ASSESSING THE EFFECTIVENESS OF INTEGRATED NON-COMMUNICABLE DISEASE AND ANTIRETROVIRAL ADHERENCE CLUBS IN CAPE TOWN, SOUTH AFRICA

BY

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A mini-dissertation submitted to the School of Public Health and Family Medicine, Faculty of Health Sciences, University of Cape Town in partial fulfilment of the requirements for the award of the degree of Master of Public Health (Epidemiology and Biostatistics)

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Submitted: December 2019

DECLARATION

I, **Blessings Gausi**, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements 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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Date: 10 December 2019

DEDICATION

To the Beit Trust Secretary, **Sir Andrew Pocock KCMG**, I cannot thank you enough for all the financial support you have given me. I never would have made it here without you. To the rest of the Beit Trust team, loads of thanks. I am glad to graduate as a Beit Trust Scholar and will raise the banner of Beit Trust wherever I will serve.

THESIS ABSTRACT

The growing burden of HIV and non- communicable disease (NCD) syndemic in Sub Saharan Africa, has necessitated introduction of integrated models of care in order to leverage existing HIV care infrastructure for NCDs. However, there is paucity of literature on long term treatment outcomes for multimorbid patients attending integrated care. We describe long term treatment outcomes among multimorbid patients who attended integrated ART and NCD clubs (IC), a novel model of care piloted in 2014 by the Western Cape Government in South Africa.

We followed up multimorbid patients for 12 months, who enrolled for IC at Matthew Goniwe and Town II clinics before September 2016.Median adherence proportions, HIV viral suppression and retention rates were calculated at 12 months before and after IC enrolment. Rates for achieving targets for blood pressure and glycosylated haemoglobin were determined at 12 months prior, at IC enrolment and at 12 months post IC enrolment. We describe demographic and clinical variables among all patients at IC enrolment and used multivariable logistic regression to evaluate for predictors of NCD control 12 months post IC enrolment.

As of 31 August 2017, 247 patients in total had been enrolled into IC for at least 12 months. Of these, 221 (89.5%) had hypertension, 4 (1.6%) had diabetes mellitus and 22 (8.9%) had both in addition to HIV. Adherence was maintained before and after IC enrolment with median adherence proportions of 1 (IQR 1-1) and 1 (IQR 1-1) respectively. HIV viral suppression rates were 98.6%, 99.5% and 99.4% at the three time points respectively. Retention in care was high with 6.9% lost to follow up at 12 months post IC enrolment.

Optimal blood pressure control was achieved in 43.1%, 58.9% and 49.4% of participants whereas optimal glycaemic control was achieved in 47.4%, 87.5% and 53.3% of diabetic participants at the three time points respectively. Multivariable logistic analyses showed no independent variables significantly associated with NCD control. Multi-morbid people living with HIV achieved high levels of HIV control in integrated HIV and NCD clubs. However, intensified interventions are needed to maintain NCD control in the long term.

ACKNOWLEDGEMENTS

I would like to thank Professor Tolullah Oni and Dr Nisha Jacob for their relentless supervisory support without which this work would not have been possible. Professor Oni guided and mentored me through every step of this thesis whereas Dr Nisha Jacob offered valueble methodological input throughout.

Many thanks should also go to Natacha Berkowitz who conducted data collection for this project.

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DISSERTATION CONTENTS

In line with the current recommendations on the structure of MPH dissertations at UCT, the contents of this dissertation are as follows:

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PART A: PROTOCOL

ASSESSING THE EFFECTIVENESS OF INTEGRATED HIV AND NON-COMMUNICABLE DISEASE ADHERENCE CLUBS IN CAPE TOWN, SOUTH AFRICA.

Investigators: Blessings Gausi; Natacha Berkowitz; Nisha Jacob; Tolu Oni

1. Background and rationale

South Africa has one of the world's largest HIV burdens, with an HIV prevalence of 12.7%[1]. Consequently, it hosts the largest antiretroviral treatment(ART) programme in the world[2], with 3.4 million patients receiving ARV care at no individual cost[3]. Since the advent of effective ARVs, HIV has become a chronic, manageable illness, with lifespans approaching that of HIV-uninfected persons[4]. This increased lifespan, along with the aging effect of HIV and drug interactions[5,6], has resulted in people living with HIV (PLHIV) to be at risk of developing lifestyle related non-communicable diseases (NCDs), thus increasing the burden of multi-morbidity (MM).

Previous research has shown that there is a significant burden of MM in South Africa with prevalence estimates ranging from 22.6% to 48.4%[7,8]. This dual epidemic of communicable and non-communicable diseases will put strain on the current health system which is ill equipped to cope with the inherent complexity of MM patients[9].

NCD care has in large been neglected at a primary care level and this has been shown through poor patient outcomes. A large study from the Western Cape Province, sampling from 18 primary care clinics, showed that over 60% of people with hypertension and over 50% of people with diabetes attending primary care facilities had poorly controlled diseases[10]. HIV/TB and NCD care services are segregated in primary health care facilities in South Africa,

which has resulted in inefficient care for multi-morbid patients, who have to attend multiple appointments at health facilities to receive care for all their conditions.

To address the inadequacies of the current health system, South Africa is undergoing complete health care reform with the planned implementation of the National Health Insurance (NHI) over the next 10 years[11]. Within this framework is the re-engineering of Primary Health Care (PHC) and the development of the ideal clinic. One of the cornerstones of this restructuring is the creation of integrated health facilities[12], where all healthcare needs are addressed at a single access point. To accomplish this, innovative methods of health care delivery are needed.

The most prevalent NCDs seen at health care facilities in the Western Cape (the setting of this study), are hypertension (HTN) and diabetes (DM)[13]. Two surveys conducted amongst the urban Black population of the Cape Town found the prevalence of hypertension and diabetes to be 35.6% [14]and 13.1%[15] respectively.

Both HTN[16] and DM[17] have been associated with HIV-infection. A study investigating MM in Khayelitsha, a peri-urban settlement in Cape Town, found a high prevalence of comorbid hypertension and diabetes associated with HIV amongst patients on ARVs[8]. This high comorbidity highlights the need to integrate care of these conditions along with routine ARV management.

To achieve integration, a novel model of care that uses community adherence clubs that integrate HIV and NCD care (ICs), has been piloted at some clinics in Cape Town. This model involves both task shifting and decentralization of care at primary health care level. Each IC consists of 25-30 people living with HIV having been on ARVs for more than 6 months with

suppressed viral loads (VL) and a diagnosis of NCD (DM, HTN or both). PLHIV without NCD diagnosis attend ordinary ART medical adherence clubs (MACs) which operate just like ICs except that only ART care is provided in these clubs. MACs have been shown to decongest facilities[18], improve retention in care[19], maintain virologic suppression[20], be cost effective[21] and be acceptable to both patients and health care workers[22].

While the effectiveness of the MACs has been well described, there has not been a formal evaluation of the clinical effectiveness of the ICs since its adoption in Cape Town, South Africa. Studies done elsewhere have assessed the feasibility and clinical benefits of integrating vertical NCD and HIV care services in primary health care clinics intended for patients with either diagnosis[23,24,25,26]. To our knowledge, no study has been done in this setting to assess the clinical effectiveness of integrating NCD and HIV care specifically for patients with multi-morbidity.

2. Study aims and objectives

This study aims to assess clinical outcomes in multi-morbid patients with HIV and comorbid DM and/or HTN after 12 months of receiving integrated care through integrated NCD and ART adherence clubs (IC) at two primary health care clinics in Cape Town.

The objectives of the study are:

1. To assess adherence to scheduled appointments for 12 months prior to, and 12 months post IC enrolment. We hypothesize that IC enrolment improves or maintains adherence to scheduled appointments.
2. To compare HIV viral loads (VL), blood pressure (BP) and haemoglobin A1c (Hba1c) control at around 12 months prior to IC enrolment, at enrolment into IC and around 12

months after enrolment into IC, at the two clinical sites. We hypothesize that IC enrolment maintains or improves clinical control of comorbidity.

3. To investigate factors that are associated with clinical control of co-morbidity in patients enrolled in IC in addition to IC enrolment.

3. Methods

3.1 Study design

We will conduct an analysis of data collected from a study that is already completed. These data were collected by Dr Berkowitz under supervision from A/Prof Oni. The study used an ambivalent design (i.e. partly retrospective and partly prospective cohort design), to enrol all HIV-infected adult patients with HTN or DM or both from three clinics (Mathew Goniwe and Town II Primary Health Care facilities) in Cape Town who attended IC appointments before September 2016. It is an observational cohort study.

3.2 Study population and set up

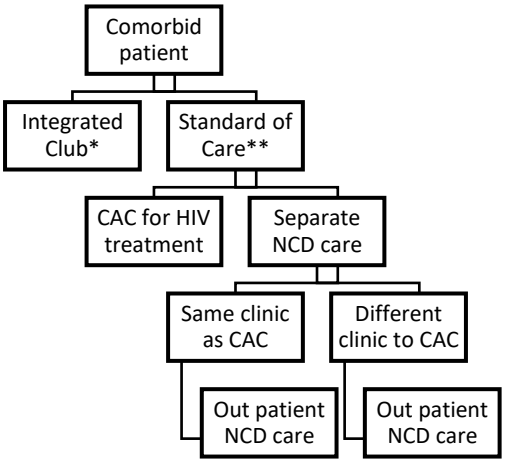
Data were collected from patients receiving integrated care at Mathew Goniwe and Town II Primary Health Care facilities under the governance of the City of Cape Town Health Department. Mathew Goniwe and Town II are facilities based in the peri-urban township of Khayelitsha. They provide, along with 11 other facilities, general, paediatric, HIV and TB care to a predominantly Black African (99%) population. The total Khayelitsha population is approximately 500 000[27]. In 2013, the City of Cape Town had an estimated antenatal HIV prevalence of 19.7%[28]. This prevalence varies by district with, in 2011, Khayelitsha (under which the two facilities fall) having an antenatal prevalence of 37.1%.

The following were inclusion criteria for the study:

- Documented HIV positive status
- Diagnosis of DM or HTN
- Attending IC at the two Primary Health Care Clinics (Mathew Goniwe and Town II) before September 2016
- Aged 18 years or more

Comorbid patients who attend IC receive ART and NCD care simultaneously whereas the standard of care for a CAC attendee who has comorbid NCD comprises of attending a CAC club for ART care and a different outpatient appointment for NCD care. Figure 1 describes these care options. For those receiving standard of care, appointments are often on a different day to the CAC appointment, and may even be at a different facility. NCD care is offered by both medical officers and professional nurses.

Figure 1: Description of care options for patients with comorbid NCDs and stable HIV at Primary Health Care Clinics in Cape Town.



*NCD and HIV care occur simultaneously in the club setting

**Patient attends ARV club care for HIV and a separate appointment for NCD care

To help fully understand similarities and differences in terms of clinical care provided in CACs and ICs, we show clinical procedures undertaken in both adherence clubs in Table 1 below.

Table 1: Adherence club procedures

	ARV adherence club (CAC)	*Integrated Club (IC)*
Club formation	Approximately 25 patients are recruited into a club simultaneously and initiated into the club process together.	
Club admission criteria	HIV infected: Stable – at least 6 months on ARVs and suppressed viral load (VL)	HIV + DM and/or HTN Stable – at least 6 months on ART and suppressed VL. Blood pressure (BP) <140/90 mmHg; HbA1c† <9% if diabetic
Number of Club visits per year	Total = 5 • 3 medication collections • 1 medication collection and clinical examination • 1 medication collection and phlebotomy	
Bloods tests conducted at phlebotomy visit	Viral Load and safety bloods (Liver function, renal function and full blood count depending on ARV regimen) *	Viral Load and safety bloods (Liver function, renal function and full blood count depending on ARV regimen HbA1c) ** Creatinine **

Procedures at each clinical visit	Weight, BP, Tuberculosis symptoms screen and ARV side effects screen, HIV and health education and adherence counselling at each visit by lay-counsellor***
Staff providing care	Lay-counsellor for medication collections Professional Nurse practitioner for clinical examination and phlebotomy Medical officer to review complicated patients

†HbA1c = glycosylated haemoglobin

*Based on provincial ARV guidelines[29]

**Based on Primary Care "PACK" guidelines[30]

***No specific NCD counselling for comorbid patients provided.

3.3 Sampling and sample size calculation

Sampling: All adult patients who attended IC at the two pilot sites and met the inclusion were enrolled (N=247). As the entire population of eligible participants was recruited, there was no sampling conducted. Patients with comorbid HTN and/or DM were identified from the club registers and clinic folders. Outcome measures (BP, VL, and HbA1c) were extracted from these comorbid patients' medical records.

Statistical power: No studies have been done to look at clinical effectiveness of IC care for patients with comorbidity. We will therefore use data for all patients enrolled into IC to maximize power.

3.4 Data collection

Data were extracted from electronic and paper records that consisted of routinely collected data from patient visits. Data were captured directly onto a RedCap electronic database by the study team. All data were anonymized, and participant identification numbers used in place of personal patient details.

Basic patient characteristics, as well as variables that may independently affect the outcome (clinical control of HIV, HTN and DM), were extracted from routinely collected data. These variables are shown in Tables 2. Clinical and adherence variables were also extracted. These are shown in Tables 3 and 4 respectively. Other variables which have been found to independently affect HTN and DM control such as income, level of education[31] and lifestyle related factors (smoking, diet and exercise)[32] were not available from routinely collected patient data and hence were not included in data collection. This will be acknowledged in analysis as well as in limitations of the study.

Table 2: Independent variables

Variable	***Format***	***Description***
Age	Continuous	Years
Sex	Categorical	Male Female
NCD diagnosis	Categorical	Diabetes Hypertension Both Neither
WHO stage at HIV diagnosis	Categorical	Stage I Stage II Stage III Stage IV
*Weight**	Continuous	Kilograms
*Height**	Continuous	Centimetres
ARVs prescribed	Categorical	Tenofovir

		Emtricitabine Lamivudine Efavirenz Zidovudine Abacavir Nevirapine Lopinavir/Ritonavir Other
Date of commencement of ARVs	dd/mm/yyyy	
Date of HIV diagnosis	dd/mm/yyyy	
Date of NCD diagnosis/diagnoses	dd/mm/yyyy	
Date of entry into integrated club	dd/mm/yyyy	
CD4 count at HIV diagnosis	Numerical	CD4 absolute cell count (cells/µl)
Facility	Categorical	Matthew Goniwe Town II

*at 12 months before IC entry, at IC entry and 12 months post IC entry

Table 3: Clinical outcome variables (at around 12 months prior, IC entry and 12 months post IC entry)

Variable	***Format***	***Description***
Blood Pressure (systolic/diastolic)	Numerical	mmHg
Hypertension Controlled (Blood pressure <140/90)	Categorical	No Yes
HbA1c	Numerical	%
Diabetes Controlled (HbA1c <7.5%)	Categorical	No Yes
Viral Load	Numerical	>1000 copies/ml
Viral Load	Categorical	Not suppressed (>1000 copies/ml) Suppressed (<1000 copies/ml)

Table 4: Adherence variables

Variable	***Format***	***Description***
Number of missed medication collection visits 1-year before IC enrolment	Numerical	

Number of missed club visits 1-year post IC entry	Numerical	
Good adherence (collection of medication≥ 80% 1-year before IC enrolment)	Categorical	Yes No
Good adherence (club attendance 1-year after IC enrolment)	Categorical	Yes No

3.5 Measurement

Attendance definition

Attendance over one year prior to IC enrolment and one-year post IC enrolment was recorded (see Table 4 above). Prior to IC enrolment, we will use medication collection as a surrogate for adherence as the participant's attendance schedule would have been variable. After IC enrolment, adherence to club visits was collected from club registers (sheets on which club patient visits are documented). Good adherence will be defined as adherence of >80%[33] (medication collection or club attendance). An acknowledged limitation to this analysis will be the lack of individual participant data on reasons for non-attendance, such as travel, illness or accessing private health care, which may affect the outcome.

Outcome measurement

Clinical outcome variables consist of BP, HbA1c and VL. These were extracted at 12 months before IC entry, at IC entry and 12 monthly for VL and HbA1c, and at IC entry and 6 or 12-monthly (dependent on facility) for BP (Table 3 above). Figures 3 – 5 describe when each

outcome variable was collected for each patient category, that is, patients with HIV, DM and HTN (HIVDMHTN), HIV and DM (HIVDM), and HIV and HTN (HIVHTN) respectively.

Figure 3: Outcome variable recording for patients with comorbid HIV, DM and HTN

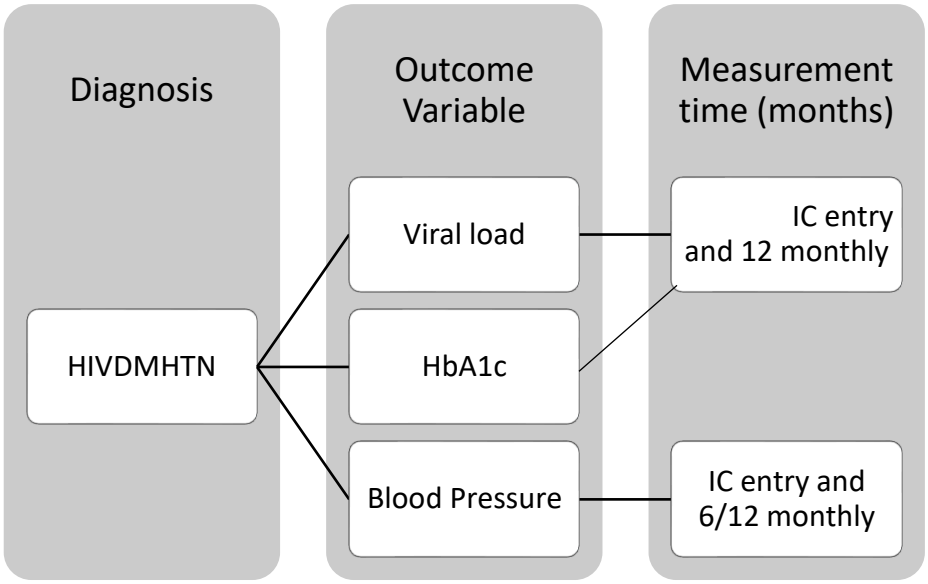


Figure 4: Outcome variable recording for patients with comorbid HIV and DM

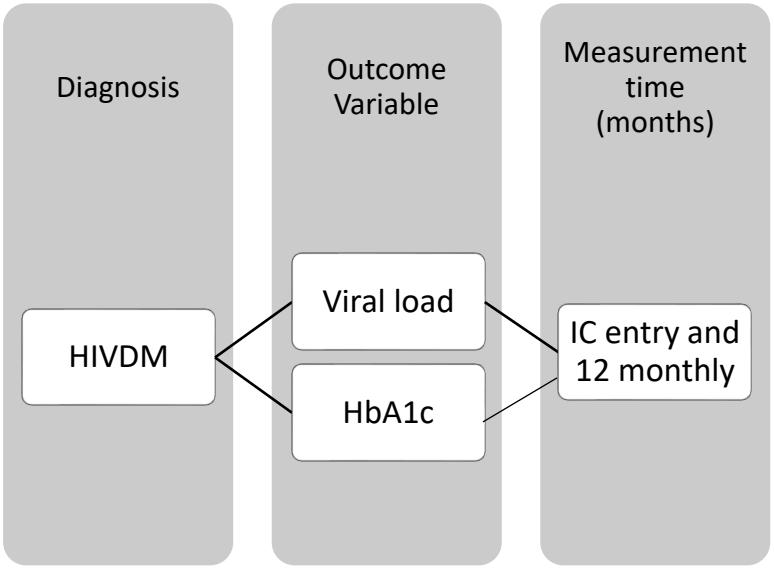
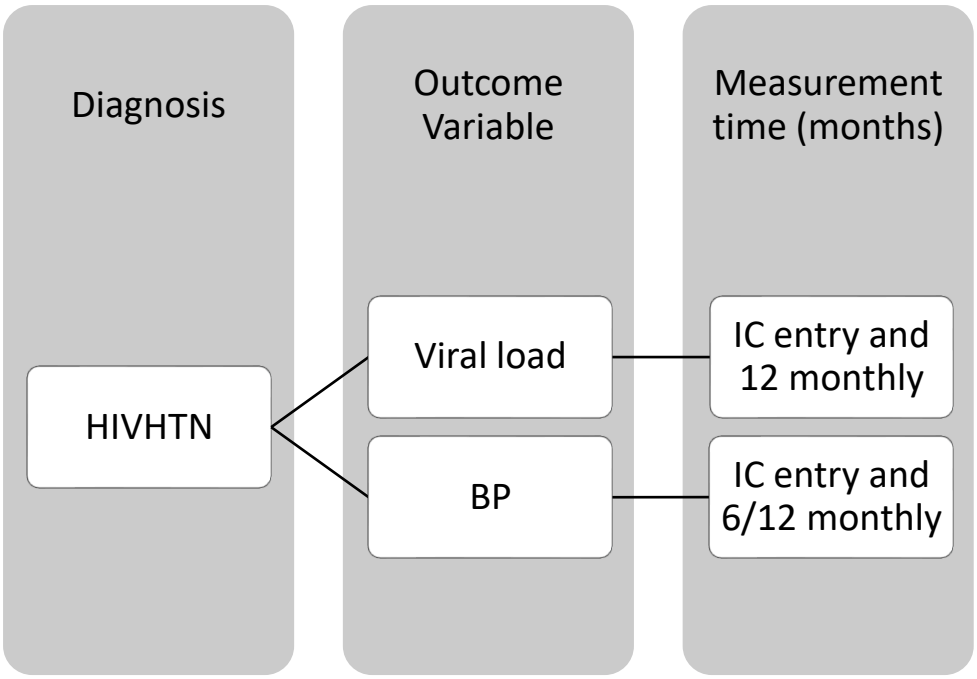


Figure 5: Outcome variable recording for patients with comorbid HIV and HTN



Clinical control definition:

Patient outcomes were assessed until 31 August 2017 (closure of data collection). HTN control was defined as having the last BP reading of <140/90mmHg[34] 12 months after IC enrolment and compared with HTN control at IC entry. DM control will be defined as the last HbA1c of <7.5%[35] 12 months after IC enrolment and compared with DM control at IC entry. Participants will be defined as virally suppressed if viral load is <1000 copies/ml [29] 12 months after IC enrolment.

3.6 Data Analysis plan

Participant data from all sites will be pooled for the purposes of analysis. Participant characteristics will be described using tables and figures. Categorical data will be described using frequency and proportions. Normally distributed continuous variables will be

described using means and confidence intervals, while medians and interquartile range will be used for non-parametric data. Significance testing will be conducted using 2-sided p-values at α of 0.05.

Objective 1: Assessing adherence to scheduled appointments for around 12 months prior to, and 12 months post IC enrolment.

Adherence to scheduled appointments will be determined by calculating the proportion of appointments attended for every participant during the study period. Mean adherence proportions will be calculated prior to IC enrolment and post IC enrolment. These will be compared using a paired t-test under the null hypothesis that IC enrolment improves adherence to care in general.

Objective 2: Clinical outcomes analysis

For the purposes of this analysis, a participant will be deemed clinically controlled if and only if both of their clinical diagnoses are controlled i.e. both HIV and NCD where NCD shall mean HTN, DM, or both. We will calculate the proportion of comorbid participants controlled at 12 months before IC enrolment, at IC enrolment and 12 months after IC enrolment. We will compare them using Chi-squared test for trend and Fischer's exact test as appropriate under the null hypothesis that IC enrolment improves or maintains clinical control of comorbidity. The primary exposure variable will be IC enrolment whereas comorbidity control will be the outcome variable.

Objective 3: Investigating factors that are associated with control of co-morbidity

We will use logistic regression to determine factors that could have additionally affected clinical control of HTN, DM and HIV other than IC enrolment.

Outcome variable: To preserve power in a multivariate model, we will collapse control of comorbidity into one outcome variable. We will model this response variable as 1 if both HIV and DM, or HIV and HTN or HIV and both DM and HTN are all optimally controlled at around 12 months post IC entry and as 0 if otherwise.

Predictors of clinical control: We will perform bivariate analyses to assess potential factors at IC entry that independently affected clinical control 12 months post IC entry. The following variables will be assessed: age, sex, WHO stage(I,II,III,IV) at ART initiation, BMI(< 18.5,18.5≤ and <25,25≤ and <30, and >30 using WHO classification of BMI[36]),duration of ART(< 1-year,≥1-year),duration of HIV diagnosis(<1-year and ≥1-year),good adherence(Yes/No), CD4 count at diagnosis(<500 and ≥500) and clinic site(Matthew Goniwe and Town II. A student's t-test, Mann–Whitney U test as well as Pearson's χ^2 and Fischer's exact test will be performed where appropriate. The univariate analyses will be shown in dummy Table 5 below.

Table 5: Predictors for clinical control apart from IC enrolment

Variable	**Clinical control (Yes)**	**Clinical control (No)**	**P value**
Age (mean± SD)			
Sex(%Male)			
WHO stage			

I			
II			
III			
IV			
BMI category			
BMI< 18.5			
18.5≤ BMI<25			
25≤ BMI <30			
ART duration			
< 1-year			
≥1-year			
Duration of HIV diagnosis			
< 1-year			
1-5 years			
> 5 years			
Good adherence			
Yes			
No			
IC enrolment			
Yes			
No			
Clinic site			

Town II			
Matthew Goniwe			

We will calculate crude odds ratios and conduct univariate logistic regression to identify all independent variables that yield a p-value of ≤0.2. These variables will be used in model building to estimate adjusted odds ratios and 95% confidence intervals for variables associated with clinical control.

Model building: We will build the multivariable logistic regression model manually and using a step-wise approach. Predictors with p-value ≤ 0.2 in univariate analyses will be selected for building the multivariable model. We will perform a Pearson's test for goodness of fit to ascertain model fit. Other variables that improve model fit with the data using the Pearson's test for goodness of fit will also be considered in the multivariable model.

Results from the multivariate logistic model will be shown in dummy Table 6 below.

All statistical analyses will be conducted in STATA 15.0 (Stata Corp LP, College Station, TX).

Table 6: Factors significantly associated with control of comorbidity

Variable	**OR (95 %CI)**	**P Value**	**Adjusted OR**	**P- Value**

4. Ethical Considerations

We plan to conduct an analysis of data that was already collected. Ethical approval for the primary study was obtained from The University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (HREC reference number 085/2017) as well as the Provincial Health Research Ethics Committee prior to data collection.

4.1 Minimizing harm

The primary study involved collection of data from patient paper and electronic records. That imposed minimal harm to the participants as all data were anonymized and all unique patient identifiers (such as names or identification numbers) were removed. This study will analyse the anonymized and de-identified data**.**

4.2 Benefit

There is no direct benefit to individual participants from which data was primarily collected. However, if the IC are found to be effective in managing stable comorbid patients, they may be implemented at more facilities, improving health care for the greater population.

4.3 Confidentiality

During primary data collection, participants were assigned study patient identifiers and entered in Redcap database that is password protected and access controlled by the primary investigator in order to ensure confidentiality. In this study we do not anticipate any breach of confidentiality since the data to be analysed is already anonymised

Since this study involves no anticipated harm to participants in the primary study, we therefore plan to obtain expedited ethical approval from the University of Cape Town Human Ethics Committee as part of good practice in ethical conduct of research as stipulated by the Declaration of Helsinki[37]. Data from the study will be kept for one year after primary analysis to allow for manuscript preparation and publication.

5. Dissemination of Results

Integration of health care is part of the mandate of the NHI. This study will provide an evaluation on a proposed model of care that may benefit patients, health care workers and facilities. Results will be reported to the facilities and adherence clubs involved, as well as dissemination to local authorities to guide systems planning. Results will also be disseminated to the academic audience locally and internationally through conference proceedings and peer-reviewed publications.

6. Logistics

Study Timeline:

	June	July	August	September	October	November	December
Ethical approval							
Data Analysis							
Write-up and dissemination							

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PART B: LITERATURE REVIEW

PATIENT OUTCOMES IN INTEGRATED HIV AND NON-COMMUNICABLE DISEASE MODELS OF CARE: A SCOPING REVIEW

Abstract

Background: High rates of non-communicable diseases (NCD) among people living with HIV have been reported in high HIV burden, low-resource settings. The growing burden of HIV and NCD syndemic has necessitated introduction of integrated models of HIV and NCD care in order to leverage existing HIV care infrastructure for NCDs. There is a paucity of evidence on the effects of integrated care on long-term patient outcomes. We sought to review literature that described effects of integration on long-term patient outcomes.

Design: Scoping review

Methods: We reviewed literature published between 01 Jan 2000 to 25 September 2019, that described long-term patient outcomes in HIV and NCD integrated models of care in order to understand the effects of integration on long-term patient outcomes. Relevant literature was searched in PubMed, Scopus, EBSCOhost and Web of Science. A manual search of abstracts in the International AIDS Society and the Journal of Acquired Immunodeficiency Syndrome was also conducted.

Results: One thousand six hundred and sixty (1660) articles were identified, 31 of which were read in full, with 11 meeting our eligibility criteria. Patient outcomes in four models of integrated care were identified: i) integration of NCD screening and treatment services into established HIV centres; ii) integration of HIV screening and treatment services into established NCD centres; iii) simultaneous integration of HIV and NCD services at health facilities and iv) integrated HIV and NCD care specifically for multi-morbid patients. Studies

reported high rates of control of HIV and NCD across the various models of integrated care. However, the majority lacked comparator groups required to ascertain superiority of integrated care over non-integrated care.

Conclusion: There is limited evidence on the effect of integration on long-term patient outcomes especially in low-resourced and high-burden settings. Well-designed clinical trials with defined comparator groups are needed to demonstrate superior benefit of integrated care over non-integrated care.

Keywords: HIV, integrated models of care, non-communicable diseases, multimorbidity, syndemics

1. Background

Human Immunodeficiency virus (HIV) is a threat to global public health with almost 40 million people living with the virus worldwide[38]. With the advent and scale up of anti-retroviral therapy (ART), HIV has become a manageable chronic condition with life expectancies of people living with HIV (PLWH) comparable to those living with other chronic conditions[4]. This increasing longevity among PLWH, and the premature aging effect of HIV is increasing the prevalence of non-communicable disease (NCD) comorbidities such as Diabetes Mellitus Type 2 (DM) and hypertension (HTN)[5],[6]. High rates of NCDs among PLWH have been reported in high HIV-burden, and low-resource settings[7],[8],[39] placing strain on the health systems in these settings which are ill equipped to cope with the inherent complexity of multi-morbid patients[9].

The growing burden of HIV and NCD syndemics has necessitated exploration of integration of HIV and NCD care in primary health care to leverage existing HIV care infrastructure for NCD care in high HIV-burden settings[40],[41]. Integrated care has been defined as the coordination, co-location, or simultaneous delivery of HIV and NCD services to patients who need it, when they need it[42]. Three models of integrating HIV and NCD care in primary health care have been previously described[43] as follows: Model 1: Integration of NCD screening and treatment services into established HIV centres; Model 2: Integration of HIV screening and treatment services into established NCD centres; and Model 3: simultaneous integration of HIV and NCD services at integrated health centres. As these models do not pre-suppose multi-morbidity, a fourth model proposed by Njuguna et al[40] includes integrated HIV and NCD care for PLWH with comorbid DM or HTN or both, which may be delivered at group (using medical adherence clubs-MACs) or individual levels.

Despite the increasing evidence to suggest feasibility of integrating HIV and NCD care, little is known about the effect of such integration on long-term patient outcomes[40,43,44]. These long-term outcomes include, but are not limited to, medication adherence, retention in care, loss to follow up, HIV viral load suppression/ improvement in CD4 counts and NCD control. It is not known if integration of HIV and NCD care in primary health care improves or at least maintains these outcomes among PLWH receiving integrated HIV and NCD care. Such evidence is needed to inform program managers and health policy makers in order to adopt, implement and scale up integrated HIV and NCD care for multi-morbid patients.

This review aims to identify literature that describes the effect of integrating HIV and NCD care on long-term patient outcomes.

2. Methods

We conducted a scoping review[45],[46] of literature that described the effect of integrating HIV and NCD care on long-term patient outcomes. This review followed the Arksey and O'Malley methodological framework for conducting scoping reviews which comprises 5 stages: identifying the research question, identifying relevant studies, study selection, charting the data and collating, summarizing and reporting results[47],[48].

2.1 Research question

This review was guided by the question 'What are the effects of integrating HIV and NCD care on long-term patient outcomes?'

2.2 Search strategy

We conducted a preliminary search of the terms 'outcomes, effects, successes, effectiveness, impact, integrated HIV, non-communicable disease, chronic disease care' in PubMed. We

then sifted through key studies for potential broader search terms and refined the search strategy (Table 1).

Table 1: Search strategy applied to PUBMED and adapted for use in other databases

Query	Fields	Search term
#1	All	Effects OR outcomes OR effectiveness OR Successes OR impact
#2	All	(Integrated OR combined) AND (care OR management OR health service delivery model)
#3	All	Chronic disease OR Non-communicable disease
#4	All	HIV OR Human Immunodeficiency Virus
#5	#1 AND #2 AND #3 AND #4	

2.3 Information sources

We performed a literature search, using the final search strategy in PubMed, Scopus, EBSCOhost and Web of Science. We also conducted a manual search of abstracts in the International AIDS Society and the Journal of Acquired Immunodeficiency Syndrome. Grey literature was sourced from Mednar and Open Grey. Bibliographies of relevant papers were also carefully searched to source journal articles unidentified through database searches.

2.4 Inclusion criteria

We included articles that reported at least one of the following patient outcomes after receiving integrated care for at least 6 months: adherence to medication, retention in care, loss to follow up, viral load measurements, CD4 counts and markers of NCD treatment outcomes including blood pressure (BP) for HTN, and glycosylated hemoglobin (HBA1c) for DM.

Inclusion criteria for this review included patients older than 18 years of age enrolled into integrated care, with a diagnosis of either HIV alone, HIV and HTN or HIV and DM or both. Longitudinal studies, case-control and cross-sectional studies published between 01 Jan 2000 to 25 September 2019 were included for review. This time frame was selected as there was little wide spread roll-out of ART programs in low- and middle-income countries, where the burden of HIV is highest, prior to 2000.

2.5 Exclusion criteria

Literature not published in English and did not report patient outcomes of interest was excluded. Literature reviews were also excluded; however, their reference lists were carefully searched for eligible studies.

2.6 Study selection

Articles retrieved using the search strategy were exported into EndNote version 9 for removal of duplicates. Thereafter, two authors (BG and PO) independently screened articles by title or title and abstract to determine if articles met the eligibility criteria. A full-text screening was then carried out. Ambiguous abstracts were also evaluated via a full text review for eligibility. Disagreements between the two reviewers were resolved through discussion to reach consensus.

2.7 Ethical considerations

As reviewed literature were published and available in the public domain, ethical approval was not sought for the purposes of conducting this review.

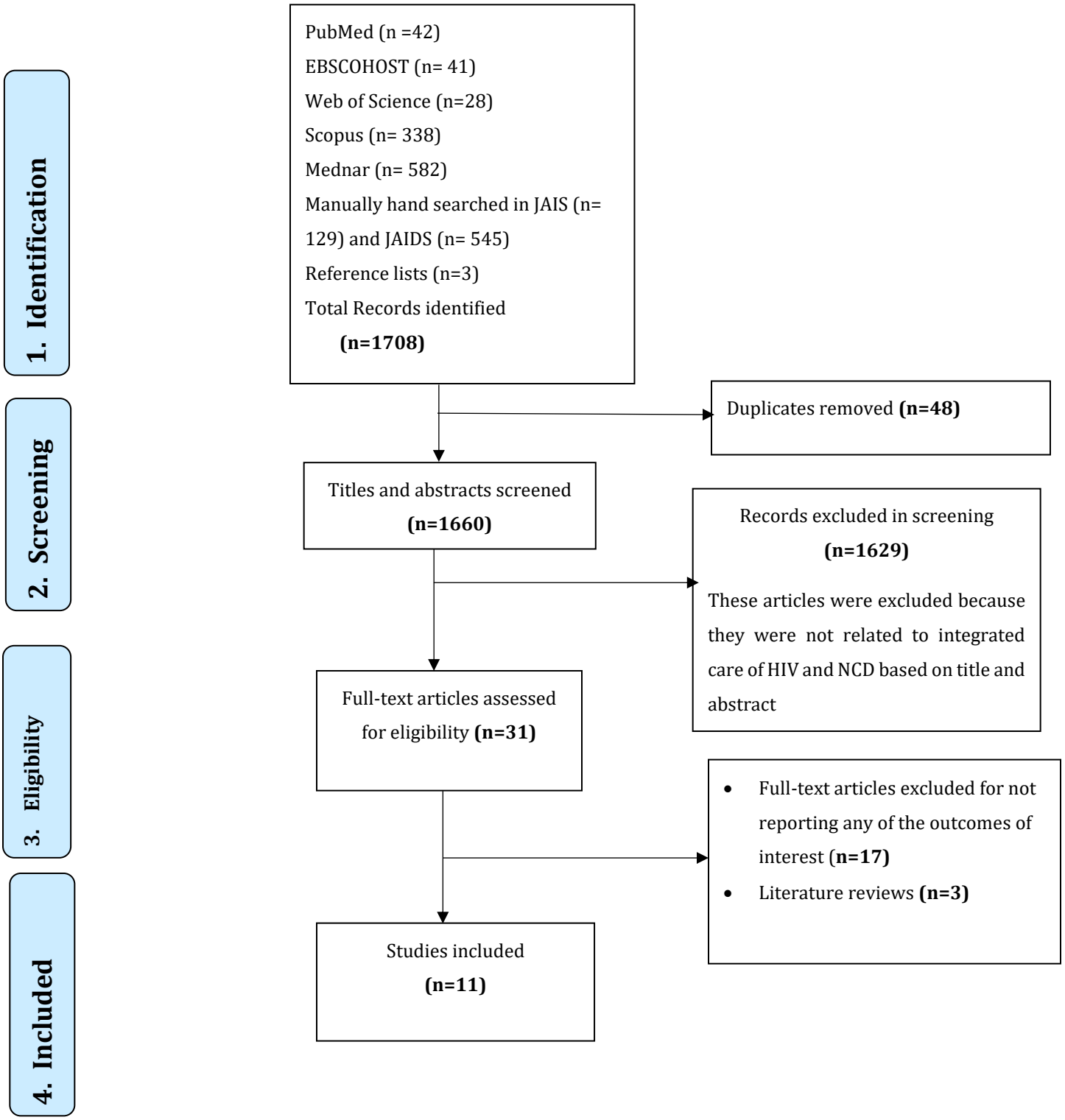
2.8 Data collection and synthesis

The following outcomes were collected and charted from selected articles using a standardized form: author, place, setting of intervention/study, model of integration utilized, intervention (services integrated), duration of intervention, study population, and results (Table 2). A narrative synthesis of the results was also performed on included studies.

3. Results

A total of 11 studies were included in the review. Results of our search strategy and process are shown in a PRISMA flow diagram in figure 1.

Figure 1: Flow diagram for selection of studies



3.1 Characteristics of included studies

Ten of the eleven studies included were full text articles[23,49–57] whereas one was an abstract article[58].Eight studies (72.7%) were published later than 2010 and the majority (n=7), were cohort studies (Table 2). There were no randomized clinical trials identified. Six of the 11 studies were conducted in developed countries (United States of America and United Kingdom) with 5 conducted in low and middle income high HIV-burden countries (Cambodia, Uganda, Kenya and South Africa) (Table 2).

3.2 Models of HIV/NCD integration

Applying the 4 model categories described by Duffy and Njuguna[40],[43], 3 of the 8 studies identified describe NCD services integrated into established HIV care centres (model 1), 5 describe simultaneous integration of HIV and NCD services (model 3), and 3 studies reported integration of HIV and NCD services for multi-morbid PLWH (model 4). No studies reported integration of HIV services into established NCD programs (model 2) (Table 2).

3.3 Patient outcomes

All studies reported HTN outcomes, 60% reported DM outcomes and 50% reported HIV outcomes. Only Janssens et al [51], reported patient outcomes for all three diseases (Table 2). Eight of the 11 studies (72.7%), reported integrated care based in primary care facilities (Table 2).

3.3 Patient outcomes by model of integration

Model 1: Integration of NCD services into established HIV care centres

The 3 studies that reported patient outcomes in the context of integration model 1,[49,50,57] offered NCD screening and treatment services to PLWH. Prevalence of comorbid HTN among PLWH studied was 26% (USA), 47.8% (Uganda) and 43% (USA) respectively[49],[50],[57]. Chu et al[49] conducted a descriptive cross-sectional study among PLWH with comorbid DM or

comorbid HTN. They found that 90% (N= 223) of PLWH with comorbid HTN had controlled BP (BP ≤140/90) and 59% (N= 103) of PLWH and DM had achieved glycaemic control (HbA1c < 7%). However, HIV related outcomes such as HIV viral suppression or CD4 counts, were not reported.

Muddu et al[50] compared HIV control rates among PLWH with no co-morbidity to PLWH with comorbid HTN. They found that after 1-year of follow up, 24.3% of those with comorbid HTN (N= 218) had controlled BP. HIV-related outcomes and retention rates did not differ between PLWH without (viral load (VL) suppressed in 90.2%; retention 71.4% (N=906)) or with comorbid HTN (VL suppressed in 91.6%; retention 65.9% (N=218)) respectively. Myerson et al[57] conducted a cross-sectional study in the USA examining control of HIV and HTN among PLWH. They found that among PLWH with comorbid HTN, 57% (N=1840) had controlled BP. In terms of HIV control, 88% of the overall cohort (N= 4278) were on ART and 67% of these had suppressed VL (mean CD4 count 468 cells /μL).

While these studies reported high rates of control of HIV and comorbid NCDs among patients who received model 1 of integrated care, they were not designed to show benefit of integrated care compared to non-integrated care. Instead, they merely reported patient outcomes upon integrating NCD screening and treatment services in established HIV programs. Comparison was not made to patient outcomes either before integration or in non-integrated care.

Model 3: Simultaneous integration of NCD and HIV services

Five studies reported patient outcomes upon simultaneous integration of HIV and NCD care[23,51–54]. Full details on study design, integrated services and results are shown in Table 2. Janssens et al[51] report treatment outcomes from 8850 participants receiving integrated care for 24 months. Of the 8850, 1419 were HIV-uninfected and received care for HTN only, 2638 were

HIV-uninfected and received care for DM only and 4793 were PLWH without comorbidities. Among PLWH, 87.7% (N=4793) were retained in care ,9.3% had died with 3% lost to follow up. Median CD4 counts after 24 months of attending integrated care rose from 53 to 316 cells/mm^3. However, viral suppression rates were not reported. Among people with HTN, 68% (N=1419) had controlled BP. Among people with DM, median HbA1c fell from 11.5% to 8.6% while 57% had HbA1c ≤ 9%.

Khabala et al[52] conducted a descriptive retrospective cohort study of 1432 HIV-infected and uninfected participants. Of the 1432, 1020 were HIV infected, 352 were HIV-uninfected with HTN whereas 60 were HIV-uninfected with DM. Participants were clinically stable for at least 12 months and recruited into MACs of 25-30 patients each. They reported an overall loss to follow up of 3.5% and high rate of compliance to clinical procedures, however, patient outcomes related to control of HIV or NCD were not reported.

Kwarisiima et al[53] conducted a descriptive cohort study which examined BP control among people with HTN without HIV and PLWH with comorbid HTN in a rural Ugandan community. After screening 34,704 individuals for HIV and HTN, 2071 had HIV while 4355 had HTN without HIV. Of the 4355, 1949 were linked to care at baseline whereas of the 2071 PLWH,199 had comorbid HTN and only 89 were linked to care at baseline. Control of BP among PLWH with HTN (48%) and people with HTN only (46%) did not differ. In this study, authors noted that NCD care was interrupted with significant stock outs for hypertension drugs during the study which may have affected clinical outcomes. Of note, investigators observed that HIV-infected patients were more likely than uninfected patients to have controlled BP at follow-up visits (aOR 1.28; 95% CI 1.00–1.77).

Ameh et al[23] conducted a controlled interrupted time series study in rural South Africa that compared the likelihood of control of HIV and HTN before and after a pilot implementation of an integrated chronic disease management (ICDM) model by the National Department of Health in selected primary health care facilities. A sample of 435 participants were enrolled in intervention facilities using proportionate sampling of which 210 had HTN and 141 were PLWH. Similarly, a sample of 443 participants were enrolled in control facilities in which 91 had HTN and 282 were PLWH. Results showed that after 30 months of follow up, patients at intervention facilities had a 6% greater likelihood of having CD4 counts >350 compared to control facilities (coefficient = 0.057; 95% confidence interval: 0.056-0.058; $P < 0.001$). In addition, patients at pilot facilities had a 1.0% greater likelihood of having patients with controlled BP (coefficient = 0.010; 95% confidence interval: 0.003 to 0.016; $P = 0.002$). However viral suppression, retention in care and loss to follow up were not reported.

The last Model 3 study was conducted by Edwards et al[54], at a primary care center in an urban informal settlement in Kenya. This was a retrospective descriptive study of 2206 participants that compared BP and diabetes outcomes among PLWH with comorbid HTN (N=200) or DM (N=10), with people living with only HTN (N=1697) or only DM (N=299). At 30 months of follow-up, the median systolic blood pressure (SBP) reduced from 151 (Interquartile range (IQR) 136-164) mmHg at baseline to 143 (IQR 129-159) mmHg, while diastolic blood pressure (DBP) reduced from 97 (IQR 86-105) mmHg to 85 (IQR 74-95) mmHg for PLWH and comorbid HTN. For people living with HTN only, median SBP reduced from 160 (IQR 144–177) mmHg at baseline to 141 (IQR 129–158) mmHg while DBP reduced from 100 (IQR 90–110) mmHg to 87 (IQR 75–95) mmHg. For PLWH and DM, mean HbA1c at last visit was 8.2% while among people with DM

only, mean HbA1c at last visit was 8.8%. Neither HbA1c at baseline nor HIV outcomes were reported.

In summary, control of HIV and comorbidities was achieved in this model of care despite logistical challenges experienced by some. Majority of studies describing this model of care did not report key HIV-related outcomes such as viral suppression. Only one study (Ameh et al[23]) compared outcomes among patients who attended integrated care with those who attended non-integrated care. The study showed some evidence that patients who attended IC were more likely to have controlled HIV or NCD compared to non-integrated care patients, suggesting superiority of IC over non-integrated care for control of morbidities. Besides that, the rest of the studies did not have comparator groups.

Model 4: Integrated care for multi-morbid patients

Three studies reported patient outcomes in model 4 of integration[55],[56],[58] (Table 1). Two of these studies (Bury et al[55] and Oluwatoyin et al[56]) undertook descriptive retrospective cohort studies among PLWH with comorbid DM who attended integrated care at HIV specialist clinics in the USA. At the end of follow up, Bury et al[55] and Oluwatoyin et al[56] report that 50% and 54% of participants respectively, had achieved American Diabetes Association targets for BP (< 140/90) and HbA1c (< 7%)[59] at last visit. These outcomes were found to be similar to those in studies with HIV-uninfected populations in the same setting[60],[61]. Lastly, Noble et al[58] conducted a cross-sectional review of PLWH with comorbid HTN in a secondary healthcare settings in Birmingham, United Kingdom. Findings showed that 63% (N=36) had controlled BP.

In summary, patients attending model 4 of integrated care are reported to demonstrate high rates of NCD control similar to HIV-uninfected populations in comparable settings. However, neither

key HIV outcomes, outcomes before integration, nor comparison with patients in non-integrated care, were reported in all three studies.

Table 2: Descriptive characteristics of selected articles

Study	Setting	Intervention	Model*	Duration (months)	Study population	Study design	Results
C, Chu (2011)	Primary care centres in the Bronx, New York, USA	Screening and treatment for HTN and DM offered to PLWH	1	N/A	PLWH, N=854 Of these, n=223 had comorbid HTN and n=108 had DM	Cross-sectional	▪ Prevalence of HTN and DM was 26% and 13% respectively ▪ 90% of PLWH and hypertension met ADA† target for BP ▪ 59% of PLWH and DM met ADA target for HbA1c ▪ Adherence to medication and viral suppression were not reported
Muddu, M (2019)	Primary health centres in Eastern Uganda	Screening and treatment of HTN among PLWH	1	12	PLWH N=1649 Of these,465 were screened for HTN, n=218 had comorbid HTN	Respective cohort	▪ Among those screened, 47.8% had HTN ▪ Among 1649, 98.5% were initiated on ART, 70.7% were retained into care, and 90.3% were suppressed ▪ Of the 1431 patients with HIV alone, 1408 (98.4%) were initiated on ART, 1005 (71.4%) were retained in care, 100% of these were monitored and 906 (90.2%) were controlled

							▪ Among PLWH with HTN, 99.5% were initiated on ART, 65.9% were retained, 91.6% were suppressed and 24.3% had controlled BP‡. HIV outcomes were similar among PLWH with HTN and without HTN
Myerson, M (2014)	Tertiary centre, The Spencer Cox Center for Health Care, New York, USA	Screening and treatment of HTN among PLWH	1	N/A	4278 PLWH, of which 1840 had HTN	Cross-sectional	▪ 88% on ART; 67% with suppressed VL (viral load less than 200 copies/mL) ▪ Among 3906 with documented recent CD4, mean CD4 was 468 cells /µL ▪ Prevalence of HTN was 43% ▪ Of the PLWH with HTN, 75% were being treated; and 57% had controlled BP ▪ No data reported on retention in care and adherence due to cross-sectional nature of the study
Janssens, B (2007)	Provincial referral hospital, Cambodia	ART treatment and care, DM treatment and care	3	24	HIV+, n=4793 DM only =2638 HTN only=1419 No HIV+DM or HIV+HTN	Prospective cohort	▪ 87.7% of HIV-infected were retained, 9.3% died and 3% lost to follow up ▪ Median CD4 count rose from 53 to 316 cells/µL ▪ 29 % lost to follow up

							▪ Median HbA1c fell from 11.5% to 8.6%, 57% had HbA1c ≤ 9% ▪ 68% of HTN had BP ≤160/90 after 6 months of regular treatment ▪ Adherence and viral suppression rates were not reported
Khabala, K (2015)	Primary care center, in urban informal settlement Kiberia, Kenya	Integrated ART and chronic disease care offered to people with DM, HTN and PLWH through MACs	3	12	Total of 1432 were enrolled in MACs PLWH n= 1020, People with HTN n = 352, People with DM = 60, 12 were PLWH and HTN	Retrospective cohort	▪ Loss to follow up was 3.5% overall ▪ High compliance to medical check-ups (99%) ▪ Markers of control of HIV and HTN or DM after follow-up were not reported
Kwarisiima, D (2019)	Primary care centres in rural Uganda	Screening and treatment for HIV, HTN and DM	3	36	34704 were screened: 2071 were PLWH 199 had HTN and only 89 were	Prospective cohort	▪ 48% of visits had controlled BP among PLWH in the entire follow up period ▪ 46% of visits had controlled BP among people not living with HIV ▪ HIV-infected patients were more likely than uninfected patients to have

					linked to care at base line. 32,633 were HIV negative, of these 4355 had HTN and 1949 were linked to care at base line		controlled blood pressure at follow-up visits (aOR 1.28; 95% CI 1.00–1.77) ▪ NCD care was interrupted with significant hypertension drug stock outs ▪ HIV related outcomes were not reported
Ameh, S (2017)	Primary care centres in rural South Africa	Integrated management of DM, HIV and HTN	3	30	435 in intervention facilities, HTN-210, PLWH -141 and 443 in control facilities HTN-91, PLWH-282	Controlled interrupted time series design	▪ Patients at intervention facilities had 6% greater likelihood of CD4 >350 cells/μL than comparison facilities (coefficient = 0.057; 95% CI: 0.056 to 0.058; P < 0.001) ▪ Patients at pilot facilities had 1.0% greater likelihood of controlled BP (coefficient = 0.010; 95% CI: 0.003 to 0.016; P = 0.002). ▪ Viral suppression, retention to care and loss to follow up were not reported

Edwards, J (2015)	Primary care center, in urban informal settlement Kiberia, Kenya	ART treatment, NCD screening, treatment and care	3	30	HIV with HTN n=200 HIV with DM n=10 HTN only n=1697 DM only n=299	Prospective cohort	▪ For PLWH and HTN, median systolic blood pressure (SBP) and interquartile range (IQR) reduced from 151 (136-164) mmHg to 143 (129-159) mmHg while diastolic blood pressure (DBP) and IQR, reduced from 97 (86-105) mmHg to 85 (74-95) mmHg. ▪ For PLWH and DM, mean HbA1c at last visit was 8.2% whereas among those with DM only mean HbA1c was 8.8% ▪ For those with HTN only, median SBP(IQR) reduced from 160 (144–177) mmHg to 141 (129–158) mmHg while DP(IQR) reduced from 100 (90–110) mmHg to 87 (75–95) mmHg. ▪ HIV outcomes were not reported

Bury, E (2007)	Tertiary center, HIV specialist clinic USA-Oklahoma	ART, Diabetes treatment in both arms, Adherence counselling in one arm	4	24	PLWH with DM n=40	Retrospective cohort	▪ Less than 50% attained ADA guidelines[59] for HbA1c ▪ Glycaemic control was similar to findings in HIV-uninfected population[62],[63] ▪ HIV outcomes were not reported
Noble, G (2012)	Secondary centre, HTN clinic, Birmingham, UK	Treatment for HTN offered to PLWH and HTN	4	N/A	PLWH plus hypertension, n=36	Cross-sectional	▪ 85% new or known hypertensive ▪ 63% had controlled BP ▪ Average decrease in 10-year cardiovascular risk was 39% (range 8% to 74%). ▪ All patients rated the clinic as good or great on all aspects and were happy with the care received. ▪ HIV related outcomes were not reported
Oluwatoyin,A (2009)	Primary care center in urban USA-Chicago	ART and Diabetes treatment and care to PLWH	4	12	PLWH and DM N=216	Respective cohort	▪ Baseline CD4 count was 516 cells/µL+/-314 cells/µL ▪ 72% had baseline viral load < 75 cells /mL ▪ No HIV outcomes reported at the end of follow up

							▪ Mean HbA1c at baseline = 7.3% +/- 1.9 % ▪ 54% had HbA1c < 7%, and 72% had HbA1c < 8% at end of follow up ▪ Rates of glycaemic control were similar to results among HIV-uninfected population (30%-44%)[60],[61] ▪ Mean SBP at baseline was 131 +/-17 mmHg, ▪ Mean DBP at baseline was 79 +/-10 mmHg ▪ 56% met ADA blood pressure goals at end of follow up
** Model 1: Integration of NCD screening and treatment services into established HIV centres; Model 2: Integration of HIV screening and treatment services into established NCD centres; Model 3: simultaneous integration of HIV and NCD services at integrated health centres. Model 4: Integration of NCD and HIV care for particularly multi-morbidity patients. This could be offered at an individual level or group level in form of medical adherence clubs for stable patients* *†ADA = American Diabetes Association, targets BP<140/90 and HbA1c < 7%. ‡ controlled BP means BP <140/90.95% CI means 95 percent confidence interval*							

4. Discussion

Studies included in our review sought to evaluate long- term patient outcomes in various models of integrated HIV and NCD care. Eleven studies were identified and of these, 3 reported outcomes in model 1 of integrated care[49,50,57], 5 reported outcomes in model 3[23,51–54] and 3 reported outcomes in model 4 of integrated care[55,56],[58]. No study was found that reported outcomes in model 2 of integrated care. Results from three model 1 studies showed that, after receiving integrated care, patients achieved high rates of control of their comorbidities[49,50,57]. Furthermore, HIV-related outcomes in one study were found to be similar among comorbid and non-comorbid PLWH[53]. This may suggest that when managed appropriately, comorbid PLWH can attain equally high levels of HIV control comparable to PLWH with no comorbidities. However, even though these studies reported high rates of HIV and NCD control after integration, a noteworthy finding was that none of these studies included a comparator group e.g. co-morbid PLWH attending non-integrated care. As such, it is not known if the reported treatment outcomes in this model of care are higher than treatment outcomes in a non-integrated setting.

Simultaneous integration of NCD and HIV services (model 3) also appeared to confer clinical benefits to PLWH. Ameh et al[23] showed that participants who attended integrated primary care facilities were found to have higher likelihood of control of their immune status as well as NCD compared to participants who never utilized integrated care. This was the only study identified that demonstrated that IC may have a positive effect on patient outcomes using a well-defined comparator group. However, while NCD outcomes were reported, the absence of HIV outcomes such as viral load suppression in most model 3 studies means the effect of this model on HIV control remains unknown.

Studies in our review also reported outcomes after integrating care for PLWH with comorbid DM or HTN (model 4)[55,56,58]. It is encouraging to note that multi-morbid patients who attended this form of integrated care achieved good clinical control of their comorbidities at rates similar to HIV-uninfected populations in their settings[60,61],[62,63]. However, similar to studies that reported patient outcomes in model 3, HIV-related outcomes were not reported in these studies. Consequently, it also remains unknown if this model of care is more effective for control of HIV among multi-morbid patients. Furthermore, these studies also did not include a control group to which patient outcomes after integration could be compared. Comparisons could take the form of before/after integration studies with the same multi-morbid PLWH or a comparison with multimorbid PLWH who received non-integrated care.

Overall, model 4 of integrated care appeared to confer the most benefit compared to the rest of the models as evidenced by relatively higher rates of clinical control of multi-morbidity among PLWH in spite of methodological challenges elucidated above.

Patient outcomes among PLWH without NCD morbidities receiving ART care through adherence clubs (MACs) have been extensively described in literature. However, our review confirms lack of evidence on the effectiveness of integrated MACs (that include HIV and NCD care) for multimorbid PLWH who have more complex healthcare needs. Our review further highlights paucity of evidence from sub-Saharan Africa, where the burden of HIV and NCD syndemic is greatest, with only 4 studies identified[23,51–53]. Given that more than two thirds of PLWH live in sub-Saharan Africa[64], studies evaluating effectiveness of integrated HIV and NCD care are urgently needed in this setting to guide healthcare policy.

To our knowledge, this is the first review to assess evidence on long-term patient outcomes in the context of various integrated HIV and NCD models of care; and we highlight the potential to leverage resources from HIV service platforms to provide effective integrated chronic disease care[44,65,66].

5. Conclusion

The potential to leverage existing HIV infrastructure to provide NCD care to multimorbid patients without jeopardizing quality of care is a key consideration for health service delivery, particularly in high HIV-burden settings undergoing rapid epidemiological transition with a rise in NCD co-morbidity. Our review has identified evidence on integration of HIV/NCD care across diverse models of care, and the potential for integration to contribute to desired long-term patient outcomes. However, we highlight the urgent need for high quality research, including clinical trials with defined comparator groups to robustly investigate the clinical impact of integrated models of care on multimorbid HIV/NCD outcomes.

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PART C: JOURNAL ARTICLE

Proposed Journal: BMC Public Health[1]

TREATMENT OUTCOMES AMONG HIV INFECTED ADULTS ATTENDING INTEGRATED HIV AND NON-COMMUNICABLE DISEASE CLUBS IN CAPE TOWN, SOUTH AFRICA.

Blessings Gausi[2]

Word counts

Abstract: 349

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[1] Instructions for authors appear in Appendix 2

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Abstract

Background: The growing burden of HIV and non- communicable disease (NCD) syndemic in Sub Saharan Africa, has necessitated introduction of integrated models of care in order to leverage existing HIV care infrastructure for NCDs. However, there is paucity of literature on long term treatment outcomes for multimorbid patients attending integrated care. We describe long term treatment outcomes among multimorbid patients who attended integrated ART and NCD clubs (IC), a novel model of care piloted in 2014 by the Western Cape Government in South Africa.

Methods: We followed up multimorbid patients for 12 months, who enrolled for IC at Matthew Goniwe and Town II clinics before September 2016.Median adherence proportions, HIV viral suppression and retention rates were calculated at 12 months before and after IC enrolment. Rates for achieving targets for blood pressure and glycosylated hemoglobin were determined at 12 months prior, at IC enrolment and at 12 months post IC enrolment. We describe demographic and clinical variables among all patients at IC enrolment and used multivariable logistic regression to evaluate for predictors of NCD control 12 months post IC enrolment.

Results: As of 31 August 2017, 247 patients in total had been enrolled into IC for at least 12 months. Of these, 221 (89.5%) had hypertension, 4 (1.6%) had diabetes mellitus and 22 (8.9%) had both in addition to HIV. Adherence was maintained before and after IC enrolment with median adherence proportions of 1 (IQR 1-1) and 1 (IQR 1-1) respectively. HIV viral suppression rates were 98.6%, 99.5% and 99.4% at the three time points respectively. Retention in care was high with 6.9% lost to follow up at 12 months post IC enrolment.

Optimal blood pressure control was achieved in 43.1%, 58.9% and 49.4% of participants whereas optimal glycaemic control was achieved in 47.4%, 87.5% and 53.3% of diabetic participants at the three time points respectively. Multivariable logistic analyses showed no independent variables significantly associated with NCD control.

Conclusion

Multimorbid people living with HIV achieved high levels of HIV control in integrated HIV and NCD clubs. However, intensified interventions are needed to maintain NCD control in the long term.

1. Background

South Africa has one of the world's largest HIV burdens, with an HIV prevalence of 12%[1]. Consequently, it hosts the largest antiretroviral treatment (ART) program in the world[2], with 3.4 million patients receiving ART care at no individual cost[3]. Since the advent of effective ART, HIV has become a chronic, manageable illness, with lifespan approaching that of HIV-uninfected persons[4]. This increased lifespan, along with the aging effect of HIV and drug interactions[5,6], has resulted in people living with HIV (PLHIV) to be at risk of developing lifestyle related non-communicable diseases (NCDs), thus increasing the burden of multi-morbidity (MM).

Previous research has shown that there is a significant burden of MM in South Africa with prevalence estimates ranging from 22.6% to 48.4%[7,8]. A study investigating MM in Khayelitsha, Western Cape (the setting of this study), found a high prevalence of comorbid hypertension and diabetes associated with HIV amongst patients on ART[8]. This dual epidemic of communicable and non-communicable diseases will put strain on the current health system which is ill equipped to cope with the inherent complexity of MM[9]. The high comorbidity among people living with HIV (PLHIV) highlights the need to integrate care of these conditions along with routine ART management. PLHIV without an NCD diagnosis attend regular ART medical adherence clubs (MACs) which comprise 25-30 PLHIV who have been on ART for at least 6 months with suppressed viral loads (VL). MACs involve both task-shifting and decentralization of care at primary health care level and have been shown to decongest facilities[10], improve retention in care[11], maintain virologic suppression[12],to be cost effective[13] and acceptable to both patients and health care workers[14].

In response to the rising burden of MM, some clinics under The Western Cape Government have sought to achieve integration; piloting a novel model of care that adapts the MAC model and integrates HIV and NCD care (IC). The structure and eligibility for the IC is similar with the inclusion of a diagnosis of NCD such as Diabetes Mellitus (DM)or hypertension (HTN) or both (DMHTN). The standard of care for a MAC attendee who has comorbid NCD comprises attending a MAC club for ART care and a different outpatient appointment for NCD care often on a different day and sometimes, a different facility. While long term patient outcomes among PLHIV attending MACs have been well described[11,12,15,16] , there has not been a formal evaluation of long term patient outcomes among PLHIV attending this model of care since its adoption in Cape Town, South Africa. These long-term outcomes include, but are not limited to, medication adherence, retention in care, loss to follow up, HIV viral suppression and NCD control. Thus, it is not known if IC improves or at least maintains desired clinical outcomes compared to MACs and separate NCD care in PLHIV. Such evidence is needed to inform health program managers and policy makers in order to adopt, implement and scale up IC for multi-morbid PLHIV globally. Therefore, in this study we sought to assess clinical outcomes in patients with HIV and comorbid DM and/or HTN before and after 12 months of receiving IC at two primary health care clinics in Cape Town, South Africa.

2. Methods

2.1 Study setting and design

We conducted a review of clinical outcomes for PLHIV before and after attending IC at two clinics (Mathew Goniwe and Town II Primary Health Care facilities) in Cape Town, South Africa. Patients had comorbid HTN and/or DM and enrolled into IC before September 2016.

The study was approved by the University of Cape Town, Faculty of Health Sciences Human Research Ethics committee (HREC Ref no: 497/2019).

2.2 Study population

Mathew Goniwe and Town II are health facilities under the governance of the City of Cape Town Health Department. They are based in the peri-urban township of Khayelitsha which has a population of approximately 500,000[17] and estimated antenatal prevalence of 37.1%[18]. Patients were adults over 18 years old, had documented HIV-infected status, documented diagnosis of DM or HTN or both and had attended MACs before they were enrolled into IC at the two clinics prior to September 2016. Clinical procedures routinely undertaken in MAC and IC clubs are summarized in Supplementary Table 1.

Supplementary Table 1: Adherence club procedures

	ART adherence club (MAC)	***Integrated Club (IC)***
Club formation	Approximately 25 patients are recruited into a club simultaneously and initiated into the club process together.	
Club admission criteria	HIV infected and stable – at least 6 months on ART and suppressed viral load (VL)	HIV infected with DM and/or HTN and stable – at least 6 months on ART and suppressed VL. Blood pressure (BP) <140/90mmHg and HbA1c†< 9%
Number of Club visits per year	Total = 5 • 3 medication collections • 1 medication collection and clinical examination • 1 medication collection and phlebotomy	

Bloods tests conducted at phlebotomy visit	Viral Load and safety bloods (Liver function, renal function and full blood count depending on ART regimen) *	Viral Load and safety bloods (Liver function, renal function and full blood count depending on ART regimen HbA1c) ** Creatinine **
Procedures at each clinical visit	Weight, BP, Tuberculosis symptoms screen and ART side effects screen, HIV and health education and adherence counselling at each visit by lay-counsellor***	
Staff providing care	Lay-counsellor for medication collections Professional Nurse practitioner for clinical examination and phlebotomy Medical officer to review complicated patients	

† HbA1c = glycosylated heamoglobin

*Based on provincial ART guidelines[19]

**Based on Primary Care "PACK" guidelines[20]

***No specific NCD counselling for comorbid patients provided.

2.3 Sampling and statistical power

All adult patients who attended IC at the two pilot sites and met the inclusion criteria were included in the study. As there are no published studies that have investigated patient outcomes among comorbid PLHIV attending IC, we enrolled all patients registered in IC clubs in our study.

2.4 Data collection

Patients with comorbid diagnosis of HTN, DM or both (DMHTN) were identified from the IC club registers and clinic folders. Outcome measures (BP, VL, and HbA1c) were extracted from

electronic and paper clinic records. Anonymized data were captured onto a RedCap electronic database by a trained study team.

Patient demographic characteristics (age, sex), anthropometric measures (weight, height), disease-related (NCD diagnoses, WHO stage at HIV diagnosis, CD4 count at HIV diagnosis, time since HIV diagnosis, duration on ART, time since NCD diagnosis), IC club-related (IC club registration date, IC clinic) variables were extracted. Clinical and adherence variables were also extracted. Adherence variables included number of scheduled and missed medication collection visits 1-year before and 1-year after IC registration. Clinical variables extracted included BP, VL and HbA1c measurements at 1-year before IC enrolment, at IC enrolment and at 1-year post IC enrolment. Patient outcomes were assessed from 1-year prior to IC enrolment up until 31 August 2017.

2.5 Definition of outcome variables

Adherence

Prior to IC enrolment, we used medication collection as a surrogate for adherence. After IC enrolment, adherence to club visits, extracted from club registers was used as a surrogate for adherence. Good adherence was defined as proportion of attended visits of > 80%, according to WHO classification of adherence to long term therapy [21].

Clinical control

HIV control was defined as having a viral load of < 1000 copies/ml [19] whereas NCD control was defined by the Society of Endocrinology, Metabolism and Diabetes of South Africa (SEMSA) targets for BP (BP < 140/90mmHg) and glycosylated hemoglobin (HbA1c < 7.5%) among diabetics[22].

2.6 Statistical analysis

We pooled participant data from both clinics for analysis purposes. Categorical variables were described using frequencies and proportions, normally distributed continuous variables using means and 95 percent confidence intervals(95% CI), and non-parametric continuous variables using medians and interquartile ranges. Adherence to scheduled appointments was calculated as the proportion of appointments attended by every participant from 12 months prior to IC enrolment up to the point of IC enrolment, and from IC enrolment to 12 months later. Median adherence proportions were calculated for the 12 months prior to IC enrolment and 12 months post IC enrolment and compared using the Wilcoxon signed rank test.

The proportion of comorbid participants with optimally controlled NCD according to SEMSA targets was calculated cross-sectionally for three time points: (i) at 12 months before IC enrolment, (ii) at IC enrolment and (iii) at 12 months post IC enrolment. The proportions of comorbid participants with optimally controlled NCD at IC enrolment and at 12 months post IC enrolment were compared using the Chi-squared test under the null hypothesis that IC enrolment maintains or improves clinical control of comorbidity.

Univariate logistic regression was used to explore factors associated with comorbidity control and crude odds ratios calculated to identify independent variables that yielded a p-value of ≤0.2. These variables were used to build a multivariate logistic model to estimate adjusted odds ratios and 95% confidence intervals for predictors of clinical control of NCD,

with the outcome variable (NCD control) categorised as 1 if HTN or DM or both, were optimally controlled at 12 months post IC enrolment and as 0 if otherwise.

Significance testing was performed using 2-sided p-values at α of 0.05.All statistical analyses were conducted in STATA 15.0 (Stata Corp LP, College Station, TX).

3. Results

As of 31 August 2017, a total of 247 patients had been enrolled into IC clubs for at least 12 months at Matthew Goniwe and Town II primary health care facilities (Table 1). There were no significant differences in demographic and clinical characteristics between patients at the two facilities at baseline, with the exception of duration with NCD and median CD4 count at HIV diagnosis. Patients who received care at Mathew Goniwe had a relatively higher median CD4 count at HIV diagnosis compared to Town II patients (Table 1). In addition, patients who received care at Town II had relatively more recent diagnosis of NCD compared to patients who received care at Matthew Goniwe facility (Table 1).

Table 1
Demographic and clinical characteristics of study participants at baseline

Variable *	**Matthew Goniwe (n=71)**	**Town II (n=176)**	**Total (N=247)**	**p-value**
Age (years), mean± SD†	48.35±8.43	45.99±8.65	46.67±8.64	0.0514
Sex, Male	18(25.35)	41(23.30)	59(23.89)	0.8651
Comorbidity				
DM	0(0)	4(2.27)	4(1.62)	
HTN	63(88.73)	158(89.77)	221(89.47)	
DMHTN	8(11.27)	14(7.95)	22(8.91)	0.326
Time with NCD (years)				
0-5	43(65.15)	124(94.66)	167(84.77)	
6--10	20(30.30)	4(3.05)	24(12.18)	
> 10	3(4.55)	3(2.29)	6(3.05)	**<0.001**
Time with HIV (years)				
0-5	31(44.29)	91(58.71)	122(54.22)	

6--10	28(40.00)	49(31.61)	77(34.22)	
> 10	11(15.71)	15(9.68)	26(11.5)	0.113
Time on ART (years)				
0-5	48(67.61)	139(78.98)	187(75.71)	
6--10	22(30.99)	36(20.45)	58(23.48)	
> 10	1(1.14)	1(0.57)	2(0.81)	0.155
WHO stage				
0	14(19.72)	60(34.09)	74(29.96)	
1	21(29.58)	53(30.11)	74(29.96)	
2	28(39.44)	43(24.43)	71(28.74)	
3	6(8.45)	15(8.52)	21(8.50)	
4	2(2.82)	5(2.84)	7(2.83)	0.103
CD4 count at Diagnosis‡				
<350	40(61.54)	89(67.94)	129(65.82)	
≥ 350	25(38.46)	42(32.06)	67(34.18)	0.374
Median CD4(IQR)‡	88(35-123)	47.5(1-108)	61(11-116)	**0.0053**

*characteristics are described as n (%) where n is number of participants with the characteristic and % is percentage of the study population with the given characteristic,† SD =standard deviation of the mean, HTN=Hypertension, DM= Diabetes Mellitus type 2,DMHTN= dual diagnosis of HTN and Diabetes Mellitus type 2, NCD = non -communicable disease which implies either DM or HTN or both in this case and ‡ = cells/μL

3.1 Patterns of multi-morbidity and treatment

Of the 247 patients, 221 (89.5%) had comorbid HTN, and 22 (8.9%) had a triple burden of HIV, DM and HTN. A small number ,4 (1.62%), of patients had DM only. The median time with comorbidity regardless of type of NCD, was 3 (IQR (2-4)) years among 197 patients with available data on duration since NCD diagnosis.

Among those with HTN, 95.48% received pharmacological therapy. The majority of patients were being treated with Hydrochlorothiazide (82.93%), Enalapril (9.95%) and Amlodipine (6.6%), All patients with comorbid DM were treated with oral anti-glycaemic agents. Pharmacological therapy for HTN among patients with HTN and DM was similar to that among patients with HTN only.

3.2 Adherence to medication

Median adherence proportions (proportion of scheduled visits attended) and their interquartile ranges before and after IC enrolment were 1 (IQR 1-1) and 1 (IQR 1-1) respectively in which an adherence proportion of 1 meant that a participant had attended approximately all scheduled appointments. Therefore, high adherence to medication was maintained before and after attending IC. There was no significant difference in median adherence proportions before and after attending IC ($p = 0.1334$) either overall or by patterns of MM.

Categorizing adherence as good or bad, there were equally high proportions of good adherence among patients before and after attending IC (91.90% and 90.28% respectively, $p = 0.305$). This observation also did not change when we sub-grouped our sample by patterns of MM.

3.3 HIV control

In our study population, 215/247 (87%) had documented viral load testing at 12 months prior to IC enrolment. Of these,212 (98.6%) were virally suppressed. Similarly, 212 patients had documented viral load testing at IC enrolment and 211 (99.5%) were virally suppressed. Likewise,164 had documented viral load testing 12 months after IC, of which 163 (99.4%) were virally suppressed. In addition,93% were retained into care at 1-year post IC enrolment with 6.9% lost to follow up. Thus, in our study population, HIV control was optimal and was maintained at 1-year post IC enrolment with high retention into care. HIV control did also not differ by patterns of MM.

3.4 Blood Pressure control

Mean Systolic Blood Pressure (SBP) was 139.9 95% CI (136.9-142.9), 132.1 95% CI (129.7-134.6) and 136.7 95% CI (133.7-139.6) at 1-year before IC, at IC enrolment and 1-year post IC enrolment respectively. Likewise, mean Diastolic Blood Pressure (DBP) was 84.7 95% CI (82.7-86.6), 79.7 95% CI (78.23-81.23) and 80.1 95% CI (78.35-81.86) at 1-year before IC, at IC enrolment and 1-year post IC enrolment respectively (Figures 1 and 2). Thus, both SBP and DBP decreased until IC enrolment and increased at 1-year post IC enrolment, though not statistically significant.

Figure 1: Mean Systolic Blood Pressure over time

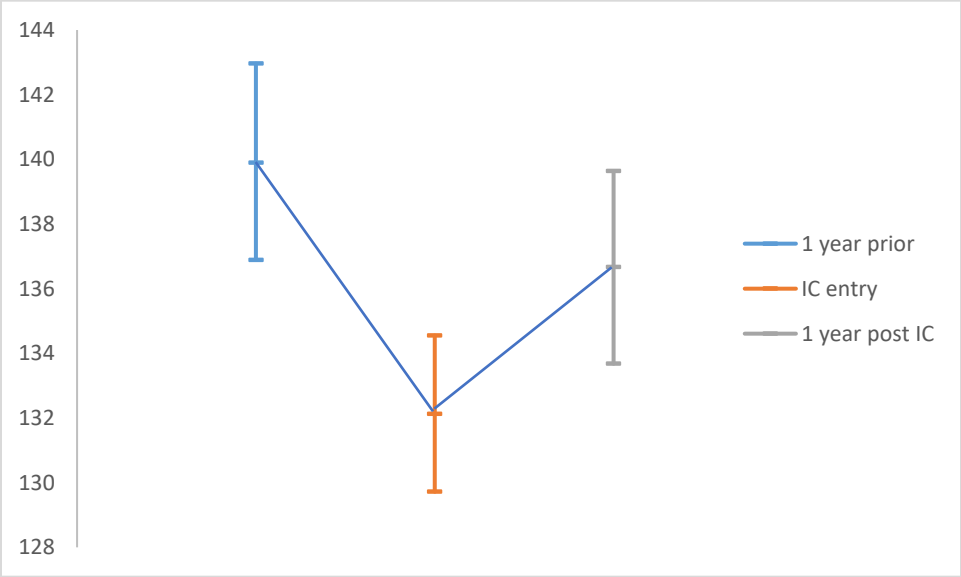
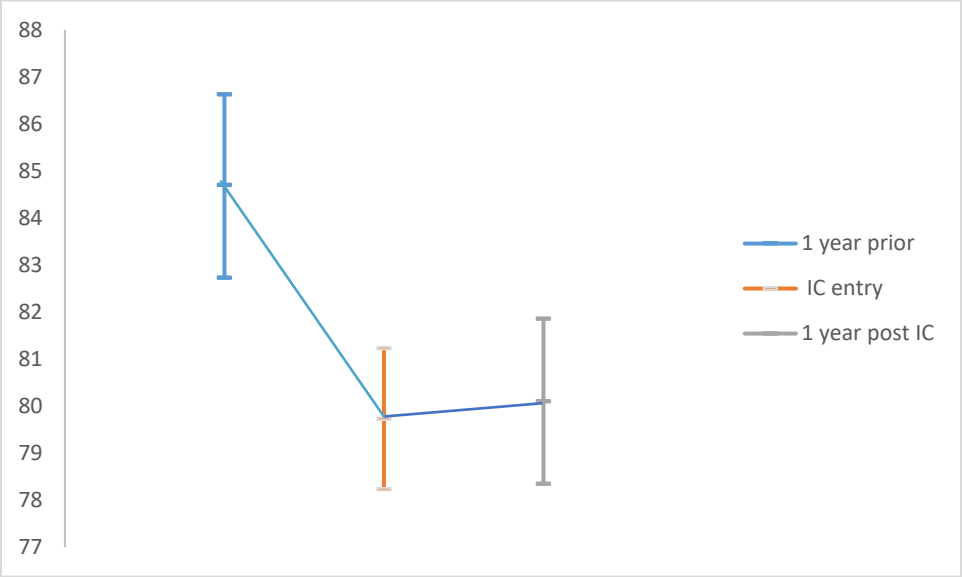


Figure 2: Mean Diastolic Blood Pressure over time



In terms of Blood Pressure (BP) control, 43.4% 95% CI (34.6,50.5), 58.9% 95% CI (52.0,65.7) and 49.4% 95% CI (41.5,57.3) had optimally controlled BP at 1-year before IC enrolment, at IC enrolment and at 1-year post IC enrolment respectively. Thus, a large proportion of our study population achieved BP control at IC enrolment ,however, BP control declined by 9.5% at 1-year post IC (p = 0.0325).When we compared proportions of BP control 1-year post IC attendance among patients with HTN only against those with DMHTN, there was no significant difference in rates of BP control among the two patient groups (64.3 vs 47.6 respectively, p = 0.1166).

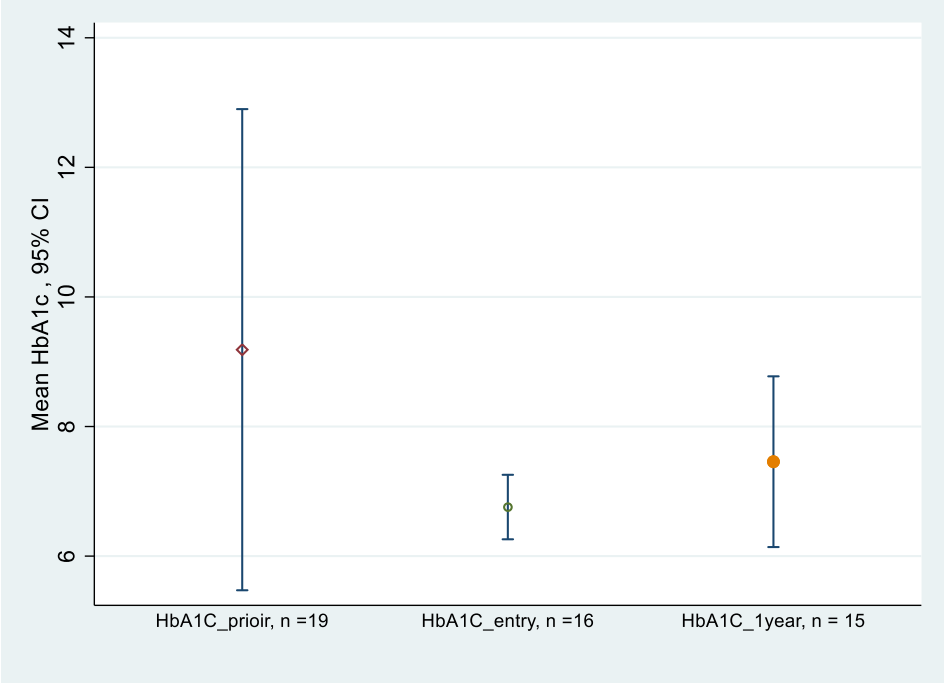
3.5 Diabetes control

Mean glycosylated haemoglobin (HbA1c) among all patients with DM (either DM or DMHTN) was 8.9 95% CI (7.3,10.5),7.0 95% CI (6.4,7.6), and 8.3 95% CI (6.8,9.9) at 12 months prior

to IC enrolment, at IC enrolment and at 1-year post IC enrolment respectively (Figure 3**)**. Thus, mean HbA1c at 1-year post IC enrolment increased slightly from mean HbA1c at IC enrolment even though not statistically significant (p = 0.3514).

Proportions of diabetic patients with optimal glycaemic control were 47.4% 95% CI (24.5,71.1), 87.5% 95% CI (61.7,98.5) and 53.3% 95% CI (26.6,78.7) at 1-year, at enrolment into IC and at 1-year post IC enrolment respectively. Thus, the proportion of diabetic patients with optimally controlled DM 1-year post IC enrolment was significantly lower compared to the point of IC enrolment (p = 0.0180). Thus, it can be seen that despite achieving high glycaemic control at IC enrolment, approximately 30% of our population did not maintain glycaemic control 1-year following IC attendance contrary to our hypothesis.

Figure 3: Glycaemic control over time



3.6 Predictors of control of comorbidity

In univariate logistic regression models, CD4 count, time with NCD, adherence status and site for IC at baseline appeared to affect control of NCD at α = 0.2 level (Table 2). However, in our multivariate logistic model, none of these variables appeared to significantly affect control of NCD 12 months post IC enrolment at α = 0.05 (Table 2).

Table 2

Predictors of NCD control in addition to IC

		Univariate Analyses			Multivariate Analyses		
Characteristic		**OR†**	**95% CI**	**P- value**	**aOR‡**	**95% CI**	**P -value**
CD4 count(cells/μL)	<350	1.00			1.00		
	≥350	0.67	(0.35,1.27)	**0.217**	0.59	(0.29,1.18)	0.138
Time with NCD (years)	0-5	1.00			1.00		
	6--10	0.27	(0.09,0.83)	**0.022**	0.35	(0.10,1.16)	0.087
	>10	0.68	(0.12,3.79)	0.656	1.42	(0.22,9.25)	0.716
Good adherence	No	1.00			1.00		
	Yes	0.47	(0.19,1.19)	**0.112**	0.47	(0.16,1.38)	0.17
Clinic site	Matthew Goniwe	1.00					
	Town II	1.56	(0.85,2.87)	**0.15**	1.50	(0.71,3.16)	0.284
Age group(years)	<40	1.00					
	40-50	1.14	(0.55,2.34)	0.729			
	>50	1.05	(0.49,2.26)	0.906			
Sex	Male	1.00					
	Female	1.09	(0.58,2.03)	0.794			
Comorbidity	DM	1.00					
	DMHTN	0.46	(0.06,3.36)	0.447			
	HTN	1.00	(0.12,8.42)	1			
BMI category	< 18.5	1.00					
	18.5–24.9	0.47	(0.026,8.52)	0.61			
	25.0–29.9	0.89	(0.05,15.44)	0.939			
	≥30	0.54	(0.032,8.90)	0.666			
WHO stage	0	1.00					
	1	0.78	(0.39,1.56)	0.483			
	2	0.94	(0.48,1.87)	0.866			
	3	2.03	(0.76,5.41)	0.157			
	4						

Time on ART (years)	0-5	1.00		
	6--10	0.96	(0.51,1.79)	0.896
	>10	1.97	(0.12,31.99)	0.634
Time since HIV Dx(years)	0-5	1.00		
	6--10	1.26	(0.69,2.28)	0.443
	>10	1.23	(0.51,2.96)	0.637

† OR = unadjusted odds ratio, ‡ aOR = adjusted odds ratio

4. Discussion

Our study is the first to report treatment outcomes among PLHIV living with other NCDs (MM) attending integrated NCD/ ART clubs piloted in Cape Town, South Africa. Several studies have reported treatment outcomes in various models of integrated HIV and NCD care (scoping review by BG et al). However, only two studies have reported treatment outcomes among PLHIV with comorbid DM or HTN[23,24]. Moreover, no study, to our knowledge, has evaluated treatment outcomes among PLHIV with comorbid NCDs attending IC in particular.

This study had several notable findings. Firstly, adherence to medication was high and sustained at 1-year of attending IC. On the same note, at 1-year post IC registration, 93% of our sample was retained in care with overall loss to follow up of 6.9%.

Second, HIV control was sustained at 1-year post IC enrolment with optimal viral suppression of near 100%. This finding is reassuring in that the viral suppression, adherence and retention rates are similar to those reported in ordinary MACs in this setting[13,15,25] .It shows good progress towards the UNAIDS 90:90:90 targets for HIV epidemic control whereby at least 90% of PLHIV receiving ART should suppress their viral loads[26] .

In addition, this finding also means that NCD care can be safely incorporated into HIV care programs without compromising HIV care, thus supporting the notion of leveraging HIV infrastructure for NCD care in the context of the rising NCD epidemic among PLHIV. Not only is integrated HIV and NCD care efficient in terms of optimizing utilization of resources, it has also been found to be convenient and acceptable to patients[27].

Thirdly, low NCD control rates were found before IC enrolment. They increased just before IC enrolment and declined at 1-year post IC enrolment.

The reason for this finding is unclear. One possible reason is insufficient exposure to regular health promotion counselling after IC enrolment and resulting lifestyle modification post IC enrolment. Patients may have been more adherent to lifestyle modification just before IC enrolment in order to benefit from the convenience of IC and potentially laxed in their life style modification commitments upon enrolment into IC. Since NCD control is not just a product of taking medication but rather to a larger extent a product of life style modification regarding diet, smoking and physical exercise, laxity in commitment to life style modification may explain the lapse in NCD control post IC enrolment[28,29,30].

The low rates of NCD control before IC enrolment show the burden of poorly controlled NCDs among PLHIV receiving disintegrated care. This has a negative impact on quality of life of PLHIV in that it increases risk of neurovascular events such as stroke and microvascular events such as renal and ophthalmic disease in addition to ART and HIV itself, thereby exacerbating mortality and morbidity among PLHIV. On the other hand, the higher rates of NCD control at IC enrolment in our study population show the potential of streamlined and intensified care in achieving greater NCD control among PLHIV with MM.

After 1-year post IC enrolment, rates of BP and glycaemic control relate favourably with those found by Bury et al[23] and Oluwatoyin et al [24] among PLHIV with comorbid NCD in the USA where approximately 50 % of PLWH with comorbid DM are reported to have achieved glycaemic control and 47% are reported to have achieved BP control. Our NCD control rates after attending IC are also consistent with findings among patients who attended integrated NCD and HIV care in Uganda in which a BP control rate of 46% was achieved after attending integrated care for three years[31].On the other hand, our NCD control rates are way higher than control rates reported among HIV -uninfected patients in Cape Town in which only 33% of patients with HTN had controlled their BP and 42% of diabetics had achieved glycaemic control[32]. Thus, BP control after 12 months of attending IC in our sample was approximately 20% higher than that reported among HIV-uninfected individuals whereas glycaemic control was at least 10 % higher than that reported among HIV -uninfected individuals who also received care at public primary health care facilities in the same setting. This may be due to increased access to adherence counselling and retention support that PLHIV have over their HIV-uninfected counterparts as also observed in Uganda by Kwarisiima et al[31].

Our study had some limitations. Variables which have been found to independently affect HTN and DM control such as income, level of education and lifestyle related factors (smoking, diet and exercise)[33,34] were not available from routinely collected patient data and hence were not included in data collection and analysis. As a result, we do not know the impact of these confounders on NCD treatment outcomes in our study population. In addition, our univariate logistic regression analyses showed that time with NCD, adherence status and clinic site at IC enrolment appeared to affect control of NCD at 1-year post IC enrolment, at

α= 0.2 level. However, in our multivariate model, no variable at IC enrolment appeared to significantly affect NCD control 1-year post IC enrolment at α= 0.05. This could be partly due to small sample size (N=247) resulting into low power in our multivariate logistic model. In future studies, a sample size of larger than 247 would be recommended to provide sufficient power for meaningful ascertainment of effect sizes.

This study has implications for policy and practice. Our findings suggest that NCD and HIV care can be safely integrated. We therefore recommend scale-up and uptake of integrated HIV and NCD clubs to other parts of the country as well as to other settings with high HIV-burden undergoing rapid epidemiological transition with a rise in NCD co-morbidity. However, models of integration should not just provide a "one stop centre" where multimorbid people living with HIV access medication for both diseases. Instead, they should also incorporate holistic NCD care that includes continuous health promotive counselling for lifestyle modification in order to achieve sustained NCD control.

5. Conclusion

Our study has demonstrated that PLHIV and NCD can sustain high levels of HIV control after attending integrated NCD and ART care clubs as evidenced by high levels of viral suppression, good retention into care and minimal loss to follow-up. This is evidence to suggest that integration of NCD care into routine HIV care in order to leverage the pre-existing HIV infrastructure for NCD care is safe. High levels of NCD control can also be achieved in integrated care, however, intensified health promoting interventions upon enrolment into integrated care are needed to sustain NCD control in the long term.

6. List of Abbreviations

HIV	Human immunodeficiency virus
NCD	Non-communicable disease
ART	Ante- retroviral therapy
PLHIV	People living with HIV
MM	Multimorbidity
DM	Diabetes Mellitus
HTN	Hypertension
DMHTN	Dual diagnosis of Diabetes Mellitus and Hypertension
IC	Integrated care clubs
SEMSA	Society of Endocrinology, Metabolism and Diabetes of South Africa
HbA1c	proportion of glycosylated haemoglobin
BP	Blood pressure
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
MACs	Medical Adherence Clubs
BMI	Body Mass Index
WHO	World Health Organisation

7. Declarations

7.1 Ethics approval

The study was approved by the University of Cape Town, Faculty of Health Sciences Human Research Ethics committee (HREC Ref no: 497/2019).

7.2 Consent for publication

Not applicable

7.3 Availability of data and materials

The dataset analysed is available from the corresponding author on reasonable request.

7.4 Competing interests

The authors declare that they have no competing interests

7.5 Funding

This project was funded from Wellcome Trust Institutional Strategic Support funds through an Imperial College Global Health Clinical Fellowship Scheme, which contributed funding to the principal investigator, Prof Tolullah Oni. However, the funder had no role whatsoever in the design of the study and collection, analysis, and interpretation of data and in writing this manuscript

7.6 Authors' contributions

Authors contributions have already been stated under acknowledgements section of this thesis as recommended by MPH dissertation guidelines. However, they will be re-instated here when submitting to the journal

7.7 Acknowledgements

Not applicable

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PART D: APPENDICES

Appendix 1: Ethical approval

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

05 August 2019

HREC REF:497/2019

Dr N Jacob
Department of Public Health & Family Medicine
Level 4
Falmouth Building-FHS

Dear Dr Jacob

PROJECT TITLE: ASSESSING THE CLINICAL EFFECTIVENESS OF INTEGRATING NON-COMMUNICABLE DISEASE AND ANTI-RETROVIRAL CARE IN CAPE TOWN, SOUTH AFRICA (MASTERS CANDIDATE - DR B GAUSI)

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

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

Approval is granted for one year until the 30 August 2020.

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)

The HREC acknowledge that the following student: Dr B Gausi 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
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

Appendix 2: Author instructions for BMC Public Health

Preparing your manuscript

The information below details the section headings that you should include in your manuscript and what information should be within each section.

Please note that your manuscript must include a 'Declarations' section including all the subheadings (please see below for more information).

Title page

The title page should:

present a title that includes, if appropriate, the study design e.g.:

"A versus B in the treatment of C: a randomized controlled trial", "X is a risk factor for Y: a case control study", "What is the impact of factor X on subject Y: A systematic review"

or for non-clinical or non-research studies a description of what the article reports

list the full names and institutional addresses for all authors

if a collaboration group should be listed as an author, please list the Group name as an author. If you would like the names of the individual members of the Group to be searchable through their individual PubMed records, please include this information in the “Acknowledgements” section in accordance with the instructions below

indicate the corresponding author

Abstract

The Abstract should not exceed 350 words. Please minimize the use of abbreviations and do not cite references in the abstract. Reports of randomized controlled trials should follow the CONSORT extension for abstracts. The abstract must include the following separate sections:

Background: the context and purpose of the study

Methods: how the study was performed, and statistical tests used

Results: the main findings

Conclusions: brief summary and potential implications

Trial registration: If your article reports the results of a health care intervention on human participants, it must be registered in an appropriate registry and the registration number and date of registration should be in stated in this section. If it was not registered prospectively (before enrolment of the first participant), you should include the words 'retrospectively registered'. See our editorial policies for more information on trial registration

Keywords

Three to ten keywords representing the main content of the article.

Background

The Background section should explain the background to the study, its aims, a summary of the existing literature and why this study was necessary or its contribution to the field.

Methods

The methods section should include:

the aim, design and setting of the study

the characteristics of participants or description of materials

a clear description of all processes, interventions and comparisons. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses

the type of statistical analysis used, including a power calculation if appropriate

Results

This should include the findings of the study including, if appropriate, results of statistical analysis which must be included either in the text or as tables and figures.

Discussion

This section should discuss the implications of the findings in context of existing research and highlight limitations of the study.

Conclusions

This should state clearly the main conclusions and provide an explanation of the importance and relevance of the study reported.

List of abbreviations

If abbreviations are used in the text, they should be defined in the text at first use, and a list

of abbreviations should be provided.

Declarations

All manuscripts must contain the following sections under the heading 'Declarations':

Ethics approval and consent to participate

Consent for publication

Availability of data and materials

Competing interests

Funding

Authors' contributions

Acknowledgements

Authors' information (optional)

Please see below for details on the information to be included in these sections.

If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.

Ethics approval and consent to participate

Manuscripts reporting studies involving human participants, human data or human tissue

must:

include a statement on ethics approval and consent (even where the need for approval was waived)

include the name of the ethics committee that approved the study and the committee's reference number if appropriate

Studies involving animals must include a statement on ethics approval and for experimental studies involving client-owned animals, authors must also include a statement on informed consent from the client or owner.

See our editorial policies for more information.

If your manuscript does not report on or involve the use of any animal or human data or tissue, please state "Not applicable" in this section.

Consent for publication

If your manuscript contains any individual person's data in any form (including any individual details, images or videos), consent for publication must be obtained from that person, or in the case of children, their parent or legal guardian. All presentations of case reports must have consent for publication.

You can use your institutional consent form or our consent form if you prefer. You should not send the form to us on submission, but we may request to see a copy at any stage

(including after publication).

See our editorial policies for more information on consent for publication.

If your manuscript does not contain data from any individual person, please state "Not applicable" in this section.

Availability of data and materials

All manuscripts must include an 'Availability of data and materials' statement. Data availability statements should include information on where data supporting the results reported in the article can be found including, where applicable, hyperlinks to publicly archived datasets analysed or generated during the study. By data we mean the minimal dataset that would be necessary to interpret, replicate and build upon the findings reported in the article. We recognise it is not always possible to share research data publicly, for instance when individual privacy could be compromised, and in such instances data availability should still be stated in the manuscript along with any conditions for access.

Data availability statements can take one of the following forms (or a combination of more than one if required for multiple datasets):

The datasets generated and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS]

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

All data generated or analysed during this study are included in this published article [and its supplementary information files].

The datasets generated and/or analysed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

The data that support the findings of this study are available from [third party name] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [third party name].

Not applicable. If your manuscript does not contain any data, please state 'Not applicable' in this section.

More examples of template data availability statements, which include examples of openly available and restricted access datasets, are available here.

BioMed Central also requires that authors cite any publicly available data on which the conclusions of the paper rely in the manuscript. Data citations should include a persistent identifier (such as a DOI) and should ideally be included in the reference list. Citations of datasets, when they appear in the reference list, should include the minimum information recommended by DataCite and follow journal style. Dataset identifiers including DOIs should be expressed as full URLs.

For example:

Hao Z, AghaKouchak A, Nakhjiri N, Farahmand A. Global integrated drought monitoring and prediction system (GIDMaPS) data sets. figshare. 2014. http://dx.doi.org/10.6084/m9.figshare.853801

With the corresponding text in the Availability of data and materials statement:

The datasets generated during and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS].[Reference number]

If you wish to co-submit a data note describing your data to be published in BMC Research Notes, you can do so by visiting our submission portal. Data notes support open data and help authors to comply with funder policies on data sharing. Co-published data notes will be linked to the research article the data support (example).

For more information please email our Research Data Team.

Competing interests

All financial and non-financial competing interests must be declared in this section.

See our editorial policies for a full explanation of competing interests. If you are unsure whether you or any of your co-authors have a competing interest please contact the editorial office.

Please use the authors initials to refer to each authors' competing interests in this section.

If you do not have any competing interests, please state "The authors declare that they have no competing interests" in this section.

Funding

All sources of funding for the research reported should be declared. The role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript should be declared.

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The individual contributions of authors to the manuscript should be specified in this section. Guidance and criteria for authorship can be found in our editorial policies.

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manuscript."

Acknowledgements

Please acknowledge anyone who contributed towards the article who does not meet the criteria for authorship including anyone who provided professional writing services or materials.

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Footnotes can be used to give additional information, which may include the citation of a reference included in the reference list. They should not consist solely of a reference citation, and they should never include the bibliographic details of a reference. They should also not contain any figures or tables.

Footnotes to the text are numbered consecutively; those to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data). Footnotes to the title or the authors of the article are not given reference symbols.

Always use footnotes instead of endnotes.

References

Vancouver reference style should be used

Preparing figures

When preparing figures, please follow the formatting instructions below.

- Figures should be numbered in the order they are first mentioned in the text and uploaded in this order. Multi-panel figures (those with parts a, b, c, d etc.) should be submitted as a single composite file that contains all parts of the figure.
- Figures should be uploaded in the correct orientation.
- Figure titles (max 15 words) and legends (max 300 words) should be provided in the main manuscript, not in the graphic file.
- Figure keys should be incorporated into the graphic, not into the legend of the figure.
- Each figure should be closely cropped to minimize the amount of white space surrounding the illustration. Cropping figures improves accuracy when placing the figure in combination with other elements when the accepted manuscript is prepared for publication on our site.

Preparing tables

When preparing tables, please follow the formatting instructions below.

- Tables should be numbered and cited in the text in sequence using Arabic numerals (i.e. Table 1, Table 2 etc.).
- Tables less than one A4 or Letter page in length can be placed in the appropriate location within the manuscript.
- Tables larger than one A4 or Letter page in length can be placed at the end of the document text file. Please cite and indicate where the table should appear at the

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- Colour and shading may not be used. Parts of the table can be highlighted using superscript, numbering, lettering, symbols or bold text, the meaning of which should be explained in a table legend.

- Commas should not be used to indicate numerical values