at each clinic are routinely recorded in the District Health Information System[12] and reported by gender and age group. For patients initiating and receiving ART, data on demographics, clinical status, and clinic visits are routinely recorded in an electronic register[17] that is compared monthly against clinic registers and a subset of clinical charts. For this analysis, anonymised patient-level data were analysed and aggregated into weekly counts of ART initiations and ART collection visits. During the COVID-19 lockdown, clinical staff, data capturers, and health information system managers were classed as essential workers. This designation meant that transport arrangements were made to enable attendance at work, minimising disruptions to data entry and data capture.

Outcomes

The primary outcomes were HIV tests per month, ART initiations per week, and ART collection visits per week at participating clinics during the study period. The number of weekly ART collection visits was a function of when visits were scheduled, and whether patients attended these scheduled visits. Because visit scheduling might also have changed during lockdown, we assessed a secondary outcome of missed ART collection visits per week. For the missed visits variable, we used the date of next scheduled ART collection visit to calculate visits that were missed by more than 2 weeks, as defined by South African guidelines.[18] Patients who attended earlier than their next scheduled visit were not defined as missing a visit, and we restricted the period of interest to end 2 weeks before the last day of data collection, because by definition a missed visit required no visit in the next 2 weeks. We stratified the outcome data by gender and by rural or urban district (according to clinic location).

Statistical analysis

We used descriptive statistics to summarise demographic and clinical data, and present crude summaries of outcomes before and after lockdown. We did not summarise HIV testing data by age, because different age categories were used for recording during the study period. We did interrupted time series segmented regression analyses by fitting a Poisson regression model with Newey–West standard errors[19,20] to account for autocorrelation and heteroskedasticity. The model included a time variable, a dummy lockdown variable indicating pre-lockdown and post-lockdown, and an interaction term between time and the lockdown variable. This approach takes account of pre-lockdown trends and allows estimation of the effect of lockdown at various timepoints by centring time at that timepoint. We used the model to estimate the immediate impact of lockdown and the effect of the lockdown by the end of the study period. We estimated the post-lockdown trend for each outcome by adding together the coefficients associated with time and the time–lockdown interaction. We did analyses for ART initiations and ART collection visits by weekly counts, but we present trends of these outcomes by monthly periods to facilitate comparisons with monthly HIV testing trends. We built separate models by gender, age, and rural and urban group. To account for seasonal changes in clinic activity (eg, holiday periods when clinics remain open but visits are typically fewer), we did a sensitivity analysis with two pairs of sine and cosine terms (Fourier terms) included in the model. We also did a sensitivity analysis of trends in positive HIV tests. We analysed data using R 4.0 (R Foundation for Statistical Computing, Vienna, Austria; appendix).

See Online for appendix

Ethical approval

This work was approved by University of Kwazulu-Natal Biomedical Research Ethics Committee (BE646/17), the KwaZulu-Natal Department of Health's Provincial Health Research Ethics Committee (KZ_201807_021), the eThekwini Municipality Health Unit, and the Bethesda Hospital Ethics Committee, with a waiver for informed consent for analysis of anonymised, routinely collected data.

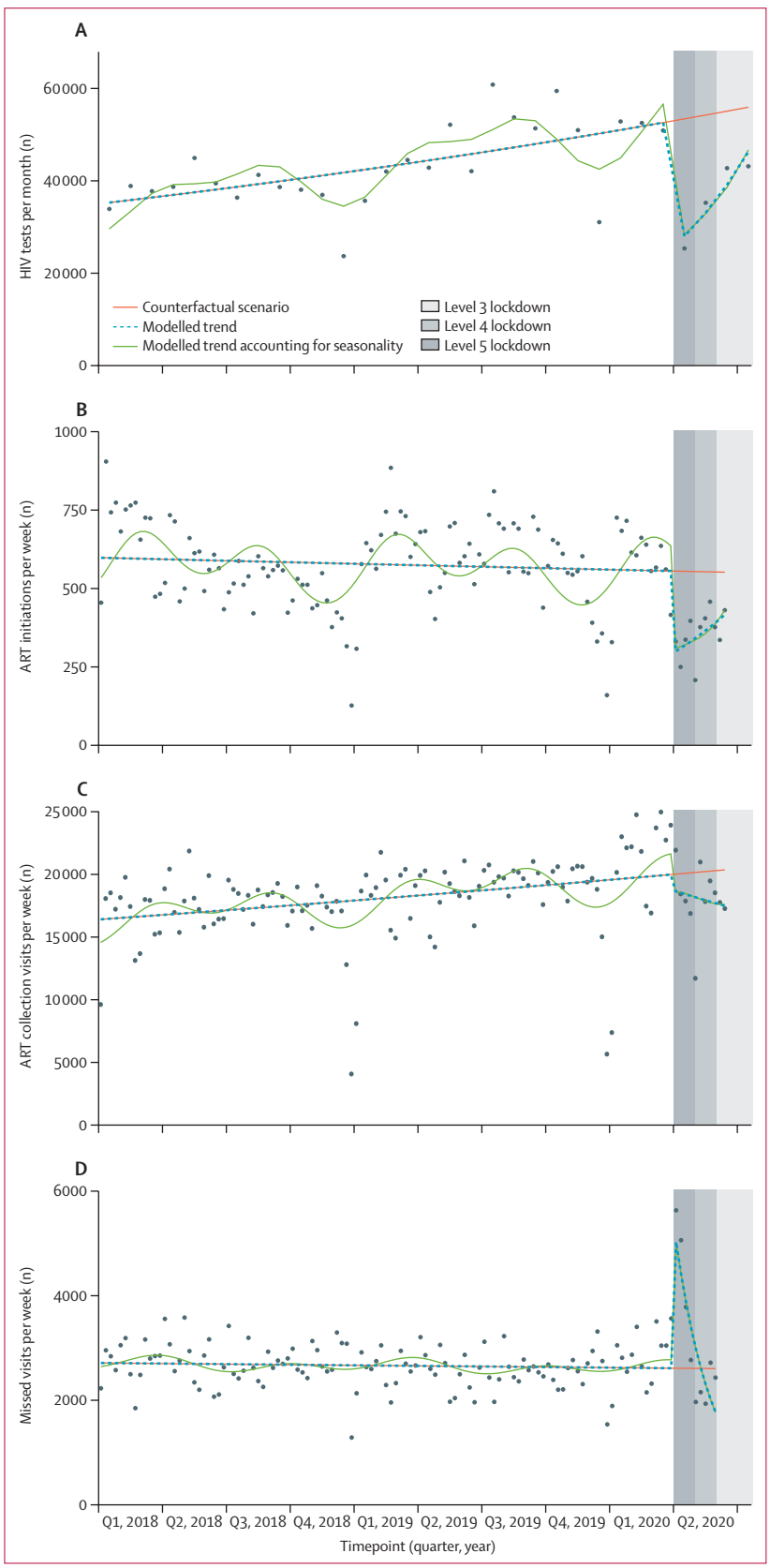
Role of the funding source

The funders had no role in the study design, data collection, analysis, interpretation, or writing of the paper.

	HIV tests*	ART initiations†	ART collection visits†	Missed ART collection visits‡
Total in study period	1 315 439	71 142	2 319 992	339 474
Median age, years (IQR)§	NA	32 (27–39)	37 (31–45)	36 (30–43)
By age group§				
0–14 years	NA	891 (1·2%)	48 440 (2·1%)	7112 (2·1%)
15–24 years	NA	9734 (13·7%)	135 649 (5·9%)	26 249 (7·7%)
25–49 years	NA	55 840 (78·5%)	1 785 187 (76·9%)	265 408 (78·2%)
≥50 years	NA	4741 (6·7%)	457 647 (15·1%)	40 705 (12·0%)
Gender				
Female	861 265 (65·5%)	46 520 (65·4%)	1 580 202 (68·1%)	224 799 (66·2%)
Male	454 174 (34·5%)	24 622 (34·6%)	739 790 (31·9%)	114 675 (33·8%)
District of clinic				
Urban	1 269 811 (96·5%)	68 821 (96·7%)	2 216 761 (95·6%)	311 746 (91·8%)
Rural	45 628 (3·5%)	2321 (3·3%)	103 231 (4·4%)	27 728 (8·2%)

Data are n (%) unless otherwise specified. ART=antiretroviral therapy. *Jan 1, 2018, to July 31, 2020. †Jan 1, 2018, to June 15, 2020. ‡Jan 1, 2018, to June 1, 2020. §Age in routine HIV testing data was recorded using varying age categories during the study period and is therefore not available.

Table 1: **Demographics of people who had an HIV test, initiated ART, or collected ART at 65 clinics in KwaZulu-Natal, South Africa**



Results

Between Jan 1, 2018, and July 31, 2020, 1 315 439 HIV tests were done at all participating clinics. Between Jan 1, 2018, and June 15, 2020, 71 142 people started ART, and 235 719 people attended 2 319 992 ART collection visits (median 9 visits per person, IQR 5–14). Between Jan 1, 2018, and June 1, 2020, 339 474 ART collection visits were missed. Demographic details are presented in table 1. 65·4–68·1% of outcomes were recorded in women, reflecting the higher prevalence of HIV among women in South Africa,[11] and 91·8–96·7% of outcomes occurred at urban clinics. Pre-lockdown, December, 2018 and 2019 had the lowest counts of HIV tests, ART initiations, ART collection visits, and missed visits (figure).

In the 27 months before the lockdown on March 27, 2020, a median of 41 926 HIV tests were done per month (IQR 37 838–51 069), compared with 38 911 tests per month (32 699–42 756) in the 4 months after lockdown (April, 2020–July, 2020). Before lockdown, a median of 2691 (2425–2906) of these HIV tests were positive per month, compared with 1638 per month (1568–1662) after lockdown. The median proportion of positive tests was 6·1% (IQR 5·4–7·0%) before lockdown and 4·3% (4·0–4·8%) after lockdown. The Poisson segmented regression analysis showed a 47·6% decrease in HIV testing in the first month of lockdown (April, 2020) (incidence rate ratio [IRR] 0·524, 95% CI 0·446–0·615; figure, table 2). After April, 2020, HIV testing increased by a trend of 18·3% per month (IRR 1·183, 95% CI 1·113–1·256), reaching 82·7% of pre-lockdown levels (0·827, 95% CI 0·704–0·972) by July, 2020. Findings were similar between women and men (table 2), and in a sensitivity analysis of positive HIV tests (appendix p 1). In the urban clinics, the decrease in HIV testing at lockdown was larger than in the rural clinics (IRR 0·515, 95% CI 0·436–0·610 in the urban centres *vs* 0·823, 0·681–0·994 in the rural centres; table 2).

In the 117 weeks before lockdown, a median of 571 ART initiations were done per week (IQR 498–678), compared with 375 per week (331–399) in the 11 weeks after implementation of lockdown. The segmented regression analysis showed a 46·2% decrease in ART initiations in the first full week of lockdown (March 30, 2020, to April 5, 2020; IRR 0·538, 95% CI 0·459 –0·630; figure, table 2). Thereafter, ART initiations gradually recovered by a trend of 15·6% per month (IRR 1·156, 95% CI 1·085–1·230; trend presented by month to allow comparisons with monthly HIV testing trends), reaching 75·3% of pre-lockdown levels (IRR 0·753, 95% CI

Figure: **Poisson segmented regression analyses of HIV testing, ART initiations, ART collection visits, and missed visits, before and after the COVID-19 lockdown in 65 clinics in KwaZulu-Natal, South Africa**
(A) HIV tests per month. (B) ART initiations per week. (C) ART collection visits per week. (D) Missed visits per week. ART=antiretroviral therapy.

0·637–0·890) by mid-June, 2020. This recovery in ART initiations occurred mainly in women (IRR 1·225 per month, 95% CI 1·118–1·341), whereas ART initiations remained low in men (1·040 per month, 0·957–1·132). The effect of lockdown on ART initiations was similar across age groups, and rural and urban clinics (table 2).

Patients attended a median of 18 519 ART collection visits per week before lockdown (IQR 17 074–19 922), compared with 17 863 per week (17 509–18 995) after implementation of lockdown. The segmented regression analysis showed weak evidence of a small decrease in the number of ART collection visits in the first full week of lockdown (IRR of lockdown effect 0·932, 95% CI 0·794–1·093; figure, table 2). After lockdown, the number of ART collections per month remained broadly constant (IRR 0·974, 95% CI 0·900–1·053), but by the end of data collection in mid-June, there was some evidence to suggest that ART collections visits were lower than pre-lockdown levels (IRR 0·859, 95% CI 0·747–0·989%). Results were similar between men and women, age groups, and for rural and urban clinics (table 2). In post-hoc analyses, we added an indicator term for the 4 weeks between the date of the first confirmed case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in South Africa and the start of the South African lockdown. The number of ART collection visits were higher in the 4 weeks between SARS-CoV-2 identification and lockdown (IRR 1·233, 95% CI 1·113–1·366), even when taking seasonality into account (1·165, 1·042–1·303). We also found that the number of early visits, in which people attended more than 7 days before their scheduled visit date, increased in this pre-lockdown period (1·271, 1·110–1·456).

Before lockdown, a median of 2637 visits per week were missed (IQR 2420–2938), compared with 2714 per week after lockdown (2151–3777; figure). The Poisson regression model showed a large increase in missed visits in the first week of lockdown (IRR 1·926, 95% CI 1·550–2·394). Thereafter, missed visits decreased rapidly as lockdown continued (0·569 per month, 0·432–0·747), and returned to pre-lockdown levels by the end of May, 2020, when the lockdown moved from level 5 to level 4 (1·006, 0·794–1·276; figure). Of the 19 183 people who missed a visit by 2 weeks during the level 5 lockdown period, 11 259 (58·7%) subsequently collected within the next month (ie, 42 days after their scheduled visit). We did not observe any marked differences in results between men and women or in different age groups. In the rural clinics, the increase in missed visits in the first week of lockdown was much less marked (IRR 1·274, 95% CI 1·076–1·509) than in the urban clinics (1·991, 1·584–2·503; table 2).

After adding two Fourier terms to account for seasonality, our findings were similar to those when seasonality was not included (table 3, figure). We also did a post-hoc analysis among people referred into a community ART delivery programme.[21] Community

	Incidence rate ratio at lockdown	Incidence rate ratio at study end	Pre-lockdown trend*	Post-lockdown trend*
HIV testing†				
Overall	0·524 (0·446–0·615)	0·827 (0·704–0·972)	1·015 (1·009–1·022)	1·183 (1·113–1·256)
Gender				
Women	0·563 (0·480–0·661)	0·865 (0·741–1·010)	1·013 (1·007–1·019)	1·169 (1·100–1·247)
Men	0·456 (0·387–0·537)	0·761 (0·638–0·907)	1·020 (1·013–1·028)	1·210 (1·147–1·277)
District				
Urban	0·515 (0·436–0·610)	0·827 (0·700–0·978)	1·016 (1·010–1·023)	1·190 (1·115–1·270)
Rural	0·823 (0·681–0·994)	0·785 (0·639–0·965)	0·996 (0·985–1·006)	0·980 (0·922–1·042)
ART initiation‡				
Overall	0·538 (0·459–0·630)	0·753 (0·637–0·890)	0·996 (0·991–1·004)	1·156 (1·085–1·230)
Gender				
Women	0·495 (0·417–0·588)	0·801 (0·651–0·985)	0·996 (0·987–1·004)	1·225 (1·118–1·341)
Men	0·616 (0·513–0·740)	0·675 (0·571–0·797)	1·000 (0·996–1·009)	1·040 (0·957–1·132)
Age, years				
0–14	0·370 (0·153–0·896)	0·544 (0·270–1·096)	0·996 (0·987–1·004)	1·175 (0·640–2·164)
15–24	0·400 (0·334–0·479)	0·772 (0·640–0·932)	1·022 (1·013–1·031)	1·363 (1·256–1·476)
25–49	0·577 (0·492–0·676)	0·739 (0·624–0·876)	0·991 (0·987–1·000)	1·108 (1·040–1·180)
≥50	0·481 (0·399–0·579)	0·796 (0·664–0·953)	0·991 (0·983–1·000)	1·230 (1·161–1·335)
District				
Urban	0·536 (0·458–0·628)	0·750 (0·631–0·892)	0·996 (0·991–1·004)	1·156 (1·080–1·230)
Rural	0·588 (0·365–0·947)	0·863 (0·625–1·191)	0·987 (0·983–0·996)	1·166 (0·869–1·560)
ART collection visits‡				
Overall	0·932 (0·794–1·093)	0·859 (0·747–0·989)	1·009 (1·000–1·013)	0·974 (0·900–1·053)
Gender				
Women	0·916 (0·780–1·075)	0·865 (0·753–0·994)	1·009 (1·000–1·013)	0·983 (0·908–1·062)
Men	0·965 (0·823–1·131)	0·847 (0·733–0·978)	1·009 (1·004–1·013)	0·953 (0·880–1·031)
Age, years				
0–14	0·908 (0·790–1·043)	0·780 (0·703–0·866)	1·013 (1·009–1·017)	0·949 (0·888–1·017)
15–24	0·875 (0·766–1·001)	0·851 (0·753–0·960)	1·026 (1·017–1·031)	1·013 (0·957–1·071)
25–49	0·933 (0·796–1·094)	0·865 (0·751–0·995)	1·009 (1·000–1·013)	0·974 (0·900–1·053)
≥50	0·946 (0·787–1·137)	0·836 (0·710–0·984)	1·004 (1·000–1·009)	0·949 (0·861–1·049)
District				
Urban	0·926 (0·786–1·090)	0·850 (0·736–0·982)	1·009 (1·004–1·013)	0·970 (0·896–1·053)
Rural	1·065 (0·969–1·171)	1·080 (0·985–1·185)	0·996 (0·991–1·000)	1·000 (0·957–1·044)
Missed ART collection visits‡				
Overall	1·926 (1·585–2·341)	0·682 (0·455–1·021)	1·000 (0·996–1·004)	0·569 (0·432–0·747)
Gender				
Women	2·045 (1·686–2·481)	0·691 (0·454–1·052)	0·996 (0·991–1·000)	0·555 (0·419–0·734)
Men	1·710 (1·399–2·090)	0·664 (0·457–0·965)	1·000 (0·996–1·004)	0·601 (0·463–0·779)
Age, years				
0–14	1·568 (1·325–1·856)	0·555 (0·429–0·717)	1·004 (1·000–1·009)	0·572 (0·472–0·690)
15–24	1·682 (1·413–2·001)	0·554 (0·374–0·820)	1·022 (1·017–1·026)	0·561 (0·430–0·727)
25–49	1·947 (1·594–2·378)	0·685 (0·451–1·042)	1·000 (0·996–1·000)	0·566 (0·428–0·751)
≥50	2·030 (1·665–2·474)	0·782 (0·552–1·109)	0·987 (0·983–0·991)	0·589 (0·463–0·751)
District				
Urban	1·991 (1·621–2·446)	0·677 (0·433–1·057)	1·000 (0·996–1·004)	0·555 (0·412–0·751)
Rural	1·274 (1·111–1·460)	0·745 (0·636–0·872)	1·004 (0·996–1·009)	0·751 (0·674–0·834)

Data are incidence rate ratio (95% CI) or trend (95% CI). ART=antiretroviral therapy. *Slope change per month †Autocorrelation addressed using Newey–West standard errors to calculate CI, with lag up to 2. ‡Autocorrelation addressed using Newey–West standard errors to calculate CI, with lag up to 3.

Table 2: **Poisson segmented regression models of the impact of COVID-19 lockdown on HIV services at 65 clinics in KwaZulu-Natal, South Africa**

	Incidence rate ratio at lockdown	Incidence rate ratio at study end	Pre-lockdown trend*	Post-lockdown trend*
HIV testing†	0·475 (0·404–0·559)	0·741 (0·631–0·872)	1·018 (1·012–1·023)	1·180 (1·090–1·279)
ART initiation‡	0·496 (0·411–0·598)	0·798 (0·645–0·987)	1·000 (0·991–1·004)	1·225 (1·113–1·352)
ART collection visits‡	0·859 (0·733–1·007)	0·852 (0·745–0·975)	1·009 (1·004–1·013)	1·004 (0·924–1·090)
Missed ART collection visits‡	1·812 (1·494–2·197)	0·693 (0·459–1·048)	1·000 (0·996–1·004)	0·595 (0·451–0·783)

Data are rate (95% CI) or trend (95% CI). ART=antiretroviral therapy. *Slope change per month. †Autocorrelation addressed using Newey–West standard errors to calculate CI, with lag up to 2. ‡Autocorrelation addressed using Newey–West standard errors to calculate CI, with lag up to 3.

Table 3: **Sensitivity analyses taking account of seasonality using two Fourier pairs in Poisson segmented regression models of the impact of COVID-19 lockdown on HIV services in KwaZulu-Natal, South Africa**

ART collections are not recorded as clinic visits, and so difficulties in collecting treatment from community pick-up points during lockdown could have led to an increase in ART collection visits at study clinics. We found no evidence of an increase in study clinic collection visits among people referred into the community ART delivery programme. The number of unscheduled clinic visits in this population decreased in the first week of lockdown (IRR 0·732, 95% CI 0·551–0·974), and was similar to pre-lockdown levels by the end of the study period (1·163, 0·973–1·391).

Discussion

We present data from a large clinic population in KwaZulu-Natal, South Africa, that show an almost 50% decrease in HIV testing and ART initiations at the beginning of the COVID-19 lockdown, with a gradual improvement over the next 3 months towards pre-lockdown levels. ART collection visits decreased slightly and missed ART collection visits increased for a short time. These trends did not differ markedly by age or gender, apart from ART initiations, which remained low among men but gradually improved among women. Overall, the impact of the lockdown tended to be less marked in the rural clinics. These findings suggest that HIV services were generally maintained for people already receiving ART. However, engaging new people into care (through HIV testing and subsequent treatment initiation) was impeded by the lockdown, particularly in urban clinics.

To date, there are few published data from low-income and middle-income countries that quantify the effect of COVID-19 lockdowns on HIV services and patient-related outcomes along the HIV care cascade. The studies that have been published were small, and unlike our analysis, they do not account for long-term trends or seasonal variations, which might have influenced outcomes. A single-site, pre-exposure prophylaxis study[22] of 455 pregnant women in South Africa reported that 34% of patients missed visits before lockdown, increasing to 57% after lockdown (odds ratio 2·36, 95% CI 1·73–3·16). In keeping with our findings, two descriptive analyses from small studies in Kenya (two sites[14] and three sites[15]) reported that 15–30% fewer HIV tests were done in April, 2020, than were done per month in January to March, 2020.[14,15] National laboratory data[23] from South Africa comparing the 2 months pre-lockdown with the first month of lockdown showed decreases of 33% in CD4 cell count (usually done at HIV diagnosis or ART initiation) and 22% in viral load testing (usually done for ART monitoring). However, decreased HIV viral load PCR testing could reflect changes in laboratory system capacity due to increased SARS-CoV-2 PCR testing, rather than changes in patient clinic attendance and ART provision.

An interrupted time series analysis[13] in 11 primary care clinics in rural KwaZulu-Natal found no difference in the number of overall clinic visits, but did show a 20% increase in HIV-related visits immediately after lockdown implementation. The study did not distinguish between HIV testing, ART initiation, or ART collection visits, although the authors hypothesise that the increase in use of HIV services reflected a rush to collect ART in anticipation of further restrictions or drug shortages. In our study, we also found that the COVID-19 lockdown affected the rural clinics less than clinics in urban areas, where lockdown restrictions might have been more heavily enforced. Furthermore, some people who had migrated to urban areas for work might have moved back to rural areas during the lockdown.

Why were HIV testing and ART initiation most affected? A qualitative study in rural Uganda,[24] and anecdotal reports from studies in Kenya,[14,15] suggest that drops in testing could be due to a paucity of personal protective equipment and space for physical distancing in clinics, as well as reduced clinic opening times and staff being redeployed from HIV testing to COVID-19 response activities.[14,24] In South Africa, 28 000 HIV community health-care workers were diverted from HIV outreach to COVID-19 symptom screening,[25] which might have led to fewer referrals to clinics for HIV testing. People without established patterns of engagement in care and regular clinic attendance to collect treatment might also have been less likely to overcome the challenges involved in attending clinics during lockdown. These include increased costs, transport difficulties, the potential need to provide proof of the reason for travel, paucity of resources, and fear of contracting SARS-CoV-2 infection at clinics.[14,15,24] The decrease

in HIV testing, positive HIV tests, and ART initiations were broadly similar, suggesting that the decrease in ART initiations was largely due to decreased testing, rather than additional attrition in the cascade between testing HIV positive and initiating ART.

The lockdown did cause some disruption to ART collections, with a short increase in missed ART collection visits in the first month of lockdown. However, collections rapidly returned to pre-lockdown levels, and most people who missed a visit did attend in the next month, meaning that overall ART collection visits did not decrease drastically in the study clinics. These findings are similar to findings from a survey[26] of 301 patients in a community ART delivery programme in urban KwaZulu-Natal, of whom only 8% reported delaying ART collection during the lockdown,[26] despite 34% reporting increased travel times or costs to collect ART and 51% reporting long waiting times to collect treatment.[26] ART collection might have been prioritised by patients already engaged in HIV care and aware of the importance of maintaining high adherence. Similar to the results of the study from rural KwaZulu-Natal,[13] we found a pre-lockdown increase in ART collection visits, suggesting that people were stocking up in preparation for potential disruptions. Clinics were also able to facilitate ART provision through strategies such as multi-month prescribing and differentiated service delivery programmes.[16,27,28] We plan further analyses to quantify how these strategies were implemented, as they might account for the slight decrease in ART collection visits after lockdown. For this analysis, any unmeasured increase in multi-month prescribing or community ART delivery would bias our results towards larger decreases in clinic ART collection visits after lockdown, rather than masking a substantial decrease in visits. We also found no evidence of an increase in people returning early to study clinics instead of collecting in the community ART delivery programme during lockdown.

Strengths of our study include the large number of routine public sector clinics from both urban and rural settings that are likely to reflect aspects of HIV programmes across southern and eastern Africa; although South Africa's large ART programme might be better resourced and hence more resilient to COVID-19 impacts.[29] Our use of long-term routine data takes into account underlying trends in HIV testing and ART use, and allows more accurate quantification of the effect of the COVID-19 lockdown. However, due to the format of HIV testing data, we were not able to assess HIV testing by weekly counts, which would have allowed a more detailed assessment of shorter-term trends. We were also unable to assess HIV viral load outcomes due to the time taken for these results to be entered into the records system.

Our findings suggest that, in one of the regions most affected by both HIV and COVID-19, the worst modelled scenarios of the impact of COVID-19 on HIV are unlikely to play out. We did not find evidence of large disruptions to ART provision, which is the main driver of morbidity and mortality in published models.[8] Instead, efforts to continue providing treatment to people in the ART programme appear to have been largely successful. Although this evidence is reassuring, COVID-19-related disruptions to ART supply chains and future COVID-19 outbreaks and lockdowns still pose a threat to HIV programmes.[30] Furthermore, our findings suggest that people who are not yet in HIV care were most affected by the lockdown. As countries in Africa consolidate health systems after the first wave of COVID-19, and manage potential second waves, efforts to catch-up with HIV testing and initiation of ART should be prioritised. Integrating HIV and SARS-CoV-2 testing programmes could be beneficial,[31] and WHO and other international organisations are now advocating for an increased focus on HIV self-testing.[28] Innovative strategies to facilitate access to treatment are also required, such as home and community-based ART initiation.[32] Research into HIV service provision in other settings, and the factors that impeded HIV testing and treatment initiation during the COVID-19 lockdown, is needed to inform public health responses to future COVID-19 outbreaks.

In conclusion, engagement of people in HIV care in South African primary care clinics through HIV testing and treatment initiation was severely impacted by the COVID-19 lockdown, with a gradual recovery towards pre-lockdown levels as restrictions eased. There were no large changes in ART collection visits. Strategies to increase HIV testing and treatment initiation should be implemented to address the current and potential future outbreaks.

Contributors

JD, TK, YS, HN, KG, CCB, and NGa conceptualised the study. TK, YS, KG, SM, HN, and NGx oversaw data collection. TK, SM, AJ, HN, and NGx oversaw curation of the data. JD, LL, CB, and KB analysed the data. JD drafted the manuscript. TK, SM, AJ, and JD verified the underlying data. All authors critically reviewed and edited the manuscript and consented to final publication. JD and NGa had full access to all the data and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

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Data sharing

The data used for this analysis cannot be shared publicly because of legal and ethical requirements regarding use of routinely collected clinical data in South Africa. Researchers may request access to the data from the eThekwini Municipality Health Unit and Bethesda Hospital (contact details obtainable upon request to corresponding author).

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19. CHAPTER 11 APPENDIX

19.1. PHILA trial protocol

The following pages contain the PHILA trial protocol which has been approved by the University of Oxford Tropical Research Ethics Committee and the University of KwaZulu-Natal Biomedical Research Ethics Committee.

Study Title: PHILA: Point of care HIV viral Load testing in a community ART programme

Internal Reference Number / Short title: PHILA

OxTREC Ref: 64-19

Date and Version No: Version 2.0 10th November 2021

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Sponsor:	University of Oxford
Funder:	Wellcome Trust PhD Programme for Primary Care Clinicians and the Countess Dowager Eleanor Peel Trust.

Chief Investigator Signature:

Conflict of interest statement

We have no conflicts of interest to declare.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the authorised individuals from the University of Oxford, the Investigator Team and members of the Oxford Tropical Research Ethics Committee (OxTREC), unless authorised to do so.

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1. SYNOPSIS

Study Title	PHILA: Point of care HIV viral Load testing in a community Antiretroviral therapy programme	
Internal ref. no.	PHILA	
Study Design	Open label, single-site, randomised implementation trial with qualitative evaluation of implementation processes	
Study Participants	HIV positive adults (≥18 years) receiving antiretroviral therapy (ART) in the Centralised Chronic Medication Dispensing and Distribution (CCMDD) programme at the Prince Cyril Zulu Clinic in Durban, South Africa.	
Planned Sample Size	Approximately 200	
Planned Study Period	One and a half years	
	Objectives To compare the effect of point-of-care viral load testing versus standard laboratory viral load testing on:	**Outcome Measures**
Primary	• Proportion of participants who have their CCMDD prescription renewed	• Proportion of participants with CCMDD prescription renewed by 3 weeks after enrolment
Secondary	• Time to renewal of CCMDD prescriptions	• Days from enrolment to renewal of CCMDD prescription
	• Time to first ART collection in CCMDD	• Days from enrolment to first ART collection recorded in CCMDD system by 16 weeks from enrolment
	• Proportion of participants retained in all HIV services (clinic and/or CCMDD)	• Proportion of participants with ART collection recorded in clinic notes or CCMDD system 6-16 weeks from enrolment
	• Time to patients receiving viral load results	• Days from enrolment until consultation when viral load results recorded in chart
	• Number of clinic visits required for CCMDD renewal	• Number of clinic visits from enrolment until CCMDD renewal
	• Cost from the patient perspective to have their CCMDD prescription renewed	• Total cost for the patient (including costs such as transport, time, childcare) to have their CCMDD prescription renewed
Tertiary	• To evaluate the diagnostic accuracy of the Xpert HIV-1 VL XC at detecting viraemia at a threshold of 50 copies/mL when operated by a nurse in a routine primary care clinic	• Sensitivity and specificity of the Xpert HIV-1 VL XC to detect viral loads ≥50 copies/mL compared to a laboratory reference assay
Qualitative evaluation	To assess what changes in clinic systems are required to implement point-of-care viral load testing	Staff perspectives regarding implementation of point-of-care viral load testing

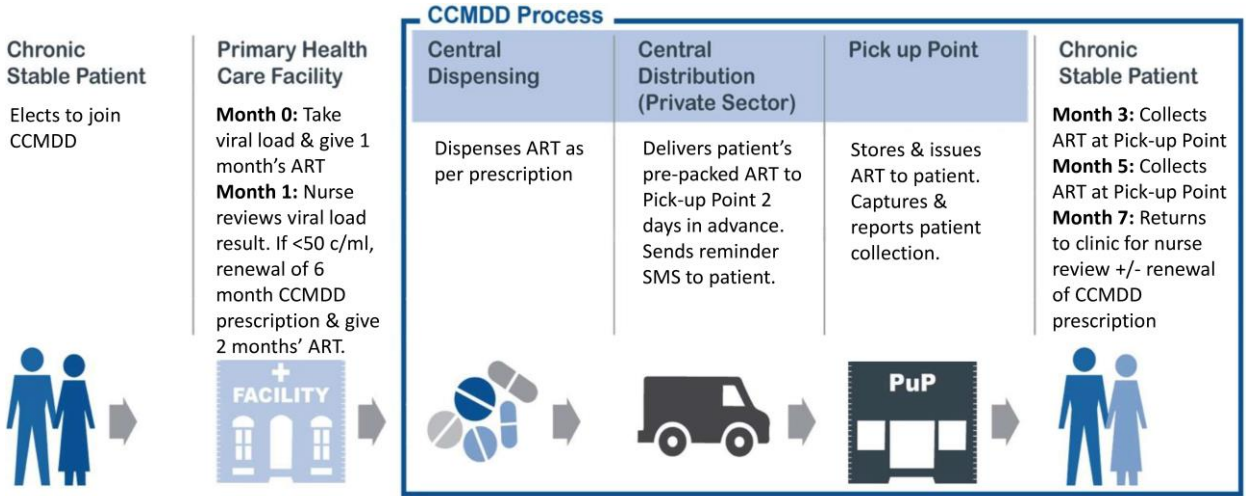
2. ABBREVIATIONS

ART	Antiretroviral Therapy
BREC	Biomedical Research Ethics Committee
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CI	Chief Investigator
CCMDD	Centralised Chronic Medication Dispensing and Distribution system
CRF	Case Report Form
eGFR	Estimated glomerular filtration rate
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
LMIC	Low- and middle-income country
MDRD	Modification of Diet in Renal Disease
NHLS	National Health Laboratory Service
OxTREC	Oxford Tropical Research Ethics Committee
PI	Principal Investigator
PIS	Participant Information Sheet
SOP	Standard Operating Procedure
WHO	World Health Organization

3. BACKGROUND AND RATIONALE

To provide life-saving antiretroviral therapy (ART) for all of its 7.9 million people with HIV[1], the South African government has developed a community ART delivery programme known as the Centralised

Figure 1: CCMDD flow diagram (adapted from[2])



Chronic Medication Dispensing and Distribution system (CCMDD).[2] CCMDD can benefit patients by allowing ART collection at pick-up points (churches, community groups, pharmacies) that are nearer, have longer opening hours and are less congested than clinics. This can improve adherence and retention in care.[3–5] However, only stable patients with a suppressed annual HIV viral load <50 copies/mL are eligible for CCMDD. Currently, taking blood and reviewing the viral load result requires two clinic visits over 7-28 days (Figure 1), as samples are sent away for testing in specialist central laboratories. Patients can struggle to attend both these visits and samples and results often get lost.[6] Without an annual viral load result, patients cannot be re-enrolled in CCMDD, so they either miss treatment or must continue collecting from crowded clinics far from home. Currently, ~300,000 of the 1 million patients in CCMDD are in this situation (so-called 'dormant'), meaning their repeat prescription has been delayed by ≥3 weeks (personal communication, Roma Ramphal, CCMDD Co-ordinator for KwaZulu-Natal).

Figure 2: GeneXpert® System & Xpert® HIV-1 viral load cartridge.



We hypothesise that using a point-of-care viral load test, to provide results in one clinic visit, could expedite CCMDD prescription renewal, reduce clinic visits and decrease the number of 'dormant' patients. The World Health Organization (WHO) recently approved the Xpert® HIV-1 (Cepheid®, Sunnyvale, USA), which can provide a viral load at the point-of-care in <2 hours (Figure 2) from 1 mL of plasma.[7,8] The assay has been validated in multiple settings, including the proposed clinical site,[9] with good correlation and accuracy in a recent meta-analysis (see Box 1, section 7.5).[10] Of note, the assay uses the fully automated molecular GeneXpert® platform, which is already widely used in low- and middle-income countries (LMICs) for diagnosing tuberculosis.[11] In 2017, an estimated 9,449 GeneXpert® instruments had been procured in 130 countries.[12] If the Xpert HIV-1 VL assay can be implemented in routine services, it could become a vital tool for HIV programmes across LMICs, particularly in Southern Africa. Recently, Cepheid has launched a newer, CE-IVD approved, dual target version, the Xpert HIV-1 VL XC, which utilises the same GeneXpert platform, and has been successfully validated in the study clinic (n = 164, Pearson correlation co-efficient 0.97 (95% CI 0.95, 0.99), mean bias -0.10 log copies/mL, (-0.54 to 0.34), specificity at viral load threshold of 50 copies/mL = 0.96 (0.91, 0.99), sensitivity = 0.93 (0.82, 0.98), manuscript in draft). The m-PIMA HIV-1/2 VL (Abbott, Chicago, USA), a similar point-of-care viral load assay, has also received WHO approval.

We performed the first pilot randomized trial of the Xpert HIV-1,[13] which demonstrated that in a research clinic amongst people recently initiated on ART, point-of-care testing increased retention in care, viral suppression, and earlier first referral into CCMDD.[14] However, we do not know whether these benefits apply in routine, non-research primary care clinics, and amongst people who need longer term viral load monitoring for renewal of CCMDD prescriptions. Implementation of point-of-care viral load testing may not be feasible in non-research settings, as it requires multiple steps including centrifuging samples, assay maintenance, quality assurance and reorganisation of clinic flow, to ensure that results are delivered and managed appropriately.

Therefore, we aim to implement point-of-care viral load testing in a routine HIV primary care clinic in South Africa, and assess whether it can improve access to ART by improving renewal of CCMDD prescriptions.

4. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure
Primary Objective To compare the effect of point-of-care viral load testing versus standard laboratory viral load testing on the proportion of participants who have their CCMDD prescription renewed	**Primary Outcome:** Proportion of participants in each arm with renewal of CCMDD prescription recorded within CCMDD database (binary)	3 weeks post enrolment
Secondary Objectives To compare the effect of point-of-care viral load testing versus standard laboratory viral load testing on:		
a) Time to renewal of CCMDD prescriptions	a) Days from enrolment to renewal of prescription in CCMDD database	a) Up to 16 weeks post enrolment
b) Time to first ART collection in CCMDD	b) Days from enrolment to first ART collection recorded in CCMDD database	b) Up to 16 weeks post enrolment
c) The proportion of participants retained in all HIV services (clinic and/or CCMDD)	c) Proportion of participants in each arm with ART collection recorded in clinic notes or CCMDD system	b) 6 - 16 weeks post enrolment
d) Time to patients receiving viral load results	d) Days from enrolment until consultation when viral load results recorded in chart	d) Up to 16 weeks post enrolment
e) The number of clinic visits required for CCMDD renewal	e) Number of clinic visits from enrolment until CCMDD renewal	e) Up to 16 weeks post enrolment
f) Cost from the patient perspective to have their CCMDD prescription renewed	f) Total cost for the patient (including costs such as transport, time, childcare) to have their CCMDD prescription renewed	f) At enrolment and subsequent visits up to and including CCMDD renewal
Tertiary Objectives To evaluate the diagnostic accuracy of the Xpert HIV-1 VL XC (or similar point-of-care viral load assay) at detecting viraemia at a threshold of 50 copies/mL when operated by a nurse in a routine clinic	Sensitivity and specificity of the Xpert HIV-1 VL XC (or similar assay) to detect viral loads ≥50 copies/mL compared to a laboratory reference assay	At enrolment
Qualitative Study Objectives:		During enrolment when point-of-care

To assess what changes in clinic systems are required to implement point-of-care viral load testing?	Staff perspectives regarding implementation of point-of-care viral load testing in a routine clinic	testing is being implemented, and after study conclusion

We hypothesise that POC VL testing will lead to faster renewal of CCMDD prescriptions due to results being available more rapidly. We have chosen to assess the primary outcome of CCMDD renewal at 3 weeks as the interval currently used within the CCMDD programme to define 'dormant' patients is not having a CCMDD prescription renewed by 3 weeks after expiration of the current prescription. Our trial primary outcome therefore aligns well with programmatic outcomes that are important to CCMDD policy makers and health system managers .

5. STUDY DESIGN

This will be a single-site, open label, individually randomised, implementation trial comparing point-of-care viral load testing with standard laboratory based viral load testing within CCMDD (Appendix A). Study implementation will be assessed using in-depth staff interviews and focus groups.

HIV positive adults who are receiving ART in CCMDD will be recruited when they are due a repeat HIV viral load to guide renewal of their CCMDD prescription. After screening, eligible, consenting participants will be enrolled and randomized 1:1 to the point-of-care intervention arm, or standard-of-care. Participants in the standard of care arm will have standard laboratory viral load and creatinine testing performed by the National Health Laboratory service. Participants in the point-of-care arm will have point-of-care viral load testing (Xpert® HIV-1 VL XC, Cepheid, Sunnyvale, CA, or similar assay) and point-of-care creatinine testing (Statsensor Xpress-I, Nova Biomedical, Waltham, MA, US, or similar assay) (Table 1). Point-of-care results will be provided in the same clinical visit, where possible. If point-of-care results are not available in the same visit, the participant will be asked to return for the result on a date scheduled at the staff and participant's discretion (normally between 1 and 28 days). In the standard-of-care arm, participants will need to return after 7-28 days to receive their results, as results may not be available before 7 days. All patients with a viral load <50 copies/mL will be given 8-12 weeks of ART and have their CCMDD prescription renewed for subsequent ART collection after 8 or 12 weeks at their community pick-up point. All prescriptions and ART collections are routinely captured electronically and recorded in a central CCMDD database, while viral load results, clinic visits and clinic ART prescriptions are documented in clinical charts and routinely captured in the clinic's TIER.net database. The research team will monitor the CCMDD and TIER.net databases, as well as clinical charts, to record all viral load results prescriptions and ART collections for each participant until 16 weeks post-enrolment (Appendix B).

During implementation of point-of-care viral load testing and after the study ends, a research assistant will perform in depth interviews and focus group discussions with clinic staff, using topic guides informed by Normalisation Process Theory to explore implementation of point-of-care testing and barriers to CCMDD prescription renewal (see section 11). Interviews and focus groups will be audio recorded, transcribed and analysed using Framework analysis.

6. STUDY SETTING

The study will take place at the Prince Cyril Zulu Clinic with support from the adjacent CAPRISA eThekwini Clinical Research Site. The Prince Cyril Zulu Clinic is a large public clinic situated next to the main transport hub in central Durban and provides HIV, tuberculosis sexual health and primary care services to a large, diverse, urban population. In 2016 the Prince Cyril Zulu Clinic was one of the first clinics to implement the CCMDD programme in Durban, and now cares for approximately 10,000 people living with HIV. However, if necessary to complete enrolment timeously, participants can be recruited from another HIV clinic or from CAPRISA's clinical research site in Vulindlela.

7. PARTICIPANT IDENTIFICATION AND RECRUITMENT

7.1. Study Participants

HIV positive adults (≥18 years old) receiving ART in CCMDD and who are due a viral load test for renewal of their CCMDD prescription.

7.2. Inclusion Criteria

The participant may enter the study if ALL of the following apply:

- Participant is willing and able to give informed consent for participation in the study.
- HIV positive adult, Male or Female, aged ≥18 years.
- Receiving ART in CCMDD and willing to continue in CCMDD
- Due a renewal of their prescription in CCMDD
- Requires an HIV viral load test for renewal of their CCMDD prescription

7.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Not eligible for CCMDD as per South African Department of Health criteria:
    - Known to be pregnant or breast feeding
    - Current tuberculosis
    - Known to have diabetes and with blood glucose >7.0mmol/L
    - Known to have hypertension with blood pressure ≥140/90 mmHg
    - Other medical condition requiring regular clinical consultations

8. STUDY PROCEDURES

8.1. Recruitment

HIV-positive patients who are in CCMDD and due viral load testing for renewal of their prescription will be identified by clinic staff and offered referral to the study team.

8.2. Informed Consent

A research assistant or research nurse will approach patients at the clinic who have been identified as awaiting CCMDD renewal. The research assistant or research nurse will describe the study, address any questions and ask for voluntary participation. If the participant is willing, they will be invited to a private room in the clinic where the research assistant or research nurse will present written and verbal versions of the Participant Information and Informed Consent detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as they wish to consider the information, and the opportunity to question the Investigator or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief Investigator. A copy of the signed Informed Consent will be offered to the participant. The original signed form will be retained at the study site.

The participant must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed.

8.3. Screening and Eligibility Assessment

After informed consent has been obtained, a research nurse will review the study inclusion/exclusion criteria with the patient. Demographics and a brief medical history will be taken. The patients clinical and laboratory record will be reviewed, and blood pressure will be measured. Pregnancy testing will be performed for all women aged 18-55 who report possible pregnancy and who have not yet had a pregnancy test on that clinic visit. Patients known to have diabetes will have a random finger prick capillary blood glucose measurement. Patients deemed eligible for the study will be enrolled on the same day as screening.

8.4. Randomisation, blinding and code-breaking

A CAPRISA statistician will generate the allocation sequence using random numbers generated in a statistical software program such as STATA 14.0 (Statacorp, Texas, USA) or SAS 9.4 (SAS Institute Inc., Cary, USA). The allocation sequence will contain variable block sizes, with participants randomised in a 1:1 ratio to the intervention or standard of care arm. The allocation sequence will be programmed into the REDCap (Vanderbilt University, Nashville, USA) enrolment electronic case report form (eCRF). All study staff apart from the statistician and data manager will be blinded to the allocation sequence. At enrolment, the research assistant or research nurse will complete the enrolment eCRF, which will automatically assign the intervention allocation and generate a unique participant identification number (PID). As this is an open label study, study staff, clinic staff and participants will not be blinded to intervention allocation.

8.5. Study enrolment visit

8.5.1 Baseline demographics and medical history

At enrolment, a research assistant or research nurse will ask participants to provide information on their demographic, social and medical history.

8.5.2 Laboratory testing

In both arms, participants will have viral load and creatinine testing to assess eligibility for CCMDD (see Table 1). Creatinine results will be used to calculate the estimated glomerular filtration rate (eGFR), using the Modification of Diet in Renal Disease (MDRD) formula.

For participants randomised to the point-of-care arm, a phlebotomist or nurse will draw venous blood for point-of-care viral load testing in the clinic. Results should be available in approximately two hours. The nurse or phlebotomist will also take a capillary finger-prick sample to perform point-of-care creatinine testing on the Statsensor Xpress-i (or similar assay), which provides a result in 90 seconds.

In the standard-of-care arm, venous blood will be drawn by a nurse or trained phlebotomist for laboratory HIV viral load and laboratory serum creatinine, and sent to the standard of care National Health Laboratory Service (NHLS) for testing as per routine clinic procedures.

8.5.3 Management of results and CCMDD prescription renewal

In both arms, clinic staff will be encouraged to act on results as soon as possible. In the point-of-care arm, results could be available in the same visit, or if not available or the client cannot wait, they will be available at the next clinic visit scheduled at staff and patient's discretion. In the standard of care arm, laboratory viral load results are normally available after 7 days, and clients typically return after 7 -28 days for results, depending on their availability, ART supply and clinic schedules.

Participants who are eligible for CCMDD with viral load <50 copies/mL and eGFR >50 mL/min/1.73 m^2 will have their prescription renewed by a nurse using the standard Department of Health CCMDD electronic prescribing form. If the electronic system is offline or unavailable, the standard Department of Health paper prescribing form will be used. The renewed prescription will allow the participant to collect their ART after 8 and 16 weeks at their community pick up point. Pick up dates will be recorded in their hand held CCMDD card. The nurse will also supply the client with ART to cover the 8 week period up to their next CCMDD pickup.

Patients with viral load ≥50 copies/mL or eGFR <50 mL/min/1.73 m^2 will not be eligible for CCMDD prescription renewal (Table 1). Participants in both arms with an eGFR of <50 mL/min/1.73 m^2 will have a repeat laboratory creatinine sample taken and will be referred to the clinic physician for assessment with the result, as is standard practice in the clinic. Participants in both arms with a detectable viral load ≥50 copies/mL will be referred to a counsellor for enhanced adherence counselling and will continue ART collection at the clinic as per South African HIV guidelines.[15,16]

Table 1: Viral load and eGFR results and CCMDD eligibility

Test	Result	CCMDD eligibility	Action
HIV Viral load	< 50 copies/mL	Potentially eligible	Renew CCMDD prescription if eGFR >50 mL/min/1.73 m^2

	≥50 copies/mL	Not eligible	Refer to counsellor for enhanced adherence counselling
eGFR	>50 mL/min/1.73 m^2	Potentially eligible	Renew CCMDD prescription if viral load normal
	≤50 mL/min/1.73 m^2	Not eligible	Take laboratory creatinine test and refer to clinician with result

8.6. Follow up and outcome assessment

Assessment of study outcomes such as subsequent CCMDD prescriptions, clinic visits, CCMDD ART pick-ups and time to availability of viral load results will be captured by the study team at 0, 8 and 16 weeks by reviewing participants routine clinical charts, laboratory results and the CCMDD electronic database (Appendix B). If no CCMDD renewal prescription is found in the CCMDD electronic database, and no ART collection is found in the clinical chart, we will follow up with the CCMDD hotline for healthcare providers to establish whether any referral was received. Between 16 and 18 weeks, any participant with no CCMDD renewal and no record of ART collection at the clinic will be contacted by the research team to establish the reason for not collecting in CCMDD. This is in accordance with standard South African guidelines for tracking patients on ART who have missed clinic appointments.

8.7. Extended follow up of routine data

For participants who agree, research staff may access routine medical records, prescription data and laboratory results for up to five years after the study exit visit, in order to determine longer term retention in care, ART adherence and viral load results. For participants who are lost to follow up, and who provided consent at enrolment, the participants vital status may be checked on the South African National Population Register.

8.8. Sample Handling

8.8.1 Point-of-care testing

Point-of-care viral load testing will be performed by a nurse, phlebotomist or technician in the clinic, who will have received comprehensive training on all aspects of performing point-of-care viral load testing and been assessed as competent by the CAPRISA laboratory site manager. All point-of-care viral load testing procedures will be performed in a specially prepared room in the clinic, using a small centrifuge and the Xpert HIV-1 VL XC assay on the GeneXpert platform, or a similar validated point-of-care assay (e.g. the m-PIMA HIV-1/2 VL). Testing will be performed following manufacturer instructions, using approximately 4 mLs of venous blood, drawn using aseptic technique. The sample will be centrifuged to separate approximately 1 mL of plasma which will be pipetted into the assay cartridge. The cartridge will be placed in the fully automated assay platform, with results available after approximately 90 minutes. In the case of an invalid result, a repeat blood sample may need to be drawn for point-of-care testing. If repeat point-of-care testing is not possible (e.g. machine failure) the repeat sample will be sent for standard laboratory

testing. Error codes will be checked regularly and reported to the CAPRISA laboratory staff and manufacturer to identify and correct sample processing or machine errors.

Point-of-care creatinine testing will be performed by a nurse or phlebotomist using the Statsensor Xpress-i, a small hand-held device similar to a glucometer that measures creatinine levels in 90 seconds. The nurse or phlebotomist will use a standard, single-use lancet to obtain a finger-prick sample of capillary whole blood, under aseptic technique, and apply it to the Statsensor test strip. Prior to use, each new lot of Statsensor® strips will be tested using manufacturer supplied linearity controls. Creatinine values will be used to calculate eGFR with a standard, validated MDRD eGFR calculator app (e.g. "eGFR Calculators" by National Kidney Foundation).

8.8.2 Standard laboratory testing

Laboratory viral load and creatinine testing will be performed by a nurse or phlebotomist in the clinic according to standard clinic procedures. In brief, approximately 9 mLs of venous blood (4 mLs for viral load testing, 5 mLs for creatinine testing) will be drawn using aseptic technique and transported on the same day to the National Health Laboratory Service for testing using their routine laboratory assays. Currently, the National Health Service performs creatinine testing on the Dimension® EXLTM 200 (Siemens Healthcare, Erlangen, Germany) at Addington Hospital, and viral load tests on either the Realtime m2000 assay (Abbott, Chicago, USA) at the Addington Hospital Laboratory, or the Cobas 6800/8800 assay (Roche, Basel, Switzerland) at the Inkosi Albert Luthuli Hospital Laboratory, depending on machine availability and capacity.

8.8.3 Storage blood

Participants who provide additional consent may also have 4 mLs of venous blood drawn for storage and retrospective ART drug level and HIV viral load and drug resistance testing. At enrolment, 5 mLs of urine will also be taken for storage and ART drug level testing. Samples will be stored in the CAPRISA biorepository according to Good Clinical Laboratory Practice for up to ten years and will be made available to the study team or other approved investigators who have obtained ethical approval for additional projects. After ten years, remaining stored samples will be disposed of.**8.8.4 Potential evaluation of newer point-of-care assays**

If new point-of-care viral load assays become available, we may use samples from this study to compare results from the new assay to the laboratory reference assay. The new assay results would be for validation purposes only and would not be used to guide clinical management.

8.9. Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or study requirements
- Withdrawal of Consent

Participants who withdraw from the study will not be replaced. Data for participants who withdraw will be included in intention to treat analysis. The reason for withdrawal will be recorded in the Case Report Form.

8.10. Definition of End of Study

The end of study is the date 18 weeks after enrolment of the last participant.

9. SAFETY REPORTING

This study does not involve an investigational medicinal product or intervention that affects physiology, and therefore will not require serious adverse event reporting. However, for completeness we will report all cases of mortality in the study to the University of KwaZulu-Natal's Biomedical Research Ethics Committee (BREC).

10. STATISTICS AND ANALYSIS

10.1. Description of Statistical Methods

At the conclusion of the study, we will test the hypothesis that point-of-care viral load testing is superior to standard laboratory testing by calculating the absolute differences in the proportion achieving study outcomes between the two arms, using intention to treat analysis.

10.2. Analysis of Outcome Measures

10.2.1 Primary outcome

We will present the absolute difference between the two arms in proportions achieving the binary primary outcome of CCMDD prescription renewal by 3 weeks. We will present 95% confidence intervals calculated using Newcombe Wilson method, and test the null hypothesis of no difference between the two arms using the chi-squared test. All participants enrolled in each arm will be included in the primary intention to treat analysis.

10.2.2 Secondary outcomes

We will use Cox proportional hazard models to compare time to receipt of viral load results, time to renewal of CCMDD prescriptions and time to first ART collection in CCMDD between the two arms. If a high proportion of events occur on days 0 to 1 post-enrolment, then a Cox model may not be suitable, and we will instead compare proportions achieving the outcome of interest at 2, 4, 8, 12 and 16 weeks post enrolment, using chi-squared tests and Newcombe Wilson 95% confidence intervals. Retention in HIV services will be defined as collecting ART from either the clinic or CCMDD between 6 and 16 weeks post enrolment. We will compare the proportion retained in HIV services between the two arms using chi-squared tests and Newcombe Wilson 95% confidence intervals. Amongst those with CCMDD renewals, we will compare the mean number of clinic visits from enrolment until CCMDD prescription renewal, and the mean total cost to the participant to attend these clinic visits, using Students t-Test. All participants enrolled in both arms will be included in intention to treat analyses of the above secondary outcomes.

10.2.3 Tertiary Objectives

We will calculate the sensitivity and specificity, with 95% confidence intervals, of the point-of-care assay to detect viral loads ≥50 copies/mL compared to a laboratory reference assay. All enrolment point-of-care viral load results will be compared to a laboratory reference viral load assay (e.g. the Cobas 6800/8800 assay (Roche, Basel, Switzerland)) using storage blood taken at the same time point.

10.3. The Number of Participants

Based on current clinic performance, we assume that 75% of patients in the standard of care arm will achieve the primary outcome of CCMDD renewal by 3 weeks. Assuming a 15% improvement in the point-of-care arm, a sample size of 100 participants per arm will have 80% power to demonstrate superiority with a two-sided alpha of 95% (Table 2). As all enrolled participants will be included in the final intention to treat analysis, we have not adjusted for loss to follow up or potential withdrawals.

Table 2: Sample size and power estimates

Proportion achieving the primary outcome	Power (beta)	Estimated total sample size
POC 90% vs lab 70%	80%	124
POC 85% vs lab 65%	80%	146
POC 80% vs lab 60%	80%	164
POC 90% vs lab 75%	**80%**	**200**
POC 90% vs lab 80%	80%	398
POC 80% vs lab 70%	80%	588

11. DATA MANAGEMENT

11.1. Access to Data

Direct access will be granted to authorised representatives from the University of Oxford and CAPRISA for monitoring and/or audit of the study to ensure compliance with regulations.

11.2. Data Handling and Record Keeping

The research team will capture study data using standardised electronic CRFs in REDCap. All data entry will undergo three stages of quality control including pre-programmed data validity checks in electronic CRFs, immediate source document review, and weekly quality reports generated by REDCap. The participants will be identified by a unique study specific number and/or code in any database. The name and any other identifying detail will NOT be included in any study data electronic file.

12. QUALITATIVE STUDY

12.1. Background

Point-of-care diagnostics have been used widely in healthcare systems in many low and middle income countries.[17] In HIV programmes, some tests such as rapid, lateral flow assays for diagnosis of HIV, have been evaluated, endorsed and incorporated into guidelines by the World Health Organization and successfully adopted in many settings.[18] However, other assays, such as more complex molecular polymerase chain reaction technologies for tuberculosis, have remained as laboratory tests despite being marketed as point-of-care assays.[17] A large systematic review of barriers to point-of-care HIV diagnostic implementation in low and middle income countries found that in 132 studies, integration of the point-of-care test into clinical work flows was the most commonly identified challenge to test utilisation.[19] However, there are few published implementation projects that have used a theory-based approach to assess implementation of point-of-care tests in healthcare systems, particularly in LMICs. One theory that has been widely used to assess implementation of new technologies in healthcare is Normalisation Process Theory. Normalisation Process Theory aims to identify what is needed to 'normalise' use of a technology in a healthcare system.

12.2. Aim

We aim to assess staff perspectives on implementation of point-of-care viral load testing as part of the CCMDD programme.

12.3. Study design

During trial enrolment when implementation of point-of-care viral load testing is taking place, a trained research assistant with experience of qualitative research will perform the first round of semi-structured interviews with approximately 8-10 staff, and a focus group with approximately 8-10 staff. After completion of enrolment, we will perform a second round of interviews and focus group, to assess perspectives on implementation of point-of-care viral load testing and integration with CCMDD.

12.4. Participants

Approximately 10-15 staff involved in viral load testing and CCMDD will be approached to participate in this qualitative study. Staff will include counsellors, phlebotomists, nurses, pharmacy staff, laboratory staff, doctors and health service managers. Focus groups and in-depth interviews may consist of the same or different staff members. However, we will endeavour to include the same staff members in the first and second round of interviews and focus groups.

12.5. Procedures

12.5.1. Informed consent

A trained research assistant will approach staff in the clinic, explain the nature of the project and offer participation. Should the staff member be interested, they will be taken to a private space and provided with written and verbal versions of the Qualitative Study Participant Information and Informed Consent. The research assistant or other study team member will answer any questions that the staff member may have, and it will be clearly stated that staff are able to refuse to participate without adverse consequences

for their working life. Once written informed consent has been provided, a copy will be offered to staff participant, and the original will remain with the research team.

12.5.2. Interviews and focus groups

Once the Informed Consent Form has been signed, the research assistant will use predetermined topic guides to conduct interviews and/or focus groups in a private room at the study clinic, or if necessary, at another suitable private venue of the participant's choice. Interviews will last approximately 30-60 minutes, and focus groups 45-75 minutes. We will make an audio recording of interviews and focus group discussions. If a participant does not consent to audio recording, we will take a written recording of the interview or focus group.

12.5.3. Analysis

Audio and written recordings will be anonymised and translated from isiZulu (when necessary) and transcribed. Data will be analysed using thematic analysis as described by Attride-Stirling and reported accordingly.[20]

13. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

Study documentation including participant information sheets, informed consent forms, regulatory files, standard operating procedures, source documentation and electronic CRFs will be subject to internal quality audits by the CAPRISA Quality Assurance team, in accordance with CAPRISA standard operating procedures. CAPRISA routinely measure quality control and retention rates on all studies. The study will be conducted in accordance with relevant regulations and standard operating procedures.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

14.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

14.3. Approvals

The protocol, participant information sheet and informed consent form, topic guides and any proposed advertising material will be submitted to OxTREC and BREC for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all amendments to the original approved documents.

14.4. Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all study documents and any electronic database. All documents will be stored in a secure cabinet in the locked research office, and will only be accessible by study staff and authorised personnel. The electronic 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. The study will comply with the General Data Protection Regulation (GDPR), which requires that personal data must not be kept as identifiable data for longer than necessary for the purposes concerned.

For the qualitative evaluation of implementation processes, interviews and focus group discussions will take place in a private room. We will make a written record during the focus group or interview, or from the recorded audio, but we will not write down any information that might identify participants or others. For example, if the participant mentions names of colleagues, we will not write those names down. The recording and notes from interviews and focus group discussions will be stored in a locked cabinet and only the staff working on this study will be able to use them. We will destroy the recordings when the research is completed. Data will never be reported in a way that could potentially reveal a single participant's identity. If during interviews or focus groups a staff member reveals practice which is not in line with professional standards and may cause harm to patients, we will discuss this with the staff member and the clinic manager.

14.5. Expenses and Benefits

Patient participants will be reimbursed ZAR150 (approximately £8.00) after the enrolment visit for their participation in the research. This is in accordance with CAPRISA Policy on Study Participant Compensation, which adhere to the Department of Health and SAPHRA guidelines, and will consider time of visits, inconvenience of study procedures, and transport expenses.[21] Reasonable travel expenses for any visits additional to normal care will be reimbursed.

Staff participants will not be reimbursed as interviews or focus groups will take place during working hours, at a mutually convenient time that has been agreed with the clinic manager.

14.6. Reporting

The CI shall submit an Annual Progress Report to OxTREC and BREC on the anniversary of the date of approval of the study. In addition, the CI shall submit an End of Study Report to OxTREC and BREC within 12 months of completion of the study. If we extend follow up of routinely collected clinic and laboratory data, for up to five years after the last study exit visit, the study will remain under annual review by OxTREC and BREC while those data are being collected.

14.7. Other Ethical Considerations

All study participants will be HIV-positive and may face HIV-related stigma. Therefore, maintaining confidentiality is particularly important in this study (see section 13.4).

For staff interviews and focus groups, there is the possibility that they will feel unable to refuse participation, or that they will feel challenged at being interviewed about aspects of their work. While every effort will be made to maintain staff confidentiality, due to the small numbers of staff participating in the study it may be possible for superiors and colleagues to infer their identity indirectly. Therefore, the option to refuse participation without implications in their work will be made clear in the informed consent process. We will also warn staff about the risk of colleagues and superiors being able to infer their identity indirectly. Staff will not be asked questions which could threaten their work position or personal questions about their lives. Questions will focus work-related issues that are already likely to have been discussed in other settings, as the clinic team have implemented point-of-care viral load testing and CCMDD.

15. FINANCE AND INSURANCE

15.1. Funding

This study is funded by a fellowship from Wellcome Trust PhD Programme for Primary Care Clinicians and the Countess Dowager Eleanor Peel Trust Medical Grants Scheme.

15.2. Insurance

The University of Oxford has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London).

16. PUBLICATION POLICY

Findings from this study will be presented at academic conferences and submitted to peer reviewed journals for Open Access publication in accordance with Wellcome Trust policies for Wellcome Trust funded research. Authorship and acknowledgements will follow the International Committee of Medical Journal Editors guidelines. Author accepted manuscripts will be posted on the investigators' institutional websites.

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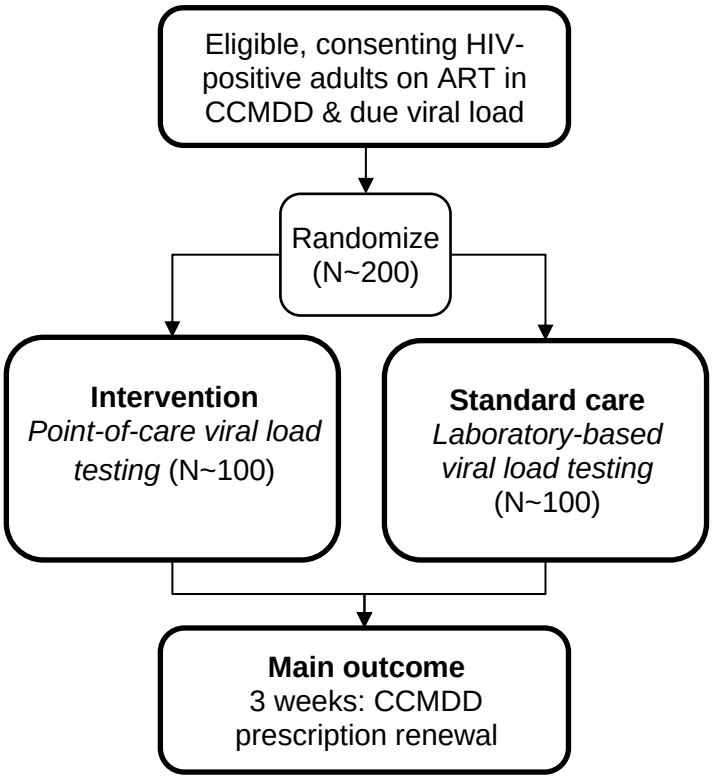
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18. APPENDIX A: STUDY FLOW CHART



19. APPENDIX B: SCHEDULE OF STUDY PROCEDURES

		Enroll	Outcome assessment	
Weeks in study		0	8	16
Informed consent		X		
Socio-demographics		X		
Medical History		X		
Vital signs +/- urine pregnancy test		X		
Eligibility screen		X		
Randomization		X		
POC Arm	**POC viral load (4 mLs venous blood) & creatinine (1.2 µL finger-prick capillary blood)**	X		
SOC Arm	**Lab viral load & creatinine (9 mL venous blood)**	X		
Optional storage blood and urine		X		
See clinic nurse for ART		X		
Outcome: Electronic CCMDD prescription renewal			X	X

POC: point-of-care, SOC: standard of care, ART: antiretroviral therapy

20. APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1.	1.1	10th November 2019	Jienchi Dorward	Addition of Mrs Hope Ngobese and Dr Yukteshwar Sookrajh as co-investigators; addition of alternative, approved point-of-care assays that could be used in the study, instead of the Xpert HIV-1 VL; addition of optional extended follow up of participants routinely collected clinic data and vital status in the South African National Population Register; simplification of the description of procedures for invalid point-of-care results; change in the duration of blood storage from 2 to 10 years; addition of the potential evaluation of new point-of-care assays

2.	2.0	10th November 2021	Jienchi Dorward	Change of planned sample size to 'approximately 200'; change of primary outcome from CCMDD renewal at 12 to 3 weeks; change of assessment of secondary outcomes from 12 to 16 weeks to reflect changes in CCMDD; addition of time to ART collection in CCMDD as secondary outcome; replacement of patient flow outcome with cost of CCMDD renewal from patient perspective outcome; addition of the novel Xpert HIV-1 VL XC instead of the Xpert HIV-1 VL; addition of potential to use another site if necessary to complete recruitment; change in inclusion criteria to allow non-annual viral loads to be used; change in exclusion criteria to 'known pregnancy'; amendment of optional stored samples at enrolment to include urine, and to allow ART drug level, and HIV drug resistance testing.

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