MORBIDITY AND MORTALITY IN THE MODERN ANTIRETROVIRAL TREATMENT ERA IN A TERTIARY TEACHING HOSPITAL IN DURBAN, SOUTH AFRICA

Dr MANIMANI RIZIKI GHISLAIN

A dissertation submitted to the College of Health Sciences, University of KwaZulu-Natal, in fulfilment of the requirements for the degree of Master of Medical Sciences.

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This is to certify that the contents of this thesis are the original research work of Dr Manimani Riziki

As the candidate's supervisor. I have approved this thesis for submission

Supervisor

Signed:… **……**

Name: Prof Nombulelo P Magula

Date: 26 June 2020

ABSTRACT

Background: Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS) is recognized as the chief cause of morbidity and mortality in Sub-Saharan Africa. South Africa is known to bear the highest number of people living with HIV globally, while KwaZulu-Natal is the worst affected province in this country.

Aim: To identify the determinant of morbidity and mortality in the modern antiretroviral therapy (ART) era in South Africa.

Study design: A cross-sectional study. To achieve the objective, a mixed data acquisition method was applied using qualitative and quantitative data. These included a systematic review and a retrospective chart review.

Data collection and analysis: For the systematic review, relevant studies were searched from the following databases: Google Scholar, PubMed, CINAHL. Two review authors independently screened titles abstracts and full-text articles in duplicate, extract data and assess the bias. Discrepancies were resolved by discussion or arbitration of a third review author. The study used the Preferred Reporting Item of Systematic Review (PRISMA 2015) guideline. This study used R software version 3.6.2. to synthesis the data, graphic displays were used to visually compare the prevalence of comorbidities across the study region.

With the retrospective chart review, we conducted a study of all patients admitted at King Edward medical wards, Durban, South Africa from January to December 2018. Data were obtained from medical records, including demographic profile, clinical attributes and laboratory records. Data were analysed using R software version 3.6.2. In addition, the association between the covariates was tested either with the Chi-Square test, Kruskal Wallis or Wilcoxon rank-sum test depending on the type of variables. A p-value < 0.05 was used as a benchmark for determining the level of statistical significance

Results: For the systematic review a total of 409 articles were obtained from the database search, finally12 articles were eligible for data extraction. All 12 studies included were published between 2008 and 2018 in English and they were conducted in Sub-Saharan Africa. Among them, three were conducted in Nigeria, two were conducted in Uganda, three were conducted in South Africa, one in Gabon, one in Ethiopia, one in Ghana, and one in Burkina Faso. In most of the included studies, tuberculosis was the first commonest causes of hospitalization accounted for 40.7% followed by anaemia with 34.2% and toxoplasmosis with

29.3%. It was as well the first cause of death accounted for 44.3% followed by anaemia with 30.2% and toxoplasmosis 27.5%. Contrary one study reported anaemia as the first causes of hospitalization and two studies reported each respectively wasting syndrome and meningitis as the first causes of death.

With regards to the chart review, a total of 577 (50.6%) females and 564 (49.4%) males were included in the study. The mean age of all the participants was 39.6±12.2, 506 (44.3%) patients had CD4 less than 200 cells /mm^3 and 273 (23.9%) had VL > 1000 copies/ml. Male gender [OR 1.39(1.07-1.8) p=0.015], age [OR1.02(1.01-1.03) p< 0.001], CD4 <200 cells/mm^3 [OR 2.14(1.37-3.45) p=0.001], VL > 1000 copies/ml [OR 1.93(1.08-3.63) p=0.032] were associated with mortality among HIV infected patients admitted in the cohort. Tuberculosis (TB) was the most common diagnosis on admission and the leading cause of death which accounted for 257 (22.5%) and 73 (24.3%) respectively, followed by kidney disease with 83(7.2%) for admission and with 38(12.6) for death. Only 70% of patients had been reported to be on ART. Age, men gender, CD4 cell and viral load were associated with mortality. Association between CD4 cell count and viral load was found.

Conclusion: Despite the recent improvement of modern antiretroviral treatment, HIV/AIDS still causes hospitalization and death among HIV infected patients. For the systematic review as well as for the chart review, tuberculosis was the commonest cause of hospitalization and death in Sub-Saharan Africa and South Africa, but it was always followed by other opportunistic infection and other non-AIDS related conditions.
There is a need to prevent opportunistic infection (especially tuberculosis) and to tackle the non-communicable disease related to HIV infection. Also, a need to start antiretroviral treatment early for patients living with HIV.

Keywords: Morbidity, Mortality, Antiretroviral therapy, Sub-Saharan Africa, South Africa.

DECLARATION 1- PLAGIARISM

DECLARATION

I, Manimani Riziki Ghislain declare that

(i) The research reported in this dissertation, except where otherwise indicated, is my original work.

(ii) This dissertation has not been submitted for any degree or examination at any other university.

(iii) This dissertation does not contain other persons' data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.

(iv) This dissertation does not contain other persons' writing unless specifically acknowledged as being sourced from other researchers. Where other written sources have been quoted, then:
a) their words have been re-written, but the general information attributed to them has been referenced;
b) where their exact words have been used, their writing has been placed inside quotation marks and referenced.

(v) Where I have reproduced a publication of which I am an author, co-author or editor, I have indicated in detail which part of the publication was actually written by myself alone and have fully referenced such publications.

(vi) This dissertation does not contain text, graphics or tables copied and pasted from the Internet, unless specifically acknowledged, and the source being detailed in the dissertation and in the References sections.

Signed: **Date**: 26 June 2020

DECLARATION 2- PUBLICATION & CONTRIBUTIONS

1. Morbidity and mortality in the antiretroviral era in Sub-Saharan Africa: a systematic review.

Contribution: Dr Manimani Riziki contributed to the project by developing the proposal, carrying out data collection, data analysis, interpretation of the results as well as manuscript preparation and writing under the supervision of Prof NP Magula. Mr Gloire -Aime Aganze Mushebenge contributed in the abstract, full article screening of the included studies.

2. Morbidity and mortality in the modern antiretroviral era in South Africa: a chart review.

Contribution: Dr Manimani Riziki contributed to the project by developing the proposal, carrying out data collection, data analysis, interpretation of the results as well as manuscript preparation and writing under the supervision of Prof NP Magula. Dr Sindy Gumede contributed also in carrying out data collection.

DEDICATION

Dedicated to my wife Furaha Bashengezi Esther, and my children Manimani Ogishwe Japhet, Manimani Ogala Agnes. Many thanks for your love and support.

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. My brother in law Bernard Balibuno Kateta and his wife Yaya Tchikoma Balibuno

. My Father Manimani Tshikoma Vincent and my mother Agnes M'Nzogero.

. My family and my friends for their support and encouragement.

ACRONYMS AND ABBREVIATION

AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Treatment
DRV	Darunavir
DTG	Dolutegravir
ETR	Etravirine
FDC	Fixed-Dose Combination
HAART	Highly Active Antiretroviral Treatment
HIV	Human Immunodeficiency Virus
InSTIs	Integrase Strand Transfer Inhibitor
MMAT	Mixed Method Appraisal Tool
NGOs	Non-Governmental Organisations
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NSP	National Strategic Plan
PI	Protease Inhibitor
PMTCT	Prevention of Mother to Child Transmission
RAL	Raltegravir
RPV	Rilpivirine
SADC	Southern African Development Community
TB	Tuberculosis
UNAIDS	Joint United Nations Programme on HIV/AIDS
VCT	Voluntary Counselling and Testing
WHO	World Health Organization

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OVERVIEW OF THE THESIS

Chapter 1: Introduction: Containing the background, the problem statement, the research questions, the aim and objectives, the literature review and the methodology.

Chapter 2: The systematic review: The manuscript is presented in the form of a journal article entitled ‘morbidity and mortality in the ART era in Sub-Saharan Africa: a systematic review’.

Chapter 3: The retrospective chart review: the chapter is presented in the form of a manuscript entitled: morbidity and mortality in the modern ART era in a tertiary teaching hospital in South African, Durban.

Chapter 4: Discussion, Conclusion, Strength, Limitation, and Recommendation

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND

Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS) remain one of the major global public health problems and cause substantial morbidity, mortality, negative socio-economic impact, and human suffering (1,2). Approximately 36.9 million persons in the world lived with HIV infection in 2017 and 1.8 million persons were newly infected in the same year (3). Nearly 940,000 persons died from AIDS-related illnesses in 2017(3).

Sub-Saharan Africa is one of the regions which is the most affected by HIV (4). The region contributes 68% of all HIV and/or AIDS patients in the world, while North America and Latin America has 4% each, Eastern Europe and Central Asia has 4% each and South-East Asia has 12% (2). UNAIDS (2018) reported that 300,000 men and 270,000 women died of AIDS-related illness in Sub-Saharan Africa in 2017 (5).

South Africa has the largest number of infected human immunodeficiency virus and the largest antiretroviral treatment program in the world (6). The prevalence of HIV has been increasing since 1990 in South Africa (7). In 2016 the national program of HIV in South Africa reached 56% of all human immunodeficiency virus-infected with 3.8 million adults on treatment (8). The Joint United Nations Programme on HIV/AIDS (UNAIDS) policy was implemented in South Africa in September 2016 (9). In the same year, the country implemented universal ART eligibility and extending it to all 7.1 million HIV-positive South Africans (9).
The country adopted also the World Health Organization (WHO) “test and treat” approach (10).

Despite the widespread antiretroviral therapy availability in South Africa, little is known about the impact of its programme on adult HIV related hospitalization and results at the level of public sector hospital (11).
The aim of the study was to identify the determinants of morbidity and mortality in the modern antiretroviral treatment (ART) era of patients of 12 years old or older admitted at King-Edward hospital, a tertiary teaching hospital in KwaZulu-Natal, Durban, South Africa.

1.2 PROBLEM STATEMENT

The antiretroviral therapy (ART) has led to a profound decrease in the morbidity and mortality among people living with AIDS (12, 13). However, despite the availability of ART, a substantial proportion of HIV infected patients has continued to die from both AIDS-related and non-AIDS-related causes (14).

Studies found that several factors may contribute to these deaths, but the mortality rate, cause of death, and risk factors for death differs between countries and depending on factors such as cultural, socio-economic, healthcare and political issues (15, 16).
In low and middle-income countries, disproportionately high mortality has been observed in the first few months after ART initiation, especially among profoundly immunosuppressed patients (16, 17). High-income countries showed decreases in death due to HIV, however, it was not the same as in low and middle-income countries (14, 18).
Therefore, the study investigated the reason for hospitalization and causes of death in the modern antiretroviral treatment (ART) era at King-Edward hospital, a tertiary teaching hospital in Durban, KwaZulu-Natal from January to December 2018.

1.3 RESEARCH QUESTIONS

Main research question

What are the determinants of morbidity and mortality in the modern antiretroviral treatment (ART) era in South Africa?

Specific research question

1. What are the research gaps on morbidity and mortality in the modern antiretroviral treatment (ART) era in Sub-Saharan Africa?

2. What are the reasons for admissions in the modern antiretroviral treatment (ART) era in a tertiary teaching hospital in South Africa?

3. What are the causes of death in the modern antiretroviral treatment (ART) era in a tertiary teaching hospital in South Africa?

1.4 AIMS AND OBJECTIVES OF THE STUDY

Main Aim

To identify the determinants of morbidity and mortality in the modern antiretroviral treatment (ART) era in South Africa.

Objectives

1. To conduct a systematic review to identify the literature available or the research gaps on the morbidity and mortality in the antiretroviral treatment (ART) era in Sub-Saharan Africa.

2. To conduct a retrospective chart review focusing on the following issues:

   a) Reasons for admissions in the modern antiretroviral treatment (ART) era at King-Edward hospital in South Africa.

   b) Causes of death in the modern antiretroviral treatment (ART) era at King-Edward hospital in South Africa.

1.5 LITERATURE REVIEW

In this Review the following sections are discussed:

1. HIV/AIDS Globally
2. HIV/AIDS in Sub-Saharan Africa.
3. HIV/AIDS in South Africa.
4. HIV/AIDS in KwaZulu-Natal.
5. HIV/AIDS Policy.
6. Morbidity and Mortality

1.5.1 HIV/AIDS GLOBALLY

Globally, the number of people infected with HIV has increased, statistics showed that 4.1 million people were newly infected by HIV and 2.8 million died from AIDS-related to HIV in 2005(19). According to Kelly (2000), AIDS is associated with the most deaths than another infectious disease in the world (20). The United Nations Joint Programme on HIV /AIDS estimated that 33 to 46 million people were infected worldwide in 2005(21). In lower-middle-

income countries, HIV/AIDS is still an ongoing problem and still causes high morbidity and mortality (22). Almost 78 million people have been infected with HIV since its discovery in 1981 (22) and as of today it has so far caused more than 34 million deaths (23). Eastern and Southern Africa with an estimated of 19 million people living with HIV and 960 000 new infections in 2015 remain the most affected region despite a global decrease in AIDS-related death and improvement of access to antiretroviral therapy worldwide (24). Data on reasons for hospitalization among children and adults with HIV globally as summarized by a systematic review identified tuberculosis and bacterial infections as the two most common causes of children and adults' HIV admissions in all geographical regions and the most common causes of death (25). United Nations Member States aimed to reduce TB deaths among people living with HIV by 75% by 2020 (92). In 2017 five low- or middle-income countries, India (84%), Eritrea (83%), Djibouti (78%), Malawi (78%) and Togo (75%), achieved or exceeded the target of a 75 % reduction in TB deaths among people living with HIV (93).

1.5.2. HIV/AIDS IN SUB-SAHARAN AFRICA

Sub-Saharan Africa has been reported as the region hardest hit by HIV and AIDS in the world. The Southern African Development Community (SADC) countries are generally the hardest hit by HIV and AIDS (26). Different factors had been identified by different authors as reasons why the African population is more susceptible to HIV and AIDS in the world. Concurrent or simultaneous sexual intercourse practices by African men is argued as a major role player in the vast spread of HIV in Sub-Saharan African countries as opposed to developed countries characterized by serial monogamy practices (27). Other authors argued that political instability, underdevelopment, widespread poverty and poor infrastructure are the major reasons for the rapid spread of HIV in African countries (28).

The 2009 AIDS epidemic update claimed that HIV and AIDS still have an enormous negative impact on business, households, communities and national economies in Sub-Saharan Africa. Sub-Sahara Africa has the biggest share of the 40 million people currently living with HIV and AIDS in the world (29, 28). In 2014 studies reported that Sub-Saharan Africa was the most affected region, 25.8 (24.0-28.7) million people were estimated living with HIV, the region accounted for nearly 70% of new infections worldwide (30). UNAIDS (2018) reported that 300.000 men and 270.000 women died of AIDS-related illnesses in Sub-Saharan Africa in 2017 (31). Cryptococcal meningitis is one of the common and often cause of death among

HIV patients in Sub-Saharan Africa. Some studies from Africa reported that 10% to 20% of deaths among HIV infected patients are attributable to cryptococcal meningitis (87, 88).
The global burden of cryptococcal meningitis has been recently re-estimated at 223,100 cases (162,500 cases in sub-Saharan Africa) leading to 181,100 annual deaths (135,900 deaths in Sub-Saharan Africa).The highest annual incidence of cryptococcal meningitis has been found in Nigeria (27,100 cases), South Africa (21,400 cases), Mozambique (18,600 cases), India (18,300 cases), Uganda (12,200 cases), Ethiopia (9600 cases), Kenya (9000 cases) and Zambia (5000 cases) (89). Tuberculosis also remains the leading cause of death among people living with HIV, causing one in three AIDS-related deaths. In ART services in Sub-Saharan Africa the proportion of patients with tuberculosis is extremely variable, ranging between 5% and 40% (90,91). Anaemia is the most common haematological manifestation of HIV disease and is frequent among HIV patients on antiretroviral therapy (ART) in Sub-Saharan Africa, with a prevalence ranging from 45- 87% (94). Among HIV infected patients, chronic kidney disease (CKD) has been observed as one of the main complications, with a prevalence ranging from 3.5 to 48.5% in Sub-Saharan Africa (95).

1.5.3. HIV/AIDS IN SOUTH AFRICA

In South Africa, the first case of AIDS was diagnosed in 1982. Since then the prevalence has increased from less than one per cent in 1990 to nearly 25 per cent in 2000 (19). In 2005, statistics showed that 5.5 million South Africans were living with HIV and therefore South Africa was claimed to be the most affected country in the world (19). Since the beginning of the epidemic, it is estimated that 1.8 million people have died of AIDS-related diseases in the country (32). From 1997 to 2005 at least 40% of all deaths were related to AIDS (32) and consequently rising death have contributed to the decline in the country's population growth rate from 1.25% in 2001 to 2002 to slightly more than 1% in 2005 to 2006 (32). The national household survey of 2005 showed young people aged between 15-24 years old as the most infected by HIV (34). South Africa launched the public-sector ART programme in 2004 (35). South Africa is identified as the largest HIV epidemic worldwide with an estimated 6.4 million people infected by HIV infection in 2012 (33).
Over the past decade, there has been an unprecedented scaling-up of the programme with more than 2.6 million people having been initiated on antiretroviral therapy (36, 37). Estimation of 3736 public health facilities across South Africa now offers free antiretroviral therapy to people (38). It has been shown that HIV mortality has decreased, and life expectancy has increased to

approximately 80% of normal life expectancy (39). The triple-drug antiretroviral therapy became available in the mid-1990s and heralded dramatic decreases in AIDS-defining diseases and hospital admissions for HIV related opportunistic infections in high-income economies countries (40, 41).

With the prioritization of widespread ART availability, HIV /AIDS accounted for approximately 50% of medical ward admissions in public sector hospitals in South Africa (42). An estimation of 2.2 million deaths has been averted in South Africa in 2016 (43).

According to the UNAIDS (2018), in 2017 in South Africa there were 7.2 million people living with HIV, among them 18.8% were aged between 15-49 years, 270,000 new HIV infections and 110,000 AIDS-related deaths (44). Sixty-one per cent of adults and 58% of children were receiving antiretroviral therapy treatment (44).

Different factors have contributed to the increase in HIV infections in South Africa. These include; women's vulnerability, lack of information and economic conditions. The lack of viable economic conditions and poverty in rural and isolated areas influence men and women to migrate and look for employment and better economic opportunities. When men and women are away from their homes for a long period, this increases the risk of HIV infection (45).

According to the world health organization, South Africa is one of 22 high tuberculosis (TB) burden countries, with a tuberculosis incidence rate of 520 per 100,00 population in 2015 (96). A study conducted in South Africa between 2011 and 2015, in total there were 2,377,676 recorded deaths, approximately 14% (188,230) of individuals aged 15 to 64 years were reported to die due to tuberculosis (97). Cryptococcal meningitis (CCM) continues to have significant mortality among HIV infected patients with low CD4 count, ranking between 30% and 50% (98). Approximately 95 of HIV-infected patients developpe anaemia during their disease (99). The cause of anaemia in HIV-infected patients is often multifactorial (100).

1.5.4. HIV/AIDS IN KWAZULU-NATAL

KwaZulu-Natal is estimated to have the highest prevalence of HIV infections in all provinces in South Africa (46). More than 55% of all South Africans infected with HIV are said to be living in KwaZulu-Natal and Gauteng provinces (47). Taylor et.al. (2002) argued that the high rate of HIV infection reported in younger women between 15-29 years suggested that many had been infected during their teens (46). They stipulated that the epidemic is mature, and deaths outstrip births in KwaZulu-Natal (46). Human Immunodeficiency Virus (HIV) prevalence among pregnant women is highest in KwaZulu-Natal and lowest in the Northern

Cape (48). Since the first antenatal HIV prevalence survey in 1990, KwaZulu-Natal has remained the centre with the highest prevalence of HIV (48). The prevalence rate of antenatal HIV in KZN as reported in 1990 was twice the national level and approximately ten per cent of the national average (48). A statement from the national department of health in South Africa reported that 47% of women who attended antenatal clinics tested positive for HIV infection in the Amajuba district and in the rural village of Umkhanyakude in the north, 51% of women aged 25 to 29 years old who had participated in the HIV survey also tested positive (47). UNAIDS (2007) reported that in keeping with current trends and no effective preventive programmes, an estimation of two-thirds of 15-year olds in this district could be infected with HIV by the time they reach their 35^{th} birthday (32). The numbers of just over 1.5 million people infected with HIV and 115483 deaths related to HIV/AIDS in 2008 placed KwaZulu-Natal as the uppermost HIV infection prevalent province of South Africa (49).

Some of the factors that make KwaZulu-Natal to have a high prevalence of HIV infection are; the lowest fraction of medical male circumcision, socioeconomic status, and education among others (50). In 2017, Statistics revealed that South Africa had a prevalence of HIV infection of 18.9% in the general population, while it was almost 12.2% in KwaZulu-Natal (44). This province is distinguished for being the worst HIV infected Sub-region in the world with a very high prevalence within certain parts of it (51).

1.5.5. HIV/AIDS POLICY

a. Global and Regional policy

Many international policies and guidelines on HIV and AIDS had been developed by the Joint United Nations Programme for HIV and AIDS (UNAIDS) and many nations adopted them in their respective countries (52). The policies include the following issues: HIV prevention and treatment; orphans and vulnerable children; gender and HIV; prevention of mother to child transmission (PMTCT); orphans and vulnerable children; testing and counselling; women and girl (52). Southern African Development Community (SADC) countries, in the year 2000 issued a policy entitled “managing the impact of HIV and AIDS in SADC” (53). The policy used a multi-sectoral approach and provided a strategic framework to tackle the HIV and AIDS epidemic in the region. The development of the framework aimed to achieve the SADC HIV and AIDS overarching goal which was: “to decrease the number of HIV and AIDS infected and affected individuals and families in the SADC region so that HIV and AIDS is no longer

a threat to public health and to the socio-economic development of member states" (53). To reach this goal, four main objectives must be followed:

1. Reducing and preventing the incidence of HIV infection among the most vulnerable groups in the region.
2. Mitigating the socio-economic impact of HIV and AIDS.
3. Reviewing, developing and harmonising policies and regarding prevention and control of HIV and AIDS transmission.
4. Mobilizing and coordinating resources for the HIV and AIDS multi-sectoral response in the region (53).

Among main actors in the HIV and AIDS response in the region, the policy recognised governments, Non-Governmental Organisations (NGOs) and the private sector (53).
South Africa participated in the formulation of these global and regional policies, adopted and adapted them within its national context, like most of the countries.

b. South Africa National Policy

South Africa has formulated many policies and legislative acts since its attainment of democracy which aim to tackle HIV and AIDS epidemic. During the first decade of reaching democracy, the policies were well documented but there was a poor response of the government against HIV and AID epidemic (54, 55, 56). On the other hand, Government and civil society demonstrate more collaboration than before in the recent policies (57).

b.1. Policies concerning women

The national department of health in 2008 released a document on the policy and guidelines. This document was for the implementation of the prevention of mother to child transmission (PMTCT) Programme to provide an update on the approach to the implementation of the PMTCT programme (58). The updated policy issued the following four stages of the PMTCT. Firstly, primary prevention of HIV especially among women of childbearing age; secondly, preventing unintended pregnancies among women living with HIV, thirdly, preventing HIV transmission from a woman living with HIV to her infant, and lastly, providing appropriate treatment, care and support to women living with HIV and their children and families (58).

Among these four goals of international basic recommendations, South Africa prioritises the primary prevention of HIV among women living with their children and families. The policy notices that the involvement of civil society in the implementation programme is very important (58).

Dual therapy with Nevirapine and AZT was introduced for PMTCT in July 2008 (59).

The department of health and the South African national AIDS Council issued guidelines on the management of PMTCT in 2010 entitled clinical guidelines: prevention of mother to child transmission (PMTCT) (60).The old policy stated that pregnant women tested HIV positive with CD4 count less than 200 cells/µl had access to antiretroviral therapy whilst in the new policy all pregnant HIV positive women with CD4 count of 350 cells/µl or presented symptoms regardless of CD4 count were eligible for treatment, this policy became applicable on 1st April 2010 (61). The policy also stipulates that all other positive pregnant women with CD4 count greater than 350 cells/µl are now eligible for treatment at 14 weeks of pregnancy to protect the baby instead of the last term of pregnancy as it was mentioned in the old policy (61).

b. 2. Policies concerning Men

The policy suggests that men should actively participate in fighting AIDS through workshops and campaigns (62). It extends voluntary counselling and testing (VCT) to men (58).

It also contains promotion of HIV and AIDS awareness, prevention and treatment among men living at high risk of HIV infection (63, 64) for example long distant truck drivers and men who have sex with men. It suggests the distribution of condoms at truck stops and toll plaza, provision of treatment and VCT at strategic points (63, 64).

Medical male circumcision helps to prevent HIV infection and the high prevalence of the epidemic in South Africa and it is suggested to be outlined in national policy (65).

b. 3. Antiretroviral therapy in South Africa

Access to antiretroviral treatment (ART) is known for improving the quality of life for infected individuals, reducing opportunistic infections and AIDS-related mortality (66).

South Africa's antiretroviral therapy guidelines are based on the World Health Organization (WHO) guidelines which include three treatment regimens:

1. The first line regimen includes two nucleoside reverse transcriptase enzyme inhibitors (NRTI) with a non-nucleoside reverse transcriptase enzyme inhibitor (NNRTI)
2. The second line regimen includes two NRTI'S with a protease enzyme inhibitor (PI) (67, 68).
3. For the third line regimen, the following drugs are available for use: InSTIs (integrase strand transfer inhibitor) [DTG (dolutegravir) and RAL (raltegravir)], the newer PI DRV (protease inhibitor darunavir) and newer NNRTIs [ETR (etravirine) and RPV (rilpivirine)]. Note that regimen choice is individualised, and expert treatment provider is always consulted before using it. World health organization recommend TLD (Tenofovir, Lamivudine and Dolutegravir) for the first-line treatment of HIV and also in second line treatment (69, 70).

Among the nucleoside reverse transcriptase enzyme inhibitors (NRTI), stavudine (D4T) was the most widely used in the first line in 2004 (71, 68) however, it was involved in causing peripheral neuropathy, hyperlactatemia and lipodystrophy (72**,** 73). Tenofovir replaced D4T as the nucleoside reverse transcriptase enzyme inhibitors (NRTI) in first-line treatment in April 2010 (74**,** 75). By mid-2011, all HIV infected patients eligible for antiretroviral therapy coverage amounted to nearly 80% (76). In 2010 and 2011 the number of patients living with HIV who started antiretroviral therapy was in excess of the number of people who became eligible to take antiretroviral therapy over the same period and that exceeding the targets set in the 2007-2011 National Strategic Plan (NSP) (76). The number of HIV infected people who have access to antiretroviral therapy in South Africa increased to 31.2% in 2012 while in 2008 it was 16.6 % (77).In the guidelines, the other overwhelming modification over the years has been the CD4 count threshold for starting of antiretroviral therapy (ART) (68). Initially, in 2004, it was set at CD4 cell count < 200 cells/μl (68), and after 2013 it was increased to a CD4 count of ≤ 350 cells/μl (75). As antiretroviral therapy was given to patient with CD4 < 500 cells/μl, death, disability and expenditure on HIV/AIDS would decrease significantly over the 40 years, and an assumption based on a well-run antiretroviral programme would appear (78). Therefore, South Africa took the decision to adopt this policy and expand its antiretroviral therapy programme to include patients with a CD4 count of ≤ 500 cells/μl in 2015 (79).

South Africa adopted the WHO guidelines in September 2016 to initiate all HIV infected individuals on antiretroviral regardless of CD4 count (80).

The country implemented 'test and treat'; if you are tested positive HIV you may access (ART) irrespective of CD4 count (81**,** 82).With that strategy South African antiretroviral therapy programme is trying to achieve targets set by Joint United Nation Programme on HIV/AIDS, to have 90% of all people tested for HIV, 90% treated and 90% virologically suppressed by 2020 (80).According to UNAIDS (2018), 4.4 million people were receiving treatment in South Africa (83), which equates to 61% of people living with HIV in the country (83).
South Africa has been reported to have the largest ART programme in the World (83).

In recent years South Africa's antiretroviral therapy services have expanded in keeping up with the WHO changing guidelines (81, 82).It was anticipated initially that the dramatic scale-up of ART would result in clinics and services becoming over-stretched and have a negative quality of care, however, after one-year, studies have shown that there was no significant effect on patients results related to the increase in antiretroviral therapy provision, either in terms of either morbidity or mortality (84).However, studies found that men were more likely to start antiretroviral therapy at an older age and later stage of infection and had almost double the mortality rate than that of women, which need to engage men in testing services and ensure that they are linked to treatment (84). Studies found also a decrease in mortality in the first year of antiretroviral therapy treatment initiation (85).

1.5.6. MORBIDITY AND MORTALITY

Morbidity and mortality are two measures commonly used for epidemiological surveillance, they describe the progression and severity of a given health event. Morbidity is the state of being symptomatic or unhealthy for a disease or condition, usually represented by prevalence or incidence. Mortality on the other hand, is related to the number of deaths caused the health event under investigation, communicated as rate or as an absolute number. Morbidity and mortality are two types of retrospective information that allows for continuous evaluation of the efficacy of either a specific health care system or an implemented intervention on place. (86).

1.6 METHODOLOGY

1.6.1. Study design

To achieve objectives, mixed data acquisition methods were applied using qualitative and quantitative data, included a systematic review and a retrospective chart review.

The study was carried out in two steps as follows:

Step 1: conducted a systematic review to identify the literature reporting on the morbidity and mortality in the antiretroviral treatment (ART) era in Sub-Saharan Africa.

Inclusion Criteria:

. Studies reporting morbidity and mortality of HIV infected patients during the antiretroviral therapy (ART) era in Sub-Saharan Africa.
. Studies published from 2008 to 2018.
. Studies reporting on males or females ≥ 18 years old HIV infected.
. Peer-reviewed English language publications.
. Observational studies on Sub-Saharan Africa only.

Exclusion Criteria:

. Studies from outside Sub-Saharan Africa
. Non-English literature
. Patients < 18 years old
. Studies reporting on morbidity or mortality in HIV-uninfected patients

Data Electronic Search:

We made use of the following databases: Google Scholar, PubMed, and CINAHL. The search strategy was based on a combination of relevant terms

Data collection and analysis

Two reviewers followed the inclusion criteria for selecting studies, they screened articles by their titles and abstracts eligibility. The full texts of articles were retrieved. The process of literature selection and reasons for exclusion and inclusion was documented by a PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis).

Data extraction and management

Data were extracted in accordance with the methods outlined in the Cochrane Handbook for the systematic review of interventions and the data extraction. Disagreements between the two review authors were resolved through discussion and by consulting a third author. R software was used for data synthesis.

Step 2: conducted a retrospective chart review focusing on:

- Reasons for admissions in the modern antiretroviral treatment (ART) era in a tertiary teaching hospital in South Africa.
- Causes of death in the modern antiretroviral treatment (ART) era in a tertiary teaching hospital in South Africa.

Inclusion criteria:

- Medical records of HIV infected patients admitted at King Edward VIII Hospital in Durban, South Africa from January to December 2018.
- Males or females ≥ 12 years old HIV with HIV infection.
- Pregnant females admitted to the medical wards at King Edward Hospital HIV infected

Exclusion Criteria:

- Patients ≥ 12 years old non-HIV infected.

1.6.2. Data Collection and Analysis:

Data were collected from the clinical records of HIV infected patients admitted at King Edward VIII hospital.

The Data collected, including age, gender, clinical parameters, history of co-morbidities (tuberculosis, candidiasis, hepatitis c, toxoplasmosis, Kaposi's sarcoma, Pneumocystis carinii etc.), laboratory data (HIV test, CD4 cell count, HIV RNA load), the reason of admissions and causes of deaths.

R software was used for analysing data. Analytical statistics including percentage and frequency were described. Categorical data were presented as tables and graphs. Prevalence of morbidity and mortality were reported as a

percentage with 95 % confidence intervals. A *p*-value of <0.05 represented statistical significance.

1.7 ETHICAL CONSIDERATIONS

Permission: Ethical clearance for the study was obtained from the University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC), reference number BE345/19. We obtained also permission from King Edward hospital and the department of internal medicine.

The risk to participants: this study consisted of a systematic review and a retrospective chart review. Therefore, it did not pose any physical, biological or emotional risk to participants.

Benefits: to identify gaps in research and to generate a hypothesis for a prospective study and to identify the determinants of morbidity and mortality in the modern antiretroviral treatment (ART) era in South Africa.

Confidentiality: we did not disclose patient identification details.

Consent: none needed because there was no interaction with patients.

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CHAPTER 2: A SYSTEMATIC REVIEW

Chapter 1 presented the background, aim, objectives, research question, the literature review and the methodology followed in this study. Chapter 2 responds to objective 1 of this study viz, to conduct a systematic review to identify the research gaps and the literature available on the morbidity and mortality in the ART era in Sub-Saharan Africa. The chapter is presented in the form of a manuscript entitled 'morbidity and mortality in the ART era in Sub-Saharan Africa: a systematic review'. This manuscript and protocol will be submitted for review at the BMC: systematic review-journal.

MORBIDITY AND MORTALITY IN THE ANTIRETROVIRAL ERA IN SUB-SAHARAN AFRICA: A SYSTEMATIC REVIEW.

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ABSTRACT

Background: Worldwide despite the availability of antiretroviral therapy (ART), Human Immunodeficiency Virus (HIV)/ Acquired immunodeficiency syndrome (AIDS) still causes morbidity and mortality among patients. The aim of this study was to establish the causes of morbidity and mortality in the modern ART era in Sub-Saharan Africa.

Method/design: We searched relevant studies from the following databases: Google Scholar, PubMed, CINAHL. Two review authors independently screened titles, abstracts and full-text articles in duplicate, extracted data and assessed bias. Inclusion criteria was based on studies reporting morbidity and mortality of HIV infected patients during the antiretroviral therapy (ART) era in Sub-Saharan Africa, studies published from 2008 to 2018, on males or females ≥ 18 years old HIV infected, Peer-reviewed English language publications. Discrepancies were resolved by discussion or arbitration of a third review author. The study used the Preferred Reporting Item of Systematic Review (PRISMA 2015) guideline.

Results: A total of 409 articles were obtained from the database search, finally12 articles met the inclusion criteria and were eligible for data extraction. Among them, three were conducted in Nigeria, two were conducted in Uganda, three were conducted in South Africa, one in Gabon, one in Ethiopia, one in Ghana, and one in Burkina Faso. In most of the included studies, tuberculosis was the leading cause of hospitalization and death, except in one which reported anaemia as the leading cause of hospitalization and in two which reported each respectively wasting syndrome and meningitis as the leading causes of death.

Conclusions: Tuberculosis is the commonest cause of hospitalization and death in Sub-Saharan Africa, but it is always followed by other infectious disease and other non-AIDS related causes.

Systematic review registration: CDR42019141933

Keywords: Morbidity, Mortality, Antiretroviral treatment, Sub-Sahara Africa.

2.1 BACKGROUND

Worldwide, despite the availability of antiretroviral therapy (ART), Human Immunodeficiency Virus (HIV)/ Acquired Immunodeficiency Syndrome (AIDS) still causes morbidity and mortality among patients. Since the first outbreak of HIV in 1981, 39 million people have died due to HIV and related diseases (1)

In Sub-Saharan Africa, HIV/AIDS is a major public health concern. In 2009, 70% of the 33 million people estimated to be infected by HIV, lived in Sub Saharan Africa (2). This region is the most affected by HIV/AIDS, 68% of the world's infected patients live there (3). According to WHO 2013, 74% of HIV related deaths is in Sub-Saharan Africa (4). In 2014 studies reported that 25.8 million people were estimated to be living with HIV (9).

According to UNAIDS (2018), Sub-Saharan Africa, particularly Eastern and Southern Africa remains the region most affected by the HIV epidemic accounting for 45% of the world's HIV infections and 53% of people living with HIV globally (5). In this region in 2017, 19.6 million of adults and children were living with HIV, 800,000 of adults and children were newly infected with HIV and 380,000 of adults and children died due to AIDS (5). In the same year in Western and Central Africa 6.1 million of adults and children were living with HIV, with 370,000 adults and children newly infected with HIV, and 280,000 adults and children dying due to AIDS (5).

Antiretroviral therapy has improved the life expectancy of patients living with HIV/AIDS (6). Maximal and durable suppression of viral replication, restoration of immunologic function, reduction of HIV-related morbidity and mortality, improvement of quality of life, and prolonging survival are the major goals of ART (7).

The fast growth in ART coverage represents one of the great public health success stories in the recent history of HIV care that lead to reduction of mortality and improvement of quality of life of people living with HIV/AIDS (PLWHA) (7). However, despite the availability of antiretroviral therapy (ART), a substantial portion of HIV infected patients have continued to be hospitalised and die from both AIDS-related and non- AIDS-related causes (8)

This study is therefore aimed at identifying the determinants of morbidity and specific causes of mortality in the modern antiretroviral treatment (ART) era in Sub-Saharan Africa.

2. 2 METHODS

We followed the Preferred Reporting Items for the Systematic Reviews and Meta-analysis Protocols (PRISMA-P) 2015 guideline (additional file1) (10). The protocol of this study is registered in PROSPERO with registration number: CRD42019141933.

We searched observational studies reporting on morbidity and mortality in the antiretroviral therapy (ART) era in Sub-Saharan Africa.

2.2.1 Eligibility criteria

Inclusion criteria:

. Studies reporting on morbidity and mortality in the antiretroviral era in Sub-Saharan Africa.

. Studies conducted in the period of 2008 to 2018.

. Studies reporting on adult males or females aged 18 years or older.

. Peer-reviewed English language publications

. Observational studies conducted in Sub-Saharan Africa.

Exclusion Criteria:

. Studies reporting on morbidity or mortality in HIV-uninfected patients.

. Studies reporting on adult males or females under the age of 18 years

2.2.2 Search Strategy for identifying relevant studies

To identify relevant studies, we searched in the following database: Google Scholar, Pub Med, CINAHL. Studies published in English from January 2008 to December 2018, conducted in Sub-Saharan Africa.

The search strategy was based on a combination of relevant terms.

Find below the main search strategy conducted in PubMed in Table1.

Table 2.1: Search strategy in PubMed

Search	Search terms
#1	(Morbidity OR Opportunistic infection related hiv) [MeSH Terms]
#2	(Mortality OR Death) [MeSH Terms]
#3	(ART OR Antiretroviral therapy) [MeSH Terms]
#4	(Sub-Saharan Africa) [MeSH Terms]
#5	#1 AND #2 AND #3 AND #4

We adapted this search strategy for a possible extension to other databases and we also contacted experts in the field to identify additional eligible studies and we manually searched reference lists from relevant studies.

2.2.3 Data collection, analysis and synthesis

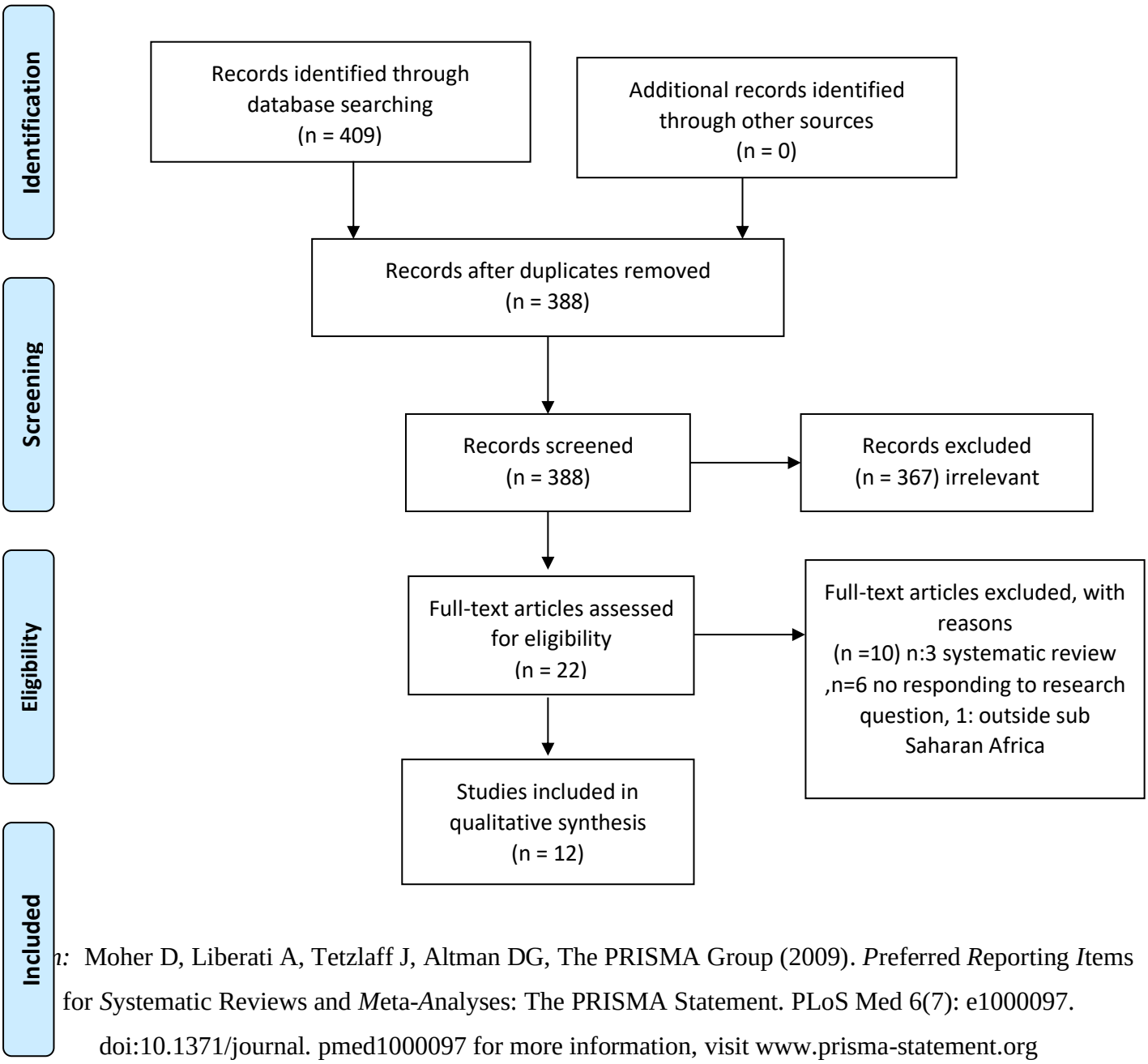
Two reviewers followed independently inclusion criteria for selecting studies, articles were identified and screened by their titles and abstracts for eligibility. The full texts of articles were retrieved. The process of literature selection and reasons for exclusion and inclusion were documented by a PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) flow diagram (figure 1) (11). We used R software version 3.6.2. to analyze the data, we captured information into a spreadsheet about the most causes of hospitalization and death related to HIV in the antiretroviral treatment, Graphic displays (figure 2) was used to visually compare the prevalence of comorbidities across the study region.

2. 3 RESULTS

For the initial search, a total of 409 articles were retained, the number of studies was reduced to 12 after applying the exclusion criteria (Figure1).

Figure2.1: literature search and selection study

Figure 2.1: PRISMA Flow Diagram



n: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal. pmed1000097 for more information, visit www.prisma-statement.org

2.3.1 Characteristics of included studies

Out of 22 reviewed articles, 12 articles were eligible for data extraction (Table 2.2). All 12 studies included were published between 2008 and 2018 in English and they were conducted in Sub-Saharan Africa. Of these, three (14, 19, 20) were conducted in Nigeria, two (15, 24)

were conducted in Uganda, three were conducted in South Africa (21, 23,25), one in Gabon (18), one in Ethiopia (17), one in Ghana (16), and one in Burkina Faso (22). The total sample size of 12 studies was 14619 participants, predominantly female. According to the study designs of the included studies, we noticed seven retrospective chart /cohort studies (14,16,18,19,20,21,22), three prospective studies (15,24,25), two cross-sectional study (17, 23). All included studies were aimed at assessing either cause of death or the most frequent diagnoses among HIV patients during the antiretroviral therapy era. In all included studies the first commonest cause of hospitalization was tuberculosis (14, 15,17,18,19,20,21,22,23,24) except in one (16) and the most cause of death was tuberculosis in all the included studies (14,15,16,18,19,20,21,23,24) except in two (17,22,). We summarised the characteristics of all included studies in Table 2, and from this list, we extracted data related to the causes of hospitalization and death in the modern ART era in Sub Saharan Africa. Most of the articles reported on death than the hospitalization, and tuberculosis was the most disease reported (figure1).

A total of 398 studies were excluded as they did not meet the inclusion criteria, of those 10 underwent a full manuscript review and were found to have no valuable data for the following reasons: Three systematic reviews (27,28,30), 1 article outside of Sub-Saharan Africa (32), 6 articles not responding to our research question (26,29,31,33,34,35).

Table 2.2. Characteristics of the included studies

TB: Tuberculosis, CCM: cryptococcal meningitis, AT: ARV toxicity, CD: Chronic diarrhoea, OM: Opportunistic malignancies, NHRI: non-HIV related illness, NSD: no specified diagnosis.

Authors And date, Geographic location	Sample Number	% female	Average Age (Years)	Intervention	Aim of the study	Study design	Outcomes	Conclusion
Agaba et al.,2011, Nigeria	354	69.2	35 ± 9	Use of ART	Determine Clinical characteristic and predictor of Mortality in hospitalized HIV infected Nigerians	Retrospective chart review	Cause of hospitalization: TB (119,33.6%) , cryptococcal meningitis (CCM) (31,8.8%) , septicaemia (13,16.4%) , ARV toxicities (AT) (41,11.6%) , chronic diarrhoea (CD) (23,6.5%), opportunistic malignancies (OM) (17,4.8%) , other infections (15, 4.2%), AIDS-demented complex (ADC) (4,1.1%) , non HIV related illness (NHRI) (32,9%), no specified diagnosis (NSD) (14,4%) Among patients who died: TB (37, 30.1%), CCM (16, 13.0%), Septicaemia (21,	Findings illustrate the need for early diagnosis of HIV infection, appropriate treatment and prevention of opportunistic infections, and improved access to ART

							17.1%), AT (4, 3.3%), CD (10, 8.1%), OM (12, 9.8%), Other infection (8, 6.5%), ADC (3, 2.4%), NHRI (7, 5.7%), NSD (5, 4%)	
Namutebi et al.,2013, Uganda	201	50	34	On ART	Determine causes and outcomes of hospitalization on in adults on ART.	Prospective cohort study	causes of hospitalization: TB (37, 18%), CCM (22, 11%), Zidovudine (AZT) - with anaemia (19, 10%), Sepsis (10, 5%) and Kaposi's sarcoma (KS) (10, 5%). 42 patients (21%) died: TB (10,24%), CCM (8,19%), Sepsis (5,12%), undiagnosed neurological syndromes (UNS) (9,21%), other illnesses (10,24%) .	Opportunistic infections, malignancy and AZT-associated anaemia contributed to most hospitalizations and Mortality. Intensify prevention, screening, and treatment for opportunistic diseases and early ART initiation. Tenofovir-based regimens, unless contraindicated should be scaled up to replace AZT based regimens

Saavedra et, al 2017, Ghana	547	53.8	41.5	Most of the patients were not on ART.	Investigate most frequent admitting diagnosis and causes of death	Retrospective study (medical records)	Causes of hospitalization: Anaemia (76, 34.2%), Toxoplasmosis: 65(29.3%), Pneumonia: (57, 25.7%), TB (45, 20.3%), HIV wasting syndrome: 44(19.8 %,), Gastroenteritis (GE) (28, 12.6%) Causes of death: TB (77, 34.7%), Anaemia (67, 30.2%), Cerebral toxoplasmosis (CT) (61, 27.5%), Pneumonia (51, 23.0%), GE (23, 10.4%)	In-patient mortality rate among HIV-infected adults admitted to the KBTH (Korle-Bu Teaching hospital) is high. Most patients not receiving ART. Earlier initiation of ART may lower the risk of opportunistic infections (OI) and HIV mortality rates. High index of suspicion and initiation of empiric treatment for TB may reduce early deaths.
Solomon et al,.2018, Ethiopia	744	40.5	24	Receiving ART	Elucidate the spectrum, magnitude	A cross-sectional study	Most common opportunistic infections: pulmonary tuberculosis (PTB) (118, 18%), severe Community-acquired pneumonia (SCAP) (107, 16.3%) and oral candidiasis	The overall prevalence of OI in the era of ART is higher.

					and determining factors of the major opportunistic infections		(OC) (103, 15.6%). The Main causes of death: bacterial meningitis (BM) (16, 28.6%), PTB (13, 23.8%), SCAP (13, 23.8%).	Significant level of AIDS defining illness was noticed. WHO stage II–IV, CD4 level, ART adherence and haemoglobin level became predictors of OIs. Skilled health professionals for proper diagnosis and management of OIs
Okome et al, 2014, Gabon	687	57	34	Administration of ART	Establish an epidemiologic profile of opportunistic diseases	A retrospective study	Hospitalizations: TB (114, 24.89%), herpes zoster (HZ) (73, 15.94%), CT (65, 14.19%), OC (65, 14.19%), and severe pneumonia (SP) (43, 9.39%), CM (2, 0.44%) and pneumocystosis (1, 0.21%), KS (9, 1.96%)	Prevalence of opportunistic diseases in Gabon remains high.

Ogoina et al.,2012, Nigeria	207	47.3	36	Administrating ART	Examine morbidity and mortality patterns of hospitalised patients	A retrospective cohort analysis of routinely collected medical records	Causes of hospitalization : TB (16,29.1%), sepsis (6, 7.3%), chronic diarrhoea (6,7.3%), KS(1, 1.8%), CT (1,1.8%),viral meningoencephalitis (VME) (1,1.8%), CCM (1,1.8%), herpes zoster (1,1.8%), AT (10, 18.1%), renal failure (RF) (2,3.6%), hypertensive heart failure (HHF) (2,3.6%) Causes of death: TB (7, 36.9%), sepsis (4, 21.1%), KS (1, 5.3%), VME (1, 5.3%) CCM (1, 5.3%), RF (1,5.3%) SP (1, 5.3%), Acute bacterial meningitis (ABM) (1, 5.3%).	In current ART era, late presentation and TB continue to fuel HIV/AIDS, with emerging challenges due to ART-related complications
Gyuse et, al 2010, Nigeria	350	61	35.4	Introduction of ART	Determine the causes of death among to plan strategies in improving mortality	Retrospective study	Causes of death: TB (24.0%), followed by sepsis and septicaemia (13.0%), meningitis, encephalitis and anaemia (11.0%), respiratory diseases (RD) (5%), hepatitis (2%), gastrointestinal disease (GID) (3%), and RF (3%).	HIV/AIDS is a major cause of mortality and morbidity.

Macpherson ,et al 2009, South Africa	1131	67	37	Initiated on ART	Determine relative contribution of death to cohort exit and causes and predictors of mortality	Retrospective cohort study	Most common causes of death: TB(47,44.3%) and diarrhoeal diseases (DD) (26,24.5%), meningitis (5,4.7%), hepatic failure (HF) (3,2.83%), opportunistic malignancies (OM) (KS, prostate, cervix, bladder, endometrium) (7,6.59%), Pneumonia (2,1.89%),septicaemia (4,3.77%), HIV encephalopathy (HE) (1,0.94%), Diabetic ketoacidosis (DKA) (1,0.94%), RF (1,0.94%)	Early HIV diagnosis, increased access to ART and early initiation, routine screening and aggressive management of OIs, particularly TB.
Kouanda et al,.2012, Burkina faso	5608	70	35	Receiving ART	Investigate causes of death and the factors associated with mortality in a cohort of patients	Retrospective cohort study	AIDS (64%) and non-AIDS related (36%). Causes of death: wasting (113, 26.9%), TB (67,16%), oesophageal /pulmonary candidiasis (O/PC) (22,5.2%), chronic diarrhoea (CD) (17,4.1%), Toxoplasmosis (16,3.8%), Cryptococcosis (7,1.7%), encephalopathy /dementia 7(1.7%), pneumocystosis (PC) (6,1.4%), OM (CC and KS) (5,1.2%), Leishmaniasis (5,1.2%), BP (4,1.0%), cytomegalovirus disease	Testing patients for HIV and starting ART earlier to reduce the mortality on patients with HIV

					on ART		(CVD) (1,0.2%), anaemia (22,5.2%), septicaemia (13,3.1%), respiratory disease (16,3.8%), AT (16,3.8%), metabolic disease (MD) (13,3.1%), myocardiopathy (MP) (14,3.3%), BM (4,1.0%), high blood pressure (HBP) (4,1.0%), depression (3,0.7%), septic abortion (2,0.5%).	
Meintjes et al, 2015, South Africa	585	57.8	35.3	ART	Describe hospital level disease burden and factors contributing to morbidity and mortality	Cross-sectional study with prospective follow-up	Most cause of hospitalization: TB(238, 40.7%), Bacterial infection (100, 17.1%), AIDS other than TB (64,10.9%). Major organ dysfunction (59, 10.1%), other diagnosis (35, 6.0%), Venous thromboembolis (VTE) (1, 5.3%), Drug related (24, 4.1%), non-communicable diseases (NCDs) (22, 3.8%), psychiatric (9, 1.5%), None diagnosed (3, 0.5%). Most causes of death: TB (37.2%) and other AIDS- (24.4%)	HIV is still accounting for nearly two-thirds of medical admissions and is associated with high mortality

Moore et al., 2011, Uganda	1132	73	38	ART	Describe mortality over time and to determine clinical conditions associated with death	Prospective study	Most common condition TB (21% of deaths), Candida disease (CD) (15%). cryptococcal disease (CCD) (12%), Pneumocystis jiroveci pneumonia (PCP) (8%) and KS (6%)	Potentially remediable conditions and preventable infections were associated with mortality while on ART
Mzileni et al 2008, South Africa	3073	67.4		ART	Describe mortality trends and causes of deaths	Prospective observational study	Causes of death: TB (42, 20.5%), CD (25, 12.2%), CCM (18, 8.8%), bacterial pneumonia/pneumocystis pneumonia (BP/PCP) (12, 5.8%), KS and lymphoma (17, 8.3%), Hepatitis (6, 2.9%).	Prevention of AIDS-defining conditions and expansion of earlier access to ART could substantially reduce mortality.

Figure 2.2: Prevalence of articles

This graph reports the prevalence of articles that described the causes of death and of hospitalization. Some articles reported both and others reported either hospitalization or death, 6 articles reported both causes of death and hospitalization, 5 articles reported causes of death and 1 reported causes of hospitalization. Tuberculosis was the most disease reported by many articles.

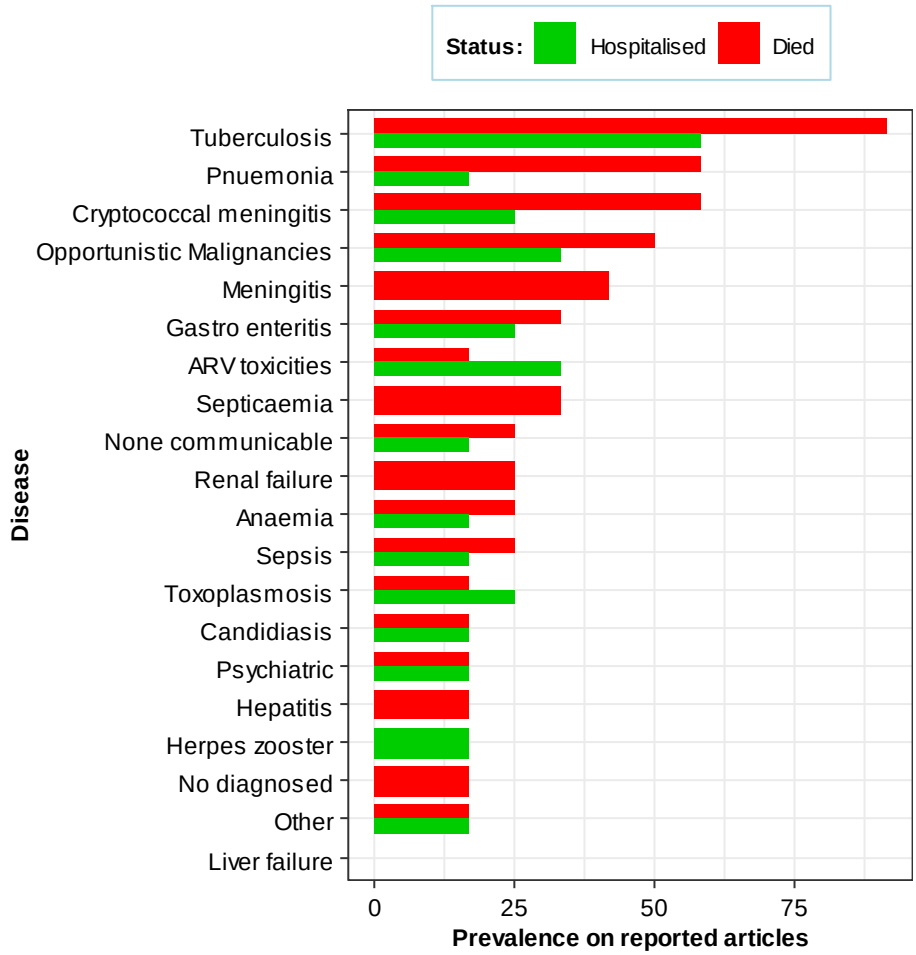


Table 2.3: Prevalence of the reason of hospitalization

Diagnosis	min	IQR			Max
		Q1	Q2	Q3	Q4
Tuberculosis	18.0	19.1	24.9	31.4	40.7
Cryptoccocal meningitis	1.8	5.3	8.8	9.9	11.0
Septicaemia	16.4	16.4	16.4	16.4	16.4
ARV_toxicities	4.1	8.5	10.8	13.2	18.1
Gastroenteritis	6.5	8.7	10.9	11.8	12.6
Malignancies	1.8	1.9	3.4	4.8	5.0
Others	4.2	5.9	7.6	9.2	10.9
No_diagnosed	4.0	4.0	4.0	4.0	4.0
Toxoplasmosis	1.8	8.0	14.2	21.7	29.3
Sepsis	5.0	5.6	6.2	6.7	7.3
Cahexia	19.8	19.8	19.8	19.8	19.8
Herpes	1.8	5.3	8.9	12.4	15.9
Pneumocystosis	0.2	0.2	0.2	0.2	0.2
Meningitis	1.8	1.8	1.8	1.8	1.8
Pneumonia	16.3	18.7	21.0	23.3	25.7
Anaemia	10.0	16.1	22.1	28.2	34.2
Renal failure	3.6	3.6	3.6	3.6	3.6
Non communicable disease	3.6	5.0	6.3	7.7	9.1
Psychiatric	1.1	1.2	1.3	1.4	1.5
Candidiasis	14.2	14.5	14.9	15.2	15.6

IQR: Interquartile range, Q2: Median

In this table above tuberculosis holds the leading reason of hospitalization with 40.7% followed by anaemia with 34.2% and toxoplasmosis with 29.3%. Non communicable disease had been also noticed with 9.1%.

Table 2.4: Prevalence of the cause of death

Diagnosis	**min**	**IQR**			**Max**
		Q1	**Q2**	**Q3**	**Q4**
Tuberculosis	16.0	22.4	24.0	35.8	44.3
Cryptoccocal meningitis	0.4	3.5	8.8	12.0	13.0
Septicaemia	3.1	3.6	8.4	14.0	17.1
ARV_toxicities	3.3	3.4	3.5	3.7	3.8
Gastroenteritis	4.1	7.1	9.2	13.9	24.5
Malignancies	1.2	5.5	6.3	7.9	9.8
Others	6.5	11.0	15.4	19.9	24.4
no_diagnosed	4.0	9.0	14.0	19.0	24.0
Toxoplasmosis	1.7	8.2	14.6	21.1	27.5
Sepsis	13.0	17.0	21.0	21.1	21.1
Pneumocystosis	1.4	1.4	1.4	1.4	1.4
Meningitis	1.0	4.7	5.3	11.0	28.6
Pneumonia	1.0	3.6	5.8	8.7	23.0
Anaemia	5.2	8.1	11.0	20.6	30.2
Hepatitis	2.0	2.2	2.5	2.7	2.9
Liver failure	2.8	2.8	2.8	2.8	2.8
Renal failure	0.9	2.0	3.0	4.2	5.3
Non communicable disease	1.4	2.1	2.8	5.1	7.4
Psychiatric	0.7	1.1	1.5	2.0	2.4
Candidiasis	5.2	7.7	10.1	12.6	15.0

IQR: Interquartile range, Q2: Median

Regarding the table above, tuberculosis is the leading cause of death with 44.3%, respectively followed by Anaemia with 30.2% and meningitis 28.6%.

2.4 DISCUSSION

The objective of this study was to identify the causes of hospitalization and causes of death among HIV patients in the ART era in Sub-Saharan Africa. The causes reported were opportunistic infections, opportunistic malignancies, and non-AIDS related. Among opportunistic infections, in most of the included studies, tuberculosis was the commonest leading cause of hospitalization and death among people living with HIV. It accounted for between 18-40.7% (table2.3) of hospitalization and 16-44.3% (table2.4) of death. The prevalence of death reported due to tuberculosis was higher than what had been reported in Thailand (38). This may be a consequence of many countries of Sub Saharan Africa, not having well developed medical analysis laboratory yet, therefore late diagnosis of tuberculosis could imply the increased rate of morbidity and mortality. Non-expanding access and late initiation of antiretroviral therapy and anti-tuberculosis treatment in some countries in Sub-Saharan Africa could also increase the burden of the disease.

Studies conducted in Rio de Janeiro; Brazil estimated 80% of reduction of tuberculosis incidence for HIV infected adults associated with the use of antiretroviral therapy (37). Many patients in Sub Saharan Africa arrived at the hospital at the later stage of disease with the rate of CD4 $\leq$ 200/cells/mm^3, many patients do not have information on disease because of lack of counselling and testing services in the region.

If patients start ART at the higher baseline CD4 count, there is potential to decrease morbidity and mortality (39).

Of the included studies, one reported from Ghana did not find tuberculosis as the first cause of hospitalization in Sub-Saharan Africa, it reported anaemia as the first cause of hospitalization (16). The included studies accounted for 34.2% of hospitalization(table2.3) and 30.2% of death (table2.4) due to anaemia. Similarly, in America, another study among HIV infected African women found almost the same result (47). Anaemia is a known independent risk factor for death among HIV/AIDS patients. It has been reported that 59% of patients who suffer from anaemia are likely to die even if other opportunistic infections associated with it are treated

appropriately (46). Anaemia is known to be multifactorial, several factors like poor nutrition, malaria, hookworm infection and other infections have been reported among its causes (48). Other studies showed a relation between the prevalence of anaemia and HIV (40, 41). This may be a result of late initiation of ART. A Study in South Africa showed that early initiation of ART resolved 66% of anaemia in HIV positive patients after just one year of treatment (45).
Two of the included studies in Burkina Faso, (22) and in Ethiopia, (17) did not find tuberculosis as the first cause of death, they found respectively wasting syndrome and bacterial meningitis. Similarly, out of the included studies, other studies did not find tuberculosis as the first leading cause of hospitalization and of death, in Europe, precisely in French Guyana, they reported that among AIDS-related deaths the most frequent diseases were histoplasmosis and toxoplasmosis (36). In Asia precisely in Taiwan, they reported that the first HIV-associated opportunistic infections were oesophageal candidiasis (43).

Opportunistic malignancies accounted between 1.8%-5% of hospitalization (table2.3) and 1.2%-9.8% of death (table2.4) in our included studies. It was noticed that Kaposi Sarcoma was the most reported (14, 15, 24, 25) as causes of hospitalization and death among HIV patients. Lack of detecting early neoplasm through screening may imply the increase of the disease in Sub-Saharan Africa because many medical laboratories in Sub-Saharan Africa do not have devices and laboratories required to support the screening.
Many people initiate ART while Kaposi sarcoma is already at advanced stages (44). Similarly, in India Kaposi Sarcoma had been reported as the most opportunistic malignancy between 2% -5 % (13).

Among non-AIDS related, in some of our included studies, ARV toxicities were shown to cause morbidity and mortality (14), (19), (15). The prevalence was almost the same in the three studies. To reduce morbidity and mortality, counselling about the adverse effects of antiretroviral drugs and aggressive monitoring of patients must be conducted before and after initiation to the antiretroviral therapy. Other non-AIDS related conditions like non-communicable disease, psychiatric, had been reported on in some of our included studies (14, 21, 22, 23). A better knowledge of the commonest comorbidities is very important to improve health promotion, prevention and care among HIV patients. Poverty, limited access to ART, malnutrition and interruption of supply at the program level had been found to be among the factors which limit the control of HIV and the effectiveness of ART in African countries (14).

2.5 CONCLUSION

In conclusion, tuberculosis was the first commonest cause of hospitalization and death in Sub-Saharan Africa according to the included studies, this was followed by other infectious diseases, opportunistic malignancies, and other non-AIDS related. To reduce morbidity and mortality in the ART era, all the different causes of hospitalization and causes of death must be attended to.

2.6 RECOMMENDATION FOR FUTURE RESEARCH

According to the findings, tuberculosis is the leading cause of hospitalization and the major killer of people living with HIV in Sub-Saharan Africa.

We recommend early HIV diagnosis and initiation of ART. Additionally, we suggest strengthening of infrastructure for screening for tuberculosis, early initiation and increased access to ART, and to conduct research on the other opportunistic infections which always accompany tuberculosis, and non-communicable diseases.

2.7 STRENGTHS AND LIMITATIONS

The strength of this study is the relevant articles finding reported on the morbidity and mortality in the antiretroviral Era in Sub Saharan Africa. There are no limitations in this study.

ABBREVIATIONS

ART: Antiretroviral therapy;

HIV/AIDS: Human Immunodeficiency Virus / Acquired Immunodeficiency Syndrome

PICO: Population, Intervention, Comparator and Outcome

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

SADC: Southern African Development Community

UKZN: University of KwaZulu-Natal

PD: prevalence of death

ph: prevalence of hospitalization

DECLARATIONS

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Availability of data and materials

All data generated from this study will be included in the published systematic review article and will also be available on request.

Authors' contributions

MRG conceptualised the study and prepared the manuscript under the guidance and supervision of NM. MRG and GAM identified, selected and screened the articles for eligibility, and the discrepancies were resolved by the intervention of NM. The process of literature selection and reasons for exclusion and inclusion were All authors contributed to the development and design of the study. MRG and NM contributed to the methodology and reviewing of the manuscript. All authors contributed to the final version. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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CHAPTER 3: A CHART REVIEW

This retrospective chart review aimed at identifying the determinants of morbidity and mortality in the modern antiretroviral treatment in South Africa. It is addressing objective 2 of the study. The results of this study will help to strengthen and influence policy and guide future research in antiretroviral treatment era. We present the chapter in the form of manuscripts entitled: 'Morbidity and mortality in the modern antiretroviral treatment era in a tertiary teaching hospital in Durban, South Africa.'

MORBIDITY AND MORTALITY IN THE MODERN ANTIRETROVIRAL TREATMENT ERA IN A TERTIARY TEACHING HOSPITAL IN DURBAN, SOUTH AFRICA.

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ABSTRACT

Introduction: Human immunodeficiency virus /acquired immune deficiency syndrome (HIV/AIDS) is a public health concern in South Africa. This study aimed at identifying the determinants of morbidity and mortality in the era of modern antiretroviral treatment (ART).

Methodology: A retrospective study was conducted; data were obtained from medical records of all HIV infected patients admitted to King Edward medical wards from January to December 2018. This included demographic profile, clinical attributes and laboratory records. Data were analysed using R software where descriptive and inferential statistics were presented. That is, five numbers summaries, box plot, Chi square, all fisher exact test and t test or rank some test

Results: A total of 577 (50.6%) females and 564 (49.4%) males aged 12 years old and older infected by HIV were included in the study. The mean age of all the patients was 39.6±12.2, 506 (44.3%) patients had CD4 less than 200 cells /mm^3 and 273 (23.9%) had VL > 1000 copies/ml. Association between CD4 cell count and Viral load ($p< 0.05$) was found. Male gender [OR 1.39(1.07-1.8) p=0.015], Age [OR1.02 (1.01-1.03) $p< 0.001$], CD4 <200 cells/mm^3 [OR 2.14(1.37-3.45) p=0.001], VL > 1000 copies/ml [OR 1.93(1.08-3.63) p=0.032] were associated with mortality in our cohort. Tuberculosis (TB) was the most common diagnosis on admission and the leading cause of death which accounted for 257 (22.5%) and 73 (24.3%) respectively, followed by kidney disease with 83 (7.2%) for admission and 38(12.6) for death. Only 70% of patients had been reported to be on ART.

Conclusion: Despite the modern antiretroviral treatment which is free, available to everyone and with fewer toxicities, HIV infected patients are still hospitalized with HIV-related complications and are also dying of AIDS. Most of the patients have been admitted with a low CD4 cell count, an indication of delayed initiation of treatment or not properly adhering to treatment. This was found to be associated with a high prevalence of TB, other opportunistic infections and non-communicable disease**.** Hence, the need for raising the awareness of early appropriate treatment, prevention of opportunistic infection and tackling non-communicable disease related to HIV. Also, these findings illustrate the need to investigate the reason for starting treatment late.

Keywords: Morbidity, Mortality, Antiretroviral therapy, South Africa

3.1 BACKGROUND

Worldwide, Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS) pandemic is a challenging public health concern (1). South Africa bears the highest number of people living with HIV/AIDS (2). Statistics showed that in 2012 approximately 6.4 million HIV infected people living in South Africa were 17% of the global burden of infection (3). In 2018 an estimation of 7.7 million people was living with HIV in South Africa (4). In the same year, 240,000 new HIV infections appeared, and 71,000 South Africans died from AIDS-related illnesses (5). South Africa implemented the National HIV/AIDS and Sexually Transmitted Infections (STI) National Strategic Plan (NSP) to tackle the HIV/AIDS epidemic. The primary objectives of this plan were to reduce HIV incidence by 50% and to expand the availability and access to ART to 80% of all HIV infected patients in the country (6).

The target of the Joint United Nations Programme on HIV/AIDS (UNAIDS) is to have 90% of all people tested for HIV, 90% treated, 90% virologically suppressed by 2020 and to end HIV infection (7). Early access to antiretroviral therapy (ART) to all people living with HIV regardless of CD4 count improve life expectancy (7). Due to the modern antiretroviral therapy which has enhanced the survival of HIV patients (8), HIV infection is no longer a fatal illness but a chronic disease which is now manageable (9). The antiretroviral therapy (ART) suppresses viral replication, restores immune function, reduces HIV associated morbidity and mortality (10).

Despite these gains, 8-26% of African patients die in the first year of initiating ART, with most deaths occurring in the first three months (11). Mortality is attributed to late initiation of ART when patients have advanced disease with increased risk of opportunistic infections and immune reconstitution inflammatory syndrome (12). The systematic review has shown the causes of morbidity and mortality in Sub-Saharan Africa in the ART era as tuberculosis, anaemia, meningitis, toxoplasmosis, gastroenteritis, pneumonia. Currently, antiretroviral treatment is freely available and modern, there is a fixed-dose combination, drugs are less toxic unlike in the past where most of the drugs were toxic with multiple treatment-related complications (8). Based on advances made in treatment, AIDS-defining illnesses related should no longer be observed, however up until today HIV infected patients still suffer and die

from AIDS. Many barriers to adherence to ART had been revealed by several studies, among them socio economic factors (such as poverty, food insecurity, unemployment and transport costs) education, cultural, political factors, stigma, discrimination, lack of social support (13, 14, 15). The goal of this study is to identify the reason of hospitalization and cause of death in this population.

3.2 METHODOLOGY

Design

We conducted a retrospective study of HIV infected patients who had been admitted in the medical ward at King Edward hospital, Durban, South Africa.

Study population

All records of patients admitted to the medical wards from January to December 2018 were reviewed. Those included in the study were all HIV infected patients aged 12 years old and older who had been hospitalized in the medical wards at King Edward hospital during the study period. Non-HIV patients and children were excluded.

Data extraction

Data extracted from medical records included socio-demographics, clinical parameters, admission date, discharged date, deceased date, causes of death, causes of hospitalization, laboratory data (CD4 cell count, RNA viral load, based on the HIV test) and ART. The reasons for admission and causes of death were based on the final diagnostic on discharge. The final diagnostic on discharge was obtained after the patients had carried out laboratory examinations. It was based on similar standardized terminology.

STATISTICAL ANALYSIS

R statistical computing software version 3.6.2. was used for data analysis. Tables and graphical displays were used to present the results. In addition, the association between the covariates was tested either with the Chi-Square test, Kruskal Wallis or Wilcoxon rank-sum test depending on the type of variables. A p-value < 0.05 was used as a benchmark for determining the level of statistical significance.

ETHICAL APPROVAL

We obtained full ethical approval from the Biomedical Research and Ethics Council

(BREC). Permission to conduct the research was provided by King Edward VIII hospital management.

3.3 RESULTS

Four thousand (4000) records of patients of 12 years and older admitted to the medical wards at King Edward hospital from January to December 2018 were examined. This study included 1 141 patients diagnosed or known HIV positive. Out of the 1 141 patients, 564 (49.4%) were males and 577 (50.6%) were females. The mean age for the entire cohort was 39.7±12.1, with a range of 12 to 92, 506 (44.3%) patients had CD4 count <200 cells /mm^3, 253 (22.2%) patients had a viral load more than 1000 copies/ml. Among the included patients 301 (26.3%) died, while 840 (73.6%) were discharged home alive (table3.1). Age, male gender, CD4 cell and Viral load were associated with mortality ($p< 0.05$) (table3.2). Association between CD4 cell count and viral load was found (table3.3). Tuberculosis was the most common diagnosis reported at admission and accounted for 257 (22.5%) of the admissions, followed by kidney disease 83 (7.2%), anaemia 75 (6.6%), cryptococcal meningitis 62 (5.4%). Tuberculosis was also the number one cause of death with 73 (24.3%) followed by acute or chronic kidney disease 38 (12.6%), Pneumonia 19 (6.3%). Other conditions that were responsible for admission 166 (14.5%) and death 43 (14.3%) are shown in table3.4 and table3.5, respectively. There was no significant difference in the duration of hospital stay between males and females (fig3.1). It was noticed that 70% of patients were reported to be on ART, among them, 53.1% was discharged and 16.9% died (fig3.2).

Table 3.1. Comparison of HIV patients in medical wards at King Edward hospital by disposition at discharge and characteristic of 1141 patients.

Characteristic	Discharged (n=840)	Died (n=301)	p-value	Overall (n=1141)
Gender			0.014	
Male (Ref)	397 (47.3%)	167(55.5%)		564(49.4%)
Age			0.007	
Mean±SD	38.9±11.7	41.8±13.1		39.7±12.1
CD4(cells /mm^3)			0.001	
<200	363 (43.2%)	143 (47.5%)		506 (44.3%)
200-<350	126 (15.0%)	34 (11.3%)		160 (14.0%)
350-<500	100 (11.9%)	20 (6.6%)		120 (10.5%)
500+	141 (16.8%)	26 (8.6%)		167 (14.6%)
Missing	110 (13.1%)	78 (25.9%)		188 (16.5%)
Length hospital stay(days)			0.003	
Mean±SD	9.46±9.43	8.65±10.5		9.25±9.72
Viral load (copies/ml)			0.049	
<50	104 (12.4%)	16 (5.3%)		120 (10.5%)
50-<1000	94 (11.2%)	17 (5.6%)		111 (9.7%)
1000+	195 (23.2%)	58 (19.3%)		253 (22.2%)
Missing	447 (53.2%)	210 (69.8%)		657 (57.6%)

The p-values are from table Stack and based on non-missing cases only.

Table 3.2. Factors associated with Mortality among HIV infected patients admitted at King Edward hospital

Explanatory	**OR(Univariable)**	**OR(Multivariable)**
Gender:		
Male (Ref)	1.39 (1.07-1.81, p=0.015)	1.12 (0.68-1.84, p=0.647)
CD4 (cells /mm^3)		
<200	2.14 (1.37-3.45, p=0.001)	4.45 (1.96-11.62, p=0.001)
200- <350	1.46 (0.83-2.59, p=0.186)	2.41 (0.87-7.16, p=0.097)
350-<500	1.08 (0.57-2.04, p=0.803)	1.00 (0.24-3.64, p=0.999)
Age(years)		
20-40	1.69 (0.74-4.57, p=0.250)	2.67 (0.40-54.12, p=0.389)
40-60	1.88 (0.82-5.09, p=0.169)	2.93 (0.29-71.84, p=0.413)
60+	3.94 (1.55-11.48, p=0.007)	8.02 (0.38-304.00, p=0.204)
Duration(weeks)		
1-2	0.60 (0.42-0.85, p=0.005)	0.49 (0.20-1.11, p=0.095)
2-3	0.70 (0.43-1.11, p=0.142)	0.25 (0.06-0.89, p=0.038)
3	0.80 (0.52-1.21, p=0.308)	0.43 (0.05-2.79, p=0.389)
Viral load (copies/ml)		
50-1000	1.18 (0.56-2.48, p=0.667)	1.08 (0.48-2.44, p=0.857)
1000+	1.93 (1.08-3.63, p=0.032)	1.36 (0.70-2.74, p=0.380)

Table 3.3. Relations between Viral Load and sex, age, CD4, duration of stay, outcome.

Viral load (copies/ml)	**<50 (n=120)**	**50-<1000 (n=111)**	**1000+ (n=253)**	**p-value**	**Overall (n=1141)**
Gender				0.609	
Male (Ref)	58 (48.3%)	49 (44.1%)	126 (49.8%)		564 (49.4%)
Age				0.675	
Mean±SD	39.4±11.4	39.5±10.5	39.1±12.5		39.7±12.1
CD4(cells/mm^3)				< 0.001	
<200	39 (32.5%)	47 (42.3%)	165 (65.2%)		506 (44.3%)
200-<350	11 (9.2%)	25 (22.5%)	38 (15.0%)		160 (14.0%)
350-<500	17 (14.2%)	19 (17.1%)	18 (7.1%)		120 (10.5%)
500+	51 (42.5%)	19 (17.1%)	28 (11.1%)		167 (14.6%)
Missing	2 (1.7%)	1 (0.9%)	4 (1.6%)		188 (16.5%)
Duration of stay(days)				0.909	
Mean±SD	10.0±9.13	9.41±8.36	10.4±10.3		9.25±9.72
Outcome				0.049	
Discharged	104 (86.7%)	94 (84.7%)	195 (77.1%)		840 (73.6%)
Died	16 (13.3%)	17 (15.3%)	58 (22.9%)		301 (26.4%)

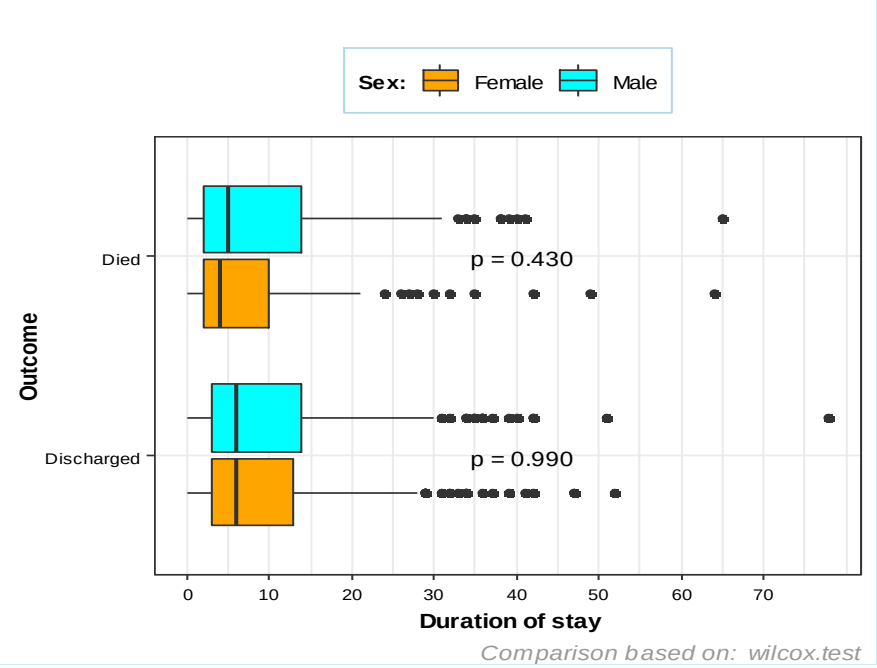
Table 3.4. Reasons for admissions among HIV patients in medical wards at King Edward hospital

Diagnosis	Frequency	Percentage
Tuberculosis	257	22.5%
Kidney disease	83	7.2%
Anaemia	75	6.6%
Cryptococcal meningitis	62	5.4%
Pneumonia	56	4.9%
Gastroenteritis	42	3.7%
Parasuicide	35	3.1%
Lymphoma	32	2.8%
Sepsis	31	2.7%
Congestive cardiac failure	29	2.5%
Cerebrovascular accident	25	2.2%
Unspecified meningitis	25	2.2%
Liver failure	24	2.1%
Bronchopneumonia	19	1.7%
Viral meningitis	19	1.7%
Hypertension	18	1.6%
Psychiatric	14	1.2%
Diabetic ketoacidosis	13	1.1%
Diabetes mellitus	10	0.9%
Headache	10	0.9%
Deep vein thrombophlebitis	9	0.8%
Epilepsy	9	0.8%
Adult onset seizures	8	0.7%
Asthma	8	0.7%
Bronchiectasis	7	0.6%
Heart failure	7	0.6%
Kaposi's sarcoma	7	0.6%
Pneumocystis pneumonia	7	0.6%
Drug-induced liver injury	6	0.5%
Nephrotic syndrome	6	0.5%
Thrombocytopenia	6	0.5%
Cholelithiasis	5	0.4%
Gastritis	5	0.4%
Hepatocellular carcinoma	3	0.3%
Toxoplasmosis	3	0.3%
Other medical illnesses non HIV related	166	14.5%
TOTAL	1141	100%

Table 3.5. Causes of death among HIV patients in medical wards at King Edward hospital

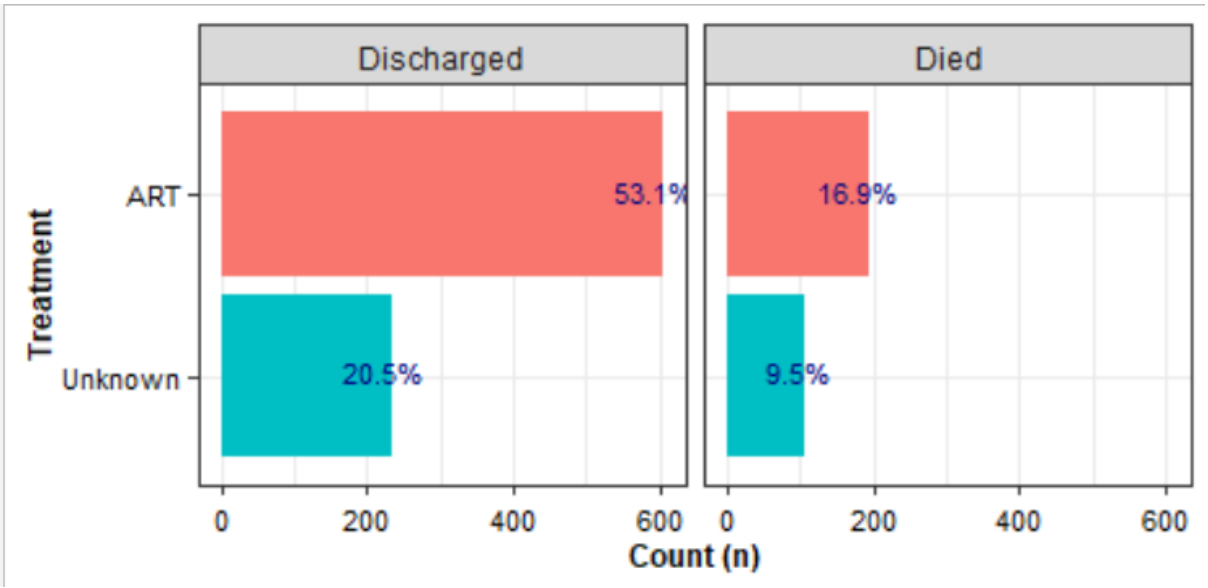
Diagnosis	Frequency	Percentage
Tuberculosis	73	24.3%
kidney disease	38	12.6%
Pneumonia	19	6.3%
Liver failure	14	4.7%
Anaemia	13	4.3%
Congestive cardiac failure	13	4.3%
Gastroenteritis	12	4.0%
Cryptococcal meningitis	10	3.3%
Lymphoma	10	3.3%
Sepsis	10	3.3%
Bronchopneumonia	9	3.0%
Unspecified meningitis	9	3.0%
Cerebrovascular accident	8	2.7%
Viral meningitis	8	2.7%
Kaposi's sarcoma	6	2.0%
Diabetic ketoacidosis	3	1.0%
Hepatocellular carcinoma	3	1.0%
Other medical illnesses non-HIV related.	43	14.3%
TOTAL	301	100%

Figure 3.1. Length of hospital stay



The p-values are more than 5% implying that there was no significant difference in the duration of stay between males and females. This applies to both the duration of stay before discharged or demising.

Figure 3.2: Relation between ART treatment and outcome



Only 70% of patients had been reported to be on antiretroviral treatment (ART) on admission or discharge.

3.4 DISCUSSION

This study aimed to identify the determinants of morbidity and mortality among HIV infected patients in the modern era of antiretroviral treatment (ART) at King Edward hospital from January to December 2018.

In this study tuberculosis was reported to be the most cause of hospitalization and of death accounting with 22.5% and 24.3%, respectively (table3.4, table3.5). Similarly, in Uganda, a study reported 18% of admissions and 24% of death due to tuberculosis (16). Other studies conducted in Nigeria (17), in Gabon (18) and in South Africa (41) had similar findings.

This may be as a result of lack of or poor TB preventative strategies, inadequate HIV counselling and testing services, also delays in referral and ART initiation are all potential reasons for late consultation and increase of TB. Other issues include, the poor infection control measures in most public spaces, lack of active case finding (ACF) and contact tracing. A study conducted in the Ivory coast showed that access to antiretroviral therapy alone or early antiretroviral treatment with isoniazid preventive therapy (IPT) respectively, decrease the risk of mortality among HIV patients (21). Another study conducted in Rio de Janeiro revealed that TB prevalence and mortality of HIV patients were significantly reduced by increasing TB screening and the implementation of IPT (22).
In addition, as in majority (44.3%) of the patients included in this study, CD4 counts were ≤ 200 cells /mm^3 and VL > 1000 copies/ml, that is a risk for developing an opportunistic infection. Other studies conducted in Gondar and India reported a high risk of developing opportunistic infection among this group (19, 20).

Anaemia and cryptococcal meningitis were also frequently diagnosed during admission. Anaemia accounted for 6.6% of admission. This was less than what had been found in Ghana (23). In this study, iron deficiency, vitamin B12 deficiency, folate deficiency and side effect of zidovudine are suspected to induce anaemia. Many patients had been admitted at the late stage of their disease that implied a delay in their initiation to antiretroviral treatment. Anaemia is known to be a significant problem among patients with HIV infection (24).
Even though anaemia can occur at any stage of HIV infection, its frequency and severity are positively correlated with progression of the disease (25). Providing an early antiretroviral treatment, in general, is known to decrease anaemia among HIV patients by inhibiting the progress of the diseases, however zidovudine an element of some antiretroviral treatment

regimens is identified as the commonest cause of drug-associated anaemia in low-income countries (26). A study conducted in Ethiopia showed that overall, ART exposure reduced anaemia prevalence among HIV patients (27).

Cryptococcal meningitis accounted for 5.4% of admission among HIV patients included in this study. Similarly, the same findings were also found in Latvia (28) and in Uganda (35). This may result as most of the HIV patients included in this study had lack of information about preventive therapy among those with low CD4 cell counts. Some of the patients had delayed initiation to ART. Cryptococcal meningitis is an opportunistic infection which occurs in HIV patients in their late stage of disease (30). Screening of cryptococcal antigenemia among persons living with HIV can allow early identification of symptomatic cases and improve health outcomes. The early access to antiretroviral treatment had improved the immune system of many HIV patients so that they do not become vulnerable to infection with cryptococcus (29). Studies conducted in the United States (31) and in Thailand (32) showed how fluconazole prophylaxis reduced the incidence of cryptococcal disease among HIV patients.

After tuberculosis, kidney disease (acute or chronic) was found as the second reason for admission and second causes of death. Among HIV infected patients admitted to King Edward, 7.2% accounted for admission and 12.6% for death, which is comparable to what had been reported in Zambia (41). Renal failure in HIV infection is associated with increased morbidity and mortality (33). Patients who were admitted at the late stage of the disease and had low CD4 less than 200 cells /mm^3 that also contributed to renal impairment. A study reported that chronic renal failure usually occurs only in advanced disease and mostly in patients with a CD4 count of fewer than 200 cells / mm^3 (34). The early access to antiretroviral treatment may improve impaired renal function among HIV patients (35). In the ART regimen, tenofovir (TDF) is the first-line treatment of HIV infection, however, it is associated with a higher risk of kidney disease (47).

The other cause of death was pneumonia with 6.3% after kidney disease. A study conducted in Uganda found almost the same prevalence of pneumonia among HIV patients (36), however, another study conducted in Malawi (37) found a high prevalence of pneumonia than this study. According to the findings of this study, pneumonia might result because of lack of preventive therapy among HIV patients who had been admitted to the hospital and most of them starting late antiretroviral treatment. It had been found that ART is independently and statistically significantly associated with decreased mortality and morbidity in pneumonia patients (38).

Some patients were admitted at the hospital with acute symptoms, such as an acute respiratory failure, a study shows that it is a complication of pneumonia and it is associated with a high risk of death among HIV patients (39).

Even though there were more women than men included, more men died while admitted to the hospital than women with ($p< 0.05$). This is comparable to that reported from another study conducted in Nigeria (40). In this study, male gender was admitted with lower CD4 cell counts and more severe opportunistic infection. Men may be presenting into care later than women with more advanced disease.

Age, male gender, CD4 cell count less than 200 cells /mm^3, HIV viral load more than 1000 copies/ml were reported to be associated with mortality in patients. These findings indicate that patients who died during hospitalization were more likely to present with poor performance status and more advanced and severe disease. A study conducted in Ethiopia reported almost the same, they found CD4 count $\leq$ 200cells/mm^3 as a prediction of mortality (43). This study found an association between CD4 cell count and HIV viral load ($p< 0.05$), low CD4 cell count implies high viral load, and this might result as most of the patients had been admitted in the advanced status of the disease. However, a study conducted in Europe had contrary findings (44).

3.5 CONCLUSION

Regarding the modern era of ART, there have been many improvements. Currently, ART regimens are well tolerated with fewer associated severe adverse events that avoid disability or permanent damage compared with older regimens used in the past (45). Numbers of patients switching or discontinuing treatment have decreased, compared to a decade ago (46), Treatment is easier to take unlike in the past. Fixed-Dose Combination (FDC) using one pill a day as opposed to two doses of three to four drugs a day can be taken (42). Despite this improvement in treatment, people living with HIV are still hospitalised and die of AIDS. This study found that many patients were admitted with a low CD4, an indication of advanced disease. Age, male gender, CD4 cell count less than 200 cells /mm^3, HIV viral load more than 1000 copies/ml were reported to be associated with mortality in patients. Tuberculosis remains the most common cause of morbidity in patients infected with HIV infection in South Africa. This study noticed that non-communicable disease such as kidney disease play a huge role in mortality among HIV patients admitted in South Africa. Not only opportunistic infection should be focused on, but the non-communicable disease also should be tackled to reduce

morbidity and mortality among HIV patients in South Africa. Health care professionals should take measures to strengthen the early diagnosis, prevention and treatment of the common opportunistic infections by investing effort into the improvement of education, screening, initial diagnosis and treatment in the community. High mortality among men was associated with more advanced disease.

3.6 LIMITATION OF THE STUDY

As the study was retrospectively designed, some detailed clinical and laboratory (CD4 and viral load) variables were not available for some patients. There were missing variables such as ART treatment, viral load and CD4 count cell of some patients on some files.

However, the missing data did not significantly affect the major outcomes of the study since the findings were comparable to those within and outside South Africa.

DECLARATION

Ethics approval and consent to participate: Ethical approval was obtained from the KZN Department of Health and UKZN BREC Ethics committee.

Consent for publication: Not applicable

Competing interests:

None declared.

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Authors' contribution

MRG, SG and NM conceptualised and designed the study. MRG prepared the first draft. MRG and SG did data collection and analysis. NM assisted with the manuscript preparation. All authors reviewed draft versions of the manuscript and gave their final approval of the manuscript.

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CHAPTER 4: SYNTHESIS: SUMMARY, CONCLUSION AND RECOMMENDATIONS.

This chapter presented a summary of the research findings, assess the strengths and limitations of the study. The conclusion, recommendations for improving existing services also are also presented.

4.1 BACKGROUND

The main aim of this study was to identify the determinants of morbidity and mortality in the modern antiretroviral treatment (ART) era in South Africa.

Many improvements have been observed in the modern ART era, such as fixed-dose combination, availability of free treatment, and fewer toxicities of drugs unlike in the past. Despite that, patients are still hospitalized and die of AIDS. According to UNAIDS, South Africa have the largest programme of antiretroviral treatment in the world (1). South Africa's antiretroviral therapy services have expanded in keeping with the WHO changing guidelines (2).

The systematic review conducted in Sub-Saharan Africa identified the research gap, suggested novel ideas for future research. The retrospective chart review gave an overview of the causes of death and admissions among HIV infected patients in the medical ward at King Edward Hospital in South Africa. There is a need for an early initiation to antiretroviral treatment and preventive therapy of AIDS. Tuberculosis remains the main commonest cause of hospitalization and death in Sub-Saharan Africa and in South Africa. The conclusion and recommendation drawn in this study will benefit the millions of HIV infected patients and health care professionals.

4.2 KEY FINDINGS OF THE STUDY

The research questions needed answers about the gaps in research on morbidity and mortality in the modern ART era in South Africa. The Chart review study has shown that 43.3% of patients were admitted with a low CD4 cell count, an indication of advanced disease. Another

study conducted in South Africa found also the same (3). Age (60 years old and older), men gender, CD4 cell count less than 200 cells /mm^3, Viral load more than 1000 copies/ml were reported to be associated with mortality inpatients. In Brazil, another study found age and male gender to be associated with mortality (4) and in Canada, CD4 cell count and Viral load were also associated with death (5). Tuberculosis was the commonest cause of admission and death in South Africa, similarly, other studies reported the same results (6, 7, 8). However, even though tuberculosis was the first commonest cause, it was always followed by other opportunistic infections and non-communicable diseases. In this study, tuberculosis was followed by chronic kidney disease as the second cause of death and it was followed by anaemia as the second cause of admission. Therefore, to reduce morbidity and mortality among HIV infected patients, focus must be drawn to non-communicable diseases. On the other hand, the systematic review revealed some studies conducted in Sub-Saharan Africa that did not find tuberculosis as the first cause of death and admission among HIV patients. Two studies, one conducted in Burkina Faso (9) and another in Ethiopia (10) revealed respectively wasting syndrome and bacterial meningitis to be the first causes of death among people living with HIV. One study conducted in Ghana (11) reported anaemia to be the first cause of admission among HIV infected patients. This difference may be due to the burden of dual HIV/TB epidemic in South Africa (12).

4.3 STRENGTHS OF THE STUDY

The systematic review was based on studies carried out in Sub-Saharan Africa. The strength of the systematic review is its rigorous methodology. Relevant studies were identified by searching in Google Scholar, Pub Med and CINAHL. A research strategy was performed based on a combination of relevant terms. Two reviewers screened abstracts and full-text articles following the inclusion and exclusion criteria as outlined in the protocol. The research team followed the Preferred Reporting Items for the Systematic Reviews and Meta-analysis Protocols (PRISMA-P) 2015 guideline (13). The process of literature selection and reasons for exclusion and inclusion were documented by a PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) flow diagram (14). In order to ensure eligibility of the research method, the research team formulated a data extraction table based on the PICO model (15).

The retrospective chart review used secondary data. The advantage of this is that the data is already available and accessible, this reduce the costs and save time during data collection. The sample size of 1 141 medical records of HIV infected patients attending the medical wards at King Edward hospital was used. Those patients had been admitted to King Edward VIII, a tertiary teaching hospital, from January to December 2018. KwaZulu-Natal is known to have the highest prevalence of HIV infections in all provinces in South Africa, and it is the epicentre of the HIV epidemic (16). The results of the chart review would impact and improve treatment of HIV patients, they would give a general overview of the morbidity and mortality in the modern ART era in South Africa.

4.4 LIMITATIONS OF THE STUDY

According to the systematic review, the objective was to identify the causes of morbidity and mortality in the ART era. Some of the selected articles were pertaining to only the causes of admission without mentioning the causes of death.

With regards to the retrospective chart review, some limitations such as missing variables such as ART treatment, viral load and CD4 count cell of some HIV patients. Some files were illegible due to the handwriting of some physicians. On the other files, HIV status of some patients was unknown and ART regimen was not specified.

4.5 CONCLUSION

The study identified the determinants of morbidity and mortality among HIV patients in the modern ART era in Sub-Saharan Africa, and particularly in South Africa. Despite the recent improvement of modern antiretroviral treatment, HIV patients still face many challenges. Early access to antiretroviral treatment and public awareness may improve the life expectancy of HIV infected patients.

Prevention of opportunistic infection (especially tuberculosis) and non-communicable disease remain important among HIV patients. There is a need to prioritise defensive prophylaxis and vaccination against major preventable opportunistic infection among people living with HIV.

4.6 RECOMMENDATIONS

1. Strengthen active case finding (ACF) and contact tracing among TB patients in the community.

2. Prevention of the main non-communicable disease which always accompany HIV/AIDS
3. Counselling and HIV test for all patients admitted in the medical ward at King Edward Hospital.

4. Monitoring renal function before initiating and while using ART in HIV patients.

5. We suggest mobile HIV counselling and testing, community-based door to door HIV counselling and testing with linkage to care will serve the dual purpose of early diagnosis of HIV and early ART initiation thus.

6. Preventive therapy of all opportunistic infections among HIV patients.

7. Early antiretroviral treatment to all HIV patients

8. Educate Patients not to use toxic herbs which can damage their kidneys

9. Test routinely, the CD4 and Viral load for each HIV patient at admission.

4.7 FUTURE STUDIES

1. Conduct the same study in the rural area where people do not have more information about HIV/AIDS.
2. Conduct a prospective study based on the association between non-communicable disease and HIV in the modern ART era.
3. Conduct a prospective study aimed to identify the reason for starting treatment late by HIV patients.

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APPENDICES

APPENDIX A: Ethical approval from KZN Department of Health.

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Physical Address: 330 Langalibalele Street, Pietermaritzburg
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Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782
Email:
www.kznhealth.gov.za

DIRECTORATE:
Health Research & Knowledge Management

Ref: KZ_201906_033

Dear Dr M R Ghislain
(UKZN)

Subject: Approval of a Research Proposal:

1. The research proposal titled **'MORBIDITY AND MORTALITY IN THE MODERN ANTIRETROVIRAL TREATMENT ERA IN A TERTIARY TEACHING HOSPITAL IN DURBAN, SOUTH AFRICA.'** was reviewed by the KwaZulu-Natal Department of Health (KZN-DoH).

   The proposal is hereby **approved** for research to be undertaken at King Edward VIII Hospital.

2. You are requested to take note of the following:

   a. *Kindly liaise with the facility manager BEFORE your research begins in order to ensure that conditions in the facility are conducive to the conduct of your research. These include, but are not limited to, an assurance that the numbers of patients attending the facility are sufficient to support your sample size requirements, and that the space and physical infrastructure of the facility can accommodate the research team and any additional equipment required for the research.*
   b. *Please ensure that you provide your letter of ethics re-certification to this unit, when the current approval expires.*
   c. *Provide an interim progress report and final report (electronic and hard copies) when your research is complete.*

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Ms G Khumalo on 033-395 3189.

Yours Sincerely

Dr E Lutge
Chairperson, Health Research Committee
Date: 27/06/19.

APPENDIX B: Ethical approval from UKZN BREC Committee

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

04 September 2019

Mr M R Ghislain (219094045)
School of Clinical Medicine
College of Health Sciences
manimanirizikif@gmail.com

Dear Mr Ghislain

Protocol: Morbidity and Mortality in the modern antiretroviral therapy era in a tertiary teaching hospital in Durban, South Africa
Degree: MMedSc

BREC Ref No: BE345/19

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 02 May 2019.

The study was provisionally approved pending appropriate responses to queries raised. Your response received on 08 August 2019 to BREC letter dated 25 July 2019 has been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have been met and the study is given full ethics approval and may begin as from 04 September 2019. **Please ensure that outstanding site permissions are obtained and forwarded to BREC for approval before commencing research at a site.**

This approval is valid for one year from 04 September 2019. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408 009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be noted by a full Committee at its next meeting taking place on **08 October 2019.**

Yours sincerely

Prof V Rambiritch
Chair: Biomedical Research Ethics Committee

cc: Postgrad Admin: kzman@ukzn.ac.za Supervisor: Mlaguilar@ukzn.ac.za