FACULTY OF HEALTH SCIENCES

UNIVERSITY OF CAPE TOWN

AN IN-DEPTH ANALYSIS OF COMORBIDITIES IN THE CONTEXT OF HIV BURDEN, IN A COHORT OF PATIENTS SEEKING HEALTHCARE AT KHAYELITSHA FACILITIES IN 2016-2017

BY

RICHARD OSEI-YEBOAH

STUDENT NUMBER: OSYRIC001

THIS THESIS IS SUBMITTED TO THE DEPARTMENT OF INTEGRATIVE BIOMEDICAL SCIENCES, FACULTY OF HEALTH SCIENCES, UNIVERSITY OF CAPE TOWN, IN FULFILMENT OF THE REQUIREMENTS FOR THE AWARD OF DOCTOR OF PHILOSOPHY DEGREE

SUPERVISOR: PROFESSOR NICKI TIFFIN

9 FEBRUARY 2023

PLAGIARISM DECLARATION

I, Richard Osei-Yeboah, hereby declare that the work presented in this thesis document is my own original work, and that I have not previously, either in its entirety or in part, submitted it to any university for degree purposes. All contributions made to the research by others, with whom I have worked at the University of Cape Town or elsewhere, is explicitly acknowledged in the thesis.

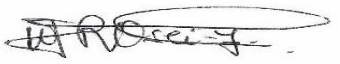
I also declare that the intellectual content of this thesis is the product of my work, except where references are made to other published data, materials, or works in which case the original authors, owners, or sources have been duly cited.

Signed... Signed by candidate Date: 9 February 2023

DECLARATION FOR INCLUSION OF PUBLICATIONS

I confirm that I have been granted permission by the University of Cape Town's Doctoral Degrees Board to include the following publication(s) in my PhD thesis, and where co-authorships are involved, my co-authors have agreed that I may include the publication(s):

1. Osei-Yeboah R., Tamuhla T., Ngwenya O., Tiffin N. (2021) Accessing HIV care may lead to earlier ascertainment of comorbidities in health care clients in Khayelitsha, Cape Town. PLOS Glob Public Health 1(12): e0000031. https://doi.org/10.1371/journal.pgph.0000031.

Signature: 

Date: 9 February 2023

Student Name: Richard Osei-Yeboah

Student Number: OSYRIC001

ABSTRACT

Prior to the introduction of antiretroviral therapy (ART) in South Africa in 2004, people living with human immunodeficiency virus (PLHIV) suffered high mortality. However, with the advancements in enhancing early detection or diagnosis, linkage to treatment, and availability of ART, PLHIV now have an increasing life expectancy. These improvements in access to care for PLHIV have resulted in the decline of HIV cause-specific mortalities, with an increase in cases of chronic diseases in this ageing population. In many developed countries, the demographics of the HIV epidemic have shifted significantly towards individuals aged over 50 years. In South Africa, where the highest burden of the HIV epidemic in sub-Saharan Africa (SSA) is recorded and about 8.45 million people are affected, the prevalence of HIV in the population aged over 50 years increased from 7.1% in 2012 to 12.5% in 2017. Recent studies outside Africa suggest higher prevalence and earlier incidence of comorbidities in PLHIV, especially those older than 50 years. More research is needed in SSA to find out if similar trends may be seen. Considering the expanding ageing population of PLHIV within SSA, it is important to understand the health needs of this population now and in the future, as well as identifying potential drivers of comorbidities that may provide avenues for future interventions. The aim of this thesis was to explore the HIV and comorbidity profiles in a virtual cohort from the healthcare client population accessing care in public facilities in Khayelitsha, Cape Town, South Africa. This virtual cohort refers to the population of healthcare clients with longitudinal data generated from routine administrative health records who were not encountered physically in this study. Their longitudinal data include both retrospective and prospective records.

Routinely collected healthcare data obtained from the Provincial Health Data Centre (PHDC) were analysed to describe ascertained tuberculosis (TB), hypertension, diabetes, chronic kidney disease (CKD), cervical cancer, lung cancer, breast cancer and mental health conditions in this population of healthcare clients, comparing the ascertainment of comorbidities in PLHIV and HIV-negative individuals. These routine health data were analysed to explore kidney function profiles in the context of HIV and other comorbidities for healthcare clients receiving kidney function test results and further assessed the kidney function profiles of PLHIV and HIV-negative healthcare clients with CKD. The risks of comorbidity occurrence in PLHIV and the

contribution of other existing disease conditions to the occurrence of common comorbidities were assessed using routine health data. This analysis included HIV metrics such as duration on ART, viral load and CD4 cell counts of PLHIV.

The findings suggest that accessing HIV care may lead to earlier ascertainment of common chronic non communicable diseases (NCDs) – hypertension, diabetes, CKD and cervical cancer compared to HIV-negative clients. Analysis of routine health data shows that ascertainment of comorbidities differs for healthcare clients due to sub-population differences including age, sex, HIV status and reasons for accessing care. Routine laboratory testing results for kidney function reflect distinct healthcare experiences by age for healthcare clients with and without HIV. Analysis of routine health data for healthcare clients with CKD shows earlier ascertainment and test with better kidney function for PLHIV. Analysis of routine data shows that existing comorbidities may contribute to the incidence of other comorbidities and unsuppressed viral load levels in PLHIV.

From real life routine health data from the general population, this study has explored comorbidities profiles of PLHIV and HIV-negative clients and has demonstrated that routine health data can depict the burden of diseases including multimorbidity and healthcare client demographics and some risk factors in PLHIV and HIV-negative healthcare clients. This study has further shown, using real life data about healthcare access and service utilisation, the overall picture of the health status and comorbidity outcomes for PLHIV and HIV-negative healthcare clients including their gender and age dynamics. The findings of this study show that routine health data could be used for evaluating public health programmes and interventions, and for monitoring treatment guidelines and policy implementation in HIV care and services and NCDs prevention, especially in resource limited settings where monitoring and evaluation options may be limited.

ACKNOWLEDGEMENTS

This PhD work was made possible through funding provided by the Africa Regional International Staff/Student Exchange II (ARISE II): Food Security and Sustainable Human Wellbeing Consortium funded by the Intra-Africa Academic Mobility Scheme of the European Union. I would like to thank the ARISE II Consortium for awarding me a scholarship to pursue this degree.

I wish to express my deepest gratitude to my supervisor, Professor Nicki Tiffin for her guidance, support, and mentorship throughout my PhD journey. I am particularly grateful to her for giving me the opportunity to pursue this degree under her supervision. It has been a wonderful journey of learning, confidence building and perseverance to reach the top.

I acknowledge the Provincial Health Data Centre, Health Impact Assessment Directorate of the Western Cape Government Health Department for providing the anonymised Khayelitsha dataset used for the analyses.

I thank the members of the Health Data Integration Research Group for their support and encouragement.

I thank my siblings, family, and friends for their continuous support and encouragement throughout my studies. A special appreciation to my dear late mother, Madam Christiana Akua Nyamekye whose sacrifices and commitments have culminated into this achievement.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
cART	combined Antiretroviral therapy
CI	Confidence Interval
CIDACS	Center for Data Knowledge and Integration for Health
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Datalink
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CVD	Cardiovascular Disease
dsDNA	double stranded Deoxyribonucleic acid
DTG	Dolutegravir
eCCR	Electronic Continuity of Care Record
eGFR	estimated Glomerular Filtration Rate
EHR	Electronic Health Record
ELISA	Enzyme Linked Immunosorbent Assay
ESRD	End Stage Renal Disease
ETP	Expanded Treatment Programme
FSGS	Focal Segmented Glomerulosclerosis
GBD	Global Burden of Disease
HbA1c	Glycated Haemoglobin
HDL-C	High Density Lipoprotein Cholesterol
HES	Health Episode Statistics
HIV	Human Immunodeficiency Virus
HIVAN	HIV-Associated Nephropathy
HPV	Human Papilloma Virus
HREC	Human Research Ethics Committee

ICD-10	International Classification of Disease-10th edition
IPT	Isoniazid Preventive Therapy
IQR	Interquartile Range
LMICs	Low- and Middle-Income Countries
LPA	Line Probe Assay
MDRD	Modification of Diet in Renal Disease
MSM	Men who have Sex with Men
NCDs	Non-Communicable Diseases
NGO	Non-Governmental Organisation
OR	Odds Ratio
PCR	Polymerase Chain Reaction
PHDC	Provincial Health Data Centre
PLHIV	People Living with HIV
PWID	People who Inject Drugs
SCr	Serum Creatinine
SD	Standard Deviation
SLE	Systemic Lupus Erythematosus
SSA	sub-Saharan Africa
SW	Sex Worker
TB	Tuberculosis
TDF	Tenofovir Disoproxil Fumarate
TEE	Tenofovir disoproxil fumarate-Emtricitabine Efavirenz
TLD	Tenofovir disoproxil fumarate-Lamivudine-Dolutegravir
UTT	Universal Test and Treat
USD	United States Dollar
WADLS	Western Australia Data Linkage System
WCGH	Western Cape Government Health Department
YLD	Years Lived with Disability

LIST OF TABLES

LIST OF FIGURES

THESIS OVERVIEW

This thesis presents an in-depth analysis of comorbidities in the context of HIV burden in a population of patients seeking healthcare in public facilities in Khayelitsha, Cape Town, from 2016 to 2017. The study explores the use of routine health data collected by the Western Cape Government Department of Health (WCGH) during the provision of healthcare, for epidemiological analysis. These routine longitudinal data are collated, linked to individuals and deduplicated by the Provincial Health Data Centre (PHDC), a health information exchange facility that collates administrative health data from public healthcare clients in the Western Cape Province in South Africa.

Chapter 1 presents literature on global and regional HIV epidemiology, ageing with HIV and the emergence of comorbidities in the era of antiretroviral therapy (ART). It explores the use of longitudinal data and data sciences approaches to explore patient comorbidity profiles. It touches on the public health response to emerging HIV comorbidities in South Africa and the possibility of moving from more disease-specific guideline interventions towards a more patient-centered approach in healthcare delivery to improve HIV and comorbidities outcomes. This chapter also presents the overarching aim of the study and the specific objectives and research questions of the various studies conducted.

Chapters 2 to 6 constitute the main body of the research undertaken for this thesis. These chapters include a publication and series of submission-ready manuscripts, and each chapter reflects the content of one manuscript. The chapters are presented as the versions of the manuscripts as would be submitted for peer-review, and therefore follow the required style of the publishing journal or the intended journal where a manuscript is being submitted. Thus, some differences in style can be found between the chapters. Chapter 2 has been published and the full citation with link to the electronic publication is presented at the start of the chapter. Chapters 3 to 6 are ready for submission to the relevant peer-reviewed journals. Supplementary material has been appended where necessary in each chapter.

Chapter 2 describes the demographics of the healthcare client population in this study and the common comorbidities ascertained in this population. This work analyses the median age of

ascertainment of a selection of common comorbidities in people living with HIV (PLHIV) and for HIV-negative healthcare clients. To better understand the relationship between age of ascertainment and the likely screening for common comorbidities, this chapter presents an additional analysis that compares the age of ascertainment of tuberculosis (TB), hypertension, diabetes, chronic kidney disease (CKD), cervical cancer, lung cancer, breast cancer, and mental health conditions in a subset of women accessing maternal care conducted under the assumption that all women accessing maternal care are likely to receive screening for comorbidities such as hypertension, diabetes, and tuberculosis at a younger age regardless of HIV and other health status. In this chapter, the relationship between ascertainment of a variety of conditions assessed in turn as outcomes of interest, and age, sex and the presence of other comorbidities assessed as risk factors, is presented.

In Chapter 2, the relationship between the occurrence of a disease condition as an outcome of interest, and ever having other comorbidities, age and sex status was modelled for healthcare clients with HIV and a variety of comorbidities. In Chapter 3, the order, and timelines of comorbidity occurrence, thus how first having HIV and other selected comorbidities may be associated with the subsequent occurrence of additional comorbidities, was analysed. The longitudinal routine health data used for this study enabled comparisons of the order of disease occurrence and was therefore possible to determine which conditions healthcare clients had at a particular time prior to occurrence of the comorbidity outcome of interest, to model this relationship. Additionally, Chapter 3 describes the timelines for the occurrence of comorbidities in healthcare clients with HIV compared to HIV-negative clients.

In view of the findings of Chapter 2 and Chapter 3 which both showed how HIV and comorbidities associate with the occurrence of other diseases under different circumstances for healthcare clients with HIV and HIV-negative clients, the following study specifically focused on kidney disease as a case study to demonstrate the use of the routine health data for a disease-specific analysis. Kidney function profiles were analysed using routine kidney function tests and results as a proxy for disease severity in healthcare clients with and without HIV. Chapter 4 describes the characteristics of healthcare clients at their first kidney function test as well as the characteristics across all the laboratory tests taken by these individuals. It further explores

the association between kidney function test results, demographics, HIV, and selected comorbidities in this population.

Considering the increasing risks of cardiovascular-related diseases among CKD patients, the known CKD-HIV relationship, and based on the findings of Chapter 4 which broadly focused on all healthcare clients who had kidney function test results, a sub-analysis was conducted for healthcare clients who were ascertained with CKD. Chapter 5 assesses the kidney function profiles in the context of HIV and other comorbidities ascertained prior to or at the time of kidney function assessment in a population of healthcare clients with CKD accessing care in public facilities, and analyses the relationship between kidney function results and sex, age, HIV, and selected comorbidities in this cohort.

As the HIV population in South Africa begins to age due to the successes of ART and following the observed comorbidities profiles in Chapter 2 and Chapter 3, and the kidney function dynamics in Chapter 4 and Chapter 5, it was important to understand how HIV-related characteristics such as duration on ART, CD4 cell count and viral load levels are associated with the occurrence of comorbidities as well as the contribution of these comorbidities, in addition to the HIV-related characteristics, to unsuppressed viral load levels. In Chapter 6, this relationship was assessed using routine health data in a population of PLHIV accessing care in public facilities.

Chapter 7 forms the conclusion of this thesis and summarises the main findings of the studies conducted as part of this thesis, presents the strength and limitation of the study, and discusses the utility of epidemiological studies using routine health data for research, policy, and practice.

CHAPTER 1: BACKGROUND

1.1 Overview

In sub-Saharan Africa (SSA), which is the epicentre of the human immunodeficiency virus (HIV) and the acquired immunodeficiency syndrome (AIDS) pandemic (Nlooto, 2017), the high HIV and AIDS mortality and morbidity posed the most challenging public health problem during the early days of the pandemic (Boulle et al., 2014). South Africa which has the highest burden of HIV in SSA is estimated to have an HIV-positive population of about 8.45 million in 2022 (Statistics South Africa, 2022). Over the decades, South Africa has experienced a health transition described as a quadruple burden of communicable – HIV/AIDS and Tuberculosis (TB), other communicable disease, non-communicable conditions, perinatal and maternal conditions, and injury-related disorders (Kahn, 2011; Mayosi et al., 2009). Over the past decades, HIV/AIDS remained the major leading cause of death in South Africa (Kabudula et al., 2021; Wyk et al., 2016). However, with enhancements in early detection/diagnosis, linkage to treatment, expanded access and success of antiretroviral therapy (ART), and general improvements in quality of life, there has been an increase in life expectancy for people living with HIV (PLHIV) and this population are now ageing (Maciel et al., 2018). Of the global 4.2 million adults aged over 50 years living with HIV, about 2.5 million are in SSA (Mahy et al., 2014). In South Africa, it is predicted that prevalence among individuals aged over 50 years would double from the current 10-15% by 2040 (Mojola et al., 2015; Negin et al., 2012). As more people with HIV live longer, comorbidities and HIV-related conditions including HIV induced inflammations and immunodeficiency from ART use negatively affect mortality rates and life course outcomes (Ruzicka et al., 2018). It is estimated that more than half of all HIV mortalities result from coinfections and age-associated non-infectious comorbidities such as malignancies, diabetes mellitus, hypertension, lipid disorders, and vascular diseases (Ruzicka et al., 2018), rather than specifically from AIDS. This study aimed to explore the profiles of a variety of comorbidities, severity, and risks associated with HIV, as the number of ageing individuals living with HIV begins to increase in South Africa.

1.2 Introduction

In 2004, the South African government responded to the HIV epidemic through its implementation of a nationwide ART programme in public health facilities (Omole et al., 2016; Stinson et al., 2016). Omole et al., report on several studies conducted in peri-urban areas, tertiary facilities, and resource-limited rural areas showing the significant gains in the reduction of HIV and AIDS-associated mortality and morbidity since the introduction of ART in South Africa (Omole et al., 2016). Additionally, Boulle et al. report a rapid decline in mortality among HIV patients with an increased duration on ART in South Africa. This study emphasises that though the rates may not be comparable to developed countries initially, after 4 years on ART, however, they approach the rates observed in high-income countries where HIV is now considered a chronic infection (Boulle et al., 2014). This gradual shift of HIV into an era of an ageing population creates complexity for the management of HIV-related conditions as well as emerging chronic comorbidities. Recent pieces of evidence highlight the incidence of HIV and ART-related chronic comorbidities, such as cancers, metabolic, cardiovascular, and mental health diseases, in addition to traditional opportunistic infections, such as TB, pneumonia, and Kaposi sarcoma co-existing with HIV and AIDS (Maciel et al., 2018; Negin et al., 2012; Nlooto, 2017; Zingmond et al., 2017).

1.3 Epidemiology of HIV and AIDS

1.3.1. Global perspective of HIV and AIDS

In 2021, a global estimate of 38.4 million (33.9 million - 43.8 million) people were living with HIV/AIDS, of which 1.5 million were new infections (UNAIDS - The Joint United Nations Programme on HIV/AIDS, 2022). About 650 000 AIDS-related deaths occurred worldwide in 2021, which was about 68% reduction since the peak in 2004 (1.9 million) and by 52% since 2010 (UNAIDS - The Joint United Nations Programme on HIV/AIDS, 2022). The regional burden of PLHIV ranged from 430 000 for the Eastern Mediterranean to 25.6 million for Africa in 2021 (World Health Organization, 2022).

1.3.2 HIV and AIDS in sub-Saharan Africa

Though SSA carries the highest burden of HIV infection, thus over 70% of the global burden (Kharsany & Karim, 2016; Nlooto, 2017), prevalence varies across countries and regions. Whilst the most severely affected East and Southern Africa collectively recorded 20.6 million PLHIV and 280 000 AIDS-related deaths in 2021, West and Central Africa recorded 5.0 million PLHIV and 140 000 AIDS-related deaths (UNAIDS - The Joint United Nations Programme on HIV/AIDS, 2022). Though the prevalence of HIV has remained steady and/or begun to decline in some countries in SSA, minority subpopulations such as sex workers (SW), men who have sex with men (MSM), people who inject drugs (PWID), and transgender women with disproportionately high HIV prevalence continue to persist and may drive the prevalence and burden of HIV (Jin et al., 2021; Kharsany & Karim, 2016).

1.3.3 Current status of HIV and AIDS in South Africa and achievement of UNAIDS 90-90-90 targets towards the new 95-95-95 target

South Africa through the expanded treatment and prevention (ETP) initiative invested USD 2.3 billion in 2016 and USD 2.9 billion in 2017 from domestic sources to run the largest ART and other HIV interventions programme worldwide (Williams et al., 2017). The rising life expectancies of PLHIV in South Africa (Boulle et al., 2014; Johnson et al., 2016), the decline in the percentage of AIDS-related mortalities from 42.1% in 2004 to 24.2% in 2018 (Statistics South Africa, 2019) and 12.9% in 2022 (Statistics South Africa, 2022) demonstrate the success of the ETP programme and investment.

Reporting the progress towards the UNAIDS targets of achieving a 90% rate of HIV diagnosis, 90% rate of ART coverage, and 90% rate of viral suppression by 2020 was a major challenge for many African countries including South Africa (Kelly & Wilson, 2015). Fractional estimations of HIV-positive individuals who have been diagnosed, as well as those achieving viral suppressions on ART, are still limited in many African countries. This is due to the failure of household surveys to include questions on whether PLHIV knew their status. It is also due to delays in introducing virological monitoring of PLHIV on ART (Johnson et al., 2017).

The “THEMBISA Model” which is a combined demographic and epidemiological model for the South African HIV/AIDS epidemic was used to estimate the progress towards the 90-90-90 targets (Johnson, 2014). Before this, accurate reporting of estimates of fractions of PLHIV who had been diagnosed was demonstrated to be possible through triangulation of HIV testing data from multiple sites (Johnson et al., 2015), and systems for reporting rates of virological suppression had been established (Takuva et al., 2017). It is reported that 85.5% of PLHIV had been diagnosed by mid-2015 (Johnson et al., 2017), leading to the achievement of the first 90% by the end of 2017. Of these individuals, 68% were on ART, of which 78% had achieved viral suppression (AVERT, 2017). Johnson et al., highlight that most provinces in South Africa faced challenges in achieving the remaining two 90% which could be attributed to multiple factors including inability to achieve high levels of ART coverage and viral suppression (Johnson et al., 2017), especially among key minority populations. It is critical to mention that lack of access to general or specialised health care by marginalised and priority populations such as women and adolescent girls, SW, MSM, and PWID who disproportionately suffer a higher burden of HIV, for fear of discrimination and victimisation (Duby et al., 2018; Ranebennur et al., 2014; Scheibe et al., 2016) poses serious threats to curtailing HIV transmission and could impact the ambition and commitment towards fully achieving the new UNAIDS fact track 95-95-95 targets by 2030 (UNAIDS - The Joint United Nations Programme on HIV/AIDS, 2020).

1.4 Ageing with HIV

1.4.1 Emerging comorbidities in the era of ART

Recent studies on the HIV epidemic in South Africa estimate that there will be a remarkable increase of PLHIV aged over 50 years in the next decade due to the wider coverage and success of ART (Hontelez et al., 2011; Johnson et al., 2016; Negin et al., 2012). Significant improvements in life expectancy for PLHIV initiating ART at different ages in South Africa have been reported (Boulle et al., 2014; Burger et al., 2022; Hontelez et al., 2011; Johnson et al., 2013). Johnson et al. report average life expectancies of 27.7 years and 10.1 years for men starting ART at ages 20 and 60 years respectively, whilst women in the same age category have even higher estimates of 36.8 years and 14.1 years respectively (Johnson et al., 2013). Additionally, men and women starting ART in 2014 at age 35 with a CD4 cell count of 200 cells/mm^3 had estimated life

expectancies of 26.7 and 33.4 years respectively (Johnson et al., 2016). This is almost comparable to PLHIV in high-income countries (Boulle et al., 2014; Katz & Maughan-Brown, 2017) who initiate ART with a CD4 cell count of 200 cells/mm^3 and are expected to live to their 70s (Cahill & Valadéz, 2013).

Ageing, regardless of HIV status, has natural consequences on the efficiency of the immune system especially with the production of T cells and T cell functionalities. These effects are worsened by HIV infection (Nguyen & Holodniy, 2008). ART poses certain risks for non-communicable diseases (NCDs) (Mills et al., 2012) such that HIV itself is an independent risk factor for NCDs. Whilst individuals on ART may now experience prolonged life into ages characterized by increased NCDs, this has been described as an "inevitable price of success" (Justice, 2010) considering that many drugs included in the standard regimens potentially increase the risk of NCDs (Valcour et al., 2005; Venkat Narayan et al., 2014).

NCDs and emerging comorbidities among PLHIV at a time of expanded ART coverage remain unsatisfactorily explored in SSA (Negin et al., 2012). The focus has been mainly on traditional HIV and AIDS-related infectious diseases. Recent evidence from developed countries and parts of Asia suggest an increase in multiple HIV and ART-related comorbidities such as coronary artery diseases, hypertension, diabetes, hyperlipidemia, cancers, and neurocognitive disorders especially among persons aged 50 years and over (Ahn et al., 2019; Maciel et al., 2018; Ruzicka et al., 2018; Tedaldi et al., 2015; Wu et al., 2014; Zingmond et al., 2017) who are more likely to develop NCDs. Upsurge in hospital admissions of PLHIV for renal and cardiovascular-related issues in Cape Town and other parts of South Africa (Meintjes et al., 2015; Moodley & Tomita, 2017; Wearne, 2015) and the report of hypertension, congestive cardiac failure, cancer, and diabetes among PLHIV in Zimbabwe (Magodoro et al., 2016) re-emphasise the observation by Maher et al. a decade ago about the presence of chronic comorbidities of African context (Maher et al., 2010). Previous studies investigating HIV comorbidities in South Africa have been based on participants' self-reporting of ever diagnosed of one or more of diabetes, hypertension, arthritis, angina, depression, asthma, stroke, epilepsy, gastric ulcers, renal disorders by a physician or healthcare professional (Negin et al., 2012; Nlooto, 2017; Zungu et al., 2019). A recent single-site retrospective cohort study in Johannesburg comparing outcomes

in older (over 50 years) and younger HIV cohorts indicates that anaemia and liver dysfunction were higher in the younger HIV cohort than the older cohort (Butler et al., 2018). Additionally, hypertension, depression, and risk factors for chronic NCDs (obesity, hyperglycemia, and hyperlipidemia) are reportedly high among HIV-positive individuals in KwaZulu Natal, South Africa (van Heerden et al., 2017).

1.4.2 Demographic trends and socio-economic impacts of HIV/AIDS and comorbidities

Socio-demographics of PLHIV and comorbidities appear similar across geographic areas with minimal variations. In the USA, males aged between 45 and 60 account for the majority of HIV-positive patients with comorbidities on Medicare (Zingmond et al., 2017), similarly, men with a median age of 45 years constitute the highest proportion of PLHIV with at least one comorbidity in Japan (Ruzicka et al., 2018). On the contrary, women constitute the majority of PLHIV reporting comorbidities in South Africa, however, the overall median age is 36-40 years, and most of this population do not have any formal income (Nlooto, 2017). The complexity of managing comorbidities and ART could be economically devastating for poor, unemployed, and low-income earning individuals given the heavy cost involved. Aside from this, the implications of the intangible cost of HIV and related comorbidities are not only suffered by individuals seeking healthcare but the government and sector players alike. For instance, the cost for HIV treatment where patients had at least one comorbidity in California amounted to about USD 47 036 (Zingmond et al., 2017). Mean hospital costs for PLHIV with 1 or ≥2 comorbidities per annum are as much as €4 422 and €9 734 respectively compared to €2 494 for those without comorbidities in the Abruzzo region, Italy (Cammarota et al., 2018). It is estimated that South Africa, in addition to other eight SSA countries with high HIV prevalence, would collectively require USD 98 billion to USD 261 billion for a long-term treatment and management of HIV and related conditions if all PLHIV should be covered by 2050 (Atun et al., 2016).

1.4.3 Common NCDs in the general population in relation to HIV status

Globally, NCDs account for about 41 million deaths each year which is equivalent to 71% of all global mortalities (Bennett et al., 2018). Cardiovascular diseases (CVDs) (17.9 million deaths annually), cancers (9.0 million), respiratory diseases (3.9 million), and diabetes (1.6 million) the top four NCDs that together account for more than 80% of premature NCD-related deaths

(Bennett et al., 2018). There has been an increase in the burden of NCDs in sub-Saharan Africa over the past two decades (Bigna & Noubiap, 2019). This surge is driven by increasing incidence of cardiovascular risk factors such as unhealthy diets, reduced physical activity, hypertension, obesity, diabetes, dyslipidaemia, and air pollution (Bigna & Noubiap, 2019; Manning et al., 2016). Reports show that NCDs are increasing in South Africa and the major NCDs are CVDs, cancer, type 2 diabetes mellitus, respiratory illnesses (such as chronic obstructive pulmonary disease) and mental health disorders (Samodien et al., 2021). It is reported that one in five South Africans above 15 years are managing more than one disease condition (Roomaney et al., 2020). Cardiovascular conditions are the leading category of NCD deaths in South Africa and deaths from renal diseases have been rising (South African Medical Research Council (SAMRC), 2017). In this population, the reported most common multimorbid profiles are combinations of cardiometabolic conditions, cardiometabolic conditions and depression, HIV and anaemia and combinations of mental disorders (Chang et al., 2019). Previous studies have reported high prevalence of hypertension in the general South African population (Kandala et al., 2021; Lynch et al., 2004; Masilela et al., 2020). Obesity, physical activity, and high density lipoprotein cholesterol (HDL-C) and increasing age are among the key risk factors for uncontrolled hypertension (Masilela et al., 2020; Peer et al., 2020). Data from the 2016 South African Demographic Health Survey show that observed prevalence of diabetes was as high as 22% among individuals aged 15 years and above (Grundlingh et al., 2022). Findings from the Global Burden of Disease (GBD) show that the largest increases among leading causes of years lived with disability (YLDs) in South Africa from 1990-2019 were from diabetes, chronic kidney disease (CKD), neonatal disorders and other musculoskeletal disorders (Achoki et al., 2022). A previous study in South Africa has reported that HIV-negative adults above 40 years are more likely to present with hypertension, diabetes, and obesity compared to PLHIV (Gaziano et al., 2017).

1.5 Public health response to emerging HIV comorbidities in South Africa

Evolving healthcare needs of PLHIV have been demonstrated to extend beyond ART and management of traditional communicable co-infections to a more integrated long-term management of chronic comorbidities (Levy et al., 2017; Pantazis et al., 2018; van Heerden et

al., 2017; Wu et al., 2014; Zungu et al., 2019). The Community Health Intervention Programme (CHIPs), the Woolworths Health Promotion Programme, the Soul City Health Promotion Programme, the Promoting Healthy Lifestyles in Khayelitsha Project, the Vuka South Africa: Move For Your Health Initiative of the National Department of Health, the Cancer Association of South Africa, the National Council Against Tobacco, and the Heart and Stroke Foundation of South Africa have been some of the interventions and programmes designed by the South African government and several non-governmental organisations (NGOs) in an attempt to tackle the upsurge of NCDs (Mayosi et al., 2009; Solomons et al., 2017) whilst strengthening HIV programmes. Despite the existence of these interventions, the impacts are yet to be established as NCDs continue to increase. Lack of shared vision and collaboration between programme managers and NGOs, disconnection between programme managers and health-service managers, inadequate review, monitoring and evaluation, as well as lack of multi-sectorial engagement may account for the failures of these programmes and interventions (Mayosi et al., 2009; Solomons et al., 2017). While efforts are progressing in combating TB and other opportunistic infections in South Africa, chronic NCD comorbidities in PLHIV have yet to garner specific attention amidst calls for scaling up primary healthcare to ensure comprehensive HIV care and services (Mayosi et al., 2009; van Heerden et al., 2017; Zungu et al., 2019).

1.5.1 Patient-centered approach to improving HIV and comorbidities: Deviation from disease-specific guidelines and interventions

Patient-centered care recognizes the individual specific health needs and the desired outcomes of healthcare clients, and these become the driving force of healthcare decision making (Catalyst, 2017). Patient-centered care promotes active engagements, collaborations and shared decision-making between patients and service providers to design and manage tailored and comprehensive healthcare plans (Catalyst, 2017). A positive association between patient-centered care and the co-creation of health care plans has been reported. This association includes satisfaction with care and improved physical and mental well-being of patients with multimorbidity in the primary care setting (Kuipers et al., 2019). Despite the importance and benefits of patient-centered care to PLHIV, it is not always prioritised in HIV care in primary

health delivery (Lanzafame & Vento, 2018). Acknowledging the personhood of the patient at every level of clinical care provides an avenue to personalise the patient's care and environment, offer shared decision making (Edvardsson et al., 2008), and foster a more responsive approach to patients' priorities which are central to patient-focused interventions (Boyd & Lucas, 2014). Owing to the evolving nature of HIV infection and evidence that HIV could be the less dominant condition co-existing in PLHIV, there is a need to adopt sustainable patient-centered interventions for the long term needs of PLHIV (Boyd & Lucas, 2014). Poitras et al. identify i) Supporting decision process and evidence-based practice; ii) Providing patient-centered approaches; iii) Supporting patient self-management; iv) Providing case/care management; v) Enhancing interdisciplinary team approach; vi) Developing training for healthcare providers, and vii) Integrating information technology as key steps to be considered to ensure a patient-centered approach for the effective management of chronic multi-morbidities (Poitras et al., 2018). They emphasize that providing patient-oriented approaches, self-management support interventions and developing training for healthcare providers potentially provide effective and positive impacts for the management of chronic diseases (Poitras et al., 2018).

Most public health interventions targeting chronic NCDs in South Africa are implemented under generalised disease guidelines (Solomons et al., 2017; van Heerden et al., 2017), however, most disease-specific guidelines lack recommendations on comprehensive treatment for patients with multiple conditions (Fortin et al., 2011). Healthcare providers may find this complexity confounding, as it is usually difficult to apply multiple interventions and guidelines to a single patient (Poitras et al., 2018).

1.6 Exploring and understanding HIV comorbidity profiles using routine health longitudinal data

The growing complexity of HIV and comorbidity inter-relationship could be a challenge for the suitability of research approaches in exploring this relationship to gain an in-depth understanding. In the past, comorbidities have been explored under cross-sectional approaches and relying on a self-reported diagnosis of diseases which may potentially affect the validity, accuracy as well as reporting of the true snapshot (Ge et al., 2016). These challenges could be

addressed using longitudinal data. The popularity of longitudinal data in research is based on the ability to capture between-individual differences and within-subjects dynamics which allow multiple measurements, observation of time trends to key events and pattern changes, ascertainments of exposures and outcomes, and control of cohort effects. (Ge et al., 2016). However, inherent difficulties such as participants follow-ups and requirement for advanced statistical and analytical skills are common with longitudinal data.

Routine health data collected from patient healthcare access or encounters are enriched with patient demographics, hospital admissions, laboratory information, pharmacy encounters, chronic comorbidity profiles and other patient characteristics; and they are not focused on a specific disease. Though routine health data are not collected for research purposes and may present huge challenges such as errors occurring from assembling large datasets from multiple sources, linking, cleaning, and retrospectively analysing data (Hemkens et al., 2016), they remain very useful for describing disease outcomes and risk factors, and provide great resources for epidemiological studies and research designs. Routine health data are increasingly becoming the mainstream option for generating evidence to support treatment choices, to appraise public health policies and interventions and to inform decision-making (Hemkens et al., 2016). In many low-and middle-income countries (LMICs) where healthcare systems are still developing and resources to conduct randomised controlled trials are limited, the benefits of routine health data could be harnessed to address several key understudied research areas, yet routine health data are largely underused (Hung et al., 2020). The advantages of using routine longitudinal data to explore HIV comorbidities may outweigh the associated cost as longitudinal HIV comorbidities studies ideally report accurate disease profiles and metrics that truly reflect the population (Achwoka et al., 2019; Ahn et al., 2019; Serrão et al., 2019).

1.6.1 Health data exchange and electronic data linkages used for research purposes

Around the world, health data exchange and data linkages have been set up for several purposes including provision of routine data to support research, develop policies, plan services, and evaluate services and government programmes. The UK Clinical Practice Research Datalink (CPRD) (Herrett et al., 2015), the UK Hospital Episodes Statistics (HES) database (Herbert et al., 2017) and the UK Office of National Statistics (ONS) mortality database and

currently the Electronic Health Record (EHR) (Wood et al., 2021) are major population-based electronic health record databases that provide data resources that include linked individual level records from national healthcare settings to enable nationwide research for the English population. Population-wide electronic health records have been used extensively for research in Sweden (Ludvigsson et al., 2016) and Denmark (Siggaard et al., 2020). In 1995, the Western Australian Data Linkage System (WADLS) was established to link up to 40 years of data from over 30 collections for a population of 3.7 million (Holman et al., 2008). The WADLS exchange has expanded and currently provides linked data to enable health and medical research (Data Linkage Western Australia, 2023; Hodges et al., 2019). In 2016, the Center for Data Knowledge and Integration for Health (CIDACS) was set up in Salvador (Bahia, Brazil) with the aim of conducting interdisciplinary studies and research, develop new scientific methodology and promote professional training using linked large-scale databases (Barreto et al., 2019). Commonly, these health data exchange and data linkages generate anonymised and deidentified longitudinal data that enable variety of epidemiological research questions to be answered.

1.6.2 Data science approaches for visualising and presenting routine HIV longitudinal data

Tufte (Tufte, 1983), outlines key characteristics and criteria any graphical display must showcase to achieve excellence, clarity, and precision, especially graphics that communicate statistical and complex ideas. Tufte emphasises that graphic displays must "induce the viewer to think about the substance rather than about the methodology, […], or something else, make large data sets coherent, reveal the data at several levels of detail, from a broad overview, encourage the eye to compare different pieces of data, and be closely integrated with the statistical and verbal descriptions of a data set". In short, graphics must reveal the data (Tufte, 1983). These essential criteria are often difficult to achieve especially with longitudinal data (Commenges et al., 2014). Longitudinal data are frequently explored using growth plots, sequence, point, bar, line, and circle graphs with limited usefulness when applied to some longitudinal data (Holzinger et al., 2014; Tueller et al., 2016). The best approach to summarise large quantitative data such as longitudinal data is obtaining a visual perception of the actual data set through high quality data display (Holzinger et al., 2014). High quality display and

interactive platforms including Forest plots, Circos, TraMineR, SLIDER, and longCatEDA for exploring longitudinal data have been implemented in R software (Commenges et al., 2014; Holzinger et al., 2014; Tueller et al., 2016), however, their applicability to routine HIV comorbidities data is yet to be fully explored.

1.7 Study aim, specific objectives, and research questions

The overarching aim of this study was to explore the HIV/AIDS and comorbidity profiles in a cohort of healthcare clients accessing care in public facilities in the Khayelitsha subdistrict, Western Cape, South Africa. The study explores the use of routine health data collected by the Western Cape Government Department of Health (WCGH) during the provision of health care, for epidemiological analysis. These routine longitudinal data are collated, linked to individuals and deduplicated by the Provincial Health Data Centre (PHDC) (Boulle et al., 2019), and HIV and common comorbidity epidemiology was analysed for an anonymised subset of data from individuals who had care at the facilities in the Khayelitsha subdistrict in 2016 and/or 2017.

The aims of this study are:

<u>Aim 1</u>

To generate a descriptive analysis of the Khayelitsha comorbidities cohort:

Objectives:

- To describe the demographics of the cohort
- To analyse the prevalence and distribution of HIV by age and sex in this cohort
- To describe the prevalence of common comorbidities – TB, hypertension, diabetes, chronic obstructive pulmonary disease (COPD)/Asthma, CKD, cervical cancer, breast cancer, lung cancer and mental health in this cohort

<u>Aim 2</u>

To better understand the order of the incidence of comorbidities – TB, hypertension, diabetes, CKD, and cervical cancer among HIV-positive and HIV-negative individuals:

Objectives:

- To analyse and compare age of comorbidity incidence in HIV-positive and HIV-negative individuals, including order of comorbidity ascertainment

Aim 3

To use routine health data to estimate disease severity for selected comorbidities - TB, hypertension, diabetes, CKD, and cervical cancer among the HIV-positive and HIV-negative individuals:

Objectives:

- To describe the characteristics of healthcare clients at their first kidney function test and across all tests taken by individuals in this cohort
- To describe comorbidity profiles and test results for HIV-positive and HIV-negative individuals receiving kidney function test
- To analyse the association between kidney function test results, demographics, and comorbidities in this population

Aim 4

To understand kidney function profiles for HIV-positive and HIV-negative individuals with chronic kidney disease (CKD)

Objectives:

- To describe the demographics of this cohort
- To describe the kidney function test results for HIV-positive and HIV-negative individuals with CKD
- To analyse the relationship between kidney function test results and age, sex and having a comorbidity - TB, hypertension, diabetes, CKD, and cervical cancer at the time of kidney function testing

Aim 5

To use routine health data to describe the relationship between the occurrence of selected comorbidities - TB, hypertension, diabetes, CKD, and cervical cancer in HIV-positive individuals and the existence of other comorbidities and HIV-related characteristics:

Objectives:

- To describe the occurrence and nature of selected comorbidities in the HIV-positive population.
- To analyse the associations between selected comorbidity ascertainment as outcomes and risk factors: sex, age at study end, comorbidities ascertained after HIV diagnosis and HIV-related characteristics.
- To describe the contribution of comorbidities ascertained after HIV diagnosis and HIV-related characteristics to unsuppressed viral load levels.

A flowchart showing the structure of the thesis is shown in Figure 1.1

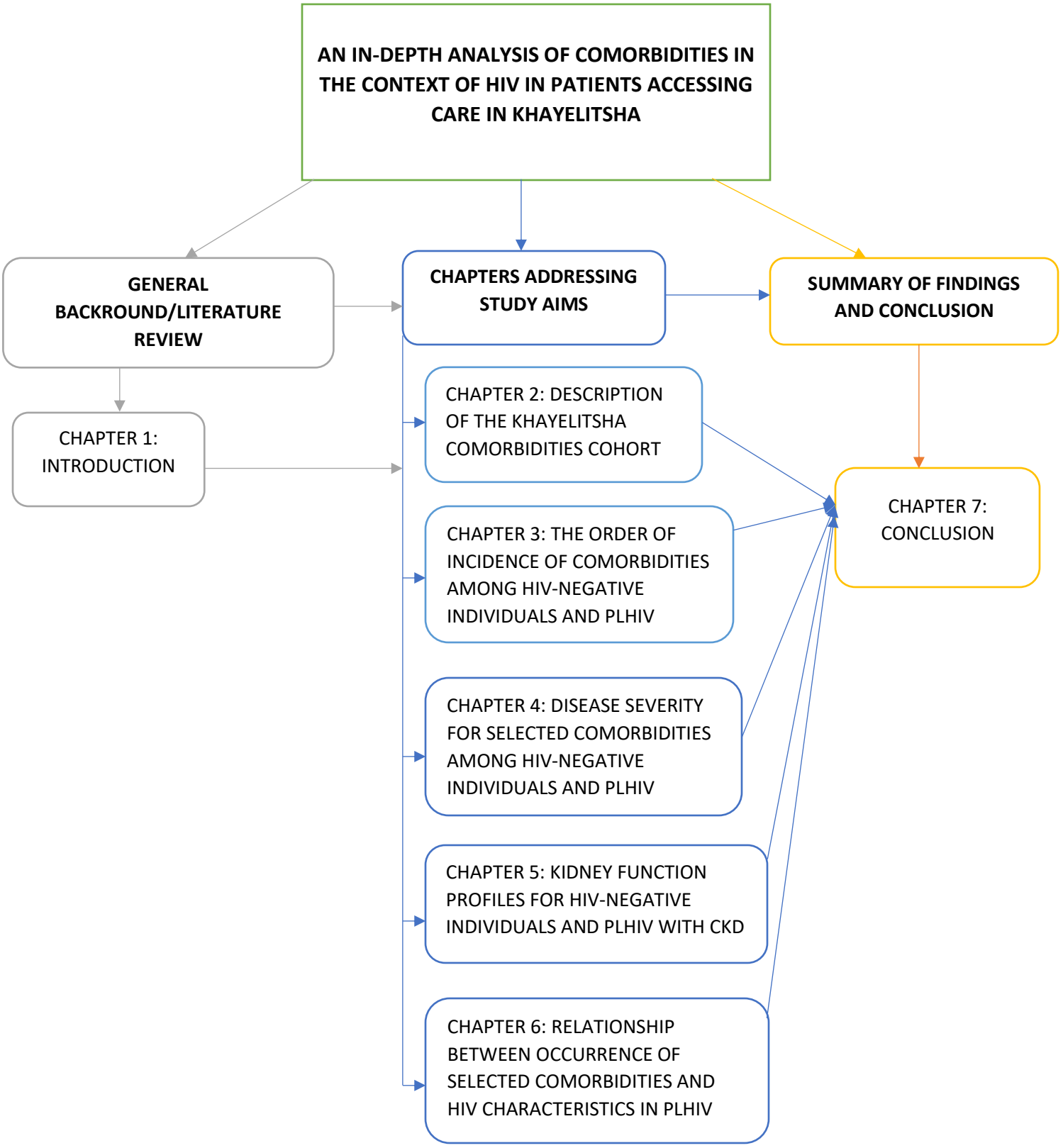


Figure 1.1: Outline of the chapters of the thesis

1.8 References

Achoki, T., Sartorius, B., Watkins, D., Glenn, S. D., Kengne, A. P., Oni, T., Wiysonge, C. S., Walker, A., Adetokunboh, O. O., Babalola, T. K., Bolarinwa, O. A., Claassens, M. M., Cowden, R. G., Day, C. T., Ezekannagha, O., Ginindza, T. G., Iwu, C. C. D., Iwu, C. J., Karangwa, I., … Naghavi, M. (2022). Health trends, inequalities and opportunities in South Africa's provinces, 1990–2019: Findings from the Global Burden of Disease 2019 Study. *J Epidemiol Community Health*, *76*(5), 471–481. https://doi.org/10.1136/jech-2021-217480

Achwoka, D., Waruru, A., Chen, T.-H., Masamaro, K., Ngugi, E., Kimani, M., Mukui, I., Oyugi, J. O., Mutave, R., Achia, T., Katana, A., Ng'ang'a, L., & De Cock, K. M. (2019). Noncommunicable disease burden among HIV patients in care: A national retrospective longitudinal analysis of HIV-treatment outcomes in Kenya, 2003-2013. *BMC Public Health*, *19*(1), 372. https://doi.org/10.1186/s12889-019-6716-2

Ahn, M. Y., Jiamsakul, A., Khusuwan, S., Khol, V., Pham, T. T., Chaiwarith, R., Avihingsanon, A., Kumarasamy, N., Wong, W. W., Kiertiburanakul, S., Pujari, S., Nguyen, K. V., Lee, M. P., Kamarulzaman, A., Zhang, F., Ditangco, R., Merati, T. P., Yunihastuti, E., Ng, O. T., … Choi, J. Y. (2019). The influence of age-associated comorbidities on responses to combination antiretroviral therapy in older people living with HIV. *Journal of the International AIDS Society*, *22*(2). https://doi.org/10.1002/jia2.25228

Atun, R., Chang, A. Y., Ogbuoji, O., Silva, S., Resch, S., Hontelez, J., & Bärnighausen, T. (2016). Long-term financing needs for HIV control in sub-Saharan Africa in 2015–2050: A modelling study. *BMJ Open*, *6*(3), e009656. https://doi.org/10.1136/bmjopen-2015-009656

AVERT. (2017). *Global HIV and AIDS statistics | AVERT*. https://www.avert.org/global-hiv-and-aids-statistics

Barreto, M. L., Rodrigues, L., Denaxas, S., Barbosa, G., Ali, M. S., Barral-Netto, M., Penna, G., Pita, R., Teles, C., Carreiro, R. P., Fiaccone, R., Cabral, L., Barreto, M. E., Almeida, B. de A., Ichihara, M. Y., & Smeeth, L. (2019). The Center for Data and Knowledge Integration for Health (CIDACS): An Experience of Linking Health and Social Data in Brazil. *International Journal of Population Data Science*, *4*(2), Article 2. https://doi.org/10.23889/ijpds.v4i2.1140

Bennett, J. E., Stevens, G. A., Mathers, C. D., Bonita, R., Rehm, J., Kruk, M. E., Riley, L. M., Dain, K., Kengne, A. P., Chalkidou, K., Beagley, J., Kishore, S. P., Chen, W., Saxena, S., Bettcher, D. W., Grove, J. T., Beaglehole, R., & Ezzati, M. (2018). NCD Countdown 2030: Worldwide trends in non-communicable disease mortality and progress towards Sustainable Development Goal target 3.4. *The Lancet*, *392*(10152), 1072–1088. https://doi.org/10.1016/S0140-6736(18)31992-5

Bigna, J. J., & Noubiap, J. J. (2019). The rising burden of non-communicable diseases in sub-Saharan Africa. *The Lancet Global Health*, *7*(10), e1295–e1296. https://doi.org/10.1016/S2214-109X(19)30370-5

Boulle, A., Heekes, A., Tiffin, N., Smith, M., Mutemaringa, T., Zinyakatira, N., Phelanyane, F., Pienaar, C., Buddiga, K., Coetzee, E., Rooyen, R. van, Dyers, R., Fredericks, N., Loff, A., Shand, L., Moodley, M., Vega, I. de, & Vallabhjee, K. (2019). Data Centre Profile: The Provincial Health Data Centre of the Western Cape Province, South Africa. *International Journal of Population Data Science*, *4*(2), Article 2. https://doi.org/10.23889/ijpds.v4i2.1143

Boulle, A., Schomaker, M., May, M. T., Hogg, R. S., Shepherd, B. E., Monge, S., Keiser, O., Lampe, F. C., Giddy, J., Ndirangu, J., Garone, D., Fox, M., Ingle, S. M., Reiss, P., Dabis, F., Costagliola, D., Castagna, A., Ehren, K., Campbell, C., … Sterne, J. A. C. (2014). Mortality in Patients with HIV-1 Infection Starting Antiretroviral Therapy in South Africa, Europe, or North America: A Collaborative Analysis of Prospective Studies. *PLOS Medicine*, *11*(9), e1001718. https://doi.org/10.1371/journal.pmed.1001718

Boyd, C. M., & Lucas, G. M. (2014). Patient-centered care for people living with multimorbidity. *Current Opinion in HIV and AIDS*, *9*(4), 419–427. https://doi.org/10.1097/COH.0000000000000073

Burger, C., Burger, R., & van Doorslaer, E. (2022). The health impact of free access to antiretroviral therapy in South Africa. *Social Science & Medicine*, *299*, 114832. https://doi.org/10.1016/j.socscimed.2022.114832

Butler, I., MacLeod, W., Majuba, P. P., & Tipping, B. (2018). Human immunodeficiency virus infection and older adults: A retrospective single-site cohort study from Johannesburg, South Africa. *Southern African Journal of HIV Medicine*, *19*(1), 8. https://doi.org/10.4102/sajhivmed.v19i1.838

Cahill, S., & Valadéz, R. (2013). Growing Older With HIV/AIDS: New Public Health Challenges. *American Journal of Public Health*, *103*(3), e7–e15. https://doi.org/10.2105/AJPH.2012.301161

Cammarota, S., Citarella, A., Manzoli, L., Flacco, M. E., & Parruti, G. (2018). Impact of comorbidity on the risk and cost of hospitalization in HIV-infected patients: Real-world data from Abruzzo Region. *ClinicoEconomics and Outcomes Research*. https://doi.org/10.2147/CEOR.S162625

Catalyst, N. (2017). What Is Patient-Centered Care? *NEJM Catalyst*. https://catalyst.nejm.org/doi/full/10.1056/CAT.17.0559

Chang, A. Y., Gómez-Olivé, F. X., Payne, C., Rohr, J. K., Manne-Goehler, J., Wade, A. N., Wagner, R. G., Montana, L., Tollman, S., & Salomon, J. A. (2019). Chronic multimorbidity among older adults in rural South Africa. *BMJ Global Health*, *4*(4), e001386. https://doi.org/10.1136/bmjgh-2018-001386

Commenges, H., Pistre, P., & Cura, R. (2014). SLIDER: Software for LongItudinal Data Exploration with R. *Cybergeo : European Journal of Geography*, 10p. https://doi.org/10.4000/cybergeo.26530

Data Linkage Western Australia. (2023). *Enabling Health & Medical Research in Western Australia*. Data Linkage WA. https://www.datalinkage-wa.org.au/

Duby, Z., Nkosi, B., Scheibe, A., Brown, B., & Bekker, L.-G. (2018). 'Scared of going to the clinic': Contextualising healthcare access for men who have sex with men, female sex workers and people who use drugs in two South African cities. *Southern African Journal of HIV Medicine*, *19*(1), 8. https://doi.org/10.4102/sajhivmed.v19i1.701

Edvardsson, D., Winblad, B., & Sandman, P. (2008). Person-centred care of people with severe Alzheimer's disease: Current status and ways forward. *The Lancet Neurology*, *7*(4), 362–367. https://doi.org/10.1016/S1474-4422(08)70063-2

Fortin, M., Contant, E., Savard, C., Hudon, C., Poitras, M.-E., & Almirall, J. (2011). Canadian guidelines for clinical practice: An analysis of their quality and relevance to the care of adults with comorbidity. *BMC Family Practice*, *12*(1), 74. https://doi.org/10.1186/1471-2296-12-74

Gaziano, T. A., Abrahams-Gessel, S., Gomez-Olive, F. X., Wade, A., Crowther, N. J., Alam, S., Manne-Goehler, J., Kabudula, C. W., Wagner, R., Rohr, J., Montana, L., Kahn, K., Bärnighausen, T. W., Berkman, L. F., & Tollman, S. (2017). Cardiometabolic risk in a population of older adults with multiple co-morbidities in rural south africa: The HAALSI (Health and Aging in Africa: longitudinal studies of INDEPTH communities) study. *BMC Public Health*, *17*(1), 206. https://doi.org/10.1186/s12889-017-4117-y

Ge, L., Tu, J. X., Zhang, H., Wang, H., He, H., & Gunzler, D. (2016). *Modern methods for longitudinal data analysis, capabilities, caveats and cautions*. *28*(5), 8.

Grundlingh, N., Zewotir, T. T., Roberts, D. J., & Manda, S. (2022). Assessment of prevalence and risk factors of diabetes and pre-diabetes in South Africa. *Journal of Health, Population and Nutrition*, *41*(1), 7. https://doi.org/10.1186/s41043-022-00281-2

Hemkens, L. G., Contopoulos-Ioannidis, D. G., & Ioannidis, J. P. A. (2016). Routinely collected data and comparative effectiveness evidence: Promises and limitations. *CMAJ : Canadian Medical Association Journal*, *188*(8), E158–E164. https://doi.org/10.1503/cmaj.150653

Herbert, A., Wijlaars, L., Zylbersztejn, A., Cromwell, D., & Hardelid, P. (2017). Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC). *International Journal of Epidemiology*, *46*(4), 1093–1093i. https://doi.org/10.1093/ije/dyx015

Herrett, E., Gallagher, A. M., Bhaskaran, K., Forbes, H., Mathur, R., van Staa, T., & Smeeth, L. (2015). Data Resource Profile: Clinical Practice Research Datalink (CPRD). *International Journal of Epidemiology*, *44*(3), 827–836. https://doi.org/10.1093/ije/dyv098

Hodges, S., Eitelhuber, T., Merchant, A., & Alan, J. (2019). Population Data Centre Profile—The Western Australian Data Linkage Branch. *International Journal of Population Data Science*, *4*(2), Article 2. https://doi.org/10.23889/ijpds.v4i2.1138

Holman, C. D. J., Bass, J. A., Rosman, D. L., Smith, M. B., Semmens, J. B., Glasson, E. J., Brook, E. L., Trutwein, B., Rouse, I. L., Watson, C. R., Klerk, N. H. de, & Stanley, F. J. (2008). A decade of data linkage in Western Australia: Strategic design, applications and benefits of the WA data linkage system. *Australian Health Review*, *32*(4), 766–777. https://doi.org/10.1071/ah080766

Holzinger, A., Schwarz, M., Ofner, B., Jeanquartier, F., Calero-Valdez, A., Roecker, C., & Ziefle, M. (2014). Towards Interactive Visualization of Longitudinal Data to Support Knowledge Discovery on Multi-touch Tablet Computers. In C. Salinesi, M. C. Norrie, & Ó. Pastor (Eds.), *Advanced Information Systems Engineering* (Vol. 7908, pp. 124–137). Springer Berlin Heidelberg. https://doi.org/10.1007/978-3-319-10975-6_9

Hontelez, J. A., Lurie, M. N., Newell, M.-L., Bakker, R., Tanser, F., Bärnighausen, T., Baltussen, R., & de Vlas, S. J. (2011). Ageing with HIV in South Africa. *AIDS (London, England)*, *25*(13). https://doi.org/10.1097/QAD.0b013e32834982ea

Hung, Y. W., Hoxha, K., Irwin, B. R., Law, M. R., & Grépin, K. A. (2020). Using routine health information data for research in low- and middle-income countries: A systematic review. *BMC Health Services Research*, *20*(1), 790. https://doi.org/10.1186/s12913-020-05660-1

Jin, H., Restar, A., & Beyrer, C. (2021). Overview of the epidemiological conditions of HIV among key populations in Africa. *Journal of the International AIDS Society*, *24*(Suppl 3), e25716. https://doi.org/10.1002/jia2.25716

Johnson, L. F. (2014). *THEMBISA version 1.0: A model for evaluating the impact of HIV/AIDS in South Africa; Centre for Infectious Disease Epidemiology and Research, University of Cape Town*. https://www.thembisa.org/content/downloadPage/WPversion1

Johnson, L. F., Dorrington, R. E., & Moolla, H. (2017). Progress towards the 2020 targets for HIV diagnosis and antiretroviral treatment in South Africa. *Southern African Journal of HIV Medicine*, *18*(1), 8. https://doi.org/10.4102/sajhivmed.v18i1.694

Johnson, L. F., Keiser, O., Fox, M. P., Tanser, F., Cornell, M., Hoffmann, C. J., Prozesky, H., Boulle, A., & Davies, M.-A. (2016). Life expectancy trends in adults on antiretroviral treatment in South Africa. *AIDS (London, England)*, *30*(16), 2545–2550. https://doi.org/10.1097/QAD.0000000000001197

Johnson, L. F., Mossong, J., Dorrington, R. E., Schomaker, M., Hoffmann, C. J., Keiser, O., Fox, M. P., Wood, R., Prozesky, H., Giddy, J., Garone, D. B., Cornell, M., Egger, M., Boulle, A., & Collaboration, for the I. E. D. to E. A. S. A. (IeDEA-S. (2013). Life Expectancies of South African Adults Starting Antiretroviral Treatment: Collaborative Analysis of Cohort Studies. *PLOS Medicine*, *10*(4), e1001418. https://doi.org/10.1371/journal.pmed.1001418

Johnson, L. F., Rehle, T., Jooste, S., & Bekker, L.-G. (2015). Rates of HIV testing and diagnosis in South Africa: Successes and challenges. *Aids*, *29*(11), 1401–1409. https://doi.org/10.1097/QAD.0000000000000721

Justice, A. C. (2010). HIV and aging: Time for a new paradigm. *Current HIV/AIDS Reports*, *7*(2), 69–76. https://doi.org/10.1007/s11904-010-0041-9

Kabudula, C. W., Houle, B., Ohene-Kwofie, D., Mahlangu, D., Ng, N., Van Minh, H., Gómez-Olivé, F. X., Tollman, S., & Kahn, K. (2021). Mortality transition over a quarter century in rural South Africa: Findings from population surveillance in Agincourt 1993-2018. *Global Health Action*, *14*(sup1), 1990507. https://doi.org/10.1080/16549716.2021.1990507

Kahn, K. (2011). Population health in South Africa: Dynamics over the past two decades. *Journal of Public Health Policy*, *32*(1), S30–S36. https://doi.org/10.1057/jphp.2011.27

Kandala, N.-B., Nnanatu, C. C., Dukhi, N., Sewpaul, R., Davids, A., & Reddy, S. P. (2021). Mapping the Burden of Hypertension in South Africa: A Comparative Analysis of the National 2012 SANHANES and the 2016 Demographic and Health Survey. *International Journal of Environmental Research and Public Health*, *18*(10), 5445. https://doi.org/10.3390/ijerph18105445

Katz, I. T., & Maughan-Brown, B. (2017). Improved life expectancy of people living with HIV: Who is left behind? *The Lancet HIV*, *4*(8), e324–e326. https://doi.org/10.1016/S2352-3018(17)30086-3

Kelly, S., & Wilson, D. (2015). HIV Cascade Monitoring and Simple Modeling Reveal Potential for Reductions in HIV Incidence. *Jaids Journal of Acquired Immune Deficiency Syndromes*, *69*(3), 257–263. https://doi.org/10.1097/QAI.0000000000000655

Kharsany, A. B. M., & Karim, Q. A. (2016). HIV Infection and AIDS in Sub-Saharan Africa: Current Status, Challenges and Opportunities. *The Open AIDS Journal*, *10*, 34–48. https://doi.org/10.2174/1874613601610010034

Kuipers, S. J., Cramm, J. M., & Nieboer, A. P. (2019). The importance of patient-centered care and co-creation of care for satisfaction with care and physical and social well-being of patients with multi-morbidity in the primary care setting. *BMC Health Services Research*, *19*(1), 13. https://doi.org/10.1186/s12913-018-3818-y

Lanzafame, M., & Vento, S. (2018). Patient-centered Care and Treatment in HIV Infection. *EClinicalMedicine*, *6*, 5–6. https://doi.org/10.1016/j.eclinm.2019.01.001

Levy, M., Greenberg, A., Hart, R., Happ, L. P., Hadigan, C., & Castel, A. (2017). High Burden of Metabolic Comorbidities in a Citywide Cohort of HIV Outpatients: Evolving Health Care Needs of People Aging with HIV in Washington, DC. *HIV Medicine*, *18*(10), 724–735. https://doi.org/10.1111/hiv.12516

Ludvigsson, J. F., Almqvist, C., Bonamy, A.-K. E., Ljung, R., Michaëlsson, K., Neovius, M., Stephansson, O., & Ye, W. (2016). Registers of the Swedish total population and their

use in medical research. *European Journal of Epidemiology*, *31*(2), 125–136. https://doi.org/10.1007/s10654-016-0117-y

Lynch, J., Smith, G. D., Harper, S., Hillemeier, M., Ross, N., Kaplan, G. A., & Wolfson, M. (2004). Is Income Inequality a Determinant of Population Health? Part 1. A Systematic Review. *The Milbank Quarterly*, *82*(1), 5–99. https://doi.org/10.1111/j.0887-378X.2004.00302.x

Maciel, R. A., Klück, H. M., Durand, M., & Sprinz, E. (2018). Comorbidity is more common and occurs earlier in persons living with HIV than in HIV-uninfected matched controls, aged 50 years and older: A cross-sectional study. *International Journal of Infectious Diseases*, *70*, 30–35. https://doi.org/10.1016/j.ijid.2018.02.009

Magodoro, I. M., Esterhuizen, T. M., & Chivese, T. (2016). A cross-sectional, facility based study of comorbid non-communicable diseases among adults living with HIV infection in Zimbabwe. *BMC Research Notes*, *9*(376). https://doi.org/10.1186/s13104-016-2187-z

Maher, D., Sekajugo, J., Harries, A. D., & Grosskurth, H. (2010). Research needs for an improved primary care response to chronic non-communicable diseases in Africa. *Tropical Medicine & International Health*, *15*(2), 176–181. https://doi.org/10.1111/j.1365-3156.2009.02438.x

Mahy, M., Autenrieth, C. S., Stanecki, K., & Wynd, S. (2014). Increasing trends in HIV prevalence among people aged 50 years and older: Evidence from estimates and survey data. *AIDS*, *28*, S453–S459. https://doi.org/10.1097/QAD.0000000000000479

Manning, K., Senekal, M., & Harbron, J. (2016). Non-communicable disease risk factors and treatment preference of obese patients in Cape Town. *African Journal of Primary Health Care & Family Medicine*, *8*(1), Article 1. https://doi.org/10.4102/phcfm.v8i1.913

Masilela, C., Pearce, B., Ongole, J. J., Adeniyi, O. V., & Benjeddou, M. (2020). Cross-sectional study of prevalence and determinants of uncontrolled hypertension among South African adult residents of Mkhondo municipality. *BMC Public Health*, *20*(1), 1069. https://doi.org/10.1186/s12889-020-09174-7

Mayosi, B. M., Flisher, A. J., Lalloo, U. G., Sitas, F., Tollman, S. M., & Bradshaw, D. (2009). The burden of non-communicable diseases in South Africa. *The Lancet*, *374*(9693), 934–947. https://doi.org/10.1016/S0140-6736(09)61087-4

Meintjes, G., Kerkhoff, A. D., Burton, R., Schutz, C., Boulle, A., Van Wyk, G., Blumenthal, L., Nicol, M. P., & Lawn, S. D. (2015). HIV-Related Medical Admissions to a South African District Hospital Remain Frequent Despite Effective Antiretroviral Therapy Scale-Up. *Medicine*, *94*(50). https://doi.org/10.1097/MD.0000000000002269

Mills, E. J., Bärnighausen, T., & Negin, J. (2012). HIV and Aging—Preparing for the Challenges Ahead. *New England Journal of Medicine*, *366*(14), 1270–1273. https://doi.org/10.1056/NEJMp1113643

Mojola, S. A., Williams, J., Angotti, N., & Gómez-Olivé, F. X. (2015). HIV after 40 in rural South Africa: A life course approach to HIV vulnerability among middle aged and older adults.

Social Science & Medicine, *143*, 204–212. https://doi.org/10.1016/j.socscimed.2015.08.023

Moodley, Y., & Tomita, A. (2017). Relationship between HIV serostatus, CD4 count and rehospitalisation: Potential implications for health systems strengthening in South Africa. *Southern African Journal of Infectious Diseases*, *32*(1), 23–28. https://doi.org/10.1080/22201181.2016.1201935

Negin, J., Martiniuk, A., Cumming, R. G., Naidoo, N., Phaswana-Mafuya, N., Madurai, L., Williams, S., & Kowal, P. (2012). Prevalence of HIV and chronic comorbidities among older adults: *AIDS*, *26*(Suppl 1), S55–S63. https://doi.org/10.1097/QAD.0b013e3283558459

Nguyen, N., & Holodniy, M. (2008). HIV infection in the elderly. *Clinical Interventions in Aging*, *3*(3), 453–472.

Nlooto, M. (2017). Comorbidities of HIV infection and health care seeking behavior among HIV infected patients attending public sector healthcare facilities in KwaZulu-Natal: A cross sectional study. *PLOS ONE*, *12*(2), e0170983. https://doi.org/10.1371/journal.pone.0170983

Omole, O. B., Semenya, M.-A. M. L., & Omole, O. (2016). Treatment outcomes in a rural HIV clinic in South Africa: Implications for health care. *Southern African Journal of HIV Medicine*, *17*(1), 1–6. http://dx. doi.org/10.4102/sajhivmed. v17i1.414

Pantazis, N., Chini, M., Antoniadou, A., Sambatakou, H., Skoutelis, A., Gargalianos, P., Kourkounti, S., Gogos, C., Chrysos, G., Psichogiou, M., Sipsas, N. V., Katsarou, O., Panagopoulos, P., Metallidis, S., & Touloumi, G. (2018). The HIV patient profile in 2013 and 2003: Results from the Greek AMACS cohort. *PLoS ONE*, *13*(9). https://doi.org/10.1371/journal.pone.0203601

Peer, N., George, J., Lombard, C., Steyn, K., Levitt, N., & Kengne, A.-P. (2020). Prevalence, concordance and associations of chronic kidney disease by five estimators in South Africa. *BMC Nephrology*, *21*(1), 372. https://doi.org/10.1186/s12882-020-02018-x

Poitras, M.-E., Maltais, M.-E., Bestard-Denommé, L., Stewart, M., & Fortin, M. (2018). What are the effective elements in patient-centered and multimorbidity care? A scoping review. *BMC Health Services Research*, *18*(1), 446. https://doi.org/10.1186/s12913-018-3213-8

Ranebennur, V., Gaikwad, S., Ramesh, S., & Bhende, A. (2014). Addressing vulnerabilities of female sex workers in an HIV prevention intervention in Mumbai and Thane: Experiences from the Aastha project. *HIV/AIDS (Auckland, N.Z.)*, *6*, 9–18. https://doi.org/10.2147/HIV.S54062

Roomaney, R. A., Wyk, B. van, Turawa, E. B., & Wyk, V. P. (2020). Prevalence of multimorbidity in South Africa: A systematic review protocol. *BMJ Open*, *10*(12), e042889. https://doi.org/10.1136/bmjopen-2020-042889

Ruzicka, D. J., Imai, K., Takahashi, K., & Naito, T. (2018). Comorbidities and the use of comedications in people living with HIV on antiretroviral therapy in Japan: A cross-sectional study using a hospital claims database. *BMJ Open*, *8*(6), e019985. https://doi.org/10.1136/bmjopen-2017-019985

Samodien, E., Abrahams, Y., Muller, C., Louw, J., & Chellan, N. (2021). Non-communicable diseases – a catastrophe for South Africa. *South African Journal of Science*, *117*(5/6). https://doi.org/10.17159/sajs.2021/8638

Scheibe, A., Makapela, D., Brown, B., dos Santos, M., Hariga, F., Virk, H., Bekker, L.-G., Lyan, O., Fee, N., Molnar, M., Bocai, A., Eligh, J., & Lehtovuori, R. (2016). HIV prevalence and risk among people who inject drugs in five South African cities. *International Journal of Drug Policy*, *30*, 107–115. https://doi.org/10.1016/j.drugpo.2016.01.004

Serrão, R., Piñero, C., Velez, J., Coutinho, D., Maltez, F., Lino, S., Sarmento e Castro, R., Tavares, A. P., Pacheco, P., Lopes, M. J., Mansinho, K., Miranda, A. C., Neves, I., Correia de Abreu, R., Almeida, J., & Pássaro, L. (2019). Non-AIDS-related comorbidities in people living with HIV-1 aged 50 years and older: The AGING POSITIVE study. *International Journal of Infectious Diseases*, *79*, 94–100. https://doi.org/10.1016/j.ijid.2018.10.011

Siggaard, T., Reguant, R., Jørgensen, I. F., Haue, A. D., Lademann, M., Aguayo-Orozco, A., Hjaltelin, J. X., Jensen, A. B., Banasik, K., & Brunak, S. (2020). Disease trajectory browser for exploring temporal, population-wide disease progression patterns in 7.2 million Danish patients. *Nature Communications*, *11*(1), Article 1. https://doi.org/10.1038/s41467-020-18682-4

Solomons, N., Kruger, H. S., & Puoane, T. R. (2017). Adherence challenges encountered in an intervention programme to combat chronic non-communicable diseases in an urban black community, Cape Town. *Health SA Gesondheid*, *22*, 70–78. https://doi.org/10.1016/j.hsag.2016.11.006

South African Medical Research Council (SAMRC). (2017). *National Burden of Disease Study: SA Medical Research Council briefing*. https://pmg.org.za/committee-meeting/24112/

Statistics South Africa. (2019). *Mid-year population estimates* (No. P0302; pp. 1–30). https://www.statssa.gov.za/publications/P0302/P03022019.pdf

Statistics South Africa. (2022). *Mid-year population estimates for 2022* (No. P03022022; pp. 1–50). https://www.statssa.gov.za/publications/P0302/P03022022.pdf

Stinson, K., Goemaere, E., Coetzee, D., van Cutsem, G., Hilderbrand, K., Osler, M., Hennessey, C., Wilkinson, L., Patten, G., Cragg, C., Mathee, S., Cox, V., & Boulle, A. (2016). Cohort Profile: The Khayelitsha antiretroviral programme, Cape Town, South Africa. *International Journal of Epidemiology*, dyw057. https://doi.org/10.1093/ije/dyw057

Takuva, S., Brown, A. E., Pillay, Y., Delpech, V., & Puren, A. J. (2017). The continuum of HIV care in South Africa: Implications for achieving the second and third UNAIDS 90-90-90 targets. *AIDS*, *31*(4), 545. https://doi.org/10.1097/QAD.0000000000001340

Tedaldi, E. M., Minniti, N. L., & Fischer, T. (2015). HIV-Associated Neurocognitive Disorders: The Relationship of HIV Infection with Physical and Social Comorbidities. *BioMed Research International*, *2015*. https://doi.org/10.1155/2015/641913

Tueller, S. J., Van Dorn, R. A., & Bobashev, G. V. (2016). Visualization of Categorical Longitudinal and Times Series Data. *Methods Report (RTI Press)*, *2016*, 1–22. https://doi.org/10.3768/rtipress.2016.mr.0033.1602

Tufte, E. R. (1983). *The Visual Display of Quantitative Information* (Second Edition). Graphic Press.

UNAIDS - The Joint United Nations Programme on HIV/AIDS. (2020). *Understanding fast-track: Accelerating action to end the AIDS epidemic by 2030* (pp. 1–12). https://www.unaids.org/sites/default/files/media_asset/201506_JC2743_Understanding_FastTrack_en.pdf

UNAIDS - The Joint United Nations Programme on HIV/AIDS. (2022). *Global HIV & AIDS statistics—Fact sheet* (pp. 1–6). https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf

Valcour, V. G., Shikuma, C. M., Shiramizu, B. T., Williams, A. E., Watters, M. R., Poff, P. W., Grove, J. S., Selnes, O. A., & Sacktor, N. C. (2005). Diabetes, Insulin Resistance, and Dementia Among HIV-1–Infected Patients. *Journal of Acquired Immune Deficiency Syndromes (1999)*, *38*(1), 31–36.

van Heerden, A., Barnabas, R. V., Norris, S. A., Micklesfield, L. K., van Rooyen, H., & Celum, C. (2017). High prevalence of HIV and non-communicable disease (NCD) risk factors in rural KwaZulu-Natal, South Africa. *Journal of the International AIDS Society*, *20*(2). https://doi.org/10.1002/jia2.25012

Venkat Narayan, K. M., Miotti, P. G., Anand, N. P., Kline, L. M., Harmston, C., Gulakowski, R. I., & Vermund, S. H. (2014). HIV and Noncommunicable Disease Comorbidities in the Era of Antiretroviral Therapy: A Vital Agenda for Research in Low- and Middle-Income Country Settings. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *67*, S2. https://doi.org/10.1097/QAI.0000000000000267

Wearne, N. (2015). Morbidity and mortality of black HIV-positive patients with end-stage kidney disease receiving chronic haemodialysis in South Africa. *South African Medical Journal*, *105*(2), 105-106–106. https://doi.org/10.7196/SAMJ.9068

Williams, B. G., Gupta, S., Wollmers, M., & Granich, R. (2017). Progress and prospects for the control of HIV and tuberculosis in South Africa: A dynamical modelling study. *The Lancet Public Health*, *2*(5), e223–e230. https://doi.org/10.1016/S2468-2667(17)30066-X

Wood, A., Denholm, R., Hollings, S., Cooper, J., Ip, S., Walker, V., Denaxas, S., Akbari, A., Banerjee, A., Whiteley, W., Lai, A., Sterne, J., & Sudlow, C. (2021). Linked electronic health records for research on a nationwide cohort of more than 54 million people in England: Data resource. *BMJ*, *373*, n826. https://doi.org/10.1136/bmj.n826

World Health Organization. (2022). *Key facts and latest estimates on the global HIV epidemic—2021* (pp. 1–7). https://cdn.who.int/media/docs/default-source/hq-hiv-hepatitis-and-stis-library/key-facts-hiv-2021-26july2022.pdf?sfvrsn=8f4e7c93_5

Wu, P.-Y., Chen, M.-Y., Hsieh, S.-M., Sun, H.-Y., Tsai, M.-S., Lee, K.-Y., Liu, W.-C., Yang, S.-P., Luo, Y.-Z., Zhang, J.-Y., Sheng, W.-H., & Hung, C.-C. (2014). Comorbidities among the HIV-Infected Patients Aged 40 Years or Older in Taiwan. *PLoS ONE*, *9*(8). https://doi.org/10.1371/journal.pone.0104945

Wyk, V. P., Msemburi, W., Laubscher, R., Dorrington, R. E., Groenewald, P., Glass, T., Nojilana, B., Joubert, J. D., Matzopoulos, R., Prinsloo, M., Nannan, N., Gwebushe, N., Vos, T., Somdyala, N., Sithole, N., Neethling, I., Nicol, E., Rossouw, A., & Bradshaw, D. (2016). Mortality trends and differentials in South Africa from 1997 to 2012: Second National Burden of Disease Study. *The Lancet Global Health*, *4*(9), e642–e653. https://doi.org/10.1016/S2214-109X(16)30113-9

Zingmond, D. S., Arfer, K. B., Gildner, J. L., & Leibowitz, A. A. (2017). The cost of comorbidities in treatment for HIV/AIDS in California. *PLOS ONE*, *12*(12), e0189392. https://doi.org/10.1371/journal.pone.0189392

Zungu, N. P., Mabaso, M. L., Kumalo, F., Sigida, S., Mlangeni, L., Wabiri, N., & Chasela, C. (2019). Prevalence of non-communicable diseases (NCDs) and associated factors among HIV positive educators: Findings from the 2015/6 survey of Health of Educators in Public Schools in South Africa. *PLOS ONE*, *14*(2), e0209756. https://doi.org/10.1371/journal.pone.0209756

CHAPTER 2: ACCESSING HIV CARE MAY LEAD TO EARLIER ASCERTAINMENT OF COMORBIDITIES IN HEALTH CARE CLIENTS IN KHAYELITSHA, CAPE TOWN

2.1 Publication details

Osei-Yeboah R, Tamuhla T, Ngwenya O, Tiffin N (2021) Accessing HIV care may lead to earlier ascertainment of comorbidities in health care clients in Khayelitsha, Cape Town. PLOS Glob Public Health 1(12): e0000031. https://doi.org/10.1371/journal.pgph.0000031

2.2 Author contribution

NT designed the study. ROY conducted the analysis and wrote the draft manuscript. NT and ROY finalised the manuscript. TT contributed to data analysis. ON provided statistical support.

2.3 Abstract

Successful antiretroviral rollout in South Africa has greatly increased the health of the HIV-positive population, and morbidity and mortality in PLHIV can increasingly be attributed to comorbidities rather than HIV/AIDS directly. Understanding this disease burden can inform health care planning for a growing population of ageing PLHIV. Anonymised routine administrative health data were analysed for all adults who accessed public health care in 2016 -2017 in Khayelitsha subdistrict (Cape Town, South Africa). Selected comorbidities and age of ascertainment for comorbidities were described for all HIV-positive and HIV-negative healthcare clients, as well as for a subset of women who accessed maternal care.

There were 172 937 adult individuals with a median age of 37 (IQR:30-48) years in the virtual cohort, of whom 48% (83 162) were HIV-positive. Median age of ascertainment for each comorbidity was lower in HIV-positive compared to HIV-negative healthcare clients, except in the case of tuberculosis. A subset of women who previously accessed maternal care, however, showed much smaller differences in the median age of comorbidity ascertainment between the group of HIV-positive and HIV-negative health care clients, except in the case of chronic kidney disease (CKD). Both HIV-positive individuals and women who link to maternal care undergo routine point-of-care screening for common diseases at younger ages, and this analysis suggests that this may lead to earlier diagnosis of common comorbidities in these groups.

Exceptions include CKD, in which age of ascertainment appears lower in PLHIV than HIV-negative groups in all analyses suggesting that age of disease onset may indeed be earlier; and tuberculosis for which age of incidence has previously been shown to vary according to HIV status.

Keywords

HIV, comorbidities, South Africa, maternal care

2.4 Introduction

South Africa bears the highest burden of the human immunodeficiency virus (HIV) epidemic in sub-Saharan Africa (SSA) (James et al., 2018) where about 7.2 million people are affected (Statistics South Africa, 2019), and is considered the current epicentre of the HIV epidemic (Hodes & Morrell, 2018). Antiretroviral therapy (ART) became available in 2004 but prior to the evolution of guidelines to the current "test and treat" policy in South Africa, many people living with HIV (PLHIV) did not reach older ages due to high mortality. Over the last decade, South Africa has expanded the ART and HIV prevention campaign by investing about USD 1.1 billion annually to run what is considered the largest programme worldwide (Williams et al., 2017). In 2014, Boulle et al., reported a rapid decline in mortality among HIV-infected patients with an increased duration on ART in South Africa and emphasised that though the rates may not be comparable to developed countries initially, after four years on ART they approach the rates observed in high-income countries where HIV is now treated as a chronic infection (Boulle et al., 2014). A decline in the percentage of acquired immunodeficiency syndrome (AIDS)-related mortalities from 42.1% in 2004 to 23.4% in 2019, (Statistics South Africa, 2019) and the rising general life expectancy (Boulle et al., 2014; Statistics South Africa, 2019) demonstrate the success of this ART programme. The prevalence of HIV in the population aged over 50 years increased from 7.1% in 2012 to 12.5% in 2017 in South Africa (Simbayi et al., 2019).

The success of the ART intervention has resulted in more older PLHIV, with improvements in their general quality of life, but in this ageing population other comorbidities still negatively affect mortality rate and life course outcome (Guaraldi et al., 2019). In addition to ongoing environmental and behavioural exposures that affect the whole population, comorbidities in

PLHIV may also include HIV-related conditions such as HIV-induced persistent immunodeficiency, inflammation, and increased toxicity from longer durations of ART use, (Silva et al., 2019) or HIV nephropathy (Husain et al., 2018). Ageing also affects the immune system and the production and function of T cells, and these effects are worsened by HIV (Leng & Margolick, 2020). Some drugs included in standard regimens may also increase the risks of some non-communicable diseases (NCDs) (Jamieson et al., 2017). A low progress in the care continuum is reported for PLHIV plus cardiometabolic conditions, (Chang et al., 2019) and a significant proportion of mortalities in PLHIV may result from co-infections and NCDs such as malignancies, diabetes mellitus, hypertension, lipid disorders, and vascular diseases.

Recent studies outside Africa suggest higher prevalence and earlier incidence of comorbidities in PLHIV, especially those older than 50 years (Ahn et al., 2019; Maciel et al., 2018), but more research is needed in SSA to see if similar trends may be seen (Negin et al., 2012). Studies in 2015 and 2017 reported risks of - and increased - hospital admissions of PLHIV for AIDS-defining illnesses, renal and cardiovascular-related issues in Cape Town and other parts of South Africa (Meintjes et al., 2015; Moodley & Tomita, 2017; Wearne, 2015), and the observations of hypertension, congestive cardiac failure, cancer, and diabetes among PLHIV in Zimbabwe (Magodoro et al., 2016) suggest a growing burden of HIV comorbidities. Given the expanding ageing population of PLHIV within SSA, we need to understand the health needs of this population group now and in the future, as well as identifying potential drivers of comorbidities that may provide avenues for future interventions. In light of the current COVID-19 pandemic, it is more important than ever to understand the background of comorbidities and co-infections in a population at high risk of COVID-19 (Boulle et al., 2020).

In this study, we analyse routine health data collected from a variety of public healthcare facilities including primary health care clinics, district level and tertiary hospitals across the Western Cape Province in South Africa. These data are used to describe ascertained comorbidities in a healthcare-seeking population from Khayelitsha, a high-density urban district in Cape Town. The Competition Commission reported that in 2018, approximately 83 per cent of the South African population who were mostly without medical insurance relied on public healthcare facilities and private healthcare facilities served the remaining 17 per cent with

medical insurance (Competition Commission, South Africa, 2019; Mhlanga & Garidzirai, 2020; Stepanikova & Oates, 2017). Govender et al., report that among low-income patients in South Africa, affordability and convenience account for the top reasons influencing healthcare-seeking behaviour in public facilities whilst the quality-of-care accounts for the key reason for private healthcare facilities, and further observed a cycling behaviour between public and private sector clinics (Govender et al., 2021). The subdistrict Khayelitsha, where this cohort originates, has a generally low-income population where we anticipate the majority of residents will access public health facilities.

We describe the median age of ascertainment for comorbidities in PLHIV and for HIV-negative health care clients. In order to better understand the relationship between age of ascertainment and likely access to screening for common comorbidities, we compare the age of ascertainment for comorbidities in the subset of women accessing maternal care under the assumption that all women accessing maternal care are likely to receive screening for comorbidities at a younger age regardless of their HIV or other health status.

2.5 Materials and Methods

2.5.1 Ethics

Ethics approval was obtained from the Human Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town (HREC ref: 482/2019). A waiver for consent was granted because the data were anonymised and perturbed, and individuals could not be identified or re-identified from the data. This means that no informed consent was given by health care clients for the use of these anonymised, perturbed data. A data access request was approved by the Health Impact Assessment Directorate at the Western Cape Department of Health, South Africa. There was no involvement of the public or patients because the data were accessed as an anonymised, perturbed dataset from routine data platforms without any interactions with individuals. The dataset was accessed in September 2018, and longitudinal data were available from 2007 to the end of 2017.

2.5.2 Data source

The Provincial Health Data Centre (PHDC) is a health information exchange facility that collates administrative health data for the Western Cape Province. Unique identifiers are used to link individuals to administrative health records (Boulle et al., 2019), and facility visit, laboratory, and pharmacy data are updated daily for about 6.6 million people currently seeking care in public facilities in the Western Cape Province. Algorithms are used to infer disease episodes from combinations of pharmacy-dispensed drugs, laboratory test results, international classification of disease-10th edition (ICD-10) diagnosis codes, and facility encounter data. These algorithms are developed and tested in collaboration with clinicians who specialise in each condition. A data set was obtained from the PHDC, Western Cape Government Health Department, with longitudinal data ranging from 2007 to 2017. The median length of time for which individuals have available data is 8 years (IQR: 3.6-10 years). The study dataset was anonymised and perturbed prior to release, to prevent identification or re-identification of individuals. The electronic confirmation of disease diagnosis resulting from administrative health record linkage is referred to as "ascertainment" rather than diagnosis, as it is derived from the electronic records rather than from a diagnosis made by a clinician during consultation.

2.5.3 PHDC definition of disease episodes

The PHDC infers diseases from routine health data using algorithms that analyse either single, or a combination of parameter(s) categorised into high, moderate, weak confidence and supporting-only evidence for having a particular disease episode. High confidence definition of HIV requires evidence for dispensed valid first line (2NRTI and NNRTI) and valid triple therapy regimen (fixed-dose combination) of antiretrovirals, and/or positive laboratory test results (viral load test, polymerase chain reaction (PCR) test, enzyme linked immunosorbent assay (ELISA) test, and ART resistance test).

High confidence definition of chronic obstructive pulmonary disease (COPD)/asthma is based on dispensed drug for treatment of COPD or asthma (Selective beta-2-adrenoreceptor agonists). High confidence definition of breast cancer includes laboratory test (SNOMED Topography Breast -ICD03T-C50) showing infiltrating duct carcinoma, comedocarcinoma,

juvenile carcinoma of the breast, intraductal papillary adenocarcinoma with invasion, intra-cystic carcinoma (not otherwise specified), medullary carcinoma (not otherwise specified), medullary carcinoma with lymphoid stroma, lobular carcinoma (not otherwise specified), infiltrating ductular carcinoma, infiltrating duct and lobular carcinoma, mucinous adenocarcinoma, pseudomyxoma peritonei, mucin-producing adenocarcinoma, tubular adenocarcinoma, papillary carcinoma (not otherwise specified), verrucous carcinoma (not otherwise specified), papillary squamous cell carcinoma, infiltrating ductular carcinoma, infiltrating duct and lobular carcinoma, infiltrating with other forms of carcinoma. Procedure or diagnosis coding such as ICD-10 malignant neoplasm of breast, ICD-10 History of malignant neoplasm of the breast, secondary malignant neoplasm of the breast, resection of quadrant of breast or subtotal mastectomy, and mastectomy.

Lung cancer high confidence definition includes attendance at bronchial radiotherapy, laboratory tests (SNOMED Topography Respiratory ICD03T C33 C34 C39) showing small cell carcinoma, non-small cell carcinoma, carcinoid tumour/tumour/Merkel cell, mesothelioma, and ICD-10 (C34) indicating malignant neoplasm of bronchus and lung. Mental health condition is defined using dispensed drug for treatment of mental health (Psycholeptics) and diagnosis code indicating mental health episode (F00) as high confidence. High confidence definition of single abnormal creatinine is based on single serum creatinine above 100, no other tests evident. Anti-dsDNA antibodies abnormally high is the main definition of systemic lupus erythematosus

For tuberculosis (TB), evidence for the episode may include admission to a specialised TB hospital, TB drug regimen dispensed, and/or laboratory test results (Positive GeneXpert, Line probe assay (LPA), Acid-Fast Bacillus positive culture, positive microscopy (Ziehl-Neelsen staining), and microbiology culture-*Toxocara canis* (using ELISA) are the main definition parameters. High confidence definition of hypertension includes dispensed hydrochlorothiazide. High confidence definitions of diabetes episodes are based on dispensed drug for the treatment of diabetes mellitus, laboratory test showing glycated haemoglobin (HbA1c) greater than 6.5%, oral glucose tolerance test result greater than 11.1mmol/l, and diagnosis coding showing an ICD-10 code indicating diabetes disease.

For chronic kidney disease (CKD), laboratory tests showing consecutive glomerular filtration rate of less than 60mL/min/1.73m^2 with 90 days between tests, dispensed kidney, or transplant medications (antithymocyte, immunoglobulin, and basiliximab), and diagnosis coding indicating kidney transplant procedure in theatre constitute a high confidence definition. It is important to note that SCr and eGFR results are used extensively in defining patients with CKD by the PHDC. This means that there is substantial overlap between having poor kidney function test results and being defined as having a CKD episode. The ascertainment algorithm in use by the PHDC, however, makes use of longitudinal eGFR results to track changes in kidney function over time, and is not based on single or stand-alone kidney function results. The PHDC algorithm uses the modification of diet in renal disease study (MDRD) GFR estimating equation to determine eGFR.

2.5.4 Study population

All adults (aged 18 years and above) who accessed public health facilities in the Khayelitsha subdistrict between 1 January 2016 and 31 December 2017, described as the 'recruitment period', were eligible in this study. We included clients who were linked across comorbidities, maternal care or HIV care records. Khayelitsha is a high-density, mixed informal/formal housing suburb in Cape Town, South Africa.

2.5.5 Statistical analysis

Descriptive statistics were generated for age, gender and burden of comorbidities in this study population. The comorbidities assessed were TB – using the age of ascertainment for first known episode, chronic obstructive pulmonary disease and/or asthma (COPD/Asthma), hypertension, diabetes, CKD, cervical cancer, lung cancer, breast cancer, and mental health diagnoses. Cardiovascular disease was not included in this study because the PHDC algorithm to infer cardiovascular disease is not yet validated.

The age at ascertainment of each comorbidity in HIV-negative and HIV-positive subgroups of the total healthcare-seeking population was determined.

In addition to describing metrics for all healthcare seekers, age at ascertainment for each comorbidity was determined in a subset of all women who had ever accessed some form of pregnancy and/or maternal care. This subset was chosen to represent individuals who would

have been linked to care independent of their HIV and general health status and are very likely to have undergone screening for common conditions as young adults. This subgroup was used to compare the age of ascertainment of comorbidities in HIV-positive and HIV-negative strata, in order to indicate whether earlier linkage to care might lead to earlier ascertainment of these comorbidities. This subset was analysed in order to ameliorate the impact of the bias in the composition of the whole study population. The significance of difference between median ages at ascertainment was calculated using Wilcoxon rank sum tests, and the significance of difference in proportions of comorbidities between PLHIV and HIV-negative groups in this subset was calculated using Fisher's exact test.

Multivariate logistic regression was used to assess the likelihood of individuals seeking healthcare for each condition to also present with HIV and other comorbidities. Each comorbidity was independently assessed as an outcome/dependent variable with independent variables age, sex, HIV, and other comorbidities. This approach was used to accommodate known bias in the dataset. The 'Enter' method of multivariate logistic regression where all input variables are entered simultaneously was used.

Data analyses were done using R Software (version 3.6.0) and RStudio (version 1.1.447); Graphical representations of age distributions at start of recruitment period for HIV-negative and -positive population, sex, age at ascertainment of HIV, and comorbidities distributions by age, HIV status, and sex were generated using the ggplot2 package in RStudio version 1.1.447.

2.5.6 Patient and public involvement

The participants in this study were healthcare seekers who visited public health facilities and generated at least one electronic health record. Retrospective data for this population spanned about 8 years. Inclusion in the study was restricted to healthcare clients who accessed care between 2016 and 2017 but included their complete retrospective data. The study questions were designed to explore the common comorbidities among these healthcare clients who seek care from public facilities. A waiver for participants' consent was granted because the data were obtained directly from digital routine health data in the PHDC and were anonymised and perturbed to prevent re-identification of participants.

2.6 Results

2.6.1 Study population characteristics

The total study population was 172 937 healthcare seekers, with a median age of 37 years (IQR: 30-48 years), of which 125 468 (73%) were females. There were 83 162 HIV-positive individuals - 48% of the total healthcare-seeking population. There were 59 164 HIV-positive females, representing 71% of all PLHIV. The median age (IQR) of HIV ascertainment differs in females and males at 35 years (IQR: 30-43 years) and 40 years (IQR: 34-47 years) respectively *(p* <0.001). There were 67 499 women with evidence of previous access to maternal care, more than half (54%) of all female healthcare seekers. Of those who had accessed maternal care, 29 828 (44.2%) were living with HIV. About 46.6% of PLHIV were seeking care for the additional comorbidities investigated in this study compared to 61.5% of individuals without HIV (Table 2.1).

Table 2.1: Demographic and baseline characteristics of healthcare seekers

Healthcare seeking population	**Total**	**HIV- (%)**	**HIV+ (%)**
	172 937	**89 775 (52%)**	**83 162 (48%)**
Female	125 468 (72.6%)	66 304 (73.9%)	59 164 (71.1%)
Has accessed maternal care	67 499 (53.8% *)	37 671 (55.8%**)	29 828 (44.2%**)
No comorbidity	78 990 (45.7%)	34 575 (38.5%)	44 415 (53.4%)
1 comorbidity	65 207 (37.7%)	36 701 (40.9%)	28 506 (34.3%)
2 comorbidities	21 514 (12.4%)	13 674 (15.2%)	7 840 (9.4%)
≥3 comorbidities	7 226 (4.2%)	4 825 (5.4%)	2 401 (2.9%)

***Proportion of females **Proportion of those who accessed maternal care**

The age distribution assessed at the beginning of the recruitment period for females and males, as well as HIV-negative and HIV-positive healthcare seekers, shows a non-uniform distribution: there were more women than men in this cohort of healthcare seekers, with more HIV-positive individuals in the younger age groups. More women in our study population were living with HIV at younger ages than men and their HIV-positive status was ascertained at earlier ages than men (Figure 2.1). More women (73%) than men were included in this study. In Figure 2.1C, we observe a double peak in the age distribution of male PLHIV. The first peak occurred early in the young adult population and the second peak occurred in the older adult population. These two populations may have unique healthcare seeking behaviours. It is likely that the first peak is

related to linkage to care and HIV services when HIV is diagnosed in the younger population whilst the second peak may be related to seeking care for or due to additional comorbidities in the older population.

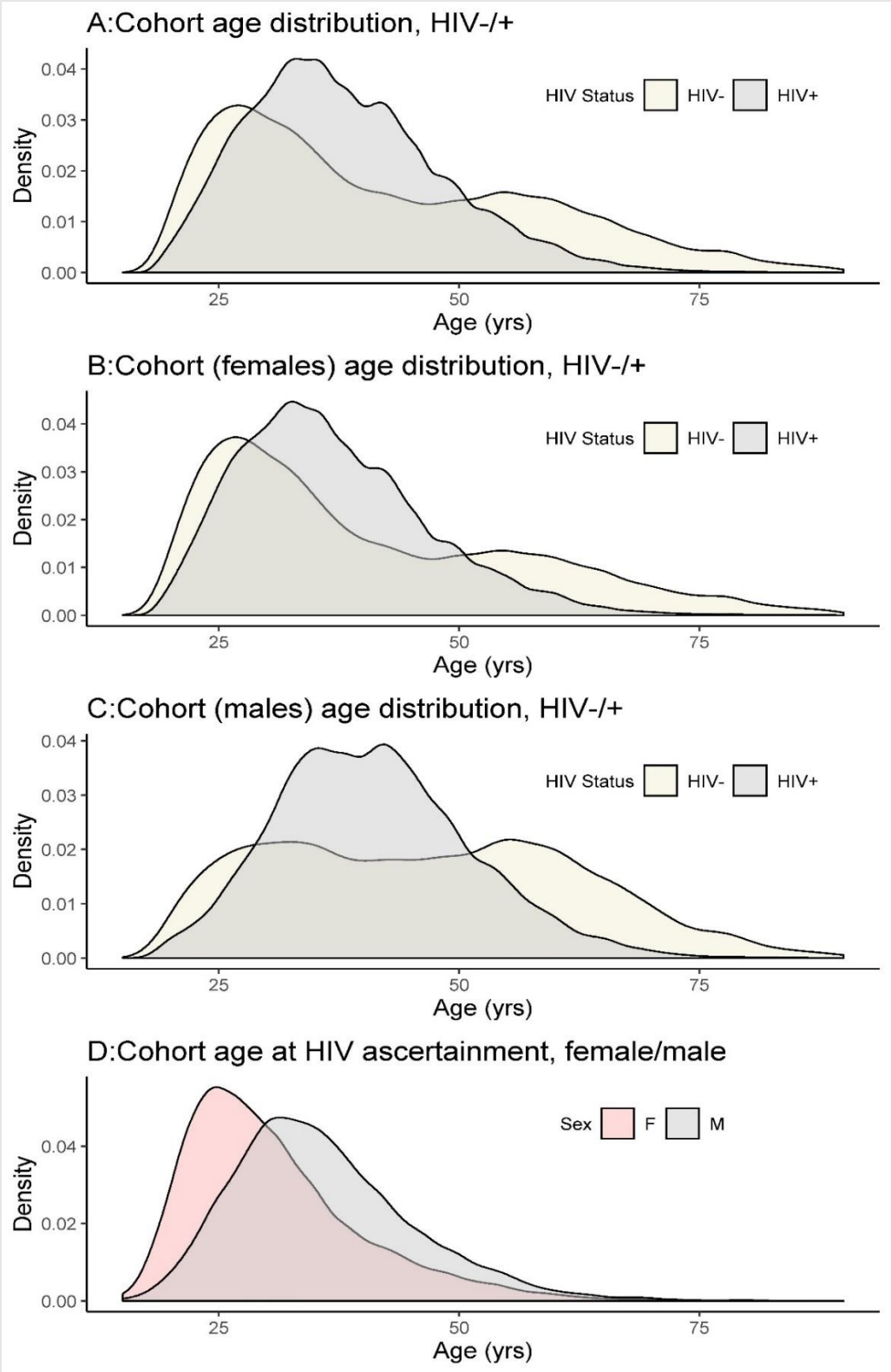


Figure 2.1: Baseline age distributions of study participants. Age in years is shown for the beginning of the recruitment period, subgroups shown are HIV status and sex.

2.6.2 The burden of comorbidities and age of ascertainment in HIV-positive and HIV-negative healthcare seekers.

The proportion of individuals seeking care in public health facilities with the assessed comorbidities were, TB (21.4%), COPD or asthma (7.4%), hypertension (26.4%), diabetes (9.7%), CKD (2.4%), cervical cancer (0.9%), lung cancer (0.5%), breast cancer (0.4%), and mental health conditions (7.2%), (Table 2.2). Except for TB, all comorbidities were ascertained earlier among people living with HIV, with large differences in the age of ascertainment seen between HIV-negative and HIV-positive healthcare seekers (Table 2.2).

Table 2.2: Comorbidities counts and median age (in years) at ascertainment in HIV-negative vs HIV-positive for all healthcare seekers

*Proportions for cervical cancer were calculated for the female population only

Condition	**Healthcare seeking population**		**HIV-negative n=89 775**		**HIV-positive n=83 162**	
	Count (%) n=172 937	Age at ascertainment (IQR)	Count (%)	Age at ascertainment (IQR)	Count (%)	Age at ascertainment (IQR)
Tuberculosis	36 837 (21.3%)	34 (27-42)	11 298 (12.6%)	33 (24-48)	25 539 (30.7%)	34 (28-41)
COPD/Asthma	12 820 (7.4%)	45 (32-56)	8 477 (9.4%)	50 (33-60)	4 343 (5.2%)	39 (32-48)
Hypertension	45 691 (26.4%)	49 (40-58)	34 090 (38%)	52 (43-60)	11 601 (14%)	43 (36-50)
Diabetes	16 979 (9.8%)	51 (41-59)	13 561 (15.1%)	52 (44-61)	3 418 (4.1%)	44 (36-51)
Chronic Kidney Disease	4 179 (2.4%)	57 (48-67)	2 833 (3.2%)	62 (55-71)	1 346 (1.6%)	46 (38-55)
Cervical Cancer*	1 180 (0.9%)	38 (32-47)	294 (0.4%)	52 (30-61)	886 (1.5%)	36 (31-42)
Lung Cancer	784 (0.5%)	47 (34-59)	443 (0.5%)	56 (40-65)	341 (0.4%)	39 (31-49)
Breast Cancer	691 (0.4%)	44 (33-54)	458 (0.5%)	47 (34-57)	233 (0.3%)	40 (33-46)
Mental Health Condition	12 512 (7.2%)	37 (27-50)	8 279 (9.2%)	39 (26-54)	4 233 (5.1%)	36 (29-45)

Within the subset of women who have ever accessed maternal care, however, the differences in the median ages at ascertainment for each comorbidity were much smaller compared to the whole population of healthcare seekers, except in the case of CKD where the median age of ascertainment was approximately 5.5 years earlier in HIV-positive women (p<0.001), and TB where the median age of ascertainment was approximately 5 years later in HIV-positive women (p<0.001) (Table 2.3). The percentage of HIV-negative and HIV-positive women presenting with each comorbidity in this subset are shown (Table 2.3). HIV-positive women were more likely to present with TB (OR: 6.78, 95% CI: 6.40, 7.18); CKD (OR: 3.48, 95% CI: 2.67, 4.58); cervical cancer (OR:9.47, 95% CI: 7.22,12.60); lung cancer (2.39, 95% CI:1.65, 3.5) and mental health conditions (OR:1.41, 95% CI:1.30, 1.53) compared to HIV-negative women. They were less likely to present with diabetes (OR: 0.69, 95% CI: 0.64, 0.75) compared to HIV-negative women.

Table 2.3: Comorbidity counts (%) with Odds Ratio (95% CI), and age at ascertainments of comorbidities (with Wilcoxon Rank Sum p-value), for HIV-negative and HIV-positive women who have accessed maternal care (IQR: Interquartile range)

Condition	**Women who accessed maternal care**		**HIV-negative women (n=37 671)**		**HIV-positive women (n = 29 828)**		**OR (C.I) Comorbidity count**	**P-value Ascertainment age**
	Count (%) n=67 499	**Ascertainment age (IQR)**	**Count (%)**	**Ascertainment age (IQR)**	**Count (%)**	**Ascertainment age (IQR)**		
Tuberculosis	8 416 (12.5%)	29 (24-34)	1 583 (4.2%)	24 (21-30)	6 833 (22.9%)	29 (25-34)	6.78 (6.40-7.18)	<0.001
COPD/Asthma	2 587 (3.8%)	32 (36-38)	1 225 (3.3%)	31 (25-38)	1 362 (4.6%)	33 (28-38)	1.42 (1.31-1.54)	<0.001
Hypertension	7 475 (11.1%)	36 (30-41)	4 202 (11.2%)	36 (30-42)	3 273 (11%)	35 (30-40)	0.98 (0.93-1.03)	0.008
Diabetes	2 434 (3.6%)	35 (29-41)	1 565 (4.2%)	36 (30-41)	869 (2.9%)	35 (29-40)	0.69 (0.64-0.75)	0.05
Chronic Kidney Disease	292 (0.43%)	39 (33-45)	78 (0.21%)	43 (36-47)	214 (0.72%)	37.5 (32-44)	3.48 (2.67-4.58)	<0.001
Cervical Cancer	504 (0.75%)	33 (29-38)	60 (0.16%)	34 (31-39·5)	444 (1.5%)	33 (29-38)	9.47 (7.22-2.60)	0.05
Lung Cancer	130 (0.19%)	31 (26-37)	45 (0.12%)	31 (26-41)	85 (0.28%)	32 (26-36)	2.39 (1.65-3.51)	0.79
Breast Cancer	212 (0.31%)	33.5 (27.8-41)	120 (0.32%)	30·5 (26-41)	92 (0.31%)	35.5 (29-40)	0.97 (0.73-1.28)	0.05
Mental Health Condition	2 480 (3.7%)	32 (26-38)	1 178 (3.1%)	31 (25-38)	1 302 (4.4%)	32 (27-38)	1.41(1.30-1.53)	<0.001

2.6.3 Distribution of ascertainment age for comorbidities in HIV-negative and HIV-positive healthcare seekers

The distributions of age at ascertainment for the comorbidities assayed are shown in Figure 2.2 for both HIV-negative and -positive groups, Figure 2.3 for PLHIV, and Figure S2.2 for HIV-negative individuals. Generally, in the HIV-positive healthcare seekers, all comorbidities are ascertained across a narrower range of ages, whilst ascertainment of comorbidities in HIV-negative healthcare seekers show a wider age range. There is a drop off in ascertainment of comorbidities in HIV-positive individuals at older ages.

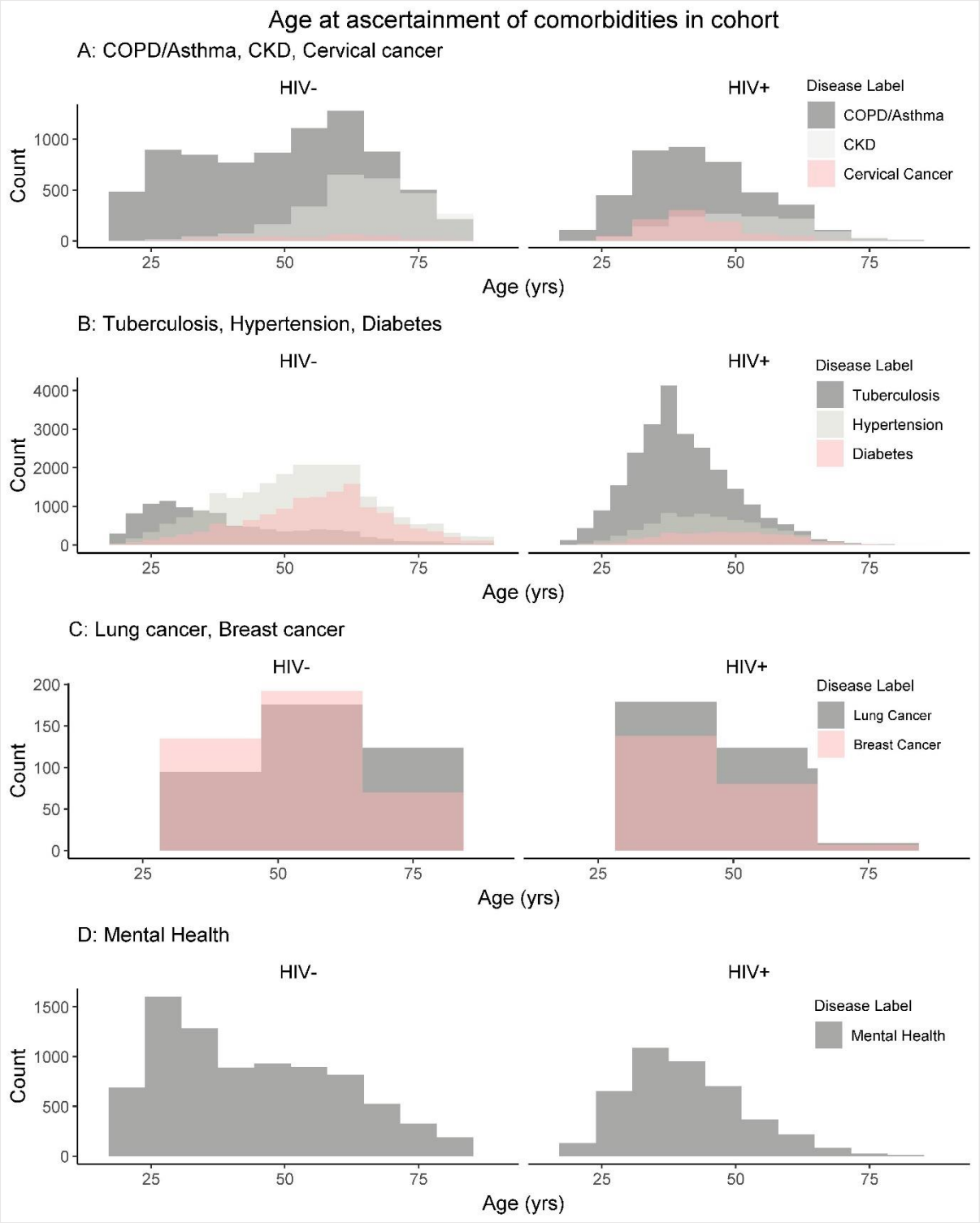


Figure 2.2: Age at ascertainment for comorbidities for HIV-positive and HIV-negative health care seekers. The absolute counts of comorbidities are shown, grouped by count range for optimal display. A. COPD/Asthma, CKD, and cervical cancer. B. Tuberculosis, hypertension, and diabetes. C. Lung cancer and breast cancer. D. Mental health condition.

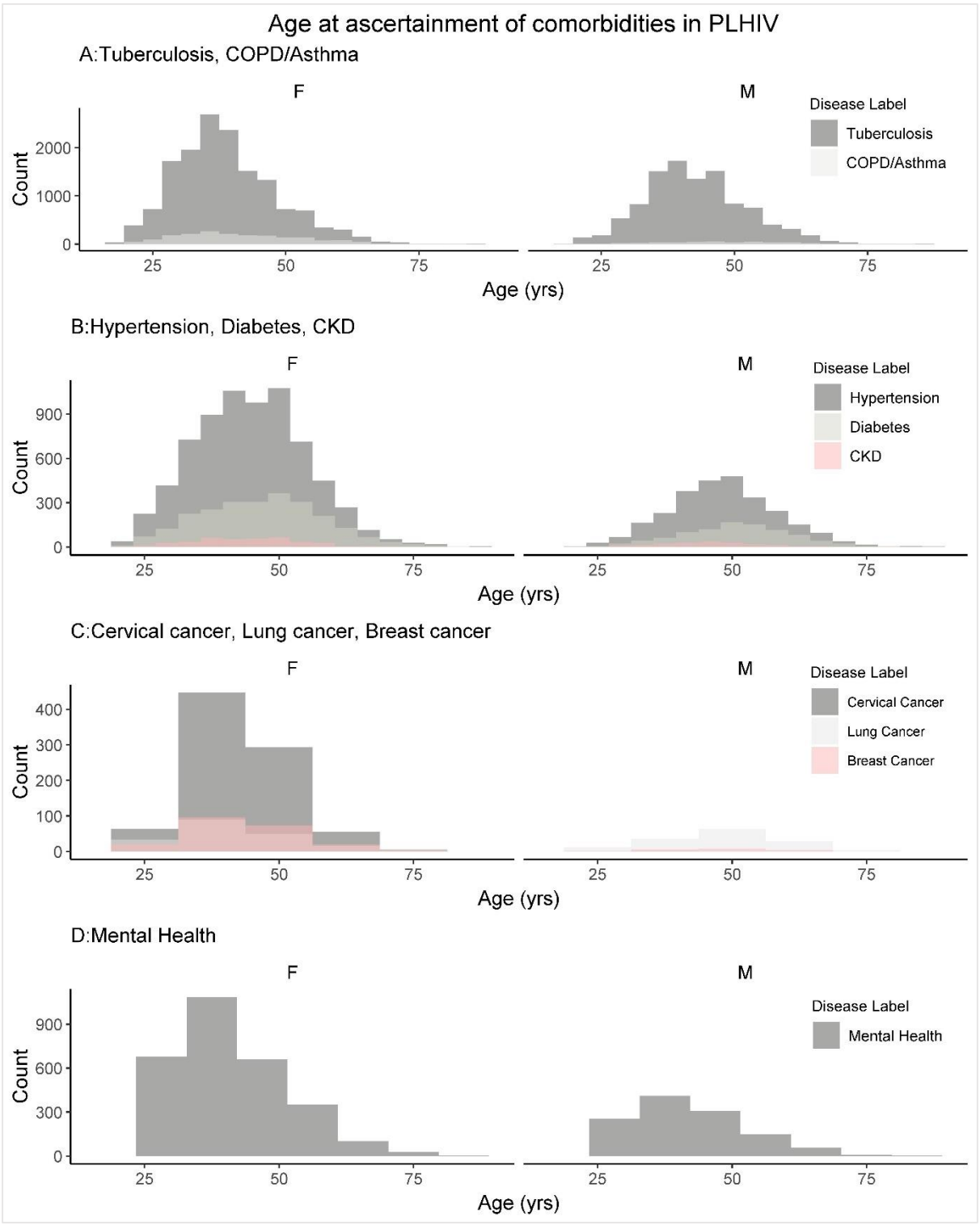


Figure 2.3: Age at ascertainment of comorbidities in HIV-positive healthcare seekers by sex. The absolute counts of comorbidities are shown, grouped by count range for optimal display. A. COPD/Asthma, CKD, and cervical cancer. B. Tuberculosis, hypertension, and diabetes. C. Lung cancer and breast cancer. D. Mental health condition

1

2.6.4 HIV status of individuals presenting with common conditions and other comorbidities

Multivariate logistic regression analysis shows the likelihood of having HIV and other comorbidities in patients presenting with each condition. The odds of having all conditions increased with age, calculated per 5-year increments. Within the whole study population, people who seek care for a first episode of TB are 2.74 (95% C.I: 2.66, 2.81) times more likely to be HIV-positive than HIV-negative. People presenting with CKD are 1.67 (95% CI: 1.54, 1.82) times likely to be HIV-positive and those presenting with cervical cancer are 4.90 (95% CI: 4.22, 5.71) times more likely to be HIV-positive. The complete data are shown in Table S2.1.

The results presented in Table 2.4, show independent analyses with each assayed comorbidity modelled as the outcome, and the contribution of HIV when adjusted for the other comorbidities. In particular, within the subset of those who have accessed maternal care, women who had TB are 6.24 (95% CI: 5.89, 6.61) times more likely than those without TB to also present with HIV; those with COPD/Asthma are 1.14 (95% CI:1.04, 1.24) and 1.76 (95% CI:1.58, 1.95) times more likely to have had HIV and TB, respectively; and maternal care seekers presenting with cervical cancer are 7.41 (95% CI:5.67, 9.7) times more likely to be HIV-positive compared to those without cervical cancer.

Table 2.4: Multivariate logistic regression for women who have previously accessed maternal care; showing odds ratio (95% Confidence interval). Odds ratio for age is shown per 5-year increments

OUTCOMES	**INDEPENDENT VARIABLES (OR [95% C.I])**										
	HIV	TB	COPD/Asthma	Hypertension	Diabetes	CKD	Cervical cancer	Lung cancer	Breast cancer	Mental Health	Age 5 yr. increment
Tuberculosis	6.24 (5.89,6.61)	-	1.74 (1.56,1.92)	0.64 (0.58,0.69)	1.18 (1.04,1.34)	2.82 (2.18,3.65)	1.33 (1.08,1.62)	3.38 (2.29,4.95)	1.28 (0.86,1.85)	1.88 (1.69,2.09)	1.15 (1.12,1.16)
COPD/Asthma	1.14 (1.04,1.24)	1.76 (1.58,1.95)	-	1.80 (1.62,2.00)	1.14 (0.96,1.35)	1.55 (1.07,2.19)	0.97 (0.65,1.38)	1.65 (0.85,2.90)	1.27 (0.73,2.06)	2.02 (1.74,2.33)	1.20 (1.18,1.24)
Hypertension	0.83 (0.79,0.88)	0.65 (0.59,0.70)	1.78 (1.60,1.98)	-	3.70 (3.37,4.07)	3.32 (2.52,4.36)	1.02 (0.80,1.30)	1.12 (0.66,1.82)	1.46 (1.02,2.06)	1.68 (1.50,1.88)	1.85 (1.82,1.89)
Diabetes	0.56 (0.51,0.61)	1.26 (1.10,1.43)	1.08 (0.91,1.29)	3.66 (3.32,4.03)	-	1.98 (1.42,2.71)	1.32 (0.91,1.87)	0.72 (0.25,1.63)	0.61 (0.30,1.10)	1.33 (1.12,1.58)	1.53 (1.50,1.58)
CKD	2.74 (1.86,3.30)	3.01 (2.33,3.90)	1.57 (1.08,2.23)	3.48 (2.66,4.54)	2.25 (1.62,3.08)	-	1.91 (1.00,3.32)	1.74 (2.79,5.78)	0.24 (0.01,1.26	1.81 (1.24,2.57)	1.70 (1.57,1.85)
Cervical cancer	7.41 (5.67,9.7)	1.33 (1.09,1.63)	0.95 (0.64,1.36)	1.03 (0.80,1.31)	1.31 (0.90,1.85)	1.52 (0.80,2.66)	-	3.42 (1.30,7.42)	1.10 (0.32,2.79)	1.77 (1.28,2.39)	1.63 (1.53,1.73)
Lung cancer	1.37 (0.92,1.07)	3.42 (2.31,5.03)	1.59 (0.82,2.81)	1.14 (0.67,1.85)	0.67 (0.23,1.55)	1.18 (0.19,3.95)	3.13 (1.20,6.71)	-	3.90 (0.92,10.9)	2.29 (1.28,3.83)	1.25 (1.11,1.41)
Breast cancer	0.73 (0.54,1.09)	1.41 (0.95,2.04)	1.28 (0.74,2.08)	1.47 (1.03,2.08)	0.62 (0.31,1.11)	0.34 (0.12,1.55)	1.36 (0.41,3.320	3.86 (0.92,10.9)	-	5.61 (3.96,7.80)	1.42 (1.30,1.56)
Mental Health Condition	1.11 (1.02,1.22)	1.90 (1.71,2.10)	2.00 (1.73,2.32)	1.71 (1.52,1.90)	1.35 (1.14,1.60)	1.63 (1.12,2.32)	1.76 (1.27,2.37)	2.34 (1.30,3.91)	5.68 (4.00,7.91)	-	1.16 (1.13,1.19)

Hypertension, diabetes, and CKD had increased odds of co-occurring (Table 2.4). Individuals with hypertension are 17% less likely to present with HIV (OR: 0.83, 95% CI: 0.79, 0.88), those with diabetes are 44% less likely to present with HIV (OR: 0.56, 95% CI: 0.51, 0.61), and those with CKD are 2.74 (95%CI: 1.86, 3.30) times more likely to present with HIV. There is no significant difference in HIV presentation between those with and without lung cancer or breast cancer. Finally, women who accessed maternal care and have mental health conditions are 11% more likely to present with HIV (OR:1.11, 95% CI: 1.02, 1.22) as well as other comorbidities compared to those without mental health conditions.

2.7 Discussion

The results reveal that PLHIV in Khayelitsha, Cape Town are seeking care for multiple chronic comorbidities in addition to co-infection with tuberculosis. Analysis of the healthcare client population in this study shows earlier ascertainment of most chronic comorbidities in PLHIV. Whilst this could be due to generally earlier incidence of comorbidities in the HIV-positive population, it could also reflect an earlier diagnosis of comorbidities in those with frequent access to health care and earlier screening due to HIV treatment visits. Ascertainment of comorbidities might occur later in people who do not normally access health care frequently and therefore only receive a diagnosis when comorbidities are sufficiently advanced to present with symptoms. Statistical metrics were not used to directly compare the prevalence of comorbidities in HIV-positive and HIV-negative subsets of the overall study population due to the known bias in this dataset which is enriched for people who are already ill or have frequent healthcare-seeking behaviour due to existing chronic conditions such as HIV. Bias also results from young healthy women attending healthcare facilities for contraceptive or maternal health services, whilst young, healthy men seldom access healthcare services. The general populations of healthcare seekers who are HIV-positive and HIV-negative are not directly comparable, accordingly.

We found that in a subset of women who accessed maternal care, there were much smaller differences in ages at ascertainment of most comorbidities in both HIV-negative and HIV-positive groups. This suggest that frequent access to healthcare may result in earlier

ascertainment of these comorbidities, rather than there being generally earlier incidence in the HIV-positive population. In all comorbidities assayed where significant differences were identified in the age of ascertainment of this group, the difference is in the range of only 1-2 years - with the notable exception of CKD which occurs an average of 5.5 years earlier in HIV positive women, in line with existing studies on HIV Nephropathy (Butler et al., 2018; Naicker, 2020). For TB, the median age of ascertainment is approximately 5 years higher in PLHIV, and it is believed that this may reflect the difference in age distribution for TB incidence in HIV-negative and HIV-positive individuals. For those without HIV, TB risk is high in young adults but decreases rapidly at older ages (Blaser et al., 2016) whereas TB risk in PLHIV remains elevated throughout adulthood, leading to a shift to an older *median* age of first TB ascertainment. It is anticipated that data for cardiovascular disease (CVD) in this population may also show earlier occurrence in PLHIV, based on prior studies (Alonso Alvaro et al., 2019), and a similar analysis will be conducted for CVD when these data are available. Multivariate analysis shows that in women, having TB or cervical cancer is highly associated with being HIV-positive. Both arise from infectious agents and are classified as HIV-related conditions (Zetola et al., 2016).

We recognise the bias in this dataset due to imbalances in the sectors of the population commonly seeking healthcare, and the exclusion of many healthy individuals (especially young men) who do not frequently attend healthcare facilities. Bias in the data means that direct comparisons of comorbidity prevalence could not be made between the total HIV-positive and HIV-negative study groups. Several sources of bias exist in our study. Healthy HIV-negative individuals without comorbidities are under-represented in people commonly seeking healthcare in public facilities. HIV-negative healthcare clients are likely to be seeking healthcare because they are ill with other conditions, so the HIV-negative group in the study population is enriched for other comorbidities. Individuals with conditions requiring frequent medication – especially HIV medication – are more likely to visit a facility during the recruitment period and subsequently be included in the dataset, so the study population is further enriched for HIV-positive individuals. In the subset analysis, women who have accessed maternal health services previously were selected to represent a subgroup of individuals who have accessed care and received screening for common comorbidities at a younger age, regardless of their HIV- or

general health status, thus providing a less-biased subset for additional analyses. Whilst this analysis can address the bias resulting from differences in accessing healthcare services, some of the limitations of the maternal subset analysis include the inability to assess comorbidities occurring more commonly in men, or much older women. In addition, it is possible that pregnant women living with HIV may have more rigorous screening and antenatal care which may lead to more frequent ascertainment of existing conditions than for HIV-negative pregnant. As more data about this cohort are collected over time, it would be possible to analyse evolving comorbidity profiles as the maternal cohort ages.

Individuals visiting healthcare facilities who are not seeking care for HIV are more likely to be accessing care for one or more other comorbidities. This explains the high prevalence of these comorbidities in healthcare clients who are HIV-negative and does not accurately represent the prevalence of those comorbidities in the general HIV-negative population, many of whom may not be currently in active care.

For these reasons, this paper does not attempt to compare the estimated prevalence of comorbidities in PLHIV with those who are HIV-negative in this study population and did not use HIV status as an outcome for multivariate regression analysis. The maternal subset was used as a proxy for a more balanced analysis, based on the assumption that women who access maternal healthcare do so at a relatively younger age regardless of their HIV status or other health conditions. Because of the time frame for which retrospective data are available, the subset who accessed maternal care had a lower maximum age than the whole group (Figure S2.1). The analysis of the maternal subset alone clearly cannot, however, be used to understand sex differences in the healthcare-seeking population. In addition, it is anticipated that there may be contributions from other confounding risk factors that we have not been able to assess in the current study because these data – for example ascertainment of less common health conditions, observational clinical data and socioeconomic status – are not currently available through the PHDC. As these data become increasingly available, it will be possible to refine these analyses to better understand the contributions of a wider range of confounding and contributing risk factors.

Differences between female and male demographics of healthcare clients may also reflect to some extent contraceptive and maternal care access by women who are not experiencing health issues or poor health, and this group of healthcare clients contributes to the relatively high proportion of younger women without HIV presenting with no comorbidities in the data set. A similar proportion of young, healthy males cannot be seen to be reflected in this dataset, accordingly. Prior studies also suggest that women are more likely to have frequent healthcare-seeking behaviours than men which may also contribute to the higher numbers of women in this study (Olanrewaju et al., 2019), and frequent access to healthcare plays a pivotal role in the ascertainment of HIV among both younger and older women (Luseno et al., 2010). The later ascertainment of HIV among men compared to women could be a result of men only presenting to facilities when they are already ill (Pulerwitz et al., 2019), and health promotion and encouraging healthcare-seeking behaviour are key in ensuring early detection of HIV in this sector of the population (Luseno et al., 2010).

A rapid fall-off in numbers of HIV-positive people aged over 60 years at recruitment is because prior to ART rollout in 2004, there was high mortality in PLHIV (Pillay-van Wyk et al., 2019) and there are few people who were diagnosed prior to 2004 and have now survived beyond 60 years of age. As the HIV-positive population now ages, however, the rising challenge of NCDs among ageing HIV-positive persons indicates that disease-specific care delivery for PLHIV may need to become more integrated and holistic to ensure that comorbidities in these patients receive the necessary attention.

2.8 Conclusion

Ascertainment of comorbidities relies on screening, which is influenced by healthcare-seeking behaviours. This analysis suggests that when women link to maternal care, or PLHIV link to HIV care, which both include point-of-care screening, they have earlier ascertainment of common conditions. This may be a more likely explanation for earlier age of ascertainment of comorbidities in PLHIV than in HIV-negative individuals, rather than earlier disease onset. If this holds true in the wider population, it would suggest that earlier screening, in general, could lead to earlier ascertainment of common comorbidities – in turn leading to earlier linkage to

care and better patient outcomes. The data also suggest that as PLHIV age, their comorbidities curve will also widen toward the older ages and share similarities with the distribution of comorbidities in HIV-negative healthcare seekers, increasing the burden on existing healthcare facilities. Careful planning can ensure that this ageing population has sufficient access to healthcare for HIV and comorbidities, into the future.

2.9 References

Ahn, M. Y., Jiamsakul, A., Khusuwan, S., Khol, V., Pham, T. T., Chaiwarith, R., Avihingsanon, A., Kumarasamy, N., Wong, W. W., Kiertiburanakul, S., Pujari, S., Nguyen, K. V., Lee, M. P., Kamarulzaman, A., Zhang, F., Ditangco, R., Merati, T. P., Yunihastuti, E., Ng, O. T., … Choi, J. Y. (2019). The influence of age-associated comorbidities on responses to combination antiretroviral therapy in older people living with HIV. *Journal of the International AIDS Society*, *22*(2). https://doi.org/10.1002/jia2.25228

Alonso Alvaro, Barnes A. Elise, Guest Jodie L., Shah Amit, Shao Iris Yuefan, & Marconi Vincent. (2019). HIV Infection and Incidence of Cardiovascular Diseases: An Analysis of a Large Healthcare Database. *Journal of the American Heart Association*, *8*(14), e012241. https://doi.org/10.1161/JAHA.119.012241

Blaser, N., Zahnd, C., Hermans, S., Salazar-Vizcaya, L., Estill, J., Morrow, C., Egger, M., Keiser, O., & Wood, R. (2016). Tuberculosis in Cape Town: An age-structured transmission model. *Epidemics*, *14*, 54–61. https://doi.org/10.1016/j.epidem.2015.10.001

Boulle, A., Davies, M.-A., Hussey, H., Ismail, M., Morden, E., Vundle, Z., Zweigenthal, V., Mahomed, H., Paleker, M., Pienaar, D., Tembo, Y., Lawrence, C., Isaacs, W., Mathema, H., Allen, D., Allie, T., Bam, J.-L., Buddiga, K., Dane, P., … Tamuhla, T. (2020). Risk factors for COVID-19 death in a population cohort study from the Western Cape Province, South Africa. *Clinical Infectious Diseases*. https://doi.org/10.1093/cid/ciaa1198

Boulle, A., Heekes, A., Tiffin, N., Smith, M., Mutemaringa, T., Zinyakatira, N., Phelanyane, F., Pienaar, C., Buddiga, K., Coetzee, E., Rooyen, R. van, Dyers, R., Fredericks, N., Loff, A., Shand, L., Moodley, M., Vega, I. de, & Vallabhjee, K. (2019). Data Centre Profile: The Provincial Health Data Centre of the Western Cape Province, South Africa. *International Journal of Population Data Science*, *4*(2), Article 2. https://doi.org/10.23889/ijpds.v4i2.1143

Boulle, A., Schomaker, M., May, M. T., Hogg, R. S., Shepherd, B. E., Monge, S., Keiser, O., Lampe, F. C., Giddy, J., Ndirangu, J., Garone, D., Fox, M., Ingle, S. M., Reiss, P., Dabis, F., Costagliola, D., Castagna, A., Ehren, K., Campbell, C., … Sterne, J. A. C. (2014). Mortality in Patients with HIV-1 Infection Starting Antiretroviral Therapy in South Africa, Europe,

or North America: A Collaborative Analysis of Prospective Studies. *PLOS Medicine*, *11*(9), e1001718. https://doi.org/10.1371/journal.pmed.1001718

Butler, I., MacLeod, W., Majuba, P. P., & Tipping, B. (2018). Human immunodeficiency virus infection and older adults: A retrospective single-site cohort study from Johannesburg, South Africa. *Southern African Journal of HIV Medicine*, *19*(1), 8. https://doi.org/10.4102/sajhivmed.v19i1.838

Chang, A. Y., Gómez-Olivé, F. X., Manne-Goehler, J., Wade, A. N., Tollman, S., Gaziano, T. A., & Salomon, J. A. (2019). Multimorbidity and care for hypertension, diabetes and HIV among older adults in rural South Africa. *Bulletin of the World Health Organization*, *97*(1), 10–23. https://doi.org/10.2471/BLT.18.217000

Competition Commission, South Africa. (2019). *Health markey inquiry: Final findings and recommendation report* (p. 260). https://www.hfassociation.co.za/images/docs/Health-Market-Inquiry-Report.pdf

Govender, K., Girdwood, S., Letswalo, D., Long, L., Meyer-Rath, G., & Miot, J. (2021). Primary healthcare seeking behaviour of low-income patients across the public and private health sectors in South Africa. *BMC Public Health*, *21*(1), 1649. https://doi.org/10.1186/s12889-021-11678-9

Guaraldi, G., Milic, J., & Mussini, C. (2019). Aging with HIV. *Current HIV/AIDS Reports*, *16*(6), 475–481. https://doi.org/10.1007/s11904-019-00464-3

Hodes, R., & Morrell, R. (2018). Incursions from the epicentre: Southern theory, social science, and the global HIV research domain. *African Journal of AIDS Research*, *17*(1), 22–31. https://doi.org/10.2989/16085906.2017.1377267

Husain, N. E., Ahmed, M. H., Almobarak, A. O., Noor, S. K., Elmadhoun, W. M., Awadalla, H., Woodward, C. L., & Mital, D. (2018). HIV-Associated Nephropathy in Africa: Pathology, Clinical Presentation and Strategy for Prevention. *Journal of Clinical Medicine Research*, *10*(1), 1–8. https://doi.org/10.14740/jocmr3235w

James, S. L., Abate, D., Abate, K. H., Abay, S. M., Abbafati, C., Abbasi, N., Abbastabar, H., Abd-Allah, F., Abdela, J., Abdelalim, A., Abdollahpour, I., Abdulkader, R. S., Abebe, Z., Abera, S. F., Abil, O. Z., Abraha, H. N., Abu-Raddad, L. J., Abu-Rmeileh, N. M. E., Accrombessi, M. M. K., … Murray, C. J. L. (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*, *392*(10159), 1789–1858. https://doi.org/10.1016/S0140-6736(18)32279-7

Jamieson, L., Evans, D., Brennan, A. T., Moyo, F., Spencer, D., Mahomed, K., Maskew, M., Long, L., Rosen, S., & Fox, M. P. (2017). Changes in elevated cholesterol in the era of tenofovir in South Africa: Risk factors, clinical management and outcomes. *HIV Medicine*, *18*(8), 595–603. https://doi.org/10.1111/hiv.12495

Leng, S. X., & Margolick, J. B. (2020). Aging, sex, inflammation, frailty, and CMV and HIV infections. *Cellular Immunology*, *348*, 104024. https://doi.org/10.1016/j.cellimm.2019.104024

Luseno, W. K., Wechsberg, W. M., Kline, T. L., & Ellerson, R. M. (2010). Health Services Utilization Among South African Women Living with HIV and Reporting Sexual and Substance-Use Risk Behaviors. *AIDS Patient Care and STDs*, *24*(4), 257–264. https://doi.org/10.1089/apc.2009.0213

Maciel, R. A., Klück, H. M., Durand, M., & Sprinz, E. (2018). Comorbidity is more common and occurs earlier in persons living with HIV than in HIV-uninfected matched controls, aged 50 years and older: A cross-sectional study. *International Journal of Infectious Diseases*, *70*, 30–35. https://doi.org/10.1016/j.ijid.2018.02.009

Magodoro, I. M., Esterhuizen, T. M., & Chivese, T. (2016). A cross-sectional, facility based study of comorbid non-communicable diseases among adults living with HIV infection in Zimbabwe. *BMC Research Notes*, *9*(376). https://doi.org/10.1186/s13104-016-2187-z

Meintjes, G., Kerkhoff, A. D., Burton, R., Schutz, C., Boulle, A., Van Wyk, G., Blumenthal, L., Nicol, M. P., & Lawn, S. D. (2015). HIV-Related Medical Admissions to a South African District Hospital Remain Frequent Despite Effective Antiretroviral Therapy Scale-Up. *Medicine*, *94*(50). https://doi.org/10.1097/MD.0000000000002269

Mhlanga, D., & Garidzirai, R. (2020). The Influence of Racial Differences in the Demand for Healthcare in South Africa: A Case of Public Healthcare. *International Journal of Environmental Research and Public Health*, *17*(14), 5043. https://doi.org/10.3390/ijerph17145043

Moodley, Y., & Tomita, A. (2017). Relationship between HIV serostatus, CD4 count and rehospitalisation: Potential implications for health systems strengthening in South Africa. *Southern African Journal of Infectious Diseases*, *32*(1), 23–28. https://doi.org/10.1080/22201181.2016.1201935

Naicker, S. (2020). HIV/AIDS and chronic kidney disease. *Clinical Nephrology*, *93*(1), 87–93. https://doi.org/10.5414/CNP92S115

Negin, J., Martiniuk, A., Cumming, R. G., Naidoo, N., Phaswana-Mafuya, N., Madurai, L., Williams, S., & Kowal, P. (2012). Prevalence of HIV and chronic comorbidities among older adults: *AIDS*, *26*(Suppl 1), S55–S63. https://doi.org/10.1097/QAD.0b013e3283558459

Olanrewaju, F. O., Ajayi, L. A., Loromeke, E., Olanrewaju, A., Allo, T., Nwannebuife, O., & Amoo, E. O. (2019). Masculinity and men's health-seeking behaviour in Nigerian academia. *Cogent Social Sciences*, *5*(1), 1682111. https://doi.org/10.1080/23311886.2019.1682111

Pillay-van Wyk, V., Msemburi, W., Dorrington, R. E., Laubscher, R., Groenewald, P., & Bradshaw, D. (2019). HIV/AIDS mortality trends pre and post ART for 1997—2012 in South Africa –

have we turned the tide? *South African Medical Journal*, *109*(11b), 41. https://doi.org/10.7196/SAMJ.2019.v109i11b.14283

Pulerwitz, J., Gottert, A., Kahn, K., Haberland, N., Julien, A., Selin, A., Twine, R., Peacock, D., Gómez-Olivé, X., Lippman, S. A., & Pettifor, A. (2019). Gender Norms and HIV Testing/Treatment Uptake: Evidence from a Large Population-Based Sample in South Africa. *AIDS and Behavior*, *23*(2), 162–171. https://doi.org/10.1007/s10461-019-02603-8

Silva, B. F., Peixoto, G. M. L., Luz, S. da, Moraes, S. de, & Peres, S. B. (2019). Adverse effects of chronic treatment with the Main subclasses of highly active antiretroviral therapy: A systematic review. *HIV Medicine*, *20*(7), 429–438. https://doi.org/10.1111/hiv.12733

Simbayi, L., Zuma, K., Zungu, N., Moyo, S., Marinda, E., Jooste, S., Mabaso, M., Ramlagan, S., North, A., Van Zyl, J., Mohlabane, N., Dietrich, C., Naidoo, I., & the SABSSM V Team, . (2019). *South African National HIV Prevalence, Incidence, Behaviour and Communication Survey, 2017: Towards achieving the UNAIDS 90-90-90 targets* (Survey No. 978-0-7969-2444–5; p. 252). HSRC Press.

Statistics South Africa. (2019). *Mid-year population estimates* (No. P0302; p. 30).

Stepanikova, I., & Oates, G. R. (2017). Perceived Discrimination and Privilege in Health Care: The Role of Socioeconomic Status and Race. *American Journal of Preventive Medicine*, *52*(1), S86–S94. https://doi.org/10.1016/j.amepre.2016.09.024

Wearne, N. (2015). Morbidity and mortality of black HIV-positive patients with end-stage kidney disease receiving chronic haemodialysis in South Africa. *South African Medical Journal*, *105*(2), 105-106–106. https://doi.org/10.7196/SAMJ.9068

Williams, B. G., Gupta, S., Wollmers, M., & Granich, R. (2017). Progress and prospects for the control of HIV and tuberculosis in South Africa: A dynamical modelling study. *The Lancet Public Health*, *2*(5), e223–e230. https://doi.org/10.1016/S2468-2667(17)30066-X

Zetola, N. M., Grover, S., Modongo, C., Chiyapo, S. P., Nsingo-Bvochora, M., Narasimhamurthy, M., Lin, L. L., Jarvis, J., Shin, S. S., & Robertson, E. (2016). Collision of Three Pandemics: The Coexistence of Cervical Cancer, HIV Infection, and Prior Tuberculosis in the Sub-Saharan Country of Botswana. *Journal of Global Oncology*, *2*(1), 47–50. https://doi.org/10.1200/JGO.2015.001701

2.10 Supplementary data

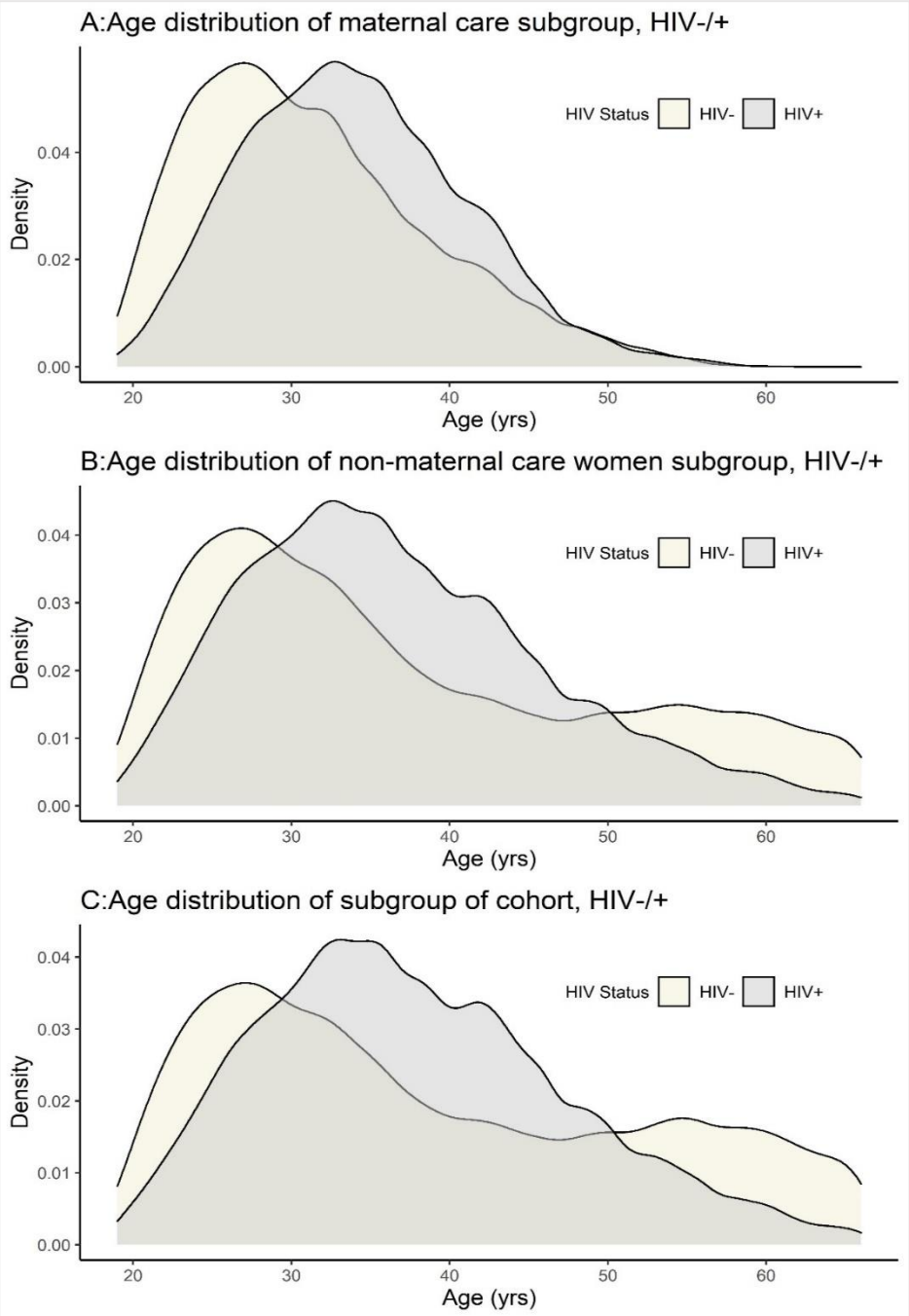


Figure S2.1: Age distribution of women in maternal subgroup, women in non-maternal subgroup, and subgroup with equivalent age range. Legend: Age (yrs.) along the x-axis is the distribution of age at the beginning of the recruitment period in HIV-negative and HIV-positive groups. A. Women who have ever accessed maternal care. B. Non-maternal women from the general healthcare-seeking population with an equivalent age range. C. The general healthcare-seeking population with an equivalent age range.

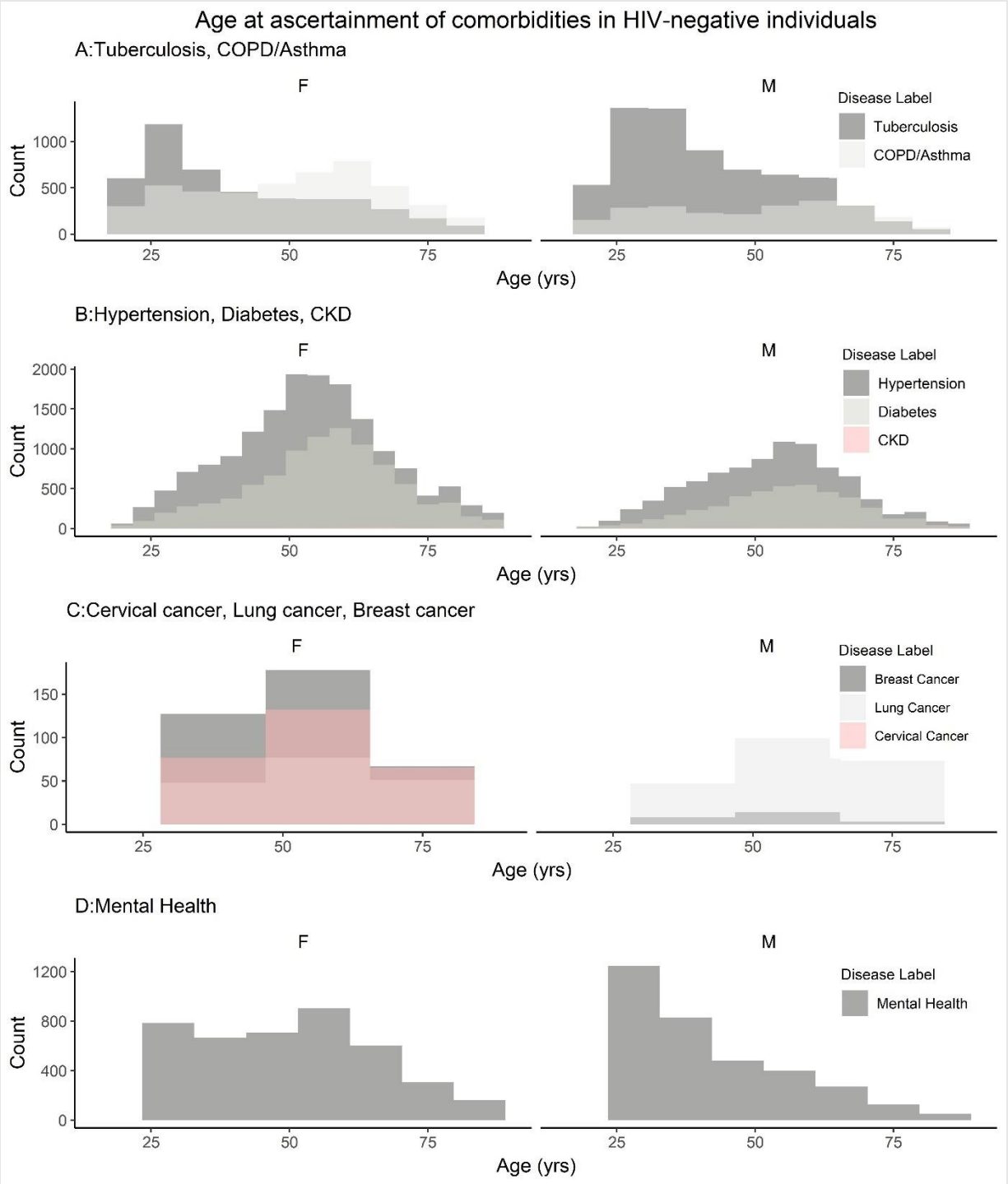


Figure S2.2: Age at ascertainment of comorbidities in HIV-negative individuals. The absolute counts of comorbidities are shown, grouped by count range for optimal display. A. Tuberculosis and COPD/Asthma. B. Hypertension, Diabetes and CKD. C. Breast cancer, Lung cancer and Cervical cancer. D. Mental health condition

Table S2.1: Multivariate logistic regression of healthcare-seeking population; Odds ratio (95% Confidence interval). Odds ratio for age is shown in 5-year increments

OUTCOMES	**INDEPENDENT VARIABLES (OR [95% C.I])**											
	HIV	Tuberculosis	COPD/Asthma	Hypertension	Diabetes	CKD	Cervical cancer	Lung cancer	Breast cancer	Mental health condition	Age 5 yr incr.	Sex M
Tuberculosis	2.74 (2.66,2.81)	-	1.39 (1.33,1.46)	0.41 (0.39,0.43)	0.75 (0.72,0.79)	1.50 (1.38,1.63)	1.45 (1.27,1.67)	3.21 (2.76,3.75)	0.94 (0.75,1.16)	0.98 (0.93,1.03)	1.08 (1.07,1.08)	3.04 (2.96,3.12)
COPD/Asthma	0.61 (0.59,0.64)	1.43 (1.36,1.50)	-	1.10 (1.05,1.15)	0.79 (0.75,0.84)	1.04 (0.96,1.15)	1.02 (0.81,1.26)	2.45 (2.06,2.91)	1.04 (0.80,1.37)	1.20 (1.12,1.27)	1.20 (1.18,1.20)	1.10 (1.06,1.15)
Hypertension	0.40 (0.38,0.41)	0.43 (0.41,0.45)	1.00 (0.96,1.05)	-	1.66 (1.59,1.73)	1.81 (1.66,1.99)	1.14 (0.97,1.32)	0.51 (0.42,0.62	0.84 (0.69,1.02)	0.82 (0.77,0.86)	1.63 (1.61,1.64)	1.10 (1.08,1.14)
Diabetes	0.43 (0.41,0.45)	0.85 (0.80,0.89)	0.77 (0.73,0.82)	2.02 (1.94,2.11)	-	2.43 (2.26,2.62)	1.14 (0.93,1.38)	0.77 (0.61,0.97)	0.87 (0.68,1.09)	0.98 (0.93,1.05)	1.28 (1.27,1.29)	0.99 (0.96,1.03)
CKD	1.67 (1.54,1.82)	1.61 (1.48,1.75)	1.08 0.98,1.19)	2.40 (2.21,2.60)	2.94 (2.75,3.16)	-	1.76 (1.33,2.30)	0.82 (0.56,1.16)	1.08 (0.72,1.55)	1.57 (1.42,1.73)	1.42 (1.40,1.44)	1.00 (0.94,1.08)
Cervical cancer	4.90 (4.22,5.71)	1.24 (1.08,1.42)	0.87 (0.60,1.08)	1.01 (0.87,1.18)	0.98 (0.80,1.19)	1.23 (0.92,1.61)	-	2.54 (1.43,4.18)	2.23 (1.35,3.49)	1.95 (1.63,2.32)	1.24 (1.21,1.27)	0.001 (0.00,0.01
Lung cancer	0.79 (0.67,0.93)	3.44 (2.95,4.02)	2.49 (2.09,2.95)	0.68 (0.57,0.81)	0.85 (0.68,1.07)	0.85 (0.59,1.20)	2.91 (1.65,4.74)	-	3.94 (2.21,6.47)	1.78 (1.44,2.17)	1.24 (1.21,1.27)	1.65 (1.42,1.92)
Breast cancer	0.71 (0.60,0.85)	0.94 (0.75,1.16)	1.00 (0.77,1.28)	0.87 (0.72,1.04)	0.82 (0.65,1.03)	0.86 (0.58,1.23)	2.42 (1.46,3.76)	3.72 (2.08,6.15)	-	4.06 (3.39,4.84)	1.18 (1.15,1.21)	0.14 (0.11,0.20)
Mental health condition	0.52 (0.50,0.54)	0.94 (0.90,1.00)	1.17 (1.09,1.24)	0.82 (0.78,0.86)	0.96 (0.90,1.02)	1.67 (1.52,1.84)	2.66 (2.22,3.15)	1.61 (1.30,1.96)	4.44 (3.72,5.29)	-	1.04 (1.03,1.05)	1.95 (1.87,2.03)

CHAPTER 3: ANALYSIS OF ROUTINE HEALTH DATA SHOWS ASCERTAINMENT OF COMORBIDITIES DIFFERS FOR HEALTHCARE CLIENTS IN KHAYELITSHA, SOUTH AFRICA DUE TO SUB-POPULATIONS DIFFERENCES

3.1 Publication status

Osei-Yeboah, R., & Tiffin, N. Analysis of routine health data shows ascertainment of comorbidities differs for healthcare clients in Khayelitsha, South Africa due to sub-populations differences (Ready for submission).

3.2 Author contribution

NT and ROY designed the study. ROY conducted the analysis and wrote the draft manuscript. NT and ROY finalised the manuscript.

3.3 Abstract

Background

As people living with human immunodeficiency virus (PLHIV) age, their health outcomes may be influenced by the roles of HIV infection and associated inflammation, the impacts of exposure to antiretroviral drugs, as well as the effects of other co-infections and chronic comorbidities. Considering the burden of disease and ongoing epidemiological transition in South Africa, and the interaction between HIV/acquired immunodeficiency syndrome (AIDS), antiretroviral therapy (ART), and non-communicable diseases (NCDs), understanding the relationships between HIV infection and comorbidities can inform planning to provide appropriate healthcare services for the ageing population of PLHIV and comorbidities.

Methods

We analysed the comorbidity profiles of PLHIV, and HIV-negative healthcare clients aged 18-80 years who accessed public health facilities in Khayelitsha, South Africa in 2016 and 2017. We compared the ascertainment dates for selected comorbidities to determine the order in which they most likely occurred and used multivariate logistic regression to determine the risk of subsequent ascertainment of a variety of disease conditions for individuals who already have HIV and at least one other condition. We used Kaplan-Meier survival curves to describe the timing of ascertainment of infectious diseases and NCDs for individuals who already had HIV.

Results

A total of 247 145 healthcare clients accessing public health facilities were included in the study, of which 154 802 (62.6%) were females. The median age of the study population in 2018 was 35 years (IQR: 28-46), and there were 81 668 PLHIV with a median age of 37 years (IQR: 31-44) of which 70 128 (85.9%) had initiated ART by the end of the recruitment period. Of the PLHIV, 58 246 (71.3%) were females. For all the comorbidities assessed in this study, the proportions of individuals with comorbidities ascertained after an HIV diagnosis were higher than for those ascertained before or at the same time as HIV; TB (72.1% vs 27.9%), cervical cancer (86.1% vs 13.9%), CKD (86.2% vs 13.8%), diabetes (65.6% vs 34.4%) and hypertension (77.1% vs 22.9%). Having a prior HIV diagnosis was associated with earlier ascertainment of TB, cervical cancer and CKD when compared to ascertainment in healthcare clients who are HIV-negative. The differences in time of comorbidity ascertainment plots show that in general, men living with HIV had diabetes, hypertension and TB ascertained at older ages when compared to women with HIV.

Conclusion

In this study population of healthcare clients, in general PLHIV had earlier ascertainment of TB, cervical cancer and CKD, but later ascertainment of hypertension and diabetes, when compared to HIV-negative individuals. These profiles suggest that aetiological factors might underlie earlier development of TB, cervical cancer, and CKD in PLHIV, in line with findings to date; but that HIV-negative individuals are possibly only attending healthcare services when physically ill from other causes and are more likely to be ascertained with an NCD accordingly. It is likely that the differences in the healthcare access patterns of the study population based on age, gender, general health and HIV status result in bias in this virtual cohort of healthcare clients; but these routine health data are still able to provide insights into the associations between an existing HIV infection and the development of subsequent comorbidities in individuals attending government healthcare facilities.

Keywords

HIV, comorbidity, ascertainment, non-communicable disease, routine health data, South Africa

3.4 Background

The roll-out and expansion of antiretroviral therapy (ART) programmes have resulted in more people living with the human immunodeficiency virus (PLHIV) gaining access to life-saving therapies in Africa (GBD 2017 HIV Collaborators et al., 2019), especially in South Africa where the impact of the HIV pandemic has been profound (Hodes & Morrell, 2018). Due to the success of these ART programmes, HIV-related morbidity and mortality are declining and more PLHIV are living to older ages (Althoff et al., 2016). Though there is a significant decline in acquired immunodeficiency syndrome (AIDS)-defining morbidities, there exist excess burden of other comorbidities among PLHIV compared with seronegative demographically comparable adults (Althoff et al., 2015; Cox et al., 2016).

Empirical evidence from sub-Saharan African (SSA) countries suggests that the prevalence of diabetes and obesity remains higher among PLHIV receiving ART than those without HIV, and receiving ART may be associated with increased prevalence of obesity (Coetzee et al., 2019). Further, prevalence of hypertension, osteoporosis, renal impairment, asthma, and cardiomyopathy are on the rise among PLHIV on ART (Kansiime et al., 2019). In South Africa, high levels of risk factors for non-communicable diseases (NCDs) among PLHIV receiving ART care are well documented in past studies (Mathebula et al., 2020; van Heerden et al., 2017).

Studies suggest that ageing and living with HIV may contribute to the rising prevalence of NCDs in PLHIV (Kato et al., 2020) and negatively affect the health-related quality of life of PLHIV compared with the general population (Miners et al., 2014; Moore et al., 2014). Hypertension, impaired glucose tolerance, diabetes mellitus, hypercholesterolemia, and hypertriglyceridemia are suggested to be associated with a long-term use of antiretroviral drugs (Kato et al., 2020). HIV-associated nephropathies arising from the prolonged use of active ART are widely studied in Africa and globally (Husain et al., 2018; Naicker, 2020; Palau et al., 2018).

Additionally, factors including ill health from HIV infection, HIV treatment toxicity, and general burden of comorbidities, albeit modifiable, contribute to a poorer quality of life in PLHIV (Althoff et al., 2016).

As PLHIV age, their health outcomes may be influenced by the roles of HIV infection and associated inflammation, the impacts of exposure to antiretroviral drugs, as well as the

effects of other viral coinfections or chronic comorbidities (Althoff et al., 2016). Considering the epidemiological transition as well as the interaction between HIV/AIDS, ART care, and NCD risk factors (Kabudula et al., 2017), it is essential to understand the relationship between HIV infections and/or ART care or having other comorbidities and the occurrence of NCDs or other related infections. This study aimed at exploring how living with HIV in the context of existing comorbidities may be associated with a higher probability of developing other additional comorbidities in a population of healthcare clients attending public health facilities in Khayelitsha, South Africa.

3.5 Methods

3.5.1 Ethics

Ethics approval was obtained from the Human Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town (HREC ref: 482/2019). A data access request was approved by the Health Impact Assessment Directorate at the Western Cape Department of Health, South Africa. A waiver for informed consent was granted because the data provided were anonymized and perturbed, and individuals could not be identified or re-identified from the data.

3.5.2 Study population

Khayelitsha is a high-density, mixed informal and formal housing suburb in Cape Town, South Africa. The analysis includes selected comorbidities ascertained by the Provincial Health Data Centre (PHDC) for all adults (18 years and above) who accessed public health facilities in the Khayelitsha subdistrict of Cape Town, South Africa, between 1 January 2016 and 31 December 2017, described as the 'recruitment period'. We included all healthcare clients who had a recorded health facility episode/encounter regardless of the condition being presented.

3.5.3 Data Source

The PHDC is a health information exchange facility that collates administrative health data for the Western Cape Province. Unique identifiers are used to link individuals to administrative health records, and facility visit, laboratory, and pharmacy data are updated daily for about 6.6 million people currently seeking care in public facilities in the Western Cape Province. Algorithms are used to infer disease episodes from combinations of

pharmacy-dispensed drugs, laboratory test results, International Classification of Disease - 10th edition (ICD-10) diagnosis codes, and facility encounter data (Boulle et al., 2019). In this study we refer to "disease ascertainment", to mean inference of the start of a disease episode as identified by an algorithm run by the PHDC, to distinguish this process of disease ascertainment from a clinical diagnosis made by a health care professional during consultation. A dataset containing routine health data was obtained from the PHDC, Western Cape Government Health Department, with longitudinal data ranging from 2007 to 2017. The records of the healthcare clients who are seeking care in public facilities included HIV and comorbidities records that were used to determine which health conditions had already been ascertained prior to ascertainment of an outcome of interest. The median length of time for which individuals have available data is 8 years (Interquartile range [IQR]: 3.6-10 years). The study dataset was anonymised and perturbed within the PHDC prior to being released for use in this analysis, to prevent identification or re-identification of individuals.

3.5.4 PHDC disease episode definition

The PHDC infers diseases from routine health data using algorithms that analyse either single, or a combination of parameters categorized into high, moderate, and weak confidence and supporting-only evidence for having a particular disease episode. High confidence definition of HIV requires evidence for dispensed valid first line (2NRTI and NNRTI) and valid triple therapy regimen (fixed-dose combination) of antiretrovirals, and/or positive laboratory test results (viral load test, Polymerase Chain Reaction (PCR) test, Enzyme Linked Immunosorbent Assay (ELISA) test, and ART resistance test). For tuberculosis (TB), evidence for the episode may include admission to specialized TB hospital, TB drug regimen dispensed, and/or laboratory test results (Positive GeneXpert, Line probe assay (LPA), Acid-Fast Bacillus positive culture, positive microscopy (Ziehl-Neelsen staining), and microbiology culture-*Toxocara canis* (ELISA) are the main definition parameters. High confidence definition of hypertension includes dispensed hydrochlorothiazide. High confidence definitions of diabetes episodes are based on dispensed drug for the treatment of diabetes mellitus, laboratory test showing glycated haemoglobin (HbA1c) greater than 6.5%, oral glucose tolerance test result greater than 11.1mmol/l, and diagnosis coding showing an ICD-10 code indicating diabetes disease.

For chronic kidney disease (CKD), laboratory tests showing consecutive glomerular filtration rate of less than 60 with 90 days between tests, dispensed kidney, or transplant medications (antithymocyte, immunoglobulin, and basiliximab), and diagnosis coding indicating kidney transplant procedure in theatre constitute high confidence definition. It is important to note that serum creatinine (SCr) and estimated glomerular filtration rate (eGFR) results are used extensively in defining patients with CKD by the PHDC. This means that there is substantial overlap between having poor kidney function test results and being defined as having a CKD episode. The ascertainment algorithm, however, makes use of longitudinal eGFR results to track changes in kidney function over time, and is not based on individual kidney function results. The PHDC algorithm uses the modification of diet in renal disease study (MDRD) GFR estimating equation to determine eGFR.

3.5.5 Data Analysis

3.5.5.1 Overview of study population, HIV and comorbidity incidence among the study participants and the order in which comorbidities were ascertained

Descriptive statistics were generated for healthcare clients with and without HIV and selected comorbidities. HIV ascertainment date was compared with the comorbidity ascertainment date to determine whether the comorbidity was ascertained prior to, on same date as, or after the ascertainment of HIV. The comorbidities considered in this study categorized as NCDs are CKD, diabetes, and hypertension; and infectious diseases are TB and cervical cancer.

3.5.5.2 Association between existing comorbidities and subsequent occurrence of disease conditions of interest

A multivariate logistic regression model was used to explore the association between already having an ascertainment of selected comorbidities and a subsequent occurrence of each of those comorbidities in turn as an outcome of interest. An individual end date of ascertainment of the outcome of interest was defined for each study participant for each disease condition in turn. The individual end dates included date of ascertainment for individuals who developed the outcome before the study ended, date of death for those who died before the study ended without recording the outcome, and a study end date for those who ended the study without experiencing the outcome. Current disease status was then defined for each condition by comparing the date of ascertainment of the condition

and the individual end dates. A positive current disease status was assigned if an individual had the condition before or at the same time as the end date of the outcome of interest. The age at inclusion into the study was used as participant age in years, for the analyses. In a supplementary analysis, multivariate logistic regression model was used to assess the risk of healthcare clients for each condition to also present with HIV and other comorbidities irrespective of the time of ascertainment. Each comorbidity was independently assessed as an outcome variable with independent variables age, sex, HIV, and other comorbidities. The complete data are shown in supplementary data. The 'Enter' method of multivariate logistic regression where all input variables are entered simultaneously was used.

3.5.5.3 Age-stratified analysis

To better understand the relationship between participant age and ascertainment of co-morbidities, we conducted age-stratified logistic regression analysis to assess the relationship between existing HIV infection and subsequent hypertension and diabetes ascertainment. Age at study end was categorized into 18-29 years, 30-44 years, 45-60 years, and 60+ years and a separate analysis was run for each age group.

3.5.5.4 Timeline of events for HIV and comorbidities ascertainment among healthcare clients

The differences in the time of ascertainment of HIV and comorbidities were determined using the 'difftime' function in RStudio. For each study participant who had HIV and a co-existing condition, the dates of ascertainment of HIV and the comorbidity were used. The unit for each time was specified as years.

3.5.5.5 Prior HIV ascertainment and the probability of developing an outcome of interest

Kaplan-Meier survival curves were used to describe how having prior ascertainment of HIV infection compares with no prior HIV infection with respect to occurrence of selected comorbidities of interest. The Kaplan-Meier method enables construction of survival curves as a function of time and takes into account censoring resulting from either death or non-occurrence of outcome of interest at study end for study population (D'Arrigo et al., 2021). The survival curves show the time (in years) to the occurrence of the outcome of interest, in this case development of the comorbidity, for healthcare clients first ascertained with HIV and indicate the number of healthcare clients at risk of developing the outcome of interest.

The log-rank test was used to compare the survival experience in the Kaplan-Meier graphs and the resulting p-values are shown in each figure.

Data analyses were done in R Software (version 4.1.2) and RStudio (2021.09.0+351 "Ghost Orchid"). Visualisations of differences in the timeline of events were done using 'ggplot2' package in RStudio. Visualisation of logistic regression output for CKD was done using 'sjPlot' package in RStudio. Kaplan-Meier survival curves were generated using the 'survival' and 'survminer' packages in RStudio.

3.6 Results

3.6.1 Overview of study population, HIV and comorbidity incidence among the study participants and the order in which comorbidities were ascertained

Description of the study population

A total of 247 145 healthcare clients were recruited into the study of which 154 802 (62.6%) were females. The median age of the study population was 35 years (IQR: 28-46). There were 165 477 (66.9%) HIV-negative clients in the healthcare client population of which 96 556 (58.4%) were females. The median age of the HIV-negative healthcare clients was 32 years (IQR: 24-46). There were 81 668 (33.0%) PLHIV with a median age of 37 years (IQR: 31-44), of which 70 128 (85.9%) had initiated ART at the end of the recruitment period. Of the PLHIV, 58 246 (71.3%) were females.

The counts and proportions of healthcare clients with comorbidities were determined for PLHIV and HIV-negative healthcare clients. Among healthcare clients with TB and cervical cancer, PLHIV had higher proportions (69.1% vs 30.9%) and (75.5% vs 24.5%) respectively, compared to individuals without HIV. Higher proportions of healthcare clients without HIV presented with CKD (68.1% vs 31.9%), diabetes (80.1% vs 19.9%), and hypertension (74.7% vs 25.3%) when compared to PLHIV (Table 3.1).

Table 3.1: Healthcare clients presenting with selected conditions, count (%) of HIV-negative and HIV-positive.

Condition	Total count	HIV-negative (%)	HIV-positive (%)
All participants	247 145	165 477 (67.0%)	81 668 (33.0%)
CKD	3 870	2 635 (68.1%)	1 235 (31.9%)
Diabetes	16 410	13 138 (80.1%)	3 272 (19.9%)
Hypertension	44 669	33 364 (74.7%)	11 305 (25.3%)
TB	35 854	11 066 (30.9%)	24 788 (69.1%)
Cervical cancer	1 144	280 (24.5%)	864 (75.5%)

Overview of HIV and comorbidity incidence among the study participants, determining 'what came first'

The counts and proportions of healthcare clients ascertained with HIV and comorbidities, and the counts and proportions of clients ascertained with the comorbidities before and after HIV ascertainment were determined. For all the comorbidities, the proportions of individuals ascertained after HIV were higher than those ascertained before HIV or on the same day. TB (72.1% vs 27.9%), cervical cancer (86.1% vs 13.9%), CKD (86.2% vs 13.8%), diabetes (65.6% vs 34.4%) and hypertension (77.1% vs 22.9%) (Table 3.2).

Table 3.2: Counts of healthcare clients living with comorbidity, comorbidity with HIV, and counts and proportions of individuals ascertained with comorbidities before and after HIV diagnosis.

Comorbidity	Total ever had comorbidity	Total had comorbidity with HIV	Total had comorbidity before HIV or on same day as HIV	Total had comorbidity after HIV
CKD	3 870	1 235 (31.9%)	170 (13.8%)	1 065 (86.2%)
Diabetes	16 410	3 272 (19.9%)	1 127 (34.4%)	2 145 (65.6%)
Hypertension	44 669	11 305 (25.3%)	2 592 (22.9%)	8 713 (77.1%)
TB	35 854	24 788 (69.1%)	6 920 (27.9%)	17 868 (72.1%)
Cervical cancer	1 144	864 (75.5%)	120 (13.9%)	744 (86.1%)

3.6.2 Association between existing comorbidities and subsequent occurrence of disease conditions of interest

Adjusting for age at study recruitment, sex, and other comorbidity status we assessed the association between subsequent comorbidity ascertainment and prior ascertainment of HIV and other comorbidities in a multivariate logistic regression analysis (Table 3.3). Additionally, we assessed the association between comorbidity ascertainment and having

HIV and other comorbidities in a multivariate logistic regression analysis and the complete data are presented in supplementary data, Table S3.1 to Table S3.5.

Chronic Kidney Disease

Our analysis shows that healthcare clients with prior diabetes are 2.69 (95% Confidence Interval [CI]: 2.48-2.91) times more likely to be subsequently ascertained for CKD compared to healthcare clients without diabetes. Subsequent CKD ascertainment for healthcare clients with prior HIV ascertainment is 1.74 (95% CI: 1.60-1.90) times more likely compared to for those without HIV. A 5-year increase in the age at study recruitment is associated with 1.61 (95% CI: 1.59-1.63) times the odds of CKD ascertainment. Healthcare clients who are first ascertained with cervical cancer are 1.53 (95% CI: 1.09-2.10) times more likely to be subsequently ascertained with CKD than healthcare clients without cervical cancer, and healthcare clients with prior TB ascertainment are 1.18 (95% CI: 1.07-1.30) times more likely to be ascertained with CKD compared to healthcare clients without TB. The analysis suggests that healthcare clients with prior hypertension are 9% less likely (Odds ratio [OR]: 0.91, 95% CI: 0.84-0.98) to be subsequently ascertained for CKD compared to healthcare clients without hypertension, and males are 14% less likely (OR: 0.86, 95% CI: 0.80-0.93) to be ascertained with CKD compared to females when age, HIV and other comorbidity status remain constant (Figure 3.1).

Diabetes

Among individuals with diabetes, a 5-year increase in the age at study recruitment is associated with higher odds of diabetes ascertainment (OR: 1.49, 95% CI: 1.49-1.50). Healthcare clients with prior ascertained CKD (OR: 0.79, 95% CI: 0.70-0.88), hypertension (OR: 0.74, 95% CI: 0.71-0.77), cervical cancer (OR: 0.74, 95% CI: 0.56-0.97), TB (OR: 0.57, 95% CI: 0.54-0.61), and HIV (OR: 0.45, 95% CI: 0.43-0.47) have lower odds of diabetes ascertainment compared to healthcare clients without these comorbidities. Our analysis shows that males have lower odds of diabetes ascertainment (OR: 0.68, 95% CI: 0.65-0.70) compared to females when age, HIV, and other comorbidity status remain constant (Table 3.3). We assessed the risk of diabetes ascertainment for healthcare clients with prior HIV ascertainment by age group. Our results show lower odds of diabetes ascertainment in all age groups for healthcare clients with prior HIV: 18-29 years (OR: 0.77, 95% CI: 0.65-0.91),

30-44 years (OR: 0.41, 95% CI: 0.38-0.44), 45-60 years (OR: 0.28, 95% CI: 0.26-0.30), and 60+ years (OR: 0.31, 95% CI: 0.25-0.36).

Hypertension

Our analysis shows that prior ascertainment of diabetes (OR: 2.17, 95% CI: 2.08-2.27) and 5-year increase in the age at study recruitment (OR: 1.62 95% CI: 1.61,1.63) are associated with subsequent hypertension ascertainment. Healthcare clients with prior CKD ascertainment (OR: 0.88, 95% CI: 0.78-0.98), HIV (OR: 0.67, 95% CI: 0.65-0.69) and TB (OR: 0.50, 95% CI: 0.48-0.52) compared to healthcare clients without these conditions, and being a male (OR: 0.66, 95% CI: 0.64-0.67) compared to being a female is associated with lower odds of hypertension ascertainment (Table 3.3). We assessed the risk of hypertension for healthcare clients with prior HIV ascertainment by age category. Our results show lower odds of hypertension ascertainment for healthcare clients with prior HIV: 30-44 years (OR: 0.62, 95% CI: 0.59-0.46), 45-60 years (OR: 0.34, 95% CI: 0.33-0.36), and 60+ years (OR: 0.34, 95% CI: 0.30-0.39) age groups. There was no significant association between prior HIV and subsequent hypertension ascertainment for healthcare clients in 18-29 years age group (OR: 1.02, 95% CI: 0.95-1.12).

Tuberculosis

Healthcare clients who are first ascertained with HIV are 3.53 (95% CI: 3.44-3.61) times more likely to have a subsequent TB ascertainment compared to HIV-negative healthcare clients. Males compared to females (OR: 1.74, 95% CI: 1.70-1.79), and a 5-year increase in age at study recruitment (OR: 1.20, 95% CI: 1.19-1.20) are associated with higher odds of TB ascertainment. Healthcare clients with prior CKD ascertainment (OR: 0.65, 95% CI: 0.57-0.75), diabetes (OR: 0.62, 95% CI: 0.58-0.66), cervical cancer (OR: 0.54, 95% CI: 0.44-0.67), and hypertension (OR: 0.18, 95% CI: 0.18-0.19) have lower odds of subsequent TB ascertainment (Table 3.3).

Cervical cancer

Healthcare clients with prior HIV ascertainment are 4.91 (95% CI: 4.30-5.61) times more likely to be subsequently ascertained with cervical cancer compared to HIV-negative healthcare clients and a 5-year increase in the age at study recruitment is associated with 1.35 (95% CI: 1.32-1.38) higher odds of cervical cancer ascertainment. Healthcare clients

with prior ascertained diabetes (OR: 0.70, 95% CI: 0.53-0.91), TB (OR: 0.60, 95% CI: 0.51-0.71), CKD (OR: 0.53, 95% CI: 0.29-0.87), and hypertension (OR: 0.37, 95% CI: 0.30-0.44) have lower odds of subsequent cervical cancer ascertainment compared to healthcare clients without these conditions (Table 3.3).

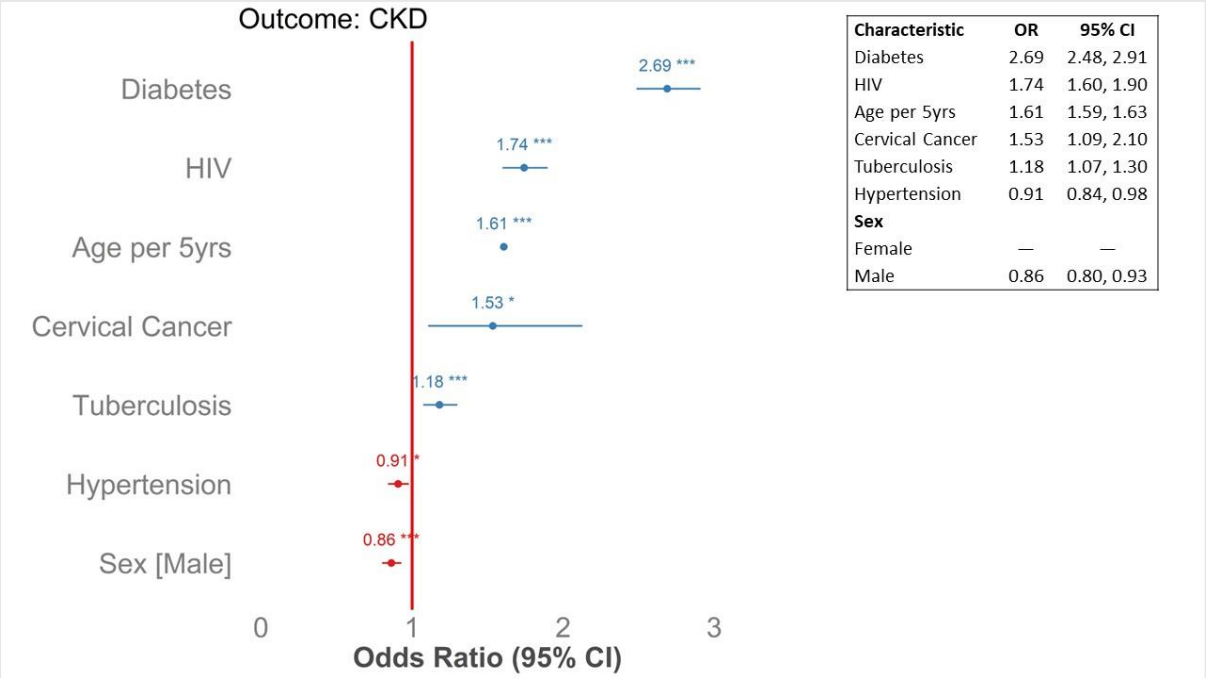


Figure 3.1: Risk of CKD for individuals with prior comorbidities showing odds ratios and 95% Confidence intervals. Odds ratios greater than one are shown in blue and odds ratios less than one are shown in red.

Table 3.3: Logistic regression to estimate the risk of comorbidities for individuals with prior ascertainment of HIV and other comorbidities.

	Risk factors (Odds ratio, 95% Confidence interval)							
Outcome	**Age in 5-year increments**	**Sex (Male)**	**HIV**	**CKD**	**Diabetes**	**Hypertension**	**TB**	**Cervical cancer**
CKD	1.61 (1.59,1.63)	0.86 (0.80,0.93)	1.74 (1.60,1.90)	-	2.69 (2.48,2.91)	0.91 (0.84,0.98)	1.18 (1.07,1.30)	1.53 (1.09,2.10)
Diabetes	1.49 (1.49,1.50)	0.68 (0.65,0.70)	0.45 (0.43,0.47)	0.79 (0.70,0.88)	-	0.74 (0.71,0.77)	0.57 (0.54,0.61)	0.74 (0.56,0.97)
Hypertension	1.62 (1.61,1.63)	0.66 (0.64,0.67)	0.67 (0.65,0.69)	0.88 (0.78,0.98)	2.17 (2.08,2.27)	-	0.50 (0.48,0.52)	0.87 (0.73,1.04)
TB	1.20 (1.19,1.20)	1.74 (1.70,1.79)	3.53 (3.44,3.61)	0.65 (0.57,0.75)	0.62 (0.58,0.66)	0.18 (0.18,0.19)	-	0.54 (0.44,0.67)
Cervical cancer	1.35 (1.32,1.38)	-	4.91 (4.30,5.61)	0.53 (0.29,0.87)	0.70 (0.53,0.91)	0.37 (0.30,0.44)	0.60 (0.51,0.71)	-

3.6.3 Timeline of events for HIV and comorbidities ascertainment among healthcare clients

The age, sex, and HIV status at time of comorbidities ascertainment and the relative time between HIV and comorbidity ascertainment were determined for NCDs – CKD, hypertension, and diabetes (Figure 3.2, Figure 3.3, and Figure 3.4) and infectious diseases – TB and cervical cancer (Figure 3.5 and Figure 3.6). There are more healthcare clients with HIV at the time of diagnosis of each comorbidity than those who were HIV-negative (Figure 3.2 - Figure 3.6). Our analysis shows the distribution of healthcare clients first ascertained with HIV before comorbidity ascertainment, and the distribution of healthcare clients ascertained with a comorbidity before HIV ascertainment. In general, the results show that for healthcare clients first ascertained with HIV, subsequent comorbidity ascertainment may occur within a 10-year period, and for healthcare clients who are first ascertained with a comorbidity, ascertainment of HIV may occur with a 7-year period (Figure 3.2 - Figure 3.6). Females and males who were living with HIV at the time of CKD, hypertension and diabetes ascertainment appear evenly distributed (Figure 3.2, Figure 3.3, and Figure 3.4). Males living with HIV and ascertained with TB, appear to be ascertained at older ages compared to females (Figure 3.5). In Figure 3.6, we observed, as expected, that prior HIV infection was common in female healthcare clients ascertained with cervical cancer.

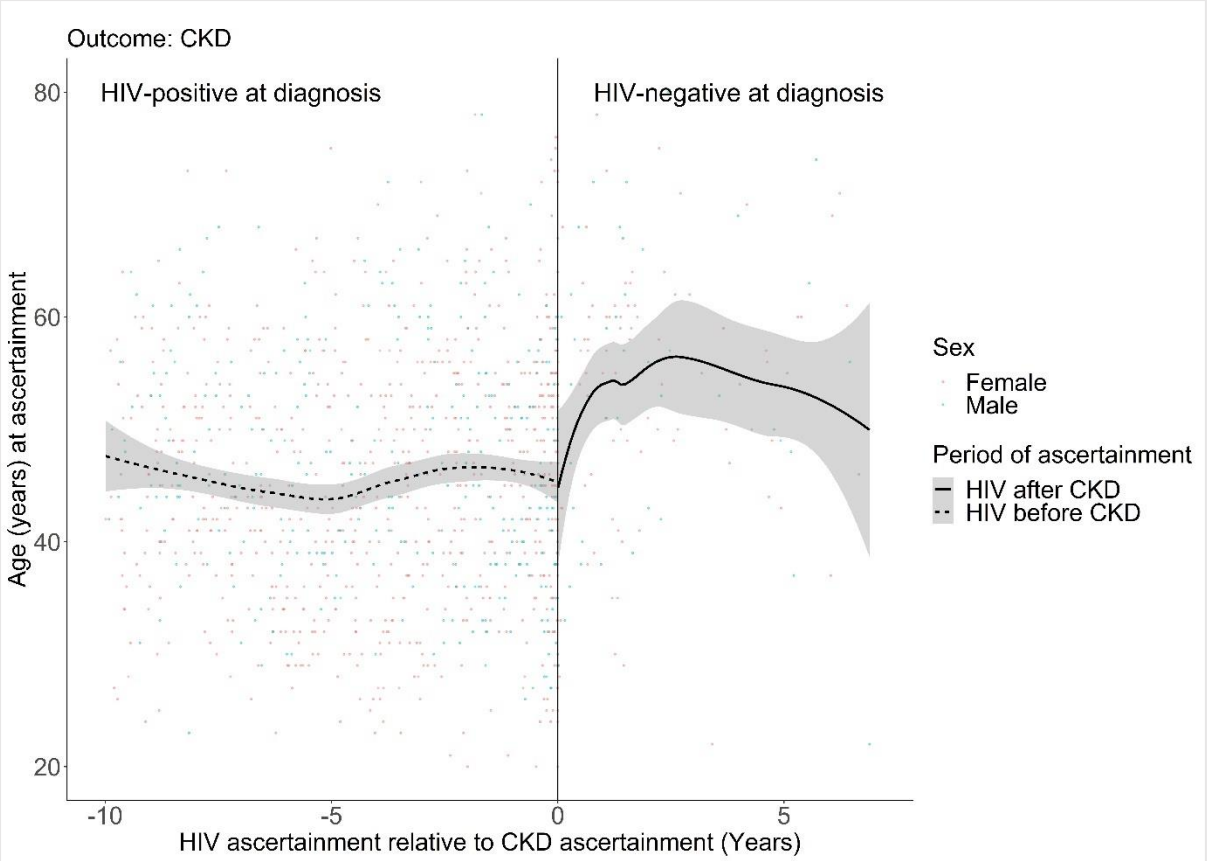


Figure 3.2: Age, sex, and HIV status at time of CKD ascertainment. Y-axis: age (in years) at ascertainment, X-axis: time (in years) of HIV ascertainment relative to CKD ascertainment. Data points are coloured by sex. Red: Female, Blue: Male.

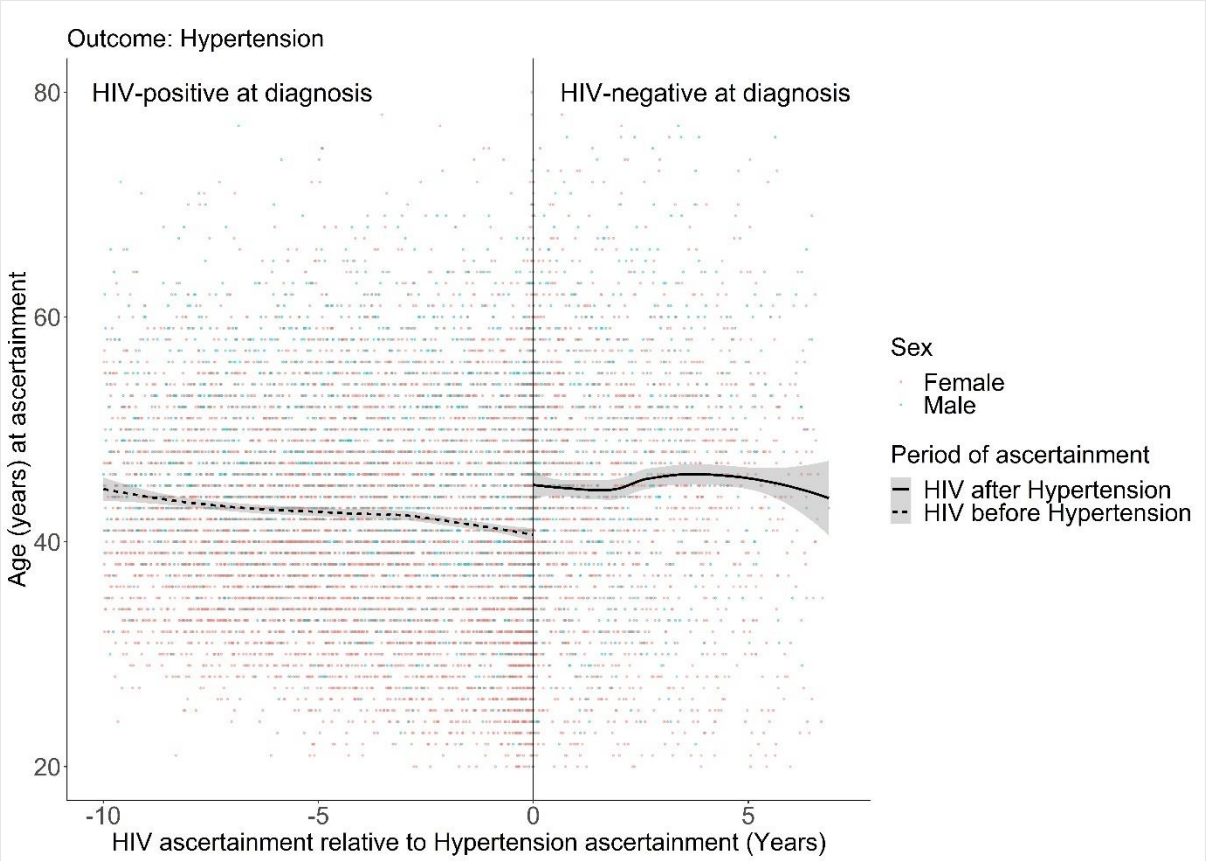


Figure 3.3: Age, sex, and HIV status at time of Hypertension ascertainment. Y-axis: age (in years) at ascertainment, X-axis: time (in years) of HIV ascertainment relative to Hypertension ascertainment. Data points are coloured by sex. Red: Female, Blue: Male.

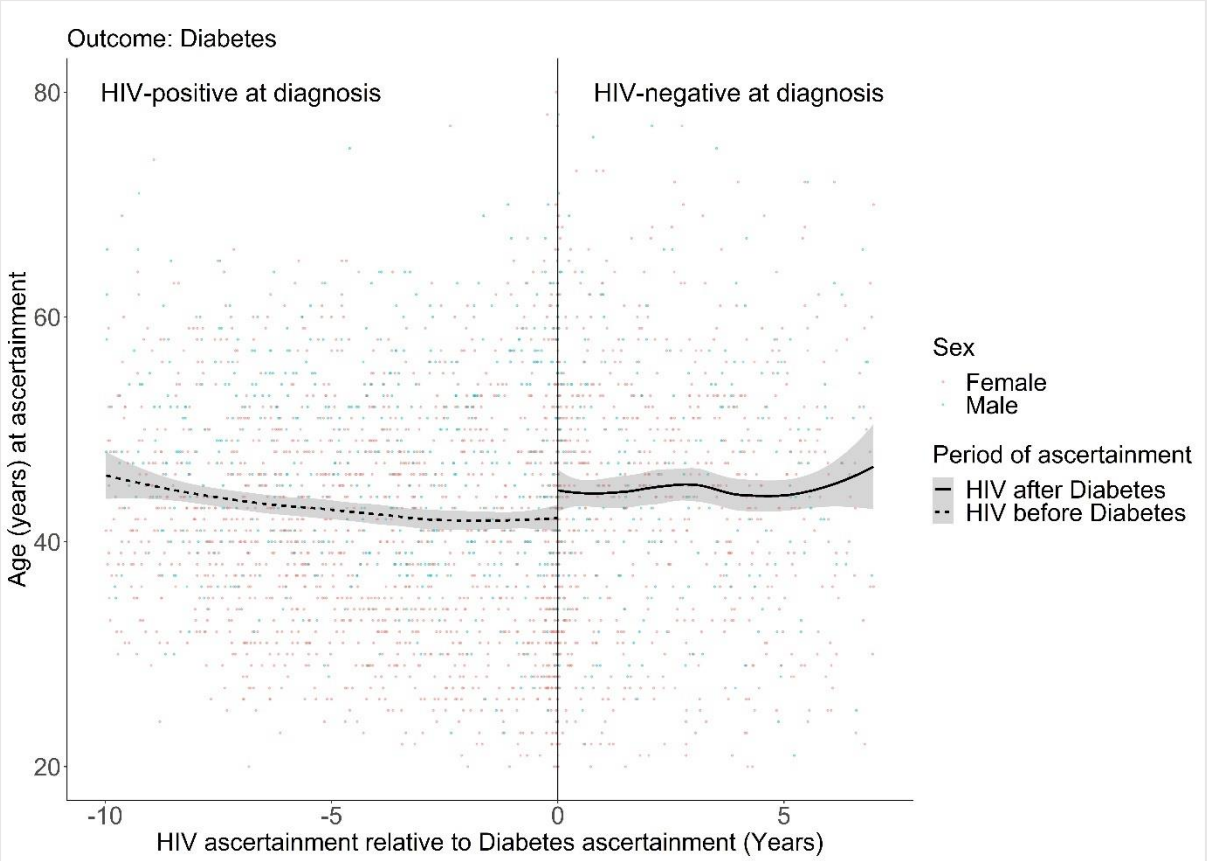


Figure 3.4: Age, sex, and HIV status at time of Diabetes ascertainment. Y-axis: age (in years) at ascertainment, X-axis: time (in years) of HIV ascertainment relative to Diabetes ascertainment. Data points are coloured by sex. Red: Female, Blue: Male.

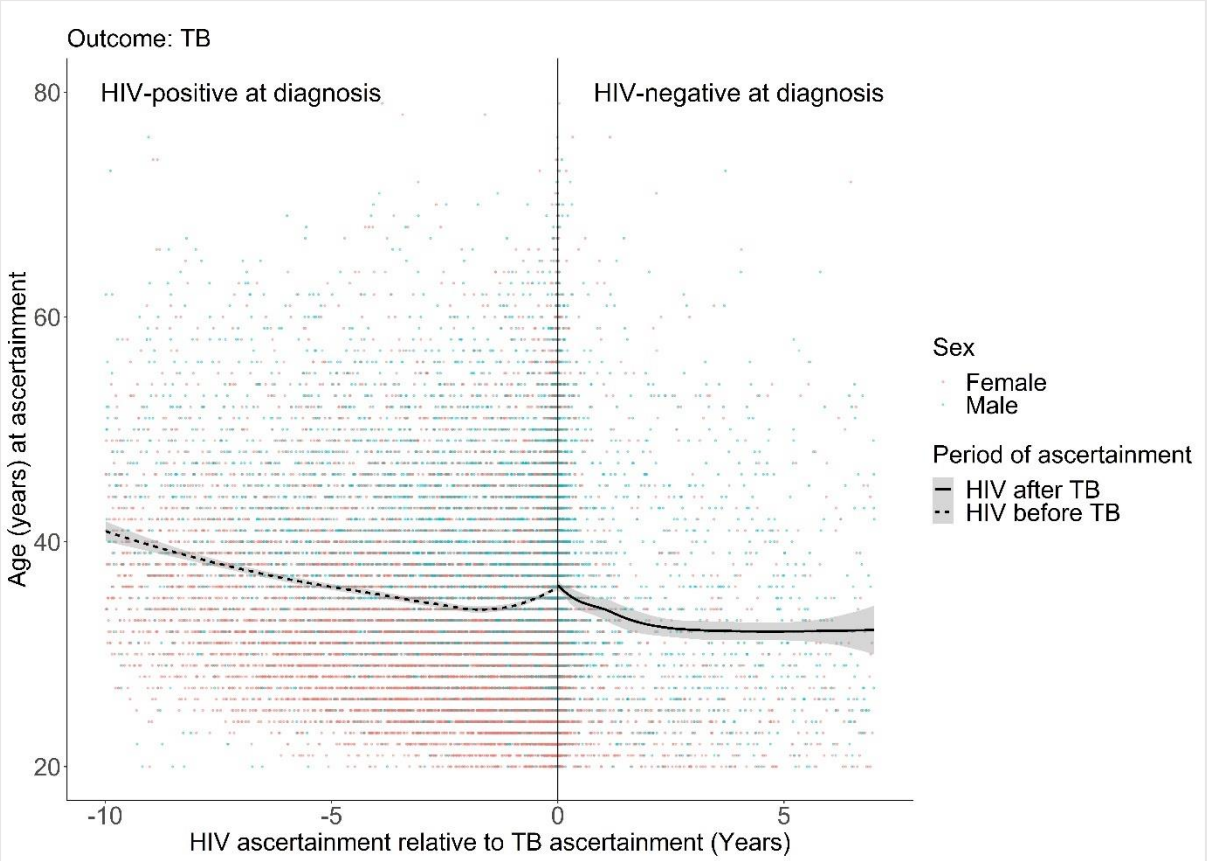


Figure 3.5: Age, sex, and HIV status at time of TB ascertainment. Y-axis: age (in years) at ascertainment, X-axis: time (in years) of HIV ascertainment relative to TB ascertainment. Data points are coloured by sex. Red: Female, Blue: Male.

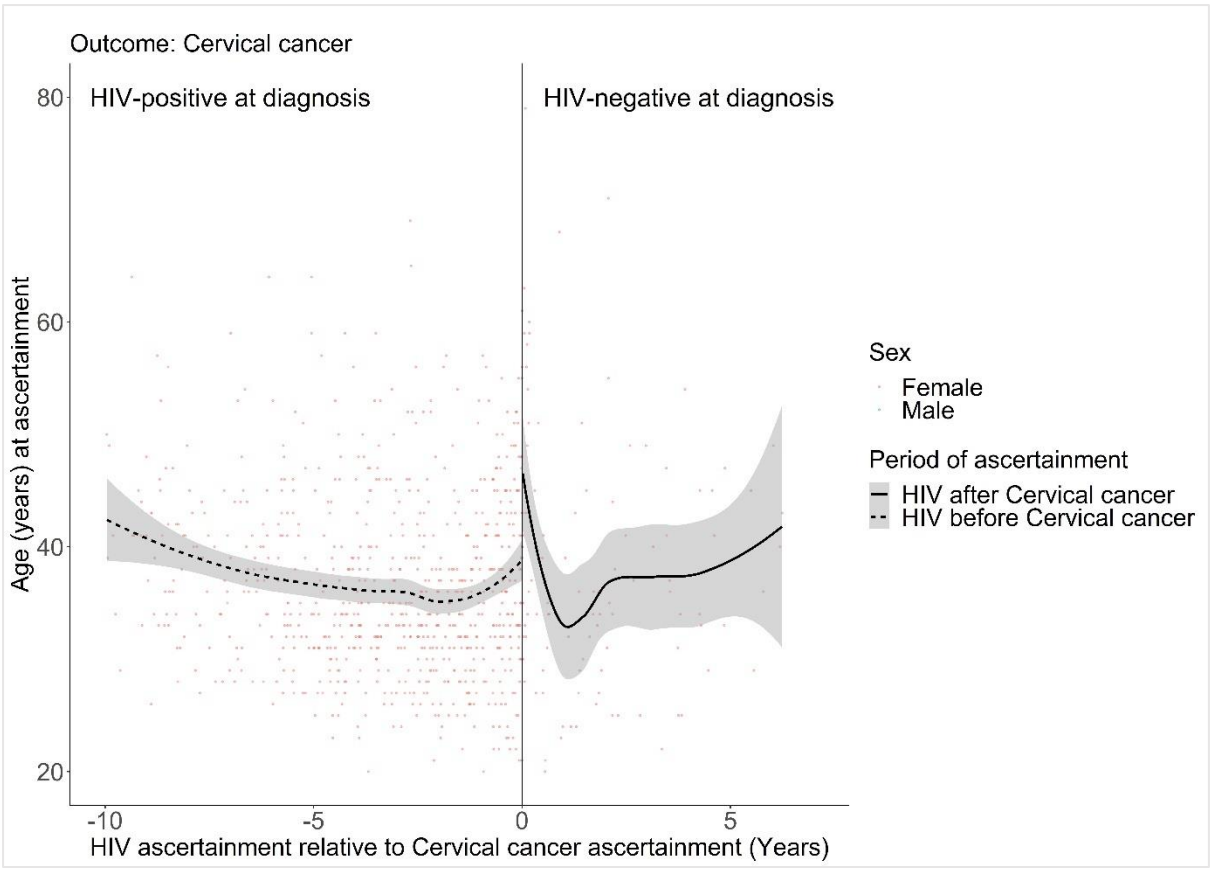


Figure 3.6: Age, sex, and HIV status at time of Cervical cancer ascertainment. Y-axis: age (in years) at ascertainment, X-axis: time (in years) of HIV ascertainment relative to Cervical cancer ascertainment. Data points are coloured by sex. Red: Female

3.6.4 Prior HIV ascertainment and the probability of developing comorbidities of interest

NCDs

From the Kaplan-Meier survival curves, it is observed among healthcare clients with prior HIV that the probability of subsequent CKD incidence is higher between 45 and 70 years than the HIV-negative healthcare clients (Figure 3.7). The number of healthcare clients at risk of CKD at 60 years shows quite a few numbers of PLHIV at risk compared to the HIV-negative healthcare clients (Figure 3.7). Generally, PLHIV appear to have slightly lower probability of hypertension incidence than HIV-negative healthcare clients. The difference is clearly seen beyond 60 years but the number of healthcare clients at risk are incomparable between PLHIV and HIV-negative clients (Figure 3.8). Our analysis shows that PLHIV have a lower probability of diabetes compared to the HIV-negative individuals (Figure 3.9). From 40 years, there is a clear difference in diabetes incidence between healthcare clients with prior HIV and HIV-negative healthcare clients.

Infectious diseases

The probability of TB incidence among healthcare clients with prior HIV is higher at all ages compared to the HIV-negative healthcare clients and a significant difference can be observed between these groups (Figure 3.10). For cervical cancer incidence, the survival curve shows a slight difference in cervical cancer incidence between PLHIV and HIV-negative healthcare clients even though PLHIV appear to have higher probability of subsequent cervical cancer incidence (Figure 3.11).

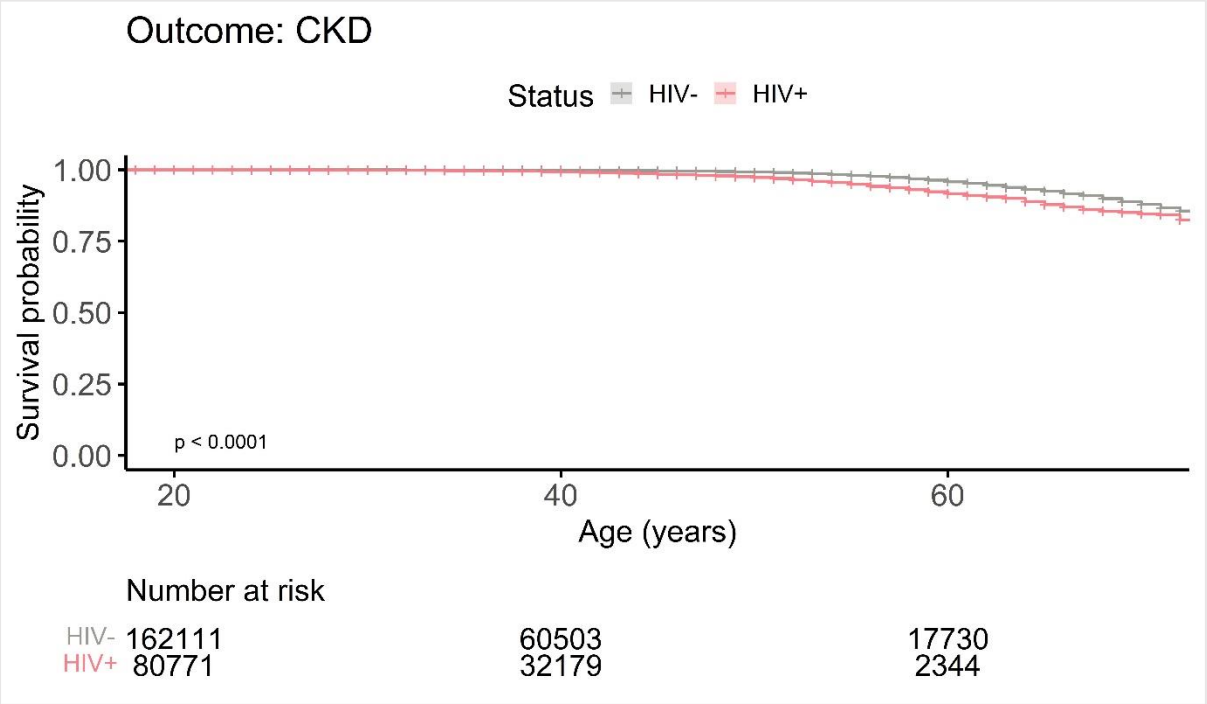


Figure 3.7: Kaplan-Meier survival curve of the probability of CKD occurrence for individuals with prior HIV ascertainment vs HIV-negative healthcare clients, and the number of healthcare clients at risk

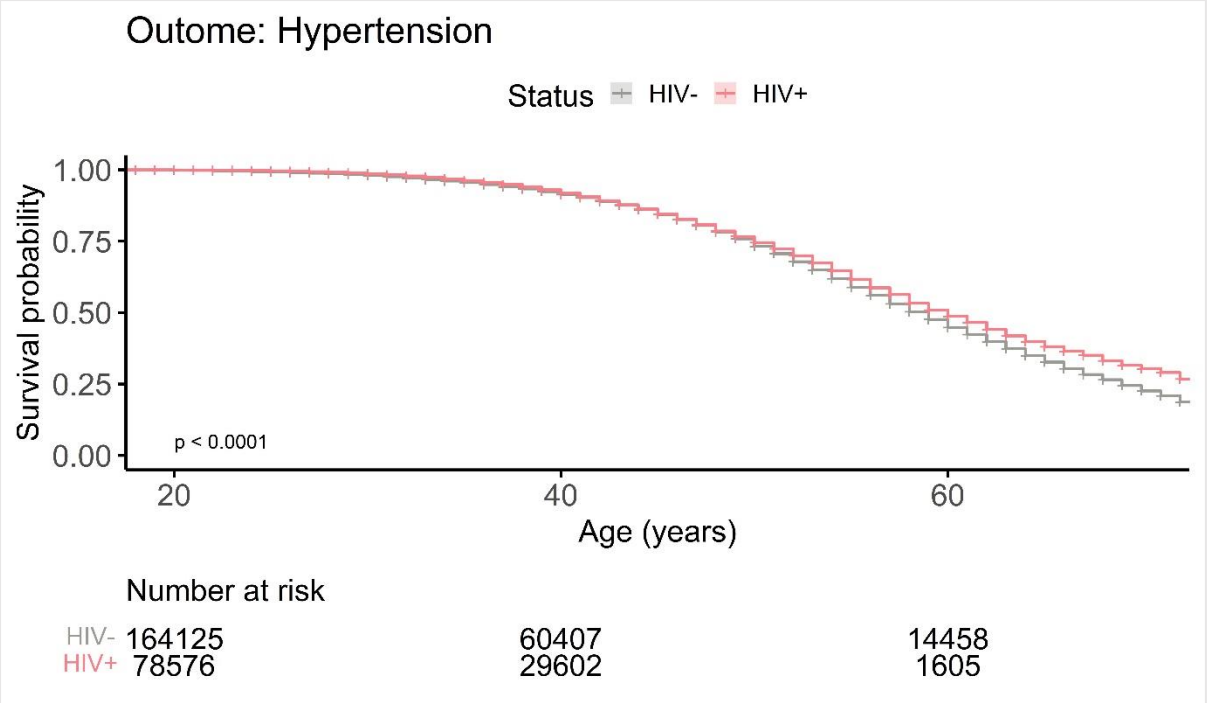


Figure 3.8: Kaplan-Meier survival curve of the probability of Hypertension occurrence for individuals with prior HIV ascertainment vs HIV-negative healthcare clients, and the number of healthcare clients at risk

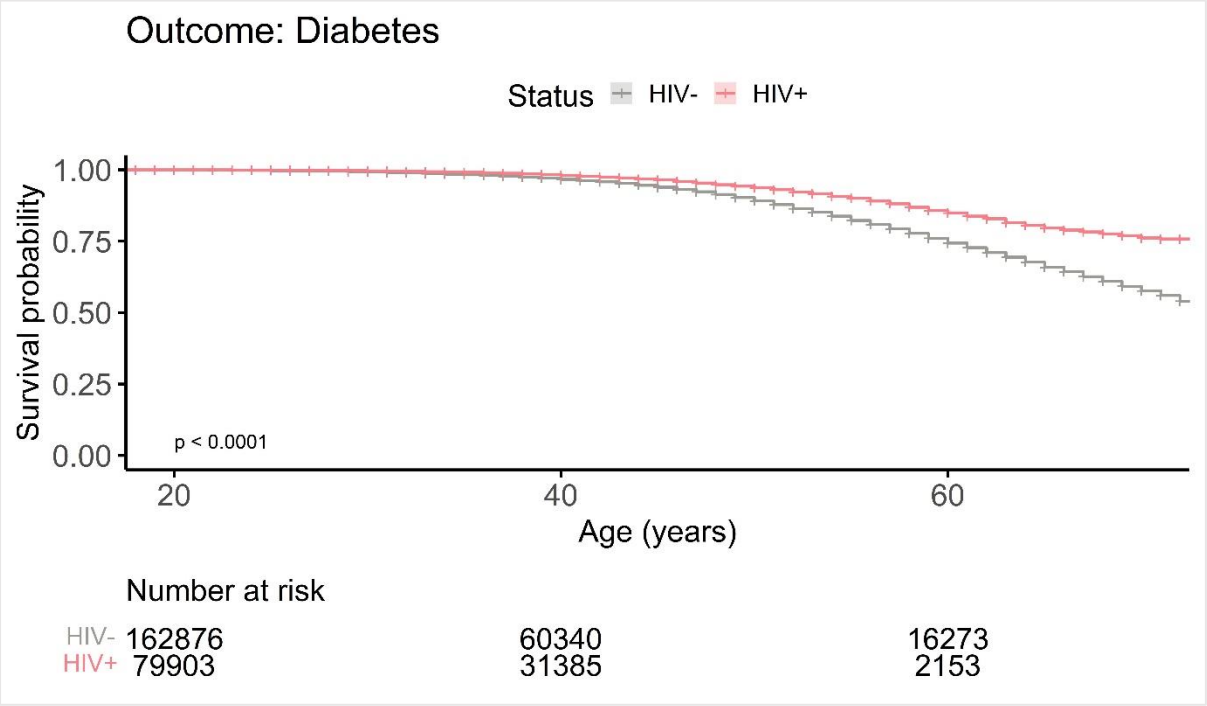


Figure 3.9: Kaplan-Meier survival curve of the probability of Diabetes occurrence for individuals with prior HIV ascertainment vs HIV-negative healthcare clients, and the number of healthcare clients at risk

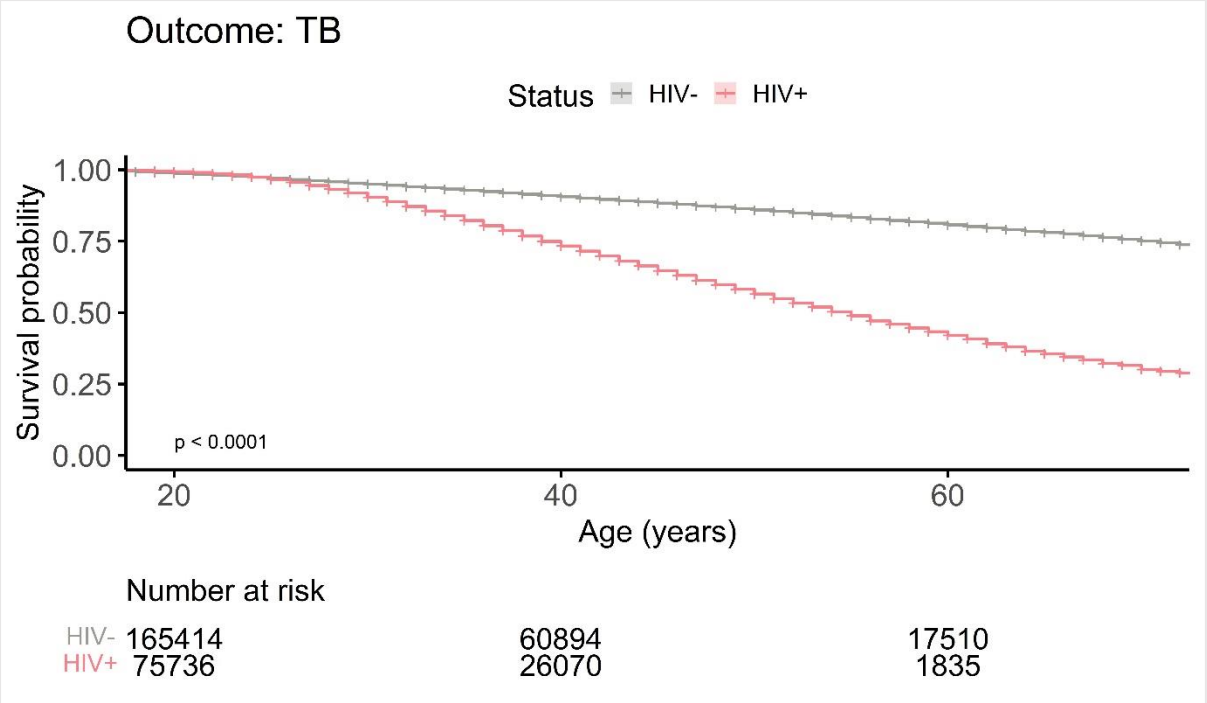


Figure 3.10: Kaplan-Meier survival curve of the probability of TB occurrence for individuals with prior HIV ascertainment vs HIV-negative healthcare clients, and the number of healthcare clients at risk

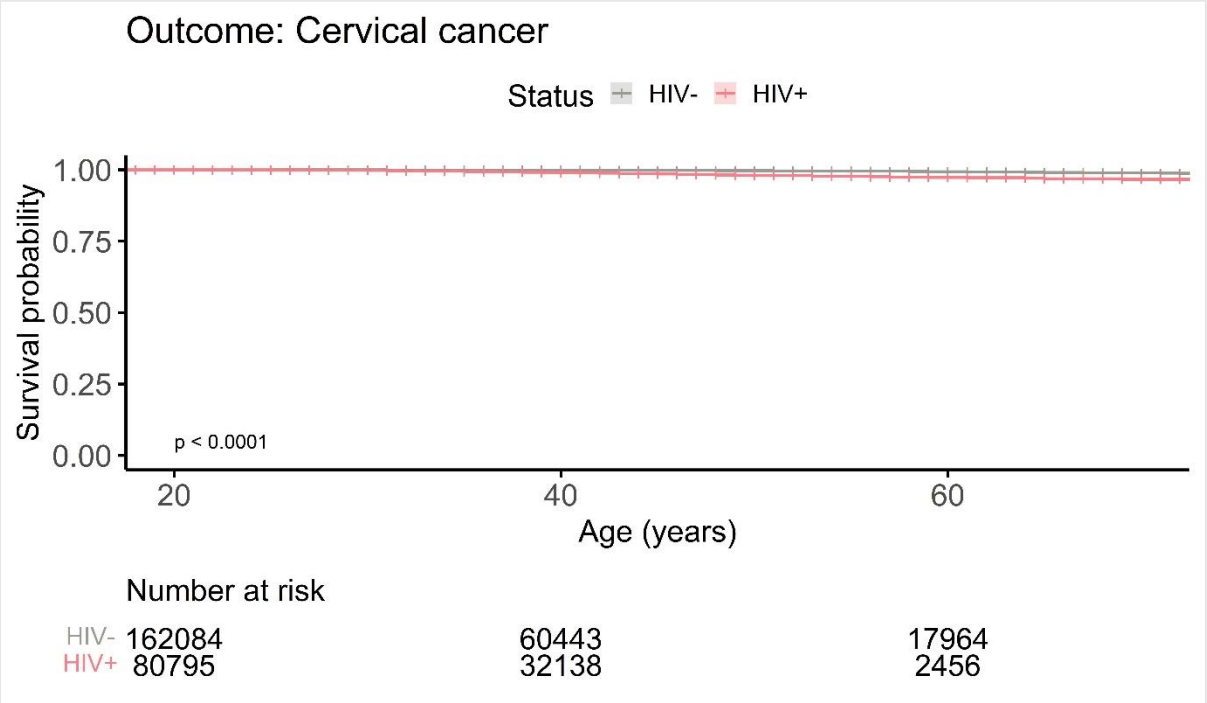


Figure 3.11: Kaplan-Meier survival curve of the probability of Cervical cancer occurrence for individuals with prior HIV ascertainment vs HIV-negative healthcare clients, and the number of healthcare clients at risk.

3.7 Discussion

The study participants represent a population of healthcare clients accessing care in public facilities for many different reasons including accessing healthcare for maternal and contraceptive services for young female healthcare clients, accessing treatment for chronic conditions for HIV-negative clients and accessing HIV care and services for PLHIV. We observed higher proportions of female healthcare clients in the overall study population, in the HIV-negative, and HIV-positive sub-populations than male healthcare clients in this study population, which is similar to a previous study that assessed HIV and comorbidity profiles in healthcare clients in Khayelitsha, Cape Town (Osei-Yeboah et al., 2021). In addition to the other reasons for healthcare access described above for women and HIV-negative healthcare clients, HIV diagnosis generally occurs earlier in females than males (Mabaso et al., 2018) and frequent healthcare access by females due to their generally early care seeking behaviours compared to late care seeking behaviours of males may lead to early HIV ascertainment in women (Luseno et al., 2010; Pulerwitz et al., 2019) and may explain the higher proportions of females than males in the HIV-positive subpopulation.

The Universal Test and Treat (UTT) guideline for PLHIV in South Africa (National Department of Health, 2016) means that improved ART services are widely available and accessible for all patients. The median age of PLHIV (37 years) and the high proportion of PLHIV on ART (85.9%) at the end of recruitment provide insights into early HIV ascertainment and the remarkable achievements of the current guideline in providing adequate care. It is important to note that the proportion of PLHIV on ART (85.9%) in our study population is higher than the 70.7% reported from the 2017 national HIV survey in South Africa (Marinda et al., 2020) and about 70% (Grobler et al., 2017; Huerga et al., 2018) reported from household-based community cross-sectional surveys in HIV endemic areas in South Africa .

Our results show that more PLHIV were ascertained with TB and cervical cancer than HIV-negative healthcare clients, whilst more HIV-negative clients were ascertained with NCDs - CKD, diabetes, and hypertension than PLHIV. Both TB and cervical cancer are common conditions associated with HIV and we expected to see this in our study population. Given that the population of PLHIV in South Africa is now ageing, NCDs which are mostly prevalent among people in the older ages may not be manifesting in this population yet compared to the HIV-negative healthcare clients (Osei-Yeboah et al., 2021). Conversely, screening for

common NCDs for PLHIV when they access HIV care and services may ensure early identification and timely treatment, unlike the HIV-negative healthcare clients who may be accessing care for these NCDs when they are already ill.

Our results show that for many healthcare clients living with HIV and other co-existing conditions, HIV ascertainment precedes the diagnosis of the co-existing conditions. This suggests an initial HIV occurrence and subsequent development of comorbidities among the healthcare clients. Whilst previous studies have reported the indirect (Zicari et al., 2019) and direct (Sviridov et al., 2020) roles of HIV in the occurrence of HIV-related comorbidities, our analysis is not able to identify whether HIV infections play biological or aetiological roles in the occurrence of these comorbidities in the healthcare client population.

The incidence and long-term treatment of both infectious and chronic NCDs have several effects on the occurrence of other diseases, including serving as risk factors.

For healthcare clients with prior HIV, diabetes, cervical cancer and TB, the long-term treatments associated with these conditions and other predisposing factors such as the contributions of multimorbidity in an individual may contribute to the incidence of CKD (Igari et al., 2015; Jitraknatee et al., 2020; Manyau et al., 2021; Palau et al., 2018; Wu et al., 2014).

Even though previous epidemiological studies have reported high prevalence of hypertension and diabetes among PLHIV (Coetzee et al., 2019; Kansiime et al., 2019; Kato et al., 2020), by using routine health data from healthcare clients, our results provide an insight and deeper understanding of the actual scenarios of the possible incidence of these conditions in a healthcare client population. Additionally, by exploring the order of the occurrence of both HIV and other comorbidities - taking into account the exact age at ascertainment of both HIV and the comorbidities – we observe the age differences between PLHIV and HIV-negative healthcare clients in relation to the ages at ascertainment of hypertension and diabetes among the healthcare clients. A recent study in South Africa reports that among persons diagnosed with hypertension and diabetes, ART and/or undetectable viral load levels are associated with lower mean systolic blood pressure and lower mean blood glucose compared to HIV-negative individuals (Manne-Goehler et al., 2017) and concludes that HIV care programmes could be used to strengthen the health

system for managing cardiometabolic conditions. A similar study noted a differential disease prevalence by sex and age group in rural South Africa such that whereas women have substantially high prevalence of HIV at 30-49 years, prevalence of multiple and poorly treated NCDs occurred at ages older than 50 years (Wong et al., 2021). The findings of the age-stratified analyses show that having a prior HIV infection does not increase the risk of hypertension and diabetes ascertainment for healthcare clients in our study population. We observed that the odds of hypertension ascertainment decreased with increasing age (per age group). The odds of diabetes ascertainment similarly decreased with increasing age groups except for 60+ years which was slightly higher than the odds for 45-60 years. For both NCDs, we observed some of the healthcare clients in our study who first had HIV and subsequently developed them. Gaziano et al., report that among adults aged 40 years and above in Mpumalanga, South Africa, HIV-negative persons were more likely to have hypertension, diabetes or be overweight compared to PLHIV, and PLHIV had consistently lower prevalence of these comorbidities (Gaziano et al., 2017). Magodoro et al., examined if HIV infection is associated with a worse profile of cardiometabolic diseases in the South African adult population and report that overall, PLHIV have lower mean systolic blood pressure than the general population and hypertension and diabetes comorbidity was less common among PLHIV (Magodoro et al., 2022). Furthermore, the study found no association between HIV, hypertension and diabetes and observed that HIV was associated with lower adjusted mean systolic blood pressure and HbA1c in women. It concluded that PLHIV have better cardiometabolic disease profiles than the general population in South Africa and highlight that social determinants could greatly influence cardiometabolic risks rather than HIV (Magodoro et al., 2022). Additionally, other previous studies in SSA found HIV infection to be associated with lower prevalence and/odds of hypertension (Dillon et al., 2013; Kayima et al., 2015; Kwarisiima et al., 2016). A population-based cross-sectional analysis comparing health conditions in adults with HIV to the general population observed that hypertension was among the individual conditions that were less likely in adults with HIV (Morales et al., 2022). These findings support the observation we have made in our healthcare client population that prior ascertainment of HIV would not necessarily be associated with subsequent occurrence of common NCDs like hypertension and diabetes. We also note, however, that the ascertainment of hypertension by the PHDC is based on hypertension treatments received by patients. This means that this ascertainment is for

treated hypertension, and does not include cases of hypertension detected by clinical observation, or undiagnosed hypertension, and we recognise that this is a potential limitation of this analysis. It is expected that the frequent HIV care and services for PLHIV would ensure adequate screening for these conditions in a timely manner for the appropriate clinical management where they are detected.

Our analysis confirms that healthcare clients in our population with prior HIV have higher risks of subsequent TB and cervical cancer ascertainment compared to healthcare clients without HIV, and as these relationships have been widely studied in previous studies (Bruchfeld et al., 2015; Chang et al., 2013; Liu et al., 2018; Stelzle et al., 2021) we expected to see this in our population.

Our analysis shows the 10-year period after an HIV ascertainment within which comorbidities may be ascertained and the 7-year period after comorbidities ascertainment within which an HIV ascertainment may occur.

In TB endemic regions like South Africa, the risk of infection may occur at younger ages for both HIV-positive and -negative populations due to high rates of exposures and active social mixing (Snow et al., 2018). Whereas the risk decreases at later ages for HIV-negative individuals, it continues through to the older ages among HIV-positive individuals and means that unlike older HIV-negative healthcare clients, older PLHIV are still highly at risk of TB infection. Therefore, longer timelines to the ascertainment of TB after HIV infection do not mean PLHIV may be living with TB infection for a longer period before ascertainment, but rather because of possible later infection.

Long-term use of antiretrovirals for HIV is associated with kidney diseases, and HIV-associated nephropathies are widely studied (Husain et al., 2018; Palau et al., 2018). This suggests that for healthcare clients in our population who are receiving ART, ascertainment of CKD may span several years after HIV diagnosis as we observed. The incidence of cervical cancer after HIV infection has been widely reported and previous studies classify cervical cancer as a HIV-related comorbidity (Manyau et al., 2021; Onohuean et al., 2022; Stelzle et al., 2021). Previous studies in SSA have reported that higher proportions of women with cervical cancer were receiving ART prior to cervical cancer diagnosis (Dryden-Peterson et al.,

2016), and HIV infection was highly associated with the development of cervical precancerous lesions (Chambuso et al., 2017).

The results of the Kaplan-Meier estimates show higher probabilities of subsequent ascertainment of CKD, TB and cervical cancer for healthcare clients who have prior HIV compared to HIV-negative healthcare clients. Previous studies have documented relationships between HIV and these conditions (Bruchfeld et al., 2015; Husain et al., 2018; Naicker, 2020; Onohuean et al., 2022; Palau et al., 2018; Stelzle et al., 2021), and we expected this relationship to reflect in our study population of healthcare clients who have prior HIV infection.

The fewer numbers of PLHIV beyond 60 years who are at risk of each of the disease conditions assessed in our study compared to the higher number of HIV-negative healthcare clients provide a clearer insight into the age differences between the PLHIV and HIV-negative healthcare clients in our population. This age difference may also contribute to the lower probabilities of hypertension and diabetes ascertainment for PLHIV as these conditions are often common in people in old ages. In addition, this may reflect the healthcare access dynamics, in which PLHIV tend to access healthcare at earlier ages, and people who are HIV-negative tend to come in because they have some other condition(s) that require care. This means that the dataset from the routine health data is enriched for younger PLHIV, and older HIV-negative individuals who have other comorbidities.

3.8 Conclusion

Our analyses of routine health data show that the population of healthcare clients seen in this study are different populations: young PLHIV are different to older PLHIV; and older PLHIV are different to older HIV-negative healthcare clients. Even though these data are enriched for healthcare clients who are HIV-negative but have other health conditions, we still see that HIV infection leads to earlier ascertainment of cervical cancer (a proxy for human papilloma virus (HPV) infection), TB and CKD, in line with findings from other studies. For NCDs, however, the differences in the makeup of the underlying subpopulations (as we described above) show how ascertainment differs, and this may agree with findings that have also been described in other studies. This study demonstrates that analysis of the

longitudinal routine health data can show known and well-recognised associations, as well as describing nuances in the different sub-populations of the healthcare client population.

3.9 Acknowledgement

We acknowledge the Provincial Health Data Centre, Health Impact Assessment Directorate of the Western Cape Government Health Department for the provision of the anonymized Khayelitsha dataset.

3.10 Data availability statement

These anonymized, perturbed data were provided for analysis by the Western Cape Department of Health, Provincial Health Data Centre. These are highly granular health data linked to individual health care clients in the province and no informed consent has been given for research use. For this reason, the Western Cape Department of Health does not permit open sharing but instead grants only primary use permission for the data. Re-use of this dataset requires approval from the Western Cape Department of Health (Provincial Health Data Centre), and Dr Moodley, Director: HIA, Western Cape Department of Health, South Africa can be contacted to advise on this process (email: melvin.moodley@westerncape.gov.za, Reference study ID 259-TIFFIN).

3.11 Funding

This research was funded in part, by the Wellcome Trust 203135/Z/16/Z. For the purpose of open access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript version arising from this submission. The Wellcome Centre for Infectious Diseases Research in Africa is supported by core funding from the Wellcome Trust [203135/Z/16/Z]. ROY receives funding from the Africa Regional Staff/Student International Exchange: Food Security and Sustainable Human Wellbeing II (ARISE II) Consortium funded by the Intra-Africa Academic Mobility Scheme of the European Union (2016-2616). NT receives funding from the NIH Common Fund (H3ABioNet, U24HG006941). NT receives funding from Wellcome CIDRI-Africa (203135/Z/16/Z). NT additionally receives support from the NIH B-Positive grant (R01HD080465).

3.12 References

Althoff, K. N., McGinnis, K. A., Wyatt, C. M., Freiberg, M. S., Gilbert, C., Oursler, K. K., Rimland, D., Rodriguez-Barradas, M. C., Dubrow, R., Park, L. S., Skanderson, M., Shiels, M. S., Gange, S. J., Gebo, K. A., & Justice, A. C. (2015). Comparison of Risk and Age at Diagnosis of Myocardial Infarction, End-Stage Renal Disease, and Non-AIDS-Defining Cancer in HIV-Infected Versus Uninfected Adults. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, *60*(4), 627–638. https://doi.org/10.1093/cid/ciu869

Althoff, K. N., Smit, M., Reiss, P., & Justice, A. C. (2016). HIV and ageing: Improving quantity and quality of life. *Current Opinion in HIV and AIDS*, *11*(5), 527–536. https://doi.org/10.1097/COH.0000000000000305

Boulle, A., Heekes, A., Tiffin, N., Smith, M., Mutemaringa, T., Zinyakatira, N., Phelanyane, F., Pienaar, C., Buddiga, K., Coetzee, E., Rooyen, R. van, Dyers, R., Fredericks, N., Loff, A., Shand, L., Moodley, M., Vega, I. de, & Vallabhjee, K. (2019). Data Centre Profile: The Provincial Health Data Centre of the Western Cape Province, South Africa. *International Journal of Population Data Science*, *4*(2), Article 2. https://doi.org/10.23889/ijpds.v4i2.1143

Bruchfeld, J., Correia-Neves, M., & Källenius, G. (2015). Tuberculosis and HIV Coinfection. *Cold Spring Harbor Perspectives in Medicine*, *5*(7), a017871. https://doi.org/10.1101/cshperspect.a017871

Chambuso, R. S., Shadrack, S., Lidenge, S. J., Mwakibete, N., & Medeiros, R. M. (2017). Influence of HIV/AIDS on Cervical Cancer: A Retrospective Study From Tanzania. *Journal of Global Oncology*, *3*(1), 72–78. https://doi.org/10.1200/JGO.2015.002964

Chang, C. C., Crane, M., Zhou, J., Mina, M., Post, J. J., Cameron, B. A., Lloyd, A. R., Jaworowski, A., French, M. A., & Lewin, S. R. (2013). HIV and co-infections. *Immunological Reviews*, *254*(1), 114–142. https://doi.org/10.1111/imr.12063

Coetzee, L., Bogler, L., Neve, J.-W. D., Bärnighausen, T., Geldsetzer, P., & Vollmer, S. (2019). HIV, antiretroviral therapy and non-communicable diseases in sub-Saharan Africa: Empirical evidence from 44 countries over the period 2000 to 2016. *Journal of the International AIDS Society*, *22*(7), e25364. https://doi.org/10.1002/jia2.25364

Cox, J. A., Kiggundu, D., Elpert, L., Meintjes, G., Colebunders, R., & Alamo, S. (2016). Temporal trends in death causes in adults attending an urban HIV clinic in Uganda: A retrospective chart review. *BMJ Open*, *6*(1), e008718. https://doi.org/10.1136/bmjopen-2015-008718

D'Arrigo, G., Leonardis, D., Abd ElHafeez, S., Fusaro, M., Tripepi, G., & Roumeliotis, S. (2021). Methods to Analyse Time-to-Event Data: The Kaplan-Meier Survival Curve. *Oxidative Medicine and Cellular Longevity*, *2021*, e2290120. https://doi.org/10.1155/2021/2290120

Dillon, D. G., Gurdasani, D., Riha, J., Ekoru, K., Asiki, G., Mayanja, B. N., Levitt, N. S., Crowther, N. J., Nyirenda, M., Njelekela, M., Ramaiya, K., Nyan, O., Adewole, O. O.,

Anastos, K., Azzoni, L., Boom, W. H., Compostella, C., Dave, J. A., Dawood, H., … on behalf of the African Partnership for Chronic Disease Research (APCDR). (2013). Association of HIV and ART with cardiometabolic traits in sub-Saharan Africa: A systematic review and meta-analysis. *International Journal of Epidemiology*, *42*(6), 1754–1771. https://doi.org/10.1093/ije/dyt198

Dryden-Peterson, S., Bvochora-Nsingo, M., Suneja, G., Efstathiou, J. A., Grover, S., Chiyapo, S., Ramogola-Masire, D., Kebabonye-Pusoentsi, M., Clayman, R., Mapes, A. C., Tapela, N., Asmelash, A., Medhin, H., Viswanathan, A. N., Russell, A. H., Lin, L. L., Kayembe, M. K. A., Mmalane, M., Randall, T. C., … Lockman, S. (2016). HIV Infection and Survival Among Women With Cervical Cancer. *Journal of Clinical Oncology*, *34*(31), 3749–3757. https://doi.org/10.1200/JCO.2016.67.9613

Gaziano, T. A., Abrahams-Gessel, S., Gomez-Olive, F. X., Wade, A., Crowther, N. J., Alam, S., Manne-Goehler, J., Kabudula, C. W., Wagner, R., Rohr, J., Montana, L., Kahn, K., Bärnighausen, T. W., Berkman, L. F., & Tollman, S. (2017). Cardiometabolic risk in a population of older adults with multiple co-morbidities in rural south africa: The HAALSI (Health and Aging in Africa: longitudinal studies of INDEPTH communities) study. *BMC Public Health*, *17*(1), 206. https://doi.org/10.1186/s12889-017-4117-y

GBD 2017 HIV Collaborators, Frank, T. D., Carter, A., Jahagirdar, D., Biehl, M. H., Douwes-Schultz, D., Larson, S. L., Arora, M., Dwyer-Lindgren, L., Steuben, K. M., Abbastabar, H., Abu-Raddad, L. J., Abyu, D. M., Adabi, M., Adebayo, O. M., Adekanmbi, V., Adetokunboh, O. O., Ahmadi, A., Ahmadi, K., … Murray, C. J. L. (2019). Global, regional, and national incidence, prevalence, and mortality of HIV, 1980–2017, and forecasts to 2030, for 195 countries and territories: A systematic analysis for the Global Burden of Diseases, Injuries, and Risk Factors Study 2017. *The Lancet HIV*, *6*(12), e831–e859. https://doi.org/10.1016/S2352-3018(19)30196-1

Grobler, A., Cawood, C., Khanyile, D., Puren, A., & Kharsany, A. B. M. (2017). Progress of UNAIDS 90-90-90 targets in a district in KwaZulu-Natal, South Africa, with high HIV burden, in the HIPSS study: A household-based complex multilevel community survey. *The Lancet HIV*, *4*(11), e505–e513. https://doi.org/10.1016/S2352-3018(17)30122-4

Hodes, R., & Morrell, R. (2018). Incursions from the epicentre: Southern theory, social science, and the global HIV research domain. *African Journal of AIDS Research*, *17*(1), 22–31. https://doi.org/10.2989/16085906.2017.1377267

Huerga, H., Van Cutsem, G., Ben Farhat, J., Puren, A., Bouhenia, M., Wiesner, L., Dlamini, L., Maman, D., Ellman, T., & Etard, J.-F. (2018). Progress towards the UNAIDS 90–90-90 goals by age and gender in a rural area of KwaZulu-Natal, South Africa: A household-based community cross-sectional survey. *BMC Public Health*, *18*(1), 303. https://doi.org/10.1186/s12889-018-5208-0

Husain, N. E., Ahmed, M. H., Almobarak, A. O., Noor, S. K., Elmadhoun, W. M., Awadalla, H., Woodward, C. L., & Mital, D. (2018). HIV-Associated Nephropathy in Africa:

Pathology, Clinical Presentation and Strategy for Prevention. *Journal of Clinical Medicine Research*, *10*(1), 1–8. https://doi.org/10.14740/jocmr3235w

Igari, H., Imasawa, T., Noguchi, N., Nagayoshi, M., Mizuno, S., Ishikawa, S., Kadomura, M., Nishimura, M., & Yamagishi, F. (2015). Advanced stage of chronic kidney disease is risk of poor treatment outcome for smear-positive pulmonary tuberculosis. *Journal of Infection and Chemotherapy*, *21*(8), 559–563. https://doi.org/10.1016/j.jiac.2015.04.008

Jitraknatee, J., Ruengorn, C., & Nochaiwong, S. (2020). Prevalence and Risk Factors of Chronic Kidney Disease among Type 2 Diabetes Patients: A Cross-Sectional Study in Primary Care Practice. *Scientific Reports*, *10*(1), Article 1. https://doi.org/10.1038/s41598-020-63443-4

Kabudula, C. W., Houle, B., Collinson, M. A., Kahn, K., Gómez-Olivé, F. X., Clark, S. J., & Tollman, S. (2017). Progression of the epidemiological transition in a rural South African setting: Findings from population surveillance in Agincourt, 1993–2013. *BMC Public Health*, *17*(1), 424. https://doi.org/10.1186/s12889-017-4312-x

Kansiime, S., Mwesigire, D., & Mugerwa, H. (2019). Prevalence of non-communicable diseases among HIV positive patients on antiretroviral therapy at joint clinical research centre, Lubowa, Uganda. *PloS One*, *14*(8), e0221022. https://doi.org/10.1371/journal.pone.0221022

Kato, I., Tumaini, B., & Pallangyo, K. (2020). Prevalence of non-communicable diseases among individuals with HIV infection by antiretroviral therapy status in Dar es Salaam, Tanzania. *PLOS ONE*, *15*(7), e0235542. https://doi.org/10.1371/journal.pone.0235542

Kayima, J., Nankabirwa, J., Sinabulya, I., Nakibuuka, J., Zhu, X., Rahman, M., Longenecker, C. T., Katamba, A., Mayanja-Kizza, H., & Kamya, M. R. (2015). Determinants of hypertension in a young adult Ugandan population in epidemiological transition—The MEPI-CVD survey. *BMC Public Health*, *15*(1), 830. https://doi.org/10.1186/s12889-015-2146-y

Kwarisiima, D., Balzer, L., Heller, D., Kotwani, P., Chamie, G., Clark, T., Ayieko, J., Mwangwa, F., Jain, V., Byonanebye, D., Petersen, M., Havlir, D., & Kamya, M. R. (2016). Population-Based Assessment of Hypertension Epidemiology and Risk Factors among HIV-Positive and General Populations in Rural Uganda. *PLOS ONE*, *11*(5), e0156309. https://doi.org/10.1371/journal.pone.0156309

LIU, G., SHARMA, M., TAN, N., & BARNABAS, R. (2018). HIV-positive women have higher risk of HPV infection, precancerous lesions, and cervical cancer: A systematic review and meta-analysis. *AIDS (London, England)*, *32*(6), 795–808. https://doi.org/10.1097/QAD.0000000000001765

Luseno, W. K., Wechsberg, W. M., Kline, T. L., & Ellerson, R. M. (2010). Health Services Utilization Among South African Women Living with HIV and Reporting Sexual and Substance-Use Risk Behaviors. *AIDS Patient Care and STDs*, *24*(4), 257–264. https://doi.org/10.1089/apc.2009.0213

Mabaso, M., Sokhela, Z., Mohlabane, N., Chibi, B., Zuma, K., & Simbayi, L. (2018). Determinants of HIV infection among adolescent girls and young women aged 15–24 years in South Africa: A 2012 population-based national household survey. *BMC Public Health*, *18*(1), 183. https://doi.org/10.1186/s12889-018-5051-3

Magodoro, I. M., Okello, S., Dungeni, M., Castle, A. C., Mureyani, S., & Danaei, G. (2022). Association between HIV and Prevalent Hypertension and Diabetes Mellitus in South Africa: Analysis of a Nationally Representative Cross-Sectional Survey. *International Journal of Infectious Diseases*, *121*, 217–225. https://doi.org/10.1016/j.ijid.2022.05.035

Manne-Goehler, J., Montana, L., Gómez-Olivé, F. X., Rohr, J., Harling, G., Wagner, R. G., Wade, A., Kabudula, C. W., Geldsetzer, P., Kahn, K., Tollman, S., Berkman, L. F., Bärnighausen, T. W., & Gaziano, T. A. (2017). The ART advantage: Healthcare utilization for diabetes and hypertension in rural South Africa. *Journal of Acquired Immune Deficiency Syndromes (1999)*, *75*(5), 561–567. https://doi.org/10.1097/QAI.0000000000001445

Manyau, P. M. C., Mabeka, M., Mudzviti, T., Kadzatsa, W., & Nyamhunga, A. (2021). Renal function impairment in cervical cancer patients treated with cisplatin-based chemoradiation: A review of medical records in a Zimbabwean outpatient department. *PLOS ONE*, *16*(2), e0245383. https://doi.org/10.1371/journal.pone.0245383

Marinda, E., Simbayi, L., Zuma, K., Zungu, N., Moyo, S., Kondlo, L., Jooste, S., Nadol, P., Igumbor, E., Dietrich, C., & Briggs-Hagen, M. (2020). Towards achieving the 90–90–90 HIV targets: Results from the south African 2017 national HIV survey. *BMC Public Health*, *20*(1), 1375. https://doi.org/10.1186/s12889-020-09457-z

Mathebula, R. L., Maimela, E., & Ntuli, N. S. (2020). The prevalence of selected non-communicable disease risk factors among HIV patients on anti-retroviral therapy in Bushbuckridge sub-district, Mpumalanga province. *BMC Public Health*, *20*(1), 247. https://doi.org/10.1186/s12889-019-8134-x

Miners, A., Phillips, A., Kreif, N., Rodger, A., Speakman, A., Fisher, M., Anderson, J., Collins, S., Hart, G., Sherr, L., & Lampe, F. C. (2014). Health-related quality-of-life of people with HIV in the era of combination antiretroviral treatment: A cross-sectional comparison with the general population. *The Lancet HIV*, *1*(1), 32–40. https://doi.org/10.1016/S2352-3018(14)70018-9

Moore, R. C., Fazeli, P. L., Jeste, D. V., Moore, D. J., Grant, I., Woods, S. P., & The HIV Neurobehavioral Research Program (HNRP) Group. (2014). Successful Cognitive Aging and Health-Related Quality of Life in Younger and Older Adults Infected with HIV. *AIDS and Behavior*, *18*(6), 1186–1197. https://doi.org/10.1007/s10461-014-0743-x

Morales, D. R., Moreno-Martos, D., Matin, N., & McGettigan, P. (2022). Health conditions in adults with HIV compared with the general population: A population-based cross-

sectional analysis. *EClinicalMedicine*, *47*. https://doi.org/10.1016/j.eclinm.2022.101392

Naicker, S. (2020). HIV/AIDS and chronic kidney disease. *Clinical Nephrology*, *93*(1), 87–93. https://doi.org/10.5414/CNP92S115

National Department of Health. (2016). *National HIV Testing Services: Policy 2016*. https://sahivsoc.org/Files/HTS%20Policy%2028%20July%20final%20copy.pdf

Onohuean, H., Aigbogun, E. O., & Igere, B. E. (2022). Meta-synthesis and science mapping analysis of HIV/HPV co-infection: A global perspective with emphasis on Africa. *Globalization and Health*, *18*(1), 36. https://doi.org/10.1186/s12992-022-00812-w

Osei-Yeboah, R., Tamuhla, T., Ngwenya, O., & Tiffin, N. (2021). Accessing HIV care may lead to earlier ascertainment of comorbidities in health care clients in Khayelitsha, Cape Town. *PLOS Global Public Health*, *1*(12), e0000031. https://doi.org/10.1371/journal.pgph.0000031

Palau, L., Menez, S., Rodriguez-Sanchez, J., Novick, T., Delsante, M., McMahon, B. A., & Atta, M. G. (2018). HIV-associated nephropathy: Links, risks and management. *HIV/AIDS (Auckland, N.Z.)*, *10*, 73–81. https://doi.org/10.2147/HIV.S141978

Pulerwitz, J., Gottert, A., Kahn, K., Haberland, N., Julien, A., Selin, A., Twine, R., Peacock, D., Gómez-Olivé, X., Lippman, S. A., & Pettifor, A. (2019). Gender Norms and HIV Testing/Treatment Uptake: Evidence from a Large Population-Based Sample in South Africa. *AIDS and Behavior*, *23*(2), 162–171. https://doi.org/10.1007/s10461-019-02603-8

Snow, K. J., Sismanidis, C., Denholm, J., Sawyer, S. M., & Graham, S. M. (2018). The incidence of tuberculosis among adolescents and young adults: A global estimate. *European Respiratory Journal*, *51*(2). https://doi.org/10.1183/13993003.02352-2017

Stelzle, D., Tanaka, L. F., Lee, K. K., Khalil, A. I., Baussano, I., Shah, A. S. V., McAllister, D. A., Gottlieb, S. L., Klug, S. J., Winkler, A. S., Bray, F., Baggaley, R., Clifford, G. M., Broutet, N., & Dalal, S. (2021). Estimates of the global burden of cervical cancer associated with HIV. *The Lancet Global Health*, *9*(2), e161–e169. https://doi.org/10.1016/S2214-109X(20)30459-9

Sviridov, D., Mukhamedova, N., Makarov, A. A., Adzhubei, A., & Bukrinsky, M. (2020). Comorbidities of HIV infection: Role of Nef-induced impairment of cholesterol metabolism and lipid raft functionality. *AIDS*, *34*(1), 1–13. https://doi.org/10.1097/QAD.0000000000002385

van Heerden, A., Barnabas, R. V., Norris, S. A., Micklesfield, L. K., Rooyen, H. van, & Celum, C. (2017). High prevalence of HIV and non-communicable disease (NCD) risk factors in rural KwaZulu-Natal, South Africa. *Journal of the International AIDS Society*, *20*(2), e25012. https://doi.org/10.1002/jia2.25012

Wong, E. B., Olivier, S., Gunda, R., Koole, O., Surujdeen, A., Gareta, D., Munatsi, D., Modise, T. H., Dreyer, J., Nxumalo, S., Smit, T. K., Ording-Jespersen, G., Mpofana, I. B., Khan, K., Sikhosana, Z. E. L., Moodley, S., Shen, Y.-J., Khoza, T., Mhlongo, N., … Harilall, S. (2021). Convergence of infectious and non-communicable disease epidemics in rural

South Africa: A cross-sectional, population-based multimorbidity study. *The Lancet Global Health*, *9*(7), e967–e976. https://doi.org/10.1016/S2214-109X(21)00176-5

Wu, P.-Y., Chen, M.-Y., Hsieh, S.-M., Sun, H.-Y., Tsai, M.-S., Lee, K.-Y., Liu, W.-C., Yang, S.-P., Luo, Y.-Z., Zhang, J.-Y., Sheng, W.-H., & Hung, C.-C. (2014). Comorbidities among the HIV-Infected Patients Aged 40 Years or Older in Taiwan. *PLoS ONE*, *9*(8). https://doi.org/10.1371/journal.pone.0104945

Zicari, S., Sessa, L., Cotugno, N., Ruggiero, A., Morrocchi, E., Concato, C., Rocca, S., Zangari, P., Manno, E. C., & Palma, P. (2019). Immune Activation, Inflammation, and Non-AIDS Co-Morbidities in HIV-Infected Patients under Long-Term ART. *Viruses*, *11*(3), Article 3. https://doi.org/10.3390/v11030200

3.13 Supplementary data

Table S3.1 Risk of CKD for individuals who were ever ascertained with other comorbidities.

Characteristic	**OR[1]**	**95% CI[1]**
Age per 5 years	1.50	1.47, 1.52
Sex		
Female	-	-
Male	0.92	0.85, 0.99
HIV	2.15	1.97, 2.34
TB	1.81	1.66, 1.98
Hypertension	3.08	2.84, 3.35
Diabetes	3.13	2.91, 3.38
Cervical cancer	1.78	1.31, 2.38

[1]OR = Odds ratio, [1]CI = Confidence interval

Table S3.2 Risk of TB for individuals who were ever ascertained with other comorbidities.

Characteristic	**OR[1]**	**95% CI[1]**
Age per 5 years	1.12	1.11, 1.13
Sex		
Female	-	-
Male	2.08	2.03, 2.13
HIV	6.96	6.78, 7.14
Hypertension	0.68	0.65, 0.70
Diabetes	1.06	1.00, 1.12
CKD	1.64	1.50, 1.78
Cervical cancer	1.32	1.15, 1.51

[1]OR = Odds ratio, [1]CI = Confidence interval

Table S3.3 Risk of Hypertension for individuals who were ever ascertained with other comorbidities.

Characteristic	OR[1]	95% CI[1]
Age per 5 years	1.58	1.58, 1.59
Sex		
Female	-	-
Male	0.67	0.65, 0.69
HIV	0.86	0.83, 0.88
TB	0.71	0.68, 0.73
Diabetes	3.61	3.46, 3.75
CKD	2.57	2.35, 2.82
Cervical cancer	1.21	1.04, 1.41

[1]OR = Odds ratio, [1]CI = Confidence interval

Table S3.4 Risk of Diabetes for individuals who were ever ascertained with other comorbidities.

Characteristic	OR[1]	95% CI[1]
Age per 5 years	1.32	1.31, 1.33
Sex		
Female	-	-
Male	0.75	0.72, 0.78
HIV	0.66	0.63, 0.69
TB	1.14	1.08, 1.20
Hypertension	3.89	3.74, 4.05
CKD	2.64	2.45, 2.86
Cervical cancer	1.12	0.91, 1.38

[1]OR = Odds ratio, [1]CI = Confidence interval

Table S3.5 Risk of Cervical cancer for individuals who were ever ascertained with other comorbidities.

Characteristic	OR[1]	95% CI[1]
Age per 5 years	1.24	1.21, 1.27
HIV	7.86	6.80, 9.12
TB	1.00	0.87, 1.14
Hypertension	1.34	1.15, 1.55
Diabetes	1.17	0.95, 1.43
CKD	1.43	1.06, 1.90

[1]OR = Odds ratio, [1]CI = Confidence interval

CHAPTER 4: KIDNEY FUNCTION IN HEALTHCARE CLIENTS IN KHAYELITSHA, SOUTH AFRICA: ROUTINE LABORATORY TESTING AND RESULTS REFLECT DISTINCT HEALTHCARE EXPERIENCES BY AGE FOR HEALTHCARE CLIENTS WITH AND WITHOUT HIV

4.1 Publication status

Osei-Yeboah, R., Ngwenya, O., & Tiffin, N. Kidney function in healthcare clients in Khayelitsha, South Africa: Routine laboratory testing and results reflect distinct healthcare experiences by age for healthcare clients with and without HIV (Ready for submission)

4.2 Author contribution

NT and ROY designed the study. ROY conducted the analysis and wrote the draft manuscript. ON provided statistical support. NT and ROY finalised the manuscript.

4.3 Abstract

Background

The incidence of HIV Associated Nephropathy (HIVAN) has declined due to improved antiretroviral therapy (ART) treatment modalities and coverage, but current research indicates that the risk of kidney disorders including chronic kidney disease (CKD) among people living with HIV (PLHIV) is substantially higher than in the general population. The Western Cape Province of South Africa has a high prevalence of PLHIV concurrent with a high burden of other infectious and non-communicable comorbidities. All PLHIV are eligible to receive free ART, and screening for kidney function is a component of the standard of care for these healthcare clients. Serum creatinine (SCr) laboratory testing is undertaken by the National Health Laboratory Service, and these data are collated at the Provincial Health Data Centre and linked with other routine health data. We describe the characteristics of healthcare clients at their first kidney function test, as well as the characteristics across all tests taken by these individuals; and explore the association between test results, demographics, and comorbidities in this population.

Methods

We analysed the SCr and estimated glomerular filtration rate (eGFR) results for PLHIV and HIV-negative healthcare clients aged 18-80 years who accessed healthcare in Khayelitsha, South Africa. We assessed their comorbidity profiles at the time of SCr and eGFR testing and

assessed the association of ascertained comorbidities with kidney function test results. We conducted age-stratified analyses of eGFR results for PLHIV and HIV-negative individuals, including analysis of a selection of comorbidities. A linear mixed effects model used all eGFR results generated for the study population over time to assess the association of HIV and other comorbidities with kidney function test results.

Results

A total of 45 640 healthcare clients aged 18-80 years who accessed healthcare in Khayelitsha public health facilities in 2016 and/or 2017 were identified as having at least one kidney function test. Of these, 22 961 (50.3%) were PLHIV. The median age at first test result for both SCr and eGFR was lower for PLHIV at 33 (IQR: 27, 41) years and 36 (IQR: 30, 43) years respectively, when compared to HIV-negative individuals aged 49 (IQR: 37 – 57) years and 52 (IQR: 44 – 59) years, respectively. PLHIV had slightly lower first median SCr results at 66 (IQR: 55 – 78) µmol/l, than HIV-negative individuals at 69 (IQR: 58 – 82) µmol/l, and this reflected in higher median eGFR results for PLHIV, as expected. When compared to PLHIV, larger proportions of HIV-negative healthcare clients receiving test results presented with hypertension, diabetes, and CKD. Among healthcare clients with eGFR results most common diseases seen in the various age groups were HIV in the 18-29 years age group, TB in the 30-44 years age group, and hypertension, diabetes and CKD in the 60+ age group. The linear mixed effect regression analysis showed that having HIV, diabetes and tuberculosis (TB) is associated with slightly higher eGFR whilst having hypertension, being a male and being in an older age category at eGFR testing is associated with lower eGFR for healthcare clients.

Conclusion

We show that renal testing patterns and results are quite distinct in younger people without HIV who tended to have worse kidney function at first testing, younger PLHIV who in general had good kidney function when tested; and older people with and without HIV who tended to have similar kidney function results. In younger people, these results most likely indicate that PLHIV are being more regularly screened for kidney function even when they show no symptoms of renal problems, whereas young people without HIV are more likely to be tested only when they present with symptoms suggestive of renal problems. In older patients, those with and without HIV appear to have similar kidney function results, but the

population of older PLHIV is very small compared to those without HIV and most likely consists of individuals who have survived into old age with HIV despite limited access to treatment before universal ART access and test and treat protocols had been rolled out, as well as individuals who contracted HIV only at a later age. From real life data about routine renal health testing, we assess kidney function testing for PLHIV which is useful for evaluating implementation of treatment guidelines and policies. We propose that it is not possible to infer the future healthcare requirements of younger PLHIV based on the health profiles of the current population of older PLHIV, but that routine health data can be used in an agile way to assess the ongoing current healthcare requirements of these sub-populations as they age.

Keywords

Serum creatinine, eGFR, kidney function, HIV, South Africa, health records

4.4 Introduction

People living with Human Immunodeficiency Virus (PLHIV) may have a wide range of kidney conditions which could be as a result of the HIV infection itself, long-term exposure to antiretroviral therapy (ART), or treatments and effects from other chronic comorbidities which also affect HIV-negative individuals (Ellis, 2017). HIV-associated nephropathy (HIVAN) is one of the most common renal disorders among PLHIV (Ellis, 2017; Naicker, 2020) and several factors including comorbidities, high viral load, low CD4+ counts and advanced kidney disease have been identified as risk factors for the occurrence of HIVAN and subsequent progression to end-stage renal disease (ESRD) (Palau et al., 2018; Waheed & Atta, 2014). Suggested mechanisms of HIV affecting renal cells include a direct infection of the renal parenchymal cells by the virus, renal cellular uptake of circulating virally encoded molecules causing indirect injury to the kidney, or indirect injury from the release of cytokines (Palau et al., 2018). Although the prevalence of HIVAN has declined due to improved ART treatment modalities and coverage, studies suggest that the risk of other renal disorders, including chronic kidney disease (CKD), among PLHIV is about 4 times higher compared to the general population (Islam et al., 2012; Kaboré et al., 2019).

The South African National Department of Health recommends a first-line HIV treatment regimen consisting of a fixed dose combination of Tenofovir disoproxil fumarate (TDF),

Lamivudine (3TC) and Dolutegravir (DTG)-TLD for all eligible adults, adolescents and children over 10 years and weighing 35kg and above, and tenofovir disoproxil fumarate-emtricitabine-efavirenz (TEE) for women of childbearing potential wanting to conceive due to safety issues of TLD in the first 6 weeks of pregnancy (National Department of Health, 2020). A major issue concerning many of these agents, especially TDF, has been nephrotoxicity and these agents are associated with the development of acute and chronic kidney diseases (Boswell & Rossouw, 2017; Ellis, 2017; Palau et al., 2018; Wyatt, 2017). Although Africa ranks highest with an estimated prevalence of CKD among PLHIV globally, at 7.9%, Southern Africa has the lowest regional prevalence estimated at 3.2% (Ekrikpo et al., 2018) and studies conducted in South Africa have reported low prevalence of renal impairment and better glomerular filtration rates among PLHIV compared to other African countries (Assaram et al., 2018; Kamkuemah et al., 2015).

Diabetes mellitus and hypertension are reported major causes of kidney disease in the general population and together account for about 70% of all ESRD (Palau et al., 2018). Considering the high prevalence of these chronic conditions in South Africa and associated long-term treatment, and the known relationship between CKD and HIV, and evidence of increased blood pressure and risk of hypertension (Nduka et al., 2016) and diabetes mellitus among PLHIV on ART, both PLHIV and seronegative populations may experience the effects of these comorbidities on kidney function.

Serum creatinine (SCr) is considered the most used endogenous marker for determining kidney function and it is widely used in clinical practice (Delanaye et al., 2017), but its sensitivity to detect early renal disorders is questioned as it might sometimes remain at normal levels despite significant kidney impairment (Fiseha et al., 2019; Hommel et al., 2012). This may be due to the fact that the production of SCr depends on lean body mass and may not accurately reflect glomerular filtration rates, especially in older patients and females who have lower muscle mass (Duru et al., 2009; Giannelli et al., 2007). It is therefore recommended that prediction equations are used to estimate glomerular filtration rate (eGFR) for reporting in conjunction with SCr to enable early detection of kidney dysfunction (Delanaye et al., 2017; Vassalotti et al., 2016). SCr may be influenced by several factors such as muscle mass, age, sex, nutritional status, and chronic illnesses, so these metrics are combined in order to calculate eGFR. Measurements of SCr and eGFR are

standard laboratory results generated during routine care when monitoring patients with kidney disease, and these results can also provide a useful profile of a patient's changing renal health over time for epidemiological research.

Given the high burden of comorbidities in South African patients (Osei-Yeboah et al., 2021), it is important to understand the relationship of kidney disease with HIV infection in the context of other comorbidities, in order to improve patient outcomes. This study explores this relationship using comorbidity records and laboratory results for SCr and eGFR from collated routine health data to describe the potential for a combined effect of HIV, hypertension, and diabetes on kidney function in patients in the Western Cape. We have used data from the Provincial Health Data Centre (PHDC), a health information exchange facility that collates administrative health data from public healthcare clients in the Western Cape Province in South Africa; and the granular laboratory test and comorbidity data provide an opportunity to link laboratory measures of kidney function with a longitudinal profile for HIV and other comorbidities in these healthcare clients (Boulle et al., 2019). We describe the characteristics of healthcare clients at their first kidney function test, as well as the characteristics across all tests taken by these individuals; and explore the association between test results, demographics, and comorbidities in this population.

4.5 Materials and Methods

4.5.1 Ethics

Ethics approval was obtained from the Human Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town (HREC ref: 482/2019). A data access request was approved by the Health Impact Assessment Directorate at the Western Cape Department of Health, South Africa. A waiver for informed consent was granted because the data provided were anonymised and perturbed, and individuals could not be identified or re-identified from the data.

4.5.2 Study population

Khayelitsha is a high-density, mixed informal and formal housing suburb in Cape Town, South Africa. The analysis includes all SCr and eGFR laboratory results generated by the National Health Laboratory Services for adults (18 years and above) who accessed public

health facilities in the Khayelitsha subdistrict of Cape Town, South Africa, between 1 January 2016 and 31 December 2017, described as the 'recruitment period'.

4.5.3 Data Source

The PHDC is a health information exchange facility that collates administrative health data for the Western Cape Province. Unique identifiers are used to link individuals to administrative health records, and facility visit, laboratory, and pharmacy data are updated daily for about 6.6 million people currently seeking care in public facilities in the Western Cape Province. Algorithms are used to infer disease episodes from combinations of pharmacy-dispensed drugs, laboratory test results, international classification of diseases 10th edition (ICD-10) diagnosis codes, and facility encounter data (Boulle et al., 2019). In this study we refer to "disease ascertainment" to mean inference of the start of a disease episode as identified by an algorithm, to distinguish this process of disease ascertainment from a clinical diagnosis made by a healthcare professional during consultation. A dataset containing routine health data was obtained from the PHDC, Western Cape Government Health Department, with longitudinal data ranging from 2007 to 2017. The records of the healthcare clients who received laboratory results included HIV and comorbidities records that were used to determine which health conditions had already been ascertained when each kidney function laboratory test was taken. The median length of time for which individuals have available data is 8 years (Interquartile range [IQR]: 3.6-10 years). The study dataset was anonymised and perturbed within the PHDC prior to being released for use in this analysis, to prevent identification or re-identification of individuals.

4.5.4 PHDC disease episode definition

The PHDC infers diseases from routine health data using algorithms that analyse either single, or a combination of parameter(s) categorised into high, moderate, weak confidence and supporting-only evidence for having a particular disease episode. High confidence definition of HIV requires evidence for dispensed valid first line (2NRTI and NNRTI) and valid triple therapy regimen (fixed-dose combination) of antiretrovirals, and/or positive laboratory test results (viral load test, polymerase chain reaction (PCR) test, enzyme linked immunosorbent assay (ELISA) test, and ART resistance test). For tuberculosis (TB), evidence for the episode may include admission to a specialised TB hospital, TB drug regimen dispensed, and/or laboratory test results (Positive GeneXpert, Line probe assay (LPA), Acid-

Fast Bacillus positive culture, positive microscopy (Ziehl-Neelsen staining), and microbiology culture-*Toxocara canis* (using ELISA) are the main definition parameters. High confidence definition of hypertension includes dispensed hydrochlorothiazide. High confidence definitions of diabetes episodes are based on dispensed drug for the treatment of diabetes mellitus, laboratory test showing glycated haemoglobin (HbA1c) greater than 6.5%, oral glucose tolerance test result greater than 11.1mmol/l, and diagnosis coding showing an ICD-10 code indicating diabetes disease.

For CKD, laboratory tests showing consecutive glomerular filtration rate of less than 60mL/min/1.73m^2 with 90 days between tests, dispensed kidney, or transplant medications (antithymocyte, immunoglobulin, and basiliximab), and diagnosis coding indicating kidney transplant procedure in theatre constitute a high confidence definition. It is important to note that SCr and eGFR results are used extensively in defining patients with CKD by the PHDC. This means that there is substantial overlap between having poor kidney function test results and being defined as having a CKD episode. The ascertainment algorithm in use by the PHDC, however, makes use of longitudinal eGFR results to track changes in kidney function over time, and is not based on single or stand-alone kidney function results. The PHDC algorithm uses the modification of diet in renal disease (MDRD) GFR estimating equation which adjusts for race/ethnicity to determine eGFR. We recognise that an update of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation without the race/ethnicity factor is now recommended (Gama et al., 2021; Inker et al., 2021).

4.5.5 Data Analysis

In order to understand when healthcare clients are first referred for SCr testing, we analysed the age at which first SCr and eGFR laboratory results are generated for adults (≥18 years) in the study population. The distribution of age at their first recorded SCr and/or eGFR test results according to HIV status was determined for all the healthcare clients in the study population.

Descriptive statistics were generated to summarise the counts and proportions for TB, hypertension, diabetes and CKD in healthcare clients who have SCr and eGFR testing done, by HIV status. The counts and proportions of the healthcare clients receiving eGFR results, and the ascertained comorbidities per 18-29 years, 30-44 years, 45-60 years, and over 60 years age groups were described.

SCr and eGFR are highly related parameters derived from the same tests. The National Health Laboratory Services of South Africa integrates SCr measures, age, sex, and ethnicity in estimating glomerular filtration rates (Levey et al., 1999, 2006). Here, we first visualise the distribution of ages at both SCr and eGFR testing for our study population, and subsequently present analyses focusing only on eGFR to assess renal disorders in our study population, because of the inbuilt adjustment for age and sex that this measurement provides. A scatter plot distribution of all SCr and eGFR results for individuals receiving test results was generated to provide a general overview of SCr and eGFR results with respect to HIV status, age and sex for all tests taken – recognising that multiple tests may arise from a single patient in this overview. Healthcare clients without identified sex status were removed from subsequent analysis.

In order to further understand the age differences in eGFR between PLHIV and HIV-negative populations, age categories were created and a boxplot distribution of all eGFR results among the age groups at eGFR testing was generated. This provides a general overview of the eGFR results per age groups among PLHIV and HIV-negative healthcare clients receiving results.

Comparisons of eGFR results for healthcare clients with described comorbidities TB, hypertension and diabetes, were made for each age category. These comparisons were based on tests conducted on specified dates for individuals who had already been ascertained with the specified comorbidity at the time the test was done. The significance of differences between the median eGFR results was calculated using Wilcoxon rank-sum tests to generate the reported p-values.

We used a linear mixed effects model to explore the relationship between eGFR results and age at testing (by age category), sex, HIV and selected comorbidities as fixed effects. The individual-level repeated eGFR tests were included as the random effect. This method takes into account the heterogeneity which may exist in the number of kidney function estimates available for each patient which must be considered when estimating kidney function trajectories (Gasparini et al., 2020; Janmaat et al., 2019). The model was run using the 'lme4' package in RStudio and the associated p-values were generated with the 'lmerTest' package.

Data analyses were done in R Software (version 4.1.2) and RStudio (2021.09.0+351 "Ghost Orchid"). Visualisations of distributions of SCr and eGFR results were done using 'ggplot2' package in RStudio (2021.09.0+351 "Ghost Orchid").

4.5.6 Patient and public involvement

The participants in this study were healthcare clients who visited public health facilities and generated at least one electronic health record. Retrospective data for this population spanned about 8 years. Inclusion in the study was restricted to healthcare clients who accessed care between 2016 and 2017 and included their complete retrospective data. The study questions were designed to explore the kidney functions and common comorbidities among these healthcare clients who seek care from public facilities. A waiver for participants' consent was granted by the University of Cape Town Faculty of Health Sciences Ethics Committee because the data were obtained directly from digital routine health data collated by the PHDC and were anonymised and perturbed prior to receipt in order to prevent the possibility of re-identification of participants.

4.6 Results

4.6.1 Comorbidities in individuals having kidney function tests

An overview of the healthcare clients receiving SCr and eGFR test results is shown by HIV status in Table 4.1. A total of 45 640 healthcare clients aged 18-80 years were identified as having at least one SCr/eGFR test. Out of these, 22 961 (50.3%) were PLHIV. Healthcare clients with subsequent eGFR results were matched to the SCr test records for further comparison: among the healthcare clients who received SCr laboratory results with or without eGFR results, 32 211 (70.6%) were females and 13 394 (29.3%) were males, the sex status of 35 (0.1%) healthcare clients was not identified. Of the total healthcare clients, 17 729 received only first SCr results without an accompanying eGFR. Apart from the high proportions of the HIV-negative healthcare clients and females in this sub-population, there are no particular characteristics indicating why they did not receive eGFR results, and it is likely that this is just a random occurrence in cases where the laboratory service did not receive sufficient additional data to calculate eGFR. The general characteristics, age distribution at first SCr testing, and distribution of first SCr results without matched eGFR results of this sub-population are provided in supplementary data, Table S4.1, Figure S4.1, and Figure S4.2.

The median age at first test result for both SCr and eGFR was lower for PLHIV at 33 (IQR: 27 - 41) years and 36 (IQR: 30 - 43) years respectively, when compared to HIV-negative individuals aged 49 (IQR: 37 – 57) years and 52 (IQR: 44 – 59) years, respectively. PLHIV had comparatively lower median SCr results at 66 (IQR: 55 – 78) µmol/l than HIV-negative individuals at 69 (IQR: 58 – 82) µmol/l, and this reflected in higher median eGFR results at their first test, accordingly, for PLHIV. Larger proportions of HIV-negative than HIV-positive healthcare clients receiving test results presented with hypertension (74.1% vs 25.9%), diabetes (79.8% vs 20.2%), and CKD (70.4% vs 29.6%) (Calculated from Table 4.1). Those living with HIV were much more likely to have TB (42% vs 8.9%), as expected (Kaplan et al., 2018; Mendelsohn et al., 2022; Swarts et al., 2021). Among the healthcare clients who received SCr laboratory results with or without eGFR results, 2 327 (5.1%) have died. Of 22 951 PLHIV in this dataset 1 262 (5.4%) have died, and of 22 689 HIV-negative healthcare clients, 1 065 (4.7%) have died.

Table 4.1: Descriptive statistics for PLHIV and HIV-negative individuals showing median age at first test and the number of individuals with comorbidities (n %) for TB, Hypertension, Diabetes, and CKD

		HIV status		
Characteristic	**Overall**	**HIV-negative**	**HIV-positive**	**p-value[2]**
	N = 45 640[1]	N = 22 689[1]	N = 22 951[1]	
Median (IQR) age (years) at recruitment	46 (36 – 57)	54 (43 – 62)	41 (34 – 48)	<0.001
Female (n,%)	32 211 (71)	15 557 (69)	16 654 (73)	<0.001
Male (n,%)	13 394 (29)	7 111 (31)	6 283 (27)	
Tuberculosis (n,%)	11 693 (26)	2 022 (8.9)	9 671 (42)	<0.001
Hypertension (n,%)	21 552 (47)	15 966 (70)	5 586 (24)	<0.001
Diabetes (n,%)	9 183 (20)	7 326 (32)	1 857 (8.1)	<0.001
CKD (n,%)	2 394 (5.2)	1 686 (7.4)	708 (3.1)	<0.001
Median (IQR) age (years) at first SCr	39 (30 – 51)	49 (37 – 57)	33 (27 – 41)	<0.001
Median (IQR) age (years) at first eGFR	40 (32 – 50)	52 (44 – 59)	36 (30 – 43)	<0.001
No eGFR test results (n,%)	17 729 (38.8)	13 221 (58.3)	4 508 (19.6)	<0.001
First SCr (µmol/l)	67 (57 – 80)	69 (58 – 82)	66 (55 – 78)	<0.001
First eGFR (mL/min/1.73m^2)	97 (81 – 117)	89 (73 – 107)	102 (85 – 122)	<0.001
Deceased (n,%)	2 327 (5.1)	1 065 (4.7)	1 262 (5.5)	<0.001
Median (IQR) age (years) at death	53 (40-64)	63 (55-70)	43 (35-52)	<0.001

[1]Median (IQR); n (%) [2]Wilcoxon rank sum test; Pearson's Chi-squared test

4.6.2 Kidney function in the healthcare client population

An analysis of the overall age distribution at first SCr and first eGFR test results for females and males per HIV status for all healthcare clients who received test results shows that whilst the age at first SCr and eGFR estimations ranged across 20-65 years for females and males with HIV, those without HIV often had their first test result at much older ages (Figure 4.1). Though a small portion of HIV-negative males have earlier screening for SCr (Figure 4.1B), males living with HIV and females in general tend to have SCr tests and eGFR results earlier in life than men without HIV (Figure 4.1, A-C and D).

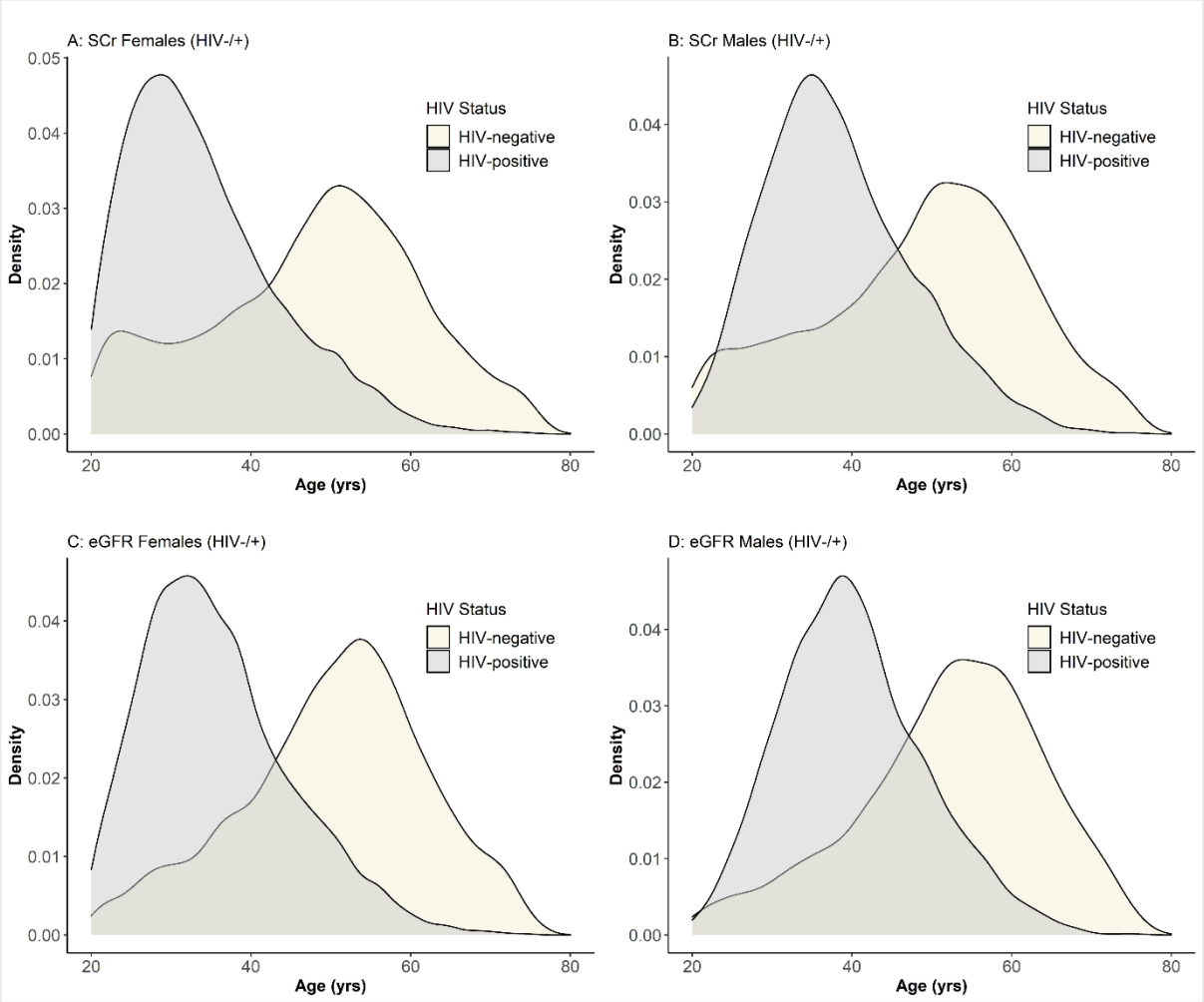


Figure 4.1: Distribution of age at first serum creatinine and estimated glomerular filtration rate testing for females and males per HIV status. The X-axis shows age (years) when the first test results were received, and the Y-axis shows the density distribution. A: Age distribution at first serum creatinine results for females by HIV status. B: Age distribution at first serum creatinine results for males by HIV status C: Age distribution at first estimated glomerular filtration rate results for females by HIV status. D: Age distribution at first estimated glomerular filtration rate results for males by HIV status, showing age (in years) at GFR estimation on the X-axis and the density distribution on Y-axis.

4.6.3 Stratification of comorbidities and kidney function by age groups

The counts and proportions of common comorbidities per age groups of healthcare clients who received eGFR results were determined. Most common diseases seen in the various age groups were HIV (89%) in the 18-29 years age group, TB (41%) in the 30-44 years age group, hypertension (86%), diabetes (47%) and CKD (24%) in the 60+ years age group (Table 4.2).

Table 4.2: Age groups, counts, and proportions of healthcare clients who received eGFR results, showing their ascertained comorbidities.

		Age category at first eGFR test				
Characteristic	Overall N = 27 907[1]	18-29 N = 4 968[1]	30-44 N = 12 276[1]	45-60 N = 8 456[1]	60+ N = 2 207[1]	p-value[2]
HIV	18 441 (66)	4 398 (89)	10 283 (84)	3 500 (41)	260 (12)	<0.001
Tuberculosis	9 228 (33)	1 907 (38)	4 986 (41)	2 055 (24)	280 (13)	<0.001
Hypertension	12 270 (44)	575 (12)	3 697 (30)	6 102 (72)	1 896 (86)	<0.001
Diabetes	5 658 (20)	212 (4.3)	1 396 (11)	3 021 (36)	1 029 (47)	<0.001
CKD	1 774 (6.4)	68 (1.4)	340 (2.8)	844 (10.0)	522 (24)	<0.001

[1]n (%), [2]Pearson's Chi-squared test; The percentage in brackets indicates proportion in each age category with the comorbidity of interest; Shaded cells represent the age group in which the comorbidity is most common

4.6.4 SCr and eGFR results in healthcare clients by age, sex and HIV status

Analysis of all SCr and eGFR test results for healthcare clients shows how the values change at older ages and differ per HIV status and sex (Figure 4.2). This comparison shows clearly how the eGFR value adjusts for age and sex so that the difference in SCr results between females and males falls away in corresponding eGFR results (Figure 4.2A compared to Figure 4.2B). Similarly, the decrease of kidney function with age is more apparent among PLHIV and HIV-negative individuals when viewing the eGFR result.

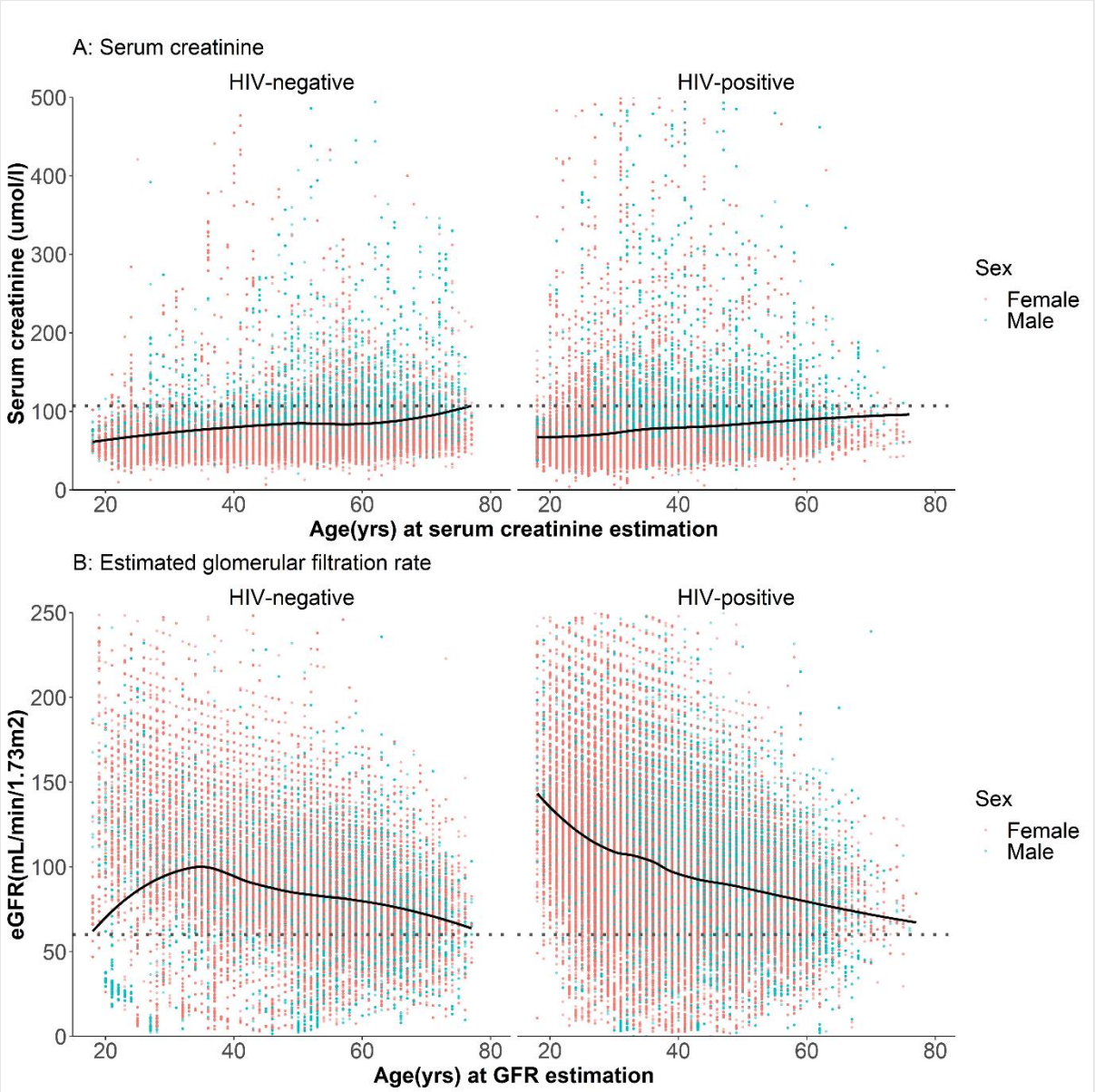


Figure 4.2: The distribution of all serum creatinine and estimated glomerular filtration rate results per HIV status and sex. Data points are coloured by sex. Red: Female, Blue: Male. A. Serum creatinine distribution by HIV status, sex, and age at measurement. Y-axis: serum creatinine results in µmol/l, X-axis: age (in years) at creatinine measurement. Dotted line: SCr value above which abnormal kidney function may be inferred. B. Estimated glomerular filtration rate distribution by HIV status, sex, and age (in years) at GFR estimation. Y-axis: eGFR (mL/min/1.73m^2) , X-axis: age (years) at eGFR measurement. Dotted line: eGFR value below which an abnormal kidney function is inferred.

4.6.5 Age stratified analysis of eGFR results in PLHIV and HIV-negative people

The eGFR distribution per age group of healthcare clients who are PLHIV and HIV-negative individuals was analysed. The analysis uses all the eGFR results recorded for all healthcare clients in our study population to make the comparisons and we recognise that multiple

results may come from one patient over time. A description of HIV-negative and HIV-positive healthcare clients is shown for each age group. Among the younger and middle age groups, the median eGFR results of the HIV-positive healthcare clients are higher compared to the HIV-negative healthcare clients in these same age groups. At older ages, the difference between the median eGFR results for the HIV-positive and HIV-negative groups is reduced (Figure 4.3).

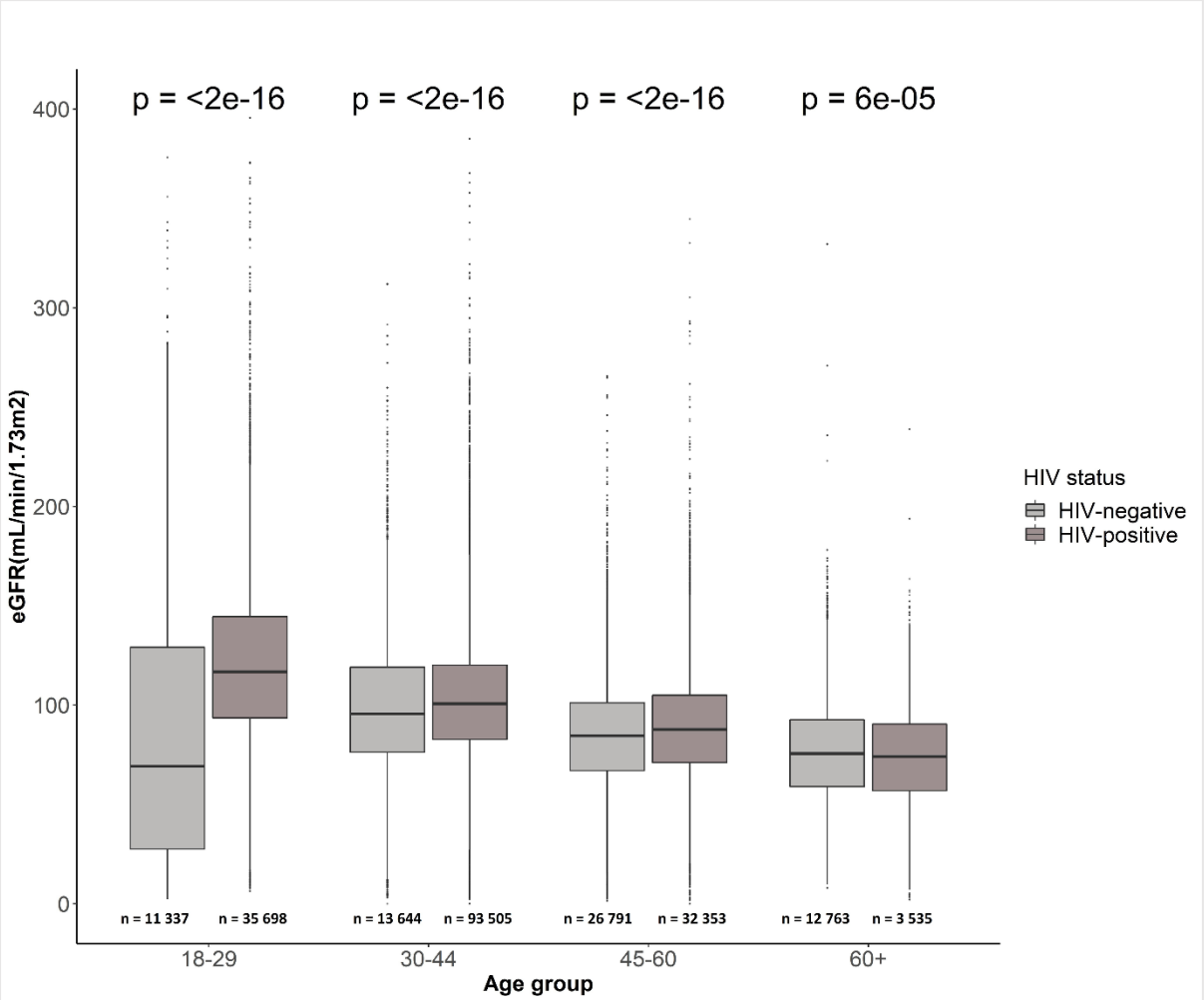


Figure 4.3: Distribution of all eGFR results per age groups and HIV status of healthcare clients receiving results. X-axis: age groups at eGFR testing; Y-axis: eGFR measures for healthcare clients. Results from PLHIV and HIV-negative healthcare clients in each age group are shown.

4.6.6 Age stratified analysis of kidney function with comorbidities TB, hypertension, diabetes, and CKD.

The number of all eGFR tests reported for PLHIV and HIV-negative individuals with comorbidities per age categories were analysed. More tests were done for PLHIV than HIV-

negative people in the 18-29 years category (11 337 vs 35 698); the 30-44 years category (13 644 vs 93 505) and the 45-60 years category (26 791 vs 32 353). Only in the category of 60+ years were more tests reported for HIV-negative individuals (12 763 vs 3 535), but in this category there is a very small numbers of PLHIV compared to those without HIV (6 916 vs 964).

Table 4.3: Median (IQR) eGFR for all tests done per age group and HIV status of healthcare clients with comorbidities

Age group: 18-29 years		**Median (IQR) eGFR value[1]**			
Comorbidity	**Counts** (% of all tests) [1]	**Overall**	**HIV-negative**	**HIV-positive**	**p-value[2]**
Tuberculosis	23 124 (49.2)	118 (99 – 141)	118 (99 – 146)	118 (97 – 141)	0.90
Hypertension	11 438 (24.3)	117 (96 – 146)	123 (100 – 153)	116 (95 – 143)	0.06
Diabetes	10 164 (21.6)	128 (107 – 153)	136 (103 – 163)	125 (107 – 142)	0.15
CKD	9 865 (21)	75 (73 – 99)	73 (39 – 85)	76 (45 – 107)	0.30
Age group: 30-44 years					
Comorbidity	**Counts** (% of all tests) [1]	**Overall**	**HIV-negative**	**HIV-positive**	**p-value[2]**
Tuberculosis	54 171 (50.6)	105 (86 – 124)	106 (88 – 126)	105 (89 – 124)	0.60
Hypertension	33 078 (30.9)	101 (85 – 121)	100 (85 – 125)	102 (85 – 120)	0.90
Diabetes	13 122 (12.2)	106 (89 – 128)	105 (89 – 130)	107 (89 – 126)	0.70
CKD	10 545 (9.8)	59 (43 – 79)	57 (40 – 79)	61 (44 – 79)	0.20
Age group: 45-60 years					
Comorbidity	**Counts** (% of all tests) [1]	**Overall**	**HIV-negative**	**HIV-positive**	**p-value[2]**
Tuberculosis	20 514 (34)	94 (77 – 112)	89 (70 – 109)	95 (79 – 112)	<0.001
Hypertension	39 620 (67)	88 (74 – 103)	87 (73 – 102)	89 (75 – 106)	<0.001
Diabetes	20 869 (35.3)	90 (74 – 107)	89 (74 – 106)	91 (75 – 112)	0.026
CKD	11 234 (19)	59 (46 – 72)	58 (45 – 72)	60 (48 – 72)	0.30
Age group: 60+ years					
Comorbidity	**Counts** (% of all tests) [1]	**Overall**	**HIV-negative**	**HIV-positive**	**p-value[2]**
Tuberculosis	2 774 (17)	83 (66 – 99)	76 (62 – 94)	87 (74 – 102)	<0.001
Hypertension	13 585 (83.4)	77 (63 – 92)	76 (63 – 91)	84 (67 – 99)	<0.001
Diabetes	7 834 (48.1)	77 (60 – 93)	76 (60 – 92)	83 (64 – 100)	0.035
CKD	5 802 (35.6)	55 (44 – 66)	55 (44 – 66)	57 (46 – 66)	0.40

[1]Median (IQR); *n (%);* [2]Wilcoxon rank sum test; Shaded cells represent statistically significant difference between PLHIV and HIV-negative individuals with the comorbidity

In each age group the comorbidity with the highest proportion of tests done in that age group reported for healthcare clients with comorbidities were TB (49.2% and 50.6%) for 18-29 years and 30-44 years age groups respectively, and hypertension (67% and 83.4%) for 45-60 years and over 60 years age groups respectively.

An analysis of the median eGFR results for PLHIV and HIV-negative healthcare clients with comorbidities in each age group showed in the younger age categories between 18 and 44 years there is no significant difference in eGFR values in those with and without TB, diabetes and CKD when comparing PLHIV and those who are HIV-negative. Although not statistically significant, PLHIV with hypertension have slightly lower eGFR values than those without HIV ($p=0.06$). In the older age categories, however, eGFR is slightly higher for PLHIV who have TB, hypertension and diabetes. For individuals with CKD, the lower eGFR values are similar regardless of HIV status.

4.6.7 Kidney function trajectories of healthcare clients with HIV and other comorbidities

Whilst previously we analysed all available test results together, we recognise that there are often multiple tests from the same individual, and that the longitudinal trajectories for the population groups might yield more detailed information about the relationship between patient characteristics and their kidney function test results. The distribution of eGFR results per age groups for individuals who had and those who did not have TB, hypertension and diabetes at the time of eGFR determination, calculating the characteristics, age and comorbidity status of the healthcare client at the time of each test result (Figure 4.4), provides an overview of these data to gain insight into the eGFR results for healthcare clients who had and did not have the selected comorbidities prior to the linear mixed effect model analysis.

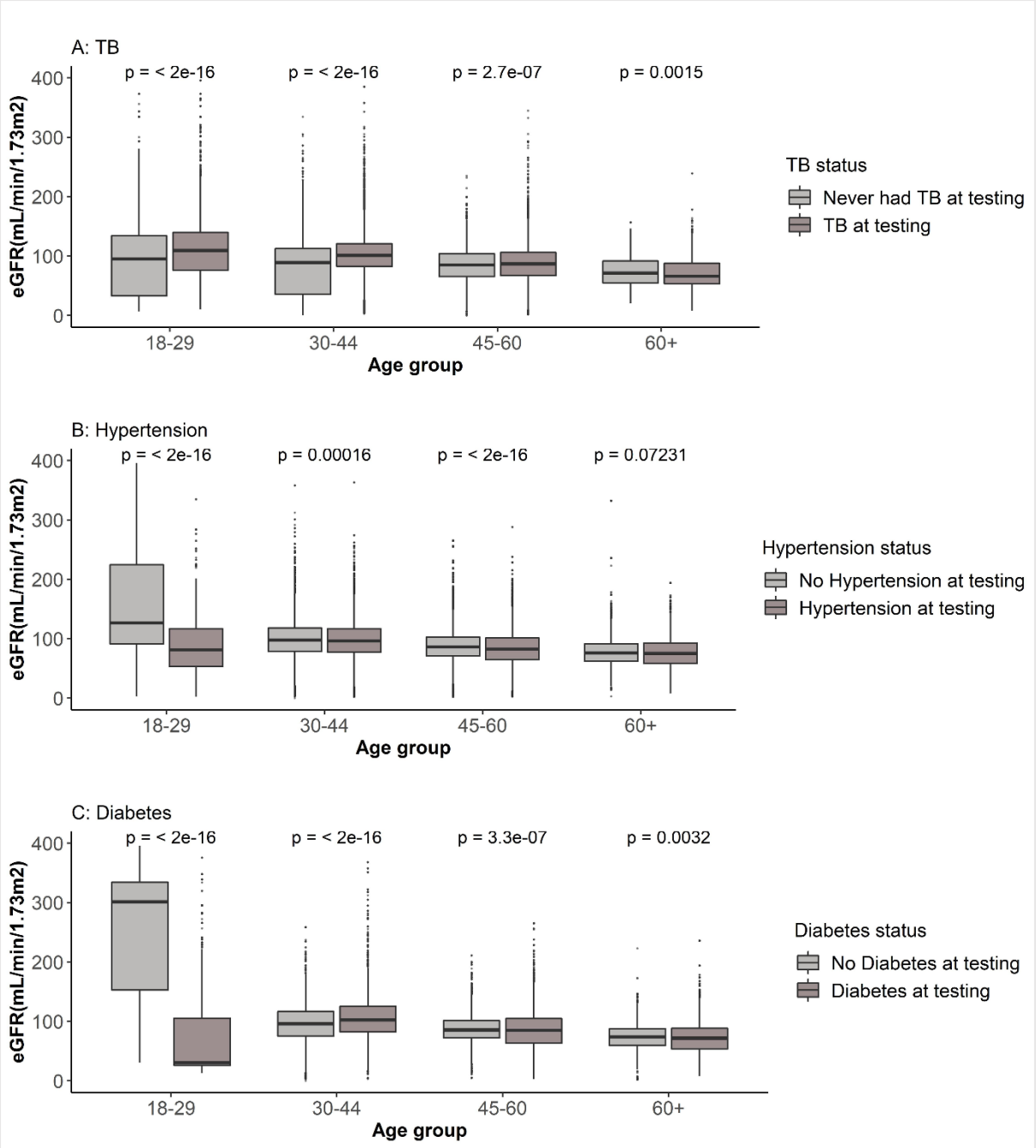


Figure 4.4: Distribution of all eGFR results per sex and comorbidity statuses at the time of testing. X-axis: Age (in groups) at GFR estimation; Y-axis: Estimated glomerular filtration rate in mL/min/1.73m^2. A. Distribution of eGFR results of healthcare clients who had or did not have TB prior to GFR estimation. B. Distribution of eGFR results of healthcare clients who had or did not have hypertension prior to GFR estimation. C. Distribution of eGFR results of healthcare clients who had or did not have diabetes prior to GFR estimation.

The distribution of eGFR results for healthcare clients who did or did not have TB prior to eGFR testing shows higher median eGFR for clients in the younger age groups (18-29 years and 30-44 years) who had TB and the difference is reduced for healthcare clients in the 45-60 years and over 60 years age groups. For healthcare clients who had hypertension and diabetes, the median eGFR results were lower for those in the 18-29 years age group, with no differences in median eGFR results for those in the 30-44 years, 45-60 years and over 60 years age groups (Figure 4.4).

The random effect part of the mixed effects model showed considerable variation of eGFR results (kidney function) between healthcare clients, with a standard deviation (SD) of 23.68 mL/min/1.73m^2 and residual variance SD of 37.09 mL/min/1.73m^2. The fixed effects part of the model is presented in Figure 4.5.

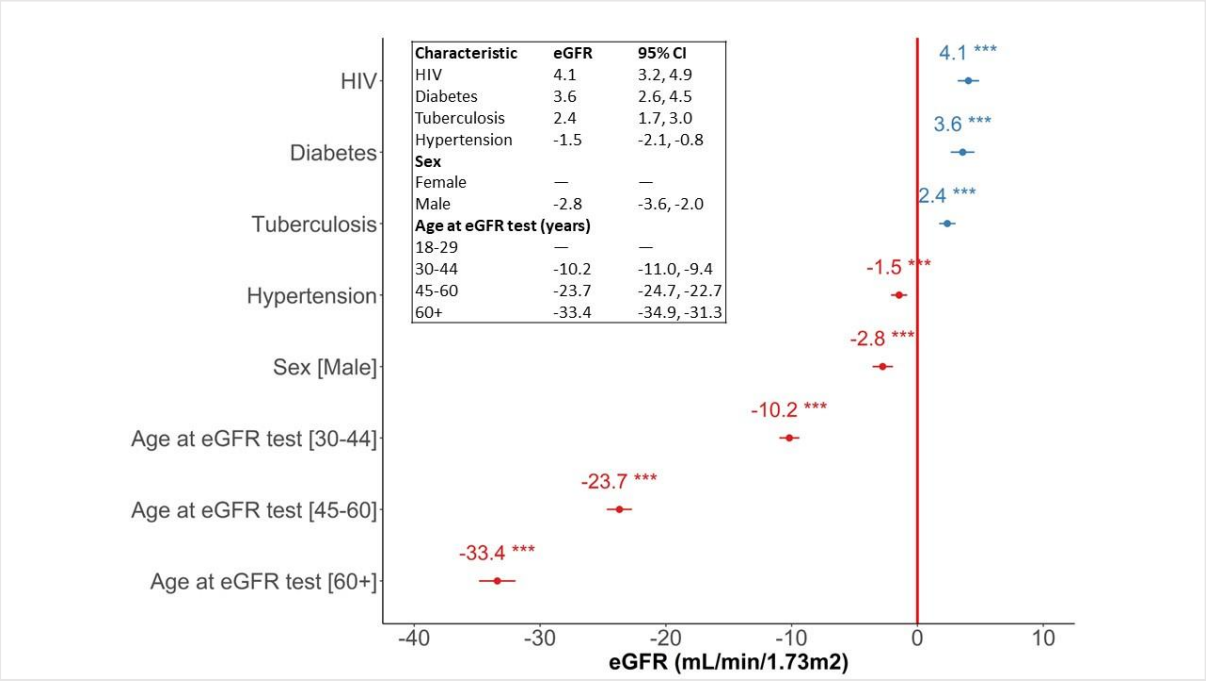


Figure 4.5: Linear mixed-effect regression results showing regression coefficients and 95% confidence interval (CI), describing the relationship between eGFR, age category at testing, HIV status and other comorbidities. X-axis: regression coefficients (eGFR in mL/min/1.73m^2); Y-axis: predictors.

The fixed effects part of the model (Figure 4.5) indicates that being in an older age category at eGFR testing is associated with lower eGFR for healthcare clients aged 30-44 years (-10.2 mL/min/1.73m^2, 95% Confidence interval [CI]: -11, -9.4), 45-60 years (-23.7 mL/min/1.73m^2;

95% CI: -24.7, -22.7), and over 60 years (-33.4 mL/min/1.73m^2; 95% CI: -34.9, -31.3) as compared to those aged 18-29 years if sex and comorbidity status remain constant. The model suggests that eGFR is lower for male healthcare clients by an average of -2.8 mL/min/1.73m^2 (95% CI: -3.6, -2.0) compared to females. Having hypertension ascertained prior to eGFR testing was found to be associated with lower eGFR results by an average of -1.5 mL/min/1.73m^2 (95% CI: -2.1, -0.82) compared to those without hypertension.

Healthcare clients already ascertained with HIV at the time of testing on average have 4.1 mL/min/1.73m^2 (95% CI: 3.2, 4.9) higher eGFR results than those who did not have HIV given that age, sex and comorbidity status remain constant. Healthcare clients with diabetes at the time of testing on average have 3.6 mL/min/1.73m^2 (95% CI: 2.6, 4.5) higher eGFR results than those without diabetes when age, sex and comorbidity status remain constant. Healthcare clients who have had TB by the time of testing on average have 2.4 mL/min/1.73m^2 (95% CI: 1.7, 3.0) higher eGFR results than those who never had TB when age, sex and comorbidity status remain constant.

4.7 Discussion

The South African 2019 ART Clinical Guidelines (updated 2020) recommend routine assessment of baseline kidney function before ART initiation. The guidelines recommend the use of eGFR calculated using Counahan Barratt formular for patients ≥ 10 and < 16 years of age, eGFR using MDRD equation for adults and adolescents above 16 years, and absolute creatinine levels for pregnant women living with HIV before initiating ART. However, results availability prior to ART initiation is not a requirement (National Department of Health, 2020). It can be seen in Figure 4.1 that HIV-negative and PLHIV sub-populations are quite different in terms of their access to kidney function tests, and are most likely getting these tests for quite different reasons: for PLHIV, it appears that individuals are being tested at a younger age, most likely as part of routine screening which forms part of the standard of care for PLHIV in South Africa; whereas in the HIV-negative population, screening at older ages is much more likely to be in response to presentation of symptoms related to kidney disease. Earlier female healthcare seeking behaviours compared to later male healthcare seeking behaviours including access to maternal care, high prevalence of CKD among women (George et al., 2019) as well as generally earlier age of HIV infection in women (Mabaso et al., 2018)] may be the reasons why more females are represented in the study

population than males. In essence, this suggests that PLHIV are being tested regardless of their apparent health, whereas those without HIV are most likely being tested only if they are symptomatic as a result of other conditions.

Early linkage to care and subsequent regular screening for kidney function even without prior related symptoms or illnesses may account for SCr and eGFR results that indicate better kidney function at first testing in PLHIV, whereas HIV-negative individuals may only start getting tested once they are identified as having high risk of renal disease or are already ill and showing symptoms suggestive of renal conditions which more commonly occurs at older ages with the advent of other non-communicable diseases (NCDs). With low median SCr results, median eGFR remains high among young PLHIV even when adjusting for age and sex, which suggests in general there are adequate metabolic processes for the excretion of SCr in these healthcare clients.

Although the overview of all raw SCr results (Figure 4.2) suggests that HIV-negative younger people having kidney function tests tend to have good kidney function. When adjusted for age and sex to generate eGFR results, it suggests that their kidney function may be more likely to be reduced. This suggests that they are referred for testing because they are presenting with clinical symptoms possibly related to kidney impairment from other causes. The plotted eGFR results shown in Figure 4.3 demonstrate this difference in kidney function between the HIV-negative and PLHIV populations in the youngest age brackets.

Poorer kidney function at an older age for first testing for healthcare clients without HIV, reflected in lower eGFR values, may reflect that this population may be presenting at health care facilities with symptoms of chronic conditions which become more common as people age and may impact kidney function. This population may only be receiving kidney function tests because kidney dysfunction is suspected due to their clinical presentation and are therefore presenting with lower kidney function results.

When PLHIV age, instead of the higher eGFR results seen when they are screened at younger ages, their kidney function results begin to approach those of the HIV-negative groups that have been referred for kidney function tests due to other health conditions, and the eGFR results between the two groups may not differ as much. This suggests that as this population of healthcare clients with HIV age, their kidney function becomes generally

similar to the kidney function of the HIV-negative healthcare clients who have non-HIV-related health conditions that affect their kidney function.

In the younger age brackets not much detectable difference is seen based on comorbidity profiles: PLHIV with the comorbidities analysed in this study do not in general appear to have kidney test results that are significantly different from those in HIV-negative clients of the same age and comorbidity profiles. As already discussed, the HIV-negative group of healthcare clients attending facilities may be presenting with one or more of the comorbidities and are likely to be attending healthcare facilities because they are feeling unwell and have symptoms due to an ongoing condition. This analysis suggests that having HIV combined with these comorbidities is not associated with greater impact on kidney function compared with the impact of these comorbidities on people without HIV.

Considering that the prevalence of HIV and TB is high in South Africa and the burden of these conditions are seen in the young to mid-aged population, PLHIV and individuals presenting with TB who have kidney function tests would most likely be in the young and middle age groups, as seen in our study population (Table 4.2). Given the high prevalence of hypertension (Kohli-Lynch et al., 2022) and diabetes (Pheiffer et al., 2021) in South Africa, it is expected that higher proportions of HIV-negative healthcare clients receiving kidney function tests but not being tested as part of routine HIV/TB care may generally reflect in the mid- to older -age population in which other chronic NCDs may be determining their healthcare seeking behaviours. Ageing with hypertension, diabetes, and CKD are known to be significant risk factors for renal disorders and this population are most likely having eGFR tests due to the impacts of these common comorbidities on kidney function. The HIV-negative subgroup of healthcare clients in this population is therefore not representative of the general HIV-negative population, as it is strongly biased towards those with other health conditions.

In the older age groups, there is not a substantial difference in average eGFR values for PLHIV and HIV-negative individuals with similar comorbidity profiles. Whilst we may have anticipated worse eGFR results in PLHIV (Campos et al., 2016), our observation in this study could be due to the much smaller number of individuals in the older age group of PLHIV – many more people with severe HIV-related disease may not have lived to this age group given the poor availability of ART when they were younger. This is supported by the

different median age at death between PLHIV, at 43 (IQR: 35-52) years and HIV-negative individuals at 63 (IQR: 55-70) years (Table 4.1). In addition, the proportion of eGFR tests for PLHIV in each age bracket (Table 4.3) are much lower in older age brackets when compared to number of tests in people without HIV who are attending healthcare facilities with other conditions. For example, in the oldest age bracket, there are only approximately 3 500 tests from PLHIV compared to 12 763 tests in the HIV-negative group in this age bracket.

Those PLHIV who have survived to the older age brackets have been screened, have perhaps had better access to health care and ART than others diagnosed at the same time, and may have experienced more mild disease or delayed onset of HIV-related symptoms. In addition, better linkage to care and/or healthcare seeking behaviours may also predispose them to better management of their additional chronic conditions and comorbidities alongside managing their HIV infection (Manne-Goehler et al., 2017).

As expected, our analysis also shows that receiving treatment for hypertension is associated with lower eGFR results. In this study, those ascertained with hypertension are identified in the PHDC data because they are receiving anti-hypertensive medications, whereas we have no way to identify unmedicated hypertensive individuals in the absence of clinical observational data. Previous epidemiological studies have reported that risks of cardiovascular diseases and events may increase in individuals with renal impairments (Bikbov et al., 2020; Gansevoort et al., 2013), but we are unable to evaluate the full impact of hypertension on this population because of our inability to identify people with hypertension from the available data.

We did not include CKD in the mixed effects model because the ascertainment of CKD by the PHDC is largely dependent on SCr/eGFR laboratory test results and may have caused modelling problems related to multicollinearity. We also note that the algorithm does not currently identify individuals with persistent proteinuria with preserved eGFR who may still qualify as having CKD. The results from the mixed effects model suggest that older age categories are associated with substantially lower eGFR results, as expected. Being male, and having hypertension were also associated with slightly lower eGFR values. In this population of healthcare clients, having HIV, TB and diabetes are associated with slightly higher eGFR results. People with TB are often also living with HIV, and therefore may also be subject to increased screening prior to having any symptoms of renal disease, and people

living with diabetes are also linked to care and undergo screening for kidney function. Our observations therefore may reflect that being linked to care and having screening for kidney function for patients with these comorbidities may result in more frequent kidney function tests before kidney function has deteriorated, with corresponding higher eGFR test results.

4.8 Conclusion

Many clinical studies have shown the relationship between HIV and subsequent nephropathy (Ekrikpo et al., 2018; Madala et al., 2014), as well as reporting improvements in kidney function for PLHIV after ART initiation (Assaram et al., 2018; Kamkuemah et al., 2015). In this study we have assessed kidney function testing and results in a population of healthcare clients in the Western Cape, South Africa, and as such are reporting on testing practices in the healthcare client population, rather than the aetiological processes by which HIV can lead to the development of other comorbidities. We also note that this virtual cohort is enriched for individuals who do not have HIV but are attending health services for other illnesses such as the comorbidities described here, and that there is an under-representation of healthy individuals who do not have HIV or other chronic conditions.

Our observations underline that not everyone being tested for kidney function are being tested for the same reasons, and we have described the differences between the subpopulations of younger and older healthcare clients, living with or without HIV.

In summary, in this study the ageing population of PLHIV who are actively seeking healthcare appear quite similar in comorbidities and kidney function to those without HIV, and it is likely that this is due to the history of access to ART in South Africa when these older individuals were first diagnosed with HIV. We believe that older PLHIV in the study population represent only a small subset of the original population of healthcare clients who contracted HIV in the 1990's and early 2000's, due to poor survival rates in those diagnosed with HIV in those decades. It is also possible a number of these older PLHIV contracted and were only diagnosed with HIV recently at older ages. This means that the current population ageing with HIV are not representative of how the same subgroup will look in the future, because those who have been diagnosed with HIV at a young age since 2004 have had improved access to ART, and since 2016 the Test and Treat approach means that they link to ART as soon as they receive a positive diagnosis, leading to better long term

patient outcomes. Whilst the older HIV population currently looks similar to the older HIV-negative population in terms of kidney disease and associated healthcare requirements, we still cannot accurately predict the future health requirements of those who linked to ART whilst young, as they age.

Our analysis of kidney test results in younger healthcare clients also suggests routine kidney function screening is being undertaken for young PLHIV in line with current guidelines and best practice, but in future studies we also need to identify where screening is not reaching those who might benefit from it.

The value of this study is that we have used real data about routine kidney health testing from healthcare clients in Khayelitsha, which offer insights into what is actually happening in facilities with respect to kidney function testing. This is useful for evaluating the implementation of treatment guidelines and healthcare delivery policies and service utilisation for PLHIV. It is encouraging to see so many younger PLHIV having kidney function tests whilst their kidney function is still good, and they do not appear to have any kidney implications. It does, however, remain difficult to predict the future kidney health needs of this population group as they age whilst living with HIV, and by analysing this real-life routine healthcare data we demonstrate that it may not be advisable to plan for future healthcare requirements of younger PLHIV based only on the profile of the current ageing population of PLHIV.

4.9 Acknowledgement

We acknowledge the Provincial Health Data Centre, Health Impact Assessment Directorate of the Western Cape Government Health Department for the provision of the anonymized Khayelitsha dataset.

4.10 Data availability statement

These anonymised, perturbed data were provided for analysis by the Western Cape Department of Health, Provincial Health Data Centre. These are highly granular health data linked to individual health care clients in the province and no informed consent has been given for research use. For this reason, the Western Cape Department of Health does not permit open sharing but instead grants only primary use permission for the data. Re-use of this dataset requires approval from the Western Cape Department of Health (Provincial

Health Data Centre), and Dr Moodley, Director: HIA, Western Cape Department of Health, South Africa can be contacted to advise on this process (email: melvin.moodley@westerncape.gov.za, Reference study ID 259-TIFFIN).

4.11 Funding

This research was funded in part, by the Wellcome Trust 203135/Z/16/Z. For the purpose of open access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript version arising from this submission. The Wellcome Centre for Infectious Diseases Research in Africa is supported by core funding from the Wellcome Trust [203135/Z/16/Z]. ROY receives funding from the Africa Regional Staff/Student International Exchange: Food Security and Sustainable Human Wellbeing II (ARISE II) Consortium funded by the Intra-Africa Academic Mobility Scheme of the European Union (2016-2616). NT receives funding from the NIH Common Fund (H3ABioNet, U24HG006941). NT receives funding from Wellcome CIDRI-Africa (203135/Z/16/Z). NT additionally receives support from the NIH B-Positive grant (R01HD080465).

4.12 References

Assaram, S., Mashamba-Thompson, T. P., & Magula, N. P. (2018). Risk factors and co-morbidities associated with changes in renal function among antiretroviral treatment-naïve adults in South Africa: A chart review. *Southern African Journal of HIV Medicine*, *19*(1), Article 1. https://doi.org/10.4102/sajhivmed.v19i1.770

Bikbov, B., Purcell, C. A., Levey, A. S., Smith, M., Abdoli, A., Abebe, M., Adebayo, O. M., Afarideh, M., Agarwal, S. K., Agudelo-Botero, M., Ahmadian, E., Al-Aly, Z., Alipour, V., Almasi-Hashiani, A., Al-Raddadi, R. M., Alvis-Guzman, N., Amini, S., Andrei, T., Andrei, C. L., … Vos, T. (2020). Global, regional, and national burden of chronic kidney disease, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*, *395*(10225), 709–733. https://doi.org/10.1016/S0140-6736(20)30045-3

Boswell, M. T., & Rossouw, T. M. (2017). Approach to acute kidney injury in HIV-infected patients in South Africa. *Southern African Journal of HIV Medicine*, *18*(1). https://doi.org/10.4102/sajhivmed.v18i1.714

Boulle, A., Heekes, A., Tiffin, N., Smith, M., Mutemaringa, T., Zinyakatira, N., Phelanyane, F., Pienaar, C., Buddiga, K., Coetzee, E., Rooyen, R. van, Dyers, R., Fredericks, N., Loff, A., Shand, L., Moodley, M., Vega, I. de, & Vallabhjee, K. (2019). Data Centre Profile: The Provincial Health Data Centre of the Western Cape Province, South Africa. *International Journal of Population Data Science*, *4*(2), Article 2. https://doi.org/10.23889/ijpds.v4i2.1143

Campos, P., Ortiz, A., & Soto, K. (2016). HIV and kidney diseases: 35 years of history and consequences. *Clinical Kidney Journal*, *9*(6), 772–781. https://doi.org/10.1093/ckj/sfw104

Delanaye, P., Cavalier, E., & Pottel, H. (2017). Serum Creatinine: Not So Simple! *Nephron*, *136*(4), 302–308. https://doi.org/10.1159/000469669

Duru, O. K., Vargas, R. B., Kermah, D., Nissenson, A. R., & Norris, K. C. (2009). High Prevalence of Stage 3 Chronic Kidney Disease in Older Adults Despite Normal Serum Creatinine. *Journal of General Internal Medicine*, *24*(1), 86–92. https://doi.org/10.1007/s11606-008-0850-3

Ekrikpo, U. E., Kengne, A. P., Bello, A. K., Effa, E. E., Noubiap, J. J., Salako, B. L., Rayner, B. L., Remuzzi, G., & Okpechi, I. G. (2018). Chronic kidney disease in the global adult HIV-infected population: A systematic review and meta-analysis. *PLOS ONE*, *13*(4), e0195443. https://doi.org/10.1371/journal.pone.0195443

Ellis, C. L. (2017). HIV associated kidney diseases: Clarifying concordance between renal failure in HIV infection and histopathologic manifestations at kidney biopsy-ClinicalKey. *Seminars in Diagnostic Pathology*, *34*(4), 377–383. https://doi.org/10.1053/j.semdp.2017.04.009

Fiseha, T., Mengesha, T., Girma, R., Kebede, E., & Gebreweld, A. (2019). Estimation of renal function in adult outpatients with normal serum creatinine. *BMC Research Notes*, *12*(1), 462. https://doi.org/10.1186/s13104-019-4487-6

Gama, R. M., Kalyesubula, R., Fabian, J., & Mahalingasivam, V. (2021). NICE takes ethnicity out of estimating kidney function. *BMJ*, *374*, n2159. https://doi.org/10.1136/bmj.n2159

Gansevoort, R. T., Correa-Rotter, R., Hemmelgarn, B. R., Jafar, T. H., Heerspink, H. J. L., Mann, J. F., Matsushita, K., & Wen, C. P. (2013). Chronic kidney disease and cardiovascular risk: Epidemiology, mechanisms, and prevention. *The Lancet*, *382*(9889), 339–352. https://doi.org/10.1016/S0140-6736(13)60595-4

Gasparini, A., Abrams, K. R., Barrett, J. K., Major, R. W., Sweeting, M. J., Brunskill, N. J., & Crowther, M. J. (2020). Mixed-effects models for health care longitudinal data with an informative visiting process: A Monte Carlo simulation study. *Statistica Neerlandica*, *74*(1), 5–23. https://doi.org/10.1111/stan.12188

George, J. A., Brandenburg, J.-T., Fabian, J., Crowther, N. J., Agongo, G., Alberts, M., Ali, S., Asiki, G., Boua, P. R., Gómez-Olivé, F. X., Mashinya, F., Micklesfield, L., Mohamed, S. F., Mukomana, F., Norris, S. A., Oduro, A. R., Soo, C., Sorgho, H., Wade, A., … Ramsay, M. (2019). Kidney damage and associated risk factors in rural and urban sub-Saharan Africa (AWI-Gen): A cross-sectional population study. *The Lancet Global Health*, *7*(12), e1632–e1643. https://doi.org/10.1016/S2214-109X(19)30443-7

Giannelli, S. V., Patel, K. V., Windham, B. G., Pizzarelli, F., Ferrucci, L., & Guralnik, J. M. (2007). Magnitude of Underascertainment of Impaired Kidney Function in Older Adults with Normal Serum Creatinine. *Journal of the American Geriatrics Society*, *55*(6), 816–823. https://doi.org/10.1111/j.1532-5415.2007.01196.x

Hommel, K., Madsen, M., & Kamper, A.-L. (2012). The importance of early referral for the treatment of chronic kidney disease: A Danish nationwide cohort study. *BMC Nephrology*, *13*(1), 108. https://doi.org/10.1186/1471-2369-13-108

Inker, L. A., Eneanya, N. D., Coresh, J., Tighiouart, H., Wang, D., Sang, Y., Crews, D. C., Doria, A., Estrella, M. M., Froissart, M., Grams, M. E., Greene, T., Grubb, A., Gudnason, V., Gutiérrez, O. M., Kalil, R., Karger, A. B., Mauer, M., Navis, G., … Levey, A. S. (2021). New Creatinine- and Cystatin C–Based Equations to Estimate GFR without Race. *New England Journal of Medicine*, *385*(19), 1737–1749. https://doi.org/10.1056/NEJMoa2102953

Islam, F. M., Wu, J., Jansson, J., & Wilson, D. P. (2012). Relative risk of renal disease among people living with HIV: A systematic review and meta-analysis. *BMC Public Health*, *12*(1), 234. https://doi.org/10.1186/1471-2458-12-234

Janmaat, C. J., van Diepen, M., Tsonaka, R., Jager, K. J., Zoccali, C., & Dekker, F. W. (2019). Pitfalls of linear regression for estimating slopes over time and how to avoid them by using linear mixed-effects models. *Nephrology Dialysis Transplantation*, *34*(4), 561–566. https://doi.org/10.1093/ndt/gfy128

Kaboré, N. F., Poda, A., Zoungrana, J., Da, O., Ciaffi, L., Semdé, A., Yaméogo, I., Sawadogo, A. B., Delaporte, E., Meda, N., Limou, S., & Cournil, A. (2019). Chronic kidney disease and HIV in the era of antiretroviral treatment: Findings from a 10-year cohort study in a west African setting. *BMC Nephrology*, *20*(1), 155. https://doi.org/10.1186/s12882-019-1335-9

Kamkuemah, M., Kaplan, R., Bekker, L.-G., Little, F., & Myer, L. (2015). Renal impairment in HIV-infected patients initiating tenofovir-containing antiretroviral therapy regimens in a Primary Healthcare Setting in South Africa. *Tropical Medicine & International Health*, *20*(4), 518–526. https://doi.org/10.1111/tmi.12446

Kaplan, R., Hermans, S., Caldwell, J., Jennings, K., Bekker, L.-G., & Wood, R. (2018). HIV and TB co-infection in the ART era: CD4 count distributions and TB case fatality in Cape Town. *BMC Infectious Diseases*, *18*(1), 356. https://doi.org/10.1186/s12879-018-3256-9

Kohli-Lynch, C. N., Erzse, A., Rayner, B., & Hofman, K. J. (2022). Hypertension in the South African public healthcare system: A cost-of-illness and burden of disease study. *BMJ Open*, *12*(2), e055621. https://doi.org/10.1136/bmjopen-2021-055621

Levey, A. S., Bosch, J. P., Lewis, J. B., Greene, T., Rogers, N., & Roth, D. (1999). A More Accurate Method To Estimate Glomerular Filtration Rate from Serum Creatinine: A New Prediction Equation. *Annals of Internal Medicine*, *130*(6), 461–470. https://doi.org/10.7326/0003-4819-130-6-199903160-00002

Levey, A. S., Coresh, J., Greene, T., Stevens, L. A., Zhang, Y. (Lucy), Hendriksen, S., Kusek, J. W., & Van Lente, F. (2006). Using Standardized Serum Creatinine Values in the Modification of Diet in Renal Disease Study Equation for Estimating Glomerular Filtration Rate. *Annals of Internal Medicine*, *145*(4), 247–254. https://doi.org/10.7326/0003-4819-145-4-200608150-00004

Mabaso, M., Sokhela, Z., Mohlabane, N., Chibi, B., Zuma, K., & Simbayi, L. (2018). Determinants of HIV infection among adolescent girls and young women aged 15–24 years in South Africa: A 2012 population-based national household survey. *BMC Public Health*, *18*(1), 183. https://doi.org/10.1186/s12889-018-5051-3

Madala, N. D., Thusi, G. P., Assounga, A. G. H., & Naicker, S. (2014). Characteristics of South African patients presenting with kidney disease in rural KwaZulu-Natal: A cross sectional study. *BMC Nephrology*, *15*(1), 61. https://doi.org/10.1186/1471-2369-15-61

Manne-Goehler, J., Montana, L., Gómez-Olivé, F. X., Rohr, J., Harling, G., Wagner, R. G., Wade, A., Kabudula, C. W., Geldsetzer, P., Kahn, K., Tollman, S., Berkman, L. F., Bärnighausen, T. W., & Gaziano, T. A. (2017). The ART advantage: Healthcare utilization for diabetes and hypertension in rural South Africa. *Journal of Acquired Immune Deficiency Syndromes (1999)*, *75*(5), 561–567. https://doi.org/10.1097/QAI.0000000000001445

Mendelsohn, S. C., Fiore-Gartland, A., Awany, D., Mulenga, H., Mbandi, S. K., Tameris, M., Walzl, G., Naidoo, K., Churchyard, G., Scriba, T. J., & Hatherill, M. (2022). Clinical predictors of pulmonary tuberculosis among South African adults with HIV. *EClinicalMedicine*, *45*. https://doi.org/10.1016/j.eclinm.2022.101328

Naicker, S. (2020). HIV/AIDS and chronic kidney disease. *Clinical Nephrology*, *93*(1), 87–93. https://doi.org/10.5414/CNP92S115

National Department of Health. (2020). *2019 ART Guideline Clinical Guidelines for the Management of HIV in Adults, Pregnancy, Adolescents, Children, Infants and Neonates* (pp. 1–26). Republic of South Africa National Department of Heath. https://sahivsoc.org/Files/2019%20ART%20Guideline%2028042020%20pdf.pdf

Nduka, C. U., Stranges, S., Sarki, A. M., Kimani, P. K., & Uthman, O. A. (2016). Evidence of increased blood pressure and hypertension risk among people living with HIV on antiretroviral therapy: A systematic review with meta-analysis. *Journal of Human Hypertension*, *30*(6), 355–362. https://doi.org/10.1038/jhh.2015.97

Osei-Yeboah, R., Tamuhla, T., Ngwenya, O., & Tiffin, N. (2021). Accessing HIV care may lead to earlier ascertainment of comorbidities in health care clients in Khayelitsha, Cape Town. *PLOS Global Public Health*, *1*(12), e0000031. https://doi.org/10.1371/journal.pgph.0000031

Palau, L., Menez, S., Rodriguez-Sanchez, J., Novick, T., Delsante, M., McMahon, B. A., & Atta, M. G. (2018). HIV-associated nephropathy: Links, risks and management. *HIV/AIDS (Auckland, N.Z.)*, *10*, 73–81. https://doi.org/10.2147/HIV.S141978

Pheiffer, C., Pillay-van Wyk, V., Turawa, E., Levitt, N., Kengne, A. P., & Bradshaw, D. (2021). Prevalence of Type 2 Diabetes in South Africa: A Systematic Review and Meta-Analysis. *International Journal of Environmental Research and Public Health*, *18*(11), Article 11. https://doi.org/10.3390/ijerph18115868

Swarts, L., Lahri, S., & van Hoving, D. J. (2021). The burden of HIV and tuberculosis on the resuscitation area of an urban district-level hospital in Cape Town. *African Journal of Emergency Medicine*, *11*(1), 165–170. https://doi.org/10.1016/j.afjem.2020.09.016

Vassalotti, J. A., Centor, R., Turner, B. J., Greer, R. C., Choi, M., & Sequist, T. D. (2016). Practical Approach to Detection and Management of Chronic Kidney Disease for the Primary Care Clinician. *The American Journal of Medicine*, *129*(2), 153-162.e7. https://doi.org/10.1016/j.amjmed.2015.08.025

Waheed, S., & Atta, M. G. (2014). Predictors of HIV-associated nephropathy. *Expert Review of Anti-Infective Therapy*, *12*(5), 555–563. https://doi.org/10.1586/14787210.2014.901170

Wyatt, C. M. (2017). Kidney Disease and HIV Infection. *Topics in Antiviral Medicine*, *25*(1), 13–16.

4.13 Supplementary data

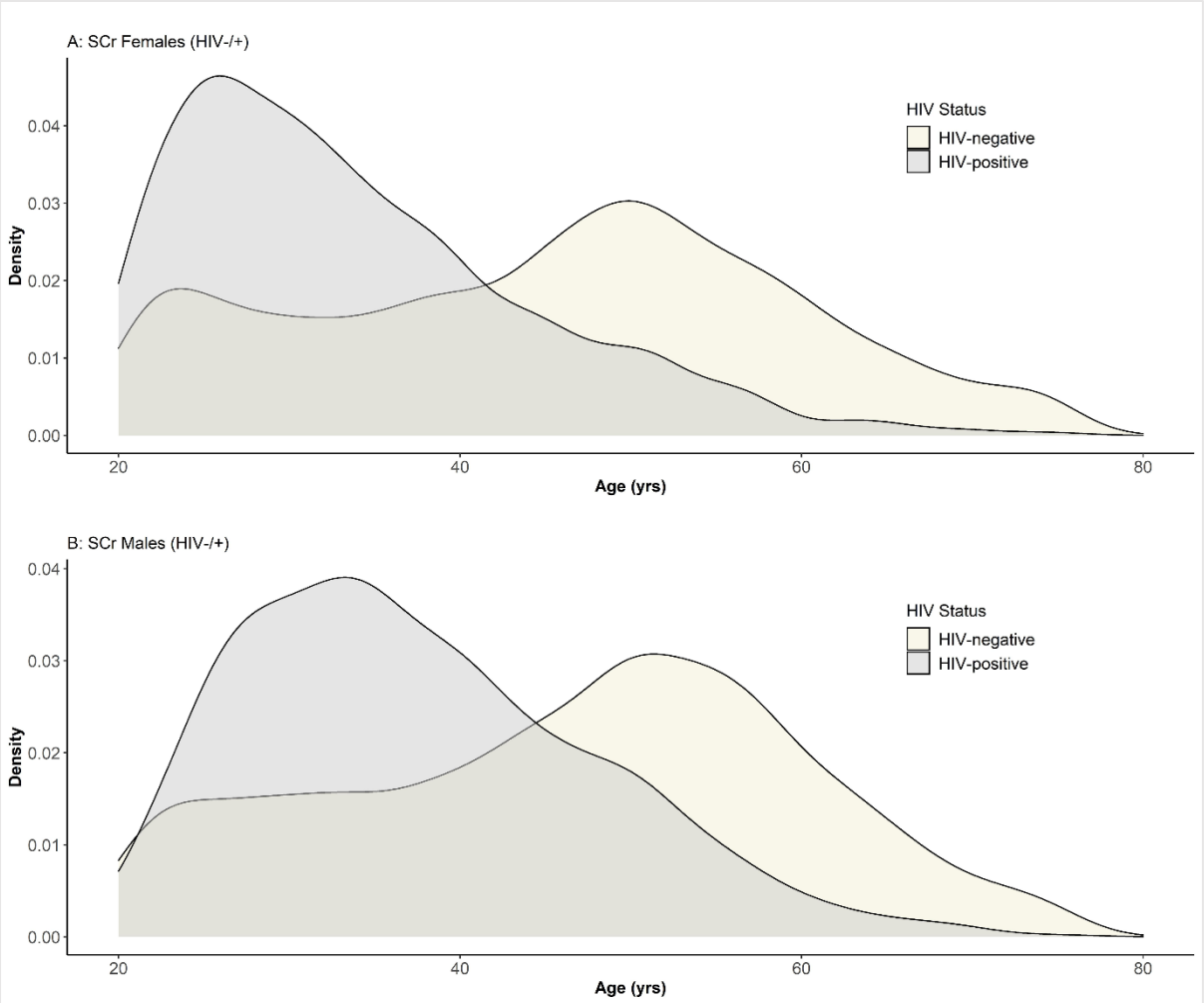


Figure S4.1: Distribution of age at first serum creatinine testing without matched estimated glomerular filtration rate for females and males per HIV status. The X-axis shows age (years) when the first test results were received, and the Y-axis shows the density distribution. A: Age distribution at first serum creatinine results for females by HIV status. B: Age distribution at first serum creatinine results for males by HIV status.

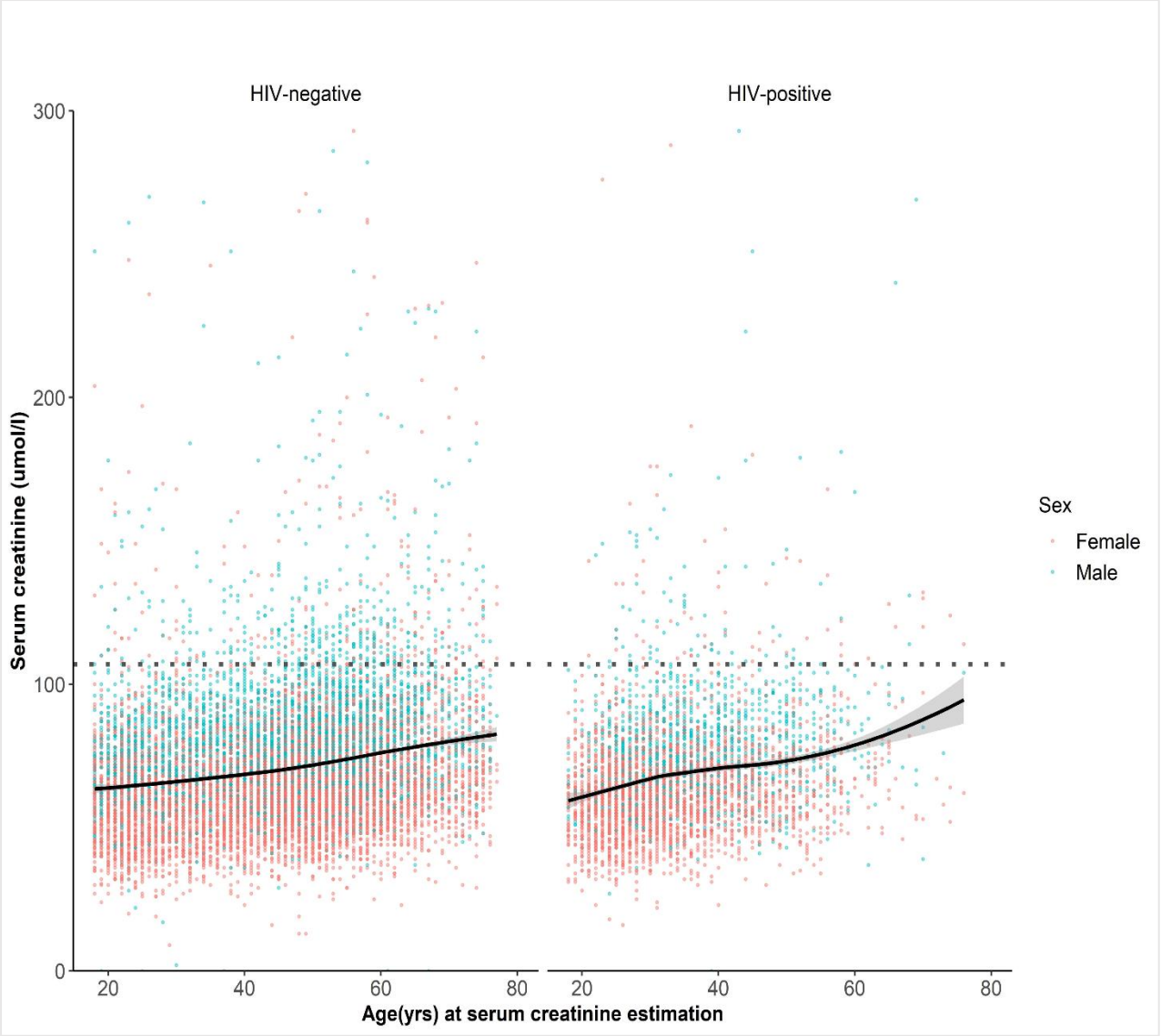


Figure S4.2: Distribution of first serum creatinine without matched estimated glomerular filtration rate results per HIV status and sex. Data points are coloured by sex. Red: Female, Blue: male. Y-axis: SCr results in µmol/l. X-axis: age (in years) at creatinine estimation. The dotted line shows the SCr value above which abnormal kidney function may be inferred.

Table S4.1: Characteristics of healthcare clients who received only SCr results without eGFR

		HIV status	
Characteristic	**Overall**, N = 17,729[1]	**HIV-negative**, N = 13,221[1]	**HIV-positive**, N = 4,508[1]
Age at SCr test	41 (29 – 53)	46 (31 – 55)	32 (26 – 40)
SCr (µmol/l)	67 (56 – 80)	67 (57 – 81)	65 (55 – 77)
Female	11,922 (67)	8,733 (66)	3,189 (71)
Male	5,793 (33)	4,476 (34)	1,317 (29)
Unknown	14	12	2
Tuberculosis	2,464 (14)	1,144 (8.7)	1,320 (29)
Hypertension	9,281 (52)	8,183 (62)	1,098 (24)
Diabetes	3,525 (20)	3,177 (24)	348 (7.7)
CKD	620 (3.5)	541 (4.1)	79 (1.8)

[1]Median (IQR); n (%)

CHAPTER 5: ANALYSIS OF ROUTINE HEALTH DATA FOR HEALTHCARE CLIENTS WITH CHRONIC KIDNEY DISEASE SHOWS EARLIER ASCERTAINMENT AND TESTING WITH BETTER KIDNEY FUNCTION TEST RESULTS FOR PLHIV IN THE WESTERN CAPE, SOUTH AFRICA

5.1 Publication status

Osei-Yeboah, R, & Tiffin, N. Analysis of routine health data for healthcare clients with chronic kidney disease shows earlier ascertainment and testing with better kidney function test results for PLHIV in the Western Cape, South Africa (Ready for submission).

5.2 Author contribution

NT and ROY designed the study. ROY conducted the analysis and wrote the draft manuscript. NT and ROY finalised the manuscript.

5.3 Abstract

Background

Chronic kidney disease (CKD) is a major comorbidity of clinical concern and contributes substantially to the burden of morbidity and mortality in people living with HIV (PLHIV). Despite the well-established relationship between HIV infection and kidney dysfunction, the incidence and presentation of CKD in PLHIV have significantly reduced due to the widespread use of antiretroviral therapy (ART), and since the introduction of combined antiretroviral therapy (cART) the occurrence of HIV-associated nephropathy (HIVAN) has declined.

Objective

To assess the relationship between estimated glomerular filtration rate (eGFR) results and HIV and selected comorbidities for healthcare clients with CKD.

Methods

We used routine health data for healthcare clients with CKD aged 18 years and above who accessed healthcare at government health facilities in Khayelitsha, South Africa, to analyse their SCr and eGFR laboratory tests. These data, accessed from the Provincial Health Data Centre at the Western Cape Department of Health, were also used to identify HIV, tuberculosis (TB), hypertension, diabetes and cervical cancer comorbidities in these

individuals. We analysed the distribution of SCr and eGFR results for PLHIV and HIV-negative healthcare clients with CKD in our study population. A linear mixed effects model was used to assess the association between kidney function test results, and HIV and other selected comorbidities.

Results

A total of 4 178 healthcare clients with CKD were included in the study, of which 2 832 (67.8%) were HIV-negative and 1 346 (32.2%) were PLHIV. Of the total healthcare client population 2 801 (67%) were females and 1 367 (32.7%) were males. Of the HIV-negative and PLHIV sub-populations, females comprised 66.2% and 68.9% respectively. In this population, PLHIV overall had lower median most recent SCr results (96 µmol/l, IQR: 78-130) than HIV-negative individuals (104 µmol/l , IQR: 82-150). The median most recent eGFR result for PLHIV (58 mL/min/1.73m^2 , IQR: 45-70) was higher than HIV-negative individuals (53.3 mL/min/1.73m^2, IQR: 40-66.2). The linear mixed effect regression analysis showed that being a male, having TB, hypertension, and being in an older age category – 30 years and above at the time of eGFR test result - is associated with lower eGFR for healthcare clients with CKD.

Conclusion

Our analysis of routine health data shows that PLHIV accessing care and services receive screening for kidney function at much younger ages. These findings suggest that PLHIV may be diagnosed with CKD and other comorbidities prior to presentation with severe disease symptoms, whereas HIV-negative healthcare clients may only be seeking care when they have physical symptoms indicating impaired kidney function or when kidney diseases have progressed. Considering median most recent eGFR and overall eGFR results, PLHIV who have confirmed CKD have better laboratory results for kidney function metrics than HIV-negative individuals who have CKD. Using routine health data, this study demonstrates kidney function profiles of a population of PLHIV and HIV-negative healthcare clients who have CKD and shows the relationship between kidney function results and HIV and selected comorbidities, providing useful insights relating to healthcare access and provision for healthcare clients with CKD. This detailed analysis suggests that routine health data can be used to evaluate the implementation of HIV care guidelines and track the development of

comorbidities in healthcare clients, whilst recognizing the limitations of these data for assessing the etiological relationship between kidney function and HIV, age, sex and the comorbidities assessed in this study.

Keywords

Chronic kidney disease, HIV, comorbidity, serum creatinine, eGFR, routine data, South Africa

5.4 Introduction

Chronic kidney disease (CKD) is a major global health burden. It is a progressive, non-communicable disease (NCD) with high morbidity and mortality which generally co-occurs in the adult population most commonly with diabetes, hypertension, obesity, and primary renal disorders (Gansevoort et al., 2013; Kalantar-Zadeh et al., 2021). In the general population, these chronic non-communicable conditions are considered the main risk factors for CKD (Cockwell & Fisher, 2020). The effect of CKD on global health could be considered in its direct contribution to global morbidity and mortality and as a key risk factor for cardiovascular diseases (GBD Chronic Kidney Disease Collaboration et al., 2020; Lv & Zhang, 2019). The Global Burden of Disease (GBD) Chronic Kidney Disease Collaboration group has reported a global CKD prevalence of 9.1% and about 1.2 million mortalities in 2017 (GBD Chronic Kidney Disease Collaboration et al., 2020). Though the GBD data indicate that the global burden of CKD is widely carried by countries in low and middle socio-demographic index quintiles, there are inter- and intra-regional differences. For instance, the burden in western, eastern and central sub-Saharan Africa (SSA) is lower than expected (GBD Chronic Kidney Disease Collaboration et al., 2020). CKD prevalence estimates from previous meta-analyses range from 2% in Cote D'Ivoire to 30% in Zimbabwe (Stanifer et al., 2014), but these estimates may be incomparable given the heterogeneity in CKD definition (George et al., 2017).

Among people living with HIV (PLHIV), CKD is a major comorbidity of clinical concern and substantially contributes to the burden of morbidity and mortality in this population in both high-income and low-middle-income countries (Heron et al., 2020). Despite the well-established relationship between HIV infection and kidney dysfunction (Ekrikpo et al., 2018), the incidence and presentation of CKD in PLHIV have significantly reduced due to the widespread use of antiretroviral therapy (ART), and with the introduction of combined

antiretroviral therapy (cART), the occurrence of HIV-associated nephropathy (HIVAN) has declined (Rosenberg et al., 2015). Clinical interventions such as weight loss, blood pressure management and treatment of dyslipidemia or hyperglycemia can also be used to slow the progression of CKD (Heron et al., 2020) and when HIV treatment guidelines and strategies include these interventions, CKD among PLHIV may even be lower than in the general population (Alfano et al., 2019; Gupta et al., 2005).

In addition to chronic NCDs, HIV-associated risk factors including viral replication measured as viral load, nadir CD4+ cell count, and age, and other viral coinfections such as hepatitis B and C contribute to CKD incidence (Heron et al., 2020). In a pooled modification of diet in renal disease study (MDRD)-based estimate, which estimates glomerular filtration based on creatinine and patient characteristics – age, sex and race/ethnicity (Levey et al., 1999, 2009), the prevalence of CKD in PLHIV in Southern Africa was lowest (3.2%) compared to Western Africa (14.6%) (Ekrikpo et al., 2018). In South Africa, a recent cross-sectional study using different estimators reports that CKD prevalence in the general population ranges from 2.3% to 5.1% for males and 1.6% to 6.7% for females (Peer et al., 2020). The prevalence of CKD in PLHIV varies widely between geographic regions and these variations are related to the reporting methods and the definition of CKD used (Rosenberg et al., 2015), as well as HIV ascertainment in different regions. Previous studies have suggested a link between CKD and tuberculosis (TB) due to immunosuppression along with demographics and comorbid factors such as diabetes (Romanowski et al., 2016; Ruzangi et al., 2020). Diabetes and hypertension are considered the common causes of CKD possibly as a result of lifestyle changes and increasing prevalence of obesity (Ghaderian & Beladi-Mousavi, 2014; Hernandez & Nasri, 2013) and the synergistic interaction between diabetes and hypertension to promote kidney injury and dysfunction (Wang et al., 2017). In a previous study, hypertension has been identified as an independent risk factor for diabetic kidney disease and alongside this, highlighted that a proportional increase in creatinine levels and eGFR may be associated with hypertension nephrosclerosis and diabetic nephropathy (Verma et al., 2016).

The aetiology of renal diseases among PLHIV includes HIV-related diseases like HIVAN, HIV immune complex kidney disease, CKD from antiretroviral toxicity, side effects of ART, or manifestation of CKD related to NCDs (Jotwani et al., 2017). Genetic risk variants *APOL1* G1

and G2 alleles which are found only in people with African ancestry have been identified as risk factors for the development of CKD and progression from CKD to end stage renal disease (ESRD) (Foster et al., 2013). These genetic variants increase rates of hypertension-associated ESRD, focal segmented glomerulosclerosis (FSGS), HIVAN, and other forms of nondiabetic kidney disease (Friedman & Pollak, 2021). *APOL1* variants have been identified as risk factors of CKD among PLHIV in SSA (Kabore et al., 2022). In South Africa, *APOL1* variants are strongly associated with HIVAN in black South Africans (Kasembeli et al., 2015). The prevalence and patterns of CKD among ART-naïve PLHIV are not comparable to ART-experienced PLHIV (Adedeji et al., 2015), which supports the suggestion that long term HIV treatment could be a significant predictor of CKD among PLHIV. Considering the increasing risks of cardiovascular diseases among CKD patients compared to individuals without CKD (Hill et al., 2016), and the contributions of HIV infection (Madala et al., 2014), ART medications (such as tenofovir and ritonavir) (Mocroft et al., 2016), in addition to a person's chronic comorbid conditions and ageing (Acquah et al., 2015; Bastida, 2017) to the occurrence of renal diseases, it is important to understand the kidney function profiles of healthcare clients with CKD in the context of HIV and other NCDs in South Africa. In this study we have analysed routine health data for healthcare clients with CKD to understand the kidney function profiles of healthcare clients in the context of HIV and other comorbidities ascertained prior to or at the time of kidney function assessment.

5.5 Methods

5.5.1 Ethics

Ethics approval was obtained from the Human Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town (HREC ref: 482/2019). A waiver for informed consent was granted because the data were anonymised and perturbed, and individuals could not be identified or re-identified from the data. A data access request was approved by the Health Impact Assessment Directorate at the Western Cape Department of Health, South Africa.

5.5.2 Study population

Khayelitsha is a high-density, mixed informal and formal housing suburb in Cape Town, South Africa. The analysis includes all SCr and eGFR laboratory results generated by the National Health Laboratory Services for adults aged 18 years and over with ascertained CKD

who accessed public health facilities in the Khayelitsha subdistrict of Cape Town, South Africa, between 1 January 2016 and 31 December 2017, described as the 'recruitment period'.

5.5.3 Data Source

The Provincial Health Data Centre (PHDC) is a health information exchange facility that collates administrative health data for the Western Cape Province. Unique identifiers are used to link individuals to administrative health records, and facility visit, laboratory, and pharmacy data are updated daily for about 6.6 million people currently seeking care in public facilities in the Western Cape Province. Algorithms are used to infer disease episodes from combinations of pharmacy-dispensed drugs, laboratory test results, international classification of diseases-10th edition (ICD-10) diagnosis codes, and facility encounter data (Boulle et al., 2019). A dataset containing routine health data was obtained from the PHDC, Western Cape Government Health Department, with longitudinal data ranging from 2007 to 2017. The records of the healthcare clients who received laboratory results included HIV and comorbidities records, and these were used to determine which conditions they already had when the laboratory test was taken. The median length of time for which individuals have available data is 8 years (IQR: 3.6-10 years). The study dataset was anonymised and perturbed within the PHDC prior to being released for use in this analysis, to prevent identification or re-identification of individuals.

5.5.4 PHDC disease episode definition

The PHDC infers diseases from routine health data using either single, or a combination of parameters categorized into high, moderate, and weak confidence and supporting-only evidence for having a particular disease episode. High confidence definition of HIV requires evidence for dispensed valid first line (2NRTI and NNRTI) and valid triple therapy regimen (fixed-dose combination) of antiretrovirals, and/or positive laboratory test results (viral load test, polymerase chain reaction (PCR) test, enzyme linked immunosorbent assay (ELISA) test, and ART resistance test). For TB, evidence for the episode may include admission to specialized TB hospital, TB drug regimen dispensed, and/or laboratory test results (Positive GeneXpert, Line probe assay (LPA), Acid-Fast Bacillus positive culture, positive microscopy (Ziehl-Neelsen staining), and microbiology culture-*Toxocara canis* (ELISA) are the main definition parameters. High confidence definition of hypertension includes dispensed

hydrochlorothiazide. High confidence definitions of diabetes episodes are based on dispensed drug for the treatment of diabetes mellitus, laboratory test showing HbA1c greater than 6.5%, oral glucose tolerance test result greater than 11.1 mmol/l, and diagnosis coding showing an ICD-10 code indicating diabetes disease.

For CKD, laboratory test showing consecutive glomerular filtration rate of less than 60mL/min/1.73m^2 with 90 days between tests, dispensed kidney, or transplant medications (antithymocyte, immunoglobulin, and basiliximab), and diagnosis coding indicating kidney transplant procedure in theatre constitute high confidence definition. It is important to note that SCr and eGFR results are used extensively in defining patients with CKD by the PHDC. This means that there is extensive overlap between having poor kidney function test results and being defined as having CKD. In defining the CKD, however, the ascertainment algorithm makes use of longitudinal eGFR results to track changes in kidney function over time and is not based on individual kidney function results but rather an individual's kidney function profile over time. The PHDC algorithm uses the MDRD GFR estimating equation to determine eGFR. We recognise that an update of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation without the race/ethnicity factor is now recommended (Gama et al., 2021; Inker et al., 2021). In this study set, all individuals with an ascertainment of CKD were included in the analysis, but their longitudinal data span the period before CKD ascertainment as well as after ascertainment. CKD staging was done based on the following description - Stage 2 - Mild CKD (GFR = 60-89 mL/min/1.73m^2); Stage 3B - Moderate CKD (GFR = 30-44 mL/min/1.73m^2); Stage 3A - Moderate CKD (GFR = 45-59 mL/min/1.73m^2); Stage 4 - Severe CKD (GFR = 15-29 mL/min/1.73m^2); Stage 5 - End stage CKD (GFR <15 mL/min/1.73m^2).

5.5.5 Data Analysis

Descriptive statistics were used to summarize the metrics for healthcare clients with confirmed CKD, and also for all kidney function laboratory tests conducted for HIV-negative healthcare clients and PLHIV. Wilcoxon rank sum tests were used to calculate the significance of differences in median age at testing, CKD ascertainment, SCr and eGFR results and Fisher's exact tests were used to calculate the significance of differences in categorical variables to generate the reported p-values.

We used a linear mixed effects model to explore the relationship between eGFR results and age at testing (by age category), sex, HIV, and selected comorbidities as fixed effects for healthcare clients with CKD. The individual-level repeated eGFR tests were included as the random effect. This method takes into account the heterogeneity which may exist in the number of kidney function estimates available for each patient which must be considered when estimating kidney function trajectories (Gasparini et al., 2020; Janmaat et al., 2019).

All data analyses were done in R Software (version 4.1.2) and RStudio (2021.09.0+351 "Ghost Orchid"). The “lme4” package in RStudio was used to run the linear mixed effect model and the associated p-values were generated with the “lmerTest” package. The visualisations of the distributions of SCr and eGFR results per HIV status and age at testing for healthcare clients with CKD were done using ‘ggplot2’ package in RStudio.

5.6 Results

5.6.1 Description of the population of healthcare clients with CKD

A total of 4 178 healthcare clients with confirmed CKD were included in the study, of which 2 832 (67.8%) were HIV-negative and 1 346 (32.2%) were PLHIV. Of the total study population, 2 801 (67%) were females, 1 367 (32.7%) were males and the sex status of 10 (0.3%) healthcare clients was not identified. Among HIV-negative healthcare clients there were 1 874 (66.2%) females and 952 (33.6%) males, and among PLHIV there were 927 (68.9%) females and 415 (30.8%) males.

Other renal disorders reported for this healthcare client population include acute kidney injury without a prior CKD diagnosis - 16 162; single abnormal creatinine, where a single SCr result is above 100µmol/l - 1 602 without a follow-up test result; and systemic lupus erythematosus patients with lupus nephritis - 315. Whereas healthcare clients could have multiple episodes of acute kidney injury, only one episode of CKD was ascertained by the PHDC algorithm, and an acute kidney injury episode could not be determined to have occurred after the start date for an ascertained CKD episode.

The median age at CKD ascertainment differed for HIV-negative healthcare clients who had higher median age of 62 years (IQR: 55-71 years) and PLHIV with median age of 46 years (IQR: 38-55 years). The median age at SCr test was higher for HIV-negative healthcare clients, 60 years (IQR: 53-68 years) than PLHIV who had a median age of 44 years (IQR: 36-

53 years). The median age at eGFR test result was higher for HIV-negative healthcare clients who had a median age of 60 years (IQR: 53-68 years) compared to 45 years (IQR: 37-53 years) for PLHIV. Of the total population with CKD, 570 (13.6%) were deceased. Of 1 346 PLHIV, 203 (15.1%) were deceased, whereas a lower proportion of 367 out of 2 832 (13%) HIV negative individuals were deceased. Almost equal proportions of HIV-negative (12.1%) individuals and PLHIV (12.6%) were at CKD Stage 5 (Table 5.1).

5.6.2 Number of laboratory tests conducted and median SCr and eGFR results for PLHIV and HIV-negative clients

A total of 39 906 SCr laboratory tests were reported for the healthcare client population with CKD, of which 20 816 (52.2%) were recorded for HIV-negative healthcare clients. There were 42 275 eGFR results for the healthcare client population and 21 685 (51.3%) results were recorded for PLHIV. PLHIV recorded lower median most recent SCr: 96 µmol/l (IQR: 78-130) than HIV-negative individuals at 104 µmol/l (IQR: 82-150) and most recent eGFR were similarly higher for PLHIV - 58 mL/min/1.73m^2 (IQR: 45-70) than HIV-negative individuals - 53.3 mL/min/1.73m^2 (IQR: 40-66.2) (Table 5.1).

Table 5.1: Baseline description of the healthcare client population with ascertained CKD, showing median (IQR), counts, and proportions per HIV status.

	Healthcare clients with CKD	**HIV-negative with CKD**	**PLHIV with CKD**	**p-value**
A: Metrics per healthcare client				
Number of healthcare clients	4 178	2 832 (67.8%)	1 346 (32.2%)	--
Median age (IQR) at CKD ascertainment	58 (48-67)	62 (55-71)	46 (38-55)	<0.001
Median age (IQR) at SCr testing	56 (48-65)	60 (53-68)	44 (36-53)	<0.001
Median age (IQR) at eGFR	54 (44-63.7)	60 (53-68)	45 (37-53)	<0.001
Sex				
Female	2 801 (67%)	1 874 (66%)	927 (69%)	<0.001
Male	1 376 (33%)	952 (34%)	415 (31%)	
Deceased	570 (13.6%)	367 (13%)	203 (15.1%)	0.074
Most recent CKD staging (% of HIV-/+ with CKD)				
NULL	32 (0.8%)	20 (0.71%)	12 (0.9%)	
Stage 2	7 (0.2%)	2 (0.07%)	5 (0.4%)	
Stage 3A	1 944 (46.5%)	1 250 (44.1%)	694 (51.6%)	0.0005
Stage 3B	1 025 (24.5%)	754 (26.6%)	271 (20%)	
Stage 4	657 (15.7%)	462 (16.3%)	195 (14.5%)	
Stage 5	513 (12.3%)	344 (12.1%)	169 (12.6%)	
B: All laboratory tests done				
Total number of serum creatinine tests	39 906	20 816 (52.2%)	19 090 (47.8%)	<0.001
Average number of SCr tests per individual	15.3	11.0	26.6	<0.001
Total number of eGFR results	42 275	20 590 (48.7%)	21 685 (51.3%)	<0.001
Average number of eGFR results per individual	15.6	12.6	20.1	<0.001
Serum creatinine Median (IQR)	98 (79-125) µmol/l	99 (82-126) µmol/l	93 (74-122) µmol/l	<0.001
Most recent serum creatinine Median (IQR)	101 (79-141) µmol/l	104 (82-150) µmol/l	96 (78-130) µmol/l	<0.001
eGFR Median (IQR)	57 (45-72) mL/min/1.73m^2	55.9 (44.6-68) mL/min/1.73m^2	60 (46.8-78) mL/min/1.73m^2	<0.001
Most recent eGFR Median (IQR)	55 (41-67) mL/min/1.73m^2	53.3 (40-66.2) mL/min/1.73m^2	58 (45-70) mL/min/1.73m^2	<0.001

5.6.3 Age at testing and distribution of all SCr and eGFR results for healthcare clients with CKD stratified by HIV status

SCr testing for HIV-negative healthcare clients with CKD were common among those aged 45-80 years while testing among PLHIV was common among those aged 25-65 years (Figure 5.1). The distribution of SCr results for the HIV-negative healthcare clients with CKD suggests that more males compared to females appear to have SCr results that are above the approximate 107µmol/l threshold, which may indicate kidney function impairment as previously defined by Hosten (Hosten, 1990), used for reporting in South Africa (Thistle, 2014) and recently referenced by Shahbaz and Gupta (Shahbaz & Gupta, 2022) (Figure 5.1). The SCr results for PLHIV appear to be more evenly distributed between females and males. Outliers above 400 µmol/l were excluded from the visualization (Figure 5.1). The eGFR results are generated from the SCr results which are adjusted for sex and age, and show a more even distribution of results among female- and -male healthcare clients with CKD for both HIV-negative individuals and PLHIV (Figure 5.2); and the observed disparity between SCr values between males that was seen in Figure 5.1 is no longer visible accordingly, due to the adjustment for female-male differences in SCr excretion which is incorporated in the eGFR calculations.

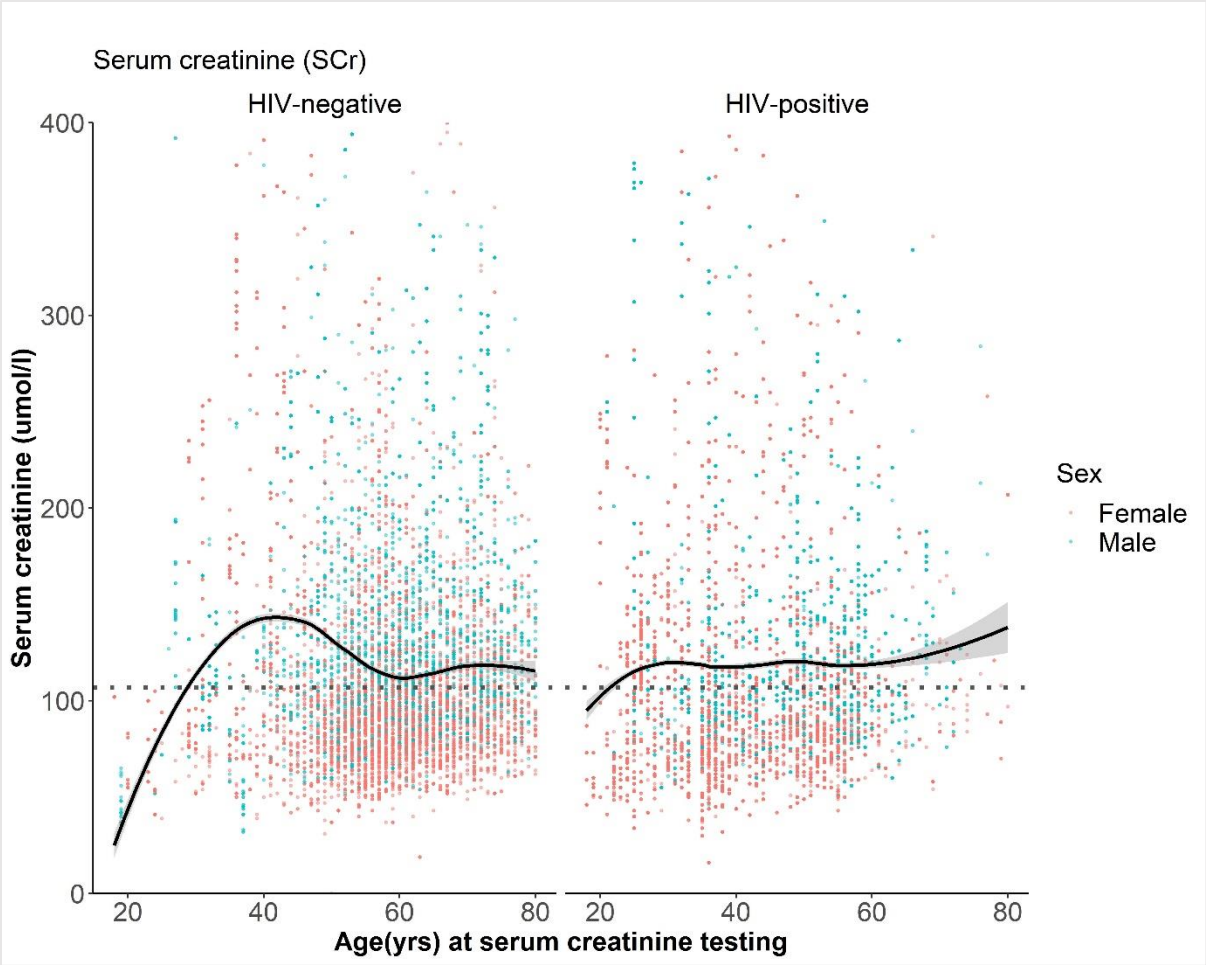


Figure 5.1: Distribution of all serum creatinine (SCr) results per HIV status and sex among healthcare clients with CKD. Data points are coloured by sex. Red: Females, Blue: Males. X-axis: Age (years) at SCr testing, Y-axis: SCr results in µmol/l. Dotted lines: the SCr value above which an abnormal kidney function is inferred.

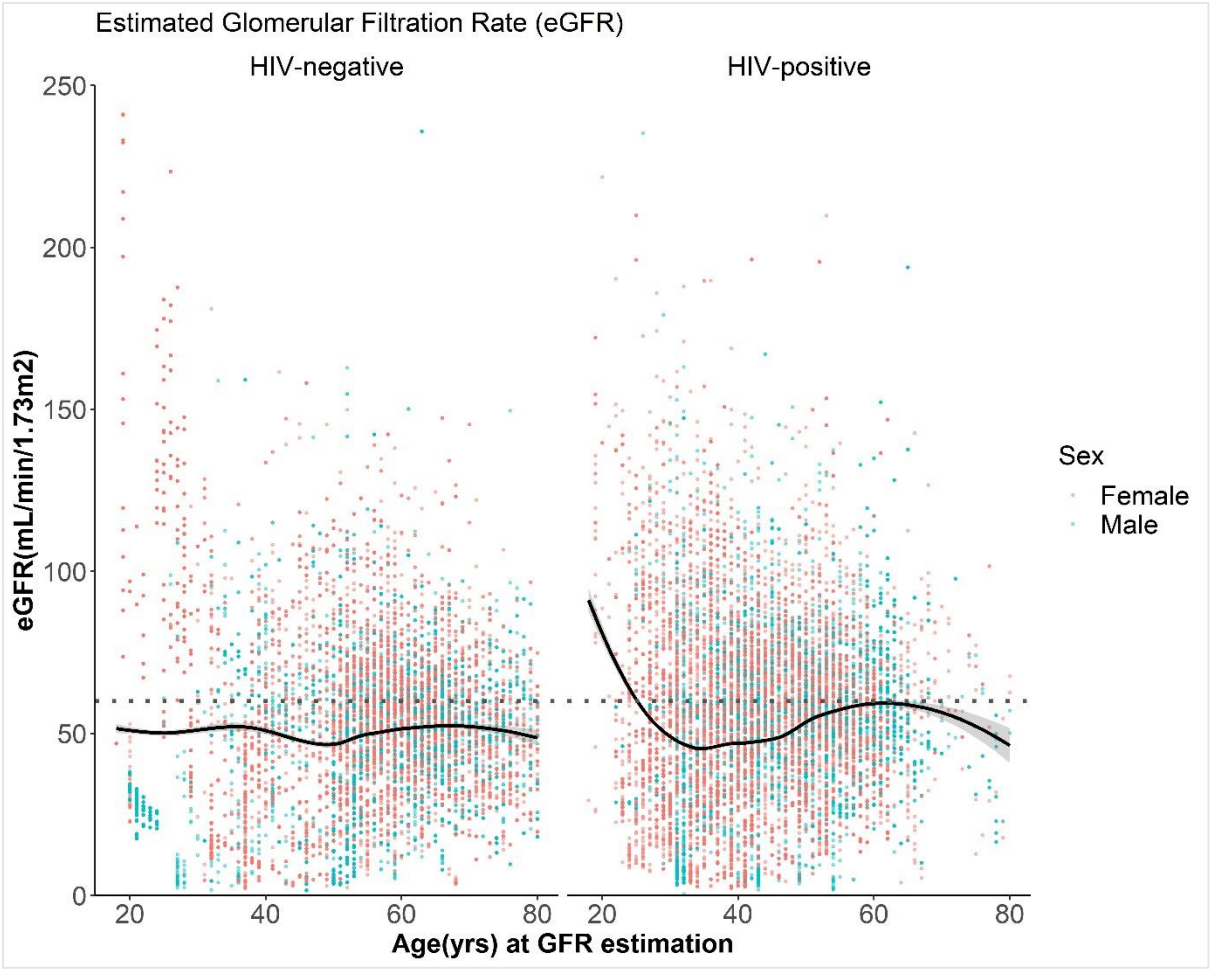


Figure 5.2: Distribution of all estimated glomerular filtration rate (eGFR) results per HIV status and sex among healthcare clients with CKD. Data points are coloured by sex. Red: Females, Blue: Males. X-axis: Age (years) at GFR estimation, Y-axis: eGFR results in mL/min/1.73m^2. Dotted lines: eGFR value below which an abnormal kidney function is inferred.

5.6.4 The relationship between eGFR results and age, sex, and having a comorbidity at CKD ascertainment.

By using all the eGFR results of healthcare clients with CKD, the linear mixed effect model demonstrates the variations in kidney function for all the study population and shows how the selected predictors impact kidney function. The test results include those from tests done prior to the date of ascertainment of CKD for all individuals in the study population. The random effect part of the models indicated a considerable variation of eGFR results (kidney function)

between healthcare clients with CKD with a standard deviation (SD) of 20.31 mL/min/1.73m^2 and residual variance SD of 17.60 mL/min/1.73m^2.

The fixed effects part of the model (Figure 5.3) indicates that being a male healthcare client is associated with lower eGFR results (-2.8/mL/min/1.73m^2, 95% CI: -4.6, -1.0) compared to being a female healthcare client when age and comorbidity status are constant. Healthcare clients with a CKD ascertainment and TB prior to laboratory testing have slightly lower eGFR results of an average -1.5mL/min/1.73m^2 (95% CI: -2.2, -0.78) than those who never had TB. Healthcare clients with CKD and prior hypertension ascertainment have substantially lower average eGFR results of -7.9 mL/min/1.73m^2 (95% CI: -8.6, -7.2) than those without hypertension when age, sex and other comorbidity status remain constant. The model indicates that being in an older age group compared to those aged 18-29 years is associated with slightly lower eGFR results for healthcare clients with CKD. Healthcare clients with CKD aged 30-44 years have an average of -7.1mL/min/1.73m^2 (95% Confidence interval - CI: -9.4, -4.7) lower eGFR results, those aged 45-60 years have an average of -9.2 mL/min/1.73m^2 (95% CI: -12, -6.7) lower eGFR results, and those aged over 60 years have on average -9.5 mL/min/1.73m^2 (95% CI: -12, -6.9) lower eGFR results than healthcare clients aged 18-29 years when sex, HIV and other comorbidities status are constant. The associations between eGFR results and prior ascertainment of HIV and diabetes for healthcare clients with CKD were not statistically significant when age, sex and other comorbidity status remain constant.

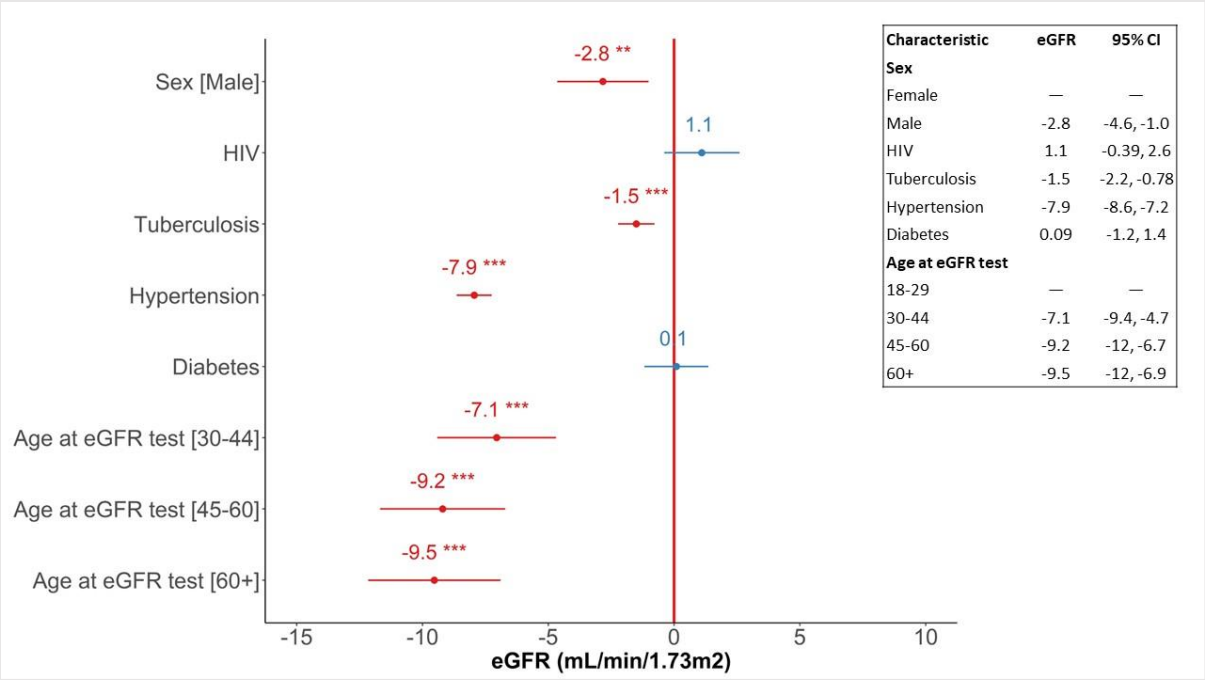


Figure 5.3: Relationship between eGFR, HIV and comorbidities of healthcare clients with CKD. Linear mixed-effect regression showing eGFR estimates and 95% confidence interval (CI)

5.7 Discussion

In this study, we have analysed routine health data about kidney function metrics for healthcare clients with CKD and compared the kidney function results for PLHIV and HIV-negative healthcare clients. Comparing the age ranges at testing in this population, we observe that PLHIV are getting tested for kidney function at much younger ages than HIV-negative individuals: 36-53 years vs 53-68 years for SCr and 37-53 years vs 53-68 years for eGFR results. The age range at CKD ascertainment also shows that PLHIV are being ascertained with CKD at much younger ages (38-55 years) compared to HIV-negative individuals (55-71 years). In the South African population, a previous study found that individuals carrying any combination of two *APOL1* risk alleles had 89-fold higher risk of developing HIVAN among PLHIV (Kasembeli et al., 2015) and the earlier ascertainment of CKD in PLHIV could be related to an earlier occurrence of CKD in PLHIV due to possible genetic risks. Considering the most recent eGFR, and the median eGFR (overall), HIV-negative individuals with CKD seem generally sicker. This may be because PLHIV are getting tested and ascertained with CKD earlier and may be receiving

timely treatment as part of HIV care and services when the disease has not yet progressed and their results improve over time, whilst HIV-negative individuals may only get tested or ascertained later with the disease and are already physically ill.

Our analysis shows that on average PLHIV receive more SCr tests (26.6 tests vs 11.0 tests) and eGFR test results (20.1 test results vs 12.6 test results) than HIV-negative healthcare clients. The median most recent SCr and eGFR results in Table 5.1 indicate that kidney function is generally better in PLHIV who have CKD and are receiving test results than HIV-negative individuals. PLHIV are routinely screened for other conditions as part of the HIV care and services and this will lead to early detection of kidney disorders (Osei-Yeboah et al., 2021). PLHIV who have CKD may be receiving adequate care for comorbidities at an earlier age and before becoming very ill with those comorbidities as result of HIV care and services, whilst HIV-negative healthcare clients with CKD may already be showing signs of severe disease progressions at the time they access healthcare services.

In this population of healthcare clients with CKD, there is a difference in age of kidney function testing between PLHIV and HIV-negative healthcare clients. The age range at kidney function testing is substantially younger for PLHIV (36-53 years for SCr and 37-53 years for eGFR) compared to HIV-negative healthcare clients (53-68 years for both SCr and eGFR). There is difference in the age of CKD ascertainment between PLHIV: 46 (38-55 years) and HIV-negative individuals: 62 (55-71 years) and shows that PLHIV are ascertained at younger ages. These observations may be related to access to care such that PLHIV accessing healthcare are regularly screened for common comorbidities and may lead to earlier ascertainment of NCDs like CKD (Osei-Yeboah et al., 2021). It could also be related to the aetiology of CKD in PLHIV where both HIV infection and prolonged exposure to ART treatment (Swanepoel et al., 2018) contribute to kidney disease occurrence through direct and indirect mechanisms which affect all parts of the nephron (Alfano et al., 2019). The cytopathic effect of HIV within the renal parenchymal cells results in the disruption of the normal cell activities; and the immune system response to HIV infections such as formation of immune complexes which are deposited in the kidneys and the hyperimmune reaction to HIV antigens pose high risks of kidney impairment in PLHIV (Alfano et al., 2019).

The mixed effect model results in Figure 5.3 show that in conjunction with other risk factors – sex, HIV, and comorbidities, being older is associated with lower eGFR results, as expected. Increasing age has been identified as a predictor of lower eGFR results in a previous study (Kavishe et al., 2021). As described above the age range at SCr testing and eGFR test results between PLHIV and HIV-negative individuals is quite different and HIV-negative individuals have higher median age at CKD ascertainment, SCr and eGFR measurements.

Our results showed that PLHIV have slightly higher most recent and overall eGFR test results compared to HIV-negative individuals (Table 5.1) and this finding is similar to a previous study in Tanzania (Kavishe et al., 2021). However, there was no significant impact of HIV on eGFR in conjunction with other risk factors assessed in the mixed effects model (Figure 5.3).

In the plotted distributions, there appears to be a difference in SCr values between men and women, with generally higher values for men (Figure 5.1), but this difference is less marked when looking at the eGFR plots for both PLHIV and HIV-negative healthcare clients most likely because eGFR values are adjusted for age and sex (Figure 5.2). This suggests that the use of glomerular filtration rate is a better metric for further analysis to compare kidney functions in this population (Fabian et al., 2019), and provides adequate basis for comparison of kidney function. The difference between males and females is observed in the mixed effects model (Figure 5.3) which shows that being a male is associated with a lower eGFR value.

The multivariate analysis shows lower eGFR results in healthcare clients in our study who have hypertension and TB in addition to CKD. Lower eGFR is a key indicator of a wide range of ongoing diseases. Due to the natural organ senescence associated with ageing, healthcare clients with kidney disorders are at increased kidney functionality impairment as they age (de Boer et al., 2011). About 1mL/min/1.73m^2 reduction of eGFR is noted to occur per a year increase in age usually starting in the third decade of life (Grams et al., 2013). The slightly lower eGFR results observed as healthcare clients with CKD fall into the older age groups in our study population may be as a result of the combined effect of the presence of kidney diseases and ageing. In addition to the physiological phenomenon of ageing-related kidney function decline, NCDs such as diabetes and hypertension further induce the rate of eGFR reduction (Russo et al., 2018). For healthcare clients with CKD lower eGFR may be a further indication of the poor

health exacerbated by the presence of other comorbidities (Fraser et al., 2020; Tartof et al., 2018) and previous studies have reported associations between kidney function decline and hypertension (Vaes et al., 2015; Yu et al., 2019), and TB (Shen et al., 2015).

In this population, we did not observe the anticipated impact of HIV on eGFR test results when considering age, sex, and other comorbidities. This suggests that HIV may not currently have significant impact on eGFR results in PLHIV. The early kidney function testing and early CKD ascertainment in PLHIV as described above possibly lead to early treatment and/or management which improves test results over time for PLHIV. We also note that the algorithm does not currently identify individuals with persistent proteinuria with preserved eGFR who may still qualify as having CKD. In relation to age, our analysis showed that being older is associated with lower eGFR results and PLHIV are generally receiving eGFR results at a younger age, which may contribute to the insignificant impact of HIV on eGFR results seen in this particular dataset with a strong age bias between PLHIV and HIV-negative subpopulations. Previous studies report that increasing age, higher body mass index and diabetes are correlated with lower eGFR (Kavishe et al., 2021; Struik et al., 2011), and as PLHIV age and present with other NCDs, the real impact of HIV on eGFR results may be observed in this population in the future.

Our analysis of kidney function metrics for individuals with CKD in terms of HIV status provides insights into how accessing care for various reasons may underline the kidney function test results for PLHIV and HIV-negative clients. The population of PLHIV in South Africa is a mixture of predominantly young individuals and a much smaller population of older adults who have survived despite been diagnosed with HIV when access to ART was not universal. It is also possible that these adults were diagnosed with HIV in the older ages. Since the population of PLHIV has generally started ageing, the lower median age of PLHIV, compared to the higher median age of HIV-negative healthcare clients at CKD ascertainment, SCr testing and eGFR reflects the age differences between PLHIV and HIV-negative healthcare clients. The HIV-negative healthcare clients are largely older individuals accessing healthcare for several chronic conditions.

5.8 Conclusion

Analysis of routine health data for healthcare clients with CKD shows substantial differences in eGFR results for PLHIV and HIV-negative individuals in terms of individual healthcare clients results and when considering all laboratory results. Our analysis shows that PLHIV who have CKD have better laboratory results of kidney function metrics than HIV-negative individuals who have CKD. PLHIV accessing care and services are generally much younger than HIV-negative clients, and also receive screening for kidney function and other comorbidities even when they do not show symptoms of kidney impairment and are identified when kidney diseases are not severe, whereas the HIV-negative healthcare clients may only be seeking care when there are symptoms indicating impaired kidney function or when kidney diseases have progressed. It is important to ensure that screening for chronic conditions is improved for individuals who are not receiving HIV services for early detection of conditions that potentially impact kidney function.

Our analyses focused on kidney function testing and reporting for healthcare clients in public facilities and our results only describe kidney function results for healthcare clients with or without HIV in the context of other comorbidities and receiving care for CKD, algorithmically ascertained by the PHDC. From routine health data, this study demonstrates kidney function profiles of a population of PLHIV and HIV-negative healthcare clients who have CKD and shows the relationship between kidney function results, age, HIV and selected comorbidities. We recognize that these routine health data are not able to demonstrate the aetiologic relationship between kidney function and HIV, age, sex, and the comorbidities assessed in this study. These routine health data can, however, provide useful insight into healthcare access and provision for healthcare clients. Our analysis of the average kidney function tests and results reflect HIV guidelines on regular laboratory screening and testing and these routine health data can be used to evaluate HIV care guidelines, monitor disease occurrences in PLHIV and in individuals who are not receiving HIV care, and determine future healthcare requirements of healthcare clients.

5.9 Acknowledgement

We acknowledge the Provincial Health Data Centre, Health Impact Assessment Directorate of the Western Cape Government Health Department for the provision of the anonymized Khayelitsha dataset.

5.10 Conflict of interest

None

5.11 Data availability statement

These anonymised, perturbed data were provided for analysis by the Western Cape Department of Health, Provincial Health Data Centre. These are highly granular health data linked to individual health care clients in the province and no informed consent has been given for research use. For this reason, the Western Cape Department of Health does not permit open sharing but instead grants only primary use permission for the data. Re-use of this dataset requires approval from the Western Cape Department of Health (Provincial Health Data Centre), and Dr Moodley, Director: HIA, Western Cape Department of Health, South Africa can be contacted to advise on this process (email: melvin.moodley@westerncape.gov.za, Reference study ID 259-TIFFIN).

5.12 Funding

This research was funded in part, by the Wellcome Trust 203135/Z/16/Z. For the purpose of open access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript version arising from this submission. The Wellcome Centre for Infectious Diseases Research in Africa is supported by core funding from the Wellcome Trust [203135/Z/16/Z]. ROY receives funding from the Africa Regional Staff/Student International Exchange: Food Security and Sustainable Human Wellbeing II (ARISE II) Consortium funded by the Intra-Africa Academic Mobility Scheme of the European Union (2016-2616). NT receives funding from the Bill & Melinda Gates Foundation.

5.13 References

Acquah, R., Graham, H., & Winter, A. (2015). Quantifying polypharmacy in a large HIV-infected cohort. *HIV Medicine*, *16*(9), 583–584. https://doi.org/10.1111/hiv.12296

Adedeji, T. A., Adedeji, N. O., Adebisi, S. A., Idowu, A. A., Fawale, M. B., & Jimoh, K. A. (2015). Prevalence and Pattern of Chronic Kidney Disease in Antiretroviral-Naïve Patients with HIV/AIDS. *Journal of the International Association of Providers of AIDS Care (JIAPAC)*, *14*(5), 434–440. https://doi.org/10.1177/2325957415587570

Alfano, G., Cappelli, G., Fontana, F., Di Lullo, L., Di Iorio, B., Bellasi, A., & Guaraldi, G. (2019). Kidney Disease in HIV Infection. *Journal of Clinical Medicine*, *8*(8). https://doi.org/10.3390/jcm8081254

Bastida, C. (2017). Polifarmacia e interacciones farmacológicas potenciales en una población envejecida con infección. *FARMACIA HOSPITALARIA*, *5*, 618–624. https://doi.org/10.7399/fh.10778

Boulle, A., Heekes, A., Tiffin, N., Smith, M., Mutemaringa, T., Zinyakatira, N., Phelanyane, F., Pienaar, C., Buddiga, K., Coetzee, E., Rooyen, R. van, Dyers, R., Fredericks, N., Loff, A., Shand, L., Moodley, M., Vega, I. de, & Vallabhjee, K. (2019). Data Centre Profile: The Provincial Health Data Centre of the Western Cape Province, South Africa. *International Journal of Population Data Science*, *4*(2), Article 2. https://doi.org/10.23889/ijpds.v4i2.1143

Cockwell, P., & Fisher, L.-A. (2020). The global burden of chronic kidney disease. *The Lancet*, *395*(10225), 662–664. https://doi.org/10.1016/S0140-6736(19)32977-0

de Boer, I. H., Rue, T. C., Hall, Y. N., Heagerty, P. J., Weiss, N. S., & Himmelfarb, J. (2011). Temporal Trends in the Prevalence of Diabetic Kidney Disease in the United States. *JAMA*, *305*(24), 2532–2539. https://doi.org/10.1001/jama.2011.861

Ekrikpo, U. E., Kengne, A. P., Bello, A. K., Effa, E. E., Noubiap, J. J., Salako, B. L., Rayner, B. L., Remuzzi, G., & Okpechi, I. G. (2018). Chronic kidney disease in the global adult HIV-infected population: A systematic review and meta-analysis. *PLOS ONE*, *13*(4), e0195443. https://doi.org/10.1371/journal.pone.0195443

Fabian, J., George, J. A., Etheredge, H. R., van Deventer, M., Kalyesubula, R., Wade, A. N., Tomlinson, L. A., Tollman, S., Naicker, S., & on behalf of the African Research in Kidney Disease (ARK) Working Group. (2019). Methods and reporting of kidney function: A systematic review of studies from sub-Saharan Africa. *Clinical Kidney Journal*, *12*(6), 778–787. https://doi.org/10.1093/ckj/sfz089

Foster, M. C., Coresh, J., Fornage, M., Astor, B. C., Grams, M., Franceschini, N., Boerwinkle, E., Parekh, R. S., & Kao, W. H. L. (2013). APOL1 Variants Associate with Increased Risk of CKD among African Americans. *Journal of the American Society of Nephrology : JASN*, *24*(9), 1484–1491. https://doi.org/10.1681/ASN.2013010113

Fraser, S. D., Barker, J., Roderick, P. J., Yuen, H. M., Shardlow, A., Morris, J. E., McIntyre, N. J., Fluck, R. J., McIntyre, C. W., & Taal, M. W. (2020). Health-related quality of life, functional impairment and comorbidity in people with mild-to-moderate chronic kidney disease: A cross-sectional study. *BMJ Open*, *10*(8), e040286. https://doi.org/10.1136/bmjopen-2020-040286

Friedman, D. J., & Pollak, M. R. (2021). APOL1 Nephropathy: From Genetics to Clinical Applications. *Clinical Journal of the American Society of Nephrology*, *16*(2), 294. https://doi.org/10.2215/CJN.15161219

Gama, R. M., Kalyesubula, R., Fabian, J., & Mahalingasivam, V. (2021). NICE takes ethnicity out of estimating kidney function. *BMJ*, *374*, n2159. https://doi.org/10.1136/bmj.n2159

Gansevoort, R. T., Correa-Rotter, R., Hemmelgarn, B. R., Jafar, T. H., Heerspink, H. J. L., Mann, J. F., Matsushita, K., & Wen, C. P. (2013). Chronic kidney disease and cardiovascular risk: Epidemiology, mechanisms, and prevention. *The Lancet*, *382*(9889), 339–352. https://doi.org/10.1016/S0140-6736(13)60595-4

Gasparini, A., Abrams, K. R., Barrett, J. K., Major, R. W., Sweeting, M. J., Brunskill, N. J., & Crowther, M. J. (2020). Mixed-effects models for health care longitudinal data with an informative visiting process: A Monte Carlo simulation study. *Statistica Neerlandica*, *74*(1), 5–23. https://doi.org/10.1111/stan.12188

GBD Chronic Kidney Disease Collaboration, Bikbov, B., Purcell, C. A., Levey, A. S., Smith, M., Abdoli, A., Abebe, M., Adebayo, O. M., Afarideh, M., Agarwal, S. K., Agudelo-Botero, M., Ahmadian, E., Al-Aly, Z., Alipour, V., Almasi-Hashiani, A., Al-Raddadi, R. M., Alvis-Guzman, N., Amini, S., Andrei, T., … Vos, T. (2020). Global, regional, and national burden of chronic kidney disease, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*, *395*(10225), 709–733. https://doi.org/10.1016/S0140-6736(20)30045-3

George, C., Mogueo, A., Okpechi, I., Echouffo-Tcheugui, J. B., & Kengne, A. P. (2017). Chronic kidney disease in low-income to middle-income countries: The case for increased screening. *BMJ Global Health*, *2*(2), e000256. https://doi.org/10.1136/bmjgh-2016-000256

Ghaderian, S. B., & Beladi-Mousavi, S. S. (2014). The role of diabetes mellitus and hypertension in chronic kidney disease. *Journal of Renal Injury Prevention*, *3*(4), 109–110. https://doi.org/10.12861/jrip.2014.31

Grams, M. E., Chow, E. K. H., Segev, D. L., & Coresh, J. (2013). Lifetime Incidence of CKD Stages 3-5 in the United States. *American Journal of Kidney Diseases*, *62*(2), 245–252. https://doi.org/10.1053/j.ajkd.2013.03.009

Gupta, S. K., Eustace, J. A., Winston, J. A., Boydstun, I. I., Ahuja, T. S., Rodriguez, R. A., Tashima, K. T., Roland, M., Franceschini, N., Palella, F. J., Lennox, J. L., Klotman, P. E., Nachman, S. A., Hall, S. D., & Szczech, L. A. (2005). Guidelines for the Management of Chronic Kidney

Disease in HIV-Infected Patients: Recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clinical Infectious Diseases*, *40*(11), 1559–1585. https://doi.org/10.1086/430257

Hernandez, G. T., & Nasri, H. (2013). World Kidney Day 2014: Increasing awareness of chronic kidney disease and aging. *Journal of Renal Injury Prevention*, *3*(1), Article 1. https://doi.org/10.12861/jrip.2014.02

Heron, J. E., Bagnis, C. I., & Gracey, D. M. (2020). Contemporary issues and new challenges in chronic kidney disease amongst people living with HIV. *AIDS Research and Therapy*, *17*(1), 11. https://doi.org/10.1186/s12981-020-00266-3

Hill, N. R., Fatoba, S. T., Oke, J. L., Hirst, J. A., O'Callaghan, C. A., Lasserson, D. S., & Hobbs, F. D. R. (2016). Global Prevalence of Chronic Kidney Disease – A Systematic Review and Meta-Analysis. *PLOS ONE*, *11*(7), e0158765. https://doi.org/10.1371/journal.pone.0158765

Hosten, A. O. (1990). BUN and Creatinine. In H. K. Walker, W. D. Hall, & J. W. Hurst (Eds.), *Clinical Methods: The History, Physical, and Laboratory Examinations* (3rd ed.). Butterworths. http://www.ncbi.nlm.nih.gov/books/NBK305/

Janmaat, C. J., van Diepen, M., Tsonaka, R., Jager, K. J., Zoccali, C., & Dekker, F. W. (2019). Pitfalls of linear regression for estimating slopes over time and how to avoid them by using linear mixed-effects models. *Nephrology Dialysis Transplantation*, *34*(4), 561–566. https://doi.org/10.1093/ndt/gfy128

Inker, L. A., Eneanya, N. D., Coresh, J., Tighiouart, H., Wang, D., Sang, Y., Crews, D. C., Doria, A., Estrella, M. M., Froissart, M., Grams, M. E., Greene, T., Grubb, A., Gudnason, V., Gutiérrez, O. M., Kalil, R., Karger, A. B., Mauer, M., Navis, G., … Levey, A. S. (2021). New Creatinine- and Cystatin C–Based Equations to Estimate GFR without Race. *New England Journal of Medicine*, *385*(19), 1737–1749. https://doi.org/10.1056/NEJMoa2102953

Jotwani, V., Atta, M. G., & Estrella, M. M. (2017). Kidney Disease in HIV: Moving beyond HIV-Associated Nephropathy. *Journal of the American Society of Nephrology*, *28*(11), 3142–3154. https://doi.org/10.1681/ASN.2017040468

Kabore, N. F., Cournil, A., Poda, A., Ciaffi, L., Binns-Roemer, E., David, V., Eymard-Duvernay, S., Zoungrana, J., Semde, A., Sawadogo, A. B., Koulla-Shiro, S., Kouanfack, C., Ngom-Gueye, N. F., Meda, N., Winkler, C., & Limou, S. (2022). APOL1 Renal Risk Variants and Kidney Function in HIV-1–Infected People From Sub-Saharan Africa. *Kidney International Reports*, *7*(3), 483–493. https://doi.org/10.1016/j.ekir.2021.10.009

Kalantar-Zadeh, K., Jafar, T. H., Nitsch, D., Neuen, B. L., & Perkovic, V. (2021). Chronic kidney disease. *The Lancet*, *398*(10302), 786–802. https://doi.org/10.1016/S0140-6736(21)00519-5

Kasembeli, A. N., Duarte, R., Ramsay, M., Mosiane, P., Dickens, C., Dix-Peek, T., Limou, S., Sezgin, E., Nelson, G. W., Fogo, A. B., Goetsch, S., Kopp, J. B., Winkler, C. A., & Naicker, S. (2015). APOL1 Risk Variants Are Strongly Associated with HIV-Associated Nephropathy

in Black South Africans. *Journal of the American Society of Nephrology : JASN*, *26*(11), 2882–2890. https://doi.org/10.1681/ASN.2014050469

Kavishe, B. B., Kweka, B. V., Nitsch, D., PrayGod, G., Jeremiah, K., Faurholt-Jepsen, D., Filteau, S., Olsen, M. F., Kitilya, B. W., Krogh-Madsen, R., Friis, H., & Peck, R. (2021). Risk factors for impaired renal function in HIV-infected and HIV-uninfected adults: Cross-sectional study in North-Western Tanzania. *BMC Nephrology*, *22*, 355. https://doi.org/10.1186/s12882-021-02563-z

Levey, A. S., Bosch, J. P., Lewis, J. B., Greene, T., Rogers, N., & Roth, D. (1999). A More Accurate Method To Estimate Glomerular Filtration Rate from Serum Creatinine: A New Prediction Equation. *Annals of Internal Medicine*, *130*(6), 461–470. https://doi.org/10.7326/0003-4819-130-6-199903160-00002

Levey, A. S., Stevens, L. A., Schmid, C. H., Zhang, Y. (Lucy), Castro, A. F., Feldman, H. I., Kusek, J. W., Eggers, P., Van Lente, F., Greene, T., & Coresh, J. (2009). A New Equation to Estimate Glomerular Filtration Rate. *Annals of Internal Medicine*, *150*(9), 604–612.

Lv, J.-C., & Zhang, L.-X. (2019). Prevalence and Disease Burden of Chronic Kidney Disease. In B.-C. Liu, H.-Y. Lan, & L.-L. Lv (Eds.), *Renal Fibrosis: Mechanisms and Therapies* (pp. 3–15). Springer. https://doi.org/10.1007/978-981-13-8871-2_1

Madala, N. D., Thusi, G. P., Assounga, A. G. H., & Naicker, S. (2014). Characteristics of South African patients presenting with kidney disease in rural KwaZulu-Natal: A cross sectional study. *BMC Nephrology*, *15*, 61. https://doi.org/10.1186/1471-2369-15-61

Mocroft, A., Lundgren, J. D., Ross, M., Fux, C. A., Reiss, P., Moranne, O., Morlat, P., Monforte, A. d'Arminio, Kirk, O., & Ryom, L. (2016). Cumulative and current exposure to potentially nephrotoxic antiretrovirals and development of chronic kidney disease in HIV-positive individuals with a normal baseline estimated glomerular filtration rate: A prospective international cohort study. *The Lancet HIV*, *3*(1), e23–e32. https://doi.org/10.1016/S2352-3018(15)00211-8

Osei-Yeboah, R., Tamuhla, T., Ngwenya, O., & Tiffin, N. (2021). Accessing HIV care may lead to earlier ascertainment of comorbidities in health care clients in Khayelitsha, Cape Town. *PLOS Global Public Health*, *1*(12), e0000031. https://doi.org/10.1371/journal.pgph.0000031

Peer, N., George, J., Lombard, C., Steyn, K., Levitt, N., & Kengne, A.-P. (2020). Prevalence, concordance and associations of chronic kidney disease by five estimators in South Africa. *BMC Nephrology*, *21*(1), 372. https://doi.org/10.1186/s12882-020-02018-x

Romanowski, K., Clark, E. G., Levin, A., Cook, V. J., & Johnston, J. C. (2016). Tuberculosis and chronic kidney disease: An emerging global syndemic. *Kidney International*, *90*(1), 34–40. https://doi.org/10.1016/j.kint.2016.01.034

Rosenberg, A. Z., Naicker, S., Winkler, C. A., & Kopp, J. B. (2015). HIV-associated nephropathies: Epidemiology, pathology, mechanisms and treatment. *Nature Reviews Nephrology*, *11*(3), Article 3. https://doi.org/10.1038/nrneph.2015.9

Russo, G. T., De Cosmo, S., Viazzi, F., Mirijello, A., Ceriello, A., Guida, P., Giorda, C., Cucinotta, D., Pontremoli, R., Fioretto, P., & the AMD-Annals Study Group. (2018). Diabetic kidney disease in the elderly: Prevalence and clinical correlates. *BMC Geriatrics*, *18*(1), 38. https://doi.org/10.1186/s12877-018-0732-4

Ruzangi, J., Iwagami, M., Smeeth, L., Mangtani, P., & Nitsch, D. (2020). The association between chronic kidney disease and tuberculosis; a comparative cohort study in England. *BMC Nephrology*, *21*(1), 420. https://doi.org/10.1186/s12882-020-02065-4

Shahbaz, H., & Gupta, M. (2022). Creatinine Clearance. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK544228/

Shen, T.-C., Huang, K.-Y., Chao, C.-H., Wang, Y.-C., Muo, C.-H., Wei, C.-C., Tu, C.-Y., Hsia, T.-C., Shih, C.-M., Hsu, W.-H., Sung, F.-C., & Kao, C.-H. (2015). The risk of chronic kidney disease in tuberculosis: A population-based cohort study. *QJM: An International Journal of Medicine*, *108*(5), 397–403. https://doi.org/10.1093/qjmed/hcu220

Stanifer, J. W., Jing, B., Tolan, S., Helmke, N., Mukerjee, R., Naicker, S., & Patel, U. (2014). The epidemiology of chronic kidney disease in sub-Saharan Africa: A systematic review and meta-analysis—ClinicalKey. *Lancet Global Health*, *2*(3), e174–e181.

Struik, G. M., den Exter, R. A., Munthali, C., Chipeta, D., van Oosterhout, J. J. G., Nouwen, J. L., & Allain, T. J. (2011). The prevalence of renal impairment among adults with early HIV disease in Blantyre, Malawi. *International Journal of STD & AIDS*, *22*(8), 457–462. https://doi.org/10.1258/ijsa.2011.010521

Swanepoel, C. R., Atta, M. G., D'Agati, V. D., Estrella, M. M., Fogo, A. B., Naicker, S., Post, F. A., Wearne, N., Winkler, C. A., Cheung, M., Wheeler, D. C., Winkelmayer, W. C., Wyatt, C. M., Abu-Alfa, A., Adu, D., Agodoa, L. Y., Alpers, C. E., Arogundade, F. A., Ashuntantang, G., … Zeier, M. (2018). Kidney disease in the setting of HIV infection: Conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney International*, *93*(3), 545–559. https://doi.org/10.1016/j.kint.2017.11.007

Tartof, S. Y., Hsu, J.-W., Wei, R., Rubenstein, K. B., Hu, H., Arduino, J. M., Horberg, M., Derose, S. F., Qian, L., & Rodriguez, C. V. (2018). Kidney Function Decline in Patients with CKD and Untreated Hepatitis C Infection. *Clinical Journal of the American Society of Nephrology*, *13*(10), 1471–1478. https://doi.org/10.2215/CJN.01530218

Thistle, Q. (2014). *Hypercreatinemia* (pp. 1–3). http://www.thistle.co.za/pdf_files/education/chemistry/chemistry_legends/2014/February%202014%20-%20Hypercreatinemia.pdf

Vaes, B., Beke, E., Truyers, C., Elli, S., Buntinx, F., Verbakel, J. Y., Goderis, G., & Pottelbergh, G. V. (2015). The correlation between blood pressure and kidney function decline in older

people: A registry-based cohort study. *BMJ Open*, *5*(6), e007571. https://doi.org/10.1136/bmjopen-2015-007571

Verma, A., Vyas, S., Agarwal, A., Abbas, S., Agarwal, D. P., & Kumar, R. (2016). Diabetic Kidney Disease and Hypertension: A True Love Story. *Journal of Clinical and Diagnostic Research : JCDR*, *10*(3), OC11–OC13. https://doi.org/10.7860/JCDR/2016/18806.7511

Wang, Z., do Carmo, J. M., Aberdein, N., Zhou, X., Williams, J. M., da Silva, A. A., & Hall, J. E. (2017). Synergistic Interaction of Hypertension and Diabetes in Promoting Kidney Injury and the Role of Endoplasmic Reticulum Stress. *Hypertension*, *69*(5), 879–891. https://doi.org/10.1161/HYPERTENSIONAHA.116.08560

Yu, Z., Rebholz, C. M., Wong, E., Chen, Y., Matsushita, K., Coresh, J., & Grams, M. E. (2019). Association Between Hypertension and Kidney Function Decline: The Atherosclerosis Risk in Communities (ARIC) Study. *American Journal of Kidney Diseases*, *74*(3), 310–319. https://doi.org/10.1053/j.ajkd.2019.02.015

CHAPTER 6: ANALYSIS OF ROUTINE HEALTH DATA SHOWS EXISTING COMORBIDITIES MAY CONTRIBUTE TO INCIDENCE OF OTHER COMORBIDITIES AND UNSUPPRESSED VIRAL LOAD IN PEOPLE LIVING WITH HIV IN KHAYELITSHA, CAPE TOWN

6.1 Publication status

Osei-Yeboah, R., & Tiffin, N. Analysis of routine health data shows existing comorbidities may contribute to incidence of other comorbidities and unsuppressed viral load in people living with HIV in Khayelitsha, Cape Town (Ready for submission).

6.2 Author contribution

NT and ROY designed the study. ROY conducted the analysis and wrote the draft manuscript. NT and ROY finalised the manuscript.

6.3 Abstract

Background

Human immunodeficiency virus (HIV) infection, long term antiretroviral therapy (ART), and other factors such as ageing may be associated with the occurrence of chronic comorbidities among people living with HIV (PLHIV). As the HIV population in South Africa begins to age due to the success of ART, it is important to understand the relationship between the occurrence of comorbidities in this population and factors such as ART initiation, CD4 cell count and viral load levels, and the contribution of pre-existing chronic comorbidities to unsuppressed HIV viral load.

Methods

Anonymised routine administrative health data were analysed for all PLHIV (aged 18 years and over) who accessed public health care in 2016 -2017 in Khayelitsha subdistrict (Cape Town, South Africa). Counts, proportions, and median (interquartile range, IQR) of selected study characteristics were described for females and males with HIV. Multivariate logistic regression analyses were conducted to assess the relationship between comorbidity occurrence and selected risk factors. A linear mixed effect model was used to assess the relationship between

unsuppressed viral load levels as an outcome, and number of comorbidities and selected HIV metrics as risk factors.

Results

A total of 82 986 PLHIV were included in the study population, of which 59 063 (71.1%) were females. The median age (IQR) of the study population was 37 years (IQR: 31-44 years). The overall median age (IQR) at HIV ascertainment for the study population was 30 years (IQR: 25-37 years). Of the PLHIV, 71 309 (85.9%) were initiated on ART. The proportions of PLHIV on ART decreased with increasing duration on ART; ≤ 3 years (43.6%), 4-6 years (26.5%), 7-9 years (17.6%), and over 10 years (12.1%). Of all the PLHIV initiated on ART, 61 818 (86.7%) ever achieved viral suppression, and of these, 23 846 (38.6%), 17 546 (28.4%), 11 982 (19.4%) and 8 444 (13.7%) had been on ART for ≤ 3 years, 4-6 years, 7-9 years and over 10 years respectively. The multivariate logistic regression analyses showed that increase in age of PLHIV, low baseline CD4 cell count, unsuppressed viral load levels, ever having CD4 cell count below 50 cells/µL and presence of other comorbidities is associated with subsequent TB and CKD ascertainment. Our analysis showed that ascertainment of hypertension and diabetes is mainly associated with increase in age of PLHIV, having other pre-existing comorbidities, and having achieved viral suppression. The linear mixed effect model showed that lower baseline CD4 cell count, increase in age at ART initiation and having one or two pre-existing comorbidities is associated with unsuppressed viral load levels.

Conclusion

In this study, we have analysed administratively collected routine health data for healthcare clients living with HIV who accessed care in public facilities in Khayelitsha, Cape Town. We conclude that the occurrence of comorbidities and unsuppressed viral load levels in an ageing population of PLHIV in our study may be largely driven by the burden of pre-existing comorbidities in addition to ageing and other HIV characteristics. From real life routine data of PLHIV accessing care in public facilities we have demonstrated the occurrence of common comorbidities in PLHIV by conducting multivariate analyses which incorporate other disease conditions as predictors. This is useful in understanding how not only HIV metrics contribute to

the occurrence of comorbidities, but also the contribution of pre-existing diseases to the occurrence of comorbidities in PLHIV. In planning care and services for an ageing population of PLHIV like we have in South Africa, potential impacts of comorbidities on HIV outcomes and the wellbeing of PLHIV should be given careful consideration.

Keywords

HIV, viral load, CD4, comorbidities, routine data, South Africa

6.4 Introduction

South Africa has been at the centre of the human immunodeficiency virus (HIV) pandemic for over two decades and remains the worst affected country globally (Hodes & Morrell, 2018). The number of people living with HIV (PLHIV) in South Africa has increased from an estimated 3.68 million in 2002 to 8.45 million in 2022 with an overall adult prevalence of 13.9% (Statistics South Africa, 2022). Almost a quarter of the women in their reproductive ages (15-49 years) in South Africa are living with HIV (Statistics South Africa, 2022). In spite of the growing proportion of PLHIV over the decades, acquired immunodeficiency syndrome (AIDS)-related deaths have declined from 31.6% in 2002, 26% in 2012 to 12.9% in 2022 (Statistics South Africa, 2022).

HIV treatment guidelines have evolved over the years and the implementation of the current universal test and treat (UTT) policy (National Department of Health, 2016) has ensured a wider coverage of antiretroviral therapy (ART) for PLHIV. A national HIV survey conducted in 2017 showed that South Africa was on track towards the first 90 target of 90% of PLHIV knowing their status but was 20 percentage points below achieving the second 90 indicator of ART coverage for all PLHIV who know their status. This was attributed to deficiencies around linkage and retention on ART (Marinda et al., 2020). Although the overall viral suppression among people on ART in South Africa was at 87.4%, interpretation of these data was to be made in the context of the uneven ART coverage across the country (Marinda et al., 2020). Reports on the progress towards the 90-90-90 targets from household-based community surveys in HIV hyperendemic areas in South Africa varied. While achievement of the third 90 target - 90% of PLHIV on ART achieving viral suppression was reported for both men and women in rural KwaZulu-Natal (Huerga et al., 2018), another study in the same region reported that none of

the targets were achieved as a whole, except the third 90 target for only women (Grobler et al., 2017).

The main goal of ART is to prevent the viral replication of HIV, decrease viral load levels, and elevate the CD4 cells which are targeted and destroyed by HIV (Ward et al., 2021). Viral load levels help monitor HIV viral replication in PLHIV, and for PLHIV receiving ART, high viral load levels may show how ART medications may be failing to suppress the virus (Ochodo et al., 2022). CD4 cell count provides good indicators of immune system functioning (Bishop et al., 2016). Viral load levels and CD4 cells are both useful for monitoring disease progression and prognosis and are significant indicators of treatment outcomes in PLHIV. Studies suggest that individuals starting ART with high viral loads or whilst severely immunocompromised may take longer to recover CD4 cells (Kranzer et al., 2013; Kufa et al., 2019), and this may be compounded by age and existing comorbidities.

HIV infection, long term ART, and other factors such as ageing may be associated with the development of comorbidities among PLHIV (Althoff et al., 2016). CD4 cell count and viral load levels are influenced by AIDS-defining events which result from the outcomes of immunologic and virologic changes which happen throughout HIV disease progression (Smurzynski et al., 2010). Low CD4 cell counts and detectable viral load levels, however, are also considered risk factors for severe non-AIDS infection among PLHIV (Collin et al., 2016).

As the HIV population in South Africa begins to age due to the success of ART, it is important to understand the relationship between the occurrence of comorbidities in this population and factors such as ART initiation, CD4 cell counts and viral load levels. This study explores this relationship in a population of PLHIV in the Western Cape Province, using routine data from the Provincial Health Data Centre (PHDC), a health information exchange facility that collates administrative health data from public health care clients in the Western Cape Province in South Africa.

6.5 Methods

6.5.1 Ethics

Ethics approval was obtained from the Human Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town (HREC ref: 482/2019). A data access request was approved by the Health Impact Assessment Directorate at the Western Cape Department of Health, South Africa. A waiver for informed consent was granted because the data provided were anonymized and perturbed, and individuals could not be identified or re-identified from the data.

6.5.2 Data source

The PHDC is a health information exchange facility that collates administrative health data for the Western Cape Province. Unique identifiers are used to link individuals to administrative health records, and facility visit, laboratory, and pharmacy data are updated daily for about 6.6 million people currently accessing care in public facilities in the Western Cape Province. Algorithms are used to infer disease episodes from combinations of pharmacy-dispensed drugs, laboratory test results, international classification of diseases-10th edition (ICD-10) diagnosis codes, and facility encounter data (Boulle et al., 2019). In this study we refer to "disease ascertainment", to mean inference of the start of a disease episode as identified by an algorithm, to distinguish this process of disease ascertainment from a clinical diagnosis made by a health care professional during consultation. A dataset containing routine health data was obtained from the PHDC, Western Cape Government Health Department, with longitudinal data ranging from 2007 to 2017. The median length of time for which individuals have available data is 8 years (Interquartile range [IQR]: 3.6-10 years). The study dataset was anonymised and perturbed within the PHDC prior to being released for use in this analysis, to prevent identification or re-identification of individuals.

6.5.3 Study population

The analysis includes all PLHIV (aged 18 years and above) who accessed public health facilities in the Khayelitsha subdistrict between 1 January 2016 and 31 December 2017, described as the 'recruitment period'. The records of the healthcare clients who received HIV services were

matched to the comorbidities records to determine which conditions they presented before and after HIV ascertainment. Khayelitsha is a high-density, mixed informal and formal housing suburb in Cape Town, South Africa.

6.5.4 PHDC disease episode definition

The PHDC infers diseases from routine health data using either single, or a combination of parameters categorized into high, moderate, and weak confidence and supporting-only evidence for having a particular disease episode. The comorbidities considered in this study are tuberculosis (TB), hypertension, diabetes, chronic kidney disease (CKD) and cervical cancer. These comorbidities were selected because they are considered HIV-related comorbidities and may be prevalent among PLHIV and based on disease episodes that are validated by the PHDC and available at this time. High confidence definition of HIV requires evidence of dispensed valid first line (2NRTI and NNRTI) and valid triple therapy regimen (fixed-dose combination) of antiretrovirals, and/or positive laboratory test results (viral load test, polymerase chain reaction (PCR) test, enzyme linked immunosorbent assay (ELISA) test, and ART resistance test). For TB, evidence for the episode may include admission to specialized TB hospital, TB drug regimen dispensed, and/or laboratory test results (Positive GeneXpert, line probe assay (LPA), Acid-Fast Bacillus positive culture, positive microscopy (Ziehl-Neelsen staining), and microbiology culture-*Toxocara canis* (ELISA) as the main definition parameters. High confidence definition of hypertension includes dispensed hydrochlorothiazide. For CKD, laboratory test showing consecutive glomerular filtration rate of less than 60mL/min/1.73m^2 with 90 days between tests, dispensed kidney, or transplant medications (antithymocyte, immunoglobulin, and basiliximab), and diagnosis coding indicating kidney transplant procedure in a theatre constitute high confidence definition. High confidence definitions of diabetes episodes are based on dispensed drug for the treatment of diabetes mellitus, laboratory test showing HbA1c greater than 6.5%, oral glucose tolerance test result greater than 11.1mmol/l, and diagnosis coding showing an ICD-10 code indicating diabetes disease.

6.5.5 Analysis

Descriptive statistics were generated to summarise the counts and proportions of baseline characteristics for females and males with HIV. Wilcoxon rank sum tests were used to

determine the significance of differences in continuous variables and Pearson's Chi Squared tests were used to determine the significance of differences in categorical variables. We conducted multivariate logistic regression analyses to assess the relationship between comorbidity occurrence and selected risk factors. We included comorbidities ascertained after HIV ascertainment and other metrics measured as part of HIV treatment and/or services to assess this relationship. The 'Enter' method of multivariate logistic regression where all input variables are entered simultaneously was used. We conducted linear mixed effect modelling by including all viral load test results per individual as random effect in the model to explore the relationship between unsuppressed viral load levels and age at HIV ascertainment, age at ART initiation, sex, baseline CD4 cell count and the number of comorbidities at the time of the last viral load testing as fixed effects. This method considers the heterogeneity which may exist in the number of viral load tests available for each participant which must be considered when estimating this relationship.

All analyses were done in R Software (version 4.1.2) and RStudio (2021.09.0+351 "Ghost Orchid"). The linear mixed effect model was run using the 'lme4' package in RStudio and the associated p-values were generated with the 'lmerTest' package. Graphical representations of logistic regression and linear mixed effect models were generated using the 'sjPlot' package in RStudio.

6.5.6 Patient and public involvement

The participants in this study were healthcare clients ascertained with HIV who visited public health facilities and generated at least one electronic health record. Retrospective data for this population spanned about 8 years. Inclusion in the study was restricted to healthcare clients who accessed care between 2016 and 2017 but included their complete retrospective data. The study questions were designed to explore the incidence of common comorbidities and the contribution of these comorbidities to unsuppressed viral load among these healthcare clients who seek care from public facilities. A waiver for participants' consent was granted because the data were obtained directly from digital routine health data in the PHDC and were anonymized and perturbed to prevent possible re-identification of participants.

6.6 Results

6.6.1 Description of the baseline characteristics of the study population

A total of 82 986 PLHIV were included in the study population, of which 59 063 (71.1%) were females, 23 923 (28.8%) were males. The median age (IQR) of the study population was 37 years (IQR: 31-44 years), females were generally younger with a median age of 35 years (IQR: 30-43 years) than males with a median age of 41 years (IQR: 34-48 years). The overall median age at HIV ascertainment for the study population was 30 years (IQR: 25-37 years), 29 years (IQR: 24-35 years) for females and 35 years (IQR: 29-41 years) for males. The differences between female-male median age at study start and HIV ascertainment were statistically significant (all p <0.001). Of female sub-population, 51 297 (86.9%) were initiated on ART whilst 20 012 (83.6%) of the male sub-population were initiated on ART, and the median age at ART initiation was lower in females [Median age (IQR): 31 years (26-37 years)] compared to males [Median age (IQR): 36 years (31-42 years)], p<0.001. The proportions of PLHIV on ART decreased with increasing duration on ART; ≤ 3 years (43.6%), 4-6 years (26.5%), 7-9 years (17.6%), and over 10 years (12.1%) and this reflected in both female and male sub-populations. Of PLHIV who initiated ART, 16 239 (22.8%) had current TB and higher proportions of males (36.0%) than females (17.6%) who initiated ART had current TB. Of all PLHIV initiated on ART, 61 818 (86.7%) ever achieved viral suppression, and of this, 23 846 (38.6%), 17 546 (28.4%), 11 982 (19.4%) and 8 444 (13.7%) had been on ART for ≤ 3 years, 4-6 years, 7-9 years and over 10 years respectively. Of PLHIV, 16 263 (19.6%) had HIV ascertained in the last 18 months and 78 406 (94.5%) had received a baseline CD4 cell count. The median baseline CD4 cell count significantly differed between females (359, IQR: 223-525) and males (246, IQR: 144-418), p <0.001. About 80.0% (66 347) of PLHIV in our study population had received viral load measurements in the last 18 months and the median time since the last viral load measurement was 8 months (IQR: 3.4-14.3), with slight differences between female [Median (IQR): 7.8 months (3.2-13.7 months)] and male [Median (IQR): 8.2 months (3.8-16.3 months)] sub-populations. Of the PLHIV, 57.7% did not have additional comorbidity, 35.4% had one comorbidity, 5.8% had two comorbidities, and 1.1% had three or more comorbidities, where the comorbidities analysed in this study were TB, hypertension, diabetes, CKD and cervical

cancer. The difference in comorbidity counts between females and males was statistically significant, p <0.001 (Table 6.1).

Table 6.1: Baseline description of the study population (2016-2017)

Characteristics	**All**	**Sex**		**p-value**
		Female, n (%)	Male, n (%)	
Study population (PLHIV)	**n= 82 986**	**59 063 (71.1%)**	**23 923 (28.8%)**	-
Age (IQR) at recruitment	37 (31-44)	35 (30-43)	41 (34-48)	<0.001
Age (IQR) at HIV ascertainment	30 (25-37)	29 (24-35)	35 (29-41)	<0.001
ART Initiated (%)	71 309 (85.9%)	**51 297 (86.9%)**	**20 012 (83.7%)**	<0.001
Median age (IQR) at ART initiation	32 (27-39)	31 (26-37)	36 (31-42)	<0.001
Duration on ART (% of total & female/male initiated on ART)				
≤ 3 years	31 118 (43.6%)	22 054 (43.0%)	9 064 (45.3%)	<0.001
4-6 years	18 916 (26.5%)	13 801 (26.9%)	5 115 (25.6%)	
7-9 years	12 517 (17.6%)	9 095 (17.7%)	3 422 (17.1%)	
Over 10 years	8 648 (12.1%)	6 260 (12.2%)	2 388 (11.9%)	
Current TB at ART start (% of ART initiated)	16 239 (22.8%)	9 044 (17.6%)	7 195 (36.0%)	<0.001
Ever achieved viral suppression (% of ART initiated)	61 818 (86.7%)	44 967 (87.7%)	16 851 (84.2%)	<0.001
Median (IQR) months since last Viral Load measurement	8.0 (3.4-14.3)	7.8 (3.2-13.7)	8.2 (3.8-16.3)	<0.001
HIV ascertainment in last 18 months (% of total/female/male)	16 263 (19.6%)	10 856 (18.4%)	5 407 (22.6%)	<0.001
Viral Load measurements in last 18 months (% of total/female/male)	66 347 (79.9%)	48 180 (81.6%)	18 167 (75.9%)	<0.001
Number with baseline CD4 cell count (%)	78 406 (94.5%)	55 978 (94.8%)	22 428 (93.7%)	<0.001
Median (IQR) Baseline CD4 cell count	333 (198-499)	359 (223-525)	246 (144-418)	<0.001
Comorbidity count (% of total & female/male)				
No comorbidity	47 875 (57.7%)	36 631 (62%)	11 244 (47%)	<0.001
1 comorbidity	29 383 (35.4%)	18 720 (31.7%)	10 663 (44.6%)	
2 comorbidities	4 811 (5.8%)	3 124 (5.3%)	1 687 (7.1%)	
3 or more comorbidities	917 (1.1%)	588 (1.0%)	329 (1.4%)	

6.6.2 Counts, proportions, and age of ascertainment of selected common comorbidities in PLHIV by sex

Of 82 986 PLHIV in this study population, 25 503 (31%) ever had TB, 11 588 (14%) had hypertension, 3 415 (4.1%) had diabetes and 1 347 (1.6%) had CKD. Similar proportions of females and males had hypertension (14% vs 14%), diabetes (4.2% vs 4.0%), and CKD (1.6% vs 1.8%), and a higher proportion of males (44%) ever had TB compared to females (25%) (Table 6.2). For all the selected comorbidities, females had lower median age of ascertainment than males and the difference in the median age of ascertainment for each comorbidity was statistically significant - TB (32 vs 37 years, p<0.001), hypertension (42 vs 46 years, p<0.001), diabetes (42 vs 47 years, p<0.001) and CKD (46 vs 47 years, p = 0.047) (Table 6.2).

Table 6.2: Counts, proportions, and age at ascertainment of PLHIV who ever had selected comorbidities

Characteristic		Sex		p-value[2]
	Overall	Female	Male	
	N = 82 986[1]	N = 59 063[1]	N = 23 923[1]	
TB	25 503 (31%)	15 059 (25%)	10 444 (44%)	<0.001
Age (years) at first TB episode	34 (28-41)	32 (27-39)	37 (31-43)	<0.001
Hypertension	11 588 (14%)	8 351 (14%)	3 237 (14%)	0.226
Age (years) at Hypertension	43 (36-50)	42 (35-49)	46 (39-53)	<0.001
Diabetes	3 415 (4.1%)	2 453 (4.2%)	962 (4.0%)	0.40
Age (years) at Diabetes	44 (36-51)	42 (34-50)	47 (40-54)	<0.001
CKD	1 347 (1.6%)	928 (1.6%)	419 (1.8%)	0.063
Age (years) at CKD	46 (38-55)	46 (37-54)	47 (39-56)	0.047

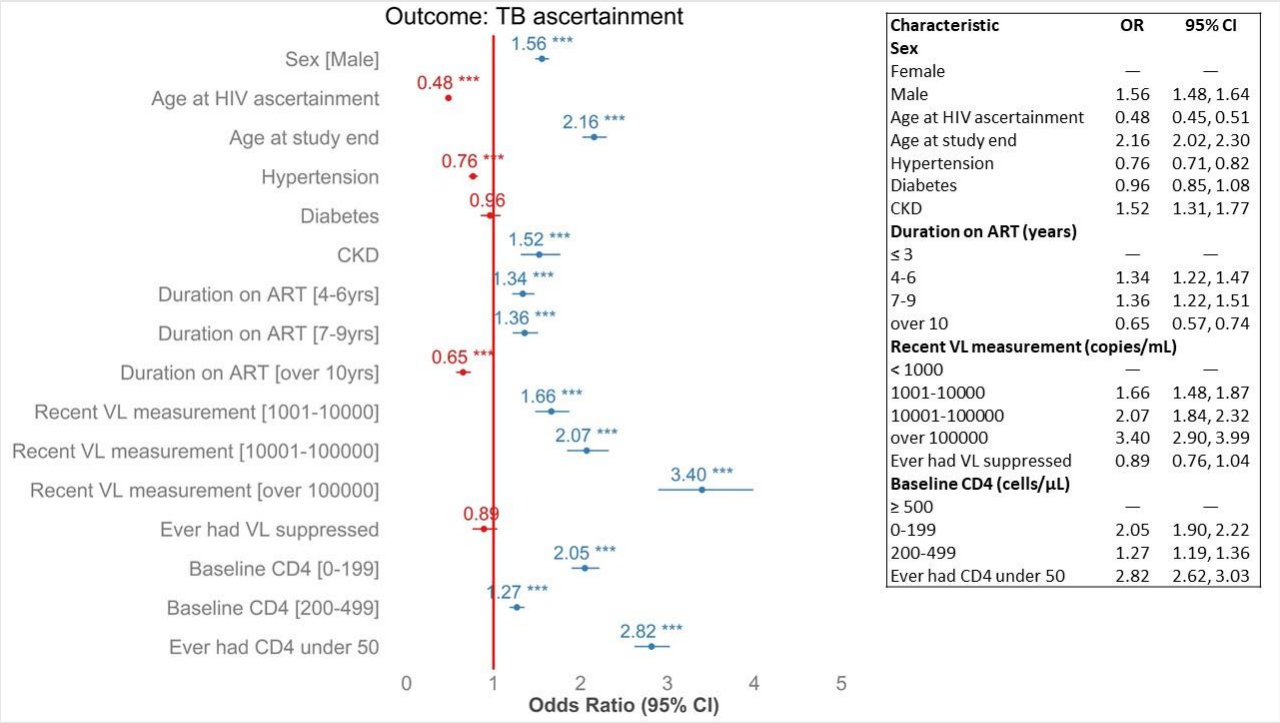
[1]n (%); Median (IQR) [2]Pearson's Chi-squared test; Wilcoxon rank sum test

6.6.3 Relationship between comorbidities occurrence and selected risk factors among PLHIV

Multivariate logistic regression analyses show the likelihood of having each condition assessed for PLHIV in the context of HIV characteristics and other pre-existing comorbidities. The results presented in Figure 6.1-6.4 show independent analyses for each assayed comorbidity modelled as the outcome, and the contribution of HIV characteristics when adjusted for the other pre-existing comorbidities.

Tuberculosis

Our analysis shows that males are 1.56 (95% Confidence Interval [CI]: 1.48, 1.64) times more likely to be ascertained with TB compared to females. A 5-year increase in the age at HIV ascertainment is associated with a 52% decrease in the risk of TB ascertainment (Odds ratio [OR]: 0.48, 95% CI: 0.45, 0.51), whilst a 5-year increase in the age at study end for PLHIV is associated with a higher risk of TB ascertainment (OR: 2.16, 95% CI: 2.02, 2.30). For PLHIV, having hypertension is associated with lower odds of TB ascertainment (OR: 0.76, 95% CI: 0.71, 0.82) and PLHIV who have CKD are 1.52 (95% CI: 1.31, 1.77) times more likely to be ascertained with TB. Our analysis shows that PLHIV who have been on ART for 4-6 years and 7-9 years are 1.34 (95% CI:1.22, 1.47) and 1.36 (95% CI: 1.22, 1.51) times more likely to be ascertained with TB respectively, whilst having been on ART for over 10 years is associated with lower odds of TB ascertainment (OR: 0.65, 95%CI: 0.57, 0.74) compared to ≤ 3 years on ART. As expected, an increase in recent viral load measurements is associated with higher odds of TB ascertainment when compared to viral load levels below 1000 copies/mL. The odds of TB ascertainment increase as the viral load levels increase; 1000-10 000 copies/mL (OR: 1.66, 95% CI: 1.48, 1.87), 10 001-100 000 copies/mL (OR: 2.07, 95 % CI: 1.84, 2.32) and above 100 000 copies/mL (OR: 3.40, 95% CI: 2.90, 3.99). PLHIV with baseline CD4 cell count of 0-199 cells/µL (OR: 2.05, 95% CI: 1.90, 2.22), and 200-499 cells/µL (OR: 1.27, 95% CI: 1.19, 1.36) have higher odds of TB ascertainment compared with those with baseline CD4 cell count of ≥ 500 cells/µL. Our analysis shows that the odds of TB ascertainment slightly reduce when PLHIV have higher baseline CD4 cell counts. PLHIV who ever have a CD4 cell count below 50 cells/µL are 2.82 (95% CI: 2.62, 3.03) times more likely to be ascertained with TB (Figure 6.1).



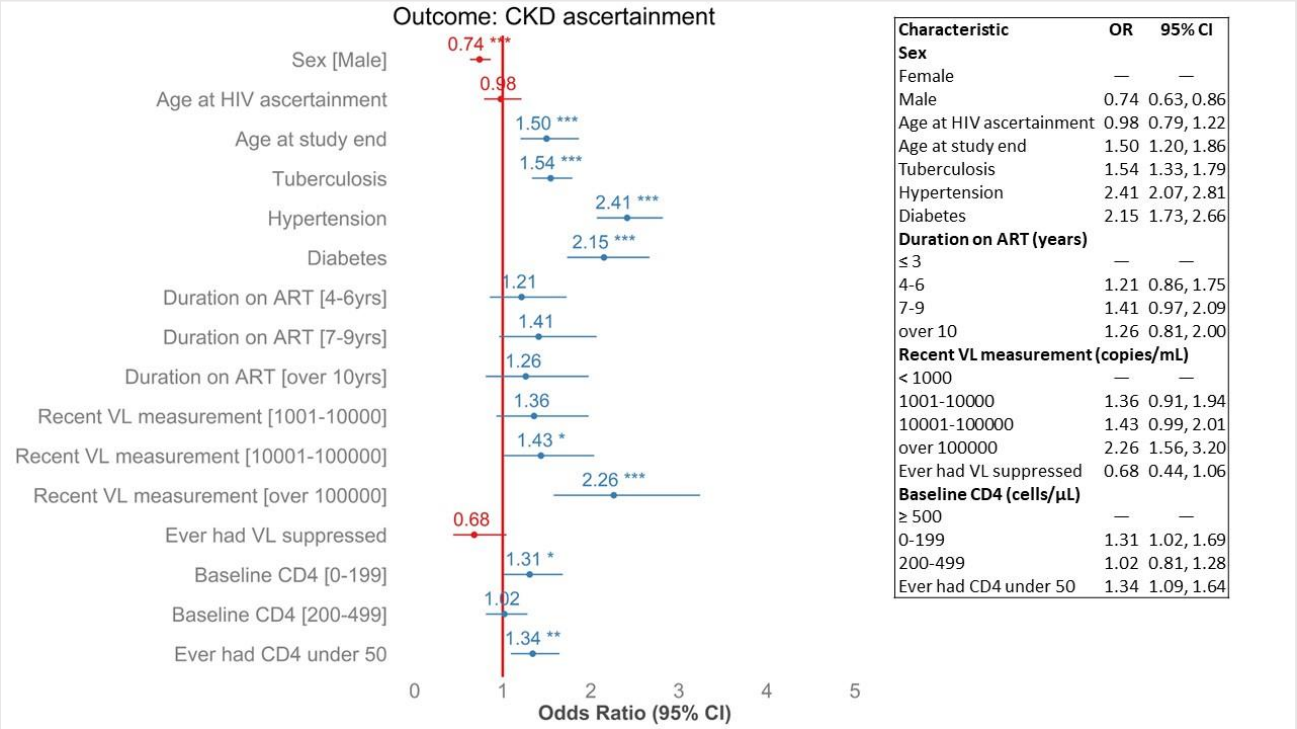
Characteristic	OR	95% CI
Sex		
Female	—	—
Male	1.56	1.48, 1.64
Age at HIV ascertainment	0.48	0.45, 0.51
Age at study end	2.16	2.02, 2.30
Hypertension	0.76	0.71, 0.82
Diabetes	0.96	0.85, 1.08
CKD	1.52	1.31, 1.77
Duration on ART (years)		
≤ 3	—	—
4-6	1.34	1.22, 1.47
7-9	1.36	1.22, 1.51
over 10	0.65	0.57, 0.74
Recent VL measurement (copies/mL)		
< 1000	—	—
1001-10000	1.66	1.48, 1.87
10001-100000	2.07	1.84, 2.32
over 100000	3.40	2.90, 3.99
Ever had VL suppressed	0.89	0.76, 1.04
Baseline CD4 (cells/µL)		
≥ 500	—	—
0-199	2.05	1.90, 2.22
200-499	1.27	1.19, 1.36
Ever had CD4 under 50	2.82	2.62, 3.03

Figure 6.1: Multivariate logistic regression showing odds ratios (ORs) and 95% confidence intervals (CI) for associations between the outcome of TB ascertainment, (n=20 463) and risk factors: sex, age at study end per 5-year increments, comorbidities ascertained after HIV diagnosis and HIV-related characteristics.

Chronic Kidney Disease

Within the study population, males are 26% (OR: 0.74, 95% CI: 0.63, 0.86) times less likely to be ascertained with CKD compared to females. A 5-year increase in the age at study end for PLHIV is associated with a 50% increase in the risk of CKD ascertainment (OR: 1.50, 95% CI: 1.20, 1.86). PLHIV who have TB - OR: 1.54 (95% CI: 1.33, 1.79), hypertension - OR: 2.41 (95% CI: 2.07, 2.81) and diabetes - OR: 2.15 (95% CI: 1.73, 2.66) are more likely to be ascertained with CKD. PLHIV with recent viral load measurements of over 100 000 copies/mL are 2.26 (95% CI: 1.56, 3.20) times more likely to be ascertained with CKD compared to those with recent viral load measurement of < 1000 copies/mL. PLHIV with baseline CD4 cell count of 0-199 cells/µL are 1.31 (95% CI: 1.02, 1.69) times more likely to be ascertained with CKD compared with those with baseline CD4 cell count of ≥ 500 cells/µL. PLHIV who ever had a CD4 cell count below 50 cells/µL are 1.34 (95% CI: 1.09, 1.64) times more likely to be ascertained with CKD. Though the

analysis shows that longer durations on ART may be associated with CKD ascertainment, these associations are not statistically significant (Figure 6.2).



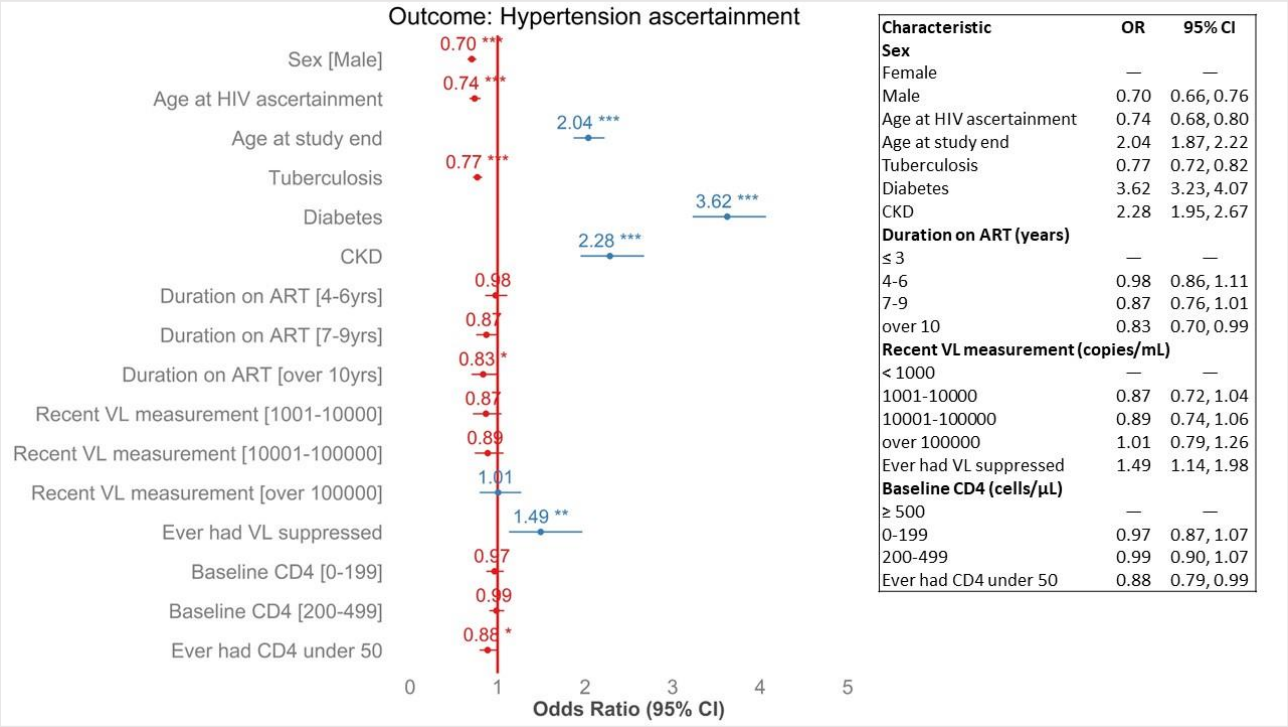
Characteristic	OR	95% CI
Sex		
Female	—	—
Male	0.74	0.63, 0.86
Age at HIV ascertainment	0.98	0.79, 1.22
Age at study end	1.50	1.20, 1.86
Tuberculosis	1.54	1.33, 1.79
Hypertension	2.41	2.07, 2.81
Diabetes	2.15	1.73, 2.66
Duration on ART (years)		
≤ 3	—	—
4-6	1.21	0.86, 1.75
7-9	1.41	0.97, 2.09
over 10	1.26	0.81, 2.00
Recent VL measurement (copies/mL)		
< 1000	—	—
1001-10000	1.36	0.91, 1.94
10001-100000	1.43	0.99, 2.01
over 100000	2.26	1.56, 3.20
Ever had VL suppressed	0.68	0.44, 1.06
Baseline CD4 (cells/µL)		
≥ 500	—	—
0-199	1.31	1.02, 1.69
200-499	1.02	0.81, 1.28
Ever had CD4 under 50	1.34	1.09, 1.64

Figure 6.2: Multivariate logistic regression showing odds ratios (ORs) and 95% confidence intervals (CI) for associations between the outcome of CKD ascertainment, (n= 1 196) and risk factors: sex, age at study end per 5-year increments, comorbidities ascertained after HIV diagnosis and HIV-related characteristics.

Hypertension

Our results show that males in our study population are 30% (OR: 0.70, 95% CI: 0.66, 0.76) times less likely to be ascertained with hypertension compared to females. A 5-year increase in the age at HIV ascertainment may be associated with a 26% decrease in the risk of hypertension ascertainment (OR: 0.74, 95% CI: 0.68, 0.80), whilst a 5-year increase in the age at study end for PLHIV is associated with higher odds of hypertension ascertainment (OR: 2.04, 95% CI: 1.87, 2.22). Having TB is associated with lower odds of hypertension ascertainment (OR: 0.77, 95% CI: 0.72, 0.82), and PLHIV who have diabetes – OR: 1.52 (95% CI: 1.31, 1.77), and CKD - OR: 2.28 (95% CI: 1.95, 2.67) are more likely to be ascertained with hypertension. Our analysis shows that PLHIV who have been on ART for over 10 years have lower odds of hypertension ascertainment (OR: 0.83, 95% CI: 0.70, 0.99) compared to having been on ART for ≤ 3 years.

PLHIV who ever had viral load suppressed are 1.49 (95% CI: 1.14, 1.98) times more likely to be ascertained with hypertension and PLHIV who ever had CD4 cell count below 50 cells/µL are 12% (OR: 0.88, 95% CI: 0.79, 0.99) less likely to be ascertained with hypertension (Figure 6.3).



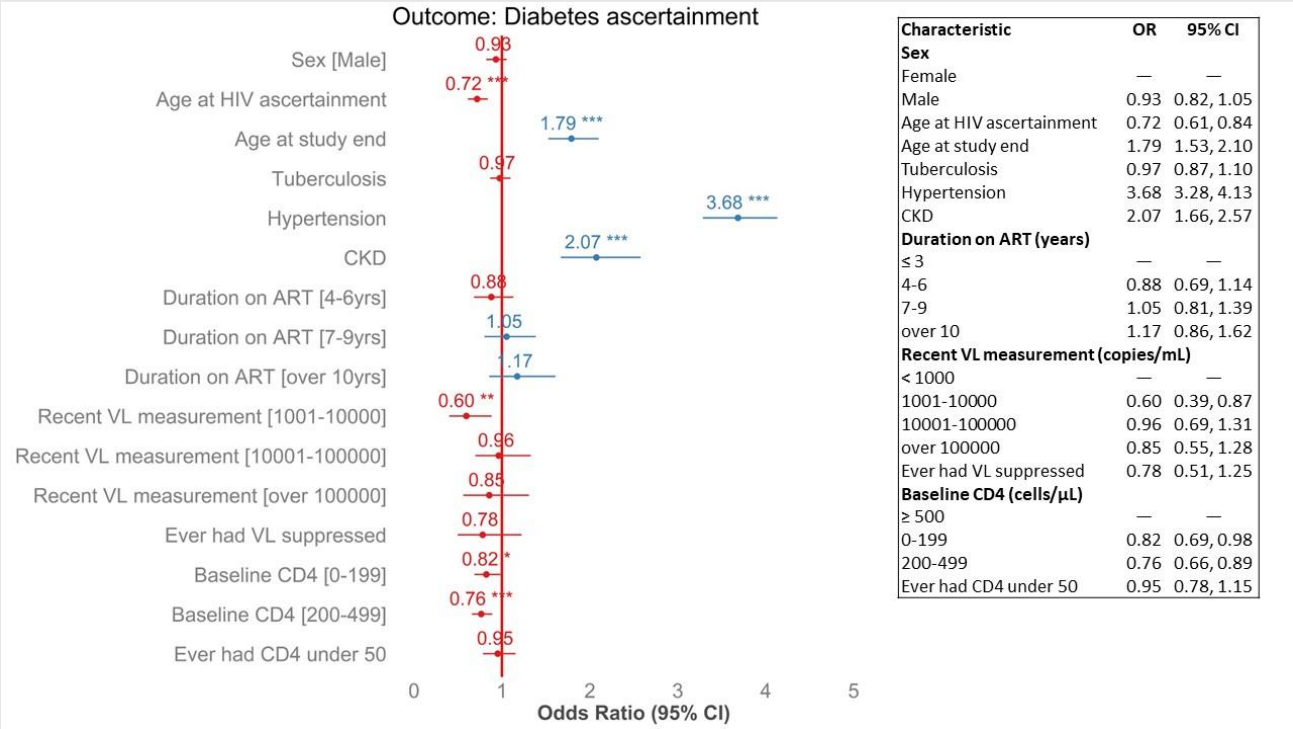
Characteristic	OR	95% CI
Sex		
Female	—	—
Male	0.70	0.66, 0.76
Age at HIV ascertainment	0.74	0.68, 0.80
Age at study end	2.04	1.87, 2.22
Tuberculosis	0.77	0.72, 0.82
Diabetes	3.62	3.23, 4.07
CKD	2.28	1.95, 2.67
Duration on ART (years)		
≤ 3	—	—
4-6	0.98	0.86, 1.11
7-9	0.87	0.76, 1.01
over 10	0.83	0.70, 0.99
Recent VL measurement (copies/mL)		
< 1000	—	—
1001-10000	0.87	0.72, 1.04
10001-100000	0.89	0.74, 1.06
over 100000	1.01	0.79, 1.26
Ever had VL suppressed	1.49	1.14, 1.98
Baseline CD4 (cells/µL)		
≥ 500	—	—
0-199	0.97	0.87, 1.07
200-499	0.99	0.90, 1.07
Ever had CD4 under 50	0.88	0.79, 0.99

Figure 6.3: Multivariate logistic regression showing odds ratios (ORs) and 95% confidence intervals (CI) for associations between the outcome of hypertension ascertainment, (n= 9 138) and risk factors: sex, age at study end per 5-year increments, comorbidities ascertained after HIV diagnosis and HIV-related characteristics.

Diabetes

Our analysis shows that a 5-year increase in the age at HIV ascertainment is associated with a 28% decrease in the risk of diabetes ascertainment (OR: 0.72, 95% CI: 0.61, 0.84), whilst a 5-year increase in the age at study end for PLHIV is associated with higher odds of diabetes ascertainment (OR: 1.79, 95% CI: 1.53, 2.10). PLHIV who have hypertension are 3.68 (95% CI: 3.28, 4.13) times more likely to be ascertained with diabetes, and PLHIV who have CKD are 2.07 (95% CI: 1.66, 2.57) times more likely to be ascertained with diabetes. PLHIV with recent viral load measurements of 1001 – 10 000 copies/mL are 40% (OR: 0.60, 95% CI: 0.39, 0.87) less likely to be ascertained with diabetes compared to PLHIV with recent viral load measurements

of < 1000 copies/mL. PLHIV with baseline CD4 cell count of 0-199 cells/µL (OR: 0.82, 95% CI: 0.69, 0.98), and 200-499 cells/µL (OR: 0.76, 95% CI: 0.66, 0.89), have lower odds of diabetes ascertainment compared with those with baseline CD4 cell count of ≥ 500 cells/µL (Figure 6.4).



Characteristic	OR	95% CI
Sex		
Female	—	—
Male	0.93	0.82, 1.05
Age at HIV ascertainment	0.72	0.61, 0.84
Age at study end	1.79	1.53, 2.10
Tuberculosis	0.97	0.87, 1.10
Hypertension	3.68	3.28, 4.13
CKD	2.07	1.66, 2.57
Duration on ART (years)		
≤ 3	—	—
4-6	0.88	0.69, 1.14
7-9	1.05	0.81, 1.39
over 10	1.17	0.86, 1.62
Recent VL measurement (copies/mL)		
< 1000	—	—
1001-10000	0.60	0.39, 0.87
10001-100000	0.96	0.69, 1.31
over 100000	0.85	0.55, 1.28
Ever had VL suppressed	0.78	0.51, 1.25
Baseline CD4 (cells/µL)		
≥ 500	—	—
0-199	0.82	0.69, 0.98
200-499	0.76	0.66, 0.89
Ever had CD4 under 50	0.95	0.78, 1.15

Figure 6.4: Multivariate logistic regression showing odds ratios (ORs) and 95% confidence intervals (CI) for associations between the outcome of diabetes ascertainment, (n= 2 339) and risk factors: sex, age at study end per 5-year increments, comorbidities ascertained after HIV diagnosis and HIV-related characteristics.

6.6.4 Relationship between having more comorbidities and unsuppressed viral load

The random effect part of the model showed major variations in unsuppressed viral load levels between PLHIV with a standard deviation (SD) of 156 843 copies/mL and residual variance SD of 2 333 copies/mL.

The fixed effect part of the model is presented in Figure 6.5. Our analysis shows that a 5-year increase in the age at ART start is associated with higher viral load levels of an average of 5 498 copies/mL (95% CI: 1 652, 9 345) when age at HIV ascertainment, sex, baseline CD4 cell count,

and the number of comorbidities remain constant. PLHIV who have baseline CD4 cell count of 0-199 cells/µL have an average increase in viral load levels of 5 746 (95% CI: 5 079, 6 413) compared to PLHIV with baseline CD4 cell count of ≥ 500 cells/µL. The results show that for PLHIV, having at least one comorbidity is associated with an increase in viral load levels by an average of 13 009 copies/mL (95% CI: 9 775, 16 244) compared with PLHIV without any additional comorbidity. Having two comorbidities is associated with increase in viral load levels by an average of 14 150 copies/mL (95% CI: 7 826, 20 474) compared to PLHIV without any additional comorbidity. Though our analysis shows an increase in viral load levels for PLHIV who have three or more comorbidities, its relationship with unsuppressed viral load levels is not statistically significant.

The results suggest that a 5-year increase in the age at HIV ascertainment is associated with low viral load levels by an average of -5 520 copies/mL (95% CI: -9 369, -1 671) (Figure 6.5).

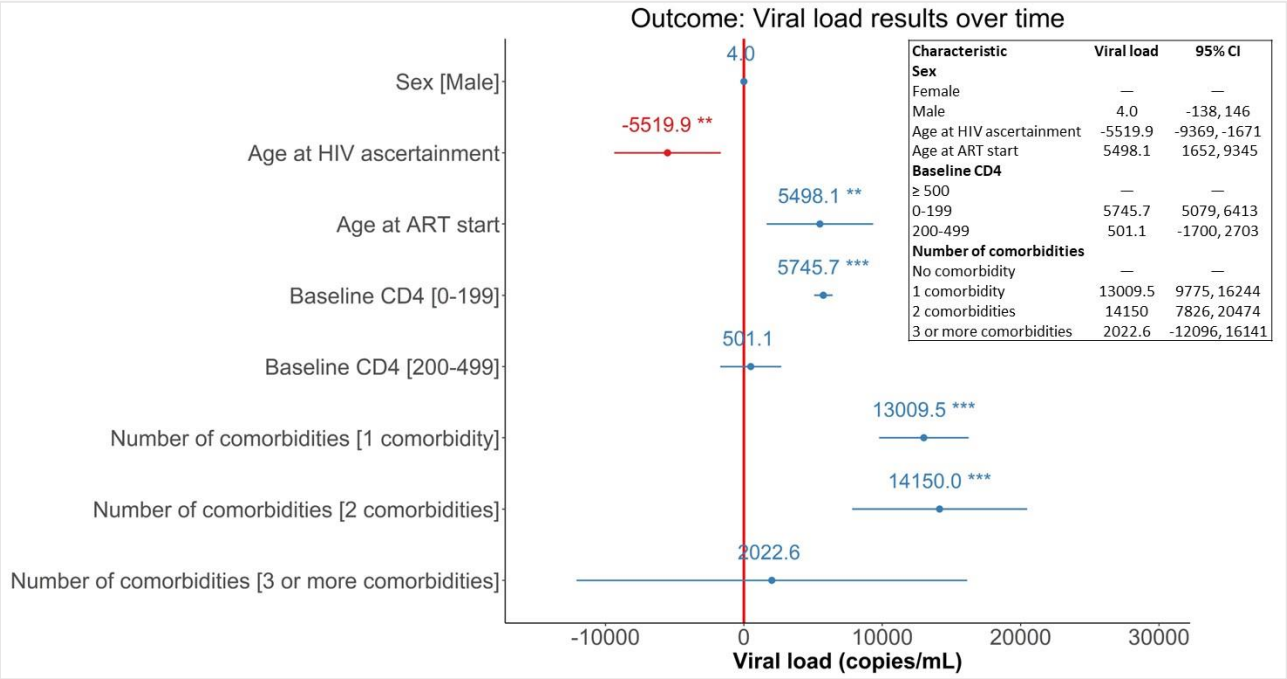


Figure 6.5: Relationship between viral load levels and sex, age at HIV ascertainment per 5-year increments, age at ART start per 5-year increments, baseline CD4 cell counts, and number of comorbidities ascertained prior to the last viral load test. Linear mixed effect regression showing viral load estimates and 95% CI.

6.7 Discussion

Prior to the introduction of the UTT guideline in South Africa in September 2016 (National Department of Health, 2016), ART initiation for PLHIV was not recommended or offered immediately after a positive test result and was based on a low CD4 cell count in addition to other clinical assessments and findings. Our results show 2-year gap between HIV ascertainment and ART initiation seen in the median age at HIV ascertainment (30 years, IQR: 25-37) and ART initiation (32 years, IQR: 27-39). The population of PLHIV in our study is a mixture of healthcare clients who were ascertained with HIV at a time treatment guidelines did not recommend immediate ART initiation and those ascertained at a time of UTT implementation. The gap is probably made up of people who have tested positive but not yet become physically ill and have not linked to treatment, as well as people who may be accessing treatment via private health care, or who moved out of the province and are not represented in our study population.

Our results show a higher proportion of females who have overall lower median ages at study recruitment and HIV ascertainment, which is similar to findings of a previous study investigating the comorbidity profiles and age at ascertainment of comorbidities for both HIV-negative and PLHIV healthcare clients in Khayelitsha, Cape Town (Osei-Yeboah et al., 2021). It has been reported that HIV diagnosis generally occur earlier in life in females than in males (Mabaso et al., 2018). Also, early healthcare seeking behaviours in women (Pulerwitz et al., 2019) in addition to other maternal and contraceptive care services provide women with frequent access to healthcare. These differences in healthcare seeking behaviours between women and men may lead to generally earlier HIV diagnosis in women than in men (Risher et al., 2021).

The expanded access to ART services in South Africa has ensured that PLHIV are initiated and maintained on ART, and the success of the ART programme has resulted in increasing proportions of PLHIV achieving viral suppression which significantly contributed toward the country's efforts toward the UNAIDS 90-90-90 target (Marinda et al., 2020). This has set the roadmap towards achieving the new UNAIDS 95-95-95 targets (UNAIDS - The Joint United Nations Programme on HIV/AIDS, 2020). Recent studies have reported that proportions of viral

suppression in PLHIV in care range between 85.7% and 94.5% across South Africa (Conan et al., 2022; Mukonda et al., 2020; Pillay et al., 2020), and it is worth noting that the proportion of our study participants with viral suppression (86.7%) is comparable to the proportions reported in other parts of South Africa. Considering the duration on ART for PLHIV in our population, our results show that the highest proportion of PLHIV have been on ART for ≤ 3 years (35.4%) compared to 12.1% who have been on ART for over 10 years. In relation to the median age at HIV ascertainment, this indicates that the population of PLHIV in our study are relatively young with a much smaller group of older PLHIV.

Though a higher proportion (57.7%) of this population did not have the additional comorbidities analysed in this study, 35.4% had at least one of those comorbidities. Our results show a significant proportion (22.8%) of PLHIV initiated on ART had current TB. HIV infection is one of the most widely recognised risk factors for TB (MacPherson et al., 2020; Mendelsohn et al., 2022) and considering the high burden of both TB and HIV in South Africa, PLHIV remain at high risks of HIV-TB coinfection (Kubjane et al., 2022). There are efforts to address the burden of TB resulting from HIV infections and PLHIV are often enrolled on isoniazid preventive therapy (IPT) (Bristow et al., 2012; Churchyard et al., 2014; Dye et al., 2013; Nel et al., 2020). This is a primary focus in HIV care and service in the Western Cape given the unusually high TB burden in the Western Cape (Claassens et al., 2013; du Toit et al., 2020). Analysis of these routine health data can accurately depict what is known from other sources – for instance TB-HIV burden/relationship like observed in this population, and as such could be used for monitoring and evaluation of interventions and progress in this area.

Our results show high proportions of females presenting with the various comorbidities, and this most likely reflects the gender differences in healthcare seeking behaviours in our population (Osei-Yeboah et al., 2021) as described above. For TB, hypertension and diabetes, females living with HIV have these conditions ascertained on average 4-5 years younger than males whereas the difference in age of ascertainment is only one year for CKD. Considering that the trend of TB diagnosis is similar to diagnosis of HIV in South Africa where in females the conditions are generally ascertained at younger ages than males (Perumal et al., 2018), we expect this difference to reflect in our population in terms of TB ascertainment among females

and males. Though HIV treatment may predispose all PLHIV to similar behaviours in terms of accessing healthcare services and/or requirements, additional maternal and contraceptive services for women include screening that can enable early detection of other non-communicable diseases (NCDs) like hypertension and diabetes (Muhwava et al., 2018; Webster et al., 2019) in the younger female healthcare client population. Our analysis shows that for comorbidities like CKD that generally occur at older ages, however, ascertainment among females and males living with HIV is likely to occur almost at the same time.

Our analysis provides insight into the ascertainment of HIV-related infectious disease and other NCDs that may be prevalent among PLHIV.

In South Africa, there is already a high burden of TB independently of HIV (Blaser et al., 2016), and considering that TB-HIV co-infection is a major challenge, the ageing population of PLHIV in our study are at increased risk of TB co-infections. Our results show that the likelihood of having had an active TB infection increases as PLHIV get older, whereas in those without HIV the risk of TB infection decreases with ageing. Males living with HIV in our study are at higher risks of TB infection compared to females living with HIV, in line with reported gender patterns of TB prevalence in South Africa which show higher prevalence in males (McLaren et al., 2015; Moyo et al., 2022). In line with existing evidence, our results demonstrate that unsuppressed viral load levels, low baseline CD4 cell count, CD4 cell count below 50 cells/µL, and comorbid CKD are associated with TB ascertainment in PLHIV. Conclusions of a study from South Africa on the continuing burden of advanced HIV disease show that ongoing HIV associated morbidities are resulting from PLHIV receiving treatment not being in continuous care and/or not being fully virally suppressed (Osler et al., 2018).

Previous studies have reported that high viral load levels (Manaye et al., 2020; Pongpirul et al., 2018), lower baseline CD4 cell counts (Ganesan et al., 2013) and longer duration on ART (Nishijima et al., 2017; Wearne et al., 2020) are predictors of kidney injury and impaired kidney function in PLHIV. Similar to these previous studies, our findings show that unsuppressed viral load levels (10001-100 000 copies/mL and over 100 000 copies/mL), baseline CD4 cell counts

(0-199 cells/μL) and CD4 cell counts below 50 cells/μL, in addition to increasing age and comorbid TB, hypertension and diabetes are the key drivers of CKD in our study population.

Our results demonstrate that the occurrence of hypertension and diabetes among PLHIV in our study population is mainly associated with increase in age at study end, presence of either hypertension or diabetes (when the other is the outcome) and presence of CKD. Additionally, having had viral load suppressed which is a key determinant of survival or a successful treatment for PLHIV is associated with hypertension occurrence. We observed that increase in age at HIV ascertainment was not significantly associated with the occurrence of any of the conditions assessed, however, increase in age at study end which relate to actual ages of study participants were significantly associated with the occurrence of all comorbidities. This suggests that as PLHIV age, their age-related risks and/or burden of common NCDs – hypertension and diabetes may tend to be similar to the population without HIV. Our previous study (Chapter 4) clearly demonstrates, however, that this ageing HIV population is not a representative of all ageing PLHIV because they are the subset of survivors who might have been diagnosed with HIV when access to ART was not yet universal and yet have survived to date.

HIV viral suppression is an important milestone for PLHIV on ART and plays significant roles in reducing HIV incidence at the population level (Tanser et al., 2017). The linear mixed effects analysis demonstrates that increase in the age at ART initiation and lower baseline CD4 cell count is associated with higher viral load levels. This suggests that when ART initiation is delayed and individuals are already physically unwell as a result of the unchecked HIV infection, achieving viral suppression may be challenging. With the implementation of the current UTT guidelines in South Africa, timely linkage, and retention in care after HIV ascertainment would significantly avert worse HIV presentations.

Our findings show that PLHIV with one or two comorbidities are more likely to be experiencing unsuppressed viral load levels. A previous study reports that PLHIV with multiple comorbidities do not have the same probability of achieving viral suppression as those without comorbidities by 36 months in medical care coordination programme (Li et al., 2020). Other studies from South Africa and Uganda emphasise the relationship between unsuppressed viral loads and

having comorbid TB (Bulage et al., 2017; Joseph Davey et al., 2018), and considering that TB is the most common comorbidity in our population, it may be significantly contributing to unsuppressed viral load levels. The non-significant relationship between PLHIV who have three or more comorbidities and unsuppressed viral load levels should be interpreted with reference to the fewer number of people with this number of comorbidities, as shown in Table 6.1, which may probably lead to lack of adequate statistical power to model this relationship.

Our study has several limitations relating to known bias in the dataset due to imbalances in the sectors of population seeking healthcare, and available comorbidities data from PHDC as described in Chapter 2 and Chapter 3. We also recognize the differences within the HIV population in terms of age. We believe that older PLHIV in the study population represent only a small subset of the original population of healthcare clients who were diagnosed with HIV in the late 1990's and early 2000's, due to poor survival rates in those diagnosed with HIV in those decades. It is also possible a number of these older PLHIV were only diagnosed with HIV recently at older ages. This means that the current population ageing with HIV are not representative of how the same subgroup will look in the future, because those who have been diagnosed with HIV at a young age since 2004 have had improved access to ART, and since 2016 the UTT approach means that they link to ART as soon as they receive a positive diagnosis, leading to better long term patient outcomes. In addition, the limited number of comorbidities assessed, based on what is available from the PHDC at this time, means that important HIV comorbidities like cardiovascular disease (CVD), which are not yet available from the PHDC have been omitted from our analyses. As these data become available, CVD will be an important comorbidity to include in further analyses.

6.8 Conclusion

In this study, we have analysed administratively collected routine health data for healthcare clients living with HIV and access care in public facilities in Khayelitsha, Cape Town.

In summary, in this study we observe higher proportions of females than males presenting with various comorbidities and an early ascertainment (4-5 years) of TB, hypertension and diabetes. Though HIV infections may predispose all PLHIV to similar health needs and services, other

reasons for accessing healthcare beyond HIV such as being pregnant (Osler et al., 2020) or accessing contraception, and the generally frequent health seeking behaviours of females than males may lead to earlier ascertainment of health conditions when women access care.

Our analysis indicates that in addition to ageing, the key predictors of the occurrence of HIV-related comorbidities such as TB and CKD are the presence of other comorbidities, lower baseline CD4 cell count and unsuppressed viral load levels. In relation to the occurrence of hypertension and diabetes in our study, we observe that as PLHIV get older and present with other comorbidities their risks of these chronic diseases increase. Our analysis of routine health data suggests that the occurrence of comorbidities in an ageing population of PLHIV in our study may be largely driven by comorbidity burden in addition to ageing and other HIV characteristics. Additionally, we observe that unsuppressed viral load levels for PLHIV in our study are associated with not only low baseline CD4 cell counts, as expected, but also the number of comorbidities with which a healthcare client is presenting.

The value of our study is that we have used routine health data from Government health service delivery in the Western Cape to analyse the occurrence and impact of common comorbidities in PLHIV, including demographics and laboratory results from healthcare clients. We have conducted multivariate analyses which incorporate multimorbidity disease conditions as independent variables together with demographic and laboratory data. This is useful in understanding not only how HIV metrics are associated with comorbidities, but also relationship of existing conditions with the subsequent occurrence of additional comorbidities in PLHIV. In planning HIV care and services for an ageing population of PLHIV, like we have in South Africa, we propose that routine health data can play a significant role in better understanding the potential impacts of comorbidities on HIV treatment success. The preliminary analysis here clearly demonstrates the importance of comorbidities in understanding HIV and viral load suppression, suggesting the need for adequate public health measures targeting reducing the incidence of comorbidities in PLHIV as part of treatment guidelines and policies to mitigate the growing burden and effects of comorbidities in PLHIV.

6.9 Acknowledgement

We acknowledge the Provincial Health Data Centre, Health Impact Assessment Directorate of the Western Cape Government Health Department for the provision of the anonymized Khayelitsha dataset.

6.10 Data availability statement

These anonymised, perturbed data were provided for analysis by the Western Cape Department of Health, Provincial Health Data Centre. These are highly granular health data linked to individual health care clients in the province and no informed consent has been given for research use. For this reason, the Western Cape Department of Health does not permit open sharing but instead grants only primary use permission for the data. Re-use of this dataset requires approval from the Western Cape Department of Health (Provincial Health Data Centre), and Dr Moodley, Director: HIA, Western Cape Department of Health, South Africa can be contacted to advise on this process (email: melvin.moodley@westerncape.gov.za, Reference study ID 259-TIFFIN).

6.11 Funding

This research was funded in part, by the Wellcome Trust 203135/Z/16/Z. For the purpose of open access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript version arising from this submission. The Wellcome Centre for Infectious Diseases Research in Africa is supported by core funding from the Wellcome Trust [203135/Z/16/Z]. ROY receives funding from the Africa Regional Staff/Student International Exchange: Food Security and Sustainable Human Wellbeing II (ARISE II) Consortium funded by the Intra-Africa Academic Mobility Scheme of the European Union (2016-2616). NT receives funding from the NIH Common Fund (H3ABioNet, U24HG006941). NT receives funding from Wellcome CIDRI-Africa (203135/Z/16/Z). NT additionally receives support from the NIH B-Positive grant (R01HD080465).

6.12 References

Althoff, K. N., Smit, M., Reiss, P., & Justice, A. C. (2016). HIV and ageing: Improving quantity and quality of life. *Current Opinion in HIV and AIDS*, *11*(5), 527–536. https://doi.org/10.1097/COH.0000000000000305

Bishop, J. D., DeShields, S., Cunningham, T., & Troy, S. B. (2016). CD4 Count Recovery After Initiation of Antiretroviral Therapy in Patients Infected With Human Immunodeficiency Virus. *The American Journal of the Medical Sciences*, *352*(3), 239–244. https://doi.org/10.1016/j.amjms.2016.05.032

Blaser, N., Zahnd, C., Hermans, S., Salazar-Vizcaya, L., Estill, J., Morrow, C., Egger, M., Keiser, O., & Wood, R. (2016). Tuberculosis in Cape Town: An age-structured transmission model. *Epidemics*, *14*, 54–61. https://doi.org/10.1016/j.epidem.2015.10.001

Boulle, A., Heekes, A., Tiffin, N., Smith, M., Mutemaringa, T., Zinyakatira, N., Phelanyane, F., Pienaar, C., Buddiga, K., Coetzee, E., Rooyen, R. van, Dyers, R., Fredericks, N., Loff, A., Shand, L., Moodley, M., Vega, I. de, & Vallabhjee, K. (2019). Data Centre Profile: The Provincial Health Data Centre of the Western Cape Province, South Africa. *International Journal of Population Data Science*, *4*(2), Article 2. https://doi.org/10.23889/ijpds.v4i2.1143

Bristow, C. C., Larson, E., Vilakazi-Nhlapo, A. K., Wilson, M., & Klausner, J. D. (2012). Scale-up of isoniazid preventive therapy in PEPFAR-assisted clinical sites in South Africa [Notes from the field]. *The International Journal of Tuberculosis and Lung Disease*, *16*(8), 1020–1022. https://doi.org/10.5588/ijtld.11.0744

Bulage, L., Ssewanyana, I., Nankabirwa, V., Nsubuga, F., Kihembo, C., Pande, G., Ario, A. R., Matovu, J. K., Wanyenze, R. K., & Kiyaga, C. (2017). Factors Associated with Virological Non-suppression among HIV-Positive Patients on Antiretroviral Therapy in Uganda, August 2014–July 2015. *BMC Infectious Diseases*, *17*(1), 326. https://doi.org/10.1186/s12879-017-2428-3

Churchyard, G. J., Chaisson, R. E., Maartens, G., & Getahun, H. (2014). Tuberculosis preventive therapy: An underutilised strategy to reduce individual risk of TB and contribute to TB control. *South African Medical Journal*, *104*(5), Article 5. https://doi.org/10.7196/SAMJ.8290

Claassens, M., Schalkwyk, C. van, Haan, L. den, Floyd, S., Dunbar, R., Helden, P. van, Godfrey-Faussett, P., Ayles, H., Borgdorff, M., Enarson, D., & Beyers, N. (2013). High Prevalence of Tuberculosis and Insufficient Case Detection in Two Communities in the Western Cape, South Africa. *PLOS ONE*, *8*(4), e58689. https://doi.org/10.1371/journal.pone.0058689

Collin, A., Marec, F. L., Vandenhende, M.-A., Lazaro, E., Duffau, P., Cazanave, C., Gérard, Y., Dabis, F., Bruyand, M., Bonnet, F., & Group, A. C. A. C. S. (2016). Incidence and Risk

Factors for Severe Bacterial Infections in People Living with HIV. ANRS CO3 Aquitaine Cohort, 2000–2012. *PLOS ONE*, *11*(4), e0152970. https://doi.org/10.1371/journal.pone.0152970

Conan, N., Simons, E., Chihana, M. L., Ohler, L., FordKamara, E., Mbatha, M., vanCutsem, G., & Huerga, H. (2022). Increase in HIV viral suppression in KwaZulu-Natal, South Africa: Community-based cross sectional surveys 2018 and 2013. What remains to be done? *PLOS ONE*, *17*(3), e0265488. https://doi.org/10.1371/journal.pone.0265488

du Toit, T., Esterhuizen, T. M., Tiffin, N., Abulfathi, A. A., Reuter, H., & Decloedt, E. H. (2020). Incident tuberculosis disease in patients receiving biologic therapies in the Western Cape, South Africa from 2007 to 2018. *BMC Infectious Diseases*, *20*(1), 900. https://doi.org/10.1186/s12879-020-05624-0

Dye, C., Glaziou, P., Floyd, K., & Raviglione, M. (2013). Prospects for Tuberculosis Elimination. *Annual Review of Public Health*, *34*(1), 271–286. https://doi.org/10.1146/annurev-publhealth-031912-114431

Ganesan, A., Krantz, E., Huppler Hullsiek, K., Riddle, M., Weintrob, A., Lalani, T., Okulicz, J., Landrum, M., Agan, B., Whitman, T., Ross, M., Crum-Cianflone, N., & Group, the I. D. C. R. P. H. W. (2013). Determinants of incident chronic kidney disease and progression in a cohort of HIV-infected persons with unrestricted access to health care. *HIV Medicine*, *14*(2), 65–76. https://doi.org/10.1111/j.1468-1293.2012.01036.x

Grobler, A., Cawood, C., Khanyile, D., Puren, A., & Kharsany, A. B. M. (2017). Progress of UNAIDS 90-90-90 targets in a district in KwaZulu-Natal, South Africa, with high HIV burden, in the HIPSS study: A household-based complex multilevel community survey. *The Lancet HIV*, *4*(11), e505–e513. https://doi.org/10.1016/S2352-3018(17)30122-4

Hodes, R., & Morrell, R. (2018). Incursions from the epicentre: Southern theory, social science, and the global HIV research domain. *African Journal of AIDS Research*, *17*(1), 22–31. https://doi.org/10.2989/16085906.2017.1377267

Huerga, H., Van Cutsem, G., Ben Farhat, J., Puren, A., Bouhenia, M., Wiesner, L., Dlamini, L., Maman, D., Ellman, T., & Etard, J.-F. (2018). Progress towards the UNAIDS 90–90-90 goals by age and gender in a rural area of KwaZulu-Natal, South Africa: A household-based community cross-sectional survey. *BMC Public Health*, *18*(1), 303. https://doi.org/10.1186/s12889-018-5208-0

Joseph Davey, D., Abrahams, Z., Feinberg, M., Prins, M., Serrao, C., Medeossi, B., & Darkoh, E. (2018). Factors associated with recent unsuppressed viral load in HIV-1-infected patients in care on first-line antiretroviral therapy in South Africa. *International Journal of STD & AIDS*, *29*(6), 603–610. https://doi.org/10.1177/0956462417748859

Kranzer, K., Lawn, S. D., Johnson, L. F., Bekker, L.-G., & Wood, R. (2013). Community Viral Load and CD4 Count Distribution Among People Living With HIV in a South African Township:

Implications for Treatment as Prevention. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *63*(4), 498–505. https://doi.org/10.1097/QAI.0b013e318293ae48

Kubjane, M., Osman, M., Boulle, A., & Johnson, L. F. (2022). The impact of HIV and tuberculosis interventions on South African adult tuberculosis trends, 1990-2019: A mathematical modeling analysis. *International Journal of Infectious Diseases*, *122*, 811–819. https://doi.org/10.1016/j.ijid.2022.07.047

Kufa, T., Shubber, Z., MacLeod, W., Takuva, S., Carmona, S., Bor, J., Gorgens, M., Pillay, Y., Puren, A., Eaton, J. W., & Fraser-Hurt, N. (2019). CD4 count recovery and associated factors among individuals enrolled in the South African antiretroviral therapy programme: An analysis of national laboratory based data. *PLOS ONE*, *14*(5), e0217742. https://doi.org/10.1371/journal.pone.0217742

Li, M. J., Su, E., Garland, W. H., Oksuzyan, S., Lee, S.-J., Kao, U. H., Weiss, R. E., & Shoptaw, S. J. (2020). Trajectories of Viral Suppression in People Living With HIV Receiving Coordinated Care: Differences by Comorbidities. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *84*(4), 387–395. https://doi.org/10.1097/QAI.0000000000002351

Mabaso, M., Sokhela, Z., Mohlabane, N., Chibi, B., Zuma, K., & Simbayi, L. (2018). Determinants of HIV infection among adolescent girls and young women aged 15–24 years in South Africa: A 2012 population-based national household survey. *BMC Public Health*, *18*(1), 183. https://doi.org/10.1186/s12889-018-5051-3

MacPherson, P., Lebina, L., Motsomi, K., Bosch, Z., Milovanovic, M., Ratsela, A., Lala, S., Variava, E., Golub, J. E., Webb, E. L., & Martinson, N. A. (2020). Prevalence and risk factors for latent tuberculosis infection among household contacts of index cases in two South African provinces: Analysis of baseline data from a cluster-randomised trial. *PLOS ONE*, *15*(3), e0230376. https://doi.org/10.1371/journal.pone.0230376

Manaye, G. A., Abateneh, D. D., & Niguse, W. (2020). Chronic Kidney Disease and Associated Factors Among HIV/AIDS Patients on HAART in Ethiopia. *HIV/AIDS - Research and Palliative Care*, *12*, 591–599. https://doi.org/10.2147/HIV.S276356

Marinda, E., Simbayi, L., Zuma, K., Zungu, N., Moyo, S., Kondlo, L., Jooste, S., Nadol, P., Igumbor, E., Dietrich, C., & Briggs-Hagen, M. (2020). Towards achieving the 90–90–90 HIV targets: Results from the south African 2017 national HIV survey. *BMC Public Health*, *20*(1), 1375. https://doi.org/10.1186/s12889-020-09457-z

McLaren, Z. M., Brouwer, E., Ederer, D., Fischer, K., & Branson, N. (2015). Gender patterns of tuberculosis testing and disease in South Africa. *The International Journal of Tuberculosis and Lung Disease*, *19*(1), 104–110. https://doi.org/10.5588/ijtld.14.0212

Mendelsohn, S. C., Fiore-Gartland, A., Awany, D., Mulenga, H., Mbandi, S. K., Tameris, M., Walzl, G., Naidoo, K., Churchyard, G., Scriba, T. J., & Hatherill, M. (2022). Clinical predictors of pulmonary tuberculosis among South African adults with HIV. *EClinicalMedicine*, *45*. https://doi.org/10.1016/j.eclinm.2022.101328

Moyo, S., Ismail, F., Walt, M. V. der, Ismail, N., Mkhondo, N., Dlamini, S., Mthiyane, T., Chikovore, J., Oladimeji, O., Mametja, D., Maribe, P., Seocharan, I., Ximiya, P., Law, I., Tadolini, M., Zuma, K., Manda, S., Sismanidis, C., Pillay, Y., & Mvusi, L. (2022). Prevalence of bacteriologically confirmed pulmonary tuberculosis in South Africa, 2017–19: A multistage, cluster-based, cross-sectional survey. *The Lancet Infectious Diseases*, *22*(8), 1172–1180. https://doi.org/10.1016/S1473-3099(22)00149-9

Muhwava, L. S., Murphy, K., Zarowsky, C., & Levitt, N. (2018). Policies and clinical practices relating to the management of gestational diabetes mellitus in the public health sector, South Africa – a qualitative study. *BMC Health Services Research*, *18*(1), 349. https://doi.org/10.1186/s12913-018-3175-x

Mukonda, E., Hsiao, N.-Y., Vojnov, L., Myer, L., & Lesosky, M. (2020). Mixed-method estimation of population-level HIV viral suppression rate in the Western Cape, South Africa. *BMJ Global Health*, *5*(8), e002522. https://doi.org/10.1136/bmjgh-2020-002522

National Department of Health. (2016). *National HIV Testing Services: Policy 2016*. https://sahivsoc.org/Files/HTS%20Policy%2028%20July%20final%20copy.pdf

Nel, J., Dlamini, S., Meintjes, G., Burton, R., Black, J. M., Davies, N. E. C. G., Hefer, E., Maartens, G., Mangena, P. M., Mathe, M. T., Moosa, M.-Y., Mulaudzi, M. B., Moorhouse, M., Nash, J., Nkonyane, T. C., Preiser, W., Rassool, M. S., Stead, D., van der Plas, H., … Woods, J. F. (2020). Southern African HIV Clinicians Society guidelines for antiretroviral therapy in adults: 2020 update. *Southern African Journal of HIV Medicine*, *21*(1), 1–39. https://doi.org/10.4102/sajhivmed.v21i1.1115

Nishijima, T., Kawasaki, Y., Mutoh, Y., Tomonari, K., Tsukada, K., Kikuchi, Y., Gatanaga, H., & Oka, S. (2017). Prevalence and factors associated with chronic kidney disease and end-stage renal disease in HIV-1-infected Asian patients in Tokyo. *Scientific Reports*, *7*(1), Article 1. https://doi.org/10.1038/s41598-017-15214-x

Ochodo, E. A., Olwanda, E. E., Deeks, J. J., & Mallett, S. (2022). Point-of-care viral load tests to detect high HIV viral load in people living with HIV/AIDS attending health facilities. *The Cochrane Database of Systematic Reviews*, *2022*(3), CD013208. https://doi.org/10.1002/14651858.CD013208.pub2

Osei-Yeboah, R., Tamuhla, T., Ngwenya, O., & Tiffin, N. (2021). Accessing HIV care may lead to earlier ascertainment of comorbidities in health care clients in Khayelitsha, Cape Town. *PLOS Global Public Health*, *1*(12), e0000031. https://doi.org/10.1371/journal.pgph.0000031

Osler, M., Cornell, M., Ford, N., Hilderbrand, K., Goemaere, E., & Boulle, A. (2020). Population-wide differentials in HIV service access and outcomes in the Western Cape for men as compared to women, South Africa: 2008 to 2018: a cohort analysis. *Journal of the International AIDS Society*, *23*(S2), e25530. https://doi.org/10.1002/jia2.25530

Osler, M., Hilderbrand, K., Goemaere, E., Ford, N., Smith, M., Meintjes, G., Kruger, J., Govender, N. P., & Boulle, A. (2018). The Continuing Burden of Advanced HIV Disease Over 10 Years of Increasing Antiretroviral Therapy Coverage in South Africa. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, *66*(Suppl 2), S118–S125. https://doi.org/10.1093/cid/cix1140

Perumal, R., Naidoo, K., & Padayatchi, N. (2018). TB epidemiology: Where are the young women? Know your tuberculosis epidemic, know your response. *BMC Public Health*, *18*(1), 417. https://doi.org/10.1186/s12889-018-5362-4

Pillay, T., Cornell, M., Fox, M. P., Euvrard, J., Fatti, G., Technau, K.-G., Sipambo, N., Prozesky, H., Eley, B., Tanser, F., & Johnson, L. F. (2020). Recording of HIV viral loads and viral suppression in South African patients receiving antiretroviral treatment: A multicentre cohort study. *Antiviral Therapy*, *25*(5), 257–266. https://doi.org/10.3851/IMP3371

Pongpirul, W., Pongpirul, K., Ananworanich, J., Klinbuayaem, V., Avihingsanon, A., & Prasithsirikul, W. (2018). Chronic kidney disease incidence and survival of Thai HIV-infected patients. *AIDS*, *32*(3), 393–398. https://doi.org/10.1097/QAD.0000000000001698

Pulerwitz, J., Gottert, A., Kahn, K., Haberland, N., Julien, A., Selin, A., Twine, R., Peacock, D., Gómez-Olivé, X., Lippman, S. A., & Pettifor, A. (2019). Gender Norms and HIV Testing/Treatment Uptake: Evidence from a Large Population-Based Sample in South Africa. *AIDS and Behavior*, *23*(2), 162–171. https://doi.org/10.1007/s10461-019-02603-8

Risher, K. A., Cori, A., Reniers, G., Marston, M., Calvert, C., Crampin, A., Dadirai, T., Dube, A., Gregson, S., Herbst, K., Lutalo, T., Moorhouse, L., Mtenga, B., Nabukalu, D., Newton, R., Price, A. J., Tlhajoane, M., Todd, J., Tomlin, K., … Eaton, J. W. (2021). Age patterns of HIV incidence in eastern and southern Africa: A modelling analysis of observational population-based cohort studies. *The Lancet HIV*, *8*(7), e429–e439. https://doi.org/10.1016/S2352-3018(21)00069-2

Smurzynski, M., Wu, K., Benson, C. A., Bosch, R. J., Collier, A. C., & Koletar, S. L. (2010). Relationship Between CD4+ T-Cell Counts/HIV-1 RNA Plasma Viral Load and AIDS-Defining Events Among Persons Followed in the ACTG Longitudinal Linked Randomized Trials Study. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *55*(1), 117–127. https://doi.org/10.1097/QAI.0b013e3181e8c129

Statistics South Africa. (2022). *Mid-year population estimates for 2022* (No. P03022022; pp. 1–50). https://www.statssa.gov.za/publications/P0302/P03022022.pdf

Tanser, F., Vandormael, A., Cuadros, D., Phillips, A. N., Oliveira, T. de, Tomita, A., Bärnighausen, T., & Pillay, D. (2017). Effect of population viral load on prospective HIV incidence in a hyperendemic rural African community. *Science Translational Medicine*, *9*(420). https://doi.org/10.1126/scitranslmed.aam8012

UNAIDS - The Joint United Nations Programme on HIV/AIDS. (2020). *Understanding fast-track: Accelerating action to end the AIDS epidemic by 2030* (pp. 1–12). https://www.unaids.org/sites/default/files/media_asset/201506_JC2743_Understanding_FastTrack_en.pdf

Ward, A. R., Mota, T. M., & Jones, R. B. (2021). Immunological approaches to HIV cure. *Seminars in Immunology*, *51*, 101412. https://doi.org/10.1016/j.smim.2020.101412

Wearne, N., Davidson, B., Blockman, M., Swart, A., & Jones, E. S. (2020). HIV, drugs and the kidney. *Drugs in Context*, *9*, 2019-11–1. https://doi.org/10.7573/dic.2019-11-1

Webster, K., Fishburn, S., Maresh, M., Findlay, S. C., & Chappell, L. C. (2019). Diagnosis and management of hypertension in pregnancy: Summary of updated NICE guidance. *BMJ*, *366*, l5119. https://doi.org/10.1136/bmj.l5119

CHAPTER 7: CONCLUSION

7.1 Summary of research findings

In Chapter 2, routine health data were analysed to describe the common comorbidities ascertained in a cohort of healthcare clients and determined the median age of comorbidity ascertainment for PLHIV and HIV-negative individuals. This analysis described associations between comorbidities incidence as outcomes, and age, sex, and existing disease conditions as risk factors. Analysis of the healthcare client population in this study showed ascertainment at earlier ages for most chronic comorbidities in PLHIV compared to HIV-negative individuals. Analysis of a subset of women accessing maternal care - under the assumption they are likely to have been screened for common comorbidities such as hypertension, diabetes, and kidney disease during their pregnancy to account for the bias in the whole population of healthcare clients - showed smaller differences in ages at ascertainment of most comorbidities among women seeking maternal care in HIV-negative and HIV-positive groups. This suggested that frequent access to healthcare may result in earlier ascertainment of these comorbidities, rather than there being generally earlier incidence in the HIV-positive population. In all comorbidities assayed where significant differences were identified in the age of ascertainment of this group, the difference was in the range of only 1-2 years - with the notable exception of chronic kidney disease (CKD) which occurred an average of 5.5 years earlier in HIV positive women, in line with existing studies on HIV Nephropathy (Butler et al., 2018; Naicker, 2020).

In Chapter 3, routine health data were analysed to describe the order and timelines for the occurrence of selected comorbidities when HIV and other disease conditions are first ascertained in a population of healthcare clients. This study showed that in general PLHIV had earlier ascertainment of tuberculosis (TB), cervical cancer and CKD as seen elsewhere (Hopkins et al., 2019; Isaguliants et al., 2021; Manaye et al., 2020; Mendelsohn et al., 2022), but later ascertainment of hypertension and diabetes (Magodoro et al., 2022), when compared to HIV-negative individuals. It was observed that the likely differences in the healthcare access patterns of the study population based on age, gender, general health, and HIV status resulted in bias in this virtual cohort of healthcare clients; however, these routine health data were still able to provide insights into the associations between an existing HIV infection and the

development of subsequent comorbidities in individuals attending government healthcare facilities.

Chapter 4 presented an analysis of routine health data for kidney function testing, including kidney function laboratory results for PLHIV and HIV-negative individuals. It was observed that PLHIV had slightly lower first median serum creatinine (SCr) results than HIV-negative individuals, and this reflected in higher median estimated glomerular filtration rate (eGFR) results for PLHIV, as expected. Among healthcare clients receiving eGFR results, most common diseases seen in the various age groups were HIV in the 18-29 years age group, TB in the 30-44 years age group, and hypertension, diabetes, and CKD in the 60+ age group. The analysis showed that having HIV, diabetes, and TB was associated with slightly higher eGFR whilst having hypertension, being a male and being in an older age category at eGFR testing was associated with lower eGFR for healthcare clients. These findings most likely reflect patterns of access to care in different subsets of the healthcare client population: this study showed that kidney function testing patterns and results were quite distinct in younger people without HIV who tended to have worse kidney function at first testing compared to younger PLHIV who in general had better kidney function when tested; and older people with and without HIV who tended to have more similar kidney function results. The ageing population of PLHIV is only a subset of surviving people who were diagnosed with HIV in the late 80's through the 90's and early 2000's, due to the limited access to ART prior to the Universal Test and Treat (UTT) policy in 2016. This is likely the reason why their profiles are more similar to those without HIV. PLHIV who were ill in the earlier era did not survive to old age. The findings from this study indicated that, most likely in younger people, PLHIV were being more regularly screened for kidney function even when they show no symptoms of renal problems, whereas young people without HIV were more likely to be tested only when they present with symptoms suggestive of kidney problems and possibly more advanced kidney disease.

In Chapter 5, routine health data were analysed for healthcare clients with CKD to understand the kidney function profiles of healthcare clients in the context of HIV and other comorbidities ascertained prior to or at the time of kidney function assessment. The finding of this study

showed substantial differences in eGFR results for PLHIV and HIV-negative individuals in terms of individual healthcare clients results and when considering all laboratory results. It showed that PLHIV who have CKD have higher laboratory results of kidney function metrics, reflected better kidney function, than HIV-negative individuals who have CKD. This observation could be because PLHIV accessing care and services also receive screening for kidney function and other comorbidities, meaning they have kidney function tests prior to exhibiting any signs of kidney disease, whereas the HIV-negative healthcare clients may only access care when they have symptoms indicating impaired kidney function or later stage kidney disease. The findings of this study showed that for healthcare clients with CKD, HIV alone did not have significant impact on eGFR results when considering other comorbidities, whereas for healthcare clients with CKD, also having TB and hypertension was associated with lower eGFR results. This study further showed that, as expected, among healthcare clients with CKD, being older – 30-44 years, 45-60 years and 60+ years was associated with slightly lower eGFR results compared to healthcare clients aged 18-29 years. The findings of this study are similar to previous studies which observed improvements in kidney function – increase in eGFR results in the first year of ART and low prevalence of renal impairment in HIV patients (Assaram et al., 2017; Bock et al., 2019; Mapesi et al., 2018). Previous studies have reported that TB and hypertension are associated with decline in kidney function (Shen et al., 2015; Vaes et al., 2015; Yu et al., 2019). These results suggest that the eGFR results generated during routine health care reflect early linkage to care and kidney function screening for PLHIV even in the absence of indications of kidney impairment. This contrasts with the likely later kidney function testing of HIV-negative individuals who are more likely only screened if they present with symptoms suggesting impaired kidney function.

In Chapter 6, routine health data for PLHIV accessing care were analysed to describe the cohort demographics and the contribution of selected comorbidities ascertained after HIV and HIV-related characteristics to the occurrence of other conditions and unsuppressed viral load levels. This study showed that in addition to the expected impact of ageing, the key predictors of the occurrence of HIV-related comorbidities such as TB and CKD are the presence of other pre-existing comorbidities, lower baseline CD4 cell count and unsuppressed viral load levels. This

finding is in line with previous studies describing the predictors of TB and CKD in PLHIV (Brito et al., 2019; Fenner et al., 2017; Geremew et al., 2020; Jose et al., 2018; Mollel et al., 2019). In relation to the occurrence of hypertension and diabetes, it was observed that as PLHIV get older (Rajagopaul & Naidoo, 2021) and present with other comorbidities their risks of these chronic diseases increase. From using routine health data about PLHIV accessing health care, it was observed that the occurrence of comorbidities and unsuppressed viral load levels in an ageing population of PLHIV in this study was largely driven by the burden of pre-existing comorbidities in addition to ageing and other HIV characteristics.

7.2 Strength of the study

This study has demonstrated how routine health data may be utilised to better understand disease occurrence and healthcare needs of PLHIV and HIV-negative individuals. From the use of routine health data, this study assessed what is happening in real life in terms of healthcare access, laboratory results, disease occurrences and key drivers of common comorbidities for PLHIV and HIV-negative individuals. For instance, this study observed that ascertainment of common chronic conditions occurs later for HIV-negative individuals, especially men, who do not have access to the kind of screening undertaken during maternal or contraceptive care. In the case of CKD, this is also accompanied by generally worse kidney function as assessed through analysis of eGFR results. Based on this observation, more accessible screening for common conditions for individuals who are not receiving HIV care and services, or maternal and contraceptive services, could be put in place to ensure timely diagnosis of chronic conditions.

From this real-life data, this study provides insight into health service use patterns of PLHIV and HIV-negative individuals in the Khayelitsha subdistrict and based on the findings of this study it is possible to better understand this population. The current subpopulation that is ageing with HIV is such a small subset of survivors and this subset is most likely individuals who either did not get as physically ill from HIV prior to ART access or were infected later in life. Whilst it is possible to better understand this population, the changing landscape of ART access over the decades means that the ageing population of PLHIV now is not necessarily reflective of the

ageing PLHIV in the upcoming decades. We can, however, use the routine health data in an agile way to monitor and assess the unfolding needs of the ageing PLHIV going forward.

The routine health data used in this study are granular individual-level data that can be used to track linkage to care and continuity of care (Litofsky et al., 2014; Whittaker & Quint, 2020). Based on these routine health data, this study does not indicate strong associations between HIV and some comorbidities such as hypertension and diabetes; but accurately demonstrates the relationship between HIV and some comorbidities such as TB, CKD and cervical cancer as well-known from other sources and prior research (Assaram et al., 2017; Chambuso et al., 2017; Kubjane et al., 2022; Kwan & Ernst, 2011; Sonnenberg et al., 2005; Stelzle et al., 2021; Vachiat et al., 2013). It is worth noting that adherence to health service policy is reflected in the routine health data used in this study in terms of screening and laboratory testing for kidney function (National Department of Health, 2020), and this indicates that these data may be effective for evaluating and monitoring public health programmes, policies, and interventions especially in settings where resources available for monitoring and evaluation are limited.

7.3 Limitations of the study

Considering that these routine health data are only administrative data which do not contain clinical observational data and therefore not primarily intended for research purposes (Boulle et al., 2019), some important limitations exist when using these data. A major limitation in this study is bias in the whole study population which is enriched for PLHIV and HIV-negative individuals who may be accessing care for various reasons such as accessing maternal care or accessing care because of ill health due to TB or chronic NCDs. This means that physically healthy HIV-negative individuals may not be represented in this population. Considering that data are collected from public health facilities in the Western Cape province, there may be missing data due to people moving out of the province and due to the use of private healthcare facilities by some sectors of the population. This may also lead to bias in terms of the socioeconomic sectors of the population represented in this study, as private health care is normally accessed by higher socioeconomic sectors of the population. The routine health data used in this study had limited number of disease conditions ascertained by the PHDC and did

not include important comorbidities like cardiovascular diseases (CVD). PLHIV have significantly higher risks of CVD, for example myocardial infarction (Freiberg et al., 2013), heart failure (Freiberg et al., 2017), pulmonary hypertension, stroke (Chow et al., 2012) and sudden cardiac death (Tseng et al., 2012) than HIV-negative individuals and will be an important comorbidity to analyse for PLHIV when data become available (Feinstein, 2022; Hsue & Waters, 2018). There are also challenges related to data linkage due to poor record keeping at facilities, which might result in situations where records cannot be linked or improperly linked together (Harron et al., 2017; Mutemaringa et al., 2023). In South Africa, the administrative health record system is still developing. The electronic continuity of care record (eCCR) for the Western Cape province which is a computer application that integrates and standardises all necessary forms, which makes it easy to capture ICD codes, prescriptions and other important data before discharge is being piloted in Cape Town (Silber, 2014) and as the system improves and data mature, these challenges will become less.

7.4 Future research direction

As mentioned above, the analysis in this study only included data on disease conditions ascertained by the PHDC and excluded several important comorbidities related to HIV and also common among HIV-negative individuals like CVD. When data on these conditions become available, it would be important to repeat the analysis for this population of healthcare clients. When data are broadened to cover healthcare clients in private healthcare facilities it would similarly be useful to analyse these data to understand the profiles of these patients and assess how healthcare clients in public and private health facilities differ. Given the benefits of routine health data utilisation in understanding health access, service use and disease profiles, more research is needed to monitor any changes in the health needs of the population of PLHIV in South Africa as they age. It remains a challenge to intuitively visualise routine health epidemiological data and more collaborative research between epidemiology and data science is needed to visualise these important data.

7.5 Contribution to knowledge, policy, and practice

The findings of this study show that screening for common comorbid conditions, including laboratory testing, are generally being implemented for PLHIV and most likely for women of childbearing age accessing maternal and/or contraceptive care. The study has contributed to knowledge about the characteristics of the different sub-populations of PLHIV and HIV-negative individuals currently accessing healthcare in Khayelitsha, in the Western Cape province of South Africa. The study has demonstrated the pronounced differences in the assessed kidney function profiles of younger PLHIV when compared to younger HIV-negative individuals and older HIV-negative individuals and PLHIV. These data accurately reflect the implementation of kidney function screening guidelines and policies for PLHIV in government care in the Western Cape. This analysis suggests that these routine health data could be used to continue to assess the needs of the current young population of PLHIV as they age, especially given that universal access to ART can ensure long and generally health lives for this population going forward. Such ongoing assessments using these data provide an affordable way to provide evidence for future policy decision making to tailor care and services to the specific and evolving needs of Western Cape healthcare clients. The findings of this study underscore the need to re-align guidelines, programmes and interventions to a more patient-centered perspective that includes routine screening for common comorbidities such as the approach for patient-centered care for PLHIV and multimorbidity (Boyd & Lucas, 2014), the approaches to providing interdisciplinary patient-centered care at HIV diagnosis (Wells et al., 2022) and the person-centred HIV prevention service approach (Pantelic et al., 2018), as generalised and disease-specific approaches may not work for the whole ageing population of PLHIV. Importantly, this study has contributed to the knowledge on the usefulness of routine health data to address key epidemiological research questions about the current healthcare client population, and demonstrates that routine health data could be leveraged for conducting large scale studies in resource limited settings to support evidence-based approaches to health care in the Western Cape.

7.6 References

Assaram, S., Magula, N. P., Mewa Kinoo, S., & Mashamba-Thompson, T. P. (2017). Renal manifestations of HIV during the antiretroviral era in South Africa: A systematic scoping review. *Systematic Reviews*, *6*(1), 200. https://doi.org/10.1186/s13643-017-0605-5

Bock, P., Nel, K., Fatti, G., Sloot, R., Ford, N., Voget, J., Gunst, C., Grobbelaar, N., Louis, F., Floyd, S., Hayes, R., Ayles, H., Beyers, N., & Fidler, S. (2019). Renal dysfunction by baseline CD4 cell count in a cohort of adults starting antiretroviral treatment regardless of CD4 count in the HIV Prevention Trials Network 071 [HPTN 071; Population Effect of Antiretroviral Therapy to Reduce HIV Transmission (PopART)] study in South Africa. *HIV Medicine*, *20*(6), 392–403. https://doi.org/10.1111/hiv.12729

Boulle, A., Heekes, A., Tiffin, N., Smith, M., Mutemaringa, T., Zinyakatira, N., Phelanyane, F., Pienaar, C., Buddiga, K., Coetzee, E., Rooyen, R. van, Dyers, R., Fredericks, N., Loff, A., Shand, L., Moodley, M., Vega, I. de, & Vallabhjee, K. (2019). Data Centre Profile: The Provincial Health Data Centre of the Western Cape Province, South Africa. *International Journal of Population Data Science*, *4*(2), Article 2. https://doi.org/10.23889/ijpds.v4i2.1143

Boyd, C. M., & Lucas, G. M. (2014). Patient-centered care for people living with multimorbidity. *Current Opinion in HIV and AIDS*, *9*(4), 419–427. https://doi.org/10.1097/COH.0000000000000073

Brito, R. M., Nguyen, D. T., Johnson, J. R., Lai, E. J., Castro, R. E., Albert, A. M., Barnes, A. S., Graviss, E. A., & Suki, W. N. (2019). Chronic kidney disease in patients infected with human immunodeficiency virus (HIV) in an urban cohort. *PLOS ONE*, *14*(4), e0215575. https://doi.org/10.1371/journal.pone.0215575

Butler, I., MacLeod, W., Majuba, P. P., & Tipping, B. (2018). Human immunodeficiency virus infection and older adults: A retrospective single-site cohort study from Johannesburg, South Africa. *Southern African Journal of HIV Medicine*, *19*(1), 8. https://doi.org/10.4102/sajhivmed.v19i1.838

Chambuso, R. S., Shadrack, S., Lidenge, S. J., Mwakibete, N., & Medeiros, R. M. (2017). Influence of HIV/AIDS on Cervical Cancer: A Retrospective Study From Tanzania. *Journal of Global Oncology*, *3*(1), 72–78. https://doi.org/10.1200/JGO.2015.002964

Chow, F. C., Regan, S., Feske, S., Meigs, J. B., Grinspoon, S. K., & Triant, V. A. (2012). Comparison of Ischemic Stroke Incidence in HIV-Infected and Non–HIV-Infected Patients in a US Health Care System. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *60*(4), 351. https://doi.org/10.1097/QAI.0b013e31825c7f24

Feinstein, M. J. (2022). HIV, Subclinical Cardiovascular Disease, and Clinical Progression: Insights From Immunologic Heterogeneity. *JAMA*, *328*(10), 931–932. https://doi.org/10.1001/jama.2022.15226

Fenner, L., Atkinson, A., Boulle, A., Fox, M. P., Prozesky, H., Zürcher, K., Ballif, M., Furrer, H., Zwahlen, M., Davies, M.-A., & Egger, M. (2017). HIV viral load as an independent risk factor for tuberculosis in South Africa: Collaborative analysis of cohort studies. *Journal of the International AIDS Society*, *20*(1), 21327. https://doi.org/10.7448/IAS.20.1.21327

Freiberg, M. S., Chang, C.-C. H., Kuller, L. H., Skanderson, M., Lowy, E., Kraemer, K. L., Butt, A. A., Bidwell Goetz, M., Leaf, D., Oursler, K. A., Rimland, D., Rodriguez Barradas, M., Brown, S., Gibert, C., McGinnis, K., Crothers, K., Sico, J., Crane, H., Warner, A., … Justice, A. C. (2013). HIV Infection and the Risk of Acute Myocardial Infarction. *JAMA Internal Medicine*, *173*(8), 614–622. https://doi.org/10.1001/jamainternmed.2013.3728

Freiberg, M. S., Chang, C.-C. H., Skanderson, M., Patterson, O. V., DuVall, S. L., Brandt, C. A., So-Armah, K. A., Vasan, R. S., Oursler, K. A., Gottdiener, J., Gottlieb, S., Leaf, D., Rodriguez-Barradas, M., Tracy, R. P., Gibert, C. L., Rimland, D., Bedimo, R. J., Brown, S. T., Goetz, M. B., … Butt, A. A. (2017). Association Between HIV Infection and the Risk of Heart Failure With Reduced Ejection Fraction and Preserved Ejection Fraction in the Antiretroviral Therapy Era: Results From the Veterans Aging Cohort Study. *JAMA Cardiology*, *2*(5), 536–546. https://doi.org/10.1001/jamacardio.2017.0264

Geremew, D., Melku, M., Endalamaw, A., Woldu, B., Fasil, A., Negash, M., Baynes, H. W., Geremew, H., Teklu, T., Deressa, T., Tessema, B., & Sack, U. (2020). Tuberculosis and its association with CD4+ T cell count among adult HIV positive patients in Ethiopian settings: A systematic review and meta-analysis. *BMC Infectious Diseases*, *20*(1), 325. https://doi.org/10.1186/s12879-020-05040-4

Harron, K., Dibben, C., Boyd, J., Hjern, A., Azimaee, M., Barreto, M. L., & Goldstein, H. (2017). Challenges in administrative data linkage for research. *Big Data & Society*, *4*(2), 205395171774567. https://doi.org/10.1177/2053951717745678

Hopkins, K. L., Hlongwane, K., Otwombe, K., Dietrich, J., Cheyip, M., Khanyile, N., Doherty, T., & Gray, G. E. (2019). Demographics and health profile on precursors of non-communicable diseases in adults testing for HIV in Soweto, South Africa: A cross-sectional study. *BMJ Open*, *9*(12), e030701. https://doi.org/10.1136/bmjopen-2019-030701

Hsue, P. Y., & Waters, D. D. (2018). Time to Recognize HIV Infection as a Major Cardiovascular Risk Factor. *Circulation*, *138*(11), 1113–1115. https://doi.org/10.1161/CIRCULATIONAHA.118.036211

Isaguliants, M., Nosik, M., Karlsen, A., Petrakova, N., Enaeva, M., Lebedeva, N., Podchufarova, D., Laga, V., Gromov, K., Nazarov, A., Chowdhury, S., Sinitsyn, M., Sobkin, A., Chistyakova, N., Aleshina, S., Grabarnik, A., & Palefsky, J. M. (2021). Prevalence and Risk Factors of Infection with High Risk Human Papilloma Viruses among HIV-Positive Women with Clinical Manifestations of Tuberculosis in a Middle-Income Country. *Biomedicines*, *9*(6), 683. https://doi.org/10.3390/biomedicines9060683

Jose, S., Hamzah, L., Jones, R., Williams, D., Winston, A., Burns, F., Phillips, A. N., Sabin, C. A., Post, F. A., & UK CHIC Study. (2018). Chronic Kidney Disease Risk in African and Caribbean Populations With HIV. *The Journal of Infectious Diseases*, *218*(11), 1767–1772. https://doi.org/10.1093/infdis/jiy397

Kubjane, M., Osman, M., Boulle, A., & Johnson, L. F. (2022). The impact of HIV and tuberculosis interventions on South African adult tuberculosis trends, 1990-2019: A mathematical modeling analysis. *International Journal of Infectious Diseases*, *122*, 811–819. https://doi.org/10.1016/j.ijid.2022.07.047

Kwan, C. K., & Ernst, J. D. (2011). HIV and Tuberculosis: A Deadly Human Syndemic. *Clinical Microbiology Reviews*, *24*(2), 351–376. https://doi.org/10.1128/CMR.00042-10

Litofsky, N. S., Farooqui, A., Tanaka, T., & Norregaard, T. (2014). Use of the Electronic Health Record to Track Continuity of Care in Neurological Surgery Residency. *Journal of Graduate Medical Education*, *6*(3), 507–511. https://doi.org/10.4300/JGME-D-13-00294.1

Magodoro, I. M., Okello, S., Dungeni, M., Castle, A. C., Mureyani, S., & Danaei, G. (2022). Association between HIV and Prevalent Hypertension and Diabetes Mellitus in South Africa: Analysis of a Nationally Representative Cross-Sectional Survey. *International Journal of Infectious Diseases*, *121*, 217–225. https://doi.org/10.1016/j.ijid.2022.05.035

Manaye, G. A., Abateneh, D. D., & Niguse, W. (2020). Chronic Kidney Disease and Associated Factors Among HIV/AIDS Patients on HAART in Ethiopia. *HIV/AIDS - Research and Palliative Care*, *12*, 591–599. https://doi.org/10.2147/HIV.S276356

Mapesi, H., Kalinjuma, A. V., Ngerecha, A., Franzeck, F., Hatz, C., Tanner, M., Mayr, M., Furrer, H., Battegay, M., Letang, E., Weisser, M., Glass, T. R., & KIULARCO Study Group. (2018). Prevalence and Evolution of Renal Impairment in People Living With HIV in Rural Tanzania. *Open Forum Infectious Diseases*, *5*(4), ofy072. https://doi.org/10.1093/ofid/ofy072

Mendelsohn, S. C., Fiore-Gartland, A., Awany, D., Mulenga, H., Mbandi, S. K., Tameris, M., Walzl, G., Naidoo, K., Churchyard, G., Scriba, T. J., & Hatherill, M. (2022). Clinical predictors of pulmonary tuberculosis among South African adults with HIV. *EClinicalMedicine*, *45*. https://doi.org/10.1016/j.eclinm.2022.101328

Mollel, E. W., Maokola, W., Todd, J., Msuya, S. E., & Mahande, M. J. (2019). Incidence Rates for Tuberculosis Among HIV Infected Patients in Northern Tanzania. *Frontiers in Public Health*, *7*. https://www.frontiersin.org/articles/10.3389/fpubh.2019.00306

Mutemaringa, T., Heekes, A., Boulle, A., & Tiffin, N. (2023). Record linkage for Routinely Collected Health Data in an African Health Information Exchange. *International Journal of Population Data Science*, *In Press*. https://doi.org/10.23889/ijpds.v7i3.2022

Naicker, S. (2020). HIV/AIDS and chronic kidney disease. *Clinical Nephrology*, *93*(1), 87–93. https://doi.org/10.5414/CNP92S115

National Department of Health. (2020). *2019 ART Guideline Clinical Guidelines for the Management of HIV in Adults, Pregnancy, Adolescents, Children, Infants and Neonates* (pp. 1–26). Republic of South Africa National Department of Heath. https://sahivsoc.org/Files/2019%20ART%20Guideline%2028042020%20pdf.pdf

Pantelic, M., Stegling, C., Shackleton, S., & Restoy, E. (2018). Power to participants: A call for person-centred HIV prevention services and research. *Journal of the International AIDS Society*, *21*(S7), e25167. https://doi.org/10.1002/jia2.25167

Rajagopaul, A., & Naidoo, M. (2021). Prevalence of diabetes mellitus and hypertension amongst the HIV-positive population at a district hospital in eThekwini, South Africa. *African Journal of Primary Health Care & Family Medicine*, *13*(1), 2766. https://doi.org/10.4102/phcfm.v13i1.2766

Shen, T.-C., Huang, K.-Y., Chao, C.-H., Wang, Y.-C., Muo, C.-H., Wei, C.-C., Tu, C.-Y., Hsia, T.-C., Shih, C.-M., Hsu, W.-H., Sung, F.-C., & Kao, C.-H. (2015). The risk of chronic kidney disease in tuberculosis: A population-based cohort study. *QJM: An International Journal of Medicine*, *108*(5), 397–403. https://doi.org/10.1093/qjmed/hcu220

Silber, G. (2014). *Winner 1.2: Electronic Continuity Of Care Record*. Inside|Out. http://insideoutpaper.org/electronic-continuity-of-care-record-winner-1-2/

Sonnenberg, P., Glynn, J. R., Fielding, K., Murray, J., Godfrey-Faussett, P., & Shearer, S. (2005). How Soon after Infection with HIV Does the Risk of Tuberculosis Start to Increase? A Retrospective Cohort Study in South African Gold Miners. *The Journal of Infectious Diseases*, *191*(2), 150–158. https://doi.org/10.1086/426827

Stelzle, D., Tanaka, L. F., Lee, K. K., Khalil, A. I., Baussano, I., Shah, A. S. V., McAllister, D. A., Gottlieb, S. L., Klug, S. J., Winkler, A. S., Bray, F., Baggaley, R., Clifford, G. M., Broutet, N., & Dalal, S. (2021). Estimates of the global burden of cervical cancer associated with HIV. *The Lancet Global Health*, *9*(2), e161–e169. https://doi.org/10.1016/S2214-109X(20)30459-9

Tseng, Z. H., Secemsky, E. A., Dowdy, D., Vittinghoff, E., Moyers, B., Wong, J. K., Havlir, D. V., & Hsue, P. Y. (2012). Sudden Cardiac Death in Patients With Human Immunodeficiency Virus Infection. *Journal of the American College of Cardiology*, *59*(21), 1891–1896. https://doi.org/10.1016/j.jacc.2012.02.024

Vachiat, A. I., Musenge, E., Wadee, S., & Naicker, S. (2013). Renal failure in HIV-positive patients—A South African experience. *Clinical Kidney Journal*, *6*(6), 584–589. https://doi.org/10.1093/ckj/sft128

Vaes, B., Beke, E., Truyers, C., Elli, S., Buntinx, F., Verbakel, J. Y., Goderis, G., & Pottelbergh, G. V. (2015). The correlation between blood pressure and kidney function decline in older people: A registry-based cohort study. *BMJ Open*, *5*(6), e007571. https://doi.org/10.1136/bmjopen-2015-007571

Wells, N., Prestage, G., Murphy, D., Medland, N., Mao, L., Howard, C., Fairley, C., Brown, G., Philpot, S. P., Wells, N., Prestage, G., Murphy, D., Medland, N., Mao, L., Howard, C., Fairley, C., Brown, G., & Philpot, S. P. (2022). Patient-centred approaches to providing care at HIV diagnosis: Perspectives from healthcare and peer-support workers. *Sexual Health*, *19*(5), 448–455. https://doi.org/10.1071/SH22052

Whittaker, H., & Quint, J. K. (2020). Using routine health data for research: The devil is in the detail. *Thorax*, *75*(9), 714–715. https://doi.org/10.1136/thoraxjnl-2020-214821

Yu, Z., Rebholz, C. M., Wong, E., Chen, Y., Matsushita, K., Coresh, J., & Grams, M. E. (2019). Association Between Hypertension and Kidney Function Decline: The Atherosclerosis Risk in Communities (ARIC) Study. *American Journal of Kidney Diseases*, *74*(3), 310–319. https://doi.org/10.1053/j.ajkd.2019.02.015