Long-term Virologic Responses to Antiretroviral Therapy Among Patients Entering Adherence Clubs in Khayelitsha, Cape Town, South Africa

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Thank you to all my loved ones for your constant support, love and belief in me. It helped me more than I can say.

Abstract

Introduction: In 2017, approximately 36.9 million people were living with HIV and 58.1% were accessing antiretroviral therapy (ART) worldwide. In South Africa, ART coverage was 48.6% in 2015, and has since increased due to the implementation of universal Test and Treat. Given the need for lifelong care for millions of individuals, differentiated models of care for ART services are required. One such model, adherence clubs (ACs) for stable ART patients, has been successfully scaled-up in the Cape Metro Health District. In this study, we describe long-term virologic outcomes of patients who have ever entered ACs.

Methods: Adult patients enrolled in ACs in Khayelitsha between January 2011 and June 2017 were eligible for inclusion. Time to, and risk factors for, an elevated viral load (first viral load >1000 copies/mL) and confirmed virologic failure (two consecutive viral loads >1000 copies/mL two to nine months apart) were estimated using the Kaplan-Meier estimator and Cox proportional hazards models. Viral load completeness was assessed at 4, 16, 28, 40 and 52 months of follow-up.

Results: Of 11 830 patients, 74% were female and 45% were aged 35-44 years at AC enrolment. The median time on ART at enrolment was 4.7 years (interquartile range (IQR) 2.7-7.1). An elevated viral load was observed in 517 patients (4%), 141 (27%) of whom subsequently experienced confirmed virologic failure. The median time from an elevated viral load to confirmed virologic failure was 137 days (IQR 112-168). Risk of an elevated viral load and confirmed virologic failure was higher among patients with a longer duration on ART and lower among older patients. The proportion of completed viral load tests ranged from 79% at 4 months to 75% at 52 months. Over 90% of patients with viral load assessments remained virologically suppressed (<400 copies/mL).

Conclusion: This study demonstrates low rates of confirmed virologic failure among patients who entered ACs. The majority of patients remained stable despite the rapid growth of ACs, supporting the continued expansion of the model, particularly for men. Monitoring was generally consistent, but suboptimal among those who experienced an elevated viral load. Patients referred to ACs, younger patients and those with longer duration of ART should be prioritised to ensure they remain stable on lifelong ART.

Part A: The study protocol was submitted for departmental and ethical approval and contains the background and methodology done for this MPH mini-dissertation.

Part B: A structured literature review about antiretroviral therapy, adherence clubs and virologic responses is presented in order to contextualise this research study.

Part C: The journal-ready manuscript is presented according the author guidelines for the Journal of the International AIDS Society.

Appendix: The appendix includes all additional documentation necessary for the presentation of the MPH mini-dissertation.

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Abbreviations

AC	Adherence club
aHR	Adjusted Hazard Ratio
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral therapy
CAC	Community based adherence club
CI	Confidence interval
DMOC	Differentiated models of care
DRC	Democratic Republic of the Congo
HIV	Human Immunodeficiency Syndrome
HR	Hazard ratio
IeDEA-SA	International epidemiology Databases to Evaluate AIDS Southern Africa
LTFU	Loss to follow-up
MSF	Médecins Sans Frontières
NNRTI	Non-nucleoside reverse-transcriptase inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitors
PLWH	People living with HIV
PMTCT	Prevention of mother-to-child transmission
SOC	Standard of care
TB	Tuberculosis
UCT	University of Cape Town
UNAIDS	United Nations Programme on HIV/AIDS
VL	Viral load
WHO	World Health Organization

PART A: PROTOCOL

1. Introduction and background

1.1 Epidemiology of HIV in South Africa

In 2016, 36.7 million individuals were living with Human Immunodeficiency Virus (HIV) worldwide (1). Most people living with HIV (PLWH) live in countries with limited resources (2). Eastern and Southern Africa experience the heaviest burden of HIV, with approximately 19.4 million HIV-positive individuals (1). In South Africa, the estimated HIV prevalence is 12.7% (3), with the highest HIV prevalence in the Gauteng (24%) and Kwa-Zulu Natal (20%) provinces (4).

1.2 Epidemiology of ART in South Africa

Effective antiretroviral therapy (ART) programmes are essential for managing the burden of HIV. By June 2017, 20.9 million PLWH were accessing ART worldwide (1). In Eastern and Southern Africa, approximately 66% of PLWH had access to ART in 2017 (5). ART coverage was 48.6% by mid-2015 in South Africa (6).

The South African ART programme began in 2004 after high-level political resistance (7,8) and expanded rapidly, with a five- and three-fold increase in ART initiation among adults and children respectively from 2003-2007 (9). The eligibility criteria were initially strict, only offering ART to patients with a CD4 count <200 cells/µL or with WHO clinical Stage IV (10). Guidelines progressively expanded to include the following patients: pregnant women regardless of their CD4 count, HIV and tuberculosis (TB) co-infected patients who had a CD4 count <350 cells/µL and children <1 year (11). In 2015, the CD4 count threshold was increased to <500 cells/µL (11).

The latest WHO Test and Treat guidelines recommend that all HIV-positive children, adolescent and adults should be initiated on long-term ART, irrespective of their CD4 count (12). On the 1st September 2016, the South African Minister of Health announced the implementation of these guidelines, expanding access to ART to anyone with a confirmed HIV diagnosis (13). Importantly, countries including South Africa which adopt the Test and Treat approach will experience an increase in the number of individuals requiring ART services. Therefore, the model of ART delivery needs to be adapted to ensure PLWH are retained in long-term care. In addition, patients currently in care should still receive quality care and remain virologically suppressed on ART despite the anticipated increase in individuals requiring these services (14).

1.3 Adherence club model

To address long-term adherence and retention in ART programmes in a context of increased demand for ART services, differentiated models of care (DMOC) are required. These models of care should ensure quick and easy access to treatment for patients who are stable on ART (15,16). Different community-based models have been piloted in various settings in Sub-Saharan Africa to improve retention and increase the availability of ART services within communities. In the Democratic Republic of Congo, community ART distribution points were established in Kinshasa for stable patients to access their medication every three months (17). In the community ART groups model of care, utilised in Mozambique, six stable patients take turns collecting ART from the clinic every month and distributing it to group members (17,18). In a similar model adopted in Malawi, the frequency of clinic visits for stable patients was reduced by allowing these patients to collect a 6-month supply of ART during their clinical assessments (17). This model of care in which pharmacy regulations have been adapted, has been used in other countries including Uganda, Zimbabwe and South Africa (17,19).

Another DMOC is adherence clubs (ACs), which aim to reduce the burden on the health system by shifting the distribution of ART services and counselling to AC meetings (20). Furthermore, this model decreases the frequency of medication collection, lessens excessive clinical consultations and improves access by decentralising ART services within the community (21). Importantly, ACs provide a rapid distribution of ART and support for groups of stable patients (16,21).

1.4 Adherence clubs in South Africa

In 2007, a pilot study of 20 ACs was conducted by Médecins Sans Frontières (MSF) at the Ubuntu clinic in Khayelitsha, Cape Town (16). Due to the success of this pilot study, ACs were adopted for the Cape Metro Health District by the Western Cape Government Department of Health in January 2011 (21).

Participation in an AC is voluntary, but patients are required to meet the eligibility criteria with regard to ART duration and virologic suppression (14,21). Initially, stable patients were defined as those who had been on ART for at least 18 months with two consecutive viral loads (VLs) <400 copies/mL (virologically suppressed) (20,21). These patients also required a referral from a clinician and it was recommended that they have a CD4 count >200 cells/μL within the last six months with no other chronic illnesses requiring regular consultation (20,21). In 2013, the CD4 criterion was removed and the required period on ART was reduced to 12 months (21). The eligibility criteria changed again in January 2015, further reducing the time on ART to a minimum of six months with only one suppressed VL (21). Although ACs may differ between facilities, there are certain fundamental components (see section 3.3).

1.5 Adherence club outcomes

To date, the performance of ACs has mostly been assessed in terms of retention and virologic suppression. In an early assessment of ACs at the Ubuntu clinic in Khayelitsha from 2007 to 2013, it was found that loss to follow-up (LTFU) and virologic rebound were reduced by 57% and 67% respectively amongst patients in ACs as compared to patients receiving clinical care (20). Notably, 97% of the patients in ACs were retained during the study period (20).

On the basis of these promising initial results, ACs were introduced on a larger scale at more facilities in the years following the 2011 pilot study (21). Similar results for retention and virologic rebound were reported when the ACs were moved to community based venues from 2012-2013 (22). During a 12-month period of club visits, LTFU was 6% and virologic rebound was experienced by less than 2% of these patients (23). The risk of LTFU in patients attending community based ACs was 67% lower than among patients receiving clinical care (22). However, it is important to note that the risk of LTFU in community based ACs was twice as likely in the age group 16-24 years compared to older age groups (22).

In an assessment of the Cape Metro Health District from 2011-2014, following the intensive scale-up of ACs, similar results were observed: retention at 12, 24 and 36 months of follow-up was 95.2%, 89.3% and 82.1% respectively (14). VL assessments were completed in 88.1% of the cohort, of which 97.2% of patients had a VL ≤400 copies/mL in the 13 months before analysis closure. Thus, the majority of patients in this cohort were able to remain stable using this model of care. However, LTFU increased from 2.6% at 12 months to 12.2% at 36 months after AC enrolment. The risk of LTFU was higher in younger patients (16-24 years adjusted hazard ratio (aHR) 2.41, 95% confidence interval (CI) 1.10-25.23 and 25-34 years aHR 1.55, 95% CI 1.03-2.33 compared to 35-44 years) and in patients accessing ART services from larger primary healthcare facilities (aHR 1.32, 95% CI 1.11-1.59) (14). Patients with a longer duration on ART (aHR 1.12, 95% CI 1.03-1.23) and aged 16-24 and 25-34 years (aHR 1.52, 95% CI 0.59-3.95 and aHR 1.74, 95% CI 1.17-2.59 respectively) were at higher risk of experiencing virologic rebound. The risk of virologic rebound was decreased by 37% when patients sent a buddy to collect their medication at least once (14).

1.6 Virologic failure

Studies have shown positive short-term results in terms of retention, virologic suppression and rebound. However, there are limited data on longer-term virologic responses including virologic failure in stable patients after enrolling in ACs. Virologic failure can be defined in a number of ways, depending on the current guidelines and the author. Western Cape guidelines define virologic failure as two consecutive VLs >1000 copies/mL within two to three months (13). However in some studies, virologic failure is defined as a VL ≥1000 copies/mL confirmed with a consecutive VL of ≥1000 copies/mL within two weeks or three months (24,25). Alternatively, virologic failure has been defined as two successive VLs >400 copies/mL with the second measurement >5000 copies/mL after adherence counselling (26).

With ART programmes expanding, the risk of failure on first-line ART has increased, and more individuals are now on second- or third-line ART (27). Non-adherence and resistance are often associated with first-line virologic failure (27,28). Within resource-limited settings, patients may be switched from first- to second-line ART late, not at all, or switched unnecessarily due to CD4 counts being used as a proxy for first-line failure rather than VLs, which are more accurate (27).

In South Africa, within 5 years of ART initiation, 14% of HIV patients failed first-line ART regimens (29). Switching to second-line ART is expensive, costing approximately two to three times more than first-line ART and therefore, switching is usually the last option (27,28). It is vital to ensure patients remain on first-line ART as long as possible to reduce costs involved with switching to second-line ART in resource-limited settings. However, it is also essential to switch patients who are on a failing regimen. VL monitoring provides an opportunity to intervene with adherence counselling, earlier detection of virologic failure and more timeous switch to second-line ART regimens if required (30).

Previous studies have identified predictors of virologic failure in a South African setting including age, sex/gender, treatment provider, first-line Non-Nucleoside Reverse-Transcriptase Inhibitors (NNRTI), CD4 count, mean corpuscular volume, haemoglobin level, TB history, missed visits to the clinic within the first six months on treatment, treatment interruptions greater than 7 days, WHO staging at ART initiation, VL at ART initiation, year of ART initiation, Nucleoside Reverse Transcriptase Inhibitors (NRTI) in ART regimens and low-level viremia (24,26,31,32).

1.7 The need for further evidence

There are several studies about the predictors of virologic failure within a clinical setting and assessments of the performance of ACs in terms of retention and virologic rebound. However, to our knowledge, there has been no research on the incidence and predictors of virologic failure in ACs in South Africa. Furthermore, studies reporting on virologic suppression and rebound have had limited follow-up time and sample sizes. Within the Cape Metro Health District over a four-year implementation period, ART was provided to 25.2% of the cohort using the AC model (21). The Western Cape Department of Health set a target for ACs to provide ART services to 50% of patients retained in care by the end 2017 (33). Given the scale-up of this model of care, longitudinal evidence on virologic responses and VL completeness in patients enrolling in ACs could inform nationwide implementation and ensure long-term quality care for stable patients.

2. Aims and objectives

We will analyse data routinely collected from the Khayelitsha cohort within the International epidemiology Databases to Evaluate AIDS Southern Africa (IeDEA-SA) collaboration to investigate the virologic responses of patients enrolling in ACs in Khayelitsha, Cape Town, South Africa between January 2011 and June 2017.

To achieve this, our specific objectives are:

- To describe the characteristics of Khayelitsha patients at entry into an AC.
- To estimate the proportions of elevated VLs, confirmed virologic failure and virologic suppression among Khayelitsha patients after entry into an AC.
- To estimate time to an elevated VL and confirmed virologic failure among Khayelitsha patients after entry into an AC.
- To examine crude and adjusted predictors of an elevated VL and confirmed virologic failure within these Khayelitsha patients.
- To estimate the percentage of VL completeness among patients entering ACs in Khayelitsha at different time points.

3. Methodology

3.1 Definitions

- The Western Cape Consolidated Guidelines for HIV Treatment define virologic failure as having two consecutive VLs >1000 copies/mL within two to three months (13). For this study, a period of two to nine months will be used to account for the delays in when these tests and adherence counselling occur in reality.
- Stable patients are defined as patients who have been on ART for a minimum of six months with one suppressed VL (14,21).
- A suppressed VL is defined as a measurement <400 copies/mL (21).
- Virologic rebound is defined as the first VL measurement ≥400 copies/mL after entry into an AC.
- An elevated VL is defined as the first VL measurement >1000 copies/mL after entry into an AC.
- LTFU is defined as 6 months or more since the last clinical visit for a patient (34).

3.2 Study design

This study will be a secondary analysis of data from the Khayelitsha cohort within the IeDEA-SA collaboration. Routine anonymised follow-up data recorded from ACs at three healthcare facilities in Khayelitsha between January 2011 and June 2017 will be utilised for this study.

3.3 Setting and study population

The study setting will be ACs within the Khayelitsha ART programme located in Cape Town, South Africa. Khayelitsha, a peri-urban township, is the largest township in Cape Town with an estimated population of 500 000 people (29,35,36). The population density is high in many areas due to frequent migration from the Eastern Cape and neighbouring countries (35). The unemployment rate is 38% and approximately 45% of the total population live in low cost formal housing (35).

The HIV burden in Khayelitsha is the highest in the Western Cape and one of the highest in the country (35,37). In 2001, the first public-sector pilot ART projects were established in three provincial primary clinics in Khayelitsha. The projects were a collaboration between MSF and the Western Cape Government (29,36–38). A total of 287 ART-naïve patients initiated ART between May 2001 and December 2002 (39). In 2004, the national ART programme was launched, with strict eligibility criteria (7). Over time, the national ART guidelines liberalised, lowing the threshold for ART eligibility. By the end of 2014, the Khayelitsha ART programme had expanded to over 40 000 patients (35).

In September 2016, South Africa adopted the World Health Organization's universal Test and Treat guidelines, significantly increasing the number of people eligible for ART nationally. To meet this demand, DMOC are being tested and evaluated. In Khayelitsha, ACs are the most recent service delivery approach that is being explored (35). Within the ART programme, stable patients are referred to ACs and participation is entirely voluntary (14,23). These stable patients are required to attend AC meetings five times annually for 30-60 minutes (14,21). ACs, comprising 25-30 members, are facilitated by a lay healthcare worker and patients collect a two-month supply of pre-packaged ART, with a four-month supply at the end of the year to support patients who migrate during this period (21,23,40). The pre-packaged ART supply is collected by the patient during the visit, but a buddy may collect the patient's medication every alternate AC meeting. Patients participate in a group discussion, are weighed and undergo a brief symptom screening during each visit (14,21,23). Four months after club entry and annually thereafter, patients have their VLs measured, and clinicians consult with club patients about their results. Symptomatic or ill patients are referred back to the health facility. If a VL exceeds 400 copies/mL, patients are referred back to the clinic for adherence counselling (14,38). These individuals may return to the AC when they return to virologic suppression (38). All paper-based registers from the ACs are captured into the electronic monitoring systems by the facility's data clerks (14,16,21).

3.4 Inclusion criteria

The following eligibility criteria will be applied for inclusion in this study:

- Patients aged 16-85 years.
- Patients who were enrolled into an AC between January 2011 and June 2017.
- Patients who had a VL ≤1000 copies/mL within 15 months before AC entry.
- Patients who initiated ART from January 2004 onwards.

3.5 Research procedures and data collection methods

Routinely recorded patient data are collected and captured at the Khayelitsha sites. A Data Transfer Protocol will be used to anonymously transfer the data to the IeDEA-SA Data Centre. All standard reports are aggregate reports that do not contain identifying information, and cannot be linked to any individual. The data are stored, cleaned and merged before analysis. The following variables for each participant will be included from the data (Tables 1 & 2):

- Demographic variables:
    - Sex
    - Age
- Clinical variables:
    - At AC entry:
        - CD4 count
        - VL measurements
        - TB history
        - Date of ART initiation
        - Duration on ART treatment
        - Date of AC entry
        - Facility
    - During follow-up
        - VL measurements
- Outcomes:
    - An elevated VL and confirmed virologic failure after entry into an AC
    - VL completeness at 4, 16, 28, 40 and 52 months after entry into an AC
    - VL completeness at 2-9 months among patients who experienced an elevated VL after entering an AC and annually thereafter

Supplementary Table 1. Variables included in this study.

Variable	**Variable type and/or format**	**Variable description**
Patient identifier	Numeric text	Unique anonymous patient identifier
Sex	Categorical	Female or male
Age	Categorical	Age, in years
Date of ART initiation	dd-mm-yyyy	
Duration of ART at AC entry	Numerical	Number of months on ART
Date of AC entry	dd-mm-yyyy	
CD4 count	Numerical	Absolute CD4 cell count (cells/µL)
Viral load	Numerical	HIV-RNA measurement (copies/mL)
TB history	Categorical	TB: yes or no
Facility	Categorical	Name of facility at which patients attend AC meetings

3.6 Statistical methods

3.6.1 Sample size and statistical power

All individuals entering ACs in Khayelitsha who meet the eligibility criteria will be included in the analysis.

3.6.2 Data analysis

Two-sided tests and 95% confidence intervals will be used in this analysis, unless otherwise indicated. The data analysis is presented below followed by dummy tables.

3.6.2.1 Descriptive statistics

We will use descriptive statistics to summarise the characteristics at enrolment in ACs (Table 1). Normally distributed, continuous variables will be described using means and standard deviations. Non-normal, continuous variables will be described using medians and interquartile ranges. Categorical variables will be described using frequencies and proportions. Normality of continuous variables will be assessed with histograms.

3.6.2.2 Survival analysis

We will estimate the median time to virologic failure from entry into an AC using Kaplan-Meier survival curves (Figure 1). We will use Cox proportional hazards models to estimate the crude and adjusted hazard ratios between the predictor variables and the outcome, virologic failure (Table 2).

3.6.2.3 Viral load completeness

We will assess the VL completeness among all eligible patients entering AC at 4, 16, 28, 40 and 52 months (Table 3). The time points chosen are in line with guidelines, which state VL tests should be done 4 months after AC enrolment and annually thereafter (21). The window for the four-month assessment will range from 0-10 months for patients followed-up for at least four months. The subsequent time points will have a year's window for patients followed-up for 16, 28, 40 and 52 months respectively.

Among patients who experienced an elevated VL after AC, VL completeness will be assessed at 2-9 months after this event for patients who are followed-up for at least three months after they have experienced an elevated VL (Figure 2). We will assess VL completeness annually thereafter at 15, 27, 39 and 51 months. A year's window will be used for patients followed-up until each time point.

Table 1. Characteristics of Khayelitsha adherence club patients at entry into adherence clubs.

Patient characteristics	At adherence club entry
Sex, n (%)	
Males	
Females	
Age (years), n (%)	
Median (IQR)	
16-34	
35-44	
≥45	
Year of entry, n (%)	
2011-2012	
2013-2015	
2016-2017	
Time on ART (years), n (%)	
Median (IQR)	
0-2	
3-4	
≥5	
CD4 count (cells/µL), n (%)	
Median (IQR)	
<250	
250-499	
500-749	
≥750	
Missing	
Viral load (copies/mL), n (%)	
<400	
400-1000	
Missing	
TB history, n (%)	
Yes	
No	
Facility	
Michael Mapongwana CDC	
Nolungile CDC	
Ubuntu HIV Clinic	

Figure 1. Kaplan-Meier survival estimates for Khayelitsha adherence club patients by time on ART.

Table 2. Univariate and multivariate Cox proportional hazard models of predictors of virologic failure among Khayelitsha adherence club patients.

	Univariate model		**Multivariate model**	
Variable	**Crude HR (95% CI)**	**p-value**	**Adjusted HR (95% CI)**	**p-value**
Variable 1				
Variable 2				

Table 3. Viral load completeness, virologic rebound and suppression in Khayelitsha adherence club patients at 4, 16, 28, 40 and 52 months.*

Follow-up time (months)	**4**	**16**	**28**	**40**	**52**
Number of patients, n					
Viral load tests completed, n (%)					
Results (copies/mL), n (%)					
<400					
400-1000					
>1000					

*Note: The window for the four-month assessment ranged from 0-10 months. The window for the 16, 28, 40 and 52 month assessment was six months before and after each time point.

Figure 2. Viral load completeness among patients who experienced an elevated viral load after entering an AC.

4. Ethical considerations

4.1 Ethical approval

The University of Cape Town (UCT) data centre of the IeDEA-SA collaboration has ethics approval from the UCT Human Research Ethics Committee (HREC 084/2006) to receive anonymised data from Khayelitsha. This study will seek specific ethics approval from the HREC, UCT (Appendix 1).

4.2 Risks and benefits

4.2.1 Risks

The data for patients attending ACs are collected at the Khayelitsha sites. There are no anticipated risks or discomfort involved with this secondary data analysis as all data transferred to the IeDEA-SA data centre are anonymised before the transfer.

4.2.2 Benefits

This study could directly benefit the participants and the wider community in improving our understanding of the predictors of elevated VLs and confirmed virologic failure within ACs in South Africa. The study may provide evidence to reduce virologic failure and retain patients in ACs on first-line ART, and inform appropriate regimen switching when required.

4.3 Privacy and confidentiality

Informed consent is not required for this study as the data are de-identified and anonymised (41). When the data are transferred from the individual sites, the identifiers are stripped and protected by password encryption. A data manager securely imports and merges the data in the IeDEA-SA data centre. Study outcomes will not be reported at an individual level, further protecting confidentiality.

5. Stakeholders

The stakeholders include:

- Southern African IeDEA cohorts.
- The Khayelitsha ART programme investigators, facility managers, and patients participating in ACs.
- Large, rapidly expanding ART programmes, particularly in resource-limited settings.
- Policy makers and the academic community working in the field of HIV treatment.

6. Dissemination of the results

The results from this study will be accessible to researchers and other stakeholders through presentation at conferences and publication in a relevant peer-reviewed journal. Furthermore, the results will be available to the site staff and academic staff through appropriate reports and abstracts. The MPH thesis will be accessible from the UCT library site.

7. Logistics

The timeline for the completion of the MPH mini-dissertation with the relevant sections and tasks is described in Table 4.

Table 4. MPH mini-dissertation timeline for completion.

Task	Duration and anticipated time of completion
Protocol	January – March 2018
Literature review	April – June 2018
Data management and analysis	May – August 2018
Manuscript write-up	August – November 2018
UCT mini-dissertation submission	December 2018
Dissemination of research findings	January 2019

8. Budget

There are no anticipated costs in this research study which will be conducted for the purpose of a MPH mini-dissertation. The analysis of the secondary data obtained from IeDEA-SA will be completed by the student researcher in her own time.

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PART B: LITERATURE REVIEW

1. Introduction

1.1 Epidemiology of HIV

Human Immunodeficiency Virus (HIV) is characterised by the weakening of the immune system due to the replication of the virus and destruction of immune cells, especially the loss of CD4 cells. This infection may result in opportunistic infections, oncological diseases, chronic diseases and comorbidities including cardiovascular, bone, renal and hepatic diseases (1). A high viral load (VL) measurement in acute HIV infections drives the transmission of HIV (2). HIV is categorised into HIV-1 and HIV-2. The majority of global HIV infections can be attributed to HIV-1, which results in immune deficiency rapidly when compared to the slow progression of HIV-2 (3,4). HIV-1 is commonly transmitted through sexual intercourse, blood, pregnancy, birth and breastfeeding (5).

1.1.1 Worldwide

HIV is a major cause of morbidity and mortality worldwide with 77.3 million HIV infections recorded globally since the start of the epidemic (6). In 2017, approximately 36.9 million people were living with HIV globally (6). Despite new HIV infections having declined by 16% among adults and 35% among children from 2010 to 2017, there were an estimated 1.8 million new HIV infections in 2017 (6). While there has been a 51% reduction in Acquired Immunodeficiency Syndrome (AIDS)-related deaths since 2004, 940 000 AIDS-related deaths occurred globally in 2017 (6).

1.1.2 Eastern and Southern Africa

Eastern and Southern Africa experience the highest burden of HIV disease, with 19.6 million people living with HIV (PLWH) in 2017. Although newly-acquired HIV infections declined by 29% from 2010 to 2016, 800 000 new HIV infections were documented in this region in 2017 (6,7). Despite a 45% decline in AIDS-related deaths from 2010-2016, 380 000 AIDS-related deaths were recorded in Eastern and Southern Africa in 2017 (6,7).

South Africa has the largest number of PLWH worldwide. It was estimated that 7.52 million individuals were HIV-positive in 2018, almost a two-fold increase from 2002 (8,9). Since 2002, there has been an increase in the prevalence of HIV among women and adults aged 15-49 years, with current estimates indicating that the HIV prevalence is 21.17% for women and 17.98% for adults (8). Among the youth (15-24 years), the prevalence of HIV has declined by 2.67% since

2002 (8). Although the number of AIDS-related deaths has declined substantially, 115 167 AIDS-related deaths occurred in 2018 (9). The burden of HIV within South Africa remains substantial in contrast with global decreased trends in HIV, and effective antiretroviral therapy (ART) programmes are required for the sustainable treatment and management of HIV.

1.2 Epidemiology of ART

ART was developed in the 1990s and allows PLWH to suppress their viral replication and manage this chronic disease (2). ART interrupts various steps of the virus's lifecycle, thus reducing both the mortality and morbidity of PLWH (2). ART initiation decreases the VL concentration in approximately three months, however the CD4 count response is variable (2). ART has increased the number of PLWH, who will require lifelong ART to maintain viral suppression.

Initially, developed countries provided patients with individualised regimens with the support of specialised doctors. However, this approach was not feasible in resource-limited settings, and in 2006, the World Health Organization (WHO) proposed a public health approach to using standardised regimens (10). Notably, similar virologic outcomes were observed among patients receiving individualised treatments in Switzerland as compared to patients receiving a public health treatment approach in South Africa (11).

1.2.1 Worldwide ART

The number of individuals accessing ART has increased from 8 million in 2010, to 17.2 million in 2015 to 21.7 million in 2017 (6). Approximately 59% of adults (≥15 years) and 52% of children (0-14 years) living with HIV had access to ART in 2017 (6).

1.2.2 Eastern and Southern Africa ART

Approximately 66% of PLWH had access to ART in Eastern and Southern Africa in 2017 (6). When stratified to adults (≥15 years) and children (0-14 years), only 66% and 59% were accessing ART respectively. Importantly, the percentage of pregnant women accessing ART for PMTCT was 93% in 2017 (6).

1.3 Differentiated models of care

Alternative approaches to ART services are necessary to support ART adherence and retention among PLWH for lifelong care. Differentiated models of care (DMOC) are a client-centred approach focused on the changing needs of individuals, allowing the simplification and adaption of HIV services along the continuum of care (12,13). This approach aims to provide better services for PLWH and importantly, to reduce the burden on the healthcare system by decongesting healthcare facilities (13). Additionally, access to HIV services is increased by effectively distributing resources (13). National policies are required for DMOC to be successful, sustainable and receive adequate funding (13).

1.4 Aims and objectives

This literature review aims to explore DMOC and their outcomes based on current global and South African ART guidelines. The objective is to review and discuss the literature on:

- Global and South African ART guidelines
- DMOC in Sub-Saharan Africa
- Virologic monitoring and responses
- Outcomes in adherence clubs (ACs) in South Africa

2. Search strategy

Literature for this review was identified using PubMed, Cochrane Library and Google Scholar. The search terms used across the databases were similar and used in combination and are listed in Table 1. PubMed was the primary source. Google Scholar and the Cochrane library were searched for additional resources. Publications in English only were included and focused mainly on adult studies in Sub-Saharan Africa and South Africa. References from the included studies were examined as a potential source of additional publications. The United Nations Programme on HIV/AIDS (UNAIDS) and WHO websites were used for current statistics and guidelines.

Table 1. **Search terms.**

Theme	Search terms
ART in South Africa	• History of antiretroviral therapy • South Africa
Differentiated models of care	• HIV and AIDS • Models of care • Differentiated models of care • Sub-Saharan Africa
Virologic failure	• Virologic/viral failure • First-line ART • Second-line ART • South Africa
Virologic suppression	• Virologic/viral suppression • South Africa • HIV/AIDS
Virologic rebound	• Virologic/viral rebound • South Africa • HIV/AIDS
Outcomes of adherence clubs in South Africa	• HIV and AIDS • Adherence clubs • South Africa

3. ART guidelines, targets and coverage

3.1 Worldwide

In 2013, UNAIDS set the 90-90-90 treatment targets to end the AIDS epidemic, which were viewed as ambitious, but achievable. These targets are that by 2020: 90% of PLWH will be diagnosed, 90% of HIV-diagnosed individuals will receive ART, and 90% of HIV-positive individuals receiving ART will be virologically suppressed (14). Based on the potential achievement of the 90-90-90 targets by 2020, modelled data suggests the AIDS epidemic could end as soon as 2030 (14).

The progress towards these treatment targets varies between the regions which have adopted these targets (Table 2). The proportion of PLWH that know their HIV status was the highest in Latin America (81%) and Eastern and Southern Africa (76%), in contrast with approximately half this proportion observed in Western and Central Africa (42%) (15). ART coverage for HIV-diagnosed individuals was the highest in Western and Central Africa (83%) and Eastern and Southern Africa (79%) (15). Approximately half of those requiring ART received it in Eastern Europe and Central

Asia (45%) and the Middle East and North Africa (41%) (15). The prevalence of virologic suppression amongst PLWH on ART was relatively similar across the majority of regions, and was highest in Eastern and Southern Africa (83%), despite the high burden of disease. In comparison, low rates of virologic suppression were observed in in the Caribbean (67%) and the Middle East and North Africa (66%) (15). The current estimates across different regions indicate that the 90-90-90 treatment targets are not being achieved at the same rate, and substantial action is required to achieve these targets by 2020.

Table 2. Progress towards the 90-90-90 treatment targets (15)**.**

	First 90: Percentage of PLWH who know their status	**Second 90: Percentage of PLWH who know their status and are on ART**	**Third 90: Percentage of PLWH on ART and virologically suppressed**
Eastern and Southern Africa	76%	79%	83%
Western and Central Africa	42%	83%	73%
Asia and the Pacific	71%	66%	83%
Latin America	81%	72%	79%
Caribbean	64%	81%	67%
Middle East and North Africa	58%	41%	66%
Eastern Europe and Central Asia	63%	45%	77%
Western and Central Europe and North America	-	-	-

3.2 South Africa

The ART programme in South Africa has had a turbulent past due to the beliefs held by the ex-President, Thabo Mbeki, and other high-ranking government officials during the early 2000s (16,17). Mbeki was a denialist who did not believe that HIV caused AIDS, suggesting that lifestyle choices and the stress of poverty were the causes (16,17). This led to lengthy delays in the implementation of effective HIV/AIDS policies, despite the growing knowledge about HIV worldwide. Due to denialism and poor policies, an estimated 330 000 premature deaths occurred during this era (18).

South Africa eventually launched an ART programme in April 2004 at accredited facilities. The expansion of the programme was extremely slow, because of the stringent criteria enforced (19). The ART programme has changed over the years to increase access to ART. In 2004, the ART guidelines stated that PLWH could be initiated on ART if their CD4 count was <200 cells/µL irrespective of their WHO staging or if they had WHO stage IV irrespective of their CD4 count (20). The ART guidelines were revised in 2010 to include pregnant women regardless of CD4 count, HIV and tuberculosis (TB) co-infected patients with a CD4 count <350 cells/µL and children under the age of one (17). In 2015, the CD4 count threshold was raised to <500 cells/µL in 2015 (17).

In 2016, the WHO issued the Treat All recommendation to ensure that all PLWH would receive ART, supporting the 90-90-90 treatment targets (21). On 1 September 2016, Dr Aaron Motsoaledi, the South African Minister of Health, announced the implementation of universal Test and Treat guidelines (22,23). The new guidelines removed all eligibility criteria, making services available to anyone with a confirmed HIV diagnosis.

Due to the changing guidelines, the number of people accessing ART has increased dramatically, from 47 500 in mid-2004 to 1.79 million in mid-2011 (24). When the CD4 count threshold was altered to <500 cells/µL, it was estimated that an additional 1.6-2 million people would require ART (25). In mid-2015, 3.39 million PLWH were accessing ART (26). At the time of the universal Test and Treat announcement, approximately 3.4 million PLWH were accessing public-sector ART in South Africa, close to half of those requiring treatment (27). The increasing size of the ART programme presents major challenges in terms of retaining people in lifelong care (28).

To accommodate the influx of eligible ART patients into the healthcare system, the number of accredited facilities in the country expanded rapidly: from 362 ART facilities in 2008 to 3 000 facilities by 2013 (25). This rapid expansion increased the burden on healthcare facilities, with a potential impact on adherence and retention of ART patients (25).

3.2.1 Progress towards 90-90-90 in South Africa

South Africa has embraced the 90-90-90 targets set out by UNAIDS (29), but progress towards these targets varies, with the most significant progress made towards the first target, 90% HIV diagnosis amongst PLWH. In mid-2015, 85% of PLWH knew their status (26). HIV diagnosis rates were fairly uniform across the nine provinces, ranging from 82.0% to 88.3% (26).

Progress towards the second treatment goal, providing ART to 90% of HIV-positive diagnosed individuals, has not been as successful. While ART coverage has more than doubled from 2010 to 2015 in South Africa, only 3.39 million (48.6%) of PLWH were receiving ART by mid-2015, ranging from 43.0% to 62.0% across provinces (26). ART coverage among men was noticeably less (43.2%) than that among women (52.0%) (26). When restricted to adults, ART coverage increased to 56.9%, ranging from 50.8% to 72.7% across the nine provinces.

Progress towards the last treatment target in South Africa has been suboptimal. In 2015, only 38.2% of PLWH were accessing ART and virologically suppressed, ranging from 31.8% to 48.3% across the nine provinces (26). This highlights the importance of effective models of care to maintain lifelong care and virologic suppression.

4. Differentiated models

Retaining patients in lifelong care for chronic diseases, such as TB, hypertension and HIV is challenging (30). As 2020 approaches, there is increased pressure to achieve the 90-90-90 treatment targets. Additionally, the Treat All recommendation has increased the number of individuals accessing ART services, intensifying the pressure on already-strained resources, particularly in countries with limited resources (13,21). To end the AIDS epidemic by 2030, a shift in HIV care is required and thus, DMOC for ART services are being explored.

4.1 Differentiated models of care

Currently, most of the DMOC for ART services have been piloted and implemented among stable HIV patients in Sub-Saharan African countries, where the burden of disease is high (13). This approach to ART services can be broadly categorised into four types: client-managed groups, healthcare worker-managed groups, facility-based individual and out-of-facility individual models.

Client-managed groups or community adherence clubs (CACs) have been utilised in Mozambique to address access to and retention in ART services (13,31). Approximately six stable patients form a group with a rotating group representative collecting the medication from the clinic each month and distributing it to group members (31,32). Uganda has implemented this model, and national polices in Kenya, Swaziland and Zimbabwe support the expansion of this model of care (13,33).

Healthcare worker-managed groups or adherence clubs (ACs) have been implemented in Cape Town, South Africa, to improve management of large numbers of patients (34,35). Piloting of ACs in the Democratic Republic of the Congo (DRC) and Zambia are underway (13). Modifications of the AC model have been supported for scale-up by national policy in Kenya (36), Swaziland (33,37) and Zimbabwe (13,38).

In Malawi, facility-based individual models or six-monthly appointments ensure that patients can collect a three-month supply of ART and attend a clinical visit every six months (13,39). Similar models have been piloted or implemented in Ethiopia, Rwanda, South Africa, Swaziland (33), Uganda and Zimbabwe (13).

Multiple out-of-facility individual models have also been piloted and/or implemented in various countries. In Kinshasa, DRC, stable patients are able to collect medication from ART distribution points within the community (40,41). Mobile outreach models for ART services are being implemented in Namibia and Swaziland (13,33). In South Africa, the central chronic medicine dispensing and distribution programme allows stable patients with chronic diseases, such as HIV, to pick up their medication from repeat scripts at an alternative location (13,42).

4.2 Adherence club model in South Africa

ACs were piloted in 2007 by Médecins Sans Frontières (MSF) at the Ubuntu clinic in Khayelitsha, Cape Town (43). Due to the success of the AC model, it was adopted for the Cape Metro Health District by the Western Cape Government Department of Health in January 2011 (35).

Briefly, these clubs generally include 25-30 stable patients who participate voluntarily and meet five times annually. Stable patients are defined as patients who have one suppressed VL (VL<400 copies/mL) and have been on ART for a minimum of six months (35). A lay healthcare worker facilitates the meetings and distributes a two-month supply of pre-packaged ART (35,44,45). During the meeting, stable patients undergo a brief symptom screening, are weighed and participate in a group discussion (35,44,45). These are important monitoring activities which are used to determine if these patients have remained stable. Ill, symptomatic or non-adherent patients are referred back to the nurse- or clinician-led care at the facility (35,43,44). Importantly, new club patients are required to have their VL measured four months after entering the club, and annually thereafter. Paper-based registers are used to capture attendance, which are subsequently transferred to an electronic monitoring system by the facility's data clerk (35,43,44).

Over time, ACs have evolved to provide services to a wider group of people. Firstly, the stringent eligibility criteria have been adapted to further decentralise services from the primary healthcare facilities. Initially, stable patients were eligible for ACs if they had a minimum time of 18 months on ART, two consecutive VLs <400 copies/mL and a referral by a clinician (34,35). In addition, it was recommended that patients had a CD4 count <200 cells/µL and no other chronic illnesses which would require regular consultation (34,35). From January 2015, a minimum of six months on ART with one suppressed VL was required for AC enrolment (35,44). Secondly, the pre-packaged ART supply changed to a four-month supply over the year-end period to facilitate stable patients who migrate during this time (46).

5. Monitoring outcomes of ART programmes

In resource-limited settings, most patients are initiated onto a standardised first-line ART regimen, which is cheaper and publicly available. First-line ART can be preserved by providing patients who have detectable and elevated VLs with adherence counselling (47,48). If elevated VLs persist in subsequent tests, patients should be switched to second- or third-line ART regimens promptly using VL monitoring with intensified adherence counselling at each step (28,48).

VL monitoring is critical in managing patients in ART programmes and assessing individual adherence and treatment responses (28,48,49). This monitoring strategy is associated with better patient outcomes due to improved accuracy (47,50). In addition, VL monitoring is associated with decreased mortality due to earlier detection of virologic failure, and prompt switching to second-line ART regimens (51). However, in resource-limited settings, switching patients is frequently done using CD4 counts as a proxy for virologic failure, rather than VL measurements (47). Therefore, patients might be switched unnecessarily, late or not at all. Switching ART regimens is the last option in resource-limited settings as second-line ART regimens cost approximately two to three times more than first-line ART regimens (47,52). In addition, second-line ART regimens often require twice-daily doses and are not tolerated well. Delaying the decision to switch patients with virologic failure is associated with poor patient outcomes and the accumulation of resistance mutations and their transmission (28,48). Patients who meet the requirement to switch ART regimens, but remain on first-line ART after confirmed virologic failure have increased mortality when compared to those who are switched (53,54). Adherence and retention are important factors in ensuring patients stay on first-line ART and avoid virologic failure, especially in resource-limited settings. Therefore, it is important to monitor and maintain patients within low-resource settings, such as South Africa, to retain patients on first-line ART, reduce costs of ART programmes and reduce the risk of resistance mutations (47).

In addition to the patient-level benefits, VL monitoring of patients can provide insight into the effectiveness of ART programmes. The proportion of completed tests at the expected test date can be used as a proxy for the quality of care within the ART programme (55). Since the beginning of the ART programme in South Africa, VL monitoring has been included in the guidelines (26,56) and surveillance systems have been established to monitor national responses to ART (57). Based on the 2017 guidelines, VL monitoring is recommended before ART initiation, three and six months after ART initiation, and every six to 12 months thereafter (48,58). Patients who maintain an undetectable VL for more than 12 months may only require VL monitoring annually (48).

5.1 Virologic responses

Virologic responses in ART programmes are assessed in terms of the percentage of patients with elevated VLs, confirmed virologic failure, virologic suppression and rebound. VL measurements that are isolated but detectable at a low level (50-1000 copies/mL) which occur in between VL measurements are termed viral blips (59,60). An elevated VL is >1000 copies/mL, after which adherence counselling is provided (28). Sustained elevated VLs result in virologic failure, which is becoming more frequent amongst patients on first-line ART regimens (47). Within South Africa, 14% of first-line ART patients experience virologic failure within five years of ART initiation (61).

The definition of virologic failure varies between different settings worldwide (62), based on local and national guidelines. South African ART guidelines define virologic failure as two consecutive VLs >1000 copies/mL within two to three months (23). South African studies typically define virologic failure as one or two consecutive VL measurements >1000 copies/mL or ≥1000 copies/mL (62–64). Other variations include restricting the definition to the first year on first-line ART, a minimum of two weeks between measurement or no re-suppression on a first-line ART regimen (47,62,65). One South African study defined virologic failure as two VL measurements ≥400 copies/mL, with the second VL measurement ≥5000 copies/mL after adherence counselling (66). Rates of virologic failure range from 4-33% across South Africa depending on the definition, time on ART or first- versus second-line ART regimens (62–64,66).

Multiple South African studies have identified predictors of virologic failure on first-line ART regimens (Table 3). Common predictors include age, sex/gender, CD4 count and WHO staging at ART initiation and first-line ART regimens including a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) (62–64,66). Other predictors include treatment provider, VL at ART initiation, ART treatment interruptions greater than seven days, mean corpuscular volume, haemoglobin level, TB history, missed visits during the first six months on ART, year of ART initiation, Nucleoside Reverse Transcriptase Inhibitor (NRTI) in ART regimen and low-level viremia (62–64,66).

Other virologic responses of interest include virologic suppression and rebound. The primary goal of ART programmes is to maintain virologic suppression, in line with the third UNAIDS target (67). Virologic suppression is critical in lowering the incidence of HIV and in order to maintain high rates of virologic suppression, consistent monitoring is required (68). South African ART guidelines define virologic suppression as a VL <50 copies/mL, however this threshold is higher for AC eligibility (<400 copies/mL) (35,48,69). Virologic suppression has been defined as a VL <400 copies/mL, ≤400 copies/mL or ≤500 copies/mL across several studies (11,26,35,44,70,71). Alternatively, virologic suppression can also be defined as a VL measurement <1000 copies/mL at one, two and three years after ART initiation (67). In South Africa, the national prevalence of virologic suppression among HIV-positive patients on ART was 38.2% in 2015 (26). Using different thresholds, rates of virologic suppression range from 83.7-96% within defined cohorts across South Africa (11,72) Notably, virologic suppression was achieved by a greater proportion of individuals using ≤400 copies/mL in ACs ranging from 94.1-96.9% (44).

Virologic rebound occurs after virologic suppression and has been defined as the first detectable VL measurement >400 copies/mL in PLWH (34,44,72). Using this definition, the proportion of patients who experienced virologic rebound after three years of virologic suppression was 26.4%

and 33.0% in older and younger patients respectively (72). Notably, virologic rebound was 9.0% after initial virologic suppression in ACs (34). In a study which used a threshold of >500 copies/mL, 25.5% of patients experienced virologic rebound at two years after virologic suppression (11). Alternatively, a VL measurement >1000 copies/mL can also be considered as virologic rebound (12,45). Lower rates of virologic rebound have been observed using this definition ranging from 1.4-3.0% in CACs (45,73).

6. Outcomes of adherence clubs in South Africa

The outcomes that have been assessed in ACs to date include retention, virologic rebound and suppression (Table 4). The initial outcomes of ACs at the Ubuntu Clinic in Khayelitsha were generally positive. Over approximately five years, retention was 12% higher in ACs as compared to the standard of care (SOC) at the clinic (34). Furthermore, patients attending ACs had a reduced risk of loss to follow-up (LTFU) (hazard ratio (HR) 0.43) and virologic rebound (HR 0.33) compared with those retained in the clinic (34). Patients in ACs are required to have an undetectable VL for six months before AC entry, and therefore may be healthier than patients receiving the SOC. Following these positive results from the pilot study, ACs were implemented at more facilities within the Cape Metro Health District in 2011 (35).

CACs were implemented at the Hannan Crusaid Treatment Centre in Gugulethu, Cape Town with 2 133 patients attending 74 CACs and assessed over an 18-month period. Over 12 months, 93.5% were retained, 6.2% were LFTU and 1.7% experienced virologic rebound (45). The risk of LTFU (adjusted hazard ratio (aHR) 2.17) and virologic rebound (aHR 2.24) was increased two-fold in patients aged 16-24 years as compared to older patients (73), highlighting the need for targeted approaches for this age group. The risk of LTFU was reduced by 67% in CACs as compared to the SOC at the facility (aHR 0.33) (73).

At the time of wide-scale implementation in the Cape Metro Health District in 2011, 7.3% of the total ART cohort in the district were in ACs (35). The number of facilities offering ACs increased from 16 to 55 between January 2011 and March 2015 (35). Of the total ART cohort in the district, 25.2% of patients accessed ART services through 1 308 active ACs by March 2015, highlighting the acceptability of this model of care after wide-scale implementation (35). One year later, the proportion of PLWH attending ACs increased to approximately 32% of the total ART cohort within the district (74).

At the Ubuntu clinic, Khayelitsha, Cape Town, retention in care was minimally higher amongst patients attending ACs as compared to the SOC. The rate of virologic suppression was similar for patients in ACs and patients receiving the SOC (75), providing additional evidence that outcomes in ACs are similar to the SOC.

For the AC model, the cost per patient year was US$300 in a cost-effective analysis, which was US$74 cheaper than the SOC (75). Although the data were from 2011 and updated research is required, ACs appear to be more cost effective than the SOC, suggesting additional benefits of this model of care.

6.1 Predictors of loss to follow-up and virologic rebound in adherence clubs

The predictors of LTFU and virologic rebound were explored in 3 216 patients across different ACs in the Cape Town Health District for a median follow-up time of 1.1 years. Retention in ACs decreased over a three-year period from 95.2% to 82.1% (44). VL assessments were completed in 88.1% of the cohort, of which 97.2% patients had a VL ≤400 copies/mL, 13 months before analysis closure (44), confirming that HIV-positive patients were able to remain stable under this model of care. Patients aged 16-24 (aHR 2.41) and 25-34 (aHR 1.55) years had a higher risk of LTFU as compared to patients aged 35-44 years (44), providing additional evidence that targeted approaches may be required for adolescents and young adults. Additionally, receiving ART services from larger facilities were predictive of LTFU (aHR 1.32). The risk of virologic rebound was greater amongst patients aged 25-34 years when compared to patients aged 35-44 years (aHR 1.74) and for patients who had been on ART for longer (aHR 1.12). Utilisation of the buddy system at least once was associated with a 37% reduction in the risk of virologic rebound (aHR 0.63) (44).

7. Future research

Over four years, ART services were provided to 25.2% of ART patients using the AC model in the Cape Metro Health District (35). The district aimed to provide 50% of ART services to patients using ACs by the end of 2017 (76). Available data indicates that within low-resource settings, ACs provide quality care to PLWH, which is often superior or comparable to the SOC. Virologic rebound and suppression has been assessed across multiple ACs within the Western Cape. However, these assessments have had limited follow-up time, especially since the scale-up of ACs. To our knowledge, the incidence and predictors of virologic failure have not yet been assessed in ACs. Longitudinal virologic responses among patients entering ACs provide important insights into the sustainability and success of this model of care and ART programmes. Furthermore, long-term outcomes on a larger sample size could inform the implementation of ACs in different settings across South Africa.

Table 3. Predictors of virologic failure in South Africa

Authors	Year of publication	Study design	Study period	Setting	Sample size	Definition of virologic failure	Predictors of first-line virologic failure	Measure of association
Fox et al	2012	Observational cohort study	January 2000 - July 2008	Themba Lethu, Johannesburg, Gauteng Gugulethu, Tygerberg Hospital and Khayelitsha, Cape Town, Western Cape, McCord Hospital Durban, KwaZulu-Natal	19 645 eligible patients	Virologic failure can be considered as two successive VLs >400 copies/mL with the second measurement >5000 copies/mL after adherence counselling (66).	• Age (older patients with every 10-year increase) • Treatment provider • Lower CD4 count at ART initiation • Higher VL at ART initiation • WHO staging at ART initiation (stage III and IV) • ART treatment interruptions greater than seven days • NNRTI in first-line ART regimen (Nevirapine (NVP) use) • Year of ART initiation (2004)	Hazard ratios
Rohr et al	2016	Observational cohort study	2004 – 2013	Gauteng and Mpumalanga (Right to Care Clinical Cohort)	72 181 eligible patients	Two consecutive VL measurements >1000 copies/mL (with the second date listed as failure) (63).	• Younger age • Male sex • Interaction between age and sex (males aged 35-40, 40-45, 45-50, 50-55 and ≥55 years) • NVP in first-line • Lower CD4 count at baseline/ART initiation • Mean corpuscular volume ≥95 fL • Haemoglobin level <12 g/dL • Confirmed history of TB • Missed visits during the first six months on ART	Beta estimates (Weibull model)
Hunt et al	2017	Cross-sectional surveillance study	August – November 2013	KwaZulu-Natal, South Africa	1299 eligible patients (540 cohort A and 759 cohort B)	VL measurement ≥ 1000 copies/mL (64).	Patients on ART for 12-15 months: • WHO stage IV at ART initiation (stage IV) • NVP in ART regimen Patients on ART for 24-36 months: • Male sex) • Age 26-49 years • WHO stage II & III at ART initiation • Stavudine & Zidovudine in ART regimen	Prevalence ratios
Hermans et al	2017	Multicentre observational study	January 2007 – May 2016	Gauteng, North West, Limpopo and Mpumalanga	70 930 eligible patients on ART	Virologic failure defined as one or more VL measurements >1000 copies/mL, which must be confirmed by no re-suppression on first-line ART (62).	• Low level viremia 51-999 copies/mL • Male sex • Older age at ART start • CD4 count <200 cells/µL at ART initiation • Year of ART initiation <2010	Hazard ratios

ART = antiretroviral therapy; NNRTI = Non-Nucleoside Reverse Transcriptase Inhibitor; NRTI = Nucleoside Reverse Transcriptase Inhibitor; NVP = Nevirapine; TB = Tuberculosis; VL = Viral load; WHO = World Health Organization

Table 4. Literature of included studies for outcomes of adherence clubs within South Africa

Author	Year of publication	Study design	Study period	City and country	Sample size	Aim	Key findings
Luque-Fernandez et al	2013	Retrospective observation study	November 2007 – February 2013	Ubuntu Clinic, Khayelitsha, Cape Town	2 829 patients (502 in ACs and 2 327 in clinic care)	To describe the effectiveness of ACs in terms of retention and viral suppression in comparison to clinic care	For the duration of the study, 97% of patients in ACs and 85% of patients in clinic care were retained in care. LTFU was reduced by 57% (HR 0.43, 95% CI 0.21-0.91) and viral rebound was reduced by 67% (HR 0.33, 95% CI 0.16-0.67) for patients in ACs when compared to clinical care patients.
Grimsrud et al	2015	Cohort study	June 2012 – December 2013	Hannan Crusaid Treatment centre in Gugulethu CHC, Cape Town	2 113 patients in CACs at the facility	Describe early outcomes and lesson about the implementation of CACs	Over an 18-month period, 2 133 patients were enrolled into one of the 74 CACs in this resource-limited setting. During a 12-month period in the club, LTFU was 6.2% (95% CI 5.1-7.4) and viral rebound was experienced by 1.7% (95% CI 1.2-2.4 of these patients. After 12 months, ART retention was 93.5% (95% CI 92.2-94.2).
Wilkinson et al	2016	Cohort study	January 2011 – March 2015	Cape Metro Health District, Cape Town	December 2011: 78 161 March 2015: 128 697	Describe the increased implementation of ACs within the Cape Metro health district	By March 2015, 25.2% of ART cohort were retained in adherence clubs compared to only 7.3% at the start of the study. The number of facilities offering ACs increased from 16 to 55 during the study period and the number of facilities offering ART services increased from 53 to 70. Over a four-year period, 25% of the ART cohort received care through ACs. The number if patients in ACs increased from 5683 to 32 425, with 1 308 ACs by the end of the study.
Bango et al	2016	Cost-effective analysis	2011	Ubuntu clinic, Khayelitsha, Cape Town	6 194 patients on ART (5 262 in SOC and 932 in ACs)	To assess the cost-effectiveness of ACs compared to SOC and assess the perceived differences between the two models of care	The cost per patient year was US$300 for the AC model, which was US$74 cheaper than the SOC. The retention of patients in care within one year was 98.03% for the ACs compared to 95.49% in the SOC. Viral suppression was noted to be higher in patients who attended ACs (99.06%) versus the SOC (97.20%).
Grimsrud et al	2016	Cohort study	May 2012 – December 2013	Gugulethu CHC, Cape Town	8 150 patients (2 113 patients in CACs 6 037 patients in SOC)	To describe LTFU and viral rebound among patients attending CACs and compare these outcomes to those patients receiving SOC	The risk of LTFU (aHR 2.17, 95% CI 1.26-3.73) and viral rebound (aHR 2.24, 95% CI 1.00-5.04) in CACs was twice as high amongst patients aged 16-24 years compared to older patients. However, there was no difference observed in these outcomes once stratified by sex. The risk of LTFU was reduced by 67% for patients attending CACs when compared to patients attending the facility (aHR 0.33, 95% CI 0.27-0.40). This observation was persevered when it was stratified by the clinics characteristics and the patients demographic variables for CACs and clinic care.

Tsondai et al	2017	Retrospective observational cohort study	January 2011 – December 2014	Cape Town Health District, Cape Town	3 216 patients in ACs	Describe and explain the predictors of LTFU and viral rebound amongst patients in ACs receiving ART within the Cape Town health district following the scale up of ACs	The median follow-up time was 1.1 years. After enrolment into an adherence club, at 1 year retention was 95.2% (95% CI 94.0-96.4), at 2 years retention was 89.3% (95% CI 87.1-91.4) and at 3 years retention was 82.1% (95% CI 77.7-91.4). VL assessments were completed in 88.1% of the cohort, of which 97.2% (95% CI 96.5-97.8) of patients had a viral load ≤400 copies/mL. Younger patients (16-24 years aHR 2.41, 95% CI 1.10-25.23 and 25-34 years aHR 1.55, 95% CI 1.03-2.33 compared to 35-44 years) and patients accessing ART services from larger facilities had a higher risk of LTFU (aHR 1.32, 95% CI 1.11-1.59). For patients aged 16-24 and 25-34 years, the risk of viral rebound was higher in an adjusted model as compared to patients aged 35-44 (aHR 1.52, 95% CI 0.59-3.95 and aHR 1.74, 95% CI 1.17-2.59 respectively). Viral rebound risk was higher amongst patients who had been on ART for longer (aHR 1.12, 95% CI 1.03-1.23). The risk of viral rebound was decreased when patients utilised the buddy system at least once (aHR 0.63, 95% CI 0.43-0.93).
ACs = adherence clubs; aHR = adjusted hazard ratio; CACs = community based adherence clubs; CI = confidence interval; LTFU = loss to follow-up; SOC = standard of care; VL = viral load							

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PART C: MANUSCRIPT

Long-term Virologic Responses to Antiretroviral Therapy Among Patients Entering Adherence Clubs in Khayelitsha, Cape Town, South Africa

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The journal manuscript is written according to the requirements for the Journal of the International AIDS Society (Appendix 2). The co-authors have not been listed in the journal manuscript, according to MPH dissertation guidelines. Contributions by the supervisor and co-authors have been noted in the acknowledgments section of this mini-dissertation.

Abstract

Introduction: In 2017, approximately 36.9 million people were living with HIV and 58.1% were accessing antiretroviral therapy (ART) worldwide. In South Africa, ART coverage was 48.6% in 2015, and has since increased due to the implementation of universal Test and Treat. Given the need for lifelong care for millions of individuals, differentiated models of care for ART services are required. One such model, adherence clubs (ACs) for stable ART patients, has been successfully scaled-up in the Cape Metro Health District. In this study, we describe long-term virologic outcomes of patients who have ever entered ACs.

Methods: Adult patients enrolled in ACs in Khayelitsha between January 2011 and June 2017 were eligible for inclusion. Time to, and risk factors for, an elevated viral load (first viral load >1000 copies/mL) and confirmed virologic failure (two consecutive viral loads >1000 copies/mL two to nine months apart) were estimated using the Kaplan-Meier estimator and Cox proportional hazards models. Viral load completeness was assessed at 4, 16, 28, 40 and 52 months of follow-up.

Results: Of 11 830 patients, 74% were female and 45% were aged 35-44 years at AC enrolment. The median time on ART at enrolment was 4.7 years (interquartile range (IQR) 2.7-7.1). An elevated viral load was observed in 517 patients (4%), 141 (27%) of whom subsequently experienced confirmed virologic failure. The median time from an elevated viral load to confirmed virologic failure was 137 days (IQR 112-168). Risk of an elevated viral load and confirmed virologic failure was higher among patients with a longer duration on ART and lower among older patients. The proportion of completed viral load tests ranged from 79% at 4 months to 75% at 52 months. Over 90% of patients with viral load assessments remained virologically suppressed (<400 copies/mL).

Conclusion: This study demonstrates low rates of confirmed virologic failure among patients who entered ACs. The majority of patients remained stable despite the rapid growth of ACs, supporting the continued expansion of the model, particularly for men. Monitoring was generally consistent, but suboptimal among those who experienced an elevated viral load. Patients referred to ACs, younger patients and those with longer duration of ART should be prioritised to ensure they remain stable on lifelong ART.

Introduction

In 2017, the estimated global prevalence of HIV was 36.9 million, with 58.1% of people living with HIV (PLWH) accessing antiretroviral therapy (ART) (1). In South Africa, ART coverage was 48.6% in 2015 (2). In September 2016, the country adopted the World Health Organization (WHO) universal Test and Treat strategy, substantially increasing the number of individuals requiring ART services (3,4). This expansion of ART has major implications in terms of service delivery and costs.

In resource-limited settings, patients are generally initiated onto a standardised first-line regimen. First-line ART is cheaper and easier to manage than second-line treatment, which costs approximately 2-3 times more and commonly requires twice-daily dosages (5). While most patients achieve virologic suppression on first-line ART, some experience virologic failure due to non-adherence or developing resistance to one or more drugs (5,6). It is important to ensure that as many patients as possible are retained on first-line ART, especially in resource-constrained settings. On the other hand, it is critical to switch resistant patients to second-line ART regimens timeously, because remaining on a failing regimen results in poor health outcomes and the accumulation of resistant mutations and their subsequent transmission (5,7). Viral load (VL) monitoring is used to guide decisions about whether a patient requires increased adherence counselling in order to remain on first-line ART, or should be switched to second-line ART due to resistance (5,7,8).

As the number of individuals who require lifelong ART grows, differentiated models of care (DMOC) for ART services are being explored to ensure PLWH are retained and remain virologically suppressed in long-term care. One such model, adherence clubs (ACs), aims to reduce the burden on patients and on the healthcare system by decentralising ART services for stable patients (9). Stable patients are defined in the AC guidelines as having one suppressed VL (<400 copies/mL) and a minimum of six months on ART (10). ACs are facilitated by lay healthcare workers and require less frequent medication collections and clinical consultations than standard of care (SOC) (10). A pilot study of ACs in Khayelitsha conducted in 2007 by Médecins Sans Frontières (MSF) reported decreased loss to follow-up (LTFU) and virologic rebound and improved retention compared to SOC (9,11). Following the initial success of this model of care, the Cape Metro Health District adopted ACs in 2011 and by March 2015, 1 308 ACs were operating at 55 of the 70 facilities (10). The scale-up of ACs increased the number of patients accessing ART services using this model of care from 7.3% at the end of 2011 to 25.2% by March 2015 (10).

Given the rapid expansion of ACs, it is important to evaluate their effectiveness over time. The proportion of completed VL tests at the expected date can be used as a proxy for the quality of care and provide an understanding into the effectiveness of ART programmes (12). In assessments following the scale-up of ACs, VLs were recorded in 88.1% of patients, with 97.2% of these virologically suppressed, 13 months before analysis closure (3).

To date, outcome assessments of ACs in the Western Cape have largely focused on virologic rebound, suppression, retention and LTFU. Virologic failure and longer-term outcomes have not yet been described. This study assesses the incidence and predictors of elevated VLs and confirmed virologic failure among adult patients who have ever entered an AC in Khayelitsha. We also describe VL completeness and virologic suppression.

Methods

Setting

Khayelitsha is a peri-urban township with an estimated population of 500 000 people (13–15). Khayelitsha has the highest burden of HIV in the Western Cape and one of the highest in South Africa (15,16). In 2012, the prevalence of HIV-positive pregnant women was 34.3% in Khayelitsha as compared to the national estimate of 29.5% (15,17). Public-sector ART services were available from 2001 through pilot projects run at three primary care clinics by MSF and the Western Cape Government (13,14,16,18). Between May 2001 and December 2002, 287 ART-naïve patients initiated ART (19). In 2004 the national ART programme was launched; by 2014, 40 000 patients were receiving ART in the Khayelitsha ART programme (15).

Adherence clubs

ACs were first piloted in Khayelitsha by MSF in 2007 and were subsequently scaled up due to their success in 2011 (10,11). At the time of analysis closure, 420 ACs were operating out of the three facilities included in this analysis: 113 in Michael Mapongwana CDC, 96 in Nolungile CDC and 211 in Ubuntu HIV Clinic.

The AC guidelines define patients as stable if they have one suppressed VL (<400 copies/mL) and have been on ART for a minimum of six months with no chronic illnesses requiring regular consultation (3,9,10). ACs consist of 25-30 stable patients who participate voluntarily and meet with a lay healthcare worker five times annually. During these visits, they are weighed, receive a two-month supply of pre-packaged ART, have a brief symptom screening and a group discussion (3,10,20). Typically patients collect their pre-packaged ART, however they may send a buddy to collect their medication at every alternate AC meeting (3,10). Patients are required to have a VL assessment four months after joining an AC, and annually thereafter. Ill, symptomatic or non-adherent patients are referred back to clinician-led care to receive the SOC at a facility. Attendance is captured using paper-based registers, which are transferred into an electronic monitoring system by the facility's data clerk (11).

Data source

Routinely recorded, anonymised data contributed to International epidemiology Databases to Evaluate AIDS Southern Africa (IeDEA-SA) from the Khayelitsha ART programme were utilised for this study. Data were aggregated before analysis.

Eligibility criteria

Patients who initiated ART from January 2004 onwards, enrolled into an AC in Khayelitsha between January 2011 and June 2017 and were aged 16-85 years with a VL ≤1000 copies/mL at AC enrolment were eligible for inclusion. Pregnant women were not included in the study, as they were not eligible for participation in the included ACs. We chose the start date of January 2011 to allow long-term virologic outcomes to be assessed since the Cape Metro Health District adopted this model of care into guidelines in 2011.

Outcomes

The primary outcome of interest was confirmed virologic failure, which was defined as two consecutive VLs >1000 copies/mL within two to three months (4), with a two to nine month window. The first VL >1000 copies/mL after entry into an AC was defined as an elevated VL, as defined in literature (7). There were patients who had VLs 400-1000 copies/mL at AC entry who were not considered as virologic failure or suppression and were included in the analysis. Virologic suppression was defined as a VL measurement <400 copies/mL. VL completeness was defined as the proportion of patients who had a VL test among those followed-up for that time period.

Statistical analyses

Characteristics at enrolment into an AC (sex, age, duration on ART, CD4 count, VL, TB history and facility) were described using medians and interquartile ranges (IQR) for continuous variables and frequencies and proportions for categorical variables. A window of 15 months before AC entry was used to determine CD4 counts and VL measurements at AC entry, accounting for the delays between guideline recommendations and testing in practice.

Time to an elevated VL and confirmed virologic failure was assessed and compared by duration on ART using Kaplan-Meier estimators. Predictors of an elevated VL and confirmed virologic failure were assessed using univariate and multivariate Cox proportional hazards models, adjusted for characteristics at enrolment. Time zero for the survival analysis was time of enrolment into an AC. Crude and adjusted hazard ratios with 95% confidence intervals (CI) are reported. Covariates included in the Cox proportional hazards model were chosen based on previous published literature. We included CD4 count in supplementary models due to the large proportion of missing data. A small proportion of patients had VL measurements >1000 copies/mL at AC and were ineligible for inclusion in our main analysis. We undertook a supplementary analysis to compare their outcomes with those of the included patients. Censoring occurred at death, transfer out to another facility, LTFU, at analysis closure (June 2017) or at the time when they experienced virologic failure. Patients were defined as LTFU if they had no contact with the facility in the six months following analysis closure (21).

VL tests are performed in batches for each AC annually. VL completeness was assessed at 4, 16, 28, 40 and 52 months for all eligible patients, in accordance with the ACs guidelines for VL testing. A 0-10 month window was used for the four-month assessment for patients followed-up for at least four months. A 12-month window was used for patients followed-up at 16, 28, 40 and 52 months. In an analysis restricted to patients who had experienced an elevated VL after AC entry, we assessed VL completeness at 2-9 months for patients followed-up for at least three months. This was based on ART guidelines which recommend a confirmatory VL test two to three months after a VL >1000 copies/mL is detected (4). VL completeness was assessed annually thereafter (15, 27, 39 and 51 months). For the subsequent time points, a 12-month window was used for patients followed-up until each time point. The proportion of patients followed up to each time period was assessed for VL measurements and categorised into <400, 400-1000 and >1000 copies/mL. Categories were chosen based on ART guidelines and studies based in this setting. Data were cleaned, coded and analysed using Stata version 15.1 (College Station, TX, USA).

Ethics

The Human Research Ethics Committee in the Faculty of Health Sciences at the University of Cape Town approved this study (HREC REF 264/2018) (Appendix 1). Participating sites in Khayelitsha had ethical approval from their institutional review board to contribute anonymised, individual-level data to IeDEA-SA.

Results

Of the 11 919 eligible patients, 89 (0.7%) patients were excluded for the following reasons: implausible dates (2), missing/undefined gender (5), unable to link on patient identifier (62) and date of death before AC entry (20) (Supplementary Figure 1). Overall, 11 830 patients were included in the analysis and followed for 17 951.9 person-years from AC entry, with a median follow-up time of 1.1 years (IQR 0.4-2.3).

Patients entering ACs were predominantly female (74.3%) and aged 35-44 years (45.0%) (Table 1). Enrolment into ACs increased over time, with the majority of AC enrolment (56.1%) occurring in 2016-2017. The median duration on ART at AC enrolment was 4.7 years (IQR 2.8-7.1). The median CD4 count was 599 cells/µL (IQR 445-779). Overall, 93.4% of patients were virologically suppressed and VLs were missing for 5.9% of patients at AC entry. Prior TB history was documented in 20.5% of patients. The majority of patients attended ACs at the Ubuntu HIV clinic (43.8%).

Table 1. Characteristics of patients entering adherence clubs in Khayelitsha.

Patient characteristics	At adherence club entry (n = 11 830)
Sex, n (%)	
Males	3 046 (25.7)
Females	8 784 (74.3)
Age (years), n (%)	
Median (IQR)	38.7 (33.4-44.4)
16-34	3 801 (32.1)
35-44	5 318 (45.0)
≥45	2 711 (22.9)
Year of entry, n (%)	
2011-2012	501 (4.2)
2013-2015	4 700 (39.7)
2016-2017	6 629 (56.1)
Duration on ART (years), n (%)	
Median (IQR)	4.7 (2.8-7.1)
0-2	3 321 (28.1)
3-4	3 074 (26.0)
≥5	5 435 (45.9)
CD4 count (cells/µL), n (%)	
Median (IQR)	599 (445-779)
<250	416 (3.5)
250-499	2 337 (19.8)
500-749	2 204 (18.6)
≥750	1 057 (8.9)
Missing	5 816 (49.2)
Viral load (copies/mL), n (%)	
<400	11 052 (93.4)
400-1000	85 (0.7)
Missing	693 (5.9)
TB history, n (%)	
Yes	2 419 (20.5)
No	9 411 (79.5)
Facility	
Michael Mapongwana CDC	2 871 (24.3)
Nolungile CDC	3 775 (31.9)
Ubuntu HIV Clinic	5 184 (43.8)

At analysis closure, 101 patients (0.8%) had died, 340 patients (2.8%) were transferred out, 812 patients (6.7%) were classified as LTFU and 10 577 (89.4%) were retained. We observed an elevated VL in 517 (4.4%) patients; of these, 141 (27.3%) patients subsequently experienced confirmed virologic failure; thus, among all patients entering ACs, 1.2% of patients experienced confirmed virologic failure. The median time from AC entry to an elevated VL was 336 days (IQR 168-673) and 137 days (IQR 112-168) from an elevated VL to confirmed virologic failure.

Among the 268 ineligible patients who had a VL >1000 copies/mL at AC entry, 150 patients (56.0%) subsequently experienced an elevated VL with a median time of 123 days (IQR 66-252) (results not shown). Among these patients, 58 patients (38.7%) subsequently experienced confirmed virologic failure and the median time from elevated VL to confirmed virologic failure was 115 days (IQR 91-154). Overall, the proportion of confirmed virologic failure was 21.6% among these patients.

Duration on ART strongly predicted both elevated VL (Figure 1A) and confirmed virologic failure (Figure 1B). In univariate analysis, the risk of experiencing an elevated VL was increased for patients with a longer duration on ART (hazard ratio (HR) 1.43, 95% CI 1.13-1.80, ≥5 years versus 0-2 years) and TB history (HR 1.29, 95% CI 1.02-1.50) (Table 2). In multivariate analysis, the association with TB history was attenuated. Older age was protective against experiencing an elevated VL: after adjustment, there was a 28% reduction in risk for patients aged ≥45 years compared with those aged 16-34 (adjusted hazard ratio (aHR) 0.72, 95% CI 0.56-0.93). Duration on ART at AC entry remained a risk factor, with patients on ART for 3-4 years (aHR 1.38, 95% CI 1.06-1.80) and ≥5 years (aHR 1.49, 95% CI 1.17-1.91) having an increased risk of experiencing an elevated VL compared with those who had been on ART for 0-2 years.

The risk of confirmed virologic failure was associated with longer durations on ART in univariate and multivariate analysis (aHR 2.39, 95% CI 1.42-4.02, ≥5 years versus 0-2 years) (Table 2). Age was protective against virologic failure: compared with patients 16-34 years, there was a 34% (aHR 0.66, 95% CI 0.45-0.97) and 48% (aHR 0.52, 95% CI 0.31-0.85) reduction in risk for patients aged 35-44 and ≥45 years respectively, after adjustment. There was no association between the health facility at which ACs were based and the outcomes of interest.

In a model which included CD4 count, increasing CD4 count at AC entry was protective against the risk of experiencing either outcome (Supplementary Table 1). Compared with patients who had a CD4 count <250 cells/µL, those entering ACs with a CD4 count ≥750 cells/µL had a 54% reduced risk of an elevated VL (aHR 0.46, 95% CI 0.29-0.72) and 77% reduced risk of confirmed virologic failure (aHR 0.23, 95% CI 0.09-0.58) respectively (Supplementary Table 1). We did not observe any of the above associations amongst patients with a VL >1000 copies/mL at AC entry (Supplementary Tables 2 and 3).

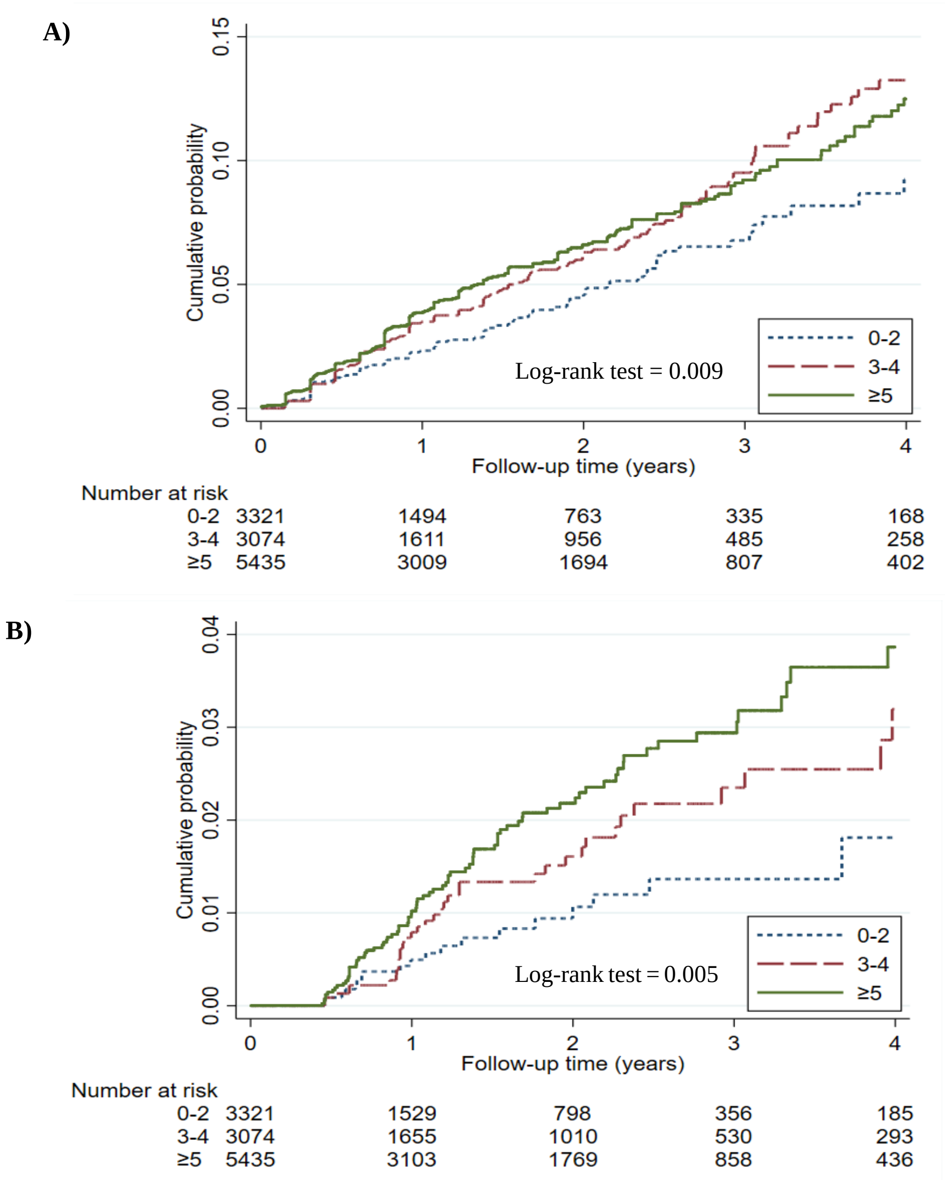

Figure 1.*
A) Cumulative probability of an elevated viral load by duration on ART at AC entry.
B) Cumulative probability of confirmed virologic failure by duration on ART at AC entry.
*Note: the y-axis scale is different for A and B.

Table 2. Crude and adjusted associations with a) an elevated viral load and b) confirmed virologic failure among patients after entry into an adherence club.

	a) Elevated viral load		b) Confirmed virologic failure	
	Univariate HR (95% CI)	**Multivariate aHR (95% CI) (n = 11 830)**	**Univariate HR (95% CI)**	**Multivariate aHR (95% CI) (n = 11 830)**
Sex				
Male	0.98 (0.81-1.20)	1.01 (0.82-1.24)	0.96 (0.65-1.41)	1.06 (0.71-1.58)
Age				
16-34	1.0	1.0	1.0	1.0
35-44	0.91 (0.75-1.11)	0.83 (0.68-1.02)	0.81 (0.56-1.17)	0.66 (0.45-0.97)
≥45	0.81 (0.64-1.04)	0.72 (0.56-0.93)	0.66 (0.41-1.07)	0.52 (0.31-0.85)
Duration on ART				
0-2	1.0	1.0	1.0	1.0
3-4	1.37 (1.06-1.77)	1.38 (1.06-1.80)	1.63 (0.94-2.86)	1.67 (0.95-2.92)
≥5	1.43 (1.13-1.80)	1.49 (1.17-1.91)	2.19 (1.33-3.60)	2.39 (1.42-4.02)
TB history				
Yes	1.29 (1.02-1.50)	1.21 (0.99-1.48)	1.19 (0.82-1.72)	1.11 (0.76-1.63)
Facility				
Michael Mapongwana CDC	1.0	1.0	1.0	1.0
Nolungile CDC	1.07 (0.83-1.37)	1.12 (0.87-1.44)	0.78 (0.48-1.26)	0.87 (0.53-1.40)
Ubuntu HIV Clinic	1.24 (0.98-1.56)	1.25 (0.98-1.58)	1.18 (0.77-1.81)	1.21 (0.79-1.87)

Among patients in ACs with sufficient follow-up at each time point, the completeness of VL tests increased from 79.4% at 4 months to 83.1% at 28 months and subsequently decreased to 75.2% at 52 months (Table 3). Almost all patients with VL tests were virologically suppressed over time: 95.9% at 4 months and 93.0% at 52 months. The proportion of patients entering ACs and ever experiencing a VL >1000 copies/mL increased over time from 2.9% at 4 months to 5.7% at 52 months.

Table 3. Viral load completeness at 4, 16, 28, 40 and 52 months after enrolment into an adherence club.

Follow-up time (months)	**4**	**16**	**28**	**40**	**52**
Number of patients, n	9 214	5 097	3 005	1 395	612
Viral load tests completed, n (%)	7 319 (79.4)	4 136 (81.2)	2 496 (83.1)	1 106 (79.3)	460 (75.2)
Results (copies/mL), n (%)					
<400	7 015 (95.9)	3 901 (94.3)	2 345 (94.0)	1 024 (92.6)	428 (93.0)
400-1000	92 (1.2)	64 (1.6)	38 (1.5)	14 (1.3)	6 (1.3)
>1000	212 (2.9)	171 (4.1)	113 (4.5)	68 (6.1)	26 (5.7)

When restricted to patients who experienced an elevated VL after AC enrolment, 55.9% of patients followed-up for three months had a subsequent VL test 2-9 months later (Figure 2). The proportion of tests not completed in this group of patients increased over time from 44.1% to 85.1% from 2-9 months to 51 months respectively. Among patients with completed VL tests, the proportion of patients re-suppressing increased from 45.0% at 2-9 months to 68.8% at 51 months (results not shown).

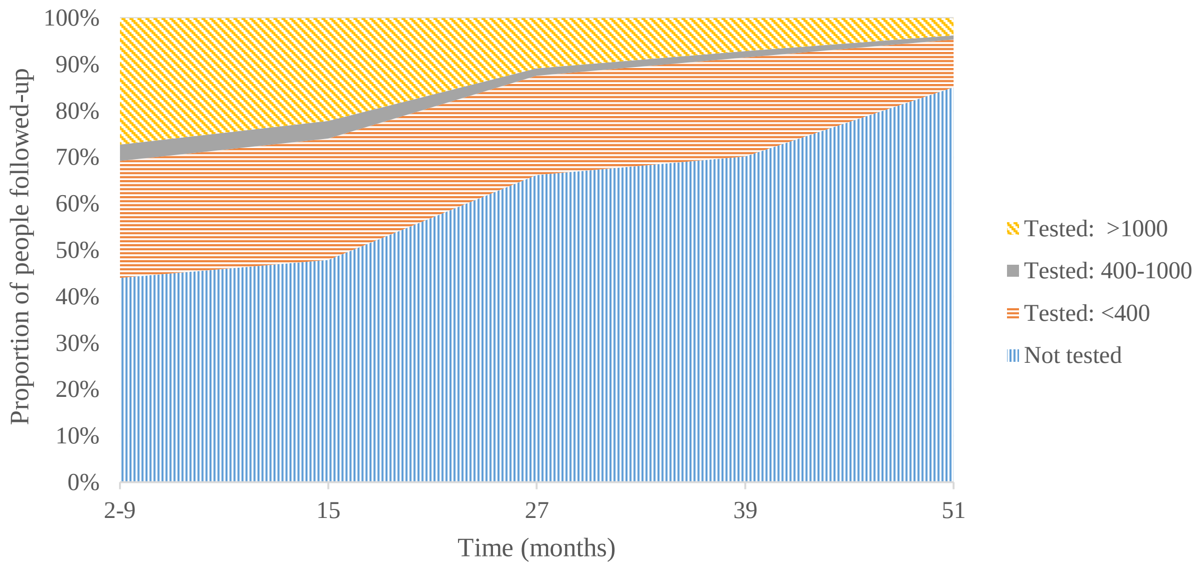

Figure 2. Viral load completeness at 2-9, 15, 27, 39 and 51 months among patients who experienced an elevated viral load after AC entry.*

*The denominator includes all patients, whether they were tested or not.

Discussion

This study demonstrated that the incidence of elevated VLs and confirmed virologic failure was low for patients who entered an AC since the scale-up of this model of care in Khayelitsha. The majority of patients were retained and remained stable over time. Younger age and longer duration on ART predicted poorer virologic outcomes. Virologic monitoring was generally consistent, although confirmatory tests were not performed on nearly half the patients experiencing an elevated VL. Nearly five years after entry into an AC, the majority of patients with an elevated VL had re-suppressed. The risk of poorer virologic outcomes was far higher in patients who were not virologically stable on entry into ACs.

Poorer health outcomes may have been expected due to the rapid expansion of ACs. However, the overall proportion of patients with confirmed virologic failure was 1.2% from January 2011 to June 2017. This is substantially lower than rates observed in several South African facility-based studies, which ranged from 4-33% based on varying times on ART, different definitions and first- or second-line ART regimens (22–25). These discrepancies may be explained by differences in the model of care (SOC versus ACs). ACs, a client-centred approach, focus on the dynamic needs of patients by offering convenient ART services with the potential benefit of increasing adherence and retention. Our study suggests that ACs may be one effective long-term solution to providing ART to many PLWH in this context.

Although most patients remained stable in ACs, our findings suggest that challenges in implementing guidelines may impact on patient outcomes. AC guidelines state that patients should be virologically suppressed (VL <400 copies/mL) before entering an AC (10). In our study, we observed some deviations from the guidelines: 0.7% of patients had VLs 400-1000 copies/mL, 268 patients had a VL >1000 copies/mL and 5.9% were missing VLs before AC enrolment. According to guidelines, these patients were not eligible for referral to ACs. Indeed, the group of patients who started ACs with a VL >1000 copies/mL were at a far higher risk of experiencing an elevated viral, and in approximately half the time compared with eligible patients. Nearly 40% of these patients subsequently experienced virologic failure, confirming that they are high risk patients who should not have been referred to ACs. Our findings emphasise the critical importance of VL testing before AC entry.

VL monitoring is critical in reducing HIV-related mortality, increasing early detection of virologic failure and timeously switching to second-line ART (26). We found that patients were generally monitored consistently over time. Approximately 80% of patients had VLs done over the study period, which was expected as VL tests are performed in batches for each club annually. Of those tested, over 90% of patients remained virologically suppressed over the study period, consistent with previous findings (3). This positive finding provides evidence of the robustness of this model of care in the context of expanding ART services. However, VL testing was suboptimal among patients with an elevated VL, approximately a quarter of whom subsequently experienced confirmed virologic failure. Among this subset of patients, the completeness of VL tests substantially deteriorated over the study period. As a result, we could have underestimated the true proportion of virologic failure. It is also possible that we underestimated the true proportion virologically suppressed, given the increasing proportion of patients re-suppressing over time. Our findings suggest that a more targeted and sustained approach to VL monitoring is required for patients who experience elevated VLs.

Duration on ART at AC entry was the most significant predictor of an elevated VL and confirmed virologic failure, with patients on ART for five years or longer having the highest risk. Our study provides additional evidence that duration on ART predicts virologic outcomes in ACs (3,9). As ACs continue to expand, it is important that patients who have been on ART for longer durations are monitored closely to ensure they remain stable and adherent.

Older patients entering an AC had a decreased risk of experiencing both an elevated VL and confirmed virologic failure, a finding that is consistent with previous studies (22–25). The increased risk of poorer virologic outcomes among younger patients suggests that they might have more difficulty transitioning between models of care and should be carefully monitored during their early stages in ACs. Adolescents and younger patients constitute a large percentage of new HIV infections and retaining these patients in care is challenging as they have to deal with a lifelong chronic illness, adhering to treatment, preventing transmission and autonomy over health-related decisions (27–30). As ACs continue to mature, it is important to understand the particular vulnerabilities of younger patients and to prioritise VL monitoring to ensure they remain stable and in care.

In our study, we found no sex difference in those experiencing either an elevated VL or confirmed failure. This is consistent with other studies which have observed no sex differences in virologic failure, LTFU, attrition and virologic rebound in both the SOC and DMOC (3,22,31,32). However, several South African studies have reported an increased risk of virologic failure amongst men (23–25,33). Furthermore, men have experienced worse health outcomes on ART than women in both the SOC and DMOC, including elevated LTFU, mortality, virologic rebound and decreased treatment success (9,34–42). Given the growing body of evidence that men are disadvantaged in access to, and outcomes on ART (34,40,43–49), our findings suggest that ACs may have a particular benefit for men, and that stable men in routine care should be referred to ACs for ongoing care.

This study is strengthened by the long duration of follow-up after the scale-up of ACs, high retention rates, the large sample size and the exploration of virologic failure after AC entry, which to our knowledge has not been analysed previously. There are several limitations to the interpretation of these results. Firstly, analysis closure was June 2017 and therefore we are missing VL measurements from 2017. The majority of patients were enrolled into ACs in 2016-2017, and the VL completeness may be underestimated, depending on when these annual assessments were scheduled. Importantly, the low rate of confirmed virologic failure should be interpreted with caution due to the missing data. This rate could potentially underestimate the outcome, especially among patients who entered ACs more recently. Secondly, key variables such as the date of AC exit, the use of a buddy, ART regimen and adherence were not available and could not be assessed. Thirdly, this analysis included adult patients from Khayelitsha, a peri-urban setting. Therefore, these study results may not be generalisable to other settings. Fourthly, it was not possible to do multiple imputation due to the large percentage of missing data. Lastly, this study is limited by the lack of a comparator group.

As the number of people requiring lifelong ART increases, DMOC will need to continue expanding. Pilot projects of ACs are underway in the Democratic Republic of Congo and Zambia (50), with national policies in Kenya, Zimbabwe and Swaziland supporting the scale-up of modified AC models (50–53). Locally, ACs have been successfully scaled up in the Cape Metro Health District and adopted into national guidelines (10,54). Our study provides additional evidence that ACs offer an effective option for long-term chronic care for stable patients in this setting. However, more data are required to understand the experiences of patients using ACs, and an updated cost-effectiveness analysis would be beneficial to policy makers.

In summary, we observed good long-term virologic responses to ART in patients who entered ACs. High rates of retention, VL testing and virologic suppression were maintained throughout the study period. VL testing should be prioritised for patients being referred to ACs, younger patients, those with longer duration on ART, and patients who experience an elevated VL after entry into an AC. These findings support the continued scale-up of ACs as an alternative for ART delivery for stable patients, particularly men, in the national ART programme.

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Supplementary material

Patients on ART and in adherence clubs

n = 15 712

Excluded:

- Age <16 or >85 (<16: 314, >85:1 & <0:1)
- AC entry after analysis closure (2 960)
- VL >1000 copies/mL at AC entry (268)
- Initiated ART before 2004 (249)

Eligible patients on ART and in adherence clubs

n = 11 919

Excluded:

- Implausible dates (2)
- Gender missing/undefined (5)
- Unable to link (62)
- Date of death before AC entry (20)

Patients included in analysis

n = 11 830

Supplementary Figure 1. Patient flow chart.

Supplementary Table 1. Crude and adjusted associations with a) an elevated viral load and b) confirmed virologic failure including CD4 count among patients after entry into an adherence club.*

	a) Elevated viral load		b) Confirmed virologic failure	
	Univariate HR (95% CI)	**Multivariate aHR (95% CI) (n = 6 014)**	**Univariate HR (95% CI)**	**Multivariate aHR (95% CI) (n = 6 014)**
Sex				
Male	0.98 (0.81-1.20)	1.00 (0.77-1.29)	0.96 (0.65-1.41)	1.09 (0.68-1.76)
Age				
16-34	1.0	1.0	1.0	1.0
35-44	0.91 (0.75-1.11)	0.72 (0.57-0.93)	0.81 (0.56-1.17)	0.61 (0.38-0.98)
≥45	0.81 (0.64-1.04)	0.60 (0.44-0.83)	0.66 (0.41-1.07)	0.44 (0.24-0.82)
Duration on ART				
0-2	1.0	1.0	1.0	1.0
3-4	1.37 (1.06-1.77)	1.43 (1.04-1.96)	1.63 (0.94-2.86)	1.91 (0.95-3.83)
≥5	1.43 (1.13-1.80)	1.52 (1.12-2.05)	2.19 (1.33-3.60)	2.90 (1.51-5.58)
TB history				
Yes	1.29 (1.02-1.50)	1.10 (0.86-1.41)	1.19 (0.82-1.72)	1.01 (0.64-1.62)
Facility				
Michael Mapongwana CDC	1.0	1.0	1.0	1.0
Nolungile CDC	1.07 (0.83-1.37)	1.16 (0.85-1.57)	0.78 (0.48-1.26)	0.83 (0.45-1.52)
Ubuntu HIV Clinic	1.24 (0.98-1.56)	1.35 (1.02-1.80)	1.18 (0.77-1.81)	1.36 (0.81-2.29)
CD4 count at AC entry				
<250	1.0	1.0	1.0	1.0
250-499	0.65 (0.44-0.96)	0.66 (0.45-0.98)	0.61 (0.31-1.21)	0.62 (0.31-1.24)
500-749	0.49 (0.33-0.73)	0.48 (0.32-0.71)	0.42 (0.21-0.86)	0.38 (0.19-0.80)
≥750	0.48 (0.31-0.76)	0.46 (0.29-0.72)	0.27 (0.11-0.66)	0.23 (0.09-0.58)

*Note: Cox proportional hazards model including CD4 count.

Supplementary Table 2. Crude and adjusted association with a) an elevated viral load and b) confirmed virologic failure among patients who had a viral load >1000 copies/mL at enrolment into an adherence club.*

	a) Elevated viral load		b) Confirmed virologic failure	
	Univariate HR (95% CI)	**Multivariate aHR (95% CI) (n = 268)**	**Univariate HR (95% CI)**	**Multivariate aHR (95% CI) (n = 268)**
Sex				
Male	1.32 (0.91-1.91)	1.37 (0.93-2.01)	1.03 (0.56-1.92)	1.03 (0.54-1.97)
Age				
16-34	1.0	1.0	1.0	1.0
35-44	1.20 (0.84-1.71)	1.14 (0.79 -1.65)	0.88 (0.50-1.56)	0.89 (0.49-1.62)
≥45	1.03 (0.64-1.64)	0.86 (0.52-1.44)	1.12 (0.55-2.31)	1.09 (0.50-2.38)
Duration on ART				
0-2	1.0	1.0	1.0	1.0
3-4	1.29 (0.80-2.07)	1.33 (0.82-2.16)	1.34 (0.63-2.87)	1.36 (0.62-2.94)
≥5	1.24 (0.81-1.88)	1.19 (0.76-1.86)	1.16 (0.58-2.32)	1.22 (0.58-2.57)
TB history				
Yes	1.04 (0.73-1.48)	0.99 (0.69-1.42)	0.84 (0.47-1.51)	0.83 (0.46-1.51)
Facility				
Michael Mapongwana CDC	1.0	1.0	1.0	1.0
Nolungile CDC	0.82 (0.48-1.38)	0.83 (0.48-1.42)	1.22 (0.51-2.95)	1.30 (0.53-3.20)
Ubuntu HIV Clinic	1.01 (0.65-1.57)	1.02 (0.65-1.58)	1.34 (0.62-2.87)	1.38 (0.64-2.98)

*Note: Cox proportional hazards model for patients who had a viral load >1000 copies/mL at AC entry.

Supplementary Table 3. Crude and adjusted association with a) an elevated viral load and b) confirmed virologic failure including CD4 count among patients who had a viral load >1000 copies/mL at enrolment into an adherence club.*

	a) Elevated viral load		b) Confirmed virologic failure	
	Univariate HR (95% CI)	Multivariate aHR (95% CI) (n = 147)	Univariate HR (95% CI)	Multivariate aHR (95% CI) (n = 147)
Sex				
Male	1.32 (0.91-1.91)	1.30 (0.78-2.15)	1.03 (0.56-1.92)	1.06 (0.44-2.55)
Age				
16-34	1.0	1.0	1.0	1.0
35-44	1.20 (0.84-1.71)	1.56 (0.94-2.61)	0.88 (0.50-1.56)	1.19 (0.51-2.80)
≥45	1.03 (0.64-1.64)	1.05 (0.50-2.19)	1.12 (0.55-2.31)	1.26 (0.37-4.31)
Duration on ART				
0-2	1.0	1.0	1.0	1.0
3-4	1.29 (0.80-2.07)	1.00 (0.53-1.88)	1.34 (0.63-2.87)	2.03 (0.68-6.07)
≥5	1.24 (0.81-1.88)	0.75 (0.40-1.41)	1.16 (0.58-2.32)	1.03 (0.35-3.21)
TB history				
Yes	1.04 (0.73-1.48)	0.82 (0.50-1.34)	0.84 (0.47-1.51)	0.79 (0.34-1.80)
Facility				
Michael Mapongwana CDC	1.0	1.0	1.0	1.0
Nolungile CDC	0.82 (0.48-1.38)	0.84 (0.43-1.66)	1.22 (0.51-2.95)	1.05 (0.33-3.32)
Ubuntu HIV Clinic	1.01 (0.65-1.57)	1.13 (0.66-1.93)	1.34 (0.62-2.87)	1.31 (0.51-3.38)
CD4 count at AC entry				
<250	1.0	1.0	1.0	1.0
250-499	0.92 (0.58-1.45)	0.99 (0.60-1.61)	0.96 (0.46-2.00)	0.90 (0.41-1.98)
500-749	0.62 (0.31-1.23)	0.71 (0.35-1.43)	0.31 (0.07-1.41)	0.30 (0.06-1.42)
≥750	0.67 (0.26-1.74)	0.81 (0.30-2.18)	0.38 (0.05-2.94)	0.31 (0.04-2.50)

*Note: Cox proportional hazards model including CD4 count for patients who had a viral load >1000 copies/mL at AC entry.

PART D: APPENDICES

Appendix 1: Ethics approval

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30/06/19
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	13/4/2018

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting the form)	10 April 2018		
HREC REF Number	084/2006	Current Ethics Approval was granted until	30/06/2018
Protocol title	International Epidemiology Databases to Evaluate AIDS in Southern Africa III (IeDEA-SA); formerly known as the Observational Antiretroviral Studies in Southern Africa Collaboration		
Principal Investigator	Mary-Ann Davies		
Department / Office Internal Mail Address	CIDER, School of Public Health & Family Medicine, 5th Floor, Falmouth Building, Anzio Rd, Observatory 7925		
1.1 Does this protocol receive US Federal funding?		☑ Yes	☐ No

2. Protocol status (tick ✓)

☑	Research-related activities are ongoing
☐	Data collection is complete, data analysis only
Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository	

HUMAN RESEARCH
ETHICS COMMITTEE
13 APR 2018
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval	N/A	
Total number of records or specimens collected, reviewed or stored since last progress report	N/A	
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	☑ Yes	☐ No

4. Signature

Signature of PI		Date	10/04/2018

23 July 2014 Page 1 of 1 FHS017
(Note: Please complete the Closure form (FHS018) if the study is completed within the approval period)

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
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25 April 2018

HREC REF: 264/2018

Dr M Cornell
Public Health & Family Medicine
CIDER
Room 5.40
5th floor
Falmouth Building

Dear Dr Cornell

PROJECT TITLE: LONG-TERM VIROLOGIC RESPONSES TO ANTIRETROVIRAL THERAPY AMONG PATIENTS ENTERING ADHERENCE CLUBS IN KHAYELITSHA, CAPE TOWN, SOUTH AFRICA (MASTERS CANDIDATE - MS K KEKOE) SUB-STUDY LINKED 084/2006

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 April 2019.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

The HREC acknowledge that the student, Kathleen Kehoe will also be involved in this study.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.

HREC 264/2018

Appendix 2: Author Guidelines for the Journal of the International AIDS Society

The *Journal of the International AIDS Society (JIAS)* welcomes submissions on HIV-related topics from various disciplines and accepts submissions of Original Research Articles, Short Reports, Reviews, Debates, Commentaries, Letters to the Editor and Viewpoints. Please carefully read through the Instructions for Authors and prepare your manuscript according to the guidelines; structure your manuscript based on the chosen article category. Manuscripts that do not follow the instructions may be returned to the authors for re-formatting. Submissions must be an original contribution, and the authors must guarantee that the content has not been previously published and is not considered for publication elsewhere. The JIAS levies a publication fee on all accepted articles to fund open-access publication. For information on editorial policies and processes, see the About JIAS page. For scientific writing resources and support, see Writing resources.

INFORMATION PRIOR TO SUBMISSION

Aims and scope

The JIAS welcomes submissions on HIV-related topics from across all scientific disciplines, including but not limited to:

- Basic and biomedical sciences
- Behavioural sciences and epidemiology
- Clinical sciences
- Health economics and health policy
- Operations research and implementation sciences
- Social sciences and humanities, including political sciences and media

The JIAS places high priority on submissions from operational research and implementation science as publication of such material can provide valuable information on various algorithms for monitoring and providing support for comprehensive, yet affordable and sustainable treatment, prevention and care programmes in different contexts.

Submission of HIV research carried out in low- and middle-income countries is strongly encouraged.

The JIAS accepts submissions in the categories of Research, Short Report, Review, Debate, Commentary and Letter to the Editor.

Ethical policies

The JIAS is a member of the Committee on Publication Ethics (COPE) and endorses the World Association of Medical Editors' (WAME's) Policy Statement on Geopolitical Intrusion on Editorial Decisions. All submitted manuscripts are scanned for plagiarism and may be rejected if significant overlap with other published material is detected. Work presented in submitted manuscripts may not have been previously published; nor may the same manuscript be submitted for consideration to another journal simultaneously. Any misconduct by authors in reporting their data, for example, falsification, will lead to rejection of their manuscript and other consequences decided on by the Editors. Please see COPE and International Committee of Medical Journal Editors (ICMJE) for further information on ethical issues in publishing.

Authorship

It is understood that all authors listed on submitted manuscripts have read and agreed to its content, and meet the authorship requirements as detailed by ICMJE here. In brief, contributors can be listed as authors if they: 1) have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; AND 2) have been involved in drafting the manuscript or revising it critically for important intellectual content; AND 3) have given final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All contributors who do not meet the criteria for authorship should be listed in the Acknowledgements section. Examples of those who might be acknowledged include a person who provided purely technical help or writing assistance, or a head of department, who provided only general support.

Ethical approval

Experimental research described in the manuscript must have been performed with the approval of an appropriate ethics review board. Research carried out on humans must be in compliance with the Helsinki Declaration, and any experimental research on animals must have followed internationally recognized guidelines. A statement on the ethical aspects, including the consent procedure followed, must be included in the Methods section of the manuscript. The Editors may reject manuscripts where the research has not been carried out within an ethical framework. For all articles that include information or photographs relating to individuals, written and signed consent from each patient to publish must also be made available if requested by the Editors. Confidentiality of study participants must be ensured at all stages of research and reporting.

Competing interests

Authors are required to submit a statement on competing interests, which exist when personal or financial relationships with persons or organizations may influence the interpretation of the data or how the author's work is presented. For details, see ICMJE's policy on competing interests here. In brief, all financial competing interests must be disclosed in this statement (reimbursements, fees, funding, salary payments from or ownership of any stocks or shares in an organization that may in any way gain or lose financially from the publication of the manuscript, either now or in the future, or applications for patents relating to the content of the manuscript), as well as non-financial competing interests (such as political, personal, religious, ideological, academic and/or intellectual interests) that are related to the work submitted. The competing interest statement should be included in the manuscript and will be published in the final article. If no competing interests exist, please state in this section, "The author declare that they have (or The author declares that he/she has) no competing interests."

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