FROM CLINIC TO COMMUNITY:

NOVEL APPROACHES FOR DECENTRALIZING HIV SERVICE DELIVERY TO IMPROVE PERSON-CENTERED CARE IN SOUTH AFRICA

Melody Wang

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Reading Committee:

Paul K. Drain, Chair

Monisha Sharma

Anjuli D. Wagner

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Abstract

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Chair of the Supervisory Committee:

Paul K. Drain

Department of Global Health

This dissertation was undertaken to investigate novel strategies and diagnostic tools for supporting decentralized health services to increase access to care for people living with HIV (PLHIV). The UNAIDS established the 95-95-95 targets to end the HIV epidemic by 2030, with the goal of having 95% of all PLHIV who are accessing antiretroviral treatment (ART) maintaining viral suppression.[1] However, among the approximately 39 million PLHIV worldwide, only half have achieved viral suppression.[2] As overburdened clinics devote limited resources to initiate and monitor millions of PLHIV on ART, there is growing consensus that a blanket model of care is no longer a sustainable strategy for providing life-long HIV services.[3]

Diagnostic services are a fundamental component of the HIV cascade of care. However, healthcare providers often rely on conventional laboratory-based testing for viral load (VL) monitoring, which can

have lengthy turnaround times that delay clinical decisions, and self-reported adherence, which can be unreliable and biased.[4-7] In **Chapter 1**, we present costing estimates for implementation of point-of-care (POC) testing technologies that allow for objective measures of adherence and VL monitoring. Microcosting of POC urine tenofovir testing was conducted within the *Simplifying Treatment & Monitoring for HIV* (STREAM HIV) study, a randomized implementation trial evaluating POC TFV and HIV VL testing in public health clinic settings in KwaZulu-Natal, South Africa. POC HIV VL testing costs were updated from the *Simplifying HIV Treatment and Monitoring* (STREAM) pilot study conducted in 2017.[8] Time and motion analysis was also conducted to capture participant and provider time needed for POC TFV testing. These POC technologies have the potential to streamline adherence support and VL monitoring and our findings may inform future policies and budgetary planning for ART monitoring in South Africa and other low- and middle-income countries (LMICs).

Compared to other countries, South Africa bears more than double the burden of the HIV epidemic, with almost one in five adults living with HIV and 5.7 million PLHIV on ART in 2022.[9] Differentiated, community-based ART delivery models may reduce the burden on the healthcare system, while also giving clinically stable PLHIV greater access to ART.[10] In **Chapter 2 and 3**, we explore the Centralized Chronic Medication Dispensing and Distribution (CCMDD) program in South Africa. The CCMDD program is a public-private partnership established over a decade ago that allows patients referred by healthcare workers in government clinics to collect ART refills at private pharmacies or community-based organizations.[11-13] This program diverts clinically stable patients from overwhelmed clinic settings and facilitates differentiated ART delivery for over 1.7 million people, becoming the largest differentiated care program in the world.[12-14]

In **Chapter 2**, we investigate the differentiated care CCMDD program in South Africa and determine how participation impacted patient clinical outcomes. We conducted a secondary analysis of cohort data from

the STREAM pilot study in Durban, South Africa and estimated the association between routine patient participation in the CCMDD program and clinical outcomes of viral suppression (<200 copies/mL) and retention in care. Our analyses in this chapter show the real-world effectiveness of the CCMDD program in maintaining these clinical outcomes compared to standard clinic-based ART provision in South Africa. These findings support national implementation of CCMDD and also highlights the need to increase differentiated care access among vulnerable sub-populations living with HIV and not just among clinically stable patients.

In **Chapter 3,** we delve deeper into gaps in the CCMDD program and employ novel barrier prioritization methods to determine which barriers are the most prevalent, frequent, and critical for ART clients, and thus pivotal to address for successful program implementation. Rapid evidence review was conducted to determine a range of barriers that were then tailored to the KwaZulu-Natal context using in-country expertise. Likert questionnaires were developed using the Theoretical Domains Framework (TDF). Primary data collection was conducted among participants in the *Point-of-care HIV Viral Load Testing in a Community Antiretroviral therapy program* (PHILA) randomized implementation trial investigating POC VL testing among PLHIV enrolled in the CCMDD program in Durban, South Africa. Our analyses identified key barriers that were frequently experienced and perceived as highly critical for continued participation in the CCMDD program. Identification of these high-priority barriers may provide guidance for future strategies addressing implementation challenges for differentiated ART delivery. Both Chapter 2 and 3 present findings that can be used to support and improve scale-up of the national differentiated care program in South Africa and other LMICs.

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DEDICATION

For the healthcare workers and community in Durban, KZN: If I ever forget why I do this work, I need only to think of your resilience and care throughout unspeakable obstacles.

CHAPTER 1. COST AND CLINICAL FLOW OF POINT-OF-CARE URINE TENOFOVIR FOR TREATMENT MONITORING AMONG PEOPLE LIVING WITH HIV INITIATIVE ART IN SOUTH AFRICA

Authors:
Melody Wang[1], Pravikrishnen Moodley[2], Mlungisi Khanyile[3], Elliot Bulo[4], Makhosazane Zondi[3], Keshani Naidoo[3], Yukteshwar Sookrajh[4], Jienchi Dorward[5], Nigel Garrett[3,8], Paul K Drain[1,6,7], Monisha Sharma[1,7]
Affiliations:

1. Department of Global Health, University of Washington, Seattle, WA
2. National Health Laboratory Service (NHLS), South Africa
3. Centre for the AIDS Program of Research in South Africa (CAPRISA), University of KwaZulu-Natal, Durban, KwaZulu-Natal, South Africa
4. eThekwini Municipality Health Unit, eThekwini Municipality, Durban KwaZulu-Natal, South Africa
5. Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, Oxfordshire, United Kingdom
6. Department of Medicine, University of Washington, Seattle, WA
7. Department of Epidemiology, University of Washington, Seattle, WA
8. Discipline of Public Health Medicine, School of Nursing and Public Health, University of KwaZulu-Natal, Durban, KwaZulu-Natal, South Africa

1.1 Abstract

Point-of-care (POC) urine tenofovir (TFV) tests can provide timely results regarding antiretroviral therapy (ART) adherence to support management of HIV treatment in clinics. However, there are a lack of data on costs and feasibility of integrating POC testing into HIV clinics in sub-Saharan Africa. We sought to characterize the clinic flow and estimate implementation costs of POC adherence testing for persons initiating ART in HIV care clinics in South Africa. We conducted a microcosting within a randomized implementation trial evaluating POC TFV in a government clinic in Durban, South Africa (STREAM HIV). Time-and-motion observation was conducted to assess staff and client time needed for POC TFV testing. We estimated both financial and economic costs for capital, clinic consumables, and personnel using a provider (ministry of health) perspective. The median total time of a clinic visit with a POC TFV test was 49:19 (minutes: seconds) and the TFV testing took 9:22 (19% of total clinic visit) including sample collection, sample loading, TFV test processing, and counselling provision based on test results. Overall, 29% of the clinic visit time included direct clinical care and assessment with a provider, with clients spending a median 14:09 getting vitals checked, receiving adherence monitoring via POC TFV testing, and collecting ART. Waiting in line for ART took most (48%) of the clinic visit time. The cost of POC TFV was USD $13 per client, assuming a clinic volume of 20 individuals initiating ART per month. The largest component cost of POC TFV testing was the test strip consumables, which accounted for 53% of the test cost. POC TFV testing can be administered at reasonable costs, requires less than 10 minutes, and therefore may be feasible to implement in South African clinics. Findings can inform the policies and budgetary planning for ART monitoring in South Africa and similar settings that are considering using POC TFV testing for adherence monitoring in complement with other diagnostic technologies.

1.2 Introduction

Routine HIV viral load (VL) monitoring and adherence to antiretroviral therapy (ART) is critical for suppressing HIV and positive clinical outcomes among the 28.7 million people living with HIV (PLHIV) accessing ART globally in 2021, which in turn reduces HIV transmission and drug resistance in the community.[2,15-17] However, initiation and management of life-long ART in low- and middle-income countries (LMICs) is challenging for PLHIV and to identify adherence issues, providers often rely on subjective measures, like self-reported behaviors, which can be unreliable and prone to recall error and bias.[18-20] Although objective assessment of ART adherence is possible through pharmacokinetic analysis of tenofovir (TFV) concentrations, broad adoption of these measures are hindered by high cost, lengthy turnaround times, and skilled personnel requirements.[7,21] Therefore, there is a demand for cost-effective, time-efficient, and scalable approaches to address uncertainty around drug adherence.[4,5,22-24]

Point-of-care (POC) urine TFV is a relatively inexpensive assay that has been developed to detect the presence of tenofovir with a short turnaround time in clinic-based settings and could complement more costly POC VL testing for monitoring.[21,25] However, the cost of routinely administering these tests and impact on clinic flow/provider time are uncertain.[21,25-27] We sought to estimate the financial and economic costs of POC TFV testing for persons initiating ART in South Africa. To contextualize our findings to that of other POC testing, we updated previously estimated costs for POC VL testing from a pilot study conducted in 2017 from the same clinic.[28] Our research investigates both the costs and clinical flow to inform the affordability of implementing POC adherence monitoring, and the sustainability and potential for scale-up within public healthcare clinics in South Africa.

1.3 Methods

Study Design

We conducted a microcosting for POC TFV from the provider perspective to estimate costs of POC adherence monitoring. Activity-based microcosting, staff interviews, and time and motion studies were conducted to estimate costs of POC TFV testing. Interviews were conducted on-site with providers, including clinicians, nurses, and hospital administration to understand work hours and responsibilities. This costing was conducted within the Simplifying Treatment & Monitoring for HIV (STREAM HIV) study (NCT04341779), a randomized implementation trial evaluating POC TFV and HIV VL testing in clinic settings in South Africa. As part of the study, adult PLHIV initiating ART are randomized to receive either monthly POC TFV testing for five months and POC VL at six and 12 months or routine lab-based monitoring as per the standard HIV care in South Africa.[26] We estimated instrument costs assuming five-year lifespans with a 3% annual discount rate.

The STREAM HIV study builds upon the first STREAM pilot study, in which our team estimated costs for implementing POC VL testing in 2017.[8,28] Thus, in addition to POC TFV microcosting, we also updated these POC VL testing costs to reflect 2022 costs using the gross domestic product (GDP) price deflator and new prices for POC HIV VL test cartridges for the GeneXpert® platform (Cepheid, Sunnyvale, USA).[29,30] Additional detail on GDP price deflator methods are provided in Appendix 1.

Study Setting

Costing activities were conducted within two government clinics in KwaZulu-Natal, South Africa. The urban study clinic was located at the Prince Cyril Zulu Communicable Disease Centre (CDC Clinic) and the adjacent CAPRISA eThekwini Clinical Research Site (ECRS), an urban

government clinic providing primary care, sexual health, HIV, and TB services. The CDC Clinic and ECRS were located near the transport hub for public commuters in central Durban, the largest city in the KwaZulu-Natal province. The CDC Clinic initiates approximately 2,000 PLHIV on ART annually. The rural study clinic was located in Vulindlela, situated approximately 25km from the provincial capital of KwaZulu-Natal (Pietermaritzburg) and home to 400,000 residents.

Data Sources and Collection

Data was collected using both the expenditure and ingredients approach. We accessed budgets and expenditure records at health facilities. To complement the expenditure approach, the more detailed ingredients approach was used to identify and value resources required for POC testing at the operational level, resulting in a comprehensive accounting of all inputs needed to deliver POC TFV testing.

Standardized cost menus were used to collect costs, including start-up training, capital, clinic consumables, and personnel time (Table 1). Staff salary and materials and instruments costs in 2022 US dollars, were obtained from expense reports, clinic invoices, published government records, laboratory price lists, health facility staff and expert interviews, and health economics literature as needed. Notably, the POC TFV test strip is not currently available for commercial purchase, thus only research use costs were calculated; the purchase price may vary when POC TFV testing becomes commercially available.

Start-up & Capital Costs

We estimated start-up training costs from expense reports and interviews with trained staff; costs incorporated the salary and time of both the trainer and trainees, and training materials. Trainings were annualized using five years of useful life based on feedback from clinic staff and

administration. Capital costs were obtained through expense reports and procurement plan contracts from the government CDC clinic.

Material & Consumables Costs of POC VL and TFV testing

Materials were identified through direct observation and interviews with healthcare workers. Consumables for POC TFV testing flow included gloves, urine sample container, sticker labels, and disposable pipette bulbs, and the unit cost of the POC TFV lateral flow test strip. We updated our prior microcosting of POC VL and adjusted for inflation and updated test cartridge costs.[28]

Time & Motion Study (TMS) for POC TFV testing

Observed activities included: 1) Clinical nurse time to collect urine, 2) Processing and running POC tests, 3) Post-test adherence counselling based on results, and 4) Completion of steps of the HIV care visit including standard clinical assessment, addressing additional medical care queries, scheduling follow-up visits. Professional Nurse health cadres, requiring a four-year degree and/or practical training program, were observed. Lower level health cadres such as Enrolled Nurse, requiring a two-year diploma, and Enrolled Nurse Assistants, requiring one-year of training, were not directly observed but responsibilities and capacity for adherence testing was discussed during staff interviews.

To reduce sampling bias, patients were observed at different parts of the work day, days of the week, and times of the year (March – May 2022 and November – December 2022). If multiple patients were in the clinic at one time, data collectors would switch and prioritize observing activities directly associated with the POC TFV testing flow. Patients with anomalous times for activities due to medical conditions needing urgent care were excluded from the analysis.

Staff time was enumerated by observing total time needed for testing and removing non-

active waiting time during POC test processing as the staff completed routine clinic activities. Observing multiple visits by various staff members allowed for more accurate estimation of the median time taken for each step. Time needed for research activities, such as informed consent and reimbursements, were removed from time estimates to estimate intervention time if implemented within routine care in a government clinic. We estimated costs for active time staff for obtaining urine and blood samples, sample transport, test processing time, data record entry, test delivery to patients, and clinical action if applicable.

Data Analysis

Analyses followed the guidelines for costing trial interventions.[31] Costs for start-up training, capital, clinic consumables, and personnel salary required for POC TFV testing were calculated. Personnel costs were calculated by multiplying the staff salary per minute with the active time spent directly collecting the urine sample, running the test, and counselling clients based on the test result. See Appendix 1 for details on POC VL cost inflation calculations.

To estimate total client volume, we assumed that a large clinic in South Africa would initiate 20 clients on ART per month.[32] Baseline estimates of per-client test costs assumed wastage of consumables for POC TFV testing to be 5% and used the median active personnel time needed for the complete test flow. We conducted one-way sensitivity analyses varying ART clinic volume, cost of POC TFV test strip, cadre of personnel conducting POC TFV testing, and percent of wastage for clinic consumables.

Ethical Approvals

Ethical approval was granted by University of Washington Institutional Review Board and the University of KwaZulu-Natal Biomedical Research Ethics Committee.

1.4 Results

Costs per POC tests

Updated POC HIV VL costs were estimated at USD $29.74 per test, assuming a clinic volume of 20 initiating ART clients per month. Assuming a higher clinic volume of 50 initiating ART clients per month, POC HIV VL test costs decreased to $21.63 per test. The main cost driver for POC HIV VL testing was the price of the consumable test cartridge, comprising 50% and 69% of the total cost, assuming a respective clinic volume of 20 and 50 ART initiations per month.

We estimated that POC TFV cost USD $12.97 per test, assuming a clinic volume of 20 initiating ART clients per month (Table 1). Costs per client were substantially higher at lower testing volumes: $17.22 for clinics initiating 10 ART clients per month, vs $10.43 and $9.58 for clinics initiating 50 and 100 ART clients per month, respectively (Table 1).

Sensitivity analyses

The largest contributor to the cost per test was the POC TFV test strip ($6.86, 53% of the total cost) (Figure 1). One-way sensitivity analyses showed changes in the POC TFV test strip price had substantial impact on the total cost (Figure 2). For example, a 20% and 10% reduction in the current POC TFV test strip cost resulted in per-client test cost of $11.60 and $12.29. Conversely, a 20% and 10% increase in the test strip cost would increase per-client test costs to $14.34 and $13.66. Reducing personnel costs by task shifting to Enrolled Nurse and Enrolled Nursing Assistant decreased the POC TFV cost per-test by just 3% and 5% respectively. Varying wastage costs also had a minimum impact on results (Figure 2).

Clinic flow for POC adherence monitoring

The patient times and clinical flow for visit including POC TFV testing is presented in Figure 3. Clinic staff arrive between 6:30AM to 7:00AM and stay until 4:00PM. Clinic opening is scheduled for 8AM, with most patients arriving earlier to queue and the majority of patients seen in the mornings until lunchtime (1:00PM). Following collection of their patient chart, the median time clients spent in the clinic for a visit with a POC TFV test was 49:19 (minutes: seconds). The POC TFV testing took a median time of 9:22 (19% of total clinic visit) including sample collection, sample loading, TFV test processing, and counselling provision based on test results (Figure 3). Urine collection was observed among 38 patients, with the median time of sample collection being 1:59 (IQR: 1:03). Among 15 samples of urine, the median time to load a plastic pipette and deposit 3 drops onto the POC TFV test strip was 0:18 (IQR: 0:33). The median time for running a POC TFV test was 5:17 (IQR: 0:36) among 32 observations. Counselling was only observed for adherent POC TFV test results in 28 patients, with a median active time of 1:48 (IQR: 4:25).

Patient Experience and Direct Interaction with Providers

Overall, only 29% of the clinic visit time included direct clinical care and assessment with a provider, clients spent a median time of 14:09 getting vitals checked, adherence monitored via POC TFV testing, and collecting ART. Patients spent 11% (5:35) of their total clinic visit registering at the front desk, walking within the clinic, and collecting urine samples, and 60% (29:35) of their total clinic visit waiting for clinical attention, either for measuring vitals or collecting ART.

Waiting in line for ART took most (48%) of the clinic visit time with a median wait time of 23:42 (IQR: 26:10, n=32). Waiting for clinical vital measurement took a shorter median time of 5:52 (IQR: 19:36, n=16). Median clinical appointment duration with the ART nurse was only 2:06 (IQR: 1:43, n=25) after the wait. Checking for clinic vitals, including measuring patient blood

pressure, body weight, and waist circumference, took a median time of 4:41 (IQR: 3:29, n=40). Personnel shortages and inefficient clinical flow between the POC TFV testing and the ART queue was noted by staff as potential areas for improvement for the future.

1.5 Discussion

We report the costs of implementing POC TFV testing for drug adherence monitoring in South Africa. The per-client test costs for POC TFV were less than half of POC HIV VL testing. The primary cost drivers for both POC tests were clinic consumables, specifically the test strip for TFV and the test cartridge for VL. POC TFV testing costs were sensitive to ART client volumes in the clinic, and the TFV test strip price. POC TFV testing flow required less than 10 minutes, and was much faster than the queues experienced by stable patients collecting ART.

A 2019 systematic review of costs of HIV services in South Africa and found that more cost analyses of non-ART interventions were needed, particularly for adherence monitoring.[33] The POC TFV testing costs and clinical flow presented in this study are the first reported in a routine implementation setting, therefore there is limited literature within which to contextualize our findings. POC VL test costs are consistent with other studies, with the estimated per-test cost of POC HIV VL testing ranging from USD $24.25 per test up to $33.71 when using the Cepheid GeneXpert four-module testing platform.[34,28,35,36] Particularly in resource-limited settings, variable assumptions on clinic infrastructure may contribute to different cost estimations.[22,23,34] Additional details on comparative cost analyses of POC testing is provided in Appendix 2.

Though there are no existing costing analyses for POC TFV testing, qualitative studies exploring perspectives on the POC urine TFV test among clients and providers in the United States found favorable acceptability among providers when used in tandem with VL testing.[7] Qualitative

results concluded that POC TFV tests should be low-cost, akin to the price of a urine-based pregnancy test, if it were to be used widely.[7] Evaluation of urine-based POC TFV assay implementation in South Africa reported positive perceptions from PLHIV regarding the ability to have constructive real-time discussions with providers, while providers noted that POC TFV testing could help identify patients at risk of treatment failure.[37,38] Healthcare workers also noted the importance of additional support staff for successful implementation in high volume health facilities.[7,37] POC technologies can accelerate adherence support and VL monitoring to create new models of patient-centered HIV care in LMICs. However, incorporating them without sufficient evidence regarding impact on clinics may overwhelm existing clinical flows and exacerbate waiting times in resource-limited healthcare facilities.

Our results are consistent with the literature showing that consumables make up a significant component of test costs.[28,34,39] Growing evidence that suggests addressing high POC testing consumable costs, most notably expensive test cartridge and test strip prices, may contribute to impactful reductions in POC testing costs for national testing programs. This can include negotiations with manufacturers to lower pricing for test cartridges, as well as greater integration on multi-disease testing platforms to enable cost-sharing between disease programs.[34] Out study used research use only costs for the POC TFV test strips and testing costs were highly sensitive to fluctuations in test strip consumable prices. Global engagement with manufacturers is needed to ensure sustainable prices for this technology if resource-limited countries are to consider implementation of POC TFV testing for adherence monitoring.

The study has several limitations. First, our analysis was conducted within a randomized control trial which may not reflect routine implementation.[40] However, to maximize external validity, the STREAM HIV trial was designed so that the study population was representative of

the population and clinical settings in which POC adherence testing will be implemented.[26,41] Following best practices, we also removed research related costs and only accounted for active personnel time delivering POC TFC testing services as intended in a government program.[31,40,42] Secondly, time and motion observation is limited by the Hawthorne effect, a phenomenon in which participants may modify their behavior when they are aware of being observed.[43] To address this, we informed participants that observation was not for worker performance evaluation and observations were conducted at varying times throughout the day, week, and across multiple seasons to improve accuracy and allow for providers to settle into normal work patterns. Lastly, implementation costs and activity time could vary by location. We tried to collect data from both urban and rural clinic locations in KwaZulu-Natal to account for variations and TMS data was collected across multiple staff members. Staff interviews were also conducted to increase understanding of site-level variation for POC TFV and aid interpretation of results. Future qualitative and microcosting studies should be conducted to determine feasibility and acceptability of implementing the POC TFV adherence test across different contexts.

In addition to its use for adherence monitoring of ART clients, POC TFV testing also has potential utility for encouraging adherence, particularly among young women, to pre-exposure prophylaxis (PrEP) and as a predictive tool for detecting drug resistance to TFV-containing ART regimens.[44-47] Consistent use of PrEP is vital for high-risk populations in order to achieve "prevention-effective" adherence, which has been shown to be modest and declining over time.[44] Studies in Kenya have shown real-time measures of PrEP adherence using a POC urine test, as opposed to more invasive and costly objective measures, was feasible in the context of routine care, acceptable to clients and providers, and could improve adherence.[46] Genotypic drug resistance (DR) testing for HIV is not commonly available in LMICs, thus treatment decisions

after repeated elevated viral load results often follow standardized national clinical guidelines without any prior DR testing.[47,48] Among people with viraemia, a positive urine TFV test may be associated with the presence of HIVDR, [45,49] but findings have been mixed.[50] Thus, our study findings contributes practical evidence on the use of a low-cost, urine-based diagnostic tool that has the potential to not only support ART adherence among PLHIV, but also high-risk populations receiving PrEP to prevent HIV infection and people struggling with potential DR.[45,47]

1.6 Conclusions

In summary, our microcosting and TMS analyses demonstrate that POC TFV testing could be feasibly implemented into routine care at a reasonable cost, particularly within clinics with higher ART client volumes and if the test is available commercially at a similar price to the research use only cost. The POC TFV testing flow is straightforward, has minimal infrastructure requirements, and is not a substantial time burden to incorporate into the overall clinical workflow. In addition to aiding drug adherence among PLHIV, our results may also encourage the use of POC TFV testing as inexpensive complementary diagnostic tools to support PrEP adherence and HIVDR testing. Our findings can inform the policy decisions and budgetary planning for ART monitoring in South Africa and other LMICs considering implementation of POC TFV and VL testing as alternatives to traditional laboratory-based testing.

1.7 Tables & Figures

Table 1. Per-test cost of POC TFV testing at varying clinic testing volumes in KwaZulu-Natal, South Africa (2022 USD). Total cost estimates assuming median personnel time for Professional Nurse cadre within a government clinic and 5% consumables wastage.

Cost Per Patient	**POC Costs by Clinic Testing Volumes (POC TFV Tests Done per Month)**			
Cost Category	10	20	50	100
Capital costs	7.42	3.71	1.48	0.74
Clinic consumables	0.29	0.29	0.29	0.29
Test strip	6.86	6.86	6.86	6.86
Start-up training	1.07	0.54	0.21	0.11
Personnel time for testing and counselling	1.58	1.58	1.58	1.58
Total cost per test	17.22	12.97	10.43	9.58

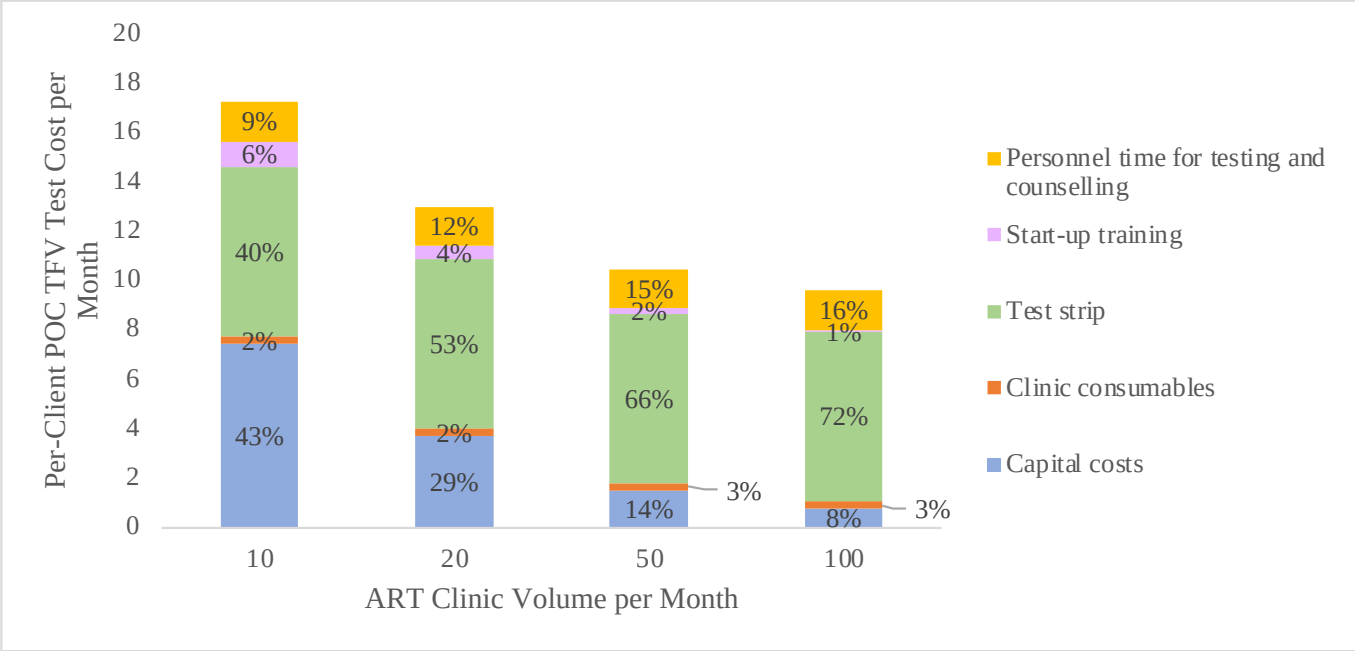


Figure 1. Percentage of total costs per category, varying monthly clinic testing volumes (2022 USD).

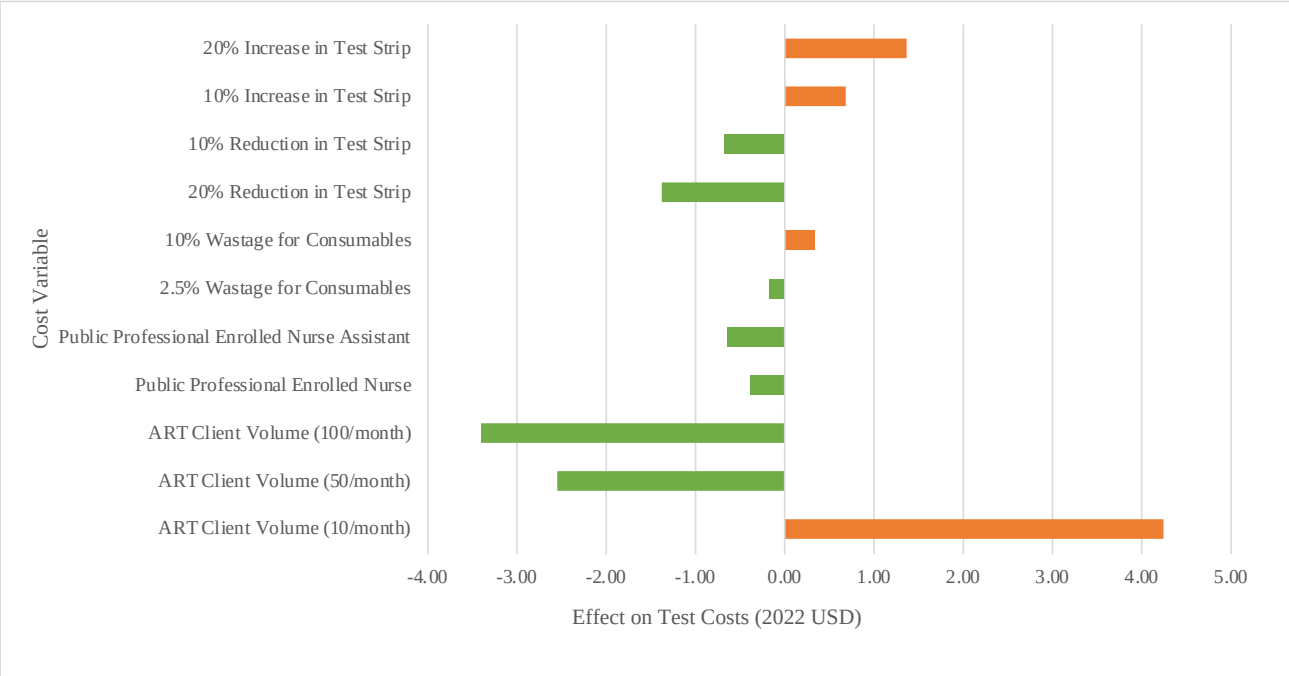


Figure 2. Sensitivity analysis assessing potential impacts of varying cost assumptions with bars displaying changes in US dollars from the total baseline POC TFV cost. Variable total costs were compared against a baseline per-client cost of POC TFV test that assumed 20 ART clients per month, median personnel time, professional nurse cadre conducting the test, 5% wastage of clinic consumables, and cost of test strip procured for the intervention.

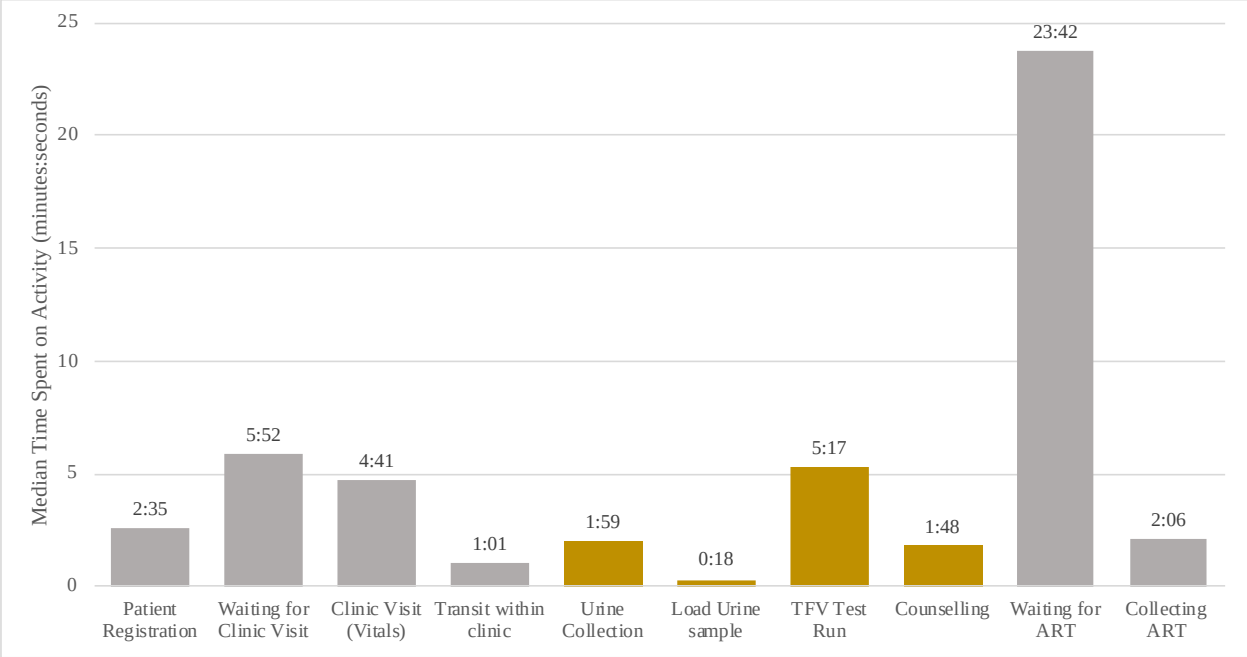


Figure 3. Clinical flow showing median time (minutes:seconds) (y-axis) participant spent during each activity type (x-axis) during a complete clinic visit including objective adherence monitoring. Activities specific for the POC urine TFV test process are shown in yellow.

CHAPTER 2. DELIVERY OF COMMUNITY-BASED ANTIRETROVIRAL THERAPY TO MAINTAIN VIRAL SUPPRESSION AND RETENTION IN CARE IN SOUTH AFRICA

Authors:

Melody Wang[1], Lauren R Violette[2,3], Jienchi Dorward[4], Hope Ngobese[5], Yukteshwar Sookrajh[5], Elliot Bulo[5], Justice Quame-Amaglo[6], Katherine K Thomas[2], Nigel Garrett[7,8], Paul K Drain[1,2,3]

Affiliations:

1. Department of Global Health, University of Washington, Seattle, WA
2. Department of Medicine, University of Washington, Seattle, WA
3. Department of Epidemiology, University of Washington, Seattle, WA
4. Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, Oxfordshire, United Kingdom
5. eThekwini Municipality Health Unit, eThekwini Municipality, Durban KwaZulu-Natal, South Africa
6. Department of Psychology, University of Washington, Seattle, WA
7. Centre for the AIDS Program of Research in South Africa (CAPRISA), University of KwaZulu-Natal, Durban, KwaZulu-Natal, South Africa
8. Discipline of Public Health Medicine, School of Nursing and Public Health, University of KwaZulu-Natal, Durban, KwaZulu-Natal, South Africa

2.1 Abstract

To determine whether the Centralized Chronic Medication Dispensing and Distribution (CCMDD) program in South Africa's differentiated ART delivery model impacts clinical outcomes, we assessed viral load (VL) suppression and retention in care between patients participating in the program compared to the clinic-based standard of care. Clinically stable people living with HIV (PLHIV) eligible for differentiated care were referred to the national CCMDD program and followed for up to six months. In this secondary analysis of trial cohort data, we estimated the association between routine patient participation in the CCMDD program and their clinical outcomes of viral suppression (<200 copies/mL) and retention in care. Among 390 PLHIV, 236 (61%) were assessed for CCMDD eligibility, 144 (37%) were eligible, and 116 (30%) participated in CCMDD. Participants obtained their ART in a timely manner at 93% (265/286) of CCMDD visits. VL suppression and retention in care was very similar among CCMDD-eligible patients who participated in the program compared to patients who did not participate in the program (aRR: 1.03; 95% CI 0.94–1.12). VL suppression alone (aRR: 1.02; 95% CI 0.97–1.08) and retention in care alone (aRR: 1.03; 95% CI 0.95–1.12) were also similar between CCMDD-eligible PLHIV who participated in the program and those who did not. The CCMDD program successfully facilitated differentiated care among clinically stable participants. PLHIV participating in the CCMDD program maintained a high proportion of viral suppression and retention in care, indicating that community-based ART delivery model did not negatively impact their HIV care outcomes.

2.2 Introduction

The UNAIDS has established the 95-95-95 targets to end the HIV epidemic by 2030, with the goal of having 95% of all people living with HIV (PLHIV) who are accessing antiretroviral treatment (ART) maintaining VL suppression.[1] Among the approximately 38 million PLHIV worldwide, roughly only half have achieved VL suppression, which is critical to reduce viral transmission and help avert the 650,000 deaths from AIDS-related illnesses reported in 2021.[51,52] The World Health Organization recommends all PLHIV receive routine clinical assessments and VL testing to monitor therapy outcomes. As high volume clinics devote resources to diagnose HIV and initiate patients on ART, service delivery models that reduce the burden of unnecessary clinic follow-up visits are needed.[3] Differentiated, community-based ART delivery models may reduce the burden on the healthcare system, while also giving clinically stable PLHIV greater access to ART.[10]

Almost one in five adults are living with HIV in South Africa, with an estimated 66% (5.1 million) PLHIV having suppressed VL in 2020.[9] In 2014, the National Department of Health (NDoH) in South Africa established the Centralized Chronic Medication Dispensing and Distribution (CCMDD) program which is a public-private partnership that allows clinically-stable patients referred by healthcare workers in government clinics to collect ART refills at private pharmacies or community-based organizations.[11-13] The CCMDD program supports patient ART adherence and retention by enabling convenient access to treatment at pick-up points, averting lengthy wait times at high volume HIV clinics, as well as diverting patients from overwhelmed clinic settings. CCMDD provides access to ART for over 1.7 million people and has become the largest differentiated care program in the world.[12,13]

However, there are mixed findings on whether decentralized community-based models of care results in similar patient loss to follow-up and adherence.[53-55] Additionally, there is growing need to better understand how patients progress along the cascade of care to access ART through alternative delivery models in routine national programs. An evaluation of the delivery of community-based ART for maintaining viral suppression and retention in care in South Africa may establish the impact of CCMDD on clinical outcomes as well as better understand the patients who are able to enroll and access differentiated care. In this dataset from a trial cohort in Durban entering the national differentiated care program in South Africa under routine conditions, we sought to evaluate participation and identify gaps in the CCMDD program enrollment cascade, and ultimately determine the impact of CCMDD program participation on HIV care outcomes among clinically stable patients compared to standard treatment within health clinic facilities.

2.3 Methods

Study Design and Participants

Participant data in this analysis was collected from the STREAM (Simplifying HIV TREAtment and Monitoring) Study cohort, an open-label randomized controlled trial in Durban, South Africa from February 2017 to October 2018. Details of the research protocol have been published elsewhere.[8] The study received ethical approval from the University of KwaZulu-Natal (BFC296/16) and University of Washington (STUDY00001466), and was registered with ClinicalTrials.gov (NCT03066128).

The study site was the CAPRISA eThekwini Clinical Research Site and the neighboring Prince Cyril Zulu Clinic, a large urban public clinic that provides HIV and primary care services for a diverse, mobile population of more than 10,000 patients. Eligible study participants were 18

years or older, living with HIV, and presented for their first routine HIV VL test six months after diagnosis. We excluded patients who were pregnant, had active tuberculosis, or required acute medical care by a physician. However, if participants became pregnant or were diagnosed with tuberculosis during follow-up, they were included in the analysis. Participants provided written consent and were enrolled in the STREAM parent study trial. After 6 months of follow-up in STREAM, study participants in both arms were then able to be assessed for enrollment into the CCMDD program as part of routine care for PLHIV in South Africa. Clinical outcomes across eligible participants who did and did not participate in the CCMDD program was measured and analyzed up to 12 months after STREAM enrollment.

Study Procedures

The data used for the current study was collected as part of a randomized trial of quarterly point-of-care VL testing on retention in care and VL suppression (the STREAM parent study).[4] At enrollment, we collected sociodemographic data, medical history, and potential risk factors for viral failure or loss to follow-up, such as method of transportation and distance to the clinic, HIV disclosure, ART adherence, and CD4 count. Mental health and substance abuse indicators were also collected, using the WHO Alcohol Use Disorder Identification Tool (AUDIT-C), WHO violence against women instrument (female participants only), and Patient Health Questionnaire-2 (PHQ-2) to screen for depression. Participants received care according to South African HIV treatment guidelines, including testing for VL and creatinine at enrollment, and VL, creatinine, and CD4 cell count after six months. Any participant with a VL>1,000 copies per mL received enhanced adherence counselling and repeat VL testing after two months. If the repeat VL was >1,000 copies per mL, the participant was offered to switch to a standard second-line ART

regimen. Participants in both comparison groups were reimbursed 100 South African Rand (ZAR) per clinic visit, per South African research guidelines.[8]

At least one year after initiating ART, stable participants in both arms of the trial qualified for the CCMDD program in South Africa, which allow clinically-stable participants to collect ART at decentralized pick-up points (PuPs).[13,56] PuPs are contracted by the NDoH and include private pharmacies and community-based adherence clubs and organizations separate from clinic settings, as well as fast-track lanes at registered health facilities.[13,56] Eligible patients may voluntarily register and select a PuP from which to collect medication every two months, and return to the clinic every six months for clinical review and prescription renewal.[56] The NDoH distributes and dispenses medication through government tender across PuPs in eight provinces in South Africa. There is no cost for patients to participate in the CCMDD program.[56]

Participants were able to be assessed for CCMDD eligibility starting from 12 months post-ART initiation. Whether the participant was assessed for CCMDD eligibility as part of the national algorithm for differentiated care, and the outcome of this assessment, was captured in electronic CRFs by study staff. In accordance with South African guidelines, participants in both trial arms were eligible for referral into the program if they were non-pregnant, clinically stable on the same treatment regimen for at least 12 months, had CD4 count >200 cells per μL, no current TB, no uncontrolled diabetes or hypertension, and had two consecutive undetectable (<20 copies/mL) VL results.[57] Once referred, participants collected ART every two months at a community pick-up point of their choice and were reviewed at the clinic by a professional nurse after six months. All blood testing occurred at the clinic. Participants not eligible for the CCMDD program or who chose not to participate continued with bi-monthly clinical visits. Any participant more than two weeks late for a scheduled clinic or community PuP visit received one phone call from the clinical team

and resumed ART collection at the clinic, per South African guidelines.[8] Laboratory and clinical records were used to assess the timing of participant referral into the community-based ART delivery program.

Study Outcomes

The primary outcome for this analysis was a composite measure of retention in care with viral suppression, defined as <200 copies per mL, at 12 months. We used this composite outcome because both components are necessary to achieve positive treatment outcomes for adults living with HIV. Patient retention in care was defined as collecting ART at the study clinic or a community pick-up point between 44-56 weeks after enrollment. Participants not retained in care at 56 weeks were tracked by the study team up to 60 weeks for VL testing. All VL testing for the primary outcome was performed using a laboratory-based Cobas 6800/8800 machine (Roche, Basel, Switzerland). We also analyzed retention in care, viral suppression (each analyzed independently), and undetectable VL at study exit.

If a participant was ever formally assessed for CCMDD participation prior to the Month 12 study exit visit, they were considered "Assessed". Of those who were considered "Assessed", those formally deemed eligible prior to the Month 12 study exit visit were considered "Eligible". Of those ever considered "Eligible", participants formally referred to the CCMDD program prior to the Month 12 study exit visit were considered "Referred". Among those referred, participants who have documentation that they picked up ART from a CCMDD pick-up point within the defined window prior to the Month 12 study exit visit are considered to have "Participated".

Statistical Analysis

The primary outcome was compared between two groups who were eligible for the CCMDD program: 1) Those who participated in the program and 2) Those who did not participate.

Relative risks and 95% confidence intervals were estimated using relative risk regression via modified Poisson regression with robust standard errors. Our pre-specified analysis adjusted for study arm, continuous age, and sex in the final model based on prior literature. We conducted two sets of sensitivity analyses: (a) adding adjustment for distance from the clinic (<5km vs ≥5km), and high alcohol use, to ensure that these factors, which differed between groups by more than 7.2% (the equivalent of two participants in the smaller group), were not confounding our results, and (b) using a modified Poisson model with identity link to model risk differences (RDs) rather than RRs, in order to ensure that modeling a common outcome did not obscure the magnitude or importance of potential differences. Statistical significance was determined using a two-sided type one error rate of 0.05. Statistical analysis was performed using SAS 9.4.[58]

2.4 Results

Screening & CCMDD Program Eligibility

Between February 24th 2017 and August 23rd 2017, the study enrolled 390 PLHIV. Among study participants, 236 were assessed for CCMDD. Of these, 144 were deemed eligible, and 140 were formally referred to the CCMDD program (Figure 1). Of those who were referred to CCMDD, 83% (116/140) of participants participated in the CCMDD program. Among the STREAM study population, 63% (246/390 enrolled) were not assessed and/or eligible for the CCMDD program.

Participant Characteristics

Across CCMDD-eligible and ineligible participants, there were no major differences in sociodemographic characteristics, travel time to clinic, HIV disclosure, and behaviors that could impact adherence to ART (Table 1). Among CCMDD-eligible participants, the median age of

those participating in the CCMDD program was 30 years [IQR: 26–37] and 68% (n=79) were female, while the median age of those not participating in the CCMDD program was 32 years [IQR: 27-38] and 71% (n=20) were female (Table 1). Almost half (45%; n=52) of CCMDD program participants did not pass secondary school (Table 1). The majority of CCMDD participants also reported a monthly income greater than 1000 South African Rand (57%; n=66), had a stable partner (79%; n=91) and at least one child (79%; n=91).

Gaps in the CCMDD program enrollment cascade

39% (154/390) of STREAM trial participants were not assessed for CCMDD program eligibility. Further investigation into baseline characteristics of patients not assessed showed they were similar to patients who were assessed for CCMDD eligibility, with a median age of 33 years (IQR: 27-38) and 34 years (IQR: 29-39), respectively. Public transportation was the main mode of transport to the clinic (88%), and the majority of unassessed patients had to travel at least 5 km to the health clinic (77%), though travel time was usually less than an hour (92%). Comparison of social-demographic characteristics, as well as mental health, drug/alcohol use, and ART adherence indicators, show this unassessed patient population was very similar to patients who were assessed, as well as patients deemed eligible for CCMDD (Table 1). The main difference observed was that unassessed participants had almost 2-fold higher prevalence of tuberculosis (21%) compared to assessed participants (12%) (Data not shown).

CCMDD program yields very similar clinical outcomes compared to standard-of-care for clinically stable patients

At study exit after 12 months of clinical follow-up, 94% (109/116) of PLHIV who were eligible and participated in the CCMDD program had achieved both VL suppression and retention in care, compared to 93% (26/28) among those who were eligible but did not participate after

adjusting for study arm, age, and sex (aRR: 1.03; 95% CI 0.94–1.12.) (Table 2). Results from the risk difference model were consistent: aRD: 0.03; 95% CI -0.06 to 0.11. These indicate very similar proportions consistent with at most a 6% lower probability of success in those participating in CCMDD. Results of the sensitivity analysis that also adjusted being ≥5km from clinic, and high alcohol use, yielded very similar results (aRR: 1.00; 95% CI 0.92-1.10). Among PLHIV who were not eligible, including those not assessed for CCMDD, 76% (188/246) were observed to achieve the composite outcome of VL suppression and retention in care at the Month 12 visit.

VL suppression alone (99% vs 96%, aRR: 1.02; 95% CI 0.97–1.08) or retention in care alone (95% vs 93%, aRR: 1.03; 95% CI 0.95–1.12) were also very similar between CCMDD-eligible PLHIV who participated and those who did not participate (Table 2). Among PLHIV who were not eligible for the CCMDD program, including those not assessed, 82.1% (n=202) were observed to achieve VL suppression and 85% (n=209) were retained in care by the Month 12 study exit visit. The proportion of participants with undetectable HIV VL (<20 copies/mL) was also similar between eligible groups who participated in CCMDD and those who did not, although this comparison rules out only at most a 19% lower probability of success (aRR: 0.96; 95% CI 0.81–1.14). Only 61% (n=150) of PLHIV who were not eligible, including those not assessed, for the CCMDD program had undetectable HIV VL at study exit visit. Sensitivity analyses for each of these outcomes produced similar results.

2.5 Discussion

In this cohort of South African adults living with HIV, the majority of patients who participated in the CCMDD program picked up ART within the expected time window and remained eligible for the CCMDD program. Enrollment in differentiated care did not negatively

impact clinical outcomes as levels of VL suppression and retention in care were equivalent between those who had received the standard-of-care compared to those who had participated in the CCMDD program. However, less than half of participants in the parent study were assessed for CCMDD program eligibility.

The observed effectiveness of CCMDD participation for maintaining the clinical outcomes of viral suppression and retention in care aligns with the expectation the CCMDD program would yield similar outcomes to the standard clinic-based ART provision in South Africa, and are consistent with findings reported in other studies across different global contexts.[59-63] In these studies among stable adult patients, participants greatly preferred decentralized pick-up points and reduced clinic visits, leading to fewer patients lost to follow-up and better retention outcomes.[53,59,60,62] However, community-based treatment is not always preferable to the clinic as there were also dissenting findings from a randomized control trial in South Africa that concluded that patients had better clinical outcomes in clinic-based adherence clubs compared to those in the community, though retention in both club models was poor.[54] Our study adds to this growing body of evidence, and is one of the first to assess the impact of the CCMDD program on the clinical outcomes of viral suppression and retention in care.

Broad models of providing monitoring and treatment to millions of unique PLHIV are not likely to adequately support patients in the long-term, thus we must consider adapting HIV services to specific population needs and contexts. Reviews on different models of differentiated care which include facets of the CCMDD program such as community-based ART groups, decentralized and more infrequent ART pick-ups, and task-shifting, suggest that adapted ART delivery strategies are acceptable alternatives to traditional clinic-based care for PLHIV.[3,53,62,64] However, access to these alternative service delivery models are often predicated on prior clinical

stability from national guidelines, thus introducing a catch-22 where patients who demonstrate poor clinical outcomes of viral suppression are ineligible to participate in programs that may increase their access to medication. Although we cannot conclude whether CCMDD participation may improve clinical outcomes for those currently excluded, research is needed to further understand the mechanism by which PLHIV drop out of care and fail to suppress VL so that implementation of ART delivery strategies can be optimized.

Our findings also show that unassessed participants had almost 2-fold higher prevalence of tuberculosis compared to assessed participants. Current tuberculosis (TB) is an exclusion criteria for CCMDD, which may explain why these participants did not have assessment of CCMDD eligibility recorded in the study database. Studies have shown that among PLHIV with comorbidities, particularly TB, there were benefits to extending intervals between clinic visits and ART pick-ups from pharmacies, however, routine TB screening was still needed and risk assessment at treatment initiation to identify factors associated with poor clinical outcomes was recommended.[65,66] Assessment and eligibility criteria may hamper access to the CCMDD program for patients who potentially have the most to gain from adaptive services. Additionally, there is also opportunity to use differentiated care not just for ART delivery, but for providing additional TB prophylaxis and screening that support both TB and HIV control measures.

Our study, and the CCMDD program in general, focused on non-pregnant, adult PLHIV who are stable on ART. This is a potential limitation of existing differentiated models of ART distribution. Key populations, such as adolescents, people who use injection drugs, and pregnant people, are particularly vulnerable to non-adherence and elevated VL.[67-70] Lack of social support, stigma, and prior loss to follow-up events were identified as essential factors that negatively impacted retention in care in a cross-sectional study that recommended home and community-

based care services be incorporated into HIV service delivery models.[71] Further research is needed to determine whether widening access to such differentiated care services through the CCMDD program could provide these disenfranchised patients with multi-month refills and lower costs for patient travel and time through decentralized ART collection.

Limitations

There were several limitations in this study, starting with the external validity of our study population. First, our study population consisted of participants from the STREAM trial, which reduces generalizability to other populations due to the types of people who are likely to join trials, and trial selection criteria. Second, retention in care in the STREAM parent study may be higher than the general population as all participants were reimbursed for study visits.[8] In addition, there is potential for selection bias as our study did not randomize participants into enrollment for the CCMDD program. However, randomization of participants was logistically and ethically objectionable as CCMDD is a national program provided across South Africa and we studied the program as it was implemented.

Analysis of baseline socio-demographic characteristics as well as health behaviors among CCMDD-eligible participants who participated in the program and CCMDD-eligible participants who did not participate in the program did not show major differences. We have adjusted for observed differences in those who participated compared to those who did not, but unmeasured differences could remain. The trial intervention (point-of-care VL testing and task sifting to enrolled nurses) may have influenced assessment procedures for CCMDD and treatment outcomes, but we also adjusted for treatment arm in the regression model. Study reimbursements may also have impacted retention in care, however, identical incentives were provided for participants in comparison groups to minimize differences.

Our study reports outcomes six months following earliest possible CCMDD enrollment, thus there could be limitations as to how these findings translate to long-term retention in care. Some participants only participated in the CCMDD program for one month which may not be long enough to adequately capture changes to VL and retention in care. Further qualitative studies on patient preferences should also be conducted to determine feasibility and acceptability of the CCMDD program and provide data on barriers to participation. A relatively small sample size, particularly among eligible participants who did not participate in the CCMDD program, as well as the fact that participants are from a single clinical site serving an urban population of PLHIV in South Africa are also noted and may encourage further studies to determine outcomes across other contexts. These research gaps will be further explored in the STREAM HIV study currently conducted in both urban and rural clinics in KwaZulu-Natal, South Africa.[26]

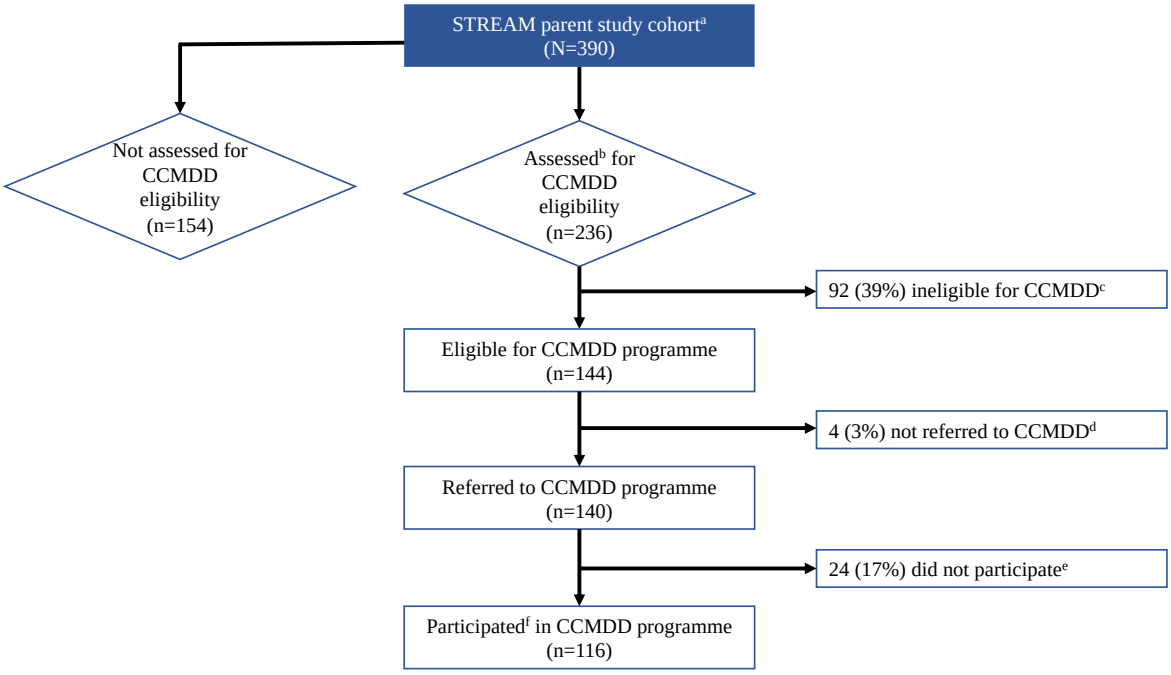
2.6 Conclusion

As universal access to ART becomes more established for millions of PLHIV worldwide, there is growing consensus that a blanket model of care is no longer an acceptable strategy for providing life-long HIV services. The CCMDD program in South Africa is an effective model for providing differentiated care for clinically stable patients, however, understanding and adapting ART delivery to unique patient contexts and needs is still needed to achieve undetectable VLs and long-term retention in care. There is a gap for a needs-based approach to servicing more vulnerable sub-populations unable to presently suppress VL, as opposed to a performance-based differentiated care model that caters exclusively to clinically stable patients.

In conclusion, we show that participation in the CCMDD program allowed stable adults

living with HIV to suppress VL, be retained in care, and have undetectable VL levels that were similar to those who received standard-of-care treatment in a clinic-based setting. These findings support national implementation of CCMDD. Further research on the long-term effectiveness of the CCMDD program on VL suppression and retention in care is needed among representative sub-populations living with HIV, and not just among clinically stable patients.

2.7 Tables & Figures



a. STREAM trial study cohort on ART for minimum of 6 months.
b. Participants assessed for CCMDD program on ART for minimum of 12 months.
c. 39% (n=92) not eligible for CCMDD program. Reasons include: detectable VL (n=38), CD4 < 200 (n=20), not clinically stable (n=4), elevated/uncontrolled blood pressure (n=14), no valid identification (n=2), no record (n=5), pregnancy (n=3), weight loss (n=2), no consent (n=1), uncontrolled diabetes (n=2), 2nd line medication (n=1)
d. 3% (n=4) not referred for CCMDD program. Reasons include: CCMDD pick-up point full (n=2), no record (n=1), participant travels often (n=1)
e. 17% (n=24) did not participate in CCMDD program. Reasons include: no record/did not attempt to get ART through CCMDD (n=22), missed appointment at pick-up point (n=2)
f. Participation in CCMDD program followed for up to 56 weeks post CCMDD enrollment.

Figure 1. Study flow and cascade of care for participants from assessment to participation in the CCMDD program. Participation was determined by documented pick-up of ART from a CCMDD pick-up point within the correct window up to 56 weeks post-CCMDD enrollment and referral.

Table 1. Cohort by eligibility and participation in CCMDD program (N=390).

	Eligible for CCMDD program		Not Eligible for CCMDD program	
	Participated	**Did not participate**	**Assessed**	**Not Assessed**
	n=116	**n=28**	**n=92**	**n=154**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Socio-demographics				
Median age - years [IQR]	30 [26, 37]	32 [27, 38]	34 [29, 39]	33 [27, 38]
Sex – Female	79 (68.1)	20 (71.4)	52 (56.5)	84 (54.6)
Highest level of education				
Did not pass secondary	52 (44.8)	11 (39.3)	49 (53.3)	81 (52.6)
Passed secondary	40 (34.5)	10 (35.7)	31 (33.7)	52 (33.8)
Tertiary or higher	24 (20.7)	7 (25.0)	12 (13.0)	21 (13.6)
Monthly income (ZAR)				
<1000	50 (43.1)	12 (42.9)	32 (34.8)	68 (44.2)
>=1000	66 (56.9)	15 (53.6)[c]	57 (62.0)[d]	80 (52.0)[e]
Has regular/stable partner	91 (78.5)	22 (78.6)	74 (80.4)	124 (80.5)
Children (1 or more)	91 (78.5)	22 (78.6)	76 (82.6)	127 (82.5)
Method of travel to clinic				
Walking	10 (8.6)	1 (3.6)	6 (6.5)	14 (9.1)
Public transportation	101 (87.1)	26 (92.9)	83 (90.2)	135 (87.7)
Private transportation	5 (4.3)	1 (3.6)	3 (3.3)	5 (3.3)
Travel >=5 kilometers to clinic	89 (76.7)	19 (67.9)	78 (84.8)	118 (76.6)
Travel < 60 minutes to clinic	108 (93.1)	28 (100.0)	81 (88.0)	142 (92.2)
HIV Disclosure, mental health, and substance use				
Disclosed HIV status to anyone	112 (96.6)	28 (100.0)	88 (95.7)	147 (95.5)
Positive Depression Screen [a]	9 (7.8)	1 (3.6)	11 (12.0)	16 (10.4)
High Alcohol Use (Audit-C) [b]	34 (29.3)	1 (3.6)	26 (28.3)	35 (22.7)
Current Tobacco smoking	15 (12.9)	2 (7.1)	19 (20.7)	28 (18.2)
Recreational drug use last 6 months	8 (6.9)	1 (3.6)	7 (7.6)	12 (7.8)
ART adherence and CD4 testing				

Self-reported 4-day ART adherence				
No missed doses	97 (83.6)	23 (82.1)	69 (75.0)	127 (82.5)
Missed any doses	19 (16.4)	5 (17.9)	23 (25.0)	27 (17.5)
Median CD4 count at enrollment [IQR]	536 [341, 719]	489 [367, 726]	348 [218, 587]	455 [314, 666][f]
Study arm				
Standard of care	13 (11.2)	21 (75.0)	14 (15.2)	147 (95.5)
Intervention	103 (88.8)	7 (25.0)	78 (84.8)	7 (4.6)

a. Depression is defined as a score greater than 1 on the PHQ-2.
b. High alcohol use is defined as an Audit-C score of greater than 2 for women and greater than 3 for men.
c. 1 participant that was CCMDD eligible but did not participate refused to disclose income.
d. 3 participants that were not CCMDD eligible and were assessed refused to disclose income.
e. 6 participants that were not CCMDD eligible and were not assessed refused to disclose income.
f. 1 participant had missing CD4 count at enrollment.

Table 2. CCMDD participation prior to month 12 study visit and the association with HIV care outcomes.

	Participation in CCMDD prior to Month 12 visit					
HIV care outcomes	Eligible but did not participate [a] N=28 n (%)	Participated [b] N=116 n (%)	Adjusted RR[c] (95% CI)	p-value	Adjusted RD[c] (95% CI)	p-value
HIV VL <200 copies/mL[e] and retained in care at the study clinic at study exit [d,e]						
Yes	26 (92.9)	109 (94.0)	1.03 (0.94-1.12)	0.545	0.03 (-0.06, 0.11)	0.551
No	2 (7.1)	7 (6.0)	REF	-	REF	
HIV VL <200 copies/mL at study exit [d]						
Yes	27 (96.4)	115 (99.1)	1.02 (0.97-1.08)	0.404	0.02 (-0.03, 0.08)	0.397
No	1 (3.6)	1 (0.9)	REF	-	REF	
Retained in care at the study clinic at study exit [e]						
Yes	26 (92.9)	110 (94.8)	1.03 (0.95-1.12)	0.478	0.03 (-0.05, 0.11)	0.478
No	2 (7.1)	6 (5.2)	REF	-	REF	
Undetectable HIV VL at study exit [d]						
Yes	24 (85.7)	102 (87.9)	0.96 (0.81-1.14)	0.68	-0.03 (-0.19, 0.13)	0.7
No	4 (14.3)	14 (12.1)	REF	-	REF	

a. Eligible for CCMDD but did not participate is defined as being appropriately assessed and eligible but has no documented receipt of ART from a CCMDD pick-up point on time at least once prior to the Month 12 study visit.
b. Participation in CCMDD is defined as being appropriately assessed, eligible, referred, and has documentation of ART pick up from CCMDD pick-up point on time at least once prior to the Month 12 study visit.
c. Relative risks and 95% confidence intervals were estimated using modified Poisson regression with robust standard errors. Risk differences and 95% confidence intervals were estimated using a risk difference (identity link) Poisson model with robust standard errors. Both types of models adjusted for study randomization arm, continuous age, and participant sex.
d. HIV VL measured using Cobas 6800/8800 machine (Roche, Basel, Switzerland).
e. Retained in care defined as collecting ART from the study clinic or CCMDD pick-up point between 44 and 56 weeks after enrollment.

CHAPTER 3. IDENTIFYING KEY BARRIERS FOR COMMUNITY-BASED ART DELIVERY AMONG STABLE ADULTS LIVING WITH HIV: A BARRIER PRIORITIZATION STUDY ON DIFFERENTIATED SERVICE DELIVERY IMPLEMENTATION IN SOUTH AFRICA

Authors*:
Melody Wang,[1,2] Yukteshwar Sookrajh,[3] Mlungisi Khanyile,[2] Kwena Tlhaku,[2] Emelda Tselana,[2] Pedzisai Munatsi,[2] Paul K Drain,[1,4,5] Nigel Garrett,[2,7] Jienchi Dorward,[2,6] Anjuli D. Wagner[1]
**Final author list and order to be confirmed for publication*

Affiliations:
1. Department of Global Health, University of Washington, Seattle, WA
2. Centre for the AIDS Program of Research in South Africa (CAPRISA), University of KwaZulu-Natal, Durban, KwaZulu-Natal, South Africa
3. eThekwini Municipality Health Unit, eThekwini Municipality, Durban KwaZulu-Natal, South Africa
4. Department of Medicine, University of Washington, Seattle, WA
5. Department of Epidemiology, University of Washington, Seattle, WA
6. Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, Oxfordshire, United Kingdom
7. Discipline of Public Health Medicine, School of Nursing and Public Health, University of KwaZulu-Natal, Durban, KwaZulu-Natal, South Africa

3.1 ABSTRACT

The differentiated care program in South Africa diverts stable people living HIV (PLHIV) to collect ART at community pick-up points. This enables existing overburdened clinics to focus their resources on those living with HIV who are not virologically suppressed and require extra support. However, questions remain on patient experiences with decentralized care programs and which barriers most affect retention and engagement in HIV care. We sought to address this by prioritizing barriers for differentiated care implementation in Durban, South Africa. We conducted a barrier prioritization sub-study within a randomized implementation trial investigating POC VL testing among PLHIV enrolled in the differentiated ART program in Durban, South Africa. Rapid evidence review was used to determine a range of barriers, which were then tailored to the local context using in-country expertise. Barriers were mapped to domains and constructs of the Theoretical Domains Framework (TDF). Participants completed a questionnaire in which barriers were evaluated in terms of their prevalence, frequency of experience, and hypothetical future criticality, using Likert scores. Go-zone bivariate plots were produced and mean Likert scores were analyzed to determine high frequency and high criticality barriers. Overall, our study found low barrier prevalence, with the majority of barriers experienced by less than 10% of participants and rare frequency of experienced barriers. However, the criticality of barriers was notably higher, with 11 out of 19 total barriers reported to affect future hypothetical continuation within the CCMDD program for over a third of participants. Go-zone mapping identified critical events and not having a form of identification as the two highest priority barriers with above average frequency and criticality scores. Environmental context and resource-related challenges were the most common barriers among participants. In conclusion, we identified key barriers that were frequently experienced and perceived as highly critical for continued participation in the CCMDD

program. Prioritized barriers identified in our study can guide future selection of implementation strategies that address differentiated ART delivery challenges in resource-limited settings.

3.2 INTRODUCTION

Universal access to antiretroviral therapy (ART) for people living with HIV (PLHIV) has been recommended by the World Health Organization for almost a decade.[72] However, as HIV services expand, sustainable management of life-long ART has necessitated differentiated service delivery models to reduce the burden of unnecessary clinic follow-up visits every month.[3,73,74] Community-based ART delivery models can redirect clinically stable PLHIV towards external pick-up points (PuPs), multi-month dispensing, and fast track services that enable reallocation of resources to increase health system capacity.[12,59,62,68,74,75]

Almost one in five adults live with HIV in South Africa and as of 2022, 5.7 million PLHIV were accessing ART.[9] The Centralized Chronic Medication Dispensing and Distribution (CCMDD) program is a public-private partnership established in South Africa in 2014 that allows clinically stable patients referred by healthcare workers in government clinics to collect ART refills at private pharmacies or community-based organizations.[11-13] By diverting stable patients from overwhelmed clinic settings, this differentiated care model frees up resources to initiate treatment in new patients and manage those with more complex needs..[12-14] CCMDD provides access to ART for over 1.7 million people and has become the largest differentiated care program in the world.[12-14]

Despite the scale of the CCMDD program, there has been mixed evidence on whether patient retention in decentralized community-based models of care impact are comparable to clinic settings and how barriers within this program influence future patient engagement in HIV care.[53-55,63,76] To better understand patient experiences in accessing differentiated care and pain points that

may impact retention in care, we identified and prioritized barriers experienced by PLHIV picking up ART through the CCMDD program. Prevalence, frequency, and criticality criteria were used to prioritize the most important barriers to successful implementation of the CCMDD program in South Africa.

3.3 METHODS

Study Design & Population

This barrier prioritization study was a cross-sectional evaluation of barriers experienced by PLHIV receiving ART through the CCMDD program. Our study was nested within the *Point-of-care HIV viral Load testing in a community Antiretroviral therapy program* (PHILA) study (PACTR202002785960123), a randomized trial comparing the effects of point-of-care (POC) viral load (VL) testing with laboratory-based VL testing in the CCMDD program in South Africa. In the trial, adults (≥18 years) living with HIV in the CCMDD program were randomized to receive either POC VL or standard laboratory VL testing to allow them to renew their CCMDD prescription for subsequent ART collection at their community pick-up point. To be eligible for the PHILA study, individuals had to have been on ART ≥12 months, then enrolled in the CCMDD program for another ≥6 months. ART clients who were ineligible for the CCMDD program were excluded from the PHILA trial and therefore also from the present study population.

Study Setting

The study site was located at the Prince Cyril Zulu Communicable Disease Centre (CDC Clinic) and the adjacent CAPRISA eThekwini Clinical Research Site (ECRS), an urban government clinic providing primary care, sexual health, HIV, and tuberculosis services. The CDC

Clinic and ECRS are located near a major transport hub for public commuters in central Durban, which is the largest city in the KwaZulu-Natal province of South Africa.

CCMDD participants received their medication from a variety of PuPs including formally staffed pharmacies, automated pharmacy dispensing units marketed as Peleboxes, clinic outreach posts, and informal community collection points. Peleboxes operated as smart lockers that dispensed medication to ART clients when they input a one-time PIN code sent directly to their phone.[77] The only Pelebox used by study participants was located within the CDC Clinic and was thus constrained by their operating hours.

Study Procedures

Clinic staff identified PLHIV in the CCMDD program who were due for viral load testing to renew their prescription and offered them referral to the study team. Study team members then introduced the PHILA parent study and ask for voluntary participation. If a participant was willing, the were invited to a private room in the clinic, informed consent would be obtained, and the participant was enrolled in the parent study. As part of this trial enrolment visit, participants were randomly assigned to intervention arm. Once randomized, participants had blood drawn for VL testing, and while the participant was waiting for their POC VL test result or before they departed and returned in a week for their laboratory VL test results, trained research assistants or research nurses administered the barrier prioritization questionnaire via RedCAP software. The barrier prioritization questionnaire was added to the PHILA parent study in March 2023, after 60 PHILA participants had already being enrolled without receiving the questionnaire. All PHILA parent study participants recruited after March 2023 participated in this barrier prioritization sub-study.

Rapid Review & Questionnaire Development

We conducted a rapid evidence review to first identify the range of implementation barriers described in literature. PubMed and Google Scholar databases were searched in January 2023 and titles and abstracts were screened for peer-reviewed primary research and systematic review articles published in the past five years reporting on patient barriers in differentiated ART programs in sub-Saharan Africa. Using barriers identified in the rapid literature review (results shown in Appendix 3), we consulted with local study staff and healthcare providers in the eThekwini research clinic to consolidate the range of barriers and only include those most relevant to the CCMDD client population in South Africa. This allowed us to leverage in-country expertise to ground our questions within the local healthcare context and refined our word choices to be better understood by the study population. We used the Theoretical Domains Framework (TDF) to guide thematic grouping of 19 identified barriers.[78] We used the OPTICC toolkit for prioritizing implementation barriers to aid questionnaire development and participants ranked barriers based on three criteria: 1) *Prevalence*, the proportion of total participants who had ever experienced each barrier in the past, 2) *Frequency* of experiencing each barrier among participants who had ever experienced each barrier in the past, and 3) *Criticality*, the extent to which the barrier would hypothetically affect the participant's continued participation in the CCMDD program in the future.[79]

Data Analysis

Study population characteristics were summarized using descriptive statistics, using medians and interquartile ranges for continuous variables and proportions for binary and categorical variables. Meaningful and small categories were collapsed together based on visual

inspection of frequencies using descriptive analyses. Barrier prevalence was measured through a binary option of whether a barrier was never experienced (questionnaire answer of "Never") or experienced at least once (encompassing questionnaire answers of "Rarely", "Occasionally", "Frequently", and "Always") and presented as a proportion. Likert scales measuring *Frequency* on a scale from 1 to 5 (Never, Rarely (less than half of visits), Occasionally (about half of visits), Frequently (more than half of visits), Always (every visit)) and *Criticality* on a scale from 1 to 5 (Not at all important, A little important, Moderately important, Very important, Necessary) were summarized using mean scores. Data were summarized in a horizonal bar plot for both criteria to visualize the pattern of responses. A Go-zone bivariate plot was generated with mean *Criticality* (x-axis) and *Frequency* (y-axis) scores plotted and the quadrants divided above and below the mean of each criterion variable.[80] All statistical analyses were conducted using R Statistical Software V4.3. To ensure that the parent trial randomization arm did not influence the barriers reported, we conducted a sensitivity analysis and stratified the main results by parent study arm and tested for differences using the chi-squared test of independence. A similar analysis was conducted for PuP type and for clients surveyed before and after the ART clinical guideline changes were implemented at our study site.

Human Subjects Protection

Ethical approval for this study was granted by the University of KwaZulu-Natal Biomedical Research Ethics Committee and Oxford Tropical Research Ethics Committee (OxTREC).

3.4 RESULTS

Study Population Characteristics

Among the 140 ART clients enrolled in our study, median age of participants was 44 years (interquartile range [IQR]: 37-48) and 66% were female (Table 1). All study participants were Black African and the majority (97%) were South African citizens. Over half (54%) of participants had at least matriculated from secondary school, while 37% had entered but not completed secondary school. Thirteen participants (9%) completed primary education or less. Less than half (43%) of study participants had full-time employment and the median monthly income among participants with any income was 4000 Rand (IQR: 2750-6350).

The majority of study participants (74%) picked up their medication from a community-based pharmacy. Thirty-two participants (23%) received their ART from the PeleBox located within the CDC clinic, while three clients used informal PuPs, and one client received ART through clinic outreach efforts. Most participants used public transport (81%), while 14% walked and 4% used private transport to reach their assigned CCMDD pick-up point. One third (34%) of study participants had disclosed their HIV status to a person other than their healthcare provider. None of the participants had a medical condition that prevented individual pick-up of ART, although 36% has had someone else pick-up their ART when they were unable.

Prevalence and Frequency of Experienced Barriers

Overall, few barriers had been experienced by many participants, and those that had been experienced had low frequency among our study participants (Figure 1). Five of 19 barriers were ever experienced by more than 10% of the study cohort (Figure 1). The most prevalent barrier was not receiving a text reminder or SMS alert that their medication was ready for pick-up, with 30% of all participants reporting having ever experienced this, although most participants who ever experienced this barrier (73%) noted it happened at less than half of visits. Among the 105

employed participants, 23% reported ever not being able to pick-up their ART due to inability to take time off of work, and of those who ever experienced this barrier, over one third (35%) reported experiencing this barrier half or more than half of visits. Not knowing how to pick-up ART (19%), critical events preventing pick-up (18%), and not having their ID (17%) were relatively prevalent barriers experienced by study participants, although there was mostly rare frequency of occurrence, with 1% of all participants experiencing each barrier at half or more than half of visits.

Unwanted HIV status disclosure (10%), not feeling confident about picking-up ART (9%), and feeling mentally unwell and unmotivated (8%) were all individual-level barriers experienced by roughly one in ten participants. Over half (60%) of participants who ever experienced fear of unwanted HIV disclosure, reported experiencing this barrier at half or more than half of visits. The remaining barriers – including PuP not having medication at the time of pick-up, extended wait times, open hours, staffing, rude behavior, relocation, and holiday breaks – were experienced by fewer than 10% of all participants (Figure 1).

Criticality of Barriers for Continued Participation in the CCMDD Program

Participants reported relatively higher criticality ratings than frequency. Of note, participants were reflecting hypothetically on whether they would continue participating in the CCMDD program and receive their ART via community pick-up points in the future if they were to experience a particular barrier. Among the 19 barriers surveyed, 11 were reported to hypothetically affect future continuation within the CCMDD program for over one third of all participants. A majority (72%) of participants stated that a rude encounter with a pick-up point provider would impact future participation in the CCMDD program. This was aligned with the fact that 60% of participants also reported that discriminatory differential treatment by staff would

affect their desire to continue receiving ART through the CCMDD program in the future. Rude and discriminatory treatment by PuP staff were also the two barriers with the highest number of participants stating experiencing these would make it hard to impossible for them to continue in the CCMDD program (57% and 50%, respectively). Two thirds of participants noted that not having medication available at their time of pick-up would affect their future participation in the CCMDD program. Notably, encountering a critical event (59%) and not having their identification at the pick-up point (50%) were in the top five barriers in terms of criticality as well as frequency.

Almost half of participants noted that having a lengthy wait time (46%) and not enough staff (43%) at the PuP would make a difference and affect their continued participation in the CCMDD program; however, only 4% report these barriers would make it impossible. Not feeling confident to ask questions, preferring to receive ART at the clinic, and feeling mentally unwell were each barriers noted by 36% of all participants to affect their continued participation in the CCMDD program. Barriers related to social pressure and support, such as unwanted HIV status disclosure and not having someone who can pick-up ART by proxy, were relatively less critical for future continuation in the CCMDD program.

Low Priority Barriers

There were several barriers that were prioritized lower for both frequency of experience and criticality for continued CCMDD program participation. Relocation and holiday travel was experienced as a barrier by only 4% and 3% of participants, respectively, and noted as making any difference in their hypothetical future decision to continue CCMDD participation by 32% and 19% of participants, respectively. The barrier of family and/or caretakers not available to help pick-up medication was experienced by only 6% of participants and noted as a relatively low

criticality barrier, with only 21% of participants saying it would make any difference in their hypothetical future pick-up of ART through the CCMDD program.

Differences Between Criticality and Frequency Among Barriers

There were several barriers that participants ranked lower in terms of criticality despite experiencing them relatively frequently (Figure 1). Although 30% and 23% of participants experienced not receiving an SMS text reminder and not being able to take time off work to pick-up ART, respectively, these two barriers were ranked lower in criticality with 38% of participants stating the lack of SMS and only 17% of participants stating that taking time off work made at least a slight difference in their hypothetical future CCMDD program participation. Not knowing how to pick-up ART was also a relatively frequently experienced barrier that was ranked lower in terms of criticality (28%).

A Pearson's correlation test was conducted to examine the relationship between mean frequency and mean criticality in the dataset. This test yielded a correlation coefficient of r = -0.26 (95% Confidence Interval [CI]: -0.64 to 0.22; p-value: 0.28), indicating negligible correlation between the average frequency and average criticality assigned to barriers.

Sensitivity analyses were conducted to see if potentially confounding variables impacted mean frequency and criticality scores for each barrier. Responses were stratified by randomization arm of the parent study, as well as PuP type. Testing for differences using the chi-squared test of independence did not show significant differences between groups.

Barriers Across Both Criticality and Frequency Criteria

The Go-Zone map visually divides barriers above and below the mean criticality score of 1.85 on the x-axis and the mean frequency score of 1.13 along the y-axis, with the upper-right quadrant defined as the "go-zone" highlighting key barriers (Figure 2). Our analysis identified two barriers, experiencing a critical event and not having a form of identification, in the go-zone with above average scores for both criticality and frequency. Figure 2 shows the majority of barriers are mapped to TDF domain of *Environment context and resources*, with both barriers in the go-zone also aligned with this predominant domain. Critical event barriers were mapped to the *Critical incident* construct, while not having identification was mapped to the *Person X environment interaction* construct.

In contrast, the lower-left quadrant highlights the barriers that scored below average for both criticality and frequency scores and encompasses half of all barriers (Figure 2). In addition to barriers in the *Environment context and resources* domain, we also see *Emotion, Beliefs about capabilities,* and *Social influence* domains represented in this low criticality and low frequency quadrant. The two other zones contain barriers with higher frequency and lower criticality scores in the upper-left quadrant and vice versa in the lower-right quadrant (Figure 2). We see the top two high frequency barriers of not receiving a SMS text alert and not being able to take time off work in the top upper-left quadrant, both of which belong within the *Person X environment interaction* construct of *Environment context and resources* domain. This high frequency low criticality quadrant also contains the individual-level barriers of unwanted HIV status disclosure, within the *Social influence* domain, and not knowing how to pick-up ART, within the *Knowledge* domain. The lower-right quadrant barriers shows the top three high criticality barriers of PuP staff being rude, discriminatory and also not having medication available for pick-up, all within the *Environment context and resources* domain on the far right of the plot.

3.5 DISCUSSION

Our study used barrier prioritization methods to quantitatively assess the prevalence, frequency, and criticality of barriers to picking-up medication from the largest differentiated ART delivery program in the world from the perspective of PLHIV. Overall, our study found that the prevalence and frequency of experienced barriers among participants enrolled in the program were relatively low. On the other hand, the criticality scores of barriers were notably higher, with over half of the barriers reported to affect hypothetical future continuation within the CCMDD program for over one third of participants. Go-zone mapping showed critical events and not having a form of identification were the two highest priority barriers (both high frequency and criticality scores). Environmental context and resource related issues were highly prioritized barriers among participants.

Understanding systemic and internal barriers that PLHIV face in community-based ART distribution programs is essential for engagement and sustainable scale-up of alternative models for HIV care. Our study provides a new perspective to this growing research landscape and is the first to quantitatively prioritize barriers identified in qualitative studies. Several qualitative studies in recent years have investigated implementation barriers of differentiated ART distribution models across Ghana,[81] Mozambique,[82] South Africa,[12,83-85] Uganda,[84,86] Zambia,[87] and Zimbabwe.[84] In line with our findings, system-level issues for out-of-facility ART pick-up have been reported in literature as major barriers; however, some studies noted more emphasis on ART drug stock-outs, staff shortages, and restrictive PuP hours than was observed in our study.[12,88-90] Patient fear of accidental HIV status disclosure, discrimination, stigma in community settings, and lack of clarity on pick-up procedures were also commonly reported individual-level barriers for differentiated care programs.[84,86,88]

Our barrier prioritization study identified critical events and lack of identification as the top two barriers for picking-up ART within the CCMDD program. Prior qualitative studies conducted in this setting noted that positive identification was strictly enforced for both registration into the program and for ART receipt, resulting in patients being turned away at the pick-up point if their ID was lost or stolen.[12] The process of replacing identity documents in South Africa is time and resource intensive, requiring multiple administrative forms, fees, and possible verification of fingerprints, thus many ART clients are hesitant to carry their ID while traveling in urban areas.[91] Although the vast majority of our study population was South African, this ID card requirement could also exclude vulnerable migrant populations. Alternative forms of identification, such as biometric fingerprint scanning, which is already used in South Africa, or allowing for copies of formal ID documents may improve access to ART for disenfranchised populations and ensure continuity of care even when formal identification is inaccessible.

Encountering critical events was unsurprisingly highly ranked as a critical barrier. However, it was also reported as occurring relatively frequently with 18% of participants experiencing this barrier. A critical event is any large-scale, unanticipated event that can disrupt implementation of a project or program.[78,92] In just the past five years, Durban has experienced several events that fit this definition. In 2020, the COVID-19 pandemic exacerbated unemployment, inequality, and food insecurity in South Africa, along with strict national lockdowns that sidelined routine HIV services for almost half a year.[93-95] In July 2021, the arrest of former president Jacob Zuma triggered widespread looting, destruction of property, and violence across Durban and most residents were forced to shelter at home as routine services were again paused for multiple weeks.[96,97] In 2022, Durban was impacted by two extreme floods, resulting in collapsed roads, disrupted electricity and water supply, and damage reported in 23

hospitals, 34 clinics, and 3 community health centers. [98-103] At the backdrop of these man-made and natural disasters, the unregulated minibus taxi industry in South Africa has been prone to high rates of accidents, violence, and crime, leaving ART clients without public transport to access decentralized healthcare services.[104,105]

Concurrent disasters experienced in Durban highlight pre-existing vulnerabilities of poor urban communities, inherited from the Apartheid regime, and show the need for effective response mechanisms to ensure continuous provision of healthcare services.[99,101,102] Compounding effects of these critical events exacerbate the socioeconomic strife, political instability, and undeveloped infrastructure context in which these participants live.[99] The economic aftermath of the pandemic, looting, and floods may also be reflected in the low proportion of participants with formal full-time employment in our study and in the downstream barriers such as not being able to take time off work and lacking money to travel to the PuP.

Not being able to take time off work was noted as a highly frequent barrier, with 23% of participants experiencing it at least once. South Africa has several legal frameworks enacted to reduce stigma and protect the rights of PLHIV, stating that all people with HIV/AIDS have a right to not disclose and not be discriminated against on the basis of HIV status.[106] However, these rights may be harder to enforce in the informal economy, especially with increased worker vulnerabilities after the socioeconomic impact of the COVID-19 pandemic.[107]

Not receiving an automated SMS text notifying ART clients of collection dates was the most frequently experienced barrier. Participant feedback noted inconsistent delivery of texts, possibly due to local connectivity issues as well as the same mobile SIM card being shared among multiple people as a cost-saving measure. As noted in our methods, participants picking-up ART from the PeleBox PuP relied on SMS texts to provide a PIN to access their medication; however

further inspection of our results show that PuP type did not impact the frequency or criticality prioritization of the lack of SMS text barrier. This may all indicate that clearer messaging is needed to inform ART clients not using the PeleBox PuP that lack of SMS receipt should not prohibit them from picking up ART.

PuP staff behavior, particularly rudeness or discrimination, emerged as the most critical barrier, indicating the significant impact of social stressors, despite their infrequent occurrence. Interestingly, unwanted HIV disclosure was rated relatively low for criticality even though qualitative studies consistently highlight fear of unintentional HIV disclosure and stigma as significant barriers to community-based treatment adherence.[12,84-86,88,108] However, it is clear that social stress and alienation are still incredibly impactful for the ART client experience.

The top eight critical barriers were all environmental context and resource-related, occurring at the PuP or health system-level and not within the individual ART client's control. In contrast, within the top eight frequency barriers, we see that almost half of the barriers were on the individual level and aligned with personal knowledge, social influences, and beliefs about capabilities. This trend may suggest that although PLHIV experience internalized barriers within their control more frequently, they may perceive external system-level issues as more critical.

There are some limitations within our study. First, our study population is limited to PLHIV who are already enrolled and participating in the CCMDD program, thus we are unable to draw conclusions on barriers to the process of referral and enrollment into the CCMDD program, which is reported to hinder access for vulnerable patients.[14] Based on the study population, participants were also asked to rank criticality of barriers based on a future hypothetical scenario, as opposed to past experiences which is how frequency of barriers was ranked. Additionally, we collected cross-sectional data which cannot detect temporal sequences in frequency and criticality of each

barrier. Finally, our study population was enrolled in a trial study in a single public urban clinic in Durban, thus our findings may have limited generalizability to other settings. However, the PHILA parent study was designed so study participants were representative of the target population and clinical settings in which CCMDD is implemented. Sensitivity analyses were also conducted to determine that trial randomization did not impact the results of the current analysis.

By employing the novel OPTICC toolkit for barrier prioritization methods, we hope this study not only enhances our understanding of the CCMDD program in South Africa, but also demonstrates the applicability of these methods for prioritizing barriers across different settings. As noted by the toolkit authors, barriers do not exist in isolation and can be influenced by dynamic and multi-level contexts.[79] Thus, another limitation was that interdependence between and co-occurrence among barriers was not addressed in our study. Future studies could use these results as a foundation to engage implementing partners in nominal group technique or free listing to explore or determine relationships between barriers; alternatively, principal components analyses could investigate patterns of barrier groupings in greater depth.[79] Quantifying associations between relevant sociodemographic characteristics and barrier frequency and criticality may also yield more insights into how barriers are experienced across different sub-populations. Additionally, future studies should consider having providers at the PuPs prioritize barriers and incorporating criteria on equity impact to explore the extent to which a barrier contributes to inequitable receipt of ART. Lastly, our study identifies high priority barriers for community-based ART delivery but does not discuss how to address them, thus we hope future studies will be able to use these findings to develop the implementation strategies needed to continue improving access to care for PLHIV.

3.6 CONCLUSION

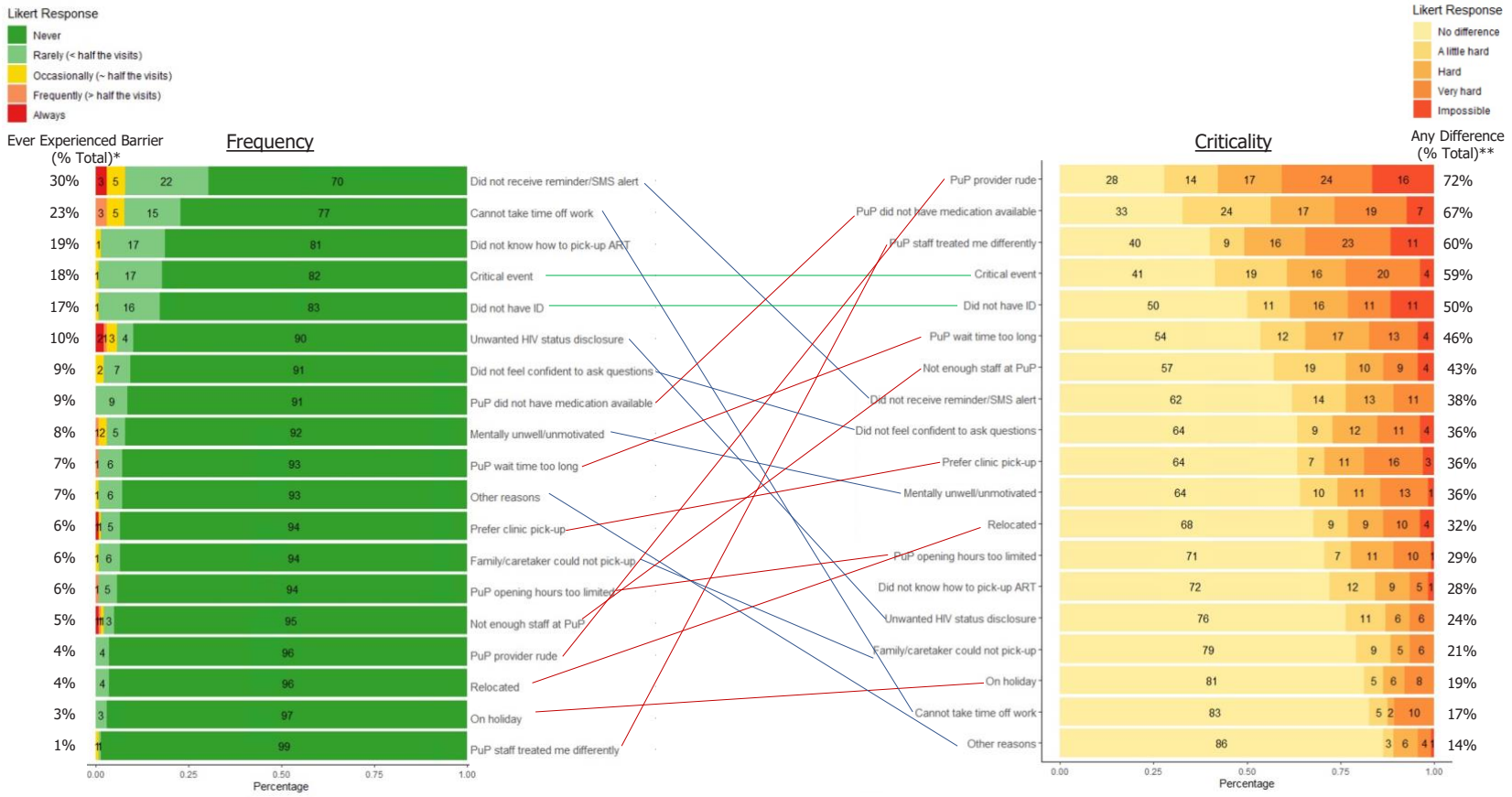
In conclusion, we identified key barriers that were frequently experienced and perceived as highly critical for continued participation in the CCMDD program. Prevalence and frequency of barriers was relatively low, while criticality was higher, particularly for environmental stressors. Critical events and lack of identification were highly prioritized barriers with above average frequency and criticality scores. Effective response measures are needed to enable uninterrupted delivery of healthcare services during critical events and allowing alternative forms of identification for ART pick-up may mitigate suboptimal care retention. Prioritized barriers identified in our study may aid selection of future implementation strategies to address high priority implementation challenges for differentiated ART delivery in resource-limited settings.

3.7 TABLES & FIGURES

Table 1. Study cohort population sociodemographic and behavioral characteristics (N=140).

Characteristic	n or Median	% or IQR
Sex (Female)	92	66
Median age (IQR)	44	37-48
Ethnicity/Race (Black African)	140	100
Citizenship		
Yes	136	97
Education (highest completed)		
None	2	1
Primary school	11	8
Secondary school but not matriculated	52	37
Matriculation	64	46
Tertiary	11	8
Employment		
Full-time	60	43
Part-time	23	16
Informal	7	5
Self-employed	10	7
Social grant recipient	5	4
Not employed	35	25
Any income*		
Yes	107	77
Median monthly income (ZAR) among persons with any income (IQR)	4000	2750-6350
HIV disclosure (aside from healthcare provider)		
Yes	48	34
PuP type		
Pharmacy	104	74
PeleBox	32	23
Clinic Outreach	1	1
Informal	3	2
Travel logistics		
Median roundtrip cost to PuP (IQR)	30	20-50
Transport method to PuP		
Walking	20	14
Public transport	114	81
Private transport	6	4

*N=139



Note: N=140 for all barriers except for "Cannot take time off work" (N=105)
*Ever Experienced includes the participants who answered either "Rarely", "Occasionally", "Frequently", and "Always" for each barrier
**Any Difference includes the participants who answered either "A little hard", "Hard", "Very Hard", and "Impossible" for each barrier

Figure 1. Participant responses regarding past experiences of barrier frequency and criticality of barriers for continued participation in the CCMDD program. Barriers for frequency are prioritized in descending order from highest to lowest proportion of population ever experiencing the barrier. Barriers for criticality are prioritized in descending order from highest to lowest proportion of population stating the barrier made any difference in their continued participation in the CCMDD program. Green lines show barriers that were ranked the same across frequency and criticality criteria. Blue lines show barriers that had lower criticality compared to frequency and red lines show barriers that had higher criticality compared to frequency.

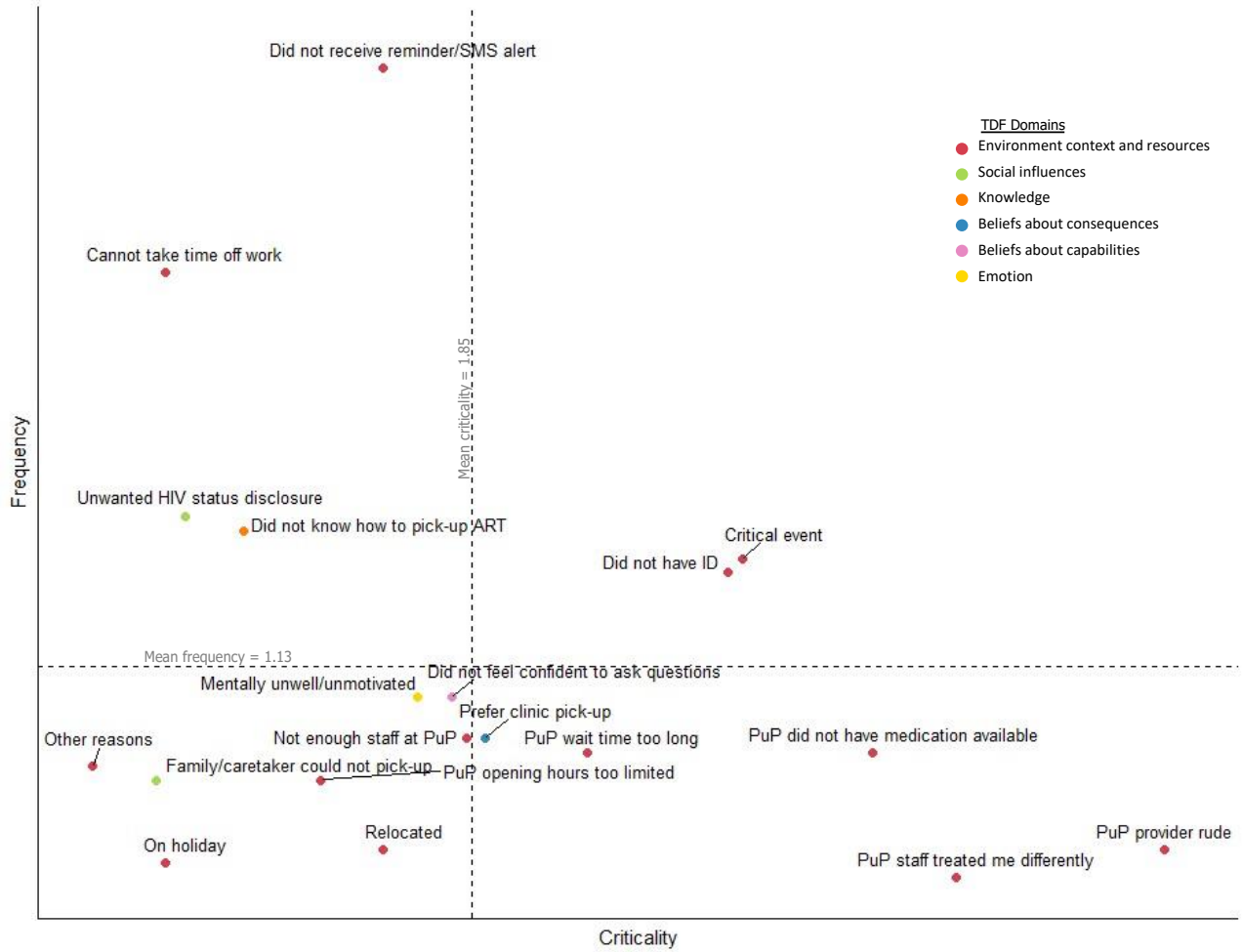


Figure 2. The Go-Zone map visually places the mean Likert score for each barrier with criticality scores increasing along the x-axis and frequency scores increasing along the y-axis. Four quadrants in the bivariate scatterplot were created by horizontally and vertically plotting the mean Likert response score across all barriers for frequency and criticality, respectively. The Go-Zone in the upper-right quadrant contains barriers that are above average in both criticality and frequency. Barriers are grouped by color according to their mapped TDF domain.

CONCLUSION

With expanded access to new highly effective ART regimens, HIV has evolved into a manageable chronic condition, thus prompting reevaluation of current models of clinic-based care. As clinics grapple with escalating resource limitations in initiating and monitoring millions of PLHIV on ART, there is a growing recognition that a one-size-fits-all model of care is no longer sustainable for providing lifelong HIV services. This dissertation presents three studies that explore innovative adherence monitoring tools and differentiated care strategies with the potential to decentralize health services into community settings, thus lessening burdens on clinic resources, and enhance access to person-centered care for PLHIV.

In **Chapter 1**, we reported results from a microcosting study on implementing POC urine TFV testing for drug adherence monitoring in South Africa. Our analyses showed that POC TFV testing could be feasibly implemented into routine care at a reasonable cost, particularly within clinics with higher ART client volumes and if the test is available commercially at an accessible price point. The POC TFV testing flow was straightforward and not a substantial time burden to incorporate into the overall clinical workflow. Our findings may also encourage the use of POC TFV testing as inexpensive complementary diagnostic tools to support PrEP adherence and HIVDR testing, in addition to aiding drug adherence among PLHIV in South Africa and other LMICs considering alternatives to traditional laboratory-based testing.

Chapter 2 analyzed the association between routine patient participation in the differentiated CCMDD program for community-based ART delivery and clinical outcomes of viral suppression and retention in care. Our analyses demonstrated that community-based ART delivery successfully facilitated differentiated care among clinically stable PLHIV, enabling maintenance of high levels of viral suppression and retention in care similar to clinic-based standard care. These

findings show the real-world effectiveness of community-based ART delivery for maintaining these clinical outcomes compared to standard clinic-based ART provision in South Africa and support national implementation of the CCMDD program.

Delving deeper into patient perspectives of the community-based ART program in South Africa in **Chapter 3**, we employed barrier prioritization methods to identify key barriers that were frequently experienced and perceived as highly critical for continued participation in the CCMDD program. Our analyses found that the prevalence and frequency of experienced barriers among participants enrolled in the program were relatively low, while criticality scores of barriers were notably higher. Go-zone mapping showed that critical events and not having a form of identification were the two highest priority barriers and that environmental context and resource related issues were highly ranked among participants.

In conclusion, this dissertation presents a body of work showing POC adherence monitoring tools and differentiated ART delivery programs are feasible to implement and have the potential to decentralize HIV service delivery. In the future, our microcosting estimates for POC urine TFV testing can inform budgetary planning for adherence monitoring. Results from our CCMDD cohort analyses support continued scale-up of the community-based ART delivery model in South Africa for clinically stable patients. Finally, key barriers identified in our barrier prioritization study may provide guidance for future implementation strategies that address high priority challenges and improve scale-up of the national differentiated care program in South Africa and other LMICs. We hope that insights gained from these findings on decentralizing HIV services from clinic to community settings will not only enhance access to healthcare for PLHIV, but also pave the way for integrated service delivery as we progress towards holistic, person-centered care.

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APPENDICES

Appendix 1. GDP price deflator methods for updating POC VL testing cost estimates.

Per-client costs from a prior POC HIV VL testing pilot study were updated using the gross domestic product (GDP) price deflator and new prices for test cartridges. Consumer price index (CPI) table values were obtained from the official World Bank data resource for the base year of 2017, when the POC VL tests were first estimated, and inflated to reflect the reported year of 2022. The 2017 POC VL test cost in USD were first converted to South African Rand using the 2017 South Africa to US exchange rate reported by the World Bank (XR: 13.2). We then adjusted for South Africa-specific inflation using CPI values with the following formula: 2022 Cost = 2017 Costs * (2022 CPI) / (2017 CPI). The final value was then converted back to USD using the 2022 South Africa to US exchange rate (XR: 16.36). All POC VL test costs were inflated using the above method except for the Cepheid POC VL test cartridge which had changed in price separate from inflation.[28] The current individual test cartridge price of USD $14.90 was inputted into the updated estimation of POC VL test costs.[34]

Appendix 2. Rapid review of costing studies conducted on POC HIV Assays.

Test Type	Geographic Region(s)	Methods	Included Costs	Key Findings	Reference
Primarily POC VL Test Costing Studies					
POC VL	Western Kenya	Micro-costing (provider perspective), Time and Motion Study (TMS)	• Personnel (staff salaries, trainings) • Equipment • Consumables • Facility & Infrastructure	Estimated POC VL testing cost USD $24.25 per test, assuming a clinic is conducting 100 VL tests per month. Centralized laboratory VL test was estimated to cost USD $25.65.	Bulterys *et. al.* (2021)
POC VL	Malawi	Gross costing (top-down) Expenditure approach: use retrospective records on the costs incurred during the study period	• Personnel (3 healthcare cadres, trainings) • Equipment **Fixed:** Cepheid GeneXpert IV device, centrifuge **Variable:** gloves, syringes, and EDTA tubes, service contract, paper etc. • Consumables • Facility overhead: uninterrupted power supply • Waste management	The “all-in” cost was $33.71 for a valid POC VL test. Compared with an international benchmark for a centralized VL test of $28.62.	Ganesh *et. al.* (2021)
POC VL	South Africa	Reported Cepheid Xpert VL cost based on instrument procurement and reagent prices as reported by the Global Fund	• Personnel: running samples, interpreting/recording results, training, support travel, Q/C, external quality assessment • Equipment: testing platform, support equipment (e.g. micro centrifuge) • Consumables	Abbott m-PIMA POC VL cost/VL test: 37.68 (29.51-45.85) Cepheid Xpert II cost/VL test: 28.33 (25.11-43.16) Centralized VL testing cost/VL test: 24.46 (in 2019 USD)	Girdwood *et. al.* (2020)

POC VL Creatinine CD4	South Africa	Micro-costing (clinical perspective), TMS, stakeholder interviews	• Personnel for clinic and lab • Equipment (GX device, centrifuge, refrigerator • Value of space • Device maintenance • Consumables for clinic and lab ⇒Cartridge/tests (variable) ⇒ QC reagents	Estimated that per-patient costs of POC HIV viral load, CD4, and creatinine tests were USD $25, $11, and $9, respectively, assuming a clinic volume of 50 patients initiated per month. At centralized laboratories, per-patient costs of POC HIV viral load, CD4, and creatinine tests were USD $26, $6, $3.	Simeon *et. al.* (2019)
Primarily POC Rapid Antibody Test Costing Studies					
POC HIV rapid antibody test POC CD4	Uganda Kenya	Micro-costing (health system perspective), TMS	• Personnel • Capital and equipment • Recurring supplies and services • Facility space	Mean cost per adult tested for HIV was $20.5 (range: $17.1 - $32.1) [2014 US$] POC CD4 test at $16 per HIV+ person identified	Chang *et. al.* (2016)
POC HIV rapid antibody test	USA*	Micro-costing (provider perspective), TMS	<u>Labor</u> Pre- and post-test interactions with clients, training, program/project admin <u>Nonlabor</u> Test kits, control reagents, rapid test supplies (gloves, biohazard bags, disposable pads), shipping costs for consumables, advertising costs to promote testing	The average cost per person tested was an estimated $47.21.	Lecher *et. al.* (2015)

*****Study did not take place in LMIC but included to show cost categories used

Appendix 3. Rapid review of barriers for differentiated care program implementation in LMICs.

Topic	**Year**	**Study Design**	**Geographic Region(s)**	**Key Takeaways**	**Barriers Identified**	**Citation**
Implementation of South Africa's central chronic medicine dispensing and distribution program for HIV treatment: A qualitative evaluation.	2022	Qualitative Conducted 109 semi-structured interviews with stakeholders (pick-up point staff, CCMDD service providers and administrators) and 16 focus groups with 138 patients.	South Africa	Recommendations included: (1) provide patient education and improve communication around refills (at the patient level); (2) provide dedicated space and staff, and ongoing training (at the organizational/clinic level); and (3) allow for prescription renewal at pick-up points and less frequent refills, and provide feedback to clinics (at the CCMDD program level).	**Patient-level barriers** included **inadequate education about CCMDD and inability to get refills on designated dates**. **Organizational-level** barriers included challenges with c**ommunication and transportatio**n, errors in medication packaging and tracking, rigid CCMDD rules, and i**nadequate infrastructure.**	Bogart, L. M., Shazi, Z., MacCarthy, S., Mendoza-Graf, A., Wara, N. J., Zionts, D., ... & Bassett, I. V. (2022). Implementation of South Africa's central chronic medicine dispensing and distribution program for HIV treatment: A qualitative evaluation. *AIDS and Behavior*, 1-13

Understanding how community antiretroviral delivery influences engagement in HIV care: a qualitative assessment of the Centralized Chronic Medication Dispensing and Distribution programme in South Africa	2020	Qualitative IDIs, FGDs with clients receiving ART and healthcare workers in Durban, South Africa. We analyzed 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.	South Africa	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.	BARRIERS FOR PATIENTS: Need for ID card Issues with electronic prescription system TB prophylaxis prohibits enrollment to CCMDD BARRIERS FOR CCMDD IMPLEMENTATION: Delayed SMS reminders ART not being available at the pickup point and a few pharmacies placing restrictions on ART pickup time Eligibility criteria for CCMDD seemed to contradict other stated aims of the healthcare system	Dorward, J., Msimango, L., Gibbs, A., Shozi, H., Tonkin-Crine, S., Hayward, G., ... & Garrett, N. (2020). 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. *BMJ open*, *10*(5), e035412.
Differentiated Antiretroviral Therapy Distribution Models: Enablers and Barriers to Universal HIV Treatment in South Africa, Uganda, and Zimbabwe	2019	Qualitative Semistructured interviews and focus group discussions with 163 stakeholders from policy, program, and patient levels	South Africa, Uganda, and Zimbabwe	DFC Benefits included perceived improved adherence, peer support, reduced stigma and discrimination, increased time for providers to spend with complex patients, and travel and cost savings for patients. Differentiated treatment distribution models can enhance treatment access for patients who are clinically stable.	Barriers: I**nsufficient drug supply**, Stigma (concerns re: unintended disclosure) Discrimination Poor care linkages (no symptom screens, inadequate LTC)	Duffy, M., Sharer, M., Davis, N., Eagan, S., Haruzivishe, C., Katana, M., ... & Amanyeiwe, U. (2019). Differentiated antiretroviral therapy distribution models: enablers and barriers to universal HIV treatment in South Africa, Uganda, and Zimbabwe. *The Journal of the Association of Nurses in AIDS Care*, *30*(5), e132.

Differentiated Care Preferences of Stable Patients on Antiretroviral Therapy in Zambia: A Discrete Choice Experiment	2019	Sample of HIV-positive adults on ART at 12 clinics in Zambia were asked to choose between 2 hypothetical facilities that differed across 6 DSD attributes. We used mixed logit models to explore preferences, heterogeneity, and trade-offs.	Zambia	Stable patients on ART primarily want to attend clinic infrequently, supporting a focus in Zambia on optimizing multi-month prescribing over other DSD features—particularly in urban areas. Substantial preference heterogeneity highlights the need for DSD models to be flexible, and accommodate both setting features and patient choice in their design.	Barriers described are **for retention in care a**nd cites DFC as a solution for these. Long waiting times, high-frequency clinic visits, and lack of support are frequently cited barriers to retention in HIV care. Note these are some of the main health care features which DSD models aim to address by adjusting visit frequency, location of services, mode of deliver, and type of service.	Eshun-Wilson, I., Mukumbwa-Mwenechanya, M., Kim, H. Y., Zannolini, A., Mwamba, C. P., Dowdy, D., ... & Geng, E. H. (2019). Differentiated care preferences of stable patients on antiretroviral therapy in Zambia: a discrete choice experiment. *Journal of acquired immune deficiency syndromes (1999)*, *81*(5), 540.
Differentiated Antiretroviral Therapy Delivery: Implementation Barriers and Enablers in South Africa	2019		South Africa	Findings suggest that creating and strengthening models that cater to client needs can achieve better health outcomes. South Africa's efforts can inform emerging models in other settings to achieve epidemic control.	BARRIERS to Novel ART delivery models: Financial (getting 2 month supplies at once etc.) Human and space resources (lack of space) TIME: need for time to allow buy-in. **Stigma** emerged as both a barrier (perceived disclosure of status) and an enabler.	Sharer, M., Davis, N., Makina, N., Duffy, M., & Eagan, S. (2019). Differentiated antiretroviral therapy delivery: implementation barriers and enablers in South Africa. *The Journal of the Association of Nurses in AIDS Care*, *30*(5), 511.

Understanding implementation barriers in the national scale-up of differentiated ART delivery in Uganda	2020	Qualitative 76 qualitative interviews with national-level HIV program managers (n = 18), District Health Team leaders (n = 24), representatives of PEPFAR implementing organizations (11), ART clinic in-charges (23) in six purposively selected Uganda districts with a high HIV burden 6 FGD	Uganda	One of the first multi-stakeholder evaluations of national DSD implementation in Uganda since initial roll-out in 2017. Multi-level interventions are needed to accelerate further DSD implementation in Uganda from demand-side (addressing HIV-related stigma, community engagement) and supply-side dimensions (strengthening ART supply chain capacities, increasing funding for community models and further DSD program design to improve patient-centeredness).	Individual-level BARRIERS: Individualized stigma and a fear of detachment from health facilities by stable patients enrolled in community- based models were reported as bottlenecks. Socio-economic status was reported to have an influence on patient selection of DSD models. Health-system BARRIERS: Insufficient training of health workers in DSD delivery and supply chain barriers to multi-month ART dispensing were identified as constraints. Patients perceived current selection of DSD models to be provider-intensive and not sufficiently patient-centered. Community BARRIERS: Community-level stigma and insufficient funding to providers to fully operationalize community drug pick-up points were identified as limitations. Context: Frequent changes in physical addresses among urban clients were reported to impede the running of patient groups of rotating ART refill pick-ups.	Zakumumpa, H., Rujumba, J., Kwiringira, J., Katureebe, C., & Spicer, N. (2020). Understanding implementation barriers in the national scale-up of differentiated ART delivery in Uganda. *BMC health services research*, *20*(1), 1-16.