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Factors associated with late HAART initiation: A retrospective study of adults living with HIV in Gauteng Province, South Africa, 2016 to 2022

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TITLE

Factors associated with late HAART initiation: A retrospective study of adults living with HIV in Gauteng Province, South Africa, 2016 to 2022

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Science in Infectious Disease Epidemiology

Johannesburg, March 2024

DECLARATION

I, Logashnee Govender, declare that this research report is my own, unaided work. It is being submitted for the Degree of Master of Science in Infectious Disease Epidemiology at the School of Public Health, Faculty of Health Science, University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signature of candidate



Date: 29 March 2024

DEDICATION

I dedicate this research project to my husband, Vijaylyn Moodley, my son, Nehalyn, my daughter, Laira, and most especially to my angel baby boy whom I said "Goodbye" to before I got to say "Hello," during this MSc. To my dearest little family, thank you for your unconditional love, your constant support, your guidance BUT most of all for being my inspiration and my giving me purpose in this life. I am eternally grateful to my parents for their sacrifices and their role in my achievements.

ABSTRACT

The nationwide implementation of antiretroviral therapy (HAART) in South Africa (SA) has been in effect since 2005. Despite the improved access to HAART, there is a persistent trend of delayed presentation for Human Immunodeficiency Virus (HIV) care, resulting in increased premature mortality. Between 2010-2011 and 2014-2015, Gauteng Province (GP) reported the highest number of patients entering HIV care with CD4 cell counts of < 200 cells/mm^3, this being the benchmark for Advanced HIV Disease (AHD). This study therefore aimed to establish the prevalence of AHD in HAART naïve adults entering the HIV HAART programme between March 2016 and March 2022. The intention was to identify the factors associated with AHD at entry into HIV care and to assess the evolution of AHD before, during and after the COVID-19 vaccination era. The secondary data analysis entailed utilizing archived specimen data from the National Health Laboratory Service Corporate Data Warehouse (NHLS CDW). Logistic regression analysis was used to determine the associations between various factors and AHD, and time series analysis to visualise the trend of AHD over time. The multivariable logistic regression model was applied to determine factors associated with AHD and trend analysis was used to investigate the impact of COVID-19 on proportion of AHD patients starting ART.

Among the 859 152 individuals included in the analysis, the median age was 39 years [IQR 32-46], 64.8% were females, and 79.2% entered the HIV care programme from clinics. There was a consistent decrease in the proportion of patients entering care over time, from 19.4% in 2017 to 11.4% in 2021. The prevalence of AHD in patients initiating HAART for the first time in Gauteng Province ranged between 24% and 27% from March 2016 to March 2022. The COVID-19 pre-vaccination period showed an increase in median CD4 counts in some districts, while others remained stable or decreased slightly. Compared to 18–24-year age group, patients in the 35 to 49 age group had a higher odds (OR =1.57, [95% CI: 1.542-1.60], p value < 0.001) of presenting with AHD at HAART initiation. Compared to females, male patients had higher odds of AHD at HAART initiation (OR=2.06, [95% CI: 2.04-2.08], p value <0.001). Patients presenting for HAART initiation in the West Rand District had a higher odds of AHD (OR =1.11, [95% CI: 1.08-1.13], p value < 0.001) compared to Johannesburg Metro. Patients presenting to clinic facilities for HAART initiation had lower odds (OR =0.61, [95% CI: 0.60-0.62], p value < 0.001) of AHD than those at hospitals.

Limitations included missing and incorrect data, which resulted in data having to be excluded. Despite the nation-wide availability of HAART, the prevalence of AHD in Gauteng Province remained high, indicating the presence of barriers hindering access to readily available HIV treatment. Further research is required to identify the barriers experienced by patients with AHD in accessing HAART across all districts, with a focus on men. HAART programmes for men need to be prioritised to encourage them to test and treat for HIV timeously. The results highlight the significant effects that pandemics and unexpected adverse events can have on people living with HIV.

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LIST OF ACRONYMS

AHD	Advanced HIV disease
AGYW	Adolescent Girls and Young Women
AIDS	Acquired immunodeficiency syndrome.
ART	Anti-retroviral treatment
BLR	Binary Logistic Regression
CCTM	Comprehensive care, treatment, and management
CDW	Corporate data warehouse
COVID-19	Coronavirus disease of 2019
CSV	Comma-separated values
FDC	Fixed drug combination
GP	Gauteng Province
HAART	Highly active antiretroviral treatment
HCW	Health Care Worker
HIV	Human immunodeficiency virus
HREC	Human research ethics committee
IDU	Injecting Drug Use
IRIS	Immune Reconstitution Inflammatory Syndrome
LIS	Laboratory Information system
LP	late presentation
MSM	Men who have sex with men.
NHLS	National Health Laboratory Service
PHC	Primary Health Care
PLWH	People Living with HIV
PCP	Pneumocystis Carinii Pneumonia
PTLC	Pre-Treatment Loss to Care
PITC	Psychologically Informed Consultation and Training
UN	United Nations
SES	Socio-economic Status
SEI	Socio-economic Index
SA	South Africa
SSA	Sub-Saharan Africa
TB	Tuberculosis
VCT	Voluntary Counselling and Testing
WHO	World Health Organization

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CHAPTER 1. INTRODUCTION

1.1 BACKGROUND

In 2010 31.5 million and in 2020, 37.8 million [1] individuals globally were living with HIV, which had increased to 39 million by 2022 [1], with 680 000 and 630 000 AIDS-related fatalities in 2020 and 2022 respectively [1], and approximately 40.4 million deaths due to HIV related illnesses since the start of the epidemic [2]. South Africa had approximately 7.6 million people living with HIV in 2022 [3] with an estimated 85 796 deaths [2], and as of March 2023, more than 5.7 million people were on treatment [4].

The 90–90–90 treatment target framework developed by the United Nations Program of HIV and AIDS (UNAIDS) stipulated that 90% of people living with HIV should know their HIV status by 2020 (Target 1), 90% of whom should be receiving sustained treatment (Target 2), 90% of whom should achieve viral load suppression (Target 3) [5]. However, as of July 2022, South Africa had not met targets 2 and 3. The 2022 UNAIDS statistics indicated that the country had achieved 94%, 75% and 69% of the targets respectively [6]. The 90-90-90 targets were recently increased to 95-95-95, these needing to be met by 2025 [7], the early access to HIV treatment reducing the viral load leading to a reduction in transmission and a reduced risk of morbidity and premature mortality [5].

Studies done in sub-Saharan Africa have shown that many patients access care late in the course of their illness, and present for HAART initiation only when they have symptoms of HIV [8]. In 2020, 55% of South African people living with HIV (PLWH) were only diagnosed when the disease was advanced [(Advance HIV Disease) (CD4 cell count < 200cells/mm^3)], while 31% were diagnosed late (CD4 cell count < 350 cells/mm^3) [9]. These high percentages of advanced and late diagnosis were noted despite the national roll-out of HAART since 2005 [10].

Gauteng Province in South Africa had the largest proportion (25.8%) of the South African population from 2002 to 2019, due in part to the high influx of migrant populations from other provinces and countries as a result of it being the country's economic hub [10]. Gauteng has remained the province with the highest proportion of the country's population as of October 2023 [11]. Research by Kim and colleagues identified Gauteng as the province with the highest HIV prevalence and number of PLWH in 2016 [12]. As of November 2023, KwaZulu-Natal Province had the highest prevalence of HIV in the country [13]. Analyses of the National

Health Laboratory Services (NHLS) data from the periods of 2010-2011 and 2014-2015 by Coetzee et al. revealed that of all the CD4 cell count tests that were done, Gauteng Province had the highest average proportion of patients with CD4 cell counts that were below 200 cells/mm³ (Advanced HIV Disease) [14]. Moreover, Kufa et al.'s investigation into CD4 cell count recovery among PLWH initiating Highly Active Anti-Retroviral Treatment (HAART) from 2010 to 2014 found that Gauteng reported the lowest median CD4 cell counts at entry into HIV care [15]. Given the high population density and significant migrant influx, Gauteng is a crucial region for targeted HIV interventions in South Africa.

Since 2009, late presentation for HIV care was defined as being diagnosed or presenting for care with CD4 cell counts of < 350 cell/mm^3 [16], while advanced HIV disease was defined a count of < 200 cell/mm³ or having an AIDS defining illness [16,17]. Early engagement in care is essential for both extending life expectancy and enhancing the quality of life for PLWH. However, despite the free and widespread availability of HIV treatment in South Africa, it is a concern that individuals are not initiating HIV treatment promptly.

In the absence of knowing the nature and extent of the AHD in PLWH in Gauteng, it is not possible to reduce the burden of HIV at an individual level and as a country as a whole. This study therefore aimed to identifying those factors associated with AHD with the intention of implementing age and gender relevant interventions where required, in addition to the districts and facilities. The results of the study are anticipated to identify areas of intervention, thus potentially decreasing the overall burden of HIV-related mortality and morbidity on both an individual and population level throughout the country. In addition, the study intended understanding to what extent the SARS-CoV-2 pandemic had any effect on HAART naïve patients with AHD presenting for HIV care.

1.2 LITERATURE REVIEW

This section reviews the local and international literature related to the prevalence of advanced HIV at HAART initiation among People Living with HIV (PLWH), if HAART initiation differed before, during and after the COVID-19 pandemic, and the factors associated with advanced HIV and HAART initiation in adults.

1.2.1 Prevalence of advanced HIV at HAART initiation among People Living with HIV

Kitenge et al. conducted a systematic review and meta-analysis of South African studies pertaining to the prevalence and trends of AHD in both HAART naïve and experienced patients [18]. The prevalence of AHD amongst HAART naïve patients between the period of 2010 and 2022 was 43.45%, however the time series analysis showed a 2% decline per year [18].

1.2.2 Difference in HAART initiation before, during and after the COVID-19 pandemic

The Coronavirus disease 2019 is an acute respiratory virus illness caused by the severe acute respiratory syndrome-related coronavirus 2 (SARS-Co-V-2). The virus was first detected in China in December 2019 and spread to other countries, resulting in a worldwide pandemic. The World Health Organisation declared a Public Health Emergency of International Concern (PHEIC) on the 30 January 2020 [19]. The pandemic affected health services worldwide, with global reports of reduced HIV testing following the implementation of COVID-19 protocols, which drastically reduced people's ability to access health services due to transport restrictions, leading to a decline in diagnosis and subsequent referrals for HAART [20]. Across Africa and Asia, there was a decrease of 41% and 37% in HIV testing, diagnosis, and treatment, respectively, during the initial COVID-19 lockdowns in 2020 [20]. Voluntary Medical Male Circumcision (VMMC), a measure known to reduce the female-to-male sexual transmission of HIV by 60%, dropped by 27%. Similarly, the percentage of mothers receiving prophylactic medication to prevent vertical transmission of HIV to the newborn decreased by 4.5% in 12 African nations [20,21].

In South Africa, increased mortality, mental health issues and substance abuse are some of the issues that impacted on the health system due to the COVID-19 pandemic [22]. The South African health care system also witnessed a decrease in HIV testing by 47.6% in April 2020, and the decline in weekly HAART initiations from 571 to 375 post-lockdown [21]. The high mortality rate of healthcare workers (HCWs) due to COVID-19 infection compromised HIV care services even further [20].

COVID-19 did not only impact HIV care services, with concurrent research from England and South Africa demonstrating elevated mortality rates of PLWH due to COVID-19 [20,23,24]. Patients with AHD exhibited a higher likelihood of mortality from COVID-19 upon

hospitalization than those who are HIV infected but do not have AHD, as evidenced by the analysis of South African cases [23]. Furthermore, patients with AHD potentially exhibited a reduced immune response to the vaccinations [25]. There was also evidence of more virulent strains of SARS-CoV-2 in patients with AHD than in those who were HIV infected but did not have AHD [26]. Tsygankova et al. found that while the mortality rate secondary to COVID-19 infection in AHD was 31%, the rate in those who were newly diagnosed was 45.5% [27].

The pathophysiology of SARS-CoV-2 involves the development of a lymphopenia, which is associated with a decrease in the CD4 cell count [28,29]. Lower CD4 T and CD8 T cells were associated with more severe disease and poor prognosis, hence in people with an existing low CD4 cell count as in AHD, this could mean an increased severity of infection and a poor outcome [28].

Given the disruption in HIV testing, the measures put in place to combat COVID-19 may have resulted in people presenting to care late, and thereby increase the percentage with AHD during the pandemic period. This study sought to compare the percentage of PLWH with AHD at entry into care before the pandemic, with those during and after the COVID-19 vaccination period.

1.2.3 Factors associated with advanced HIV and HAART initiation in adults

Various local and international studies have identified factors associated with the AHD entry into HIV care, with a combination of patient and health system factors being noted. Some studies defined late presentation as presenting for HIV care with CD4 cell count of less than 200cells/mm^3 [30], others used a benchmark of less than 350cells/m^3 [31,32,33] The different definitions of AHD with respect to the CD4cell count was as per the WHO definitions at the time the study was conducted. Bedert et al. identified two broad categories of factors, these being psychosocial and health system related. [34] We identified a host of both health system and patient factors that were associated with AHD and HAART initiation. Whilst dissatisfaction with the healthcare provider was noted an associated factor for AHD [34,35], other factors related to health care service provision were also noted. Such factors included not being tested at the healthcare facility [34], despite presenting numerous times for health care. Stigmatization and discrimination [35,36], fear of lack of confidentiality [36] were some of the concerns experienced by HIV positive patients presenting for HAART with AHD. Age was found to be associated with HAART initiation in AHD in numerous studies, in particular those

patients in the 50 years and older age group [32,33,34,37,38,39]. This was followed by 24 years and older age group [30,37,40]. With respect to gender, being male were more likely to associated with AHD and HAART association [19,23,24,25,28] [30,32,33,35,38] though females were also associated factors in some studies [32,34,37]. Whilst men who have sex with men (MSM) was an associated factor [40], heterosexual people were also noted to be an associated factor with HAART initiation in AHD [32,34,38]. Time at presentation for HAART initiation also played a role, as patients who presented 6 months or more after being diagnosed with HIV were more likely to have AHD than those who presented within 6 months of being diagnosed [31]. While there was no clear association between race and AHD entry into care, four of the studies identified migrants as patients who were more likely to be affected [30,32,71]. The three of the four studies conducted in Europe found that migrants of Sub-Saharan African descent in particular were more likely to have AHD [30,32,71]. Whilst locally in Lephalale, King et al analysed CD4 cell counts to establish the burden of AHD in this industrial hub.[70] Community survey and census data established that a significant number of migrants resided in Lephalale with an excessively high number of males compared to females. Even though the median CD4 cell count had increased during the study period, males persistently had the lower median CD4 cell counts compared to females.[70] These findings were largely suggestive that the migrant population was an associated factors with AHD. Co-morbidities such as diabetes [30] and tuberculosis [37] were also documented associated factors and importantly, not having previously tested for HIV was also associated with AHD when initiating HAART [31,37,40]. Those who were newly diagnosed at a hospital facility were more likely to have AHD when presenting for first time HAART initiation [38]. Our study focused on both patient factors (age and gender) and health system factors (type of facility and district) with regards to AHD and HAART initiation in HAART naïve patients.

1.4 PROBLEM STATEMENT

Despite the national availability of HAART in South Africa, patient outcomes differ across facilities, districts, and provinces due to late presentation for commencement of HAART, which is associated with a high mortality rate. The problem of AHD at entry into HIV care could have been worsened during the COVID-19 pandemic, as evident by decrease in HAART initiations [20]. Multiple factors have been associated with the elevated likelihood of late-stage HIV disease presentation, including geographic distance to the testing site, competing healthcare demands, work obligations outside of home, perceived barriers to health services, and suboptimal emotional health [35]. Migrant status [30, 22], illiteracy and advanced age have also been identified as contributing factors [42]. Clinical indicators, such as missed diagnostic opportunities, inadequate screening, circumstances of diagnosis and disease staging [43] play a role, alongside demographics such as pregnancy, women over 40 years and a history of physical abuse [41]. Moreover, individuals experiencing high-HIV related stigma demonstrated a higher likelihood of AHD at presentation for HAART [35]. In the absence of knowing the prevalence of and factors associated with advanced HIV (CD4 cell count < 200cells/mm^3) at HAART initiation in adults living with HIV in Gauteng Province, South Africa, from March 2016 to March 2022, it will not be possible to improve the quality of life of those affected, decrease the associated morbidity and mortality, and reduce the economic burden on the health system.

1.5 JUSTIFICATION

Statistics from 2022 revealed that South Africa has approximately 7.6 million PLWH [4] and an estimated 85 796 HIV/AIDS related deaths [3]. While more than 5.7 million people were on HAART as of March 2023 [5], a South African study conducted between 2010 and 2021 showed that that prevalence of AHD in HAART naïve patients was 43.5% [18]**.** Despite increasing access to treatment, the number of people with AHD at the time of diagnosis remains high. In addition to a high mortality rate, AHD is also associated with increased health care costs. In South Africa, the mean monthly cost per patient varies with CD4 count: $31.61 for <100 cells/mm3, $12.78 for 101-350 cells/mm3, $12.65 for 351 -500 cells/mm3, and $11.93 for >500 cells/mm3 [44]. There is also increased risk of opportunistic infections, immune reconstitution inflammatory syndrome (IRIS), incomplete immune reconstitution, higher viral

reservoirs, higher inflammation, increased risk of AIDS-related and non-AIDS-related comorbidities in patients with AHD [45].

In South Africa, data for 2010-2011 and 2014-2015 revealed that Gauteng Province reported the highest average proportion of CD4 cell counts that were below 200 cells/mm^3 of all the CD4 cell counts test that were done [14], while in 2016 it had the highest density of HIV prevalence and PLWH [12]. In addition, the CD4 cell count recovery among PLWH initiating HAART from 2010 to 2014 who had the lowest median CD4 cell counts was from Gauteng [15].

Patients with AHD had a higher risk of mortality from COVID-19 upon hospitalization [23, 46], with the SARS-CoV-2 virus causing lymphopenia in patients with AHD [28,29]. To further exacerbate the problem of the decreased CD4 cell count, people with AHD had significantly lower anti-spike antibody rates after being vaccinated for COVID-19 [25, 47]. The onset of the COVID-19 pandemic in South Africa led to a significant decrease in HIV diagnosis and HAART initiation and was associated with a significant decline in national testing volumes in 2020/21 compared to the previous year.

1.6 RESEARCH QUESTION

What was the prevalence of AHD and what were the factors associated with having advanced HIV disease at HAART initiation among adults living with HIV in Gauteng Province, South African, from March 2016 to March 2022?

1.7 AIM

To investigate the prevalence of and factors associated with advanced HIV (CD4 cell count <200cells/mm^3) at HAART initiation in adults living with HIV in Gauteng Province in South Africa from March 2016 to March 2022**.**

1.8 OBJECTIVES

1. To determine the prevalence of advanced HIV at HAART initiation among People Living with HIV (PLWH).
2. To determine if HAART initiation in patients with advanced HIV disease differed in the periods before, during and after the COVID-19 pandemic state of disaster alert levels.

3. To determine the factors associated with advanced HIV disease among adults initiating HAART.

1.9 STUDY STRUCTURE

This study is presented in the following four chapters:

Chapter 2. Methodology: this chapter details the methods used to conduct the study and address the three objectives. It details the study design, setting and sample, data collection process as well as the analysis and ethical considerations.

Chapter 3. Results: this chapter presents the results of the data analysis done to address the three study objectives, including regression analysis.

Chapter 4. Discussion: this chapter discusses the implications of the study results and compares them to local and international studies.

Chapter 5. Conclusion: this chapter addresses the extent to which the problem was addressed, and the Aim achieved by reviewing the findings for each of the three objectives. It notes the limitations that may have affected the results and presents recommendations for practice and research.

CHAPTER 2: METHODOLOGY

2.1. INTRODUCTION

The study methods are detailed with respect to the three objectives (Table 2.1), this chapter outlining the study design, setting, that being Gauteng Province, South Africa,

2.2 STUDY DESIGN

The study was a retrospective analysis of secondary data that is routinely collected by the South African National Health Laboratory Services (NHLS). The study included HIV positive adults (18 years or older), who initiated HAART for the first time in Gauteng from March 2016 to March 2022.

2.3 STUDY SETTING

The NHLS is the largest diagnostic pathology service in the South African public health care sector, providing services to over 80% of the population in all nine provinces [48]. The laboratory plays a vital role in many programmes, one of them being The National Antiretroviral roll-out programme through CD4 cell count testing, viral load studies and HIV Treatment Monitoring, which was implemented in 2005. More than 38 million CD4 cell count tests have been done since then, with approximately 3.5 million being conducted per annum [49]. In 2019/2020 and 2020/2021, approximately 600 000 and 500 000 CD4 cell test counts were conducted respectively in Gauteng [48,50], with eight of the 47 CD4 cell testing facilities across the country being located in the province [48,50].

HIV counselling and testing (HCT) provides an entry point to HIV treatment, care, and support [51], with the HIV test being a point of care rapid test that is done at the clinic level [51]. Those who test HIV-positive on a rapid screening test should have a second confirmatory HIV test using a second rapid testing device, a positive outcome resulting in the patient being confirmed to be HIV infected [51]. The cell counts (CD4 cell count and VL) are done on the day of the HIV infection confirmation when the patient consults with the HCW at the health care facility [52]. A blood specimen is collected from the patient and sent via courier to NHLS. If the laboratory is attached to a district hospital, the sample is analyzed and CD4 result generated, and if not, the sample is registered and referred to a CD4 laboratory. The sample is then received as a referral, analyzed and the CD4 result generated [52]. All patient results are made available to HCW via the online NHLS Trakcare service [53], the CD4 cell testing instruments

being interfaced through a digital Laboratory Information Systems (LIS) [49, 53]. All sites across South Africa are connected through this LIS that automatically uploads data into a single data warehouse, the CDW, where raw test data is cleaned, transformed, and archived [49, 53].

2.4 STUDY SAMPLE

The study sample included all HIV-positive adults 18 years of age and older, presumed to have entered the Comprehensive Care Treatment Management (CCTM) programme for HIV for the first time between March 2016 and March 2022 in all five districts of Gauteng Province (Figure 2.1). The number of HAART initiations in adults living in Gauteng for the year 2014 was 223 080 [15].



Figure 2.1 The five districts that make up Gauteng Province [54]

The 2022 census survey reported that Gauteng Province has the highest population in South Africa at 15 099 422 [55]. The districts of City of Johannesburg, City of Tshwane, Ekurhuleni, Sedibeng, and the West Rand (Figure 2.1) are home to 4 803 262, 4 040 315, 4 066 691, 1 190 687 and 998 466 people, respectively [56]. Males comprised 50.5% while females made up the

remaining 49.5% [56]. As of 2022, Gauteng had a total of 369 primary health care clinics, with 116 in the CoJ, 73 in CTM, 93 in EKM, 38 in Sedibeng and 49 in the West Rand [57].

Test data from 859 152 unique individuals were analysed, with Figure 2.2 outlining the final sample determination. Data was only included if information was available on the patients CD4 count and their viral load. Data was separately collected for viral load (VL) and CD4 count CD4), after which it was checked for duplication. The VL and CD4 data were stored as string variables and converted into numerical variable (destringing) so that we could perform our analysis. Destringing, de-duplicating and removing patients who were in special studies, for which data was excluded, resulted in a total 6 376 6980 records. Of the 7 425 737 records originally identified for viral load analysis, the process resulted in 1 048 757 remaining, and of the 3 399 295 identified for CD4 cell count analysis, only 2 485 644 remained. We identified unique individuals with first ever VL and CD4 cell count done and excluded all others, with a resultant 854 844 and 913 651 in the VL and CD4 cell count datasets, respectively.

Missing gender data were excluded, with 843 4230 remaining in the VL dataset and 899 306 in the CD4 cell count dataset. The VL and CD4 cell count datasets were then merged into one set with a total of 1 742 729, and after excluding missing facility data, 1 462 368 remained. Unique individuals that had a CD4 cell count with at least one VL test done 5 to 15 months later were identified, and we excluded those that did not have a CD4 cell count with a corresponding VL 5 to 15 months later, the final sample size being 859 152.

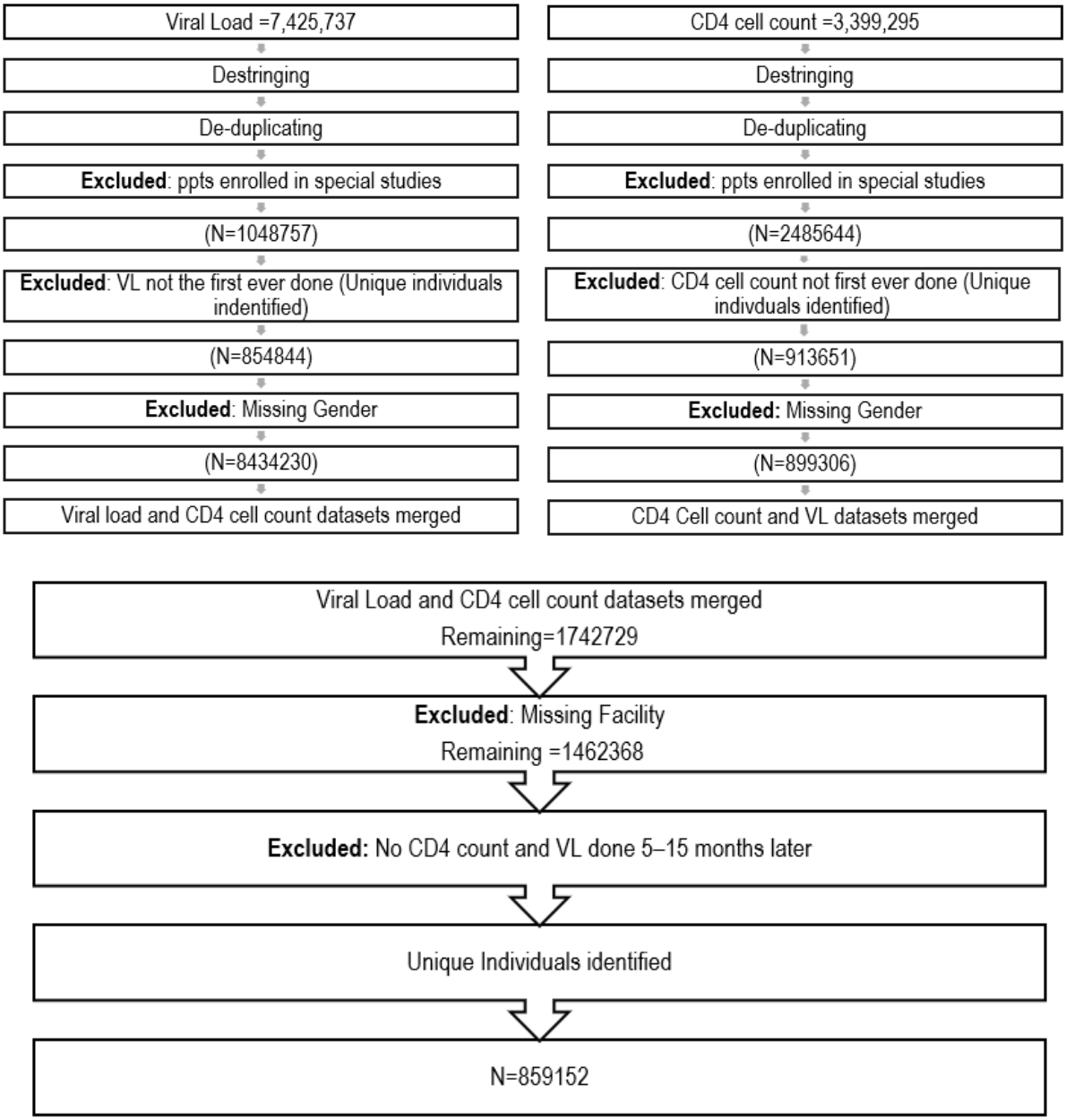

Figure 2.2 Data collection process

2.5 DATA COLLECTION

Specimen data archived in the NHLS CDW was utilized in this analysis, the data for each objective being indicated in Table 2.1 Objectives 1 data related to the prevalence of AHD, while Objective 2 was more focused on the association between AHD and the COVID-19 periods. Both sets of data were used for Objective 3. The test data was provided by the CDW in a CSV file and imported into the analysis software Stata® [version 17.0, College Station, Texas, USA]. Data cleaning was done by initially checking the completeness of the data using descriptive commands, the data fields being examined separately for errors and missing values, then checking for duplicate test records or entries. If two or more test records had the same age and CD4 cell count with the accompanying viral load (VL) it was considered as a potential duplicate and removed from the dataset. From the test records (episodes), individuals were identified based on their patient identity numbers that were generated and assigned by the CDW based on the likelihood of them belonging to the same patient (probabilistic record linkage). Each person had to have had at least one CD4 cell count with at least one or two viral loads done 5 - 15 months after the initial CD4 count to be included in the study. This was based on the assumption that the entry into HIV care was done as per the 2016 HIV South African treatment guidelines, which stipulated that CD4 counts were to be done at treatment initiation and at 12 months if the entry level count was < 200 cells/mm³. Further CD4 counts are not routinely done but are recommended if patients re-enter after disengaging from care and if there is a suspected immunological or clinical failure. VL are done at six and 12 months and then annually, hence those with just a VL or a CD4 cell count without a corresponding VL done 5 - 15 months later were removed, as they were regarded as already being in the system, and not a newly entered care. From the multiple test data, individuals having their first ever CD4 count in the study period were identified for inclusion.

2.5.1 Variables

a. Demographic characteristics

The demographic data used for this study consisted of age, (18 years and older) and gender (males and females). in the age groups 18-24 years, 25 to 34 years, 35 to 49 years and 50 + years accounted for 9%, 33.6%, 43.1% and 14.2%, respectively. Female patients comprised 64.8% of the total population, while male patients were the remaining 35.2%.

b. Objective 1

The variables used to address Objective 1 were median CD4 cell count and various demographic details. After determining the first ever CD4 count done for each person, the remaining counts were not included in the analysis. The exposure demographic variables (age, facility, gender, district, and COVID-19 period) associated with the first ever CD4 count were recoded and re-categorized where necessary. Individuals with unspecified or missing gender or facility type were not included in the analysis. The outcome variable was a numerical variable (CD4 counts at entry), which was further classified as binary i.e., whether or not the patient entered HIV care at an advanced stage of HIV, as identified from this first ever CD4 count. AHD entry into care was defined as having a CD4 cell count of < 200 cells/mm^3 at entry and was determined as an eligible first ever CD4 count. Non-advanced HIV entry into care was defined as a CD4 cell count of 200 cells/mm^3 or more.

c. Objective 2

The variables accessed for this objective were the median CD4 count, the district and the COVID-19 period. The outcome variable (Advanced or Non-advanced HIV at entry into care) was analyzed with respect to the period of entry into the HAART programme i.e., pre COVID-19, COVID-19 pre-vaccination period or COVID-19 post vaccination period, to determine if the pandemic had had any influence on treatment initiation. The main exposure variables were the time, as measured by calendar years, and periods before, during and after the onset of the COVID-19 pandemic. Calendar years included each year from 2016 to 2022, with 2016 including individuals from March to December. The subsequent years, i.e., 2017 - 2021, each included individuals from January to December, whereas 2022 only included records from January to March. As the first case of the COVID-19 infection occurred in South Africa in March 2020, the time of entry into care was categorized into three time periods with respect to the COVID-19 pandemic: Pre COVID-19 (01 March 2016 - 01 March 2020), COVID19 pre-vaccination (02 March 2020 - 31 July 2021) and COVID-19 post- vaccination (01 (August 2021 - 01 March 2022).

Another key exposure variable was 'District' which indicated the geographical location of the facility where the patients first initiated HAART in Gauteng Province. The five districts of being the City of Johannesburg Metro (hereafter referred to as Johannesburg Metro), City of Tshwane Metro (hereafter referred to as Tshwane Metro), Ekurhuleni

Metro, Sedibeng, and West Rand Districts. Other exposure variables were age (18-24, 25-34, 35-49 and 50 years and above) gender (Female and Male) and type of facility, which described where patients initiated HAART for the first time, either a clinic or hospital.

c. Objective 3

The data used to address Objective 3 consisted of both data sets from Objectives 1 and 2 above, as well as a number of demographic variables.

2.6 DATA ANALYSIS

The analysis consisted of both descriptive and statistical components.

Table 2.1 Study Objectives and associated methods

Objectives		Methods
1	To determine prevalence of advanced HIV at HAART initiation among People Living with HIV residing in Gauteng Province from 2016 to 2022	Descriptive analysis Contingency Tables Chi-Square test of Independence
2	To determine if HAART initiation in patients advanced HIV disease differed in the periods before during and after the COVID-19 pandemic associated state of disaster alert levels	Descriptive analysis Time series analysis Binary Logistic Regression Contingency Tables Chi-Square test of Independence
3	To determine the factors associated with advanced HIV and HAART initiation in adults from 2016 to 2022 in Gauteng Province	Logistical regression Binary Logistic Regression Contingency Tables Chi-Square test of Independence

a. Objectives 1

Descriptive analyses were used to analyse all the variables, with medians and interquartile ranges being used to describe age and CD4 cell count at HAART initiation. Frequency and proportions were used for categorical variables such as gender, district, and facility. A time series analysis was also conducted to determine trends in monthly median CD4 cell counts over time. Kruskal-Wallis test used to compare the median CD4 cell counts.

b. Objective 2

Contingency tables were used to explore the relationship between each of the categorical independent variables i.e. age group, district, gender, facility type and the year and the binary dependent variable i.e. AHD or no AHD. They were also used to explore the relationship between the COVID-19 periods (pre-COVID-19, pre-vaccination, and post-vaccination) and the presence of AHD. After analysing each contingency table, Chi-square test of independence was applied to assess if the relationship between each of the categorical independent variables, i.e. age group, district, gender, facility type, year, and the binary outcome (AHD or No AHD) were statistically significant. The Chi-square test of independence was also used to assess if the relationship between each of the COVID-19 periods and the presence of AHD or not was statistically significant.

c. Objective 3

Logistic regression analysis was conducted to determine if calendar period or year was associated with advanced HIV, with HAART initiation being adjusted for the effect of all potential confounders. A second logistic regression was conducted to establish if there was an association between the time of HAART initiation as per COVID-19 periods and the outcome variable of AHD Since the lab dataset did not have many variables available, (i.e. age, sex, district, sub-district, facility)we used all available variables *a priori* in both models.

2.7 ETHICAL CONSIDERATIONS

Ethical approval was provided by the Witwatersrand Human Research Ethics Committee (HREC) prior to conducting the study (M220664) **(Appendix 2).** The protocol was also submitted to the Academic Affairs, Research and Quality Assurance office at the NHLS, the custodian of the NHLS CDW data. HREC approval was submitted to the NHLS CDW custodian after which access was granted to the relevant data. The data was assigned unique identity numbers that were linked to the individual or patient data by the CDW, this identifier being known as the patient episode number. As this was a retrospective data review, no permission was required from any of the individuals whose data was available on the database.

CHAPTER 3: RESULTS

3.1 INTRODUCTION

This chapter presents the results using descriptive statistics, graphical representations and various figures relevant to the quantitative data and is presented with respect to the three objectives once the population characteristics have been addressed. Contingency tables and chi-square tests were applied, which were clarified through their corresponding p-values that deemed the result significant if the p-value was less than 0.05. A Binary logistic regression (BLR) was used to determine the impact of various factors on the presence or absence of advanced HIV disease in HIV positive but HAART naïve patients in the pre-COVID-19, COVID-19 pre-vaccination period and COVID-19 post vaccination period.

3.2 DEMOGRAPHIC CHARACTERISTICS

The characteristics of the study population are presented in Table 3.1, which indicates that of the 859 152 patients, over one third (n=330 466, 38.5%) resided in Johannesburg Metro, and the two other metros of Tshwane and Ekurhuleni jointly accounting for 47.5% (n=408 237). The median age was 39 years (IQR 32-45), the largest age group being those 35-49 years old at 43.1% (n=357 205), followed by those 18-34 at 42.6% (n=353 047). Most of the patients were females (64.8%), and the majority initiated HAART for the first time via clinics (79.2%), their first point of contact with the health system. The number of those presenting for HAART initiation showed a consistent decrease over time, from 19.2% in 2016 to 3.1% in 2022. The numbers presenting for HAART initiation changed over the course of the COVID-19 pandemic, with three quarters (n=638 505, 74.3) being recorded during the pre-COVID-19 years, this decreasing during the height of the pandemic to 18% (n=154 797), and to 7.7% (n=65 850) once vaccinations were provided. Overall, there was no significant changes in the median CD4 count of the patients who initiated HAART between the pre-COVID-19 and the pre- and post-vaccination periods in the various districts **(Table 3.4).**

Table 3.1: Characteristics of the study population with AHD initiating HAART in Gauteng from March 2016 to March 2022 (n=859 152)

Variable	Characteristics	No. (%)
District	Johannesburg Metro	330 466 (38.5)
	Tshwane Metro	184 367 (21.5)
	Ekurhuleni Metro	223 871 (26.1)
	Sedibeng District	58 173 (6.8)
	West Rand District	62 275 (7.2)
Age (years)	**Median (IQR)**	**39 (32-46)**
	18-24	74 740 (9.0)
	25-34	278 307 (33.6)
	35-49	357 205 (43.1)
	50 and above	117 645 (14.2)
Gender	Female	556 466 (64.8)
	Male	302 686 (35.2)
Facility Type	Hospital	179 125 (20.8)
	Clinic	680 027 (79.2)
Study Period	2016	164 823 (19.2)
	2017	166 976 (19.4)
	2018	145 891 (17.0)
	2019	137 956 (16.1)
	2020	116 238 (13.5)
	2021	100 434 (11.7)
	2022	26 834 (3.1)
COVID-19 Period	Pre-COVID-19 (03/2016 – 03/2019)	638 505 (74.3)
	COVID-19 Pre-vaccination (03/2019-03/2020)	154 797 (18.0)
	COVID-19 Post-vaccination (03/2020-03/2022)	65 850 (7.7)

Table 3.2 presents the study population by district, while Table 3.3 illustrates the median CD4 count by district, those from Sedibeng having the highest median CD4 count at 394 cells/mm³ compared to the West Rand with a 356 cells/mm³ count (Table 3.3). Patients of the 18–24-year age group from the Tshwane Metro had a higher overall median CD4 cell count than all other age groups. Patients from the 34–49-year age group in the West Rand had the lowest median CD4 count, and female patients had higher median CD4 counts for all five districts than the males. Female patients from the Sedibeng District had a median CD4 cell count of 459, which was the highest overall, while male patients from the West Rand had the lowest median count. When comparing the median CD4 counts in each year from 2016 to 2022, patients presenting for HAART initiation in 2016 had the highest median counts compared to all the other years.

There were no obvious trends in median CD4 counts noted from 2016 to 2022 in the various districts. Compared to the COVID-19 pre- and post-vaccination periods, patients presenting for HAART initiation in the pre-COVID-19 period had the highest median CD4 count. An increasing trend in the median CD4 count was noted in the Johannesburg Metro, and a slight decrease was noted in Sedibeng from the Pre-COVID-19 to the post-vaccination era. No trends in the median CD4 count were noted in any of the other districts from the pre-COVID-19 to the vaccination eras. Overall, patients presenting to clinics for HAART initiation had higher median CD4 counts than those going to hospitals throughout all five districts.

Table 3.2 Description of Study Population by District *Variables with missing data

Variable	Category	Johannesburg Metro N= 330466 (38.5%)	Tshwane Metro N= 184367 (21.5%)	Ekurhuleni Metro N= 223871 (26.1%)	Sedibeng N= 58173 (6.8%)	West Rand N= 62275 (7.2%)
Median age (IQR)	39 (32-46)	39 (33-47)	39 (32-46)	37 (31-45)	39 (32-46)	40 (33-48)
Age Group*		N=313485	N=177411	N=219164	N=56919	N=60918
	18-24	26037 (7.9%)	16052 (8.7%)	21678 (9.7%)	5764 (9.9%)	5209 (8.4%)
	25-34	104097 (31.5%)	57346 (31.1%)	79797 (34.6%)	17961 (30.9%)	19106 (30.7%)
	35-49	139212 (42.1%)	76852 (41.7%)	90632 (40.5) %	24172 (41.6%)	26337 (42.3%)
	50+	44139 (13.4%)	27161 (14.7%)	27057(12,1%)	9022 (15.5%)	10266 (16.4%)
Gender						
	Female	216120 (65.4%)	119813 (65.0%)	144429 (64.5%)	35740 (61.4%)	40364 (64.8%)
	Male	114346 (34.6%)	64554 (35.0%)	79442 (35.5%)	22433 (38.6%)	21911 (35.2%)
Facility Type						
	Clinic	255671 (77.4%)	137880 (74.8%)	189454 (84.6%)	47017 (80.1%)	50005 (80.3%)
	Hospital	74795 (22.6%)	46487 (25.2%)	34417 (15.4%)	11156 (19.9%)	12270 (19.7%)
Year						
	2016	57760 (17.5%)	36247 (19.7%)	46044 (20.6%)	13526 (23.3%)	11246 (18.1%)
	2017	61803 (18.7%)	36985 (20.1%)	44806 (20.0%)	11788 (20.3%)	11594 (18.6%)
	2018	56014 (16.9%)	32179(17.5%)	37520 (16.8%)	9459 (16.2%)	10719 (17.2%)
	2019	54559 (16.5%)	29681 (16.1%)	35250 (15.7%)	8383 (14.4%)	10083 (16.2%)
	2020	47163(14.3%)	23385(12.7%)	29985(13.4%)	7146 (12.3)	8559 (13.7%)
	2021	42024(12.7%)	20230 (10.9%)	24127 (10.8%)	6158 (10.6%)	7895 (12.7%)
	2022	11143 (3.4%)	5660 (3.0%)	6139(2.7%)	1713 (2.9%)	2179(3.5%)
COVID-19 Period						
	Pre-COVID 19	239042 (72.3%)	139707(75.8%)	169694 (75.8%)	44784 (77.0%)	45278 (72.7%)
	Pre-vaccination	64100 (19.4%)	30816(16.7%)	39061 (17.4%)	9213 (15.8%)	11607 (18.6%)
	Post-vaccination	27324 (8.3%)	13844 (7.5%)	15116 (6.8%)	4176 (7.2%)	5390 (8.7%)

Table 3.3: CD4 cell count distribution across districts (N=859 152)

Variable	Category	Johannesburg Metro		Tshwane Metro		Ekurhuleni Metro		Sedibeng		West Rand	
		N	Median (IQR)	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)
All		330466	374 (186- 581)	184367	388 (196-6140	223871	369 (189-585)	58173	394 (203-616)	62275	356 (183-565)
Age	18- 24	26037	419 (253-612)	16052	447 (272-656)	21678	437 (267-640)	5764	446 (272-651)	5209	403 (241-587)
	25-34	104097	382 (206-587)	57346	404 (214-625)	79797	390 (209-603)	17961	410 (222-634)	19106	370 (195-578)
	35- 49	139212	361 (182-586)	76852	363 (173-590)	90632	339 (165-558)	24172	377 (186-603)	26337	343 (169-554)
	50+	44139	382 (203-592)	27161	387 (190-624)	27057	353 (175-575)	9022	381 (192-604)	10266	357 (186-563)
Gender	Female	216120	424 (235-632)	119813	440 (240-663)	144429	425 (234-640)	35740	459 (257-678)	40364	415 (228-623)
	Male	114346	291 (141-474)	64554	299 (136-506)	79442	279 (130-467)	22433	302 (143-494)	21911	265 (123-442)
Year	2016	57760	376 (195-575)	36247	400 (206-610)	46044	397 (213-601)	13526	432 (240-641)	11246	361 (185-561)
	2017	61803	368 (189-572)	36985	393 (201-612)	44806	380 (195-594)	11788	400 (212-622)	11594	337 (171-535)
	2018	56014	377 (199-583)	32179	379 (190-608)	37520	361 (182-577)	9459	383 (195-611)	10719	357 (186-566)
	2019	54559	360 (189-563)	29681	378 (191-599)	32550	344 (175-554)	8383	374 (190-587)	10083	358 (190-562)
	2020	47163	375 (199-588)	23385	386 (195-619)	29985	348 (176-562)	7146	365 (183-601)	8559	368 (183-580)
	2021	42024	395 (207-611)	20230	393 (192-644)	24127	369 (185-600)	6158	365 (181-603)	7895	362 (184-592)
	2022	11143	388 (197-614)	5660	382 (184-640)	6139	397 (192-636)	1713	398 (193-639)	2179	368 (190-595)
COVID-19 Period	Pre-COVID -19	239042	370 (193-573)	139707	388 (197-608)	169694	371 (192-583)	44784	401 (211-619)	45278	353 (182-556)
	COVID-19 Pre-vaccination	64100	386 (205-597)	30816	390 (195-630)	39061	355 (182-576)	9213	359 (180-594)	116607	371 (187-587)
	COVID-19 Post-vaccination	27324	392 (201-615)	13844	384 (185-644)	15116	379 (182-620)	4176	382 (184-630)	5390	357 (177-597)
FACILITY	Hospital	74795	361 (150-590)	46487	370 (140-645)	24417	242 (77-489)	11156	349 (133-580)	12270	279 (91-516)
	Clinic	255671	378 (207-579)	137880	393 (212-605)	189454	388 (213-597)	47017	403 (219-624)	50005	372 (205-574)

The median CD4 count is indicated in Figure 3.1 and shows that in 2016, at the start of the study, the level is slightly below 350 cells/mm³ and decreased slightly in the first 19 months (October 2017) during the pre-COVID-19 pandemic. The start of the pandemic at month 48 shows a slight peak in the median CD4 count, this changing in month 60 with the onset of the post-vaccination era.

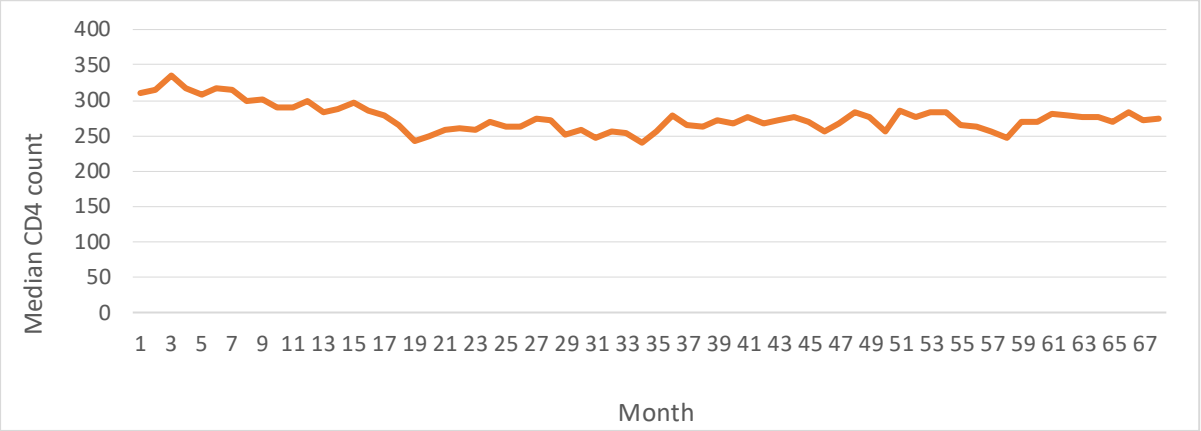

Figure 3.1 Time series of the monthly median CD4 count of the study population between 1 March 2016 and 31 March 2022

3.3 OBJECTIVE 1. PREVALENCE OF AHD IN ADULTS THAT INITIATED HAART

The prevalence of AHD in patients initiating HAART in Gauteng Province between 2016 and 2022 was 25.8% (n=221,732), with 74.2% of the patients presenting for first time HAART initiation (n=637 420) not having AHD. Figure 3.2 is an overview of the distribution of individuals with AHD of each year from 2016 to 2022 in Gauteng, with a slight increase in from 2016 (24.4%) to 2019 (26.9%), followed by a slight decrease for the remaining years from 26.9% in 2020 to 25.9% in 2022.

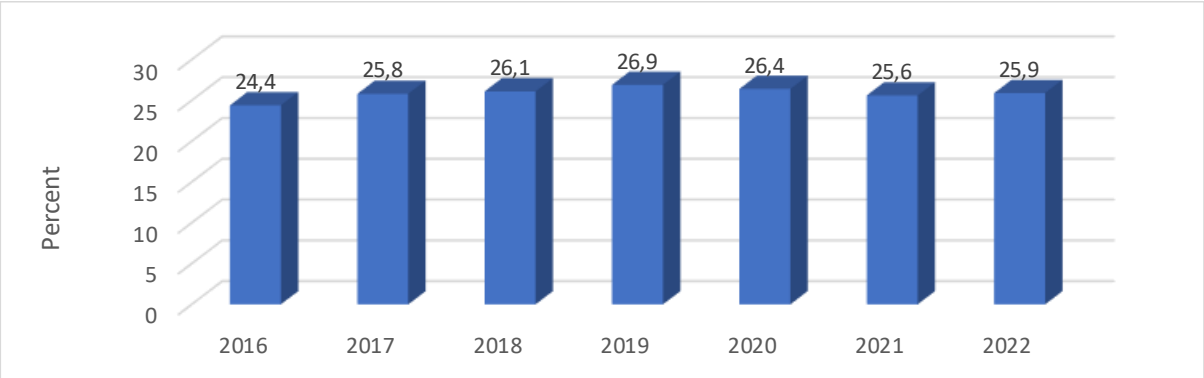

Figure 3.2: Percentages of AHD from 1 March 2016 to 31 March 2022 in Gauteng

3.4 OBJECTIVE 2. PROPORTION OF PATIENTS PRESENTING WITH AHD FOR HAART INITIATION IN EACH DISTRICT BEFORE THE COVID-19 PANDEMIC, AND BEFORE AND AFTER THE VACCINATION PERIOD

Table 3.4 shows that the proportion of HAART initiation across the three metros of Johannesburg, Tshwane and Ekurhuleni and the West Rand District stayed fairly consistent across the three time periods, varying less than 2%. The uptake of HAART increased over time in the Sedibeng District, starting at 23.6% pre-COVID-19 and increasing to 26.8% during the post-vaccination period. The West Rand District had the highest proportion with AHD initiating HAART in both the pre-COVID-19 and post-vaccination periods at 27.5% and 27.4%, respectively. There was a marginal decline in the proportion of patients with AHD initiating HAART in Johannesburg from 25.9% to 24.8%, a slight increase in Tshwane Metro from 25.3% to 26.8%, and no obvious trend in the Ekurhuleni Metro or the West Rand District. Overall, there were no significant differences in the proportion of patients with AHD initiating HAART in all five districts during the various time periods (Pre-COVID-19, COVID-19 Pre-vaccination and COVID-19 Post-vaccination). (**Table 3.4**)

Table 3.4: Percentages of AHD in each district by COVID-19 Period

Districts	Pre-COVID-19	COVID-19 Pre-vaccination	COVID-19 Post-vaccination	X^2 p-value
	No. (%)	No. (%)	No. (%)	
Johannesburg Metro	61 962 (25.9)	15 575 (24.3)	6 770 (24.8)	0.95
Tshwane Metro	35 355 (25.3)	7 891 (25.6)	3 710 (26.8)	0.97
Ekurhuleni Metro	44 242 (26.1)	10 783 (27.6)	4 105 (27.1)	0.96
Sedibeng District	10 566 (23,6)	2 589 (28.1)	1 120 (26.8)	0.95
West Rand District	12 434 (27.5)	3 099 (26.7)	17 064 (27.4)	0.94

3.5 OBJECTIVE 3. FACTORS ASSOCIATED WITH ADVANCED HIV AND HAART INITIATION

In the bivariate analysis (Table 3.5), factors associated with AHD HAART initiation were: the 35-49 year age group [OR 1.92, 95% CI 1.88 - 1.96 , p-value < 0.001] compared to the 18-24 year age group, males [OR 2.14, 95% CI 2.12 - 2.16, p-value < 0.001] compared to females, those in the West Rand District [OR 1.10, 95% CI 1.08-1.12 , p-value <0.001] and Ekurhuleni Metro [OR 1.05, 95% CI 1.04-1.06 , p-value <0.001] compared to the Johannesburg Metro, and in 2019 [OR 1.14 , 95% CI 1.12-1.16 , p-value < 0.001] compared to 2016. Patients presenting to the clinic for HAART initiation [OR 0.58, 95% CI 0.57-0.59, p-value < 0.001] were less likely to have AHD than those initiating at hospitals (Table 3.5).

In the multivariable analysis (Table 3.5), the odds of AHD in patients in the 35–49-year age group was 1.57 times higher that of those in the 18–24-year age group [aOR 1.57, 95% CI 1.54 - 1.61, p-value < 0.001]. Regarding gender, the odds of male patients initiating HAART with AHD were 2.06 times more than that of female patients [aOR 2.06, 95% CI 2.04 - 2.08, p value < 0.001]. Patients from the West Rand district were 1.11 times more likely to have AHD when initiating HAART than those from the Johannesburg Metro [aOR 1.11, 95% CI 1.09-1.13, p-value < 0.001].

The odds of patients having AHD were reduced by 39% if patients initiated HAART at clinics [aOR 0.61, 95% CI 0.60 - 0.62, p-value< 0.001]. Those presenting for HAART initiation in 2019 had the highest odds of AHD compared the year 2016 [aOR 1.16, 95% CI 1.14-1.18, p value, < 0.001) (Table 3.5). However, when compared to 2016, all other years had higher odds of patients presenting with AHD for HAART initiation, 2017 [aOR 1.08, 95% CI 1.06-1.10, p-value < 0.001], 2018 [aOR 1.10, 95% CI 1.08-1.16 p-value < 0.001], 2020 [aOR 1.11, 95% CI 1.03-1.16 p-value < 0.001], 2021 [aOR 1.07, 95% CI 1.05-1.08 p-value < 0.001] and 2022 [aOR 1.09, 95% CI 1.06-1.12 p-value < 0.001].

In the second multivariable logistic regression model (Table 3.6), patients presenting for HAART initiation in the pre-vaccination [aOR 1.01, 95% CI 0.99-1.02; p-value 0.45] and post-vaccination periods [aOR 1.00, 95% CI 0.98-1.01; p-value -0.84] had almost the same odds of patient presenting with AHD in the pre-COVID-19. There were no changes in association of the covariates in this model compared to the first model, which contained the calendar years.

Table 3.5: Factors associated with AHD and HAART initiation in Gauteng from 1 March 2016 to 31 March 2022, in calendar years

Variables	% with AHD	Unadjusted			Adjusted		
		Univariable OR	95% CI	p-value for univariable OR	Multivariable OR	95% CI	p-value for multivariable OR
Age (years)							
Reference = 18-24	17.1	1,00					< 0.001
25-34	23.8	1,51	1.48 - 1.54	< 0.001	1,42	1.39 - 1.45	< 0.001
35-49	28.4	1,92	1.88 - 1.96	< 0.001	1,57	1.54 - 1.61	< 0.001
50 and above	26.2	1,72	1.68 - 1.76	< 0.001	1,30	1.27 - 1.34	< 0.001
Gender							
Reference = Females	20.5	1,00					
Males	35.6	2,14	2.12 - 2.16	< 0.001	2,06	2.04 - 2.08	< 0.001
District							
Reference = Johannesburg	25.5						
Tshwane Metro	25.5	1,00	0.98 - 1.01	0.74	0,99	0.97 - 1.00	0.07
Ekurhuleni Metro	26.4	1,05	1.04 - 1.06	< 0.001	1,08	1.07 - 1.10	< 0.001
Sedibeng District	24.5	0,95	0.93 - 0.97	< 0.001	0,94	0.92 - 0.96	< 0.001
West Rand District	27.4	1,10	1.08 - 1.12	< 0.001	1,11	1.09 - 1.13	< 0.001
Facility Type							
Reference = hospital	34.5						
Clinic	23.5	0,58	0.57 - 0.59	< 0.001	0,61	0.60 - 0.62	< 0.001
Year							
Reference = 2016	24.4						
2017	25.5	1,08	1.06-1.10	< 0.001	1,09	1.07- 1.10	< 0.001
2018	26.1	1,10	1.08-1.16	< 0.001	1,10	1.09-1.12	< 0.001
2019	26.9	1,14	1,12-1,16	< 0.001	1.16	1.14-1.18	< 0.001
2020	26.4	1,11	1,09-1,13	< 0.001	1.13	1.10-1.15	< 0.001
2021	26.6	1,07	1,05-1,08	< 0.001	1.07	1.05-1.09	< 0.001
2022	25.9	1,09	1.06-1.12	< 0.001	1.07	1.04-1.10	< 0.001

Table 3.6: Factors associated with AHD and HAART initiation in Gauteng from 1 March 2016 to 31 March 2022 (COVID-19 Periods)

			Unadjusted			Adjusted	
	% with AHD	Univariable OR	95% CI	p-value for univariable OR	Multivariable OR	95% CI	p-value for multivariable OR
Age (years)							< 0.001
Reference = 18-24	17.1	1.00					
25-34	23.8	1,51	1.48 - 1.54	< 0.001	1,42	1.39 - 1.45	< 0.001
35-49	28.4	1,92	1.88 - 1.96	< 0.001	1,57	1.54 - 1.61	< 0.001
50 and above	26.2	1,72	1.68 - 1.76	< 0.001	1,30	1.27 - 1.34	< 0.001
Gender							
Reference = Females	20.5	1.00					
Males	35.6	2,14	2.12 - 2.16	< 0.001	2,06	2.04 - 2.08	< 0.001
District							< 0.001
Reference = Johannesburg	25.5						
Tshwane Metro	25.5	1,00	0.98 - 1.01	0,74	0,99	0.97 - 1.00	0,07
Ekurhuleni Metro	26.4	1,05	1.04 - 1.06	< 0.001	1,08	1.07 - 1.10	< 0.001
Sedibeng District	24.5	0,95	0.93 - 0.97	< 0.001	0,94	0.92 - 0.96	< 0.001
West Rand District	27.4	1,10	1.08 - 1.12	< 0.001	1,11	1.09 - 1.13	< 0.001
Facility Type							
Reference = hospital	34.5						
Clinic	23.5	0,58	0.58 - 0.59	< 0.001	0,61	0.60 - 0.62	< 0.001
Covid Period							
Reference=Pre COVID-19	25.8						
COVID-19 Pre-vaccination	25.8	1,00	0.99 - 1.01	0,84	1,01	0.99 - 1.02	0,45
COVID-19 Post-vaccination	26.2	1,02	1.00 - 1.04	0,02	1,00	0.98 - 1.02	0,84

CHAPTER 4: DISCUSSION

4.1 INTRODUCTION

This chapter discusses the implications of the results and reviews them with respect to local and international studies, related to the three objectives.

The decrease in AHD between 2016 and 2019 indicates that lack of sustained testing, which may vary between districts over time, but suggest the need for ongoing public health messaging about the disadvantages of late presentation. **Table 3.6** (Model 2) demonstrates the factors associated with AHD and HAART initiation in Gauteng from 1 March 2016 to 31 March 2022 with respect to the different COVID-19 periods.

The HAART uptake during the different COVID-19 eras shows the effect that lack of access to health services can have on testing, and the importance of not forgetting chronic conditions when crises arise due to the severe health implications for those who could be affected by severe morbidity and premature mortality if HIV services cannot be accessed. These figures are similar to those in other SSA countries, where HAART uptake declined considerably over the COVID-19 state of emergency and needs to be monitored to establish if the pre-COVID levels have been achieved.

4.2 Objective 1. Prevalence of AHD in adults that initiated HAART

The high prevalence of patients initiating HAART with AHD in Gauteng is concerning, these findings being similar to those of Carmona et al. in 2016, who predicted that 32.9% of patients initiating HAART in South Africa will do so with AHD [58]. In view of the freely available HAART in the public sector, but poor uptake, factors such as psycho-social, health system are likely to influence or deter patients from entering HAART programmes. HAART initiation programmes to encourage and increase early HAART commencement have been implemented in South Africa [59,60]. Such programmes include the MINA campaign [61], Multidisease National Wellness Campaign [59], and the Undetectable=Untransmissible (U=U) campaigns [60] launched in 2020, 2018 and 2022, respectively.

Some of the reasons for patients initiating HAART with AHD that were noted in the review of the literature included not being aware of their HIV status [62], lack of clinical symptoms, lack of testing due to the stigma attached to being diagnosed with HIV [33,35], delays in the diagnosis of HIV [31], non-disclosure of previous HAART use, and disengagement from care. In South Africa, suggested interventions included improving HIV testing approaches, using the

WHO recommended oral self-testing kits, implementing community-based testing, especially for men, and promoting HIV testing programmes in school for younger males [61].

The MINA (an isiZulu word meaning "I" or "Me") campaign is aimed at encouraging men to access HIV testing, ensure linkage of HIV treatment, and provide support groups and counselling [61,63]. This campaign was part of an effort to decrease HIV infection and promote healthy living in men diagnosed with HIV and has been implemented across 400 public health facilities in South Africa [63]. Prioritising HIV programmes for males was recommended in international studies, [32] such as implementing interventions described in the Centre for Disease Control (CDC) Serostatus Approach to Fighting the HIV Epidemic (SAFE) initiative [31]. SAFE is a programme being aimed at HIV infected persons, including those currently unaware of their serostatus, and who have been tested and found to be uninfected but are considered high risk [64].

The five SAFE principles are based on the following: (1) increase the number of HIV-infected persons who know their serostatus; (2) increase the use of health care and preventive services; (3) increase the availability of high-quality care and treatment; (4) increase adherence to therapy by individuals with HIV, and (5) increase the number of individuals with HIV who adopt and sustain HIV–STD risk reduction behaviour [64]. As AHD is associated with a high rate of mortality and morbidities, it is essential that men be tested and treated early in the disease, our current study figures showing that they only account for one third of those tested. Our study found that although the proportion of males initiating HAART was less than that of females, they were more likely to present with AHD when initiating HAART than females. Policy makers should focus on establishing the challenges and barriers experienced by males in accessing HIV treatment, specifically early in the disease, to ensure that they are able to access regular HIV testing timeously.

Some of the existing disease management measures in South Africa include policies that do not require parental consent for HIV testing in children aged 12 and above. Policies also encourage community-based approaches, such as mobile outreach campaigns and events, workplace, and home-based testing, as well as testing in educational settings and places of worship [65]. Community approaches increase early diagnosis by reaching first-time testers and people who seldom use clinical services, such as men. Furthermore, the South African Pharmacy Council (SAPC) has approved over-the-counter distribution and use of HIV self-test

kits [66]. Health care workers are encouraged to provide the necessary post-test counselling if patients self-test and the results are positive [66]. While Gauteng is known to have the highest influx of migrants in the country, [10] refugees and asylum seekers are entitled to free primary healthcare services, such as access to free HAART, and should be encouraged to do so without prejudice by health care workers [65]. Migrant status was also noted as an associated factor for patients initiating HAART with AHD in some European countries. This factor needs to be investigated in Gauteng and across South Africa, given its large migrant population [10]. This is because some studies have found migrant status of SSA descent to be an associated factor with HIV infection itself and not just AHD [71]. Access to HAART based on nationality should therefore not be a limiting factor for migrants in South Africa.

4.3 OBJECTIVE 2. PROPORTION OF PATIENTS PRESENTING WITH AHD FOR HAART INITIATION IN EACH DISTRICT BEFORE THE COVID-19 PANDEMIC, AND BEFORE AND AFTER THE VACCINATION PERIOD

A significant decline in percentage of patients with AHD presenting for HAART initiation from the pre-COVID-19 to the post-vaccination period was noted in the results, together with a consistent decrease in the number of patients over time, from 19.4% in 2017 to 11.4% in 2021, which may be due to the large sample size. These findings are nevertheless in keeping that of both Msomi [20] and the 2020/2021 NHLS annual report [67], in which the number of HIV tests done declined during the COVID-19 pandemic. Although the trend is persistent from 2016 through to 2022, the two years of 2016 and 2022 were not included as a discussion point due to limited data in both years

The decrease in HIV testing can be attributed to several factors, including lockdown restrictions, staff shortages at facilities and a scarcity of resources in the under-resourced health care system. Another important consideration for this decrease in HIV testing can be the high mortality rate associated with COVID-19 infections in patients with AHD, the number of COVID related deaths being regarded as under-reported by the SA Medical Research Council [68] It might also be inferred that the social restrictions during lockdown lowered the transmission of HIV, making this an important area for further research [20,69]. South Africa implemented various contingency measures in an attempt to avoid interruption of the life saving HIV services required, which included providing HAART through multi-month prescription at local clinics, and reallocating PHC services to district hospitals.

Patients from the West Rand District presented with the lowest median CD4 cell counts across all categories throughout the study period. In addition, the West Rand District had the highest proportion of patients with AHD presenting for HAART initiation in both the pre-COVID-19 period and the COVID-19 post-vaccination period. Further research and investigations regarding barriers and challenges experienced in accessing HIV care would benefit patients across the region, but in the West Rand District specifically.

4.4 OBJECTIVE 3. FACTORS ASSOCIATED WITH AHD IN PATIENTS WHO INITIATED HAART

The two regression models indicated that patients presenting to hospitals for HAART initiation were more likely to present with AHD than those without. Distance has also been noted as a factor affecting the uptake of HIV testing, the results of this study indicating that most people accessed care at their local clinic, which is likely to be located where other goods and services can be accessed, making it possible for them to be tested. The distance from a primary health care facility is one of the main issues related to encouraging people to test, with those living less than 10 km away being more likely to make the effort to seek health care and therefore test for HIV [12]. Furthermore, South Africa has stringent referral policies [65], with preliminary serviced being provided at the primary health care (PHC), including HIV testing (and pre- and post-test counselling). In the public sector, people are required to use the health services that are close to their home, which could account for 80% of testing being done in the clinic setting. South Africa has revised its National Strategic Plan (NSP) four times since 2000 in an attempt to allocate HIV resources to identified underserved areas [12]. Kim et al. recommended targeting areas requiring HIV service through the use of statistical modelling and high-resolution maps to identify underserved areas or areas of high prevalence [12] to enable issues related to distance to be accommodated. Patients who are critically ill and referred to specialised clinics or for admission at hospital level may be the reason for so many being tested outside the clinic environment, which may be due to their having co-morbidities that require more specialised care [65].

The findings of Jardim and colleagues showed that HIV services in the South African public health sector were significantly negatively impacted by budget, resource, and staffing constraints [69]. Op de Coul recommended starting the use of indicator-condition guided HIV testing, this removing individual HIV risk assessments and testing as part of routine patient management [32]. The use of such an approach can negate the need to establish possible

reasons for testing, for example, due to a partner tested positive, or because the patient had symptoms of HIV etc. Such information could be used to assess other factors associated with AHD in HAART naïve patients.

CHAPTER 5: CONCLUSION

5.1 INTRODUCTION

South Africa is home to the highest number of PLWH, with HAART having been made freely and widely available since 2005 and irrespective of the CD4 cell count from 2016. Despite this national roll-out of HAART and various programmes to promote its uptake, patients with HIV continue to present late for treatment initiation, which can result in the development of AHD. In addition, the onset of the COVID-19 pandemic resulted in decreased HIV testing and HAART initiation globally and locally. Patients with AHD are associated with a higher premature mortality as well as numerous morbidities than those without. Patients with AHD also place a significant economic burden on the South African health system as they require more specialised care that could have been prevented had they tested and initiated HAART timeously. The study therefore aimed to identify AHD prevalence and its associated factors in patients who presented for HAART initiation, and to assess the impact of the COVID-19 pandemic on those which AHD initiating HAART in Gauteng, from March 2016 to March 2022.

With respect to Objective 1, the prevalence of AHD was found to be 25.8%, this being approximately twice the prevalence of HIV in South Africa, which was 12.7% in 2022. This indicates the alarming fact that delayed testing and treatment is having a serious effect on people's quality of life, likely resulting in preventable morbidity and premature mortality.

Regarding Objective 2, there was a slight decline in the proportion of patients with AHD initiating HAART in Johannesburg Metro from the pre-COVID-19 and post-vaccination period, and a slight increase in the proportion with AHD in Tshwane Metro. However, no obvious trends of AHD in patients were noted in Ekurhuleni Metro, Sedibeng, or the West Rand Districts from the pre COVID-19 to the post-vaccination periods. The patterns of these differences suggest variability in the impact of the COVID-19 pandemic on CD4 cell counts in the different districts.

In terms of Objective 3, the West Rand District was identified as having the highest odds for patients to present with AHD when initiating HAART for care, male patients, patients in the 35 to 49-year group and those presenting at hospitals having the higher odds for presenting for HAART initiation with AHD.

5.2 STUDY IMPLICATIONS

Our study has several implications for HIV treatment programs, the high prevalence of patients with AHD initiating HAART highlights a major public health concern, reflecting the challenges of managing HIV at an advanced stage. It also underscores the importance of early detection of HIV infection and treatment interventions to prevent the progression to AHD. The findings also provide motivation for health professionals and researchers to monitor the health status and immune function of the population during and after adverse events such as the COVID-19 pandemic, as CD4 counts are a key measure of immune competence, particularly in the context of HIV/AIDS. The findings highlight the need for targeted public health strategies in districts with significant disparities with respect to AHD in the different age groups, gender, and facilities, to address potential long-term effects of the pandemic on immune health.

5.3 LIMITATIONS AND STRENGTHS

The findings for this study may have been affected by a number of limitations, such as missing (e.g. age groups) and incorrect data that could not be rectified. Secondly, the quality of the NHLS data depends on the performance of the record-linkage algorithm, as poor linkage can result in the one patient being identified as two unique persons, which can lead to over or under-estimating the numbers of patients seeking care. Thirdly, psycho-social and health systems factors are not assessed in the secondary data analysis, as those variables are not routinely collected at specimen request. Ideally, the HAART initiation should be viewed relative to the post COVID-19 period, the data being limited to during the COVID-19 period. Despite the analysis being based on a large provincially representative database from patients accessing the public-sector healthcare services, the NHLS database does not include those who seek access to clinical care in the private sector and/or at some non-governmental organizations. As data was only included from 2016, it is possible that patients could have been included who were already in the HIV treatment programme. The year of 2016 includes data from March to December, and not for the full year, while for 2022 it includes data from January to March, which means that those years contain less data than the other years. The data therefore cannot be assumed to be nationally representative, with implications for the generalizability of the results to other provinces in South Africa.

Patients were not included if they did not have at least one follow-up viral load, which could pose a limitation as it is possible that some patients who had severely advanced HIV disease died prior to a later viral load being done. The analysis was limited to first time HAART initiating patients only, with those who re-started HAART after disengaging from care being omitted, the results therefore being unlikely to reflect total burden of advanced HIV disease in Gauteng. The absence of clinical data correlation was also a recognised limitation.

Despite the limitations, the study has several strengths, including being a representative sample of the densely populated Gauteng Province, which has highest number of lowest CD4 cell count for HIV care in the country. In addition, the large sample size cannot be ignored, the consistency of the results across the districts indicating the importance of having large number for analysis. Furthermore, the temporal scope of the study spans from 2016 to 2022, thereby capturing trends over a significant time period.

5.4 RECOMMENDATIONS

Based on the findings from this retrospective study, several strategic recommendations are proposed to enhance the management and treatment of advanced HIV disease (AHD) and address identified systemic gaps:

1. Identification of barriers to HIV service access: We recommend conducting comprehensive research to elucidate personal, social, logistical, and healthcare system barriers that impede access to HIV services, with a particular emphasis on middle-aged men. Understanding these barriers is critical for the development of targeted interventions aimed at improving service uptake and patient retention in care.
2. Expansion of research to other provinces: We recommend replicating this epidemiological study across the remaining eight provinces of South Africa to ascertain whether similar AHD prevalence rates are observed. This is essential for informing and driving national health promotion strategies across diverse regions.
3. Deployment of Mobile Testing Units: We recommend the implementation mobile HIV testing units to enhance accessibility, particularly in remote and underserved areas. Early detection and timely initiation of HAART through mobile units can mitigate the incidence of late presenters and reduce the burden of AHD.
4. Community and faith-based engagement: We recommend engaging community leaders and faith-based organizations to advocate for HIV testing, particularly targeting male

populations. Leveraging their societal influence can help to reduce stigma and promote health-seeking behaviours, thereby encouraging early testing and treatment initiation.

5. Sustained management of chronic conditions during crises: We recommend the development of robust strategies to ensure the continuous management of chronic conditions, such as HIV, during crises like the COVID-19 pandemic. This includes maintaining uninterrupted access to diagnostic and therapeutic services to prevent disease progression and reduce mortality rates.
6. Qualitative research on HAART initiation delays: We recommend conducting qualitative studies to investigate the underlying factors contributing to delayed initiation of HAART. Insights gained from these studies can inform the design of effective interventions to encourage earlier treatment initiation and improve clinical outcomes.
7. AHD in migrant populations living in South Africa : Given the large migrant population in Gauteng, the burden of AHD in migrant populations warrants investigation not just in Gauteng but in SA.

These recommendations aim to optimize HIV treatment programs, decrease the prevalence of AHD, and improve health outcomes for individuals living with HIV in South Africa by addressing both systemic and individual-level barriers to care.

5.5 CONCLUSION

South Africa is likely to remain the epicentre of the SSA HIV pandemic for many years to come, with an ongoing focus on prevention and treatment being required to prevent people from becoming complacent about the implications of being infected. While considerable strides have been done regarding the availability, accessibility and affordability of HIV testing and treatment, overcoming issues such as stigma and discrimination, disbelief in its severity, and inappropriate health care attitudes to those infected or wanting testing need to be ongoing. With HIV now being a manageable chronic condition, preventing avoidable progression of the disease to AHD is possible, thereby reducing the possibility of premature mortality, with the inconveniences and suffering that it can cause. Promote the early uptake of HIV testing and treatment will assist in ensuring that people are able to enjoy a good quality of life, be productive members of their families and communities, and break the stigma of living with the virus.

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APPENDICES

Appendix 1: Plagiarism Declaration

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Logashnee Govender (Student number: 2486055) am a student registered for the degree of Masters In Epidemiology (Infectious Diseases) in the academic year 2024.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature:  Date: 31 March 2024

Appendix 2: Ethics Clearance Form

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Dr L Govender

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M220664

NAME: (Principal Investigator)	Dr L Govender
DEPARTMENT:	School of Public Health Department of Epidemiology and Biostatistics Medical School University
PROJECT TITLE:	*Factors associated with late Highly Active Anti-Retroviral Treatment initiation: a retrospective study of adults living with Human Immunodeficiency Virus in Gauteng, South Africa, 2016 to 2012*
DATE CONSIDERED:	2022/06/24
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Dr T Kufa-Chakezha
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2022/10/26

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. I agree to submit a yearly progress report. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in June and therefore reports and re-certification will be due in the month of June each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

28 Oct 2022
Date

Appendix 3: Turnitin Report

Research Report for Turnitin.pdf 02/04/2024

ORIGINALITY REPORT

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