A Retrospective Cohort Study comparing Retention and Viral suppression between Co-morbidity Adherence Clubs and HIV-Only Adherence Clubs in Cape Town, South Africa

By

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Declaration

I, *Joanna Allerton*, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgments indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Dissertation Abstract

In South Africa, there is an increasing population of those with both Human Immunodeficiency Virus (HIV) and one or more non-communicable diseases (NCDs). This is thought to be due to a number of factors, including both the successful Antiretroviral Therapy (ART) programme (which has increased the life-expectancy of those with HIV) and the increasing prevalence of NCDs (due to an aging population, lifestyle changes and urbanisation). This co-morbid population has been shown have poor health outcomes especially in terms of adherence (due to pill burden, multiple appointments etc). There are currently very few models of integrated care for those with both HIV and NCDs, despite well-documented potential benefits of this approach for both the patient and the health system (in terms of efficiency). One such model of care, the co-morbidity adherence clubs (for those with both HIV and hypertension and/or diabetes), was implemented in 2016 in South Africa and this study aims to compare the key outcomes of retention and viral suppression between these clubs and the established HIV-only adherence clubs.

Part A is the study protocol which lays the foundation for the need for this research, and explains how the research will be conducted. Part B forms the literature review which gives a summary of the existing literature and provides context for the dissertation. Part C is the manuscript, presenting the analysis of the retrospective cohort study, and includes a discussion on the implications of key findings.

The study sample comprised 602 HIV-positive adults (501 from the HIV-only club model and 101 from the co-morbidity club model). The overall female proportion was 70.3% and the median age was 38 years. The results showed that there was no difference in the proportion of those retained (84.2% vs 85.6%, p=0.703) or the proportion who were virally suppressed (97% vs 97%, p=0.999) in the co-morbidity club compared to the HIV-only club. In multivariable logistic regression models, adjusted for age, sex and duration on ART, there was no significant difference in retention (adjusted odds ratio [aOR] 0.75 95% confidence interval [CI] 0.38, 1.47) or viral suppression (aOR 0.98 95% CI 0.23, 4.14) by club model. The most common reason for loss of retention from the HIV-only club was non-attendance whereas for the co-morbidity club it was being sent back to clinic for high blood pressure.

This study provides early evidence of comparable short-term patient outcomes between HIV-only and co-morbidity club models and provides reassurance that co-morbidity clubs can be implemented without affecting the outcomes of HIV care. It also provides early promise that, whilst the differential reasons for loss of retention by club model merit further investigation, patients with HIV and hypertension and/or diabetes can safely be managed in co-morbidity clubs.

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Part A: Protocol

A Retrospective Cohort Study comparing Retention and Viral suppression between Co-morbidity Adherence Clubs and HIV-Only Adherence Clubs in Cape Town, South Africa

Background

Human Immunodeficiency Virus (HIV) is now recognised by WHO as a chronic disease as it fits the description of a condition requiring ongoing management over years [1]. This is due to the introduction and subsequent scale-up of anti-retroviral therapy (ART) which has decreased mortality and increased life-expectancy, and has been aided by ambitious targets for ART uptake and adherence such as the UNAIDS 90-90-90 guidelines [2,3]. This vertical programme global public health success, however, has had the consequence of generating increasingly large numbers of people living with HIV (PLHIV). These PLHIV are at risk of developing non-communicable diseases (diseases without an infective cause, often referred to as NCDs) due not only to their increasing age and decreasing mortality but also to the HIV infection itself and ART side-effects [4]. Reported prevalence of diabetes and hypertension in PLHIV in low-and-middle-income countries are estimated at 1.3-18% and 21.2% respectively, and this prevalence increases with age [5].

Whilst the increase in prevalence of NCDs is a global phenomenon, with 36 million deaths annually, low-income countries carry the highest burden of both morbidity and mortality. In Africa alone, the number of people with diabetes was estimated at around 16 million in 2017, and 80% of NCD deaths occur in low-income countries [6,7]. Sub-Saharan Africa, with its well-documented high burden of HIV, is thus experiencing a dual disease burden and a relatively new population of adults with co-existing chronic disease in the form of HIV and NCDs [8]. There is therefore a necessity to address the health needs of this population.

The scale-up of the ART programme has been largely successful and so there is a growing interest in harnessing this model to address the needs of this new population by integrating NCD care into the existing HIV health systems [9]. Such a horizontal programme approach is potentially more sustainable (in terms of resources and finances) as well as being more patient- and adherence-centred (through reduced appointment frequency) [8,10]. There are also shared characteristics between chronic HIV and NCDs in terms of progression over time, the importance of adherence and retention in services, and the need for continuous follow-up and support [11].

Although WHO calls for integrated NCD programmes, there is little research evidence currently on the outcomes of such systems, with the few studies being descriptive or implementation-focussed [12,13]. However, some early evidence has been encouraging. In a study of patients with both HIV and diabetes at an HIV clinic in the USA, the proportion of patients who met HbA1c goals was reported to be comparable (at 54%) to those people with diabetes without HIV, demonstrating that HIV infection need not be a barrier to the achievement of good glycaemic control [14]. This was further demonstrated in a retrospective record review in Kenya which found that NCD outcomes (blood pressure and HbA1c) were similar between HIV positive and HIV negative patients [15]. A prospective cohort study in Cambodia which looked at patients with HIV, hypertension or diabetes treated in newly implemented chronic disease clinics found reasonable retention outcomes at two years, being 87.7% of HIV patients, 71% of those with diabetes and 68% of those with hypertension [2]. Whilst not including specific data on patients with co-existing chronic disease, this study showed that integrating chronic disease care was feasible. It also found that the service was well-accepted by patients and that health care staff used similar skills (particularly those regarding chronic disease and adherence) in managing NCDs and HIV, demonstrating an overlap and potential increased efficiency in use of staff. Another study in Kenya also found that up-skilling staff to provide a cardiovascular disease service in an HIV setting was feasible and well-accepted by staff [16]. Importantly, a large study from Uganda combined NCD care into existing HIV services and found this to be a feasible model for managing those with co-existing HIV and NCDs, reporting improved NCD diagnosis and management [17].

One method by which ART scale-up has been successfully achieved in South Africa is the Adherence Club ("club") system whereby PLHIV receive their antiretroviral mediation 2-monthly in a counsellor-led non-clinic environment run by trained counsellors. To qualify for the clubs, patients must be virally suppressed (defined as ≤400 copies/ml) and have been on their antiretroviral mediation for at least six months. Within this system, patients meet five times a year for a weight, a symptom check and to receive their pre-packed medication. Each club member receives an annual blood test followed by a clinical visit at which results and any symptoms are reviewed by a clinician. Outcomes to date have been good, albeit on an observational rather than analytical level. A recent retrospective cohort analysis of clubs in the Cape Town health district showed retention of 95.2% (95% CI, 94.0-96.4) at 12 months and 89.3% (95% CI, 87.1-91.4) at 24 months after club enrolment, together with 94.1% (95% CI, 91.6-96.0) viral suppression (defined as ≤400 copies/ml) at month 28 after joining the club. [18]. These encouraging outcomes (although still reasonably short-term with a median time in clubs in this study of 1.1 years) add weight to the argument for using ART scale-up models to encompass those patients with co-existing NCDs and HIV. In addition, such patients are currently excluded from the club system and so are an increasingly large under-served population. A retrospective descriptive study carried out in Kenya assessed retention, amongst other indicators, in patients enrolled into clubs. These clubs comprised patients with HIV, hypertension or diabetes or various combinations of these. Retention in the club system was good, at 94.5% at 1 year, and in addition there was a high degree (99%) of compliance with protocols, demonstrating early feasibility of these mixed-disease clubs [19].

Building on this evidence, various facilities within Cape Town have informally implemented co-morbidity clubs over the last few years. These initiatives (based on the ART club model but serving those patients with both HIV and diabetes and/or hypertension) have been pragmatic in nature, often having been developed at a facility level as a consequence of the increasing need to address the needs of this population. They are thus somewhat fragmented with no standardised guidance or model, and outcomes have not as yet been assessed. There is therefore a basic need to evaluate these co-morbidity clubs to inform best practice at a local level. This study hopes to achieve this by analysing routinely

collected data from both the HIV-only clubs and the newer co-morbidity clubs at Gugulethu Community Health Centre (CHC) to compare outcomes, specifically retention in the club and viral suppression. This will address the current lack of analytical research on this topic. By comparing these newly-implemented co-morbidity clubs to the successful and established HIV-only club model, it is hoped that evidence will be generated to inform not only policy locally but also the wider potential to integrate NCD and HIV services at a national or global level.

Purpose of the Study

This study seeks to compare key outcomes between HIV-positive adults enrolled in a HIV-only adherence club and those enrolled in a co-morbidity adherence club (for those with diabetes and/or hypertension in addition to HIV) during 2016. The key outcomes are retention in the club system and viral suppression.

Primary objectives

- To compare club retention at 12 months amongst adults enrolled into the HIV-only adherence club model compared to those enrolled into the co-morbidity club model
- To compare the proportions of adults who have viral suppression, defined as not having experienced a club viral load > 400 copies/ml within 12 months of enrolment, between club models

Primary Hypotheses

- There will be no difference in retention proportions between the two club models.
- There will be no difference in proportions of adults with viral suppression between club models.

Secondary objectives

- To describe reasons for being sent back to clinic care, overall and by club model.
- For those enrolled into co-morbidity clubs, to describe primary outcomes (retention and viral suppression) in terms of chronic disease indicators.

Study Design

Overview

The proposed study design will be a retrospective cohort study using clinical data routinely collected by the HIV service at Gugulethu CHC. Data from the Gugulethu clubs have been collected since their inceptions in June 2012 (for the HIV-only clubs) and February 2016 (for the co-morbidity clubs). These data comprise patient demographics such as sex and age as well as scheduled and attended club visit dates and current retention status within the club.

For the purposes of this study, the data used will be that concerning all adults enrolled into a club in 2016 (either HIV-only or co-morbidity). The date of enrolment will be defined as the date of the first attended club appointment and the study follow-up time will be 12 months post-enrolment plus a seven day grace period. Thus routine data will be used from January 2016 until December 2017.

Setting

The proposed study will use routinely collected data from the Gugulethu HIV clinic and the associated off-site clubs.

Gugulethu has a population of approximately 100 000 (with a catchment area population of approximately 400 000) and is predominantly of low-socioeconomic status. The vast majority of the population uses free local public sector health services. By the end of December 2017, approximately 5875 adults on antiretroviral therapy (ART) were under the care of the HIV services at the Gugulethu CHC (encompassing both the clinic and the clubs), with approximately 60% of these adults being retained in club care (from local data). Since the implementation of clubs at Gugulethu in June 2012, the number of adults retained in club care has steadily increased. From January 2014 until December 2017, the number of adults retained in club care increased by 45% from 2420 to 3509 (from local data).

The Club Model of Care

There are, as of December 2017, 119 HIV-only clubs operating at Gugulethu CHC together with seven co-morbidity clubs and two adolescent clubs. The adult clubs meet in the nearby off-site community hall named “iKwezi”.

HIV-only clubs

The local standard of care is clinic-based care from ART initiation, with potential club referral from six months post-initiation for those patients who are virally suppressed and have no co-morbidities that require additional health care. Club referral is at the clinician’s discretion.

Each club consists of around 30 individuals and meets every two months with the exception of the December/January holidays when the appointment interval is four months. The clubs are run by counsellors who give a health promotion and adherence talk, promote condom use, weigh and check symptoms for each club member and dispense two months of pre-packed ART (four months over the December/January holiday period) at each visit. Each

club member receives an annual blood test visit (referred to as a Blood Visit) at which point a professional nurse performs routine phlebotomy for viral load and ART safety bloods. The following visit is a Clinical visit, at which the nurse checks the blood results and performs a clinical assessment. The remaining visits are known as Standard. Patients in clubs may send someone (a "buddy") to collect their ART for them, but this is permitted only every alternate visit and never on a blood or clinical visit. If a patient misses a club visit, there is a grace period of seven days after the scheduled session for them to collect their medication. Those who have not collected their medication within this period are identified as DNA (Did Not Attend). These patients are followed up by the counsellors via phone calls and home visits, depending on resources, and are removed from club. Patients are removed from club and sent back to clinic (BTC) if they have a high viral load (>400 copies/ml), are pregnant, or have any symptoms meriting further clinical assessment.

Co-morbidity clubs

These clubs are for those patients on both ART and medication for diabetes and/or hypertension, all for more than six months. The usual HIV inclusion criteria still apply, as per the HIV-only clubs, but there are additional disease indicator criteria as shown in Table 1. To enable correct inclusion, a screening form was implemented in April 2016 (see Appendix A). Patients are removed from co-morbidity clubs for the same reasons as the HIV-only clubs but also if their chronic disease indicators are above prescribed thresholds, as shown in Table 1. Co-morbidity clubs are run by club counsellors with additional training in health promotion and lifestyle advice pertaining to diabetes and hypertension. The structure of visits in the co-morbidity clubs is a little different from the HIV-only clubs, most obviously in that there are two scheduled annual clinical visits rather than one, and that a Clinical Nurse Practitioner conducts the clinical visits. The visit structure is shown in Table 1.

Table 1. Comparison of Club Models

AREAS OF CARE	CLUB MODEL	
	HIV-ONLY CLUB	**CO-MORBIDITY CLUB**

Eligibility	• ≥6 months on ARVs
	• Viral load < 400 copies/ml
	• No other co-morbidities
	• CD4 > 100
	• Not pregnant
		• ≥6 months on ARVs
		• Viral load < 400 copies/ml
		• ≥6 months on medication for diabetes and/or hypertension
		• CD4 > 100
		• Not pregnant
		• BP (mmHg) less than target
		  ○ 150/95 for hypertension
		  ○ 150/90 for diabetes
		• HbA1c < 9% for diabetes
		• Creatinine Clearance >50 ml/min (or eGFR† > 60)

Criteria for Removal	• DNA • Viral load > 400 copies/ml • Pregnant • Symptoms meriting further assessment	• DNA • Viral load > 400 copies/ml • Pregnant • Symptoms meriting further assessment • BP > 160/100 for all • HbA1c > 10% for diabetes • Step up in meds needed

Structure of Visits	• Standard
	• Standard
	• Blood *(viral load, safety bloods)*
	• Clinical *(blood results, symptom check)*
	• Standard
	• Standard
		• Standard
		• Standard
		• Blood
		  ○ *Viral load, safety bloods, creatinine, cholesterol if previous cholesterol > 5 mmol/l for all*
		  ○ *HbA1c for diabetes*
		• Clinical 1
		  ○ *Blood results, random glucose, BP for all*
		• Standard
		• Standard
		• Clinical 2
		  ○ *BP for all*
		  ○ *Foot screen, random glucose, urine, date for retinal screening for diabetes*

Staff present	• Standard Visits - Counsellors • Blood and Clinical Visits – Professional Nurse	• Standard Visits - Counsellors • Blood and Clinical Visits – Clinical Nurse Practitioner

*eGFR= Estimated Glomerular Filtration Rate; BP: Blood Pressure

Study Population

Study participants will be HIV positive persons referred to attend an HIV-only or a co-morbidity club at Gugulethu CHC in 2016.

Inclusion criteria

- Age 18 or older
- Attended their first club visit in 2016

Exclusion criteria

- First viral load blood test scheduled within 121 days (four months) of the first club visit
- No scheduled club clinical visit within the follow-up period of 1 year (plus seven days grace period)
- Those enrolled into adolescent clubs

The first two exclusion criteria are in place for the following reasons:

All those enrolled into the co-morbidity clubs had a scheduled first viral load blood test at four months after enrolment. This is because all these clubs were newly implemented (see Table 2). However, those enrolled into the HIV-only clubs had their first scheduled viral load blood tests at any point from enrolment to 12 months, due to the nature of some of these clubs existing prior to 2016. To adjust for this, individuals enrolled in the HIV-only club system who had a viral load blood test prior to four months (121 days) will be excluded.

For similar reasons, some of those enrolled into HIV-only clubs did not have a scheduled clinical visit within the 12 months of follow-up (due to the four month visit interval towards the end of the year) and so these individuals were also excluded.

Data Collection

Standard of Care

Each club (HIV-only and co-morbidity) visit is recorded, as per the Gugulethu CHC standard of care, on a paper register, held by the club counsellors and kept locked in the club room in the clinic when not in use. A data clerk captures the data on a weekly basis into a password-protected Excel spreadsheet. The data is backed up on a weekly basis and the computer used is kept in a locked room at the clinic. The data clerk has undergone training in data-capturing as well as Good Clinical Practice and ethical research conduct, and is supervised by a UCT staff member to ensure accuracy of data capturing.

The co-morbidity club data collection involves additional indicators, and these are recorded in the individual club members' clinic folders.

Research Study

Electronic records, as mentioned above, and patient clinic folders (particularly for those enrolled into the co-morbidity clubs) will be used for this proposed study. This study data will only be accessed by the study investigators and will be password-protected following standard password safety procedures. The routinely collected data, as per standard of care, contain identifiers (names and folder numbers) but these will be removed, and replaced with anonymous identifiers, once the data have been cleaned and are ready for analysis. In the case of both clubs, patient clinic folders and laboratory records may be used to address missing data. All study investigators are trained in Good Clinical Practice and ethical research conduct.

Data Analysis

The total number of individuals included in the study will be all those enrolled in clubs in 2016 and who fulfilled the criteria as previously described. This will be 602 in total; 501 from HIV-only clubs and 101 from co-morbidity clubs. This represents all patients currently enrolled in the comorbidity clubs thus sample size estimation was not needed. However, this sample size will give 90% power to detect a 15% difference in retention between HIV-only and co-morbidity clubs using a two-sided alpha of 0.05 and assuming retention in the HIV-only club of 85% (from programme data).

Primary outcome analyses

The primary outcomes are retention in club care at 12 months post-enrolment and viral suppression (no club viral load >400 copies/ml within 12 months post-enrolment). Reasons for not being retained in club will be defined based on the club standard of care as follows: DNA (Does Not Attend), BTC (sent Back to Clinic), TFO (is Transferred Out of the club) or RIP (passed away). In addition, age, sex and time on ART for each patient will be abstracted from the club registers and patient folders.

The analyses will be based on pure-count methods, beginning with a description of baseline variables (both demographic and clinical) by club model. Descriptive statistics will include medians with interquartile ranges, means with standard deviations, and proportions. Comparisons of distributions and retention proportions by club model will employ t-, rank-sum, chi-squared or Fisher's exact tests, as appropriate. The date assigned to loss of retention will be the first scheduled club date at which the patient is recorded as DNA, BTC, TFO or RIP. The date assigned to the loss of viral suppression will be the date of the first post-enrolment club viral load blood test showing >400 copies/ml. In addition, survival analysis will be used as a secondary approach to primary outcome data analyses and will include Kaplan-Meier estimates of the proportion of retained patients by club model and a log-rank test to compare time to loss from club by club model.

Secondary outcome analysis

The secondary analyses will describe known reasons for non-retention overall and by club model. Univariable and multivariable logistic regression models, overall and by club model, will be used to examine predictors of the primary outcomes of interest

Throughout the analyses, statistical tests will be 2-sided at $\alpha=0.05$. Model fit will be compared using the AIC, and all modelling will employ standard diagnostic procedures [20].

Description of Risks and Benefits

Risks

As this is a retrospective cohort study using data previously collected as per the Gugulethu CHC standard of care, it is a minimal risk study. However, there still remain potential risks should loss of confidentiality occur during study data collection and analysis. Specific measures to minimize this risk include confidentiality training for all personnel involved in data collection and analysis. Anonymous identifiers will be used during all study data collection and analysis and all electronic records will be kept in password-protected files. Access to the study data will be limited to the study investigators.

Benefits

There are no specific *direct* benefits to the patients in this study as the data will be collected on patients who have already been enrolled in a club model at a clinician's discretion as per the standard of care. However, there are *indirect* benefits. The HIV-only clubs already have evidence showing, at minimum, comparable viral suppression and retention rates compared to clinic care. So, by comparing the co-morbidity clubs to the standard of these existing clubs, it will be possible to potentially identify whether these co-morbidity clubs are an

optimal strategy for delivering care to adults with co-morbidities. There is clinical equipoise regarding co-morbidity club outcomes and, if shown to have successful outcomes, there is potential for this club model to be scaled-up throughout Cape Town, the Western Cape Province, and across South Africa. This would potentially result in providing an integrated, more efficient service to this currently underserved population. To this end, the involvement of policy makers involved in HIV care and treatment will help maximize the indirect benefits of the study through strengthened public sector health care services for individuals affected by co-morbidity as described.

Informed Consent process

No specific informed consent will be taken from participants, as the data being analysed is routinely collected by the Gugulethu CHC as part of the standard of care. For the same reason, there will be no compensation for participants. Of note, all patients who attend the Gugulethu CHC HIV services (from where patients are referred to the clubs) sign a simple consent form informing all patients that standard of care data will be captured for research purposes and that their confidentiality will be maintained (see Appendix B).

Privacy and Confidentiality

As previously discussed, confidentiality will be preserved throughout the study. All routine standard of care data collection was done in a closed room at the Gugulethu CHC, and the same procedures will be followed for any addition data collection necessary to fill address missing data. The clinic-based data-entry clerk and all investigators have been trained in Good Clinical Practice (GCP) and ethical research conduct to ensure that they uphold confidentiality on all study information. The data will contain anonymous participant identifiers and all data sets are, and will continue to be, password-protected and stored on a clinic computer in a locked room.

Ethical Considerations

As previously discussed, this study is using routinely collected data from these two Gugulethu club models which will be anonymised and password-protected. No additional contact with patients will be conducted. Approval for this research is being sought from the University of Cape Town Human Research Ethics Committee.

Following from the successfully implemented HIV-only clubs, the co-morbidity clubs were implemented pragmatically in various facilities in the Cape Town area based on a perceived need to provide a service for those HIV infected patients who also had diabetes and/or hypertension. It was soon after implementing the HIV-only clubs that this need was perceived. It was agreed at the Steering committee (an official body convened by the Western Cape Government) that these HIV patients with co-morbidities could be put in clubs as long as clinicians took responsibility for ensuring the extra review. Following this, Dr Cathy Kalombo, at Gugulethu CHC, implemented specific co-morbidity clubs at the Gugulethu site in 2015, with the first club meeting in February 2016.

Use of information and publications

The proposed study will be submitted as a mini-dissertation in partial fulfilment of the requirements for Masters in Public Health degree at the University of Cape Town. A publishable manuscript describing the findings of this study will be prepared for submission to a relevant peer reviewed journal for publication. The proposed study results will also be shared with Gugulethu CHC managers and the Provincial Department of health.

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Part B: Literature Review

Introduction

The Problem of Co-morbidity

Globally, deaths from non-communicable diseases (NCDs) are increasing both in number and as a proportion of all deaths, with the majority occurring in low and middle income countries [1]. On top of this public health concern, the prevalence of HIV in South Africa continues to rise, largely due to the successful anti-retroviral therapy (ART) roll-out programme, and thus a cohort of ageing adults with chronic HIV infection is emerging [2]. There is therefore a growing number of people living with HIV (PLHIV) who also have one or more NCDs. Currently, this population is poorly served by vertical programmes and there are few examples of integrated care.

Models of Care

The scale-up of the ART programme has generally been deemed to have been successful and so there is a growing interest in harnessing this programme to address the needs of this new co-morbid population by integrating NCD care into the existing HIV health system [3]. One model of care by which ART scale-up has been successfully achieved in South Africa is the club system, whereby PLHIV receive their ART 2-monthly in a counsellor-led environment [4]. On the back of the success of this and other global programmes integrating NCDs and HIVs, various facilities in Cape Town have recently informally implemented co-morbidity clubs catering for those with both HIV and one or more NCDs, most commonly diabetes and hypertension.

The Research Gap

There is very little research evidence regarding outcomes of integrated models of care, with few South African analytical studies looking at outcomes for this specific population. The primary aim of this review is to explore and appraise the existing research on integrated models of care for HIV, hypertension and diabetes. This review will briefly describe the

landscape of HIV and NCDs before synthesising the available literature on integrated models of care. This review will set the background for the manuscript which focuses on describing the local implementation of co-morbidity clubs and then comparing various outcomes between adults in these clubs (who have both HIV and hypertension and/or diabetes) with those in the HIV-only ART clubs.

Literature Review Search Strategy

Full text papers published in English, from January 2000 – March 2018 were included. The full strategy is outlined below in Table 1. Included studies focused on integrated care of adults with both HIV and hypertension and/or diabetes, and were discussed in the following themes: the public health burden, arguments for integrated care, the feasibility of integrated care, benefits and challenges of integrated models of care, and the existing club model itself.

Table 1. Literature Search

Database	Number	Strategy
Pubmed	1	MeSH HIV Infection OR MeSH Acquired Immunodeficiency syndrome OR MeSH HIV
	2	HIV OR Human Immune Deficiency Syndrome OR Acquired Immune Deficiency syndrome OR Immunodeficiency syndrome
	3	1 OR 2
	4	MeSH Adult
	5	Adult
	6	4 OR 5
	7	MeSH Antiretroviral Therapy, Highly Active OR MeSH Anti-Retroviral Agents
	8	Antiretroviral OR Anti-retroviral OR Antiviral OR Anti-HIV OR ART OR HAART OR ARV
	9	7 OR 8
	10	MeSH Medication Adherence OR MeSH Patient Compliance
	11	Adherence OR Compliance OR Medication Persistence
	12	10 OR 11
	13	Model* of care OR Club* OR Adherence Club*
	14	MeSH Diabetes Mellitus OR MeSH Hypertension
	15	Diabetes OR Hypertension OR Non-communicable diseases
	16	14 OR 15
	17	Integrated HIV care
	18	MeSH Delivery of Health Care
	19	Integrated HIV care OR MeSH Delivery of Health Care
	20	3 AND 6 AND 9 AND 12 AND 13 AND 16 AND 19*
Cochrane		HIV AND (hypertension OR diabetes)
EBSCO		HIV AND Hypertension AND adherence then HIV AND Diabetes AND adherence
Google Scholar		HIV AND Hypertension AND adherence HIV AND Diabetes AND adherence
Conferences		Sites searched included IAS, AIDS2014 and CROI

The Public Health Burden

The burden of NCDs

This burden of NCDs can be enumerated in terms of prevalence, incidence, mortality and morbidity.

Diabetes is increasing in prevalence. It is estimated that around 16 million adults in Africa were living with diabetes in 2017 and this number is expected to rise to around 41 million by 2045 [5]. Regarding hypertension, the trend in prevalence is less clear but, as of 2015, stands at 26.1% for women and 27.4% for men in South Africa [6]. There is thus a substantial burden of both mortality and morbidity from NCDs in South Africa.

The estimated incidence of diabetes in people with HIV varies widely between studies and the data available are limited. A recent African systematic review reports a combined incidence rate of 17.4 per 1000 person years and concludes that this seems no higher than in those without HIV [7]. Regarding hypertension, a prospective cohort study of people with HIV in Tanzania recently found an incidence rate of hypertension of 120 per 1000 person years [8].

Globally, deaths from NCDs are increasing in number, killing 40.5 million people in 2016, with 17.9 million of these deaths being attributable to cardiovascular disease and 1.6 million to diabetes. In South Africa, 39% of deaths were caused by NCDs in 2010, with the absolute number of deaths due to NCDs being similar to the number due to HIV and TB combined [9]. By 2030, NCDs are predicted to be the biggest cause of death in Africa [9].

Whilst Global Disability-Adjusted Life Years (DALYs) remained stable from 1990 to 2010, the proportion of these DALYs accounted for by NCDs increased from 43% in 1990 to 54% in 2010 [10]. In addition, the global distribution of NCDs is heterogenous, with low- and middle-income countries shouldering the greatest burden. In fact, 80% of the deaths due to chronic disease occur in these countries [1]. In addition, on this background of mortality transition there exists the undiminishing prevalence of HIV.

The burden of HIV

Globally, as of 2017, there were around 36.9 million PLHIV and 940,000 HIV-related annual deaths [11]. An astounding 19% of these PLHIV are living in South Africa, and the HIV prevalence in the country is certainly not decreasing [11]. A STATS SA release in 2017 found a mid-year HIV prevalence of 12.6%, compared with 12.1% in 2012 and 10.6% in 2008 [12, 13]. This increase in prevalence, despite a decrease in new HIV infections since 2010, is due to the introduction and subsequent scale-up of ART which has decreased mortality and increased life-expectancy not only in South Africa but world-wide [14, 15]. In South Africa, ART became widely and freely available in 2004 and a large cohort study from KwaZulu-Natal showed an overall life-expectancy (not just in those with HIV) increase of 11.3 years from 2003 to 2011 [2].

This welcome drop in HIV mortality is, however, generating a new health challenge – that of the increasingly large and ageing cohorts of PLHIV who are less vulnerable to HIV-related opportunistic infections but more vulnerable to NCDs. In fact, HIV has been recognised by the WHO as being a chronic disease as it fits the description of a condition requiring ongoing management over years [16]. South Africa is therefore increasingly experiencing the dual burdens of NCDs and HIV, chronic diseases which are not without their similarities and which are often experienced as comorbid diseases.

Dual burden of HIV and NCDs

As can be inferred from the WHO's definition of HIV as a chronic disease, HIV shares some characteristics with other chronic diseases. The main risk factor for HIV infection is behavioural (unsafe sex) as are the main risk factors for NCDs (alcohol use, smoking, obesogenic diet, inactivity) [17]. Whilst the risk factors themselves differ, the behavioural interventions necessary to try and modify these lifestyles have similarities. Both HIV and NCDs tend to be progressive over time and effective treatments of both include an emphasis on self-management with community support and a need to monitor adherence as well as to maintain retention in health services over time [18].

As well as the shared characteristics, PLHIV are thought to be at increased risk of developing NCDs over time due to several reasons: the virus itself via chronic inflammation mechanisms, ART (both the incidence of diabetes and the prevalence of hypertension have been shown to increase with cumulative exposure to ART), and the simple fact of ageing ie survival from previously deadly HIV-related opportunistic infections and thus vulnerability to NCDs [19–23]. It is predicted that the majority of PLHIV (up to 84%) will have at least one NCD by 2030 [24]. Therefore, there are not only shared characteristics between NCDs and HIV but there appears to be an increased prevalence of NCDs amongst PLHIV which further drives up the number of people with these comorbidities.

There have been a number of studies looking at the question of the prevalence of NCDs in PLHIV. A cross-sectional survey in Cambodia found that, of 510 adults attending HIV clinics, 8.8% had diabetes and 15.1% hypertension [25]. Similar studies in Malawi and Zimbabwe showed somewhat differing results with the prevalence of co-morbidity (with common NCDs) in the HIV population being 26.6% and 15.3% respectively [26, 27]. A 2012 systematic review looked at African and Asian populations and assessed the magnitude of NCD and HIV co-morbidity. The results showed that the prevalence of diabetes was less than 5% in all the included studies and that of metabolic syndrome 13-28% [28]. There are three basic limitations to these data – firstly all studies included were cross-sectional therefore there is no temporality thus no basis on which to judge causality. Secondly there are no comparison groups and thirdly there is no Africa-specific disaggregation. There exists one prospective study which found an incidence of diabetes in PLHIV of 5.72 (5.31-6.13) per 1000 PYFU but this is relatively old (2008) and contained no African cohorts [19]. Regarding comparison groups, some of the clearest evidence comes from Italy where one case-control study showed a significantly higher prevalence of NCDs in PLHIV compared to HIV-negative adults and another found a significant two-fold increased prevalence (4.1% vs 2.5%) of diabetes in those with HIV compared to those without [29, 30].

So not only are these chronic diseases independently increasing in prevalence but there is an increase in co-morbidity over and above that expected, due to this excess of NCDs in PLHIV. In addition, it is thought that these comorbidities actually have multiplicative damaging effects on health outcomes, and are thus best managed by primary care clinicians

skilled in this particular area [31]. Because of the above-mentioned increasing population, the shared principles of management and the specific health-care needs, there is growing interest and urgency in implementing integrated care for this population. However, it is not only this that points to the benefits of integrated care. The need for horizontal programmes can also be supported from the point of view of minimising both the individual and the health system burden.

The Arguments for Integrated Care

Integrated care may be beneficial for both the individual and for the health system [26].

Individual Benefits

Patients with co-morbidities carry a large burden in terms of understanding their diseases, clinic appointments and medication. Those with co-morbidities have been shown to be at increased risk of poor adherence due to the large numbers of medications prescribed for each individual involved, with the degree of this polypharmacy being a predictor of mortality [32, 33]. It has also been shown that patients with co-morbidities use health care more frequently, and suffer poorer outcomes [31]. One qualitative study from the USA, specifically carried out on those with both HIV and either diabetes or hypertension, found that comorbidities frustrate patients, with poor understanding exacerbating adherence problems [33]. In addition, a recent South African qualitative study assessed the experiences of patients with both HIV and diabetes and found a dissatisfaction with having to attend separate clinics for HIV and diabetes as well as difficulty managing the pill burden [34].

Also of note, there is evidence that HIV clinicians are not always comfortable treating general comorbidities [35]. Such individuals currently have to attend multiple appointments and are often seen by multiple different health professionals thereby putting extra strain on the achievement of adherence and retention, compromising optimal care as well as resulting in a suboptimal patient experience in terms of time spent accessing health care [36]. An all-too-common outcome is patient deferral of vital routine visits. Integrated

models of care would allow individuals with both HIV and NCDs to receive care from a clinician specifically trained in this population and would reduce the individuals' burden of clinic visits.

Health System Benefits

Co-morbidities also place a burden on the health system that could, at least in part, be alleviated with integrated care. It is thought that integrated management would be more cost-effective and efficient than multiple vertical programmes [17]. Health systems, in low- and middle- income countries especially, are already under-resourced and so any increased efficiency in cost, time, resources and staff is much needed [37]. It has also been argued that integrated management potentially increases community self-reliance [18].

The Call for Research

There are many arguments for integrated care: innate shared characteristics and management needs, an increasingly large population, a need to optimise patient adherence and experience, potentially improved clinical care and lastly health system efficiencies. Horton in the Lancet argues that HIV and NCDs should not be seen as separate entities in research, and Narayan et al describes a key research priority entitled, "Development of innovative and effective models of integrated NCD and HIV care" [38, 39]. In addition, a report from South Africa in 2009 called for a national initiative for integrated care and a recent Lancet article describes HIV and NCDs as "increasingly intertwined" and highlights the urgent need for research (including health system research) on this population in sub-Saharan Africa [40, 41]. Questions must thus be asked about the current evidence regarding models of NCD and HIV co-management, how to best assess these models, and whether such integrated care is feasible in practice.

The Feasibility of Integrated Care

Co-management of HIV and NCDs

A retrospective cohort study from the USA looked at the associations in women (from 2006 to 2014) between HIV status and the control of any coexisting diabetes and/or hypertension [42]. The results showed better control of these NCDs in HIV positive women compared to HIV negative women. This better management was postulated to be due to an increased propensity for HIV positive women to be receiving routine health care, often with a consistent provider. Another retrospective cohort study, more generalisable to the African context, compared NCD outcomes over one year between HIV positive and HIV negative adults in Nairobi, Kenya [43]. The results showed no significant differences in blood pressure or HbA1c between the two groups, again supporting the idea that it should be possible to integrate NCD and HIV care together in a primary care clinic.

Harnessing the HIV Infrastructure

A UNAIDS report from 2011 argues that this integration will be best achieved by leveraging the HIV experience and describes an Ethiopian before and after study in which local existing HIV approaches (including record-keeping approaches, staff training etc) were used and outcomes (such as increased monitoring and assessment of adherence) were thereby improved [23, 44]. The scale-up of the ART programme has generally been deemed to have been successful, especially in South Africa, and so there is potential to leverage this programme to manage those with both HIV and NCDs [4]. Using the existing HIV infrastructure enables harnessing of this successful programme in terms of location, staff expertise, multi-disciplinary teams, adherence and retention support, monitoring and evaluation, task-shifting, community-based care as well as patient acceptance. It also has the potential to limit extra costs and staffing, and is relatively well-funded especially when compared to funding for NCD programmes [36]. Attempting to collate the existing evidence on models of integration, a recent literature review described 15 such programmes in low income countries. The results varied from model to model, but the review concluded that it is feasible to use the existing HIV infrastructure and systems to provide care for those with

NCDs in an integrated environment [45]. There is also some evidence that individual outcomes for NCDs and HIV are often associated.

Outcome Assessment

There is little clear evidence on the optimum outcome measures for this co-morbid population. A study from Uganda assessed disease control (in terms of viral suppression, blood pressure control and HbA1c control as appropriate) in those with both HIV and hypertension and/or diabetes who attended multi-disease community health fairs over 3 years [46]. The results showed that 67-69% of those with HIV and hypertension or diabetes achieved control compared to 90% of those with HIV alone, and thus the authors argue for the importance of using a composite endpoint [47]. However, there is also evidence that that determinants of adherence don't differ widely within patients and that there is a strong correlation between ART adherence and adherence to medication for NCDs [48, 49]. In addition, a USA study looked at the association between poor HIV control and poor control of diabetes or hypertension. Their linear regression analysis demonstrated a link and they conclude that this correlation points to a common factor of poor adherence [50]. It is therefore likely that markers of ART adherence (such as viral load) can help predict adherence to NCD medication and so such HIV outcomes can provide useful proxy markers of overall outcomes in this population. So, having established reasonable feasibility of co-management and of harnessing the existing HIV infrastructure as well as having discussed outcome measurement, it is important to look for more specific evidence related to outcomes from these models.

Benefits and Challenges of Integrated models of care

There is a startling lack of large-scale models of any chronic care in low- and middle-income countries [36]. There is therefore little outcome evidence currently for the co-morbid population, with the few published studies being descriptive or implementation-focused [45]. However, some early evidence has been encouraging, with most existing studies in Africa and Asia finding integrated care for HIV and NCDs to be acceptable and feasible for both clinic staff and patients [46, 51–53].

Benefits for the Clinic Staff and Health Systems

Benefits for health care workers were shown in a study from Kenya that found that up-skilling these workers to provide a cardiovascular disease service in an HIV setting was feasible and well-accepted by staff [53]. There is also some evidence of potential increased efficiency in use of staff. For example, in Cambodia, chronic disease clinics (accepting adults with HIV, diabetes or hypertension or any combination of these) were set up with the aim of treating HIV and NCDs within one system and using complementary adherence support strategies. It was found that health care staff used similar skills (particularly those regarding chronic disease and adherence) in managing NCDs and HIV, demonstrating an overlap and possible improved efficiency [51]. Adding to the evidence on increased efficiency is a study from Malawi of the implementation of an integrated chronic care clinic which found that no additional human or financial resources were needed compared to treating the chronic diseases separately [52].

Benefits for the Patients

The Cambodian study mentioned above demonstrated reasonable retention at 24 months of care (87.7% for PLHIV, 71% for those with diabetes and 68% for those with hypertension) which is comparable to or better than African retention rates for those with HIV alone which stands at 65% of adults retained at 3 years [54]. It also found that the services were well-accepted by the patients. An African study with similar findings comes from Uganda and found that combining NCD care into existing HIV services was a feasible model for managing those with co-morbidity, reporting improved NCD diagnosis and management since implementation of this integrated approach [46]. This finding was backed up by the afore-mentioned Malawian case-control implementation study which described the set-up of chronic disease clinics providing care for HIV and common NCDS. This study also found early evidence, albeit it descriptive, that an integrated approach was efficient and reduced some patient attendance barriers [52].

Challenges

However, some challenges have been recorded. A case study in South Africa evaluated the 2011 pilot implementation of an integrated chronic disease management (ICDM) model, the aim of which was to use existing HIV programmes to also manage those with NCDs. Although this pilot was situation-specific with limited generalizability, it did fail to find the model sufficiently acceptable from the perspectives of both patients and staff with many reported inadequacies such as poor defaulter-tracing, equipment and drug availability [55]. Of note, a later interrupted time-series study on the ICDM model, published in 2017, found a small but significant improvement in CD4 count and blood pressure over time but no overall clinical benefit [56]. Other studies also mention various challenges to the implementation of integrated care [36, 53, 57]. These include the need for increased human resources, the increase in patient demand, drug stock-outs and poor infrastructure and equipment amongst others. Despite these challenges, the majority of the patchy evidence available points to the achievability of integrated care. Some of the most compelling early evidence for the feasibility of integrated care comes from Kenya and is based on the club system developed in South Africa.

The Club Model

The club model was developed in South Africa from 2007 onwards and is a system whereby PLHIV (who are stable on their medication but have no other co-morbidities) receive their antiretroviral mediation two-monthly in a counsellor-led non-clinic group environment run by trained counsellors. A recent retrospective cohort analysis of such clubs in the Cape Town health district showed retention of 95.2% (95% CI, 94.0-96.4) at 12 months and 89.3% (95% CI, 87.1-91.4) at 24 months after club enrolment, together with 94.1% (95% CI, 91.6-96.0) viral suppression (defined as ≤400 copies/ml) at 28 months after club enrolment [5]. Although there was no suitable comparison group in this study, and the definition of retention included those who left club but continued clinic care, these retention rates were shown to be well above South African estimated retention rates of around 72% at 4 years post ART-initiation [58]. Of note, the retention remained comparable (77.6%) if one used the stricter definition of retention in the club system itself. These good outcomes (although

still reasonably short-term with a median time in clubs in this study of 1.1 years) add weight to the argument for using ART scale-up models to encompass those patients with co-existing NCDs and HIV. In addition, the club model has been shown to be acceptable to patients and more cost-effective than clinic care [59] [60].

The Kenyan Experience

Building on the success of the South African model and to address the agenda of integrated care, Medication Adherence Clubs (MACs) were implemented in Nairobi, Kenya with the aim of using this club system to provide care for adults with one or any combination of hypertension, diabetes and HIV [61]. A study of 1432 such adults found a high retention rate of 96.5%, a high degree of compliance (99%) to protocols and that only 2% of club patients had to be referred back to the clinic for medical reasons during the one year follow-up time. Although this study was descriptive only, nurse- rather than counsellor-facilitated, and provided no specific data regarding co-morbidities, the sample size was reasonable and it appears generalisable to the South African context in terms of the population being from a resource-constrained urban area. A later qualitative study on the same population found MACs to be acceptable to both patients and health care workers, the main benefits being cited as reduced waiting time and number of appointments [62]. This early encouraging evidence regarding models of integrated care together with the unmet need for effective care for this growing co-morbid population has led to the informal implementation of co-morbidity clubs in various facilities within Cape Town.

The Co-morbidity clubs

The Cape Town co-morbidity clubs have been implemented pragmatically at a facility level, largely due to an increase in individuals who were excluded from HIV-only ART clubs due to hypertension and/or diabetes. With the approval of the Provincial Department of Health Steering Committee, the co-morbidity clubs at Gugulethu Community Health Centre, Cape Town started enrolling patients with both HIV and hypertension and/or diabetes from February 2016, with the admission criteria following that of the HIV-only ART clubs with the

addition of chronic disease criteria. Table 2 outlines the two local club models in terms of eligibility, removal criteria, visit structure and human resources.

Table 2. Comparison of the Club Models

AREAS OF CARE	CLUB MODEL	
	NORMAL CLUB	**CO-MORBIDITY CLUB**
Eligibility	• ≥6 months on ARVs • Viral load < 400 copies/ml • No other co-morbidities • CD4 > 100	• ≥6 months on ARVs • Viral load < 400 copies/ml • ≥6 months on medication for diabetes and/or hypertension • BP < 150/95 mmHg (<150/90 if diabetic) • HbA1c < 9% • Creatinine Clearance >50 ml/min (or eGFR > 60) • CD4 > 100
Criteria for Removal	• Defaulted • Viral load > 400 • Pregnant • Symptoms meriting further assessment	• Defaulted • Viral load > 400 • Pregnant • Symptoms meriting further assessment • BP > 160/100 • HbA1c > 10% • Step up in medication needed
Structure of Visits	• Standard • Standard • Blood • Clinical • Standard • Standard	• Standard • Standard • Blood • Clinical (1) • Standard • Standard • Clinical (2)
Staff present	• Standard Visits - Counsellors • Blood and Clinical Visits – Professional Nurse	• Standard Visits - Counsellors • Blood and Clinical Visits – Clinical Nurse Practitioner

With this pragmatic implementation has come some fragmentation, a lack of standardised guidance or model as well as unassessed outcomes. There is therefore a basic need to evaluate these co-morbidity clubs not only to inform best practice at a local level but also to fill a wider research need. Two key predictors of better health outcomes are adherence to medication and successful continuity of care and so the manuscript that follows looks at the important outcomes of viral load and retention data in these co-morbidity clubs [36]. As previously discussed, the viral load can help to predict not only adherence to ART but also potentially adherence to medication for NCDs.

Conclusion

There is a growing and complex population of individuals with both HIV and NCDs in low- and middle-income countries which is currently underserved in the health system. There are compelling arguments for integrated care for this population from the perspective of the shared characteristics (for example the behaviour change needed for chronic disease management), the individual (in terms of adherence and acceptability) and the health system (in terms of resource- and system-effectiveness). In many affected countries there is HIV system infrastructure in place and the HIV scale-up has been successful. Because of this, there is increasing interest in harnessing this programme and its existing infrastructure to help address the needs of these co-morbid patients.

One successful programme in South Africa has been the ART adherence club system and so this provides an ideal starting point for providing integrated care. Co-morbidity clubs have been informally implemented in Cape Town, born out of a growing realisation of the unmet needs of this population, and so these clubs are well positioned to provide information on the effectiveness of integrated management of this population. However, to date there has been no evaluation of patient outcomes from the co-morbidity clubs. The study that follows aims to address this research gap by comparing outcomes of HIV viral load and retention in the club model between those in HIV-only clubs and those in co-morbidity clubs. These results are likely to not only inform local policy but to help address the need for analytical evidence on the outcomes of patients in integrated care and to thus inform NCD and HIV services at a national level [39, 63].

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Part C: Manuscript

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A Retrospective Cohort Study comparing Retention and Viral suppression between Co-morbidity Adherence Clubs and HIV-Only Adherence Clubs in Cape Town, South Africa

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A Retrospective Cohort Study comparing Retention and Viral suppression between Co-morbidity Adherence Clubs and HIV-Only Adherence Clubs in Cape Town, South Africa

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Keywords: Antiretroviral therapy, Medication Adherence, Delivery of Health Care, Diabetes Mellitus, Hypertension, South Africa

Abstract

Introduction: Antiretroviral therapy (ART) adherence clubs have become an important model of care for those with Human Immunodeficiency Virus (HIV) who are stable on medication. With effective ART there is also a growing population of patients living with HIV as well as hypertension and/or diabetes and an urgent need for effective models of integrated care for this group. However, there is little evidence on differentiated models of care for HIV-positive patients with co-morbidities. We compared patient outcomes in the recently implemented co-morbidity adherence club model and the established HIV-only adherence club model in Gugulethu, Cape Town.

Methods: Adults who were stable on ART and enrolled in an adherence club model (co-morbidity or HIV-only) during 2016 were eligible for analysis. Using data from the routine club registers we assessed both retention in the club models and viral suppression (whilst in the club) from club enrolment through 12 months. We compared these outcomes using Chi-squared tests and Fishers exact tests where appropriate, and outcome predictors were assessed using multivariable logistic regression models. Kaplan-Meier estimates were also calculated to assess time to loss from club.

Results: Of 602 adults enrolled, 501 were from the HIV-only clubs and 101 from the co-morbidity clubs. Those enrolled into the co-morbidity clubs were significantly older and had been on anti-retroviral therapy (ART) for longer. There was no difference in the proportion of those retained (84.2% vs 85.6%, p=0.703) or the proportion who were virally suppressed (97% vs 97%, p=0.999) in the co-morbidity club compared to the HIV-only club. In multivariable models, adjusted for age, sex and duration on ART, there was no difference in retention (adjusted odds ratio [aOR] 0.75 95% confidence interval [CI] 0.38, 1.47) or viral suppression (aOR 0.98 95% CI 0.23, 4.14) by club model.

Conclusion: This novel study provides the first preliminary results for the integrated co-morbidity club model, and shows comparable short-term patient outcomes between HIV-only and co-morbidity clubs. Although larger studies are needed, our findings provide reassurance that co-morbidity clubs can be implemented without affecting the outcomes of HIV care.

Introduction

The introduction and scale-up of antiretroviral therapy (ART) has dramatically decreased mortality and increased life-expectancy of people living with HIV [1]. This program success has had the unanticipated consequence of generating a large population of people living with HIV who are, due to their increasing age as well as the direct effects of HIV and ART, at risk of developing non-communicable diseases (NCDs). The incidence of NCDs, particularly hypertension and diabetes, is increasing disproportionately in low and middle-income countries [2]. South Africa, with its well-documented high burden of HIV, is thus experiencing the dual burdens of NCDs and HIV, two chronic conditions which are not without similarities and which are often experienced as comorbidities.

The estimated prevalences of diabetes and hypertension in people living with HIV in low-and-middle-income countries are high at 1.3-18% and 21.2% respectively [3]. There are powerful arguments for integrated care for this population [4]. Firstly, NCDs and HIV are both chronic conditions that tend to be progressive over time and thus effective treatments share an emphasis on self-management with community support and a need to monitor adherence and retention in health services [5]. Secondly, it is thought that these co-morbidities have multiplicative damaging effects on health outcomes and thus present specific health-care needs [6]. Thirdly, those with co-morbidities have been shown to be at increased risk of poor adherence and the current patient burden of attending multiple appointments in vertical programmes puts extra strain on this [7–9]. Lastly, there is evidence that integrated management would be more cost-effective and efficient than multiple vertical programmes [10]. Health systems, in low- and middle- income countries especially, are already under-resourced and any increased efficiency in cost, time, resources and staff is much needed [11].

Despite these calls, there is a striking lack of any large-scale integrated care models (particularly of an analytical nature) in low- and middle-income countries [9], with a corresponding dearth of evidence regarding optimal models of care for the comorbid

population [9, 12]. Existing descriptive and implementation-focused studies have provided an encouraging foundation for further research, with integrated chronic disease clinics in Ugandan and Cambodia demonstrating outcomes which were comparable to, or better than, African retention rates for those with HIV alone [13–15].

With the successful scale-up of the South African ART programme comes the potential to leverage the existing infrastructure to respond to the call for integrated co-morbidity care [16]. One method by which ART scale-up has been achieved is through the adherence club system, whereby PLHIV receive their antiretroviral mediation two-monthly in a non-clinic environment led by trained counsellors [17]. These clubs have demonstrated good retention and viral suppression outcomes in observational studies but currently exclude individuals with co-morbidities [18, 19]. This successful club model was adapted in Kenya in 2013 to encompass those with NCDs and demonstrated a high club retention of 96.5% at one year [20]. Building on this, various facilities within Cape Town have informally implemented co-morbidity clubs into which those with HIV and hypertension and/or diabetes can enrol. These initiatives have been pragmatic in nature with no standardised or recommended model and, to date, the outcomes of patients in the co-morbidity club model have not been evaluated. To address this gap, this retrospective cohort study compares the outcomes of both retention in the club model and HIV viral suppression between the newly-implemented co-morbidity clubs and the established HIV-only clubs [21]

Methods

A retrospective cohort study was conducted of patients who enrolled in the co-morbidity and HIV-only adherence club models at Gugulethu Community Health Centre (CHC), Cape Town during 2016. Outcomes of club retention and HIV viral suppression for adults were compared between club models.

Setting

Gugulethu has a population of approximately 100 000 and is predominantly of low-socioeconomic status [22]. The Gugulethu CHC, which has a catchment area population of approximately 400 000, provides routine ART services in both clinic based and adherence club models. From January 2014 until December 2017, the number of adults retained in club care increased by 45% from 2420 to 3509, and by the end of 2017, 60% of the 5875 adults in ART services at Gugulethu CHC were being managed in the club system [23]. Co-morbidity clubs, for those with both HIV and hypertension and/or diabetes, were implemented in February 2016 following a perceived local need.

ART Adherence Clubs

The ART adherence clubs are well-established counsellor-run models whereby groups of around 30 patients meet five times a year to receive ART care. As of December 2017, 119 HIV-only clubs were operating at Gugulethu CHC together with 7 co-morbidity clubs and 2 adolescent clubs. At the Gugulethu CHC, suitable patients (those who are stable and virally suppressed) are referred to the clubs from the ART clinic. All clubs meet in a nearby off-site community hall and a full comparison of the HIV-only and co-morbidity club model structure and criteria is presented in Additional File 1. The details of the HIV-only club model have been described previously [24] but, briefly, a standard visit comprises health promotion, patient weight and symptom check as well as the dispensing of pre-packed ART. The additional checks performed for the blood and clinical visits are shown in Additional File 1.

The newer co-morbidity clubs use the same inclusion criteria as the HIV-only clubs, but there are additional chronic disease indicator criteria including blood pressure, HbA1c and random glucose. Following some incorrect enrolments in early 2016, a screening form with these criteria was implemented in April 2016. Patients are removed from co-morbidity clubs as for the HIV-only clubs but also if their chronic disease indicators are above

prescribed thresholds. Co-morbidity clubs are run by club counsellors with additional training in health promotion and lifestyle advice pertaining to diabetes and hypertension. The structure of visits is a little different, most obviously in that there are two scheduled annual clinical visits rather than one.

As per the standard of care, the details of each club visit (HIV-only or co-morbidity) are entered into a paper register by the counsellors and these data are then captured electronically by a data clerk at the CHC. For each club visit the retention status is recorded as one of the following: Current (the patient attended the club visit), DNA (the patient Did Not Attend the club visit or collect their medication within seven days of their scheduled visit), BTC (the patient was sent Back To Clinic care for further assessment), TFO (the patient requested a Transfer Out of the club), or RIP (the patient passed away). For the co-morbidity clubs, additional chronic disease indicators are captured from the patient folders.

Participants

All adults who successfully enrolled (attended their first scheduled club appointment after referral from the CHC) into either the HIV-only or the co-morbidity clubs during 2016, and who had a routine HIV viral load scheduled after at least four months (121 days) in the club, were eligible for inclusion in this analysis. Those who had no scheduled club clinical visit within the 12 months follow-up period were excluded (as per Figure 1). Of note, there was no cross-over between the two club models within the time-period of the study.

Measures

For each enrolled adult, the primary outcomes of club retention status and viral suppression were assessed using routinely collected data through 12 months (plus a seven day grace period) post-enrolment in the club.

Retention is an important outcome by which to judge the effectiveness and acceptability of any patient model of care. Retention in the club was defined using the club status recorded at their last scheduled club visit whereby patients are considered retained if they attended the club visit within 7 days of the scheduled visit and had not been recorded as BTC or TFO. The date of loss of retention was defined as the first scheduled club date at which the patient's club status was recorded as DNA, BTC, TFO or RIP.

Viral suppression is a useful outcome by which to assess not only HIV control (particularly adherence to ART) but also control of NCDs by virtue of the association of adherence to ART with that to medication for NCDs [21, 25]. Viral suppression was defined as no viral load >400 copies/ml at a club clinical visit. The date of loss of viral suppression was defined as the date of the first viral load >400 copies/ml taken during the follow-up period.

Of note, there was no tracking of patients who were not retained in the club system and so these patients may or may not have continued their care outside of the club models. All the patients were managed by Gugulethu CHC as per the usual standard of care over the study period.

Statistical Analysis

Patients entered the analysis at their first club visit and exited 12 months (plus a seven day window period) post-enrolment.

Baseline characteristics, demographic and clinical, of enrolled adults were described overall and by club model using medians with interquartile ranges (IQR) and proportions. Comparisons of medians and proportions by club model were performed using Wilcoxon rank-sum and chi-squared tests respectively. Whilst the cohort was assembled retrospectively, a cross-sectional analysis of retention by club model at 12 months post-enrolment was conducted to determine both the proportion of patients in each model retained in the club system and the proportion of patients who were virally suppressed. These proportions were compared using chi-squared tests or Fishers exact tests as appropriate. The median time spent in club was described by club model type and retention status. In addition, Kaplan-Meier estimates of time to loss from club in both models are presented in supplementary material.

Multivariable logistic regression models were fitted to examine the associations between baseline characteristics and outcomes of interest by club model and overall. In *a priori* model design, the current literature was taken into account which describes lower viral suppression and higher loss of retention among young patients and males [18, 26]. It was also hypothesised that enrolment in the HIV-only and co-morbidity clubs may differ by age and sex. Because of this potential for confounding, the variables of age and sex were included in all models regardless of statistical significance. The association of adherence with duration on ART is not clear-cut in the literature but because of an possible association with retention, duration was also included as a variable in all multivariable models [27].

For those enrolled into the co-morbidity clubs, retention was also described by chronic disease (hypertension, diabetes or both). All statistical tests were two-sided at alpha=0.05.

The study was powered at 90% for a 15% effect size. Data were analysed using STATA 14.0 (STATA Corporation, College Station, TX, USA).

Ethics

This study obtained ethical approval from the University of Cape Town Human Research Ethics Committee. Informed consent was not sought from individual patients as this study was a retrospective cohort analysis of routinely collected data, although the local standard of care involves all patients attending the ART clinic at Gugulethu CHC signing a simple consent form on arrival thus agreeing to their data being used in operational research.

Results

A total of 602 patients were included in the analysis; 501 from the HIV-only club model and 101 from the Co-morbidity club model. Figure 1 presents the participant selection for this analysis.

Figure 1. Flow diagram of Eligibility Evaluation for those Enrolled into a Club in 2016

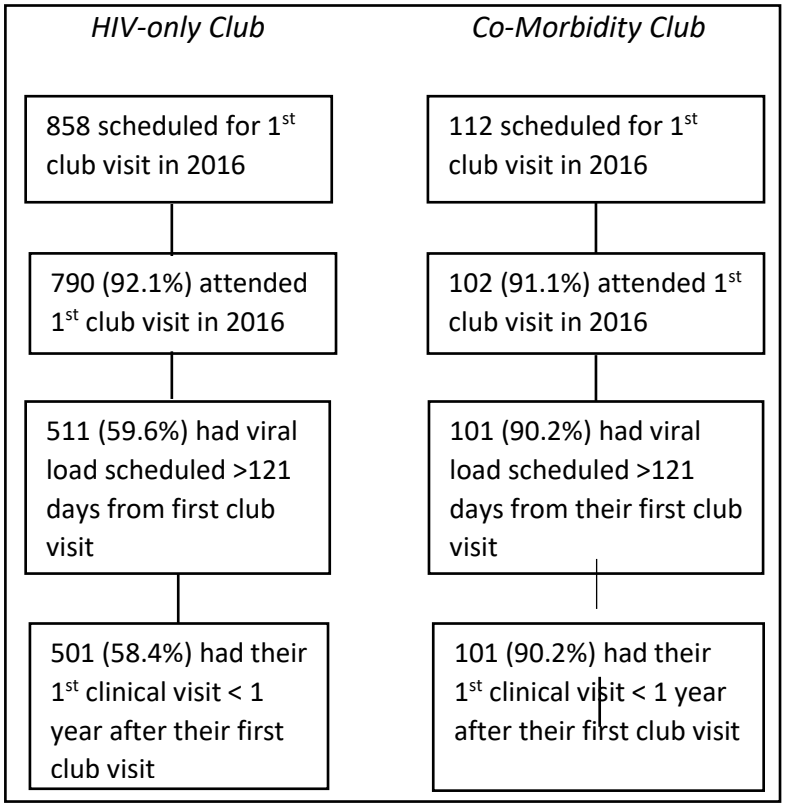


Table 1 describes the baseline characteristics of the patients overall and by club model. The median age at enrolment (38 years overall) differed significantly between the club models, being 36.5 years (IQR 30.5, 42.7) for the HIV-only clubs and 50.7 years (IQR 42.0, 56.0) for the co-morbidity clubs ($p<0.001$). The overall female proportion was 70.3%, with no significant difference by club model. The overall median duration on ART at enrolment was 2.6 years (IQR 1.4, 5.7), this being significantly longer in the co-morbidity club (4.5 years [IQR 2.4, 8.3]) than the HIV-only clubs (2.3 years [IQR 1.3, 5.0]). Of the 101 individuals enrolled into the co-morbidity clubs, 81 (80.2%) had hypertension, 7 (6.9%) diabetes and 8 (7.9%) both. There were 5 patients (5.0%) who had neither hypertension nor diabetes due to incorrect enrolment into the clubs by clinic staff.

Table 1. Demographic and Clinical Characteristics of those Enrolled into Club in 2016, Overall and by Club Model

Variable (at club enrolment)	Overall	HIV-only club	Co-morbidity club	p-value
Number of individuals (%)	602	501 (83.2)	101 (16.8)	-
Median (IQR) age in years	38.0 (31.6, 45.1)	36.5 (30.5, 42.7)	50.7 (42.0, 56.0)	<0.001
Female, n (%)	423 (70.3)	353 (70.5)	70 (69.3)	0.817
Median (IQR) years on ART	2.6 (1.4, 5.7)	2.3 (1.3, 5.0)	4.5 (2.4, 8.3)	<0.001

Table 2 presents retention and viral suppression overall and by club model. At 12 months post-enrolment, the overall retention in club care was 85.4%. The retention in the HIV-only clubs was 85.6% and that in the co-morbidity clubs was 84.2% with no statistically significant difference between these proportions (p = 0.703). Of note, survival analysis also showed no statistically significant difference by club model in the proportion retained over time (p=0.340). The Kaplan-Meier estimates are presented in Additional File 2. The proportion of patients who were virally suppressed was 97.0% overall as well as in both club models. Eight patients from the co-morbidity clubs (7.9%) and 36 patients from the HIV-only clubs (7.2%) had no club viral load result and were included as virally suppressed but results did not change substantially in sensitivity analyses assuming missing viral loads were not virally suppressed (data not shown). The median time in the club model at the viral load blood test differed significantly between club models, being 5.5 months for the HIV-only clubs and 3.7 months for the co-morbidity clubs (p<0.001). Among those who were not retained in club at 12 months, the median time in club appeared similar between club models. The reasons for loss of retention differed significantly by club model (p=0.004). The commonest reason for loss of retention from the HIV-only clubs was failure to attend (DNA) whereas for the co-morbidity clubs it was being sent back to clinic (BTC). The reasons for being BTC also differed between club models, with a high viral load being the commonest cause for HIV-only clubs (70.6%) and high blood pressure for the co-morbidity clubs (54.5%). The small

sample size precluded further statistical analysis. Further information regarding reasons for being sent back to clinic, by club model, is presented in Additional File 3.

Table 2. Retention in Club and Viral Rebound by 12 months Post-enrolment in HIV-only and Co-morbidity clubs. All cells are presented as n (%) unless specified otherwise

Outcome	**Overall**	**HIV-only Club**	**Co-morbidity Club**	**p-value**
Retention	514 (85.4)	429 (85.6)	85 (84.2)	0.703
Not retained	88 (14.6)	72 (14.4)	16 (15.8)	
Did Not Attend	43 (7.1)	39 (7.8)	4 (4)	0.004
Back to Clinic	28 (4.7)	17 (3.4)	11 (10.9)	
Transfer Out	17 (2.8)	16 (3.2)	1 (1)	
Median (IQR) months in club if not retained	5.5 (5.5, 7.4)	5.5 (5.5, 7.4)	5.5 (3.7, 6.4)	0.050
Viral suppression	584 (97.0)	486 (97.0) ‡	98 (97.0)†	0.999
Median (IQR) months in club at time of viral load measure	5.5 (3.7, 5.5)	5.5 (3.7, 5.5)	3.7 (3.7, 3.7)	P<0.001

†8 (7.9%) viral load results missing, ‡ 36 (7.2%) viral load results missing

In both univariable and multivariable logistic regression models there were no statistically significant predictors of retention in club or viral suppression in this cohort (Table 3). In the multivariable model, adjusted for age, sex and increasing duration on ART, there was a 25% decreased odds of retention for those in the co-morbidity clubs compared to those in the HIV-only clubs (aOR 0.75 (0.38, 1.47)). There was a very small decreased odds of viral suppression in the co-morbidity clubs compared to the HIV-only clubs (aOR 0.98 (0.24, 4.14)). Age at enrolment did not seem to be associated with retention or viral suppression in either club model. Increasing duration on ART didn't appear associated with either HIV-only or co-morbidity club retention but appeared to have a positive effect on viral

suppression overall (aOR 1.20 (0.97, 1.47)) and in both club models. The effect of sex on retention and viral suppression appeared to differ by club model, with females being more likely to be retained than males in both club models. Sensitivity analyses were performed for the overall primary outcomes with and without the five individuals in the co-morbidity club model who were incorrectly enrolled and no differences in outcomes were found (data not shown).

Table 3. Crude and Adjusted Logistic Regression Results predicting Retention in Club and Viral Suppression Overall and by Club Model. Results expressed as odds ratios (OR) with 95% confidence intervals

	Overall		**HIV-only Clubs**		**Co-morbidity Clubs**	
	Unadjusted	*Adjusted*	*Unadjusted*	*Adjusted*	*Unadjusted*	*Adjusted*
Retention in club						
Increasing age (years)	1.01 (0.98,1.03)	1.01 (0.98, 1.04)	1.03 (0.99,1.06)	1.02 (1.00, 1.06)	0.96 (0.90,1.02)	0.96 (0.90, 1.03)
Female	1.05 (0.65,1.72)	1.12 (0.66, 1.89)	0.90 (0.52,1.58)	1.06 (0.58, 1.92)	1.98 (0.66,5.91)	1.62 (0.52, 5.04)
Increasing years on ART	1.03 (0.96, 1.11)	1.03 (0.95, 1.11)	1.04 (0.95, 1.13)	1.01 (0.92, 1.11)	1.04 (0.89, 1.22)	1.06 (0.90, 1.25)
Co-morbidity club	**0.89** (0.49,1.61)	**0.75** (0.38, 1.47)				
Viral suppression†						
Increasing age (years)	1.00 (0.95, 1.05)	0.97 (0.92, 1.03)	1.00 (0.94, 1.05)	0.96 (0.90, 1.02)	1.05 (0.93, 1.19)	1.03 (0.90, 1.17)
Female	0.46 (0.13,1.62)	0.38 (0.10, 1.41)	0.36 (0.08, 1.61)	0.27 (0.06, 1.29)	1.13 (0.10, 12.98)	1.10 (0.08, 15.06)
Increasing years on ART	1.20 (0.97, 1.47)	1.24 (1.00,1.55)	1.17 (0.93, 1.47)	1.21 (0.96, 1.53)	1.40 (0.80, 2.43)	1.36 (0.77, 2.39)
Co-morbidity club	**1.01** (0.28,3.55)	**0.98** (0.23,4.14)				

† All patients classified as virally suppressed if no recorded viral load>400 copies/ml

Primary outcomes for those in the co-morbidity clubs, described by chronic illness, are shown in Table 4. The numbers of patients with diabetes or both hypertension and diabetes were very small but retention and viral suppression proportions did not appear to differ between the different categories of comorbid illness. Only three participants in the co-

morbidity club experienced a viral load >400 copies/ml and all three had hypertension alone.

Table 4. Retention and Viral Suppression in the Co-morbidity Club Model recorded by Illness. All cells are n (%)

	Hypertension	**Diabetes**	**Both**	**Neither**
Total	81 (80.2)	7 (6.9)	8 (7.9)	5 (5)
Retention	67 (82.7)	6 (85.7)	7 (87.5)	5 (100.0)
Did Not Attend	4 (4.9)	0 (0)	0 (0)	0 (0)
Back To Clinic	9 (11.1)	1 (14.3)	1 (12.5)	0 (0)
Transfer Out	1 (1.2)	0 (0)	0 (0)	0 (0)
Viral suppression	78 (96.3)	7 (100.0)	8 (100.0)	5 (100.0)

Discussion

This analysis provides preliminary insights into important outcomes for HIV-positive patients in a co-morbidity club model, comparing them to patients in the well-described HIV-only club model at 12 months post-enrolment. In this first analysis of a co-morbidity club model in this setting, we found no differences in 12 month retention in club or viral suppression between the two club models.

Compared to the HIV-only club model, we found that those who enrolled into the co-morbidity club tended to be older and to have been on ART for longer. This is an expected finding due to the increased prevalence of co-morbidities with age and duration on ART as well as the delay in implementing co-morbidity clubs. Once enrolled, those in the co-morbidity club were more likely to be BTC but less likely to be DNA than those in the HIV-only club. BTC from the co-morbidity club was predominantly NCD-related (mostly for high

blood pressure) and likely reflects the increased frequency of clinical monitoring, particularly that of blood pressure. The fewer DNAs likely reflect a satisfaction with the co-morbidity club model of care but may also reflect an element of reduced stigma associated with attending a co-morbidity club compared to an HIV-only club.

Although no statistically significant differences in retention in club were found, multivariable models from this analysis suggest that there is a tendency towards poorer retention among the co-morbid group. Of note, there was a negligible difference in odds of viral suppression between club models. This points to comparable control of HIV in both models and supports the finding that the reasons for loss of retention in the co-morbidity club were mostly NCD-related.

Our findings in the HIV-only club model are comparable to those in the literature with a recent study on HIV-only clubs finding a club retention of 77.6% and a viral suppression proportion of 95.7% at 16 months [18]. The demographics of those enrolled into the HIV-only club were similar to those in other club literature in terms of sex and age. The duration on ART was, however, shorter in this study than other club literature, probably owing to the fact that the club model is now an established standard of care in this setting [19]. Although there are few available studies on co-morbidity models of care, the retention proportions in this study compare favourably to mixed chronic disease clinics such as those in Cambodia and Uganda [14, 28]. The Kenyan MACs also found high retention rates at 1 year of 96.5% but their definition of retention included all those still in in either club or clinic-based care and very few of the patients had co-existing HIV and NCDs [20].

In this study, age was not associated with retention or viral suppression in either club model. This is not in keeping with the majority of the literature, but may be explained by the fact that comparable studies involved larger ranges of ages and more adolescents [18, 29]. Increasing duration on ART increased the odds of viral suppression overall and in each

club model. This is notable as other studies on HIV-only clubs have found a decreased viral suppression with increased time on ART [18, 19].

The following limitations must also be considered. Firstly, these results come from a newly-implemented project and the sample size was reasonably small. Even though the model associations were not statistically significant, the wide confidence intervals around some reasonably large effect sizes point to a lack of power and we cannot preclude the existence of an association. For this reason, the non-significantly reduced odds of retention in a co-morbidity club compared to a HIV-only club needs further evaluation with a larger sample size and ideally a longer follow-up period. Secondly, the median time in the club model at the viral load blood test was significantly higher for the HIV-only clubs compared to the co-morbidity clubs. This was due to the new implementation of the co-morbidity clubs meaning that all patients entered these clubs at the first standard visit (see Additional File 1). It was therefore possible that those in the HIV-only clubs had more time in which to lose viral suppression. Thirdly, all missing viral loads were classed as virally suppressed in the analyses leading to a possible underestimation of viral suppression, although sensitivity analyses did not significantly change the results. Future analyses of larger cohorts may warrant a competing risks approach, or consideration of retention as a confounder for viral suppression. Fourthly, no potential clustering effect by club membership within each club model was accounted for. Lastly, whilst the control group is appropriate and allows meaningful comparison, potential alternative control groups would be those patients with both HIV and NCDs who are being managed in clinics (thereby assessing the direct impact of the club system for this population) and those patients who have NCDs alone and are being managed in a club system (thus assessing the effect of the HIV on NCDs).

Conclusion

This study, to our knowledge, is the first to directly compare club clinical outcomes between adults with HIV alone and those with HIV and hypertension and/or diabetes. These findings

provide early evidence of comparable outcomes for the co-morbidity and HIV-only club models and provide reassurance that co-morbidity clubs can be implemented without affecting the outcomes of HIV care.

Although further evidence on larger cohorts with longer follow-up are required, as well as further investigation regarding the differential reasons for loss of retention by club model, these findings provide reassurance that the under-served population with HIV and co-morbidities can safely be managed in an integrated adherence club model.

Competing Interests

The authors declare no competing interests.

Acknowledgements

The authors would like to acknowledge Gugulethu Community Health Centre and the National Health Laboratory Services of South Africa for providing access to these data.

Authors' Contributions

JA conceived the design, conducted the analysis and drafted the manuscript.

Additional File 1: Comparison of Club Models

AREAS OF CARE	CLUB MODEL	
	HIV-ONLY CLUB	**CO-MORBIDITY CLUB**

Eligibility	• ≥6 months on ARVs
	• Viral load < 400 copies/ml
	• No other co-morbidities
	• CD4 > 100
	• Not pregnant
		• ≥6 months on ARVs
		• Viral load < 400 copies/ml
		• ≥6 months on medication for diabetes and/or hypertension
		• CD4 > 100
		• Not pregnant
		• BP (mmHg) less than target
		  ○ 150/95 for hypertension
		  ○ 150/90 for diabetes
		• HbA1c < 9% for diabetes
		• Creatinine Clearance >50 ml/min (or eGFR > 60)

Criteria for Removal	• Did Not Attend • Viral load > 400 copies/ml • Pregnant • Symptoms meriting further assessment	• Did Not Attend • Viral load > 400 copies/ml • Pregnant • Symptoms meriting further assessment • BP > 160/100 for all • HbA1c > 10% for diabetes • Step up in medication needed

Structure of Visits	• Standard
	• Standard
	• Blood *(viral load, safety bloods)*
	• Clinical *(blood results, symptom check)*
	• Standard
	• Standard
		• Standard
		• Standard
		• Blood
		  ○ *Viral load, safety bloods, creatinine, cholesterol if previous cholesterol > 5 mmol/l for all*
		  ○ *HbA1c for diabetes*
		• Clinical 1
		  ○ *Blood results, random glucose, BP for all*
		• Standard
		• Standard
		• Clinical 2
		  ○ *BP for all*
		  ○ *Foot screen, random glucose, urine, date for retinal screening for diabetes*

Staff present	• Standard Visits – Counsellors • Blood and Clinical Visits – Professional Nurse	• Standard Visits - Counsellors • Blood and Clinical Visits – Clinical Nurse Practitioner

eGFR: Estimated glomerular filtration rate; BP: Blood Pressure

Additional File 2: Survival Analysis

A survival analysis was performed for all those enrolled into the club model (either HIV-only or co-morbidity) during 2016. The analysis end date was the 1st December 2017, the date of the last scheduled club visit for 2017 plus 7 days grace period. The outcome ("event") was loss of retention in the club (defined as a status of DNA, BTC, TFO or RIP) and the survival time was the time from club enrolment until a recorded loss of retention or until the 1st December 2017 depending on which came first.

The sample size of 601 individuals contributed 9493.2 person months and 119 lost retention in club. One individual in the co-morbidity club model requested transfer out at the first scheduled appointment so was not included in the survival analysis. The Kaplan-Meier survival curves are shown in Figure 1.

Figure 1. Kaplan-Meier estimates of the proportion of patients who did not reach the primary outcome of loss of retention in the HIV-only and Co-morbidity club model

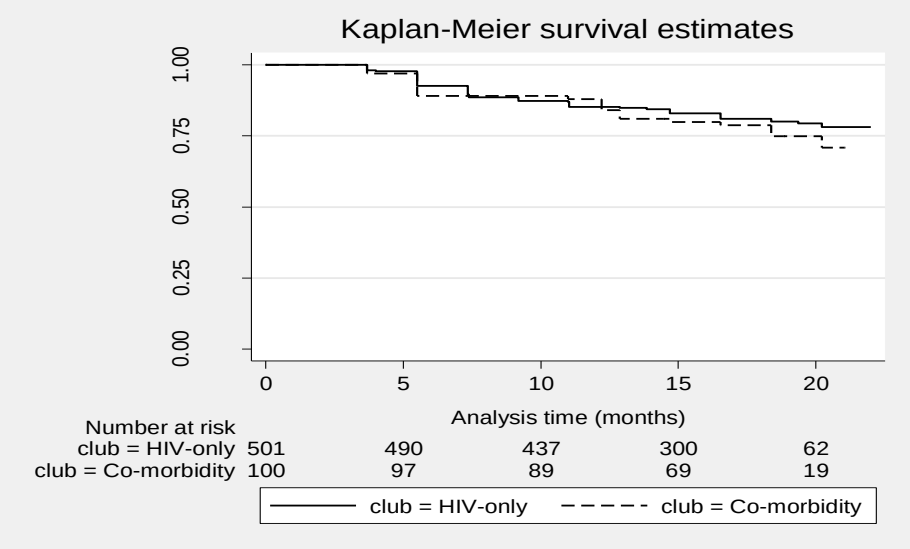
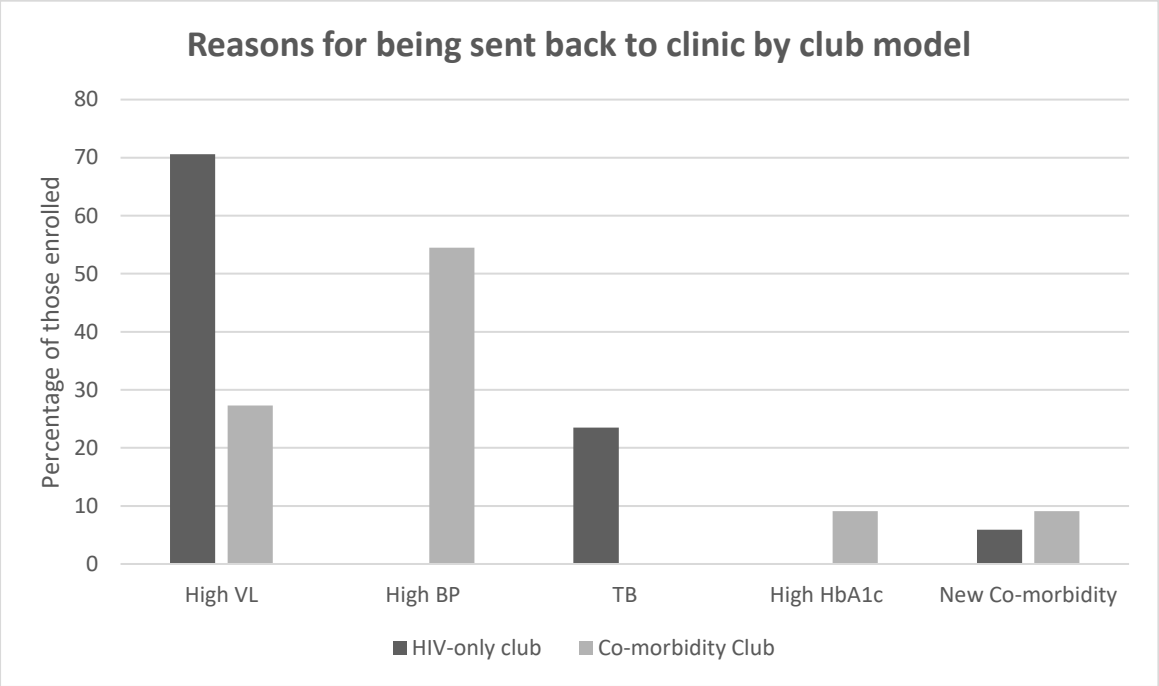


Figure 1 shows a reduction in proportion retained over time in the Co-morbidity club compared to the HIV-only club but a log-rank test for equality of survivor functions showed this difference to be non-statistically significant (p=0.340). Although the lines show increased divergence after around 20 months, this is likely to be due to the small numbers of patients after this time.

Additional File 3: Reasons for being sent back to clinic (BTC) from the HIV-only and co-morbidity clubs



VL=viral load; BP=blood pressure; TB=tuberculosis

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Part D: Appendices

Appendix A. Screening Form for Co-Morbidity Clubs

Date: □□/□□□/2 0□□

Patient Name: _____

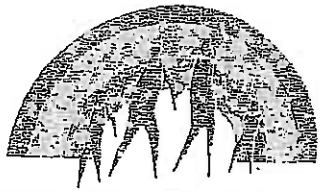
Patient Folder Number: _____

Has the patient been on ARVs for >6 months?	Yes □ No □
Is the latest viral load <400?	Yes □ No □
Is the CD4 >100?	Yes □ No □
Does the patient have either diabetes, hypertension or both?	Yes □ No □
Does the patient have any other chronic diseases that require regular clinical review?	Yes □ No □
Is the BP (within 6 months) < 150/95?	Yes □ No □
If diabetic, is the BP (within the last 6 months) < 150/90?	Yes □ No □
If diabetic, is the HbA1c (within 1 year) < 9%?	Yes □ No □
Is the eGFR>60 or the Creatinine clearance >50 (within the last 6 months)	Yes □ No □
Has the patient been on their chronic disease (diabetes or hypertension) medication for > 6months?	Yes □ No □

If all white boxes ticked – ELIGIBLE for Chronic Club

If any grey boxes ticked – INELIGIBLE for Chronic Club

Appendix B. Simple informed consent for all patients attending Gugulethu CHC HIV clinic



RESEARCH CONSENT FORM Patient Folder number:.....

Doctor or Sister _____ of _____ HIV clinic has explained to me that I am attending a clinic where tuberculosis and HIV are being studied. The care I will receive will be the same or better than that at any other primary care clinic in the Western Cape.

I understand that some of my personal details (including my age, sex, date of diagnosis of TB/HIV, employment and financial standing, as well as details of my illness) will be collected to increase the understanding of HIV and TB in this area. All this information will be kept CONFIDENTIAL and in a separate place from my clinic folder. Only the clinic doctors and nursing sister have access to this information. If it is used later (for further research or publication) my name will not be attached to it in any way.

I give permission for any blood or sputum samples that are sent for my health care to be kept once the test needed is completed. These samples may be used again to increase information on HIV and TB in this area. If the results of these research test are relevant to my health care, my doctor and I will be informed of them. If the information is used more widely, my name will not be attached to it in any way.

Patient sign: _____ Date: _____
Printed name: _____

Health care worker sign: _____ Date: _____
Printed name: _____

Witness sign: _____ Date: _____
Printed name: _____
(Only needed if patient is under 18 years).

Appendix C. Ethics committee approval for this study

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

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

06 March 2018

HREC REF: 156/2018

Ms T Phillips
Centre for Infectious Disease Epidemiology & Research
(CIDER-)
School of Public Health & Family Medicine
FHS

Dear Ms Phillips

PROJECT TITLE: A RETROSPECTIVE COHORT STUDY COMPARING RETENTION AND VIRAL SUPPRESSION BETWEEN CO-MORBIDITY ADHERENCE CLUBS (FOR THOSE ADULTS WITH CO-EXISTING HIV AND DIABETES AND /OR HYPERTENSION) AND THE TRADITIONAL ADHERENCE CLUBS (FOR THOSE WITH HIV ALONE) IN CAPE TOWN, SOUTH AFRICA (Master's candidate- Dr J Allerton)

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

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 March 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)

We acknowledge that the student: Dr J Allerton will also be involved in this study.

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.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

HREC:156/2018

Appendix D. JIAS Author Guidelines

Research - full reports of data from original research studies

Headings: Introduction, Methods, Results, Conclusions

Word limit: 350 words

Main text:

Headings: Introduction, Methods, Results, Discussion, Conclusions

Word limit: 3500 words

Numbers of figures and tables: Unlimited

Additional files: Yes

Main Text File

The text file should be presented in the following order:

1. Title page
2. Keywords
3. Abstract
4. Main text
5. Conflict of Interest Statement
6. Authorship
7. Acknowledgments
8. References
9. Tables
10. Figures

Title page

The title should not contain abbreviations, except commonly used abbreviations such as HIV or AIDS (see Wiley's best practice SEO tips).

On the title page, you should mention the title of the manuscript, list all authors' names in full, and list any study groups if applicable. Each authors' affiliation should be numbered in superscript consecutively and listed underneath, including department, institution, city and country.

The corresponding author should be marked with the symbol § in superscript and full contact details should be provided, including a telephone number with country code. Authors who have contributed equally to the work should be marked with the symbol * in superscript. Deceased authors should be marked with the symbol ^ in superscript. The email addresses of all authors should be listed by their initials.

Keywords

Pease provide six keywords. Keywords should be taken from those recommended by the US National Library of Medicine's Medical Subject Headings (MeSH) browser list at https://www.nlm.nih.gov/mesh/. Preferably alternate words to those found in the abstract in order to improve search hits for the article in repositories.

Abstract

The Abstract should not exceed 350 words and should be structured according to the headings of the selected article category (see above), excluding the heading “Discussion” for Research articles. Avoid using abbreviations and do not cite references in the Abstract. If you are reporting results from a controlled health care intervention, please include your trial

registry, together with your unique identifying number at the end of the Abstract. For randomized controlled trials, follow the CONSORT extension for abstracts.

Main Text

Article sections

Introduction

The Introduction section should introduce the topic to readers without specialist knowledge in that area and must clearly outline the current state of knowledge in this field, the motivation and the aim of the study or the article.

Methods

The Methods section should include all information necessary to repeat the study, in particular, the study design, how data was collected and analyzed, clarifying the choice of methods that were made. If applicable, you should describe the setting of the study, the dates the study were conducted, and the sample or participants, as well as necessary power calculations and materials, including statistical packages, used. Interventions and programmes should be described in detail. Generic names for drugs or any molecules should be used.

All studies involving humans or animals require a statement on ethical approval, and for the former, the consent procedure that was followed. Please include the names of the ethics review board(s) that approved the study. If the research study was specific to one sex/gender, the reasons for this should be clearly stated.

Results

This section should include only data and findings from the authors' study. Presentation of statistical results should mention confidence intervals and levels of significance where appropriate. Quotes from qualitative study participants of less than three lines should be quoted in the text using quotation marks. For quotes longer than three lines, place the quote in a separate, indented paragraph and introduce it with a colon. No quotation marks are needed in this case. Details of the participant can be added in round brackets following the quote, but should not contain identifiable information to ensure confidentiality. Clarifications within the quotation should be placed in square brackets.

Submitting authors are strongly encouraged to include data disaggregated by sex (and, whenever possible, by race) and provide a comprehensive analysis of gender and racial differences. The authors should include the number and percentage of men, women and, if appropriate, transgender persons who participated in the research study. Anatomical and physiological differences between men and women (height, weight, body fat-to-muscle ratios, cell counts, hormonal cycles, etc.), as well as social and cultural variables (socio-economic, education, access to care, etc.), should be taken into consideration in the presentation of data and/or analysis of the results.

Discussion

In the Discussion section, you should discuss your main findings and place these within the context of the current body of knowledge in the field. Limitations of the study, for example, selection bias, can also be discussed, and should address how these influence the results and conclusions. If statistically significant differences were found between men and women or between different racial or cultural groups in the effects of the studied intervention, the implications, if any, for clinical and/or public health should be adequately discussed.

Conclusions

In your Conclusions section, state your key messages from the study and explain their importance and relevance, as well as implications. Future studies and recommendations can

be included in this section. The conclusions drawn must be strictly based on the data provided.

Conflict of Interest Statement

Authors will be asked to provide a conflict of interest statement during the submission process. For details on what to include in this section, see the 'Conflict of Interest' section in the Editorial Policies and Ethical Considerations section below. Submitting authors should ensure they liaise with all co-authors to confirm agreement with the final statement.

Authorship

Please refer to the journal's Authorship policy in the Editorial Policies and Ethical Considerations section for details on author listing eligibility. The individual contributions of each author must be specified in the Authors' Contributions section. Please use authors' initials and state that all authors have read and approved the final manuscript. An example of a suitable statement is: "S.W., N.J., D.W. and S.S. performed the research. S.W., N.J., H.H. and T.L. designed the research study. H.H. and S.S. contributed essential reagents or tools. S.W., N.J. and D.W. analysed the data. S.W. and N.J. wrote the paper." Please see the 'Authorship' section in the Editorial Policies and Ethical Considerations section below for what constitutes authorship.

Acknowledgments

Contributions from anyone who does not meet the criteria for authorship should be listed, with permission from the contributor, in an Acknowledgments section. Financial and material support should also be mentioned. Thanks to anonymous reviewers are not appropriate.

References

All external sources of information should be referenced within the text, the tables and figures, using consecutive numbering in square brackets, e.g. [1], [3-5], [3,4]. The references should be up to date and adequately reflect the current state of knowledge in the field. Citation bias, for example, by country or point of view must be avoided. Numbers of references are unlimited for all article categories and should be formatted in standard Vancouver style; see Sample references from ICMJE . Unpublished observations, personal communications and manuscripts currently under consideration should be cited in the text in round brackets and not in the reference list.

Tables

They should be supplied as editable files, not pasted as images. Tables should be inserted into the text. They should have the header: "Table 1. Title of table". All tables should be cited in the text in consecutive order. The tables should not contain colour or shading, and no vertical, visible lines. If tables are copied or adapted from another source, permission must be sought by the authors prior to publication and these should be clearly cited as such. If a table spans more than one page, authors may want to consider uploading the table as an additional file instead. Tables should be self-contained and complement, not duplicate, information contained in the text. A legend can be provided underneath the title, listing any abbreviations or meanings of symbols used. If several tables are included, please ensure that symbols are used consistently. Legends should be concise but comprehensive – the table, legend, and footnotes must be understandable without reference to the text. All abbreviations must be defined in footnotes. Footnote symbols: †, ‡, §, ¶, should be used (in that order) and *, **, *** should be reserved for P-values. Statistical measures such as SD or SEM should be identified in the headings.

Figures

Figures should be cropped as closely as possible and have the header: "Figure 1. Title of figure". All figures need to be cited in the text in consecutive order.

Although authors are encouraged to send the highest-quality figures possible, for peer-review purposes, a wide variety of formats, sizes, and resolutions are accepted. Click here for the basic figure requirements for figures submitted with manuscripts for initial peer review, as well as the more detailed post-acceptance figure requirements.

Figure legends should be concise but comprehensive – the figure and its legend must be understandable without reference to the text. Include definitions of any symbols used and define/explain all abbreviations and units of measurement. If several figures are included, please ensure that symbols are used consistently.

Additional Files

Appendices

Appendices will be published after the references. For submission, they should be supplied as separate files but referred to in the text.

Supporting Information

Supporting information is information that is not essential to the article, but provides greater depth and background. It is hosted online and appears without editing or typesetting. It may include tables, figures, videos, datasets, etc. Click here for Wiley's FAQs on supporting information.

Note: If data, scripts, or other artefacts used to generate the analyses presented in the paper are available via a publicly available data repository, authors should include a reference to the location of the material within their paper.

General Style Points

The following points provide general advice on formatting and style:

• Abbreviations: In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Initially, use the word in full, followed by the abbreviation in parentheses. Thereafter use the abbreviation only.

• Acronyms: Acronyms should be used sparingly, and not in headings or in the Abstract. Only commonly known acronyms may be used, and they should be spelt out at first use followed by the abbreviation in brackets. SI units should be used, with litre and molar being permitted.

• Units of measurement: Measurements should be given in SI or SI-derived units. Visit the Bureau International des Poids et Mesures (BIPM) website here for more information about SI units.

• Numbers: Numbers under 10 are spelt out, except for: measurements with a unit (8mmol/l); age (6 weeks old), or lists with other numbers (11 dogs, 9 cats, 4 gerbils).

• Trade Names: Chemical substances should be referred to by the generic name only. Trade names should not be used. Drugs should be referred to by their generic names. If proprietary drugs have been used in the study, refer to these by their generic name, mentioning the proprietary name and the name and location of the manufacturer in parentheses.

• Footnotes: Footnotes are not allowed in the text, the information shall be included directly into the text, where it fits best, and if these are references, to include in the reference section at the end.

• Language: All submissions must be in UK English (International) and UN-accepted terminology should be followed. No capitalization should be used except for grammatically correct use, official names and titles, and abbreviations.

• General recommendation: Use line spacing of 1.5 and an easily readable font, for example, Times New Roman, size 12. Your manuscript should contain line numbers to facilitate editors' and reviewers' comments