EVALUATION OF THE MANAGEMENT OF HIV/AIDS WITH DIABETES AS A CO-MORBID CONDITION IN PUBLIC HEALTH FACILITIES IN ETHEKWINI METRO OF KWAZULU-NATAL: DEFINING CONTRIBUTORY FACTORS TO PATIENT OUTCOMES

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SUBMITTED IN FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPY BY RESEARCH THESIS IN THE SCHOOL OF HEALTH SCIENCES, DISCIPLINE OF PHARMACEUTICAL SCIENCES, UNIVERSITY OF KWAZULU-NATAL, WESTVILLE, DURBAN, SOUTH AFRICA.

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DECLARATION

I David Mohammed Umar, declare as follows: That the work described in this thesis has not been submitted to any other tertiary institution for purposes of obtaining an academic qualification, whether by me or any other party. This research is my original work. Where use has been made of the work of others, it has been duly acknowledged. This thesis does not contain text, graphics or tables copied and pasted from the Internet or any other sources, unless specifically acknowledged, and the source being detailed in the thesis and in the References sections.

That my contribution to the project was as follows:

I conceptualized and drafted the intellectual work being presented in this thesis by publications and manuscripts with the guidance and support of my supervisor. I trained 3 research assistants to help me with my data collection. I captured the data onto SPSS version 26 and analyzed the data guided by a statistician, which enabled me to make conclusions and recommendations as outlined in this thesis.

Signed Student: David Mohammed Umar Date: June 7, 2020

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DEDICATION

This thesis is dedicated to God for absolutely everything, to my late mom who sacrificed a lot to get me educated, and to my entire family for their unquantifiable support.

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ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired Immune Deficiency Syndrome
aOR	Adjusted Odd Ratio
ART	Antiretroviral Therapy
ARV	Antiretroviral
ATV/r	Atazanavir/Ritonavir
AZT	Azidothymidine (also known as Zidovudine)
BREC	Biomedical Research Ethics Committee
CCR5	Chemokine Receptor Antagonist
CDC	Centre for Disease Control and Prevention
COR	Crude Odd Ratio
d4T	Stavudine
DDI	Didanosine
EFV	Efavirenz
FBS	Fasting Blood Sugar
FDC	Fixed Dose Combination
FI	Fusion Inhibitor
FTC	Emtricitabine
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immuno-deficiency Virus
INSTI	Integrase Inhibitor
LPV/r	Lopinavir/Ritonavir
LTDL	Lower Than Detectable Level
MS Word	Microsoft word
NCDs	Non-Communicable Diseases
NDoH	National Department of Health
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
PAD	Peripheral Arterial Disease
PCP	Pneumocystis pneumonia
PCR	Polymerase Chain Reaction
PI	Protease Inhibitor
PLWH	Persons Living With HIV
QOL	Quality of life
SPSS	Statistical Package for Social Sciences
SSA	Sub-Saharan Africa
STGs/EML	Standard Treatment Guidelines and Essential Medicines List
TDF	Tenofovir
VL	Viral load
WHO	World Health Organization
ZDV	Zidovudine

ABSTRACT

Introduction

HIV/AIDS has remained a huge burden. It is still affecting large population of people globally with mortality of over 35 million people. South Africa is the most affected country. Substantial progress has been made in HIV antiretroviral therapy which is now capable of suppressing viral replication and prevent transmission. Great efforts and significant successes have been recorded in the fight against HIV/AIDS especially in South Africa. With effective medications, PLWH now have increased longevity, this makes them susceptible to chronic diseases like diabetes. The burden of diabetes is also high in KwaZulu-Natal, which also comes with its attendant complications. Despite the progress made, the scourge of HIV/AIDS and diabetes still persists. Hence this study aimed to evaluate the management of HIV/AIDS and diabetes as a comorbid condition, and to determine factors that contribute to patient outcomes.

Methodology

The study was conducted in 4 HIV clinics attached to Public Sector Hospitals in the eThekwini Metro of Kwazulu-Natal (KZN) South Africa after obtaining ethical approval. A total of 1,203 adult, non-pregnant patients living with HIV and were receiving antiretroviral therapy for at least 6 months between 2005 and 2019 were randomly selected and recruited in the study after obtaining written consent from them. Data was collected using questionnaire and from patient chart. The statistical package for social sciences (SPSS) software version 26 was used to analyze the data using descriptive statistics, Chi square and logistic regression. Results were presented, discussion and conclusion were made as appropriate.

Results

There were 770 (64%) females and 405 (33.7%) males included in this study, with 29 to 48 years as the largest age group (60.2%). Clinicians prescribed the recommended add regimens in all cases. TDF + FTC + EFV was the most recommended regimen at 65%. On the average 43.85% of HIV patients were initiated on ART at CD4 count <200 cells/μL. Male gender and baseline CD4 count were the predictors of ART regimen changes.

It was found that 40.8% of PLWH on ART were virally suppressed. The probability of achieving viral suppression was significantly less in younger patients, the less educated and those with baseline CD4 cells count less than 200cells/μL, while the likelihood of achieving viral suppression was about 4 times higher for those that received encouragement from family to adhere to ART.

The prevalence of immunologic failure among PLWH on ART was 8.6 % (CD4 cell count <200 cells/μL). CD4 cells count outcome was statistically significantly associated with gender, poor adherence to ART and baseline CD4 cells count. The probability of immunologic decline for those who did not strictly adhere to ART was more than 3 folds higher than those who adhered to ART; and the probability of immunologic failure was more than 8 folds higher for those who had baseline CD4 cells <200 cells/μL than those who had baseline CD4 cells ≥200 cells/μL.

The prevalence of diabetes among PLWH on ART was 9%. Over 47% of those who had diabetes, had uncontrolled blood sugar, with a mean fasting blood sugar (FBS) of 11.7 mmol/L. The predictors of diabetes among PLWH on ART were, gender and age. Male PLWH had 65% less chances of having diabetes and those who were between the ages of 18 and 48 years were 88% less probable to have diabetes compared to those who were older than 48 years.

Conclusion and Recommendations

Clinicians adhered to the national treatment guidelines, but significant percentage of the patients were initiated on ART late resulting in poor outcome. Those who test positive for HIV should be informed on the benefits of initiating ART early, the possible consequence of late initiation of ART and Clinicians must ensure everyone who needs ART is offered one without delay.

The prevalence of immunologic failure was 8.6%. Predictors to immunologic failure were non-adherence and late initiation of ART (CD4 cells <200 cells/µL).

Prevalence of viral suppression was low (40.8%). The chances of virological failure was higher among younger, less educated, patients who started ART late (<200cells/µL) and patients who received encouragement from family to adhere to ART. Young PLWH should be regularly counselled on the benefits of adherence to ART, those that are not educated should be taught in languages they best understand, and pictorial illustrations should be used for counselling and family members should be involved in the follow up and encouragement of patients. That should be done with the permission of patients.

The prevalence of diabetes among PLWH was high (9%) and 47% of these did not have glyacemic control (mean FBS was 11.7 mmol/L). The predictors were male gender and older age. Those who test positive to HIV should also be screened for diabetes before commencement of ART and treatment for diabetes should be initiated as ART is initiated and blood sugar should be monitored regularly to ensure glycaemic control, which is essential for the prevention of diabetic complications.

CHAPTER 1

INTRODUCTION

HIV/AIDS is a health scourge that is still a heavy burden of the 21st century. It has continued to affect large population globally. From the onset of the epidemic, over 70 million people have been infected, the mortality is in the range of 35 million people. [1] The population within the productive age bracket of 15 to 49 years of age are the most affected.[1]

Sub-Saharan Africa, which has a record of approximately 67% of global burden, remains the most acutely affected; with South Africa being the country that is most affected.[1]

Diabetes Mellitus, on the other hand, is a protracted non-infectious disease. It has acute and chronic complications, especially without the right management. It results in complications such as retinopathy, neuropathy, peripheral arterial diseases, and the diabetic foot, which can lead to amputations and cardiovascular diseases, among others. [2,3]

The occurrence of diabetes mellitus is rising at a disturbing rate, particularly in developing countries, with South Africa having the highest recorded cases; besides the larger (over 70%) population of the undiagnosed.[4, 5]

1.1 Background and Literature Review

Human immunodeficiency virus (HIV) is carried in the blood. It is mainly acquired via sex, intravenous medication tools sharing, as well as transmission from mother to child, this can happen in the course of birth or breastfeeding. HIV disease is brought about by infection with the retroviruses HIV-1 or HIV-2.

HIV-2 has a little bit lower transmission risk. People who are have HIV-1 are likely to have higher viral load than persons who have HIV-2.[6,7] Higher viral load is linked with an accelerated deterioration to AIDS in persons with HIV-1.[8,9]

The prevalence of HIV-2 in the developed world is very low; therefore research, vaccine, and development of drug have been concentrated on HIV-1. Infections with HIV have affected Sub-Saharan Africa (SSA) more, compared with other regions of the world. Non-communicable diseases (NCDs) have become more important in-hospital admissions and mortality globally. Among other NCDs in affected populations in both developed and developing countries, diabetes mellitus has become the most concern.[10]

1.2 Phases of HIV Infection

Acute Seroconversion

The rapid incidence of plasma viremia with widespread virus spread is seen in humans 4 to 11 days after the virus' mucosal entry. There is no fixed synthesis site, but the virus appears to incorporate into active transcription areas, likely because these areas have more open chromatin and DNA that is more readily accessible.[11,12] This severely hinders the host's eradication of the virus, as latent proviral genomes can stay without immune system detection and cannot be targeted by antivirals. During this process, the infection is discovered and a proviral reservoir is developed.[13,14] This reservoir consists of intensely infected cells, usually macrophages, and tends to increasingly discharge viruses. Some of the viral discharge replenish the reservoir, creating some more effective infection. As calculated by DNA polymerase chain reaction (PCR), the pro-viral reservoir appears quite stable. Though it does decline with combative antiviral therapy, the half-life is such that eradication is not a prospect. The pro-viral reservoir scale corresponds with the steady-state viral load and is associated with the anti-HIV CD8 + T-cell reaction. Combative

prompt treatment of severe infection can reduce the burden on the provirus. Mostly in newly infected cases, the viral load is excessive, and the number of CD4 + T-cells suddenly drops. With the production of anti-HIV antibodies and CD8+T-cell responses, the viral load decreases to a steady-state, and the CD4+T-cell count rises to levels within the reference range, albeit slightly lower than before infection. Seroconversion can take several months to complete, some weeks. Symptoms can include fever, flu-like illness, lymphadenopathy and rash during this time. For about half of all people infected with HIV, such symptoms occur.[15]

Asymptomatic HIV Infection

People infected with HIV at this point of infection show few to no signs or symptoms for a few years to a decade or more. Viral replication continues throughout this period,[16] and the immune response to the virus is both favourable and strong. In certain cases, chronic systemic lymphadenopathy is an obvious symptom of infection. This rate of decrease is related to, but not easily presaged by, the steady-state viral load. It is reported that late initiation of therapy results in less effective therapy response and a lower degree of immune reconstitution.

AIDS

Once the immune system has been amply compromised to begin leading to severe opportunistic infections, the patient is considered to have AIDS. A CD4 + T-cell count of less than 200 / μL is often used as an criterion for the diagnosis of AIDS for surveillance purposes in the United States, however some opportunistic infections occur when CD4 + T-cell counts are greater than 200 /μL, and some individuals with a CD4 count lower than 200/μL may stay relatively healthy.

Numerous opportunistic infections and conditions are used to identify when HIV infection has advanced to AIDS. The overall prevalence of these infections and conditions varies from rare to

common but they are all uncommon or mild in immunocompetent people. AIDS can be recognized if one of these is serious or chronic in a person diagnosed with HIV and there are no other explanations for immune suppression. [17]

1.3 CD4 Count and Viral Load

Regardless of the clinical and CD4 count, antiretroviral therapy should be started in children, adolescents, pregnant and breastfeeding women, and adult persons living with HIV.[18] (WHO, 2017). With 4,4 million people taking treatment by 2018, this has made South Africa the biggest ART program. After ART treatment initiation, testing of viral load should be carried out every 6 and 12 months, then every 12 months after that. As the favoured mode of diagnosing and validating treatment failure, WHO highly recommends viral load.[18] In a period of 4-8 weeks of treatment, a clinical goal of 1-2-log reduction should be reached; without achieving suppression or reduction of the viral load, it should be adjudged as to be drug resistance.[19]

1.4 History of HIV

HIV disease was first identified in San Francisco and in New York City in 1981. Some young homosexual men presented with opportunistic infections usually associated with extreme immune deficiency at the time: pneumocystis pneumonia (PCP) and Kaposi aggressive sarcoma.[20]
HIV remained unknown for the next 2 years.[21] Chronic drug abuse, lifestyle and other infection causing agents, were considered as factors during that period.[22] In the absence of testing, the epidemy of HIV spread fast and quietly.

Nonetheless, cogent clinical effects were obtainable before the disease was well-known to society; for example, just a single incident of Pneumocystis pneumonia, specifically not related to immune suppression was diagnosed in the US from January 1976 and June 1980, before HIV was identified.

There were 42 similar diagnoses made in 1981 alone; By December 1994, the CDC had already reported 127,626 cases of PCP with HIV infection as the sole cause of immune suppression. Kaposi sarcoma is also up to 30,000 times more probable to occur in people with HIV than in people who were not immunocompromised.[23]

1.5 The Stigma of HIV Infection

Much stigma has been related to HIV infection, because the virus is generally associated with sexual acquisition and implies sexual promiscuity. This stigma led to the discrimination and rejection of HIV infection screening. There is stigma also as a result of fear of getting infected through casual contact with a HIV infected person.

These behaviors are not right because without sexual contact or contact with blood, HIV is poorly transmissible. In addition, the likely life expectancy of HIV-infected patients that get treatment is high. HIV is not transmitted in the course of casual contact and easily destroyed by simple cleaning agents. Much of the fear about HIV infection is because it is incurable and the gradual immune failure and subsequent premature mortality in those not receiving treatment.[15]

1.6 AIDS Denial

A small but vocal faction, inclusive of some scientists, keep on the argument that there is no HIV, or that HIV does not lead to AIDS, and that the HIV tests cannot be trusted or that the treatments are toxic. This misreport is, for the most part, as a result of lack of understanding of the scientific literature, purposive distortion, or compelling falsehood rooted in pseudoscientific dissention.
In the scientific literature and public symposium, all of the variances advanced by these dissidents were discussed and disproved and tested and rebuffed in the legal system. However, they remain

resolute, and these kinds of opinions can negatively affect people who are unavoidably at risk of exposure to HIV infection or who refuse to accept therapy for their advancing infection.

Likewise, political denial and apathy have doubtlessly resulted in momentous damage. Various governments in countries with high HIV infection rates acceded gradually that they had an HIV epidemic, and at the beginning rejected, for example, South Africa initially rejected that AIDS was even a problem, then that the disease was as a result of infection; and, that antiretroviral therapy was efficacious in the treatment of HIV infection and holding off MTCT. Now changes have occurred, but they were apathetic, and it cost many thousands of lives.[15]

1.7 Epidemiology

1.7.1 Global

As reported by the Joint United Nations Programme on HIV/AIDS[24] (UNAIDS 2019), in 2018, about 37.9 million persons were living with HIV worldwide. The global HIV prevalence among adults was 0.8%. UNAIDS estimates that about 21% of the persons infected with HIV do not know they have the infection.[24] In 2018, 770,000 people died as a result of illnesses related to AIDS.[24]

Large proportion of persons living with HIV (68%) live in sub-Saharan Africa, mostly in low- and middle-income countries. 20.6 million of this population live in East and Southern Africa, with 800,000 new HIV infections in 2018.[24] In 2018, there were approximately 1.7 million new infections.[24] Young women are notably susceptible,, with approximately 6,200 new infections occurring in this group weekly.[25] In sub-Saharan Africa, 80% of new infections are among girls aged 15-19, and young women aged 15-24 are twice as probable to be living with HIV as men. More than 35% of women globally experienced physical and sexual abuse at some point. Women who experience abuse in some regions are one and a half times more predisposed to eventually be diagnosed with HIV.

1.7.2 South Africa

The HIV epidemic started spreading in the early 1990s in South Africa.[26] having the world's largest HIV epidemic, of the 37.9 million people living with HIV in 2018, approximately 7.7 million (over 20%) were in South Africa alone.[24] South Africa accounts for 33% of all new HIV infections in Southern Africa[27], 14% of new infections worldwide in 2018.

South Africa has taken giant strides in managing the HIV epidemic; it has the world's largest antiretroviral therapy (ART) programme and has mainly, for the most part, financed from its domestic capital. The nation spent over $1.34 billion in running its HIV services in 2015.[27] The ART programme was relatively successful as it led to a boost in life expectancy to 67.7 years in 2015.[28]

Nonetheless, the prevalence of HIV among the general population remains high (20.4%), even though it differs appreciably between regions.[27] For example, the prevalence is set at an estimate of 5.6% in the Western Cape and 6.8% in Northern Cape.[29] with the prevalence of 12.2% in KwaZulu-Natal.[30] And mortality due to AID-related illnesses was 71,000 in 2018.[24]

Regardless of the giant strides made in South Africa to combat the HIV epidemic with some meaningful progress, the target of achieving the vision 90-90-90 by 2020 is not successful, this makes it essential to investigate the likely factors contributing to the slow progress as well as treatment failure in some.

Also, as more people with HIV who adhere to treatment live longer, non-chronic communicable diseases become common among PLWH. One cogent example of such diseases is diabetes. Diabetes is particularly important because South Africa is among the highest prevalent nations in Africa. The convergence of HIV and diabetes in same patients makes it crucial to investigate the

extent and the risk factors causing the comorbidity, especially as data on the prevalence and risk factors of diabetes in PLWH in KwaZulu-Natal is limited.

1.8 Complications of diabetes

1.8.1 Diabetic Neuropathy

Diabetic peripheral neuropathy is defined as "the presence of symptoms and signs of peripheral nerve dysfunction in people with diabetes after exclusion of other causes."[31,32] Feature of neuropathies is prolonged loss of function of nerve fiber. Neuropathies gravely decrease patients' quality of life (QOL) and can introduce severe secondary complications such as falls, fractures, foot ulcers, cardiac arrhythmias, amputations, and death.[33]A study carried out in India showed a meaningful association in peripheral arterial disease (PAD) patients to be with complications like retinopathy and neuropathy. PAD is affecting diabetic patients; age as one of the host factors also the duration of diabetes in the patient. PAD comes with many risks to diabetic patients, which may bring about lower limb amputations. PAD patients have a higher possibility of having a stroke, or even death may occur.

1.8.2 Diabetic Foot Infections

Infections of the foot commonly occur in patients with diabetes who are susceptible to such infections due to altered vascular supply. Local trauma and compression, mostly combined with numbness as a result of neuropathy, along with microvascular disease, can give rise to diverse different diabetic foot infections ranging from simple to severe ones.

Treatment of infections in diabetic patients is challenging. This is because they have poor microvascular circulation, which prevents phygocytic cells from reaching infected tissues. They can also have linked infections affecting bone and tissue called fetid foot, peripheral macrovascular

diseases as well as peripheral microvascular and capillary disease with gangrene.[35,36,37,38,39] In addition, the number of people having diabetes among HIV positive patients is also increasing. This is by reason of factors such as an increase in life expectancy owing to the availability of antiretroviral drugs as well as metabolic side effects of some antiretrovirals, which are implicated in causing insulin resistance.[40,41] This makes diabetes a significant co-morbidity in persons living with HIV, which requires a critical attention and an integrated management strategy.

1.9 Management of HIV

The guideline for the management of HIV has gone through a metamorphosis. Since the first antiretroviral Zidovudine, was approved in 1987, there have been repeated alteration in the antiretroviral treatment guidelines, as more drugs are found. The current guideline requires the use of three antiretroviral drugs that belong to different classes (HAART).[46]

There have been adjustments also in pill burden, starting with a Zidovudine the only regimen to multi-dose regimen to the current fixed-dose regimen.[47]

The guideline for the commencement of treatment has also undergone changes; at the beginning, patients were started with ART when they had CD4 count $\leq$ 200 cell/μL, then switched to CD4 count $\leq$ 500 cell/μL, but now clinicians are encouraged to treat everyone that tests positive to the virus.[48]

While all these guidelines are developed to achieve maximum therapeutic results in managing HIV/AIDS, a successful antiretroviral therapy, to a great extent, depends on patient adherence to medications, clinician's adherence to guidelines, amongst other factors. Several suitable approaches could be employed to enhance medication adherence.[49,50]

1.10 Description of the Core Research Problem and its Significance

Despite the availability of effective ART and having the biggest anti-retroviral therapy universally, the strain of HIV remains utmost in South Africa, with Kwazulu-Natal carrying the highest burden, [41,42,43,44] and many patients not attaining viral suppression. Also, many diabetic patients are not achieving enough glycaemic control at both private and public health institutions.[5,45,2] (Pillay, Adous & Mahomed, 2015; Amod, Riback & Schoeman, 2012; Pillay et al. 2016)

1.11 The Rationale of the Study

Considering the huge resources spent in providing anti-retroviral therapy to those living with HIV, the provision of Post Exposure Prophylaxis to people who have been exposed to the risk of infection; as well Pre-Exposure Prophylaxis for those at high risk, it is crucial to survey the various factors that could impact on patient management outcomes with the view to finding the likely reasons for the failure to achieve optimal treatment outcomes for many of those on ART.

1.12 Research questions, aim, and objectives

1.12.1 Research Questions

The main research question: Do clinician factors such as adherence to HIV management protocol, patient factors such as adherence to ARVs, and diabetes affect HIV management outcomes, and how do they affect it?

The specific research questions are:

- Do clinicians adhere to the HIV management protocol?
- What are the patient factors that are associated with HIV management outcomes?
- What are the effects of these patient factors on HIV management outcomes?

- What is the prevalence of diabetes among PLWH?
- What are the predictors of diabetes in PLWH?

1.12.2 Aims and Objectives of the Study

This study aimed to assess adherence to HIV management protocols, effects of patient factors, and clinician factors on HIV patient management outcomes. Also, to determine the prevalence and predictors of diabetes mellitus among persons living with HIV.

1.12.3 The specific objectives of the study were:

- To assess clinician's adherence to the HIV management protocols
- To determine patient factors that could influence management outcomes such as viral suppression and immunological recovery.
- To determine the effects of patient factors on management outcomes such as viral suppression and immunological recovery.
- To evaluate the prevalence and predictors of diabetes mellitus among PLWH

1.13 Research Methodology

A detailed methodology is included in each of the papers/manuscripts that appear in chapters 2, 3, 4 and 5.

1.13.1 Study Design

This study was a retrospective and prospective study, based on analysis of sampled PLWH, which used questionnaires and patient hospital files for data.

1.13.2 Study setting and data source

The study was conducted at the HIV clinics of four public sector hospitals in the eThekwini health district of KwaZulu-Natal that are situated at former designated racial settlements. Random sampling technique was used to obtain data from persons living with HIV (PLWH) who have been on antiretroviral therapy (ART) for at least 6 months between 2005 and 2019.

1.13.3 Inclusion criteria

- Persons living with HIV (PLWH) who may or may not have diabetes
- Receiving ART for at least 6 months between 2005 and 2019.
- Adults (18 years and above)
- Male and female (not pregnant)

1.13.4 Exclusion criteria

- Persons living with HIV (PLWH) who are below 18 years.
- Persons living with HIV (PLWH) who started receiving ART before 2005 or have not been on ART for at least 6 months.
- Pregnant women
- Persons who were initially included but opted out of the study in the course of data collection.

1.13.5 Sampling technique and sample size

Random sampling technique was used to avoid bias and to obtain a sample that is a true representation of the population of the study. This was achieved as follows: PLWH were approached, the purpose of the study was explained to them and their consent to participate in the

study was requested by reading out the BREC consent form for those who could not read, in a language of their choice and those who could read were given the form to read. Each person who consented to participate in the study by signing the consent form was asked to pick randomly, squeezed piece of paper in a pool of small pieces of paper on which the letters Y or N was written, the papers were squeezed and mixed. Anyone who happened to pick a paper with letter Y was included in the study, provided he or she met the inclusion criteria.

The minimum sample size for this study was calculated as 249 participants per hospital, and this gave a total of 996 participants from the 4 hospitals.

The following statistical parameters were used to arrive at the minimum sample size: Odds ratio = 1.25, type 1 error = 0.05, type 2 error = 0.2 and statistical power = 0.80. Assuming a population variance of 1 and a population mean of 0 (normal distribution). A minimum sample size of 996 was determined for the 4 hospitals with a critical Z value = 1.96.

However, the actual sample size collected was 281, 286, 345, and 291 from the 4 hospitals, respectively, giving a total sample size collected as 1203

1.13.6 Data collection

Data collection took place between the period of 3rd October 2018 and 10th August 2019. Data was collected using two instruments, questionnaire and patient chart, which were designed using MS Word 2016.

The questionnaire was designed to obtain information on patient demographics such as name, gender, age among others, and patient factors such as education level, adherence to medications,

consumption of alcohol, use of supplements, use of traditional medicine, patients' knowledge of the disease, patients' attitude towards treatment among others.

The questionnaire was pretested among a few of the persons living with HIV (PLWH) who were attending ARV clinics. The pretesting was done to ensure the validity and reliability of the questionnaire to obtain accurate responses from the respondents. The pretested questionnaires that were in isiZulu and English languages were administered according to the language of choice of each respondent and were retrieved after the respondents completed them. Those who participated in the pretest were not included into the main study participants during the actual data collection.

The patient chart was used to obtain data that were relevant to the management of HIV from the hospital record. The data obtained included CD4 counts, viral loads, clinical stages, ARV commencement dates, ARV regimens used. Adverse effects experienced, diabetes status, among other information.

1.13.7 Data analysis

Data analysis was performed using the Statistical Package for Social Sciences (SPSS) version 26 using descriptive statistics; frequencies of all categorical variables were obtained. A chi-square test was used to determine the relationship between variables, univariate and multivariate logistic regressions were used to determine the relationships and the extent of relationships between variables as appropriate. All levels of significance were kept at $p < 0.05$.

1.14 Ethics consideration

The study obtained approval from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal with the ethics reference number BE314/18**.**

1.15 Structure of the thesis

Chapter 1: Introduction, literature review and methodology

Chapter 2: Presentation of manuscript titled: Adherence to treatment protocols/guidelines by clinicians in the management of HIV, submitted to BMC Infectious Diseases for publication.

Chapter 3: Presentation of a manuscript submitted for publication in AIDS Care and it is under review on 'patient factors and viral suppression in HIV management'. The manuscript is presented in line with the specific guidelines of the journal.

Chapter 4: Published paper in Ponte Journal titled: Patient factors and immunologic recovery in HIV management.

Chapter 5: Presentation of a manuscript titled: Prevalence and predictors of diabetes among persons living with HIV, submitted to BMC Public Health for publication.

Chapter 6: Discussion and synthesis

Limitations of the study

Conclusion and recommendations

Annexures

Chapter 1 provided the background and literature review on HIV and the global epidemic, diabetes and HIV co-infection and the challenges associated with them globally and in South Africa. The rationale to do the study together with the problem statement was also included and concluded with its stated aims and objectives. The methodology used in the study was also detailed.

In Chapter 2, one of the stated objectives viz 'To assess clinician's adherence to the HIV management protocols' is presented.

Adherence to HIV treatment guidelines by clinicians is critically important in order to achieve the desired outcomes in the management of HIV. An important first step in this study therefore was to ascertain if the treatment guidelines were adhered to by clinicians in the management of HIV in PLWH**.** The findings are presented in this chapter.

The chapter is presented in the format of a manuscript.

The manuscript titled 'Adherence to HIV Treatment Protocols by Public Sector Clinicians in the eThekwini Metro of KwaZulu-Natal': A Retrospective Study' is presented according to submission guidelines of BMC Infectious Diseases.

Submission Date: 11TH June 2020.

Manuscript Number: INFD-D-20-02030

CHAPTER 2

Manuscript submitted to BMC Infectious Diseases

BMC Infectious Diseases

ADHERENCE TO HIV TREATMENT PROTOCOLS BY PUBLIC SECTOR CLINICIANS IN THE ETHEKWINI METRO OF KWAZULU NATAL: A RETROSPECTIVE STUDY

--Manuscript Draft--

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Abstract:	Abstract Background: There were estimated 7.7 million people living with HIV in South Africa in 2018 and 71,000 AIDS-related deaths in the same year. Remarkable progress has been made in the management of HIV as it is now a manageable chronic condition with the use of HAART. Appropriate use of these medicines is essential for successful management of HIV and optimum outcomes. Treatment guidelines are developed to aid clinicians optimize patient care. This study therefore aimed to investigate the extent to which clinicians adhere to these guidelines in KwaZulu-Natal. Method: The study was conducted in 4 HIV clinics in public healthcare facilities in the eThekwini Metro of KwaZulu-Natal, South Africa. Total of 1203 adult PLWH who have been on ART for at least 6 months, between 2005 and 2019 were randomly selected and recruited. Data was collected from patients' hospital charts. SPSS version 26 was used to analyze the data using descriptive statistics, Chi square and logistic regression. Results: There were 770 (64%) female participants. Though clinicians prescribed the recommended regimens in all cases, about 40% of the HIV patients were initiated late on ART. TDF + FTC + EFV was the most prescribed regimen at 65%. Male gender and baseline CD4 count were the predictors to switching ART regimens. Conclusion: Clinicians generally adhered to the National treatment guidelines but generally initiated ART later than recommended. Steps must be taken to ensure those who test positive are initiated early for treatment, then and only then can optimum treatment outcomes be achieved. Keywords: HIV/AIDS, Clinicians, Adherence, Antiretroviral, Treatment, ART, Regimen, Protocols, Guidelines, PLWH
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ADHERENCE TO HIV TREATMENT PROTOCOLS BY PUBLIC SECTOR CLINICIANS IN THE ETHEKWINI METRO OF KWAZULU NATAL: A RETROSPECTIVE STUDY

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Abstract

Background: There were estimated 7.7 million people living with HIV in South Africa in 2018 and 71,000 AIDS-related deaths in the same year. Remarkable progress has been made in the management of HIV as it is now a manageable chronic condition with the use of HAART. Appropriate use of these medicines is essential for successful management of HIV and optimum outcomes. Treatment guidelines are developed to aid clinicians optimize patient care. This study therefore aimed to investigate the extent to which clinicians adhere to these guidelines in KwaZulu-Natal.

Method: The study was conducted in 4 HIV clinics in public healthcare facilities in the eThekwini Metro of KwaZulu-Natal, South Africa. Total of 1203 adult PLWH who have been on ART for at least 6 months, between 2005 and 2019 were randomly selected and recruited. Data was collected from patients' hospital charts. SPSS version 26 was used to analyze the data using descriptive statistics, Chi square and logistic regression.

Results: There were 770 (64%) female participants. Though clinicians prescribed the recommended regimens in all cases, about 40% of the HIV patients were initiated late on ART. TDF + FTC + EFV was the most prescribed regimen at 65%. Male gender and baseline CD4 count were the predictors to switching ART regimens.

Conclusion: Clinicians generally adhered to the National treatment guidelines but generally initiated ART later than recommended. Steps must be taken to ensure those who test positive are initiated early for treatment, then and only then can optimum treatment outcomes be achieved.

Keywords: HIV/AIDS, Clinicians, Adherence, Antiretroviral, Treatment, ART, Regimen, Protocols, Guidelines, PLWH.

Introduction

There were estimated 7.7 million people living with HIV in South Africa in 2018 [1], with 20.4% HIV prevalence among adults aged 15 to 45 years of age alone and 71,000 AIDS-related deaths same year [1]. South Africa has the largest HIV epidemic and antiretroviral therapy programme` globally [2], with 62% of adult HIV positive people on treatment.

Remarkable progress has been made since the start of monotherapy with Zidovudine in 1987. Currently HIV is a manageable chronic condition with the use of highly active antiretroviral therapy (HAART) constituting of ≥3 medicines [3]. The pharmacologic classes to which the antiretroviral drugs in the combination therapy belong, include:

Nucleoside reverse transcriptase inhibitors (NRTIs),

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Protease inhibitors (PIs)

Integrase inhibitors (INSTIs)

Fusion inhibitors (FIs)

Chemokine receptor antagonists (CCR5 antagonists)

Entry inhibitors (CD4-directed post-attachment inhibitors)

Treatment guidelines are developed to aid clinicians in optimizing patient care. The National Department of Health of South Africa printed the first edition of the Standard Treatment Guidelines and Essential Medicines List (STGS/EML) in 1998 and have continuously updated these guidelines as new knowledge and new regimens became available [4]. They guide clinicians on the use of antiretroviral therapy.

Adherence to ART initiation guidelines focuses on 3 important questions. 'When to start', 'What to start' and comorbid disease assessment [5].

To answer the question 'when to start', the South African antiretroviral treatment guidelines recommended various baseline CD4 cells counts and other patient considerations at which antiretroviral therapy should commence and treatments are guided, as these recommendations were updated over time [6,7,8,4,9,10]. However, the current recommendation is 'treat all', that is to start treatment for every person who tests positive for HIV as soon as possible irrespective of the CD4 count, if the person is ready to start the treatment [11,10].

Regarding the question 'what to start', the South African antiretroviral treatment guidelines currently recommends ART regimen which contains 2 nucleoside reverse transcriptase inhibitors (NRTIs) together with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI). [4].

There are different antiretroviral medicines with different pharmacokinetic and pharmacodynamic properties within the pharmacologic classes mentioned above, which are combined to form different regimens in order to meet different patient needs. These ART combinations are classified into first, second and third regimen. The regimens and recommendations are as shown in table 1 below

High level of adherence to antiretroviral therapy by PLWH is required to achieve long-term success in treatment [12]. For the purpose of this study, adherence to the South African antiretroviral treatment guidelines was defined as commencement of treatment for persons who test positive for HIV at the recommended time, with a recommended first line ART regimen and

maintaining treatment with same but changing to another suitable regimen whenever the initial regimen is not suitable for the specific patient. Adherence to treatment guidelines by clinicians is essential in order to optimize patient care and treatment outcomes. However, a lot have been studied about patient's adherence to ART, but little is known about adherence to the South African antiretroviral treatment guidelines by clinicians. Hence this study was undertaken to investigate the degree to which clinicians adhere to HIV management protocols as outlined in the antiretroviral treatment guidelines for South Africa.

Method

This was a quantitative, retrospective study aimed to investigate the degree to which clinicians adhered to HIV management protocols as outlined in the antiretroviral treatment guidelines for South Africa. The study was conducted in 4 HIV clinics in Public Sector Hospitals in the eThekwini Metro of Kwazulu-Natal (KZN), South Africa. These hospitals were selected based on the different previously designated racial groupings. A total of 1,203 patients living with HIV that have been on antiretroviral therapy (ART) for at least 6 months, between 2005 and 2019 were randomly selected as follows; letters 'Y' and 'N' were written on separate folded pieces of paper. The patients who consented to participate in the study were asked to pick a folded piece of paper. Those who picked 'Y' were included in the study. The participants had to be 18 years and above, and not pregnant. Those satisfying the criteria were recruited into the study after obtaining their written consent to participate in the study.

The following statistical parameters were used to arrive at the minimum sample size of 249 per hospital: Odds ratio = 1.25, type 1 error = 0.05, type 2 error = 0.2 and statistical power = 0.80. Assuming a population variance of 1 and population mean of 0 (normal distribution). A minimum sample size of 996 was determined with a critical Z value – 1.96. Though 996 was required for

this study, the number that selected Y was more than the required sample size resulting in a sample size of 1203 which was accepted to allow for dropouts in the study.

Data was collected from the patient's chart in the hospitals. Information on patient management was obtained. These included data on when patient commenced ART, what ART regimen was prescribed, changes in ART regimen, comorbidities, baseline and current CD4 counts, baseline and current viral load and data on diabetes were extracted from the patient charts into a table designed using Microsoft word.

The statistical package for social sciences (SPSS) software version 26 was used to analyze the data. Logistic regression was used to identify factors associated with change of regimen as well as predictors for regimen change and descriptive statistics were used to get other results relevant to the study.

Results

Table 2. Demographic information of patients on antiretroviral therapy

Variable	Frequency	Percentage (%)
Gender		
Female	770	64.0
Male	405	33.7
Not indicated	28	2.3
Age in years		
18-28	145	12.5
29-48	694	60.2
>48	313	27.2
Baseline CD4		
<200 cells/µL	275	45.5
200-350 cells/µL	156	25.8
351-500 cells/µL	75	12.4
>500 cells/µL	98	16.3

There were more females (64%) than males. The age group 29 to 48 years was the largest age group of the participants with just over 60%. Over 45% of the participants had baseline CD4 count of less than 200 cells/µL.

Table 3: Baseline CD4 cell count distribution at the commencement of ART, from 2005 to 2018.

Year ART started	Baseline CD4 cell count							
	<200 cells/μl.		200 - 350 cells/μL		500 cells/μL		>500 cells/μl.	
	n	%	N	%	n	%	n	%
2005-2012	169	55.8	70	23.1	23	7.6	41	13.5
2013-2014	14	29.8	26	55.3	4	8.5	3	6.4
2015	9	30	8	26.7	7	23.3	6	20
2016-2018	56	44.4	23	18.3	22	17.5	25	19.8

Table 4. Distribution of ART regimens prescribed by clinicians (n=669)

ART Regimen	Frequency	Percentage (%)
ABC/3TC/EFV	90	13.5
ABC/FTC/EFV	1	0.1
D4T/3TC/EFV	5	0.7
TDF/3TC/NVF	2	0.3
TDF/FTC/ATVr	22	3.3
TDF/FTC/EFV	435	65
TDF/FTC/LPVr	30	4.5
TDF/FTC/NVP	21	3.1
ZDV/3TC/ATVr	13	1.9
ZDV/3TC/EFV	3	0.4
ZDV/3TC/LPVr	47	7

Each regimen prescribed constituted 2 NRTIs together with either a NNRTI or a PI.

The most prescribed regimen was TDF/FTC/EFV (65%).

The least prescribed regimen was ABC/FTC/EFV (0.1%).

Table 5. Changes from initial ART regimens to current ART regimens.

FROM	TO									
	ABC + 3TC + EFV, n *	TDF + FTC + EFV, n *	ZDV + 3TC + LPVr, n **	TDF + FTC + LPVr, n **	TDF − FTC − ATVr, n **	ZDV + 3TC + ATVr, n **	TDF + 3TC + NVP, n *	TDF − FTC − NVP, n *	ABC + FTC + EFV, n *	d4T + 3TC + EFV, n *
ABC+3TC+ATVr **	1									
ABC+3TC+EFV *		7	3							
ABC+3TC+LPVr **	1		1	1						
ZDV−3TC+EFV *	5	11		1	1					
d4T+3TC+EFV *	11	87	8	6	4	1				
d4T+3TC+LPVr *	2			1						
d4T+3TC+NVP *	3	32	4	4	5		1	3		
TDF+3TC+LPVr **	1	1		2	2					
TDF+3TC+NVP *	1	27	4	1				7		
TDF+3TC+EFV *	10	68	5	2	1			1	1	
TDF+FTC+EFV *	10		10	1	1			2		1
TDF+FTC+NVP *		1								
ZDV−3TC+LPVr **	1	2		2	1					1
Total (%)	46 (12.4)	236 (63.8)	35 (9.4)	21 (5.7)	15 (4.0)	1 (0.3)	1 (0.3)	13 (3.5)	1 (0.3)	1 (0.3)

*First line regimen ** Second line regimen.

Sometimes patients were switched from a first line ART regimen to another first line ART regimen, for example TDF + 3TC + NVP to TDF + FTC + EFV. TDF+FTC+EFV was the preferred regimen by clinicians to switch to, 63.8% of all regimen changes made switched from other regimen to this regimen (TDF+FTC+EFV).

Table 6: Reason(s) for regimen change and current regimen. N=46

REASON(S) FOR CHANGING REGIMEN	CURRENT REGIMEN				
	ABC/3TC/EFV	TDF/FTC/ATVr	TDF/FTC/EFV	TDF/FTC/LPVr	ZDV/3TC/LPVr
Renal impairment, n (%)	12 (70.6)	-	2 (10.5)	1 (50)	-
Defaulted treatment, n (%)	1 (5.9)	1 (33.3)	6 (31.6)	-	3 (60)
Availability of New drugs, n (%)	-	-	2 (10.5)	-	1 (20)
Regimen failure, n (%)	1 (5.9)	-	1 (5.3)	-	-
TB diagnosis, n (%)	-	-	2 (10.5)	-	-
TDF toxicity/Side effect, n (%)	1 (5.9)	-	-	-	-
Shift worker, n (%)	-	-	1 (5.3)	-	-
Lipodystrophy, n (%)	1 (5.9)	-	3 (15.8)	-	-
EFV toxicity/Side effect, n (%)	-	1 (33.3)	-	-	-
Virological failure, n (%)	1 (5.9)	1 (33.3)	-	-	-
Hepatitis B infection, n (%)	-	-	-	-	1 (20)
Neurosis, n (%)	-	-	-	1 (50)	-
Proteinuria, n (%)	-	-	5.3	-	-
Allergy, n (%)	-	-	5.3	-	-
Total, n (%)	17 (100)	3 (100)	19 (100)	2 (100)	5 (100) Grand Total = 46

Renal impairment was the highest reason for regimen changes with 15 individuals switched to other regimens due to it.

Table 7: Multi-covariate and uni-covariate analysis results for factors associated with change of ART regimen.

Variables	COR (95%CI)	COR P-Value	aOR (95%CI)	aOR P-Value
Gender				
Male	0.57(0.36-0.92)	0.022*	0.60(0.34-0.97)	0.037*
Female	1		1	
Age				
18 – 28	0.38(0.18-0.82)	0.013*		
29-48	1.01(0.60-1.73)	0.959		
>48	1			
Alcohol consumption				
Yes	0.47(0.27-0.81)	0.007*		
No	1			
Taking herbal/traditional medicines				
Yes	0.52(0.25-1.11)	0.090		
No	1			
Having diabetes				
Yes	1.68(0.69-4.07)	0.257		
No	1			
Baseline CD4 cells count				
<200 cells/µ/L	1.89(1.14-3.13)	0.013*	1.99(1.18-3.34)	0.010*
≥200 cells/µ/L	1		1	
Duration on ART				
	1.05(1.04-1.06)	0.000*		

In a univariate logistic regression, the gender, age, alcohol consumption, baseline CD4 count and duration of treatment of PLWH on ART were significantly associated with changing of patient's ART regimen from first line to a second line.

In a stepwise forward likelihood ratio multivariate logistic regression model, gender and baseline CD4 counts were predictors of changing from first line ART regimen to second line.

Discussion

Clinicians generally adhered to the ART treatment guidelines in prescribing ART regimens that consisted of 2 nucleoside reverse transcriptase inhibitors (NRTIs) together with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI). They initiated therapy with first line ART regimens as recommended in all the cases [6,7,8,4,9]. (Table 4 and 5) This finding however slightly differed from another study which indicated a 95% adherence to recommended ART combinations by clinicians [13].

The percentage of PLWH who were initiated late on ART (baseline CD4 count <200 cells/μL) was 29.8% (in 2013-2014), 30% (in 2015) [4] and 44.4% (in 2016-2018). These were contrary to the recommendations within those periods, as the South African antiretroviral therapy guidelines recommended that ART should commence at baseline CD4 count ≤350 cells/μL in 2013-2014 [8] and baseline CD4 count of 500 cells/μL in 2015 [4]. Alarmingly the period from 2016 to 2018, witnessed the highest percentage of late initiation of ART as 44.4% of HIV positive persons were started on ART at CD4 count <200 cells/μL, despite the policy of 'Treat all' which the guidelines recommended from 2016 [9]. This shows that a significant percentage of persons who tested positive for HIV were often initiated late on ART and it is similar to another study which showed that 39% of PLWH in Johannesburg and 35% in Mopani were initiated late on ART (CD4 count <200 cells/μL) [14]. These late initiations of ART could be due to late diagnosis of HIV or late presentation of patients at the clinic, as studies have shown that many people present late at clinics [15], or it could be due to delayed implementation of guidelines by hospital managers and clinicians. Late initiation of ART makes immunological recovery less likely [16], virological failure more likely [17], which leads to a need for regimen change, thereby decreasing available treatment regimen options for such patients [14], and increases all-cause mortality rate [18,19,14].

Furthermore, strong evidence has shown that early initiation of ART in HIV positive persons results in excellent treatment outcomes [16,20,21,22,23].

The increased coverage of HIV testing in South Africa [1] is quite commendable. However, it is not enough to have great policy, large coverage of testing or even available effective medicines if everything is not done to ensure early treatment initiation. This remains a major challenge in the fight against HIV/AIDS, which must be addressed to beat the epidemic.

Almost 56% of those who tested positive for HIV in 2005-2012, 55.3% in 2013-2014 and 23,3% in 2015 were initiated on ART at their recommended CD4 cell counts as stipulated in the guidelines [6,7,8,4]. Although, 44.8% % of individuals in 2005-2012, 14.9% in 2013-2014 and 43.3% in 2015 were initiated on ART at CD4 counts higher than the normal recommendations, it was still considered acceptable as patients with HIV/TB co-infection, pregnant or breast feeding women, HIV/hepatitis co-infection and HIV WHO clinical stage 3 or 4 were to be initiated on ART at higher CD4 counts than the ones recommended for other patients, according to the antiretroviral treatment guidelines [6,7,8,4].

From this study, TDF/FTC/EFV was the most prescribed ART regimen (65%) and the regimen most switched to from other regimens (63.8%). This high prescription of TDF/FTC/EFV by clinicians was in accordance with the South African antiretroviral treatment guidelines which recommend this regimen as a first line, first choice regimen for naïve patients since 2010 [7,8,4,9]. Another study has also found that TDF/FTC/EFV was the most tolerated, most prescribed ART regimen and having a high rate of virological suppression [24], suggesting why clinicians most frequently switched patients who probably did not tolerate other ART regimens to TDF/FTC/EFV.

Another finding in this study that is worthy of note is that, 13.5% of PLWH were prescribed the first line ART regimen comprising of ABC + 3TC + EFV. This regimen was recommended for

patients who had kidney failure (eGFR <50 mL/min), as TDF-containing regimens were contraindicated in patients with kidney failure or patients on additional nephrotoxic drugs such as the aminoglycosides. [4]. This suggests that prevalence of renal failure or some form of renal impairment was high (13.5%) among PLWH on ART in KZN. This is similar to another study which found a prevalence of 13.3% of chronic kidney disease among PLWH on ART [25]. This substantially high prevalence of kidney disease among PLWH on ART is worrisome as it limits clinician's choice of ART regimen and other medications used for co-morbid conditions, since many medicines are primarily metabolised via the kidneys.

Reasons given for switching regimens were renal impairment, defaulting on treatment, routine regimen change to a newer and better regimen, lipodystrophy, tuberculosis and being a shift worker. However, a study by Soorju and Naidoo in 2016 in KwaZulu-Natal found that ART regimen switching was mainly due to adverse drug reactions [26].

This study also found that female gender and baseline CD4 count <200 cell/μL were predictors to ART regimen switching.

Male PLWH on ART were 40% less likely to be switched from their initial ART regimen to a second regimen (aOR = 0.60, 95% CI= 0.34-0.97, P-value= 0.037) (Table 7). This is similar to a study from the US which also found that females were more likely to have regimen change due to poor adherence [27]. Another study with a large sample size, covering seven regions of the world also found that women from North America and Southern Africa had higher chance to switch ART regimen compared to men [28]. Therefore, it is evident from this study and from literature that females had significantly higher probability to switch from initial ART regimen. This may partly be due to gender-specific factors such as pregnancy. More studies are recommended in order to

understand the cause(s) and tailor treatments to minimize the chances to switch regimens by female patients on ART.

Patients on ART who had baseline CD4 count below 200 cell/μL had 2 folds likelihood of being changed from one regimen to another (aOR = 1.99, 95% CI= 1.18-3.34, P-value= 0.010) (Table 7). This is expected, as baseline CD4 count has been generally shown to influence HIV treatment outcomes [17,16] This however could be limited if people who test positive for HIV initiate ART early, since all who test positive to HIV are now eligible for treatment based on the current South African antiretroviral treatment guidelines [10].

Conclusions

Clinicians prescribed the appropriate ART regimen constituting the right drug class combinations to persons who tested positive to HIV. However, there was high percentage of patients who were initiated late on ART from 2013 to 2018. Unless the cause(s) of late initiation of ART in South Africa are vigorously identified and appropriately addressed, the efforts of government in making available HIV tests and antiretroviral drugs for all who need them, will fall short of achieving the desired optimum treatment outcomes.

Female gender and late initiation of ART were predictors to switching from initial ART regimen to another regimen. It is therefore essential to develop strategies to increase the durability of initial regimens in order to avoid exhausting the available treatment options which would be detrimental not only to the patients concerned but could also be a public health challenge.

List of abbreviations

3TC - Lamivudine

ABC - Abacavir

AIDS - Acquired Immune Deficiency Syndrome

aOR - Adjusted Odd Ratio

ART - Antiretroviral Therapy

ARV - Antiretroviral

ATV/r - Atazanavir/Ritonavir

AZT - Azidothymidine (also known as Zidovudine)

BREC - Biomedical Research Ethics Committee

CCR5 - Chemokine Receptor Antagonist

CDC - Centre for Disease Control and Prevention

COR - Crude Odd Ratio Efavirenz

d4T - Stavudine

DDI - Didanosine

EFV - Efavirenz

FBS - Fasting Blood Sugar

FDC - Fixed Dose Combination

FI - Fusion Inhibitor

FTC - Emtricitabine

HAART - Highly Active Antiretroviral Therapy

HIV - Human Immuno-deficiency Virus

INSTI - Integrase Inhibitor

KZN - KwaZulu-Natal

LPV/r - Lopinavir/Ritonavir

LTDL - Lower Than Detectable Level

NCDs - Non-Communicable Diseases

NDoH - National Department of Health

NNRTI - Non-nucleoside Reverse Transcriptase Inhibitor

NRTI - Nucleoside Reverse Transcriptase Inhibitor

NVP - Nevirapine

PAD - Peripheral Arterial Disease

PCP - Pneumocystis pneumonia

PCR - Polymerase Chain Reaction

PI - Protease Inhibitor

PLWH - Persons Living With HIV

SPSS - Statistical Package for Social Sciences

STGs/EML - Standard Treatment Guidelines and Essential Medicines List

TDF - Tenofovir

VL - Viral load

ZDV - Zidovudine

Declarations

Ethics approval and consent to participate

Before the commencement of this study, ethical approval was obtained from the biomedical research ethics committee (BREC) of the University of KwaZulu-Natal (UKZN) (Reference number BE 314/18).

Each participant read or was read to, the Informed Consent Form from BREC and consented to participate in the study and signed the form before being included in the study.

Consent for publication

Not applicable

Availability of data and materials

The dataset used and/or analyzed during the current study is available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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The College of Health Sciences Research office of the university of KwaZulu-Natal provided stipends to the corresponding author, funded logistics such as transportation to collect data and funded the cost of printing the research instrument (information sheet). But the office was not

involved in any way in the design of the study, was not involved in the data collection. Was not involved in any way in the analysis, interpretation of data or in writing the manuscript.

Authors' contribution

DMU conceptualized the study, designed the work, collected data alongside 2 research assistants, analyzed and interpreted the data with the guidance of a statistician.

DMU has approved the submitted version of this manuscript and has agreed both to be accountable for his contributions and to ensure that questions related to the accuracy or integrity of any part of the work even ones in which he was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature

PN revised, the proposal, the information sheet, draft manuscript and the final manuscript.

PN has approved the submitted version of this manuscript and has agreed both to be accountable for her contributions and to ensure that questions related to the accuracy or integrity of any part of the work even ones in which she was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature

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Chapter 2 provided information on the level of clinician's adherence to the South African HIV treatment protocols, rate of late initiation of ART, most prescribed and most switched to ART regimen and predictors to switching from one ART regimen to another.

In chapter 3, one of the objectives, that is, 'To determine effects of patient factors on HIV management outcomes' is presented ('Viral suppression' is the outcome presented in this chapter).

Viral suppression is the main determinant of a successful management of HIV infection. Some specific patient factors such as adherence can influence this outcome despite clinician's adherence to antiretroviral protocols. The findings are presented in this chapter.

The chapter is presented in the format of a manuscript.

This manuscript titled 'Patient Factors and Viral Suppression in HIV Management' is presented according to author's guide of AIDS care journal.

Submission Date: 11th January 2020. It is currently under review.

CHAPTER 3

Manuscript under review

Health Sciences

PATIENT FACTORS AND VIRAL SUPPRESSION IN HIV MANAGEMENT

Journal:	*AIDS Care - Psychology, Health & Medicine - Vulnerable Children and Youth Studies*
Manuscript ID	AC-2019-12-1164
Journal Selection:	AIDS Care
Keywords:	HIV, viral suppression, transmission, Patient factors, HAART

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PATIENT FACTORS AND VIRAL SUPPRESSION IN HIV MANAGEMENT

Abstract

The burden and impact of the HIV/AIDS epidemic remains enormous, especially in South Africa; and the war against it is still on. Great efforts and substantial success has been recorded. Significant advances in HIV antiretroviral therapy have been made. HAART is capable of suppressing HIV replication and sustained viral suppression can eliminate HIV transmission. Nevertheless, effective management and prevention of new infections remain a challenge.

The study was conducted among persons living with HIV (PLWH) in four hospitals in eThekwini, South Africa, with a sample size of 1203 (64% female), aimed at identifying possible patient factors associated with viral suppression.

The result indicated that 40.8% were virally suppressed. The probability of achieving viral suppression was significantly less in younger patients, the less educated and those with baseline CD4 cells count less than 200cells/ml, while the likelihood of achieving viral suppression was about 4 times higher for those that received encouragement from family to adhere to ART.

More should be done to counsel and follow up younger and the less educated PLWH, to adhere to ART; test for HIV to ensure early detection and treatment before CD4 count drops; provide information on the effect of encouragement to PLWH on viral suppression.

Key words: HIV management, viral suppression, transmission, patient factors, encouragement, HAART

Introduction

Significant advances in HIV antiretroviral therapy have been made since the introduction of Zidovudine (AZT) in 1987 (AIDS.gov, 2017). The advent of highly active antiretroviral therapy (HAART) has even brought us into a more exciting and promising era in the effort to combat the HIV epidemic. HAART is capable of suppressing viral replication and has transformed HIV infection from life-threatening disease with 100% mortality into a chronic, medically manageable condition in patients who have access to medication (Palella et al., 1998 and Rathbun, Liedtke, & Miller, 2019).

There is now definite scientific evidence that sustained HIV suppression using the highly active antiretroviral therapy eliminates the risk of HIV transmission (Cohen et al., 2016 and Cohen et al., 2011, Palella et al., 1998, Smith, Powers, Muessig, Miller & Cohen, 2012, Vernazza, Hirschel, Bernasconi, & Fleff, 2008 and Walensky et al., 2010). This has made achievement of HIV viral suppression in persons living with HIV (PLWH) not only an important means to improve the quality of life of persons living with HIV (PLWH) and prolong their life span but also an integral component of preventing new infections (Cohen et al., 2011, Hamers, Sigaloff, Kityo, Mugyenyi & de Wit, 2013, Lingappa et al., 2010 and Price et al., 2011). This could be key to halting the epidemic.

In spite of these progress made with antiretroviral therapy, the morbidity and mortality due to HIV, as well as transmission of HIV remains high globally (UNAIDS, 2018).

Sub-Saharan Africa remains the most severely affected, which accounts for about 67% of the global prevalence, where South Africa is by far the most affected country, which alone accounts for the biggest epidemic in the world with 7.2 million people living with HIV with a prevalence of 18.9% (UNAIDS 2018). In 2017, there were 270,000 new HIV infections and 110,000 people died from AID-related illnesses in South Africa (UNAIDS, 2018).

However, South Africa has taken giant strides in an effort to combat the heaviest of the HIV and AIDS burden any nation had to face and has made huge improvements. It has the largest antiretroviral treatment (ART) programme in the world and its funded largely from domestic resources and has even undergone further expansion recently with the implementation of the 'test and treat' guidelines (UNAIDS, 2018). It is the first country in sub-Saharan Africa to fully approve Pre-Exposure Prophylaxis (PreP) which is available to people at high risk of infection (UNAIDS, 2018). With the success in the ART programme there is a resultant increase in life expectancy up to 67.7 years in 2015 (SANAC, 2017). In spite of all these commendable giant strides, South Africa is not close to meeting the third component of the WHO "90-90-90" target for 2020, which is to achieve viral suppression in 90% of the people who are on ART, as South Africa is committed to meeting. Failure to meeting this desired goal of viral suppression might have been influenced by some factors that are patient dependent, resulting in still having high rate of new infections as well as poor rate of viral suppression. Hence the need to study the possible associations/influence of various patient factors on viral suppression in the given settings, as these factors and the outcomes may differ from one culture and setting to another.

Aim

This study aims to determine the effects of patient factors on HIV management outcome.

Objectives

1. To determine patient factors associated with viral suppression in persons living with HIV taking antiretroviral therapy
2. To evaluate the effects of patient factors on viral suppression

Materials and Method

This is a quantitative, observational and analytical study. Before the commencement of this study, approvals were obtained from the biomedical research ethics committee (BREC) of the university of KwaZulu-natal (Reference number BE 314/18) and the department of health KwaZulu-natal.

The study was conducted in 4 HIV clinics attached to Public Sector Hospitals in the eThekwini District of Kwazulu-Natal (KZN), South Africa. These hospitals were selected based on the different former ethnic/racial settlements. A total of 1,203 Patients living with HIV and were receiving antiretroviral therapy for at least 6 months were randomly selected and recruited in the study after obtaining written consent from each patient to participate in the study using the BREC consent form.

The following statistical parameters were used to arrive at the minimum sample size of 249 per hospital: Odds ratio = 1.25, type 1 error = 0.05, type 2 error = 0.2 and statistical power = 0.80. Assuming a population variance of 1 and population mean of 0(normal distribution). A minimum sample size of 994 was determined with a critical Z value = 1.96.

Included in the study were HIV patients receiving antiretroviral therapy, adults (18 years and above), male and female (not pregnant) and who started receiving ARVs between 2007 and 2018.

Excluded in the study were HIV patients who were below 18 years of age, pregnant women and those who started receiving ARVs before 2007 or after 2018.

Data was collected using pretested and validated questionnaire and from patient chart.

The questionnaire was designed to obtain information on patient demographics such as name, gender, age e.t.c. and patient factors such as education level, adherence to medications,

consumption of alcohol, use of supplements, use of traditional medicine, patients' knowledge of the disease, patients' attitude towards treatment while information on patients management outcomes such as baseline and current CD4 counts, initial and current viral load e.t.c were extracted from the hospitals' patient charts into a table designed using Microsoft word.

The statistical package for social sciences (SPSS) software version 26 was used to analyze the data. Results were tabulated, discussion and conclusion were made as shown below

Results

A total of 1203 adult persons living with HIV from four hospitals were included in this study. 770 (64%) were female, 405 (33.7%0 male, while 28 (2.3%) did not indicate their gender. 145(12.6%) were between the ages 18 to 28 year, 694(60.2%) between the ages 29 to 48 years and 313(27.2%) ages greater than 48 years. Baseline viral load was as follows; 25(15.6%) high (≥100,000 copies/μL), 24(15.0%) low (10,000 to 99,999 copies/μL) while 111 (69.4%) lower (<10,000 copies/μL but higher than 'undetectable' level). Their viral loads at the time of study were as follows; 384 (59.2%) had higher than undetectable level while 265 (40.8%) had (Lower than detectable level) LTDL of viral load, which is a viral load between 20 to 70 copies/ml.

Chi-square analysis showed the following factors were significantly associated with patient current viral load. These are: age of the patients, forgetting to take ARVs along when travelling or leaving home, feeling inconvenienced sticking to treatment plan, taking herbal/traditional medicine, encouragement from family members to take ART, receiving care and assistance from family when sick and receiving financial assistance from family when needed. As shown in table 1.

Predictors of Achieving Viral Suppression (LTDL) in PLWH on Anti-retroviral therapy (ART).

In a univariate analysis, the current viral load of patients on anti-retroviral medications was significantly related to age of the patients, level of education, forgetting to take HIV medications when travelling or leaving home, feeling inconvenienced sticking to treatment plan, taking herbal/traditional medicines, encouragement from family members to take HIV medications, receiving care and assistance from family when sick, receiving financial assistance from family when needed for transportation to the clinic and initial CD4 count.

In stepwise forward likelihood ratio multivariate logistic regression models, age, level of education, encouragement from family members to take their medications and current CD4 cell counts were the determinant factors that affect viral load among PLWHIV on ART.

The probability of achieving viral suppression for HIV patient on ART between the ages of 18 to 28 years old was 73% less than HIV patients who were older than 48 years old (aOR = 0.27, 95% CI= 0.13-0.60, P-value=0.001).

The probability of achieving viral suppression for HIV patient on ART between the ages of 29 and 48 years old was 39% less than HIV patients who were older than 48 years old (AOR = 0.61, 95% CI= 0.39-0.95, P-value=0.028).

Patients on ART that have primary school level of education were 57% less likely (aOR = 0.43, 95% CI= 0.22-0.83, P-value=0.012) to achieve viral suppression than those who had tertiary level education, while patients on ART that have high school level of education were 50% less likely (aOR = 0.50, 95% CI=0.28-0.87. P-value=0.014) to achieve viral suppression than those who had tertiary level education.

HIV patients on ART, who had encouragement from family members to adhere to their medications were about 4 times likely to achieve viral suppression than those who did not receive family encouragement (aOR = 3.74, 95% CI= 1.30-10.70, P-value= 0.014. Furthermore, patients on ART that had baseline CD4 count <200 cell/ml were 53% less likely to achieve viral suppression than those who had ≥200 cells/ml (AOR = 0.47, 95% CI= 0.31-0.70, P-value= 0.000) as shown in table 2.

Discussion

Based on this study which was conducted in high HIV prevalent South Africa, virological suppression among PLWH who were on highly active antiretroviral therapy (HAART) was 40.8% which is still far off from achieving the third of UNAIDS " 90-90-90" by 2020.

Factors that are significantly associated with viral suppression in persons living with HIV who were on highly active antiretroviral therapy (HAART) are; age of patient, poor adherence to ART (sometimes forgetting to take ART), inconvenience of sticking to treatment plan, taking herbal/traditional medicines, encouragement from family to take medicines, receiving care and assistance from family when sick as well as financial assistance from family when needed.

This study showed that the probability of achieving viral suppression for HIV patients on ART between the ages of 18 to 28 years old is 73% less than that of HIV patients who were older than 48 years old (aOR = 0.27, 95% CI= 0.13-0.60, P-value=0.001), while for those between the ages of 29 and 48 years old is 39% less than that HIV patients who were older than 48 years old (aOR = 0.61, 95% CI= 0.39-0.95, P-value=0.028). This shows that viral suppression is higher among older age groups and it is similar to a report by Hess and Hall, (2014). This lower chances of achieving viral suppression in younger patients may be due to lower adherence to antiretroviral medications by younger patients compared to older patients. This could possibly be due to younger persons' awareness that HIV infection is no longer a 'dead sentence'. However, this possible attitude could lead to drug resistance which is a public health concern. Another reason may be that older patients are more concerned about their health, overcome stigma easily, stay at home more, which result in better adherence to their medication hence higher rate of viral suppression.

Patients on ART that have primary school level of education were 57% less likely (aOR = 0.43, 95% CI= 0.22-0.83, P-value=0.012) to achieve viral suppression than those who had tertiary

level education, while patients on ART that have high school level of education were 50% less likely (AOR = 0.50, 95% CI=0.28-0.87. P-value=0.014) to achieve viral suppression than those who had tertiary level education. This is expected, as higher level of education could make an individual understand instructions and counselling better, be able to seek for further clarification from health professionals and trained counsellors, they could also read written materials that are meant to enlighten patients and the general public about HIV, its management and outcomes. Other possible reason for this difference in viral suppression outcomes may be that the higher educated an individual is, the higher the chance of being employed hence less financial limitations to regularly visit ARV clinic for medication refill and/or consultation whenever necessary.

HIV patients on ART, who had encouragement from family members to adhere to their medications were about 4 times likely to achieve viral suppression than those who did not receive family encouragement (aOR = 3.74, 95% CI= 1.30-10.70, P-value= 0.014. This is similar to another study conducted in South Africa which indicated an improved viral suppression among patients on ART who received community based adherence support (Fatti et al., 2016). The effect of encouragement from family is likely mediated through a variety of mechanisms such as greater disclosure, reduction in stigma, decrease in psychological problems, which in turn are likely to increase adherence to medications (Hodgson et at., 2014 and Lowther, Selman, Harding, & Hagginson, 2014). These, most likely were responsible for the desired outcome of viral suppression

Furthermore, patients on ART that had baseline CD4 count <200 cell/ml were 53% less likely to achieve viral suppression than those who had ≥200 cells/ml (aOR = 0.47, 95% CI= 0.31-0.70, P-value= 0.000), that is, virological failure is higher with patient who initiated ART at a lower baseline CD4 cell count. This finding supports the WHO recommendation that ART should be initiated in everyone living with HIV at any CD4 cell count (WHO, 2015).

Declaration of interest statement: There is nothing to declare

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Table 1: Chi-square analysis results showing different variables associated with viral suppression

Variables	Current viral load n (%)		Total frequency, n (%)	Chi-square P-value
	Detectable	LTDL		
Gender				
Male	124(60.5)	81(39.5)	205(32.3)	0.486
Female	247(57.6)	182(42.4)	429(67.7)	
Age				
18 - 28	43(67.2)	21(32.8)	64(10.3)	0.015*
29 - 48	222(60.8)	143(39.2)	365(59.0)	
>48	95(50.0)	95(50.0)	190(30.7)	
Education				
Primary school	87(63.0)	51(37.0)	138(22.8)	0.082
High school	207(60.5)	135(39.5)	342(56.5)	
Tertiary level	49(49.5)	50(50.5)	99(16.4)	
No formal education	12(46.2)	14(53.8)	26(4.3)	
Employment Status				
Employed	138(61.1)	88(38.9)	226(35.2)	0.514
Unemployed	243(58.4)	173(41.6)	416(64.8)	
Skipped taking ARVs any day within the last 1 month?				
Yes	54(60.7)	35(39.3)	89(14.1)	0.807
No	322(59.3)	221(40.7)	543(85.9)	
Sometimes forgetting to take ARVs along when travelling or leaving home				
Yes	62(70.5)	26(29.5)	88(13.9)	0.027*

No	316(58.0)	229(42.0)	545(86.1)	
Feeling inconvenienced sticking to treatment plan				
Yes	74(67.9)	35(32.1)	109(18.2)	0.028*
No	276(56.4)	213(43.6)	489(81.8)	
Alcohol consumption				
Yes	72(64.3)	40(35.7)	112(17.6)	0.220
No	304(58.0)	220(42.0)	524(82.4)	
Taking herbal/traditional medicines				
Yes	34(73.9)	12(26.1)	46(7.3)	0.036*
No	338(58.2)	243(41.8)	581(92.7)	
Encouragement from family members to take ARVs				
Yes	322(58.5)	228(41.5)	550(94.3)	0.021*
No	26(78.8)	7(21.2)	33(5.7)	
Receiving care and assistance from family when sick				
Yes	344(57.8)	251(42.2)	595(94.4)	0.009*
No	28(80.0)	7(20.0)	35(5.6)	
Financial assistance from family when needed				
Yes	280(56.5)	216(43.5)	496(79.6)	0.009*
No	88(69.3)	39(30.7)	127(20.4)	

Table 2: Multi-covariate and uni-covariate analysis results for different socio-demographic, clinical and risk variables that affect viral suppression.

Variables	COR(95%CI)	COR P-Value	AOR(95%CI)	AOR P-Value
Gender				
Male	0.89(0.63-1.25)	0.486	0.75(0.49-1.14)	0.171
Female	1		1	
Age				
18 – 28	0.49(0.27-0.89)	0.018*	0.27(0.13-0.60)	0.001*
29-48	0.64(0.45-0.92)	0.015*	0.61(0.39-0.95)	0.028*
>48	1		1	
Level of Education				
No formal education	1.14(0.48-2.72)	0.762	1.16(0.40-3.40)	0.786
Primary	0.57(0.34-0.97)	0.038*	0.43(0.22-0.83)	0.012*
High school	0.64(0.41-1.00)	0.051	0.50(0.28-0.87)	0.014*
Tertiary	1		1	
Employment Status				
Employed	0.90(0.64-1.25)	0.514	----	---
unemployed	1			
Skipped taking ARVs any day within the last 1 month?				
Yes	0.94(0.60-1.5)	0.807	-----	---
No	1			
Sometimes forgetting to take ARVs along when travelling or leaving home				
Yes	0.58(0.36-0.94)	0.028*	0.64(0.35-1.18)	0.155
No	1		1	
Feeling inconvenienced sticking to treatment plan				
Yes	0.61(0.40-0.95)	0.029*	---	--
No	1			

Alcohol consumption				
Yes	0.22(0.50-1.17)	0.221	---	--
No	1			
Taking herbal/traditional medicines				
Yes	0.49(0.25-0.97)	0.040*	---	
No	1			
Encouragement from family members to take ARVs				
Yes	2.63(1.12-6.16)	0.020*	3.74(1.30-10.70)	0.014*
No	1		1	
Receiving care and assistance from family when sick				
Yes	2.92(1.26-6.79)	0.013*	--	
No	1			
Financial assistance from family when needed for transportation to the clinic				
Yes	1.74(1.15-2.64)	0.009*	--	
No	1			
Having diabetes				
Yes	1.16(0.68-1.98)	0.587	--	
No	1			
Initial CD4 count				
<200	0.47(0.33-0.65)	0.000*	0.47(0.31-0.70)	0.000*
≥200	1		1	

Keys: (1) the reference category; COR: Crude Odd Ratio; CI: Confidence interval; AOR: Adjusted Odd Ratio

Chapter 3 provided information on the 'patient factors and viral suppression in HIV management', thus percentage of PLWH on ART who achieved viral suppression, patient factors significantly associated with viral suppression and predictors to achieving viral suppression is presented.

In chapter 4, another aspect of the stated objective as in chapter 3 viz 'To determine patient factors on HIV management outcomes' is presented ('immunologic recovery' is the outcome presented).

Immunologic recovery usually occurs as viral suppression is achieved. Immunologic recovery is indicated by increase in CD4 cell counts to normal range. This prevents the presence of opportunistic infections which are a hallmark of immune suppression.

Some specific patient factors may influence how well and sustained CD4 cells count increases resulting in good immunologic recovery. The findings are presented in this chapter.

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This manuscript titled 'Patient Factors and Immunologic Recovery in HIV Management' has been published in PONTE Journal.

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CHAPTER 4

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PATIENT FACTORS AND IMMUNOLOGIC RECOVERY IN HIV MANAGEMENT

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ABSTRACT

Individuals infected with HIV and are having low CD4 cells count are vulnerable to attack by opportunistic infections. These infections occur more frequently and more severely in persons living with HIV (PLWHIV) than in the general population.

Highly active antiretroviral therapy (HAART), when adhered to by PLWHIV, is capable of suppressing HIV viral replication, thereby reducing the viral population to 'lower than detectable level' which eventually results in immunologic recovery and restoration of normal immune function as the number of CD4 cells increases.

However, not all PLWHIV achieve immunologic recovery. There are factors that affect immunologic recovery. This study, with a sample size of 1203 PLWHIV, was aimed at determining patient factors which could affect immunologic recovery in PLWHIV on antiretroviral therapy in public health care facilities in KwaZulu-Natal. Data was collected using hospital patient charts. 64% of the participants were female. The prevalence of immunologic failure among PLWHIV on ART was 8.6 % (CD4 cell count <200 cells/μL). CD4 cells count outcome was statistically significantly associated with gender, poor adherence to ART and baseline CD4 cells count. The probability of immunologic failure for those who did not strictly adhere to ART was more than 3 folds higher than those who adhered to ART; and the probability of immunologic failure was more than 8 folds higher for those who had baseline CD4 cells <200 cells/μL than those who had baseline CD4 cells ≥200 cells/μL. These therefore affirms the absolute necessity of strict adherence to ART by PLWHIV as well as highlights the necessity of the WHO HIV treatment policy of 'Treat all'.

Key words: Patient, Immunologic, CD4, HIV, Factors, failure, recovery

INTRODUCTION AND LITERATURE REVIEW

CD4 cell count is an essential pointer of immune function. (Bouteloup et al., 2017) When an individual is infected with the human immunodeficiency virus (HIV), the virus attacks the CD4 cells in their blood. This process damages the CD4 cell and leads to drop in their number in the body, This makes it hard for the immune system of PLWHIV to combat infections. (Moncivaiz and Alexander, 2018), All people diagnosed with HIV are therefore vulnerable to a number of opportunistic infections and are at increased risk of pathogenic organisms that affect the general population. (Haburchak, 2019), The frequency and morbidity of HIV-related infections and malignancies increases, as the absolute CD4 T-lymphocyte count declines to and below 200 cells/μL. Therefore, those who are infected with HIV, having declining CD4 count are at increased risk of life-threatening, AIDS-defining opportunistic infections. (Ford N et al., 2017 and Thompson et al., 2010).

CD4 count is an important guide for the commencement and stoppage of primary and seconcodary prophylaxis against opportunistic infections such as Pneumocystic carinii, Cytomegalovirus and other opportunistic pathogens during antiretroviral therapy (ART) in patients with HIV infection. Prophylaxis against opportunistic infections can be stopped safely, the moment CD4 count increases above 500 cells/μL. (Battegay et al., 2006, Bouteloup et al., 2017)

In past, antiretroviral therapy (ART) was delayed in those who tested positive for HIV until their CD4 cells count dropped to 200 cells/μL according to the guidelines and recommendations. However, the current recommendation is that antiretroviral therapy should be commenced for all persons who test positive for HIV irrespective of CD4 counts to minimize HIV related morbidity and mortality (WHO, 2015). Studies have shown that early commencement antiretroviral therapy

(ART) with CD4 count > 200 cells/μL increases survival and prevents progression of the disease relative to delayed commencement of ART (Zolopa et al. 2010).

Even when these guidelines and recommendations are adhered to by clinicians, there are other factors that may influence the outcomes of treatment which are specific to patient population. This study therefore was aimed at assessing such patient specific factors that can affect immunologic recovery among PLWHIV on antiretroviral therapy in KwaZulu-Natal.

Aim

This study aimed to determine the effects of patient factors on immunologic recovery in HIV management.

Objectives

1. To determine the prevalence of immunologic failure (CD4 count <200 cells/μL) among PLWHIV on ART in public hospitals in KwaZulu-Natal.
2. To determine patient factors that are associated with immunologic recovery in persons living with HIV, on antiretroviral therapy
3. To evaluate the effects of patient factors on immunologic recovery

METHODOLOGY

This is a quantitative, observational and analytical study. The study was conducted in 4 HIV clinics attached to Public Sector Hospitals in the eThekwini District of KwaZulu-Natal (KZN), South Africa. These hospitals were selected based on the different former ethnic/racial settlements. A total of 1,203 Persons living with HIV and were receiving antiretroviral therapy for at least 6 months were randomly selected and recruited in the study after obtaining written consent from each patient to participate in the study using the biomedical research ethics committee (BREC) consent form.

The following statistical parameters were used to arrive at the minimum sample size of 249 per hospital: Odds ratio = 1.25, type 1 error = 0.05, type 2 error = 0.2 and statistical power = 0.80. Assuming a population variance of 1 and population mean of 0(normal distribution). A minimum sample size of 996 was determined with a critical Z value = 1.96.

Included in the study were HIV patients receiving antiretroviral therapy, adults (18 years and above), male and female (not pregnant) and who started receiving ARVs between 2005 and 2019.

Data was collected using pretested and validated questionnaire and from patient chart in the hospitals.

The questionnaire was designed to obtain information on patient demographics such as name, gender, age e.t.c. and patient factors such as education level, adherence to medications, consumption of alcohol, use of supplements, use of traditional medicine, patients' knowledge of the disease, patients' attitude towards treatment while information on patients management

outcomes such as baseline and current CD4 counts, baseline and current viral load among others were extracted from the hospitals' patient charts into a table designed using Microsoft word.

The statistical package for social sciences (SPSS) software version 26 was used to analyze the data. Results were tabulated, discussion and conclusion were made as shown below

ETHICAL CONSIDERATION

Before the commencement of this study, approvals were obtained from the biomedical research ethics committee (BREC) of the University of KwaZulu-Natal (Reference number BE 314/18) and the department of health KwaZulu-Natal.

RESULTS

Table 1: Demographic information

Variable	Frequency	Percentage (%)
Gender		
Male	405	34.5
Female	770	65.5
Age in years		
18 – 28	145	12.6
29 – 48	694	60.2
>48	313	27.2
Level of education		
No formal education	48	4.3
Primary school	208	18.6
High school	672	60.0
Tertiary level	192	17.1
Employment status		
Yes	384	32.4
No	801	67.6

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Table 2: Chi-square analysis results showing different variables associated with CD4 cell count (immunologic recovery).

Variables	Current CD4 cells n (%)		Total frequency, n (%)	Chi-square P-value
	<200	≥200		
Gender				
Male	24 (11.9)	177 (88.1)	201 (31.5)	0.032*
Female	30 (6.9)	407 (93.1)	437 (68.5)	
Age				
18 – 28	7 (10.8)	58 (89.2)	65 (10.4)	0.676
29 – 48	31 (8.4)	336 (91.6)	367 (58.8)	
>48	14 (7.3)	178 (92.7)	192 (30.8)	
Education				
Primary school	15 (10.9)	122 (89.1)	137 (22.5)	0.530
High school	26 (7.6)	315 (92.4)	341 (56.0)	
Tertiary level	9 (8.7)	95 (91.3)	104 (17.1)	
No formal education	1 (3.7)	26 (96.3)	27 (4.4)	
Employment Status				
Employed	23 (10.0)	206 (90.0)	229 (35.5)	0.362
Unemployed	33 (7.9)	383 (92.1)	416 (64.5)	
Forgetting to take HIV medicines sometimes				
Yes	14 (12.8)	95 (87.2)	109 (17.0)	0.080
No	41 (7.7)	492 (92.3)	533 (83.0)	
Skipped taking ARVs any day				

within the last 1 month?				
Yes	11 (13.3)	72 (86.7)	83 (13.1)	0.125
No	45 (8.1)	508 (91.9)	553 (86.9)	
Sometimes forgetting to take ARVs along when travelling or leaving home				
Yes	10 (11.4)	78 (88.6)	88 (13.8)	0.240
No	42 (7.7)	506 (92.3)	548 (86.2)	
Feeling inconvenienced sticking to treatment plan				
Yes	10 (9.2)	99 (90.8)	109 (18.1)	0.658
No	39 (7.9)	455 (92.1)	494 (81.9)	
Alcohol consumption				
Yes	6 (5.5)	104 (94.5)	110 (17.2)	0.195
No	49 (9.3)	480 (90.7)	529 (82.8)	
Taking herbal/traditional medicines				
Yes	3 (6.0)	47 (94.0)	50 (7.9)	0.498
No	51 (8.8)	529 (91.2)	580 (92.1)	
Stopping to take HIV medicines after taking it for a long time, like 2 to 3 years				
Yes	9 (15.8)	48 (84.2)	57 (9.1)	0.027*
No	42 (7.4)	528 (92.6)	570 (90.9)	
Disclosure of HIV status to family members				
Yes	47 (7.9)	548 (92.1)	595 (92.8)	0.085

No	7 (15.2)	39 (84.8)	46 (7.2)	
Encouragement from family members to take ARVs				
Yes	43 (7.8)	510 (92.2)	553 (94.4)	0.719
No	2 (6.1)	31 (93.9)	33 (5.6)	
Receiving care and assistance from family when sick				
Yes	52 (8.7)	544 (91.3)	596 (94.3)	0.509
No	2 (5.6)	34 (94.4)	36 (5.7)	
Financial assistance from family when needed for transportation to the clinic				
Yes	44 (8.9)	451 (91.1)	495 (79.2)	0.315
No	8 (6.2)	122 (93.8)	130 (20.8)	
Baseline CD4 cell count				
<200	40 (14.9)	229 (85.1)	269 (46.3)	0.000*
≥200	12 (3.8)	300 (96.2)	312 (53.7)	

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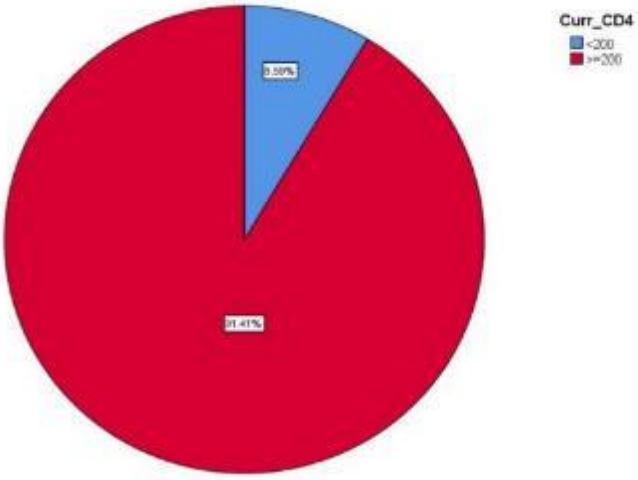
Table 3: Multi-covariate and uni-covariate analysis results for different socio-demographic, clinical and risk variables that affect CD4 cells count (immunologic recovery).

Variables	COR (95%CI)	COR P-Value	aOR (95%CI)	aOR P-Value
Gender				
Male	1.84(1.05-3.24)	0.034*	1.34(0.63-2.83)	0.450
Female	1			
Age				
18 – 28				
29-48				
>48				
Level of Education				
No formal education	0.41(0.05-3.35)	0.403		
Primary	1.30(0.54-3.09)	0.556		
High school	0.87(0.40-1.92)	0.733		
Tertiary	1			
Employment Status				
Employed	1.30(0.74-2.27)	0.363		
unemployed	1			
Forgetting to take HIV medicine sometimes				
Yes	1.77(0.93-3.37)	0.083	3.06(1.28-7.33)	0.012*
No	1		1	
Skipped taking ARVs any day within the last 1 month?				
Yes	1.73(0.85-3.49)	0.129		
No	1			
Sometimes forgetting to take ARVs along when travelling or leaving home				
Yes	1.55(0.75-3.20)	0.243		
No	1			
Feeling inconvenienced sticking to treatment plan				
Yes	1.18(0.57-2.44)	0.658		

No	1			
Alcohol consumption				
Yes	0.57(0.23-1.35)	0.201		
No	1			
Taking herbal/traditional medicines				
Yes	0.66(0.20-2.20)	0.501		
No	1			
Taking supplement				
Yes	0.55(0.29-1.03)	0.061		
No	1			
Stopping to take HIV medicines after taking for a long time, like 2 to 3 years				
Yes	2.36(1.08-5.13)	0.031*	1.37(0.44-4.27)	0.585
No	1			
Encouragement from family members to take ARVs				
Yes	1.30(0.30-5.64)	0.720		
No	1			
Receiving care and assistance from family when sick				
Yes	1.63(0.38-6.96)	0.513		
No	1			
Financial assistance from family when needed for transportation to the clinic				
Yes	1.49(0.68-3.24)	0.318		
No	1			
Baseline CD4 count				
<200	4.37(2.24-8.51)	0.000*	8.03(3.28-19.67)	0.000*
≥200	1		1	
Duration of treatment	0.98(0.98-0.99)	0.000*	0.98(0.97-0.99)	0.000*

Keys: (1) the reference category; COR: Crude Odd Ratio; CI: Confidence interval; AOR: Adjusted Odd Ratio.

Figure 1: Prevalence of immunologic failure (CD4 count <200 cells/μL)



A total of 1203 adult persons living with HIV from four hospitals were included in this study.

Baseline CD4 cells count was as follows; 275(45.5%) immunologic failure (<200 cells/μL), while 156 (25.8%) had CD4 cells between 200 cells/μL and 350 cells/μL, 75 (12.4%) had CD4 cells between 351 and 500 cells/μL, as well as 98 (16.2%) had CD4 cells >500 cells/μL (these are within the reference range of 500 – 2000 cells/μL)

CD4 cells counts at the time of study were as follows; 56 (8.6%) immunologic failure (<200 cells/μL) while 596 (91.4%) no immunologic failure ((≥200 cells/μL). Among those that were not having immunologic failure at the time of the study 112 (17.2%) had CD4 cells between 200 cells/μL and 350 cells/μL, 149 (22.9%) had CD4 cells between 351 and 500 cells/μL, while 335 (51.4%) had CD4 cells >500 cells/μL which is within the refence range of 500 – 2000 cells/μL (Bennett, 2019).

This study, based on the Chi-square analysis (Table 2 as shown above) found that there is statistically significant association between immunologic status of PLWHIV on antiretroviral therapy and gender of the patient, stopping of medication after a long time (2 to 3 years) of adherence as well as CD4 cells count at the commencement of ART.

In a univariate analysis (Table 3 as shown above), CD4 cells count of patients on anti-retroviral medications was significantly related to patient's gender, stopping to take antiretroviral medicine after adherence for a long time (2 to 3years), baseline CD4 cells count and duration on antiretrovirals since commencement of therapy.

In a stepwise forward likelihood ratio multivariate logistic regression model (Table 2), forgetting to take medicines sometimes, baseline CD4 cells count and duration on therapy were the predictors for immune recovery among PLWHIV on ART.

The probability of immunologic failure for HIV patient on ART who sometimes forget to take their medicines was more than 3 folds higher that those who strictly adhered to their medications (aOR = 3.06, 95% CI=1.28-7.33, P-value = 0.012).

The probability of immunologic failure for HIV patient on ART who had baseline CD4 cells count <200 cells/µL was more than 8 folds higher that those who had CD4 cells count ≥200 cells/µL. (AOR = 8.03, 95% CI= 3.28-19.67, P-value = 0.000).

DISCUSSION/CONCLUSION

Our study among persons living with HIV on antiretroviral therapy in public health care facilities in eThekwini, KwaZulu-Natal showed that, the higher the baseline CD4 cells count at the commencement of antiretroviral therapy, the higher the percentage increase in CD4 cells towards the reference range of 500 – 2000 cells/μL, hence the better the chances for achieving full immunologic recovery. This corresponds with a study by Adewumi et al., in 2015.

There was significant association between immunologic failure and patient's failure to continue adherence to medications after some 2 to 3 years of adherence, also the probability of immunologic failure for HIV patient on ART who sometimes forget to take their medicines was more than 3 folds higher that those who strictly adhered to their medications (aOR = 3.06, 95% CI=1.28-7.33, P-value = 0.012). These show that any form non-adherence to ART, either occasional forgetfulness or a break after a long period of adherence, results in immunologic failure. This is similar to an earlier study. (Nachega et al., 2009). This finding further underscores the necessity of strict adherence to antiretroviral therapy by PLWHIV to prevent immunologic failure, achieve and maintain immunologic recovery as well as prevent resistance to ART, which could be a public health threat, as affirmed by other studies. (Paterson et al., 2000 and Nachega et al., 2009).

it is therefore important that health care providers do not to concentrate their follow up efforts only on the patients who are having challenges achieving treatment success, but rather also as a matter of priority to design follow up strategies at intervals for patients who are doing well with viral suppression and immunologic recovery. Such strategy could be by organising forums to educate PLWHIV again and again, emphasizing on the importance of continues strict adherence, in other to prevent treatment failure after a long period of successful management.

There was 8.6% prevalence of immunologic failure (CD4 count <200 cells/μL) among PLWHIV on antiretroviral therapy attending public health facilities in eThekwini, KwaZulu-Natal. There is scarcity of data in South Africa on prevalence of immunologic failure among PLWHIV on ART. However, studies have shown that there is a pattern of decrease in CD4 cells after some years on ART. (Tsegaye and Worku, 2011, Kassa et al., 2013 and Reda et al, 2013). This may be due to apathy towards adherence after some years of successful adherence to medications by some patients on ART, as shown in a study conducted in 2020 by Umar and Naidoo.

The probability of immunologic failure for HIV patient on ART who had baseline CD4 cells count <200 cells/μL was more than 8 folds higher that those who had baseline CD4 cells count ≥200 cells/μL (AOR = 8.03, 95% CI= 3.28-19.67, P-value = 0.000). This strongly supports the current recommendation of 'Treat all', rather than allowing patient's CD4 cells count to drop before treatment is commenced (WHO, 2015).

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Chapter 4 provided information on the 'effects of patient factors on immunologic recovery', thus, prevalence of immunologic failure among persons living with HIV on ART, patient factors significantly associated with immunologic recovery and predictors of immunologic failure among persons living with HIV were highlighted.

In chapter 5 the final stated objective viz 'To Evaluate the Prevalence and Predictors of Diabetes among PLWH' is presented.

Successful management of HIV increases longevity among PLWH, however co-morbidities like chronic non-communicable diseases [NCD] sometimes interfere with positive health outcomes. One such NCD is diabetes. Therefore, evaluating the prevalence and the predictors of diabetes among PLWH is an important step in understanding the challenge of such comorbidities and managing them. The findings are presented in chapter 5.

The manuscript titled 'Prevalence and predictors of Diabetes Mellitus among Persons Living with HIV (PLWH)' is presented according to the submission guidelines of BMC Public Health.

Manuscript Number: PUBH-D-20-03462

Submission Date: 11TH June 2020.

CHAPTER 5

Manuscript submitted to BMC Public Health

BMC Public Health

PREVALENCE AND PREDICTORS OF DIABETES MELLITUS AMONG PERSONS LIVING WITH HIV (PLWH)

--Manuscript Draft--

Manuscript Number:	PUBH-D-20-03462
Full Title:	PREVALENCE AND PREDICTORS OF DIABETES MELLITUS AMONG PERSONS LIVING WITH HIV (PLWH)
Article Type:	Research article
Section/Category:	Chronic Disease Epidemiology
Funding Information:	
Abstract:	Abstract Background: Diabetes mellitus is a chronic non-infectious medical condition which is evident by raised levels of glucose in the blood, because the body cannot produce any or enough of the hormone insulin or use insulin effectively. Diabetes, if not well managed leads to complications such as neuropathy, retinopathy, nephropathy which can be fatal. Some of the factors that predisposes to diabetes include older age, higher body mass index, heredity and hypertension. With the availability of HAART for the managing HIV/AIDS infection, life span of persons living with HIV (PLWH) has increased significantly. With increased longevity, the aging population of PLWH also face chronic diseases such as diabetes in addition to HIV. The burden of both HIV and diabetes is high in South Africa, particularly in KwaZulu-Natal. Nevertheless, the prevalence of diabetes among PLWH in KwaZulu-Natal and its predictors is not well understood. Therefore, this study was conducted to determine the prevalence, predictors of diabetes and the outcome of managing diabetes among PLWH. Methods: The study was conducted in four public health care facilities in KwaZulu-Natal after ethical approval and informed consent were obtained. A pretested questionnaire and hospital patient charts were used to collect data. SPSS version was used to analyze the data using descriptive statistics and logistic regression. Results: Th e prevalence of diabetes among PLWH was 9%. This was higher than the prevalence of diabetes of 5.4% among the general population in South Africa. Just over 47% of those who had diabetes, had uncontrolled blood sugar, with a mean fasting blood sugar (FBS) of 11.7 mmol/L. The predictors of diabetes among PLWH were, male gender and older age. Male PLWH had 65% less chances of having diabetes and those who were between the ages of 18 and 48 years were 88% less probable to have diabetes compared to those who were older than 48 years. Conclusion: Public sector health care facilities in KwaZulu-Natal need to do much more to manage diabetes in PLWH in order to prevent diabetic complications and possible negative impact on the outcome of HIV management.
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PREVALENCE AND PREDICTORS OF DIABETES MELLITUS AMONG PERSONS LIVING WITH HIV (PLWH)

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Abstract

Background: Diabetes mellitus is a chronic non-infectious medical condition which is evident by raised levels of glucose in the blood, because the body cannot produce any or enough of the hormone insulin or use insulin effectively. Diabetes, if not well managed leads to complications such as neuropathy, retinopathy, nephropathy which can be fatal. Some of the factors that predisposes to diabetes include older age, higher body mass index, heredity and hypertension.

With the availability of HAART for the managing HIV/AIDS infection, life span of persons living with HIV (PLWH) has increased significantly. With increased longevity, the aging population of PLWH also face chronic diseases such as diabetes in addition to HIV. The burden of both HIV and diabetes is high in South Africa, particularly in KwaZulu-Natal. Nevertheless, the prevalence of diabetes among PLWH in KwaZulu-Natal and its predictors is not well understood. Therefore, this study was conducted to determine the prevalence, predictors of diabetes and the outcome of managing diabetes among PLWH.

Methods: The study was conducted in four public health care facilities in KwaZulu-Natal after ethical approval and informed consent were obtained. A pretested questionnaire and hospital patient charts were used to collect data. SPSS version was used to analyze the data using descriptive statistics and logistic regression.

Results: The prevalence of diabetes among PLWH was 9%. This was higher than the prevalence of diabetes of 5.4% among the general population in South Africa. Just over 47% of those who had diabetes, had uncontrolled blood sugar, with a mean fasting blood sugar (FBS) of 11.7 mmol/L. The predictors of diabetes among PLWH were, male gender and older age. Male PLWH

had 65% less chances of having diabetes and those who were between the ages of 18 and 48 years were 88% less probable to have diabetes compared to those who were older than 48 years.

Conclusion: Public sector health care facilities in KwaZulu-Natal need to do much more to manage diabetes in PLWH in order to prevent diabetic complications and possible negative impact on the outcome of HIV management.

Key words: Diabetes, Patient, Factors, HIV, Predictors, Prevalence. PLWH

Introduction

"Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both" [1].

Insulin is an essential hormone produced in the body's pancreas gland and carries glucose from the bloodstream into the cells of the body where the glucose is transformed into energy. Deficiency of insulin or the cell's failure to respond to insulin results in hyperglycemia, which is a key feature of diabetes.

If no intervention is done, hyperglycemia can cause damage to different body organs, resulting to the development of debilitating and life-threatening health problems such as cardiovascular disease, neuropathy, nephropathy and eye disease, resulting in retinopathy and blindness. These complications, however, can be slowed down or avoided if diabetes is appropriately managed.

Besides the main types of diabetes, viz Type 1, type 2 and gestational, there is secondary diabetes which arises as a complication of other diseases like pancreatitis, and hormonal disturbances such as Cushing's disease [2].

The development of combined antiretroviral therapy has led to the increase in the life span of persons living with HIV (PLWH) with treatment, similar to the expected age of the general population [3,4,5]. With longevity, however, PLWH are developing other chronic medical conditions [6,7,8,9]. One of these chronic comorbidities is diabetes mellitus

Factors associated with the development of diabetes in PLWH are the same as those in persons without HIV; they include older age, heredity, higher Body Mass Index [BMI], higher triglyceride, lower total cholesterol and hypertension. However, PLWH have the additional risk factors of HIV and HIV medicines [10,11,12]. Antiretroviral medications, such as nucleoside

reverse transcriptase inhibitors (NRTI) and protease inhibitors (PI), have been implicated in causing disorders such as insulin resistance, hyperglycaemia and diabetes [11,13].

Irrespective of the factors linked with the development of diabetes in PLWH, understanding the magnitude of the problem and proper management are essential, not only for the prevention of diabetic complications, reduction of mortalities due to the complications or for the improvement in the quality of life but also to prevent possible negative impact on the outcomes of managing HIV. Hence, this study was therefore conducted with the following aim.

Methods

This was a retrospective and a prospective study, aimed at determining the prevalence and predictors of diabetes among persons living with HIV (PLWH) and assessing the outcome of managing diabetes. The study was conducted in 4 HIV clinics at Public Sector Hospitals in the eThekwini Metro of KwaZulu-Natal (KZN), South Africa. These hospitals were selected based on the different former designated racial settlements. A total of 1,203 patients living with HIV that have been on antiretroviral therapy (ART) for at least 6 months, between 2005 and 2019 were randomly selected as follows; letters 'Y' and 'N' were written on separate folded pieces of paper. The patients who consented to participate in the study were asked to pick a folded piece of paper. Those who picked 'Y' were included in the study.

The participants had to be 18 years and above, and not pregnant. Those satisfying the criteria were recruited into the study after obtaining their written consent to take part in the study. The following statistical parameters were used to arrive at the minimum sample size of 249 per hospital: Odds ratio = 1.25, type 1 error = 0.05, type 2 error = 0.2 and statistical power = 0.80. Assuming a population variance of 1 and population mean of 0 (normal distribution). A minimum sample size of 996 was determined with a critical Z value = 1.96. Though 996 was required for this study, the

number of participants that selected Y was more than the required sample size resulting in a sample size of 1203 which was accepted to allow for dropouts in the study.

Data was collected by using both pretested and validated questionnaire and patient chart.

The questionnaire was designed to obtain information on patient demographics, other information such as diabetes screening at the clinic, diabetes status, diabetes medication, adherence to hypoglycemic medications by the patients, and life style modification while information on patients management outcomes such as baseline and current CD4 cell counts, baseline and current viral load, initial and current blood sugar were obtained from the hospitals' patient charts and transcribed into a table designed using Microsoft word.

The statistical package for social sciences (SPSS) software version 26 was used to analyze the data. Descriptive statistics and logistic regression were used in the analyses of data.

Results

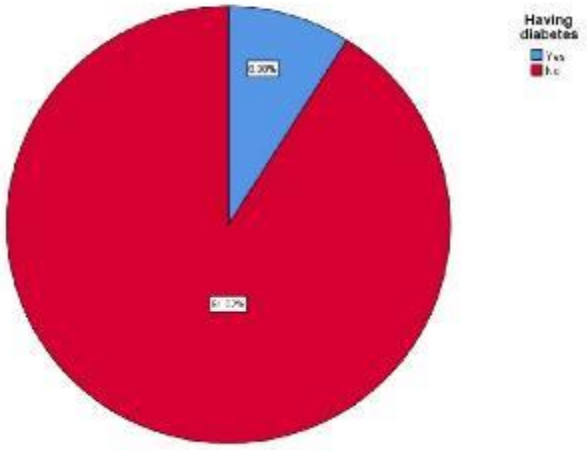
Table 1. Demographic information of patients

Variable	Frequency	Percentage (%)
Gender		
Female	770	64.0
Male	405	33.7
Age in years		
18-28	145	12.6
29-48	694	60.2
>48	313	27.2
Baseline CD4		
<200 cells/μL	275	45.5
200-350 cells/μL	156	25.8
351-500 cells/μL	75	12.4
>500 cells/μL	98	16.2

Of the 1203 participants, there were more females by close to fifty percent than males, while 28 (2.3%) did not indicate their gender. The age group 29 to 48 years was the majority age group of

the participants with just over 60%. Over 45% of the participants still had a CD4 count of less than 200.

Figure 1: Prevalence of diabetes among persons living with HIV



The prevalence of diabetes among persons living with HIV (PLWH) was 9%, [Fig 1]

Over 61% of those having diabetes were diagnosed while already on ART.

Over 47% of those with diabetes remained with uncontrolled blood sugar, having a mean FBS of 11.7 mmol/L.

Discussion

In this study 9% of the participants living with HIV (PLWH) had diabetes. South Africa, where the study was conducted has a high HIV prevalence as 20.4% of adults between the ages of 15 and 49 live with HIV [14]. In addition, the prevalence of diabetes among South Africa's adult general population was 5.4%. [15], yet the prevalence of diabetes among PLWH was much higher at 9%. As shown in this study.

This high prevalence of diabetes among PLWH as shown in our study, is consistent with findings by some other earlier studies [16,17,18,12]. However, a study by Diabetes Focus eMag [19] indicated that prevalence of diabetes among PLWH is similar to that among the general population. This difference in findings by different studies may be due to differences in the prevalence of diabetes amongst different populations, or differences in participant's lifestyles.

Another finding from this study relating to gender has shown that the prevalence of diabetes among females PLWH was higher (9.5%) than that of males (7.4%). This finding is similar with a study by Hernandez-Romieu et al, where in 2017 [20], it was shown that the prevalence of diabetes among females living with HIV was higher than that of males living with HIV. However, the same study showed that the prevalence of diabetes is higher in males among the general population. Furthermore, in this South African study it was found that female gender is a predictor for diabetes in PLWH, as males living with HIV were 65% less likely to have diabetes than females. This finding was similar with other studies which indicated that female who are HIV positive are more likely to have non-communicable diseases (NDC) co-morbidity. [21,22]. Hence, females living with HIV should be screened for diabetes repeatedly at close interval, in other to detect diabetes early and manage them accordingly.

Though this study found that 61% of the PLWH were diagnosed with diabetes after the commencement of antiretroviral therapy, there was no significant association between when ART was commenced and the incidence of diabetes mellitus. Earlier studies vary in their findings with regards to the association between ART and diabetes, with some studies showing similar results to this study [19], while other studies were contrary to the findings of this study, in that, they showed association between ART and diabetes [23,16,17,18]. While the question whether ART predisposes PLWH to diabetes or not remain controversial, people who test positive for HIV should be tested for diabetes before the commencement of ART and periodically thereafter.

Almost half (47.1%) of the PLWH with diabetes in this study remained with uncontrolled blood sugar (Mean FBS of 11.7 mmol/L), this is particularly of concern, as this predisposes them to diabetic complications such as retinopathy, neuropathy, nephropathy among others. These complications, if allowed to occur will further increase the disease burden and pill burden for this group of patients. Therefore, this study further sheds light on this issue to help clinicians understand the burden of diabetes among PLWH and appreciate the possible impact of uncontrolled blood sugar among these patients, with a view to mitigating the impact of the convergence of these chronic conditions by ensuring effective management of diabetes among persons living with HIV.

This study also showed that older age is a predictor to diabetes in PLWH, such that the likelihood of diabetes for those older than 48 years of age was 88% compared to those that are younger than 48 years of age. This is similar with other studies which showed that old age is a risk factor to chronic comorbidities in PLWH. [21,22]. As ART increases the life span of PLWH, predisposing them to chronic medical conditions such as diabetes, clinicians should give adequate attention to diabetes in PLWH as they do to other comorbidities.

However, the current (at the time of the study) blood sugar measurement for some of the patients with diabetes were missing, this might have affected the level of accuracy of the mean fasting blood sugar found in this study (11.7 mmol/L).

Conclusion/recommendations

In KwaZulu-Natal, the prevalence of HIV among PLWH (9%) was higher than that of the general population (5.4%), the prevalence among females was higher (9.5%) than that of males (7.4%) and predictors of diabetes among PLWH were female gender and older age. About half (47.1%) of the people with diabetes had uncontrolled blood sugar with a mean FBS of 11.7 mm/L. There was no association between ART and diabetes. People who test positive to HIV should be tested for diabetes before the commencement of ART, this is to further study the possible association between ART and HIV as some studies indicated. Regular and continuous testing for diabetes should be carried out and those found to be diabetic should be adequately managed to prevent diabetic complications as well as prevent possible interference with the outcomes of managing HIV.

List of abbreviations

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PLWH Persons Living With HIV

HIV – Human Immunodeficiency Virus

AIDS – Acquired Immunodeficiency Syndrome

FBS - Fasting Blood Sugar

HAART – Highly Active Antiretroviral Therapy

BMI – Body Mass Index

NRTI - Nucleoside Reverse Transcriptase Inhibitors

PI - Protease Inhibitors

KZN - KwaZulu-Natal

ART - Antiretroviral Therapy

SPSS - Statistical Package for Social Sciences

BREC - Biomedical Research Ethics Committee

Declarations

Ethics approval and consent to participate

Before the commencement of this study, ethical approval was obtained from the biomedical research ethics committee (BREC) of the University of KwaZulu-Natal (UKZN) (Reference number BE 314/18).

Each participant read or was read to, the Informed Consent Form from BREC and consented to participate in the study and signed the form before being included in the study.

Consent for publication

Not applicable

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests

Funding

The College of Health Sciences Research office provided stipends to the corresponding author, funded logistics such as transportation to collect data and funded the cost of printing the research instruments (questionnaire and information sheet). But it was not involved in any way in the design

of the study, was not involved in the data collection. Was not involved in any way in the analysis, interpretation of data or in writing the manuscript.

Authors' contribution

DMU conceptualized the study, designed the work, collected data alongside 2 research assistants, analyzed and interpreted the data with the guidance of a statistician.

DMU has approved the submitted version of this manuscript and has agreed both to be accountable for his contributions and to ensure that questions related to the accuracy or integrity of any part of the work even ones in which he was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature

PN revised, the proposal, the questionnaire, the information sheet, draft manuscript and the final manuscript.

PN has approved the submitted version of this manuscript and has agreed both to be accountable for her contributions and to ensure that questions related to the accuracy or integrity of any part of the work even ones in which she was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature

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Table 2. Association between patient variables and diabetes among PLWH taking ART.

(Table 2 should appear below table 1 in the text file)

Variables	Diabetes, n (%)		Total frequency, n (%)	Chi-square P-value
	No	Yes		
Gender				
Male	363(92.4)	30(7.6)	393(34.6)	0.219
Female	669(90.2)	73(9.8)	742(65.4)	
Age				
18 – 28	139 (99.3)	1(0.7)	140(12.5)	0.000*
29-48	643(95.3)	32(4.7)	675(60.5)	
>48	233(77.4)	68(22.6)	301(27.0)	
Level of Education				
No formal education	40(87.0)	6(13.6)	46(4.2)	0.109
Primary	175(87.1)	26(12.9)	201(18.5)	
High school	601(92.2)	51(7.8)	652(60.0)	
Tertiary	173(92.0)	15(8.0)	188(17.3)	
Employment Status				
Employed	349(93.6)	24(6.4)	373(32.6)	0.030*

unemployed	692(89.6)	80(10.4)	772(67.4)	
Alcohol consumption				
Yes	189(92.2)	16(7.8%)	205(18.1)	0.505
No	841(90.7)	86(9.3)	927(81.9)	
Initial CD4 count (cells/mm3)				
<200	234(88.6)	30(11.4)	264(44.9)	0.414
200 - 350	142(91.0)	14(9.0)	156(26.5)	
351 - 500	68(93.2)	5(6.8)	73(12.4)	
>500	89(93.7)	6(6.3)	95(16.2)	
Current CD4 count (cells/mm3)				
<200	50(94.3)	3(5.7)	53(8.3)	0.386
200 - 350	99(93.4)	7(6.6)	106(16.7)	
351 - 500	133(90.5)	14(9.5)	147(23.1)	
>500	293(88.8)	37(11.2)	330(51.9)	
Initial viral load (copies/mm3)				

High (>100,000)	22(95.7)	1(4.3)	23(14.6)	0.137
Low (10,000 – 99,000)	19(79.2)	5(20.8)	24(15.3)	
Lower (<10,000)	100(90.9)	10(9.1)	110(70.1)	
Current viral load (cells/mm3)				
'Detectable'	340(90.9)	34(9.1)	374(59.0)	0.587
LTDL	233(89.6)	27(10.4)	260(41.0)	

Key: * = Statistically significant

As can be seen from table 2 above, there was statistically significant association between the age and employment status of PLWH and having diabetes, at 95% confidence level.

Table 3: Predictors of diabetes in PLWH on ART (Multi-covariate and uni-covariate logistic regression).

(Table 3 should appear below table 2 in the text file)

Variables	COR (95%CI)	COR P-Value	aOR(95%CI)	aOR P-Value
Gender				
Male	0.76(0.49-1.18)	0.220	0.35(0.15-0.82)	0.016*
Female	1		1	
Age				
18 – 48	0.14(0.09-0.22)	0.000*	0.12(0.06-0.26)	0.000*
>48	1		1	
Duration on ART				
			1(0.99-1.01)	0.473
Level of education				
No formal education	1.73(0.63-4.74)	0.286		
Primary	1.71(0.88-3.35)	0.115		
High school	0.98(0.54-1.78)	0.944		
Tertiary	1			

Employment Status				
Employed	0.60(0.37-0.96)	0.032*		
unemployed	1			
Alcohol consumption				
Yes	0.83(0.48-1.44)	0.506		
No	1			
Baseline CD4 cells count				
>200 cells/µL			1.90(0.91-3.98)	0.088
≤200 cells/µL			1	
Current CD4 cells count				
>200 cells/µL			1.04(0.25-4.32)	0.957
≤200 cells/µL			1	

393 Keys: 1 = the reference category; COR= Crude Odd Ratio; CI= Confidence interval; aOR =

394 Adjusted Odd Ratio (Logistic regression).

395

In a stepwise forward likelihood ratio multivariate logistic regression model (as shown in table 3 above), female gender and age were predictors of diabetes in PLWH on ART.

The probability for diabetes mellitus in male PLWH on ART was 65% less than that of females (aOR = 0.35, 95% CI= 0.15-0.82, P-value=0.016).

The likelihood of diabetes mellitus in PLWH on ART who were between the ages 18 and 48 years was 88% less than those that were older than 48 years. (aOR = 0.12, 95% CI= 0.06-0.26, P-value=0.000)

Chapter 5 provided information on the prevalence and predictors of diabetes mellitus among persons living with HIV (PLWH), thus highlighting the prevalence of diabetes among PLWH, association between the prevalence of diabetes and commencement of ART, glycemic control among PLWH and the predictors of diabetes among PLWH.

In chapter 6 the thesis is discussed, synthesized, concluded with subsequent recommendations. The limitation of the study is also included in this chapter.

CHAPTER 6

DISCUSSION/SYNTHESIS

This study investigated and reported on the adherence of clinicians to HIV treatment guidelines, patient factors that could influence HIV management outcomes and their specific effects on the outcomes, as well as determined the prevalence, treatment outcomes and predictors of diabetes among PLWH.

Clinicians' adherence to treatment guidelines including regimen change.

Antiretroviral treatment guidelines were developed to guide HIV/AIDS clinicians on the use of ARV therapy in order to optimize patient care.[53] The metamorphosis in the HIV treatment guidelines over the few decades shows the evolving challenges in the field of antiretroviral therapy.[52]

The finding that the average annual prevalence of ART initiation at CD4 cell count <200 cells/μL was 40% from 2005 to 2018 is in contrast to a study in Thailand where 19% had a baseline CD4 count below 200 cells/μL.[54] This is concerning because as far back as 2013, the South African HIV treatment guidelines had moved away from recommending late initiation of ART (at CD4 count ≤200 cells/μL), to initiating ART early at CD4 ≤350 from 2013 to 2015. The current recommendation is 'Treat all', that is, initiate ART for everyone who tests positive for HIV.[55] Early initiation of ART in persons who tests positive to HIV has been proven to improve treatment outcomes such as viral suppression, prevention of transmission, reduction in morbidity and mortality.[56,57] It is therefore not enough to have effective medicines available or test widely but also to initiate ART early for everyone who tests positive for HIV, in other to optimize treatment

outcomes, prevent transmissions and to reduce morbidity and mortality.[58,59,60] This is essential to win the war against HIV/AIDS in South Africa and globally.

Prescribers adhered to treatment guidelines with respect to the recommended ARV regimens, and prescribed ART regimens constituting 2 NRTIs with either a NNRTI or a PI.[61,62,63,53,64] This is excellent, however the problem of late initiation of ART must be overcome to derive the potential optimal treatment outcomes as a result of using the right drugs combinations.

The most prescribed first line ART regimen was TDF/FTC/EFV (65%) as well as the most switched to regimen (63.8%). This could be due to the tolerability and high rate of viral suppression of this regimen as shown by other studies.[65] It also shows the adherence to the guidelines by clinicians in prescribing it as the first line, first choice regimen as recommended.[62,63,53,64.]

An interesting finding regarding switching of regimens was also made in this study. Male patients on ART were 40% less likely to be switched from ART regimen to another (aOR = 0.60, 95% Cl= 0.34-0.97, P-value= 0.037), a finding supported by other studies, such as the US study which found that females were more likely to have regimen change due to poor adherence.[66] and the study on women from Southern Africa which also showed that females had a higher chance to change regimen.[67] This may be due to gender-specific factors such as pregnancy as evidenced in another study from South Africa that found the predictors of non-adherence to ART by pregnant women were marital status, non-disclosure to sexual partner and family, cigarette smoking and alcohol use.[68] Regimen change leads to less available options of ART regimen for clinicians to choose from for the specific patients and regimen changes that are prompted by resistance to antiretroviral medicine poses a public health challenge. More studies are recommended in order to better understand the causes and tailor treatments to minimize the chances to switch regimen by females. It is also necessary to come up with strategies to increase durability of initial regimens.[69]

In addition, it was found that patients on ART who had baseline CD4 count below 200 cell/µL had 2 folds likelihood of being switched from one regimen to another (aOR = 1.99, 95% Cl= 1.18-3.34, P-value = 0.010). This is expected, as baseline CD4 cells count has been generally shown to influence HIV treatment outcome.[70,56] However, the problem of late initiation of ART could be overcome or minimized if people who test positive for HIV are initiated on ART early, as all who test positive are now eligible for treatment.[55]

The most prominent finding in this section is that there has been consistently late initiation of ART (at CD4 <200 cell/µL) all through from 2005 to 2018. This must be addressed to win the fight against HIV/AIDS.

Patient factors and viral suppression

Highly active antiretroviral therapy (HAART) has made HIV a medically manageable condition in patients who have access to medication.[71,72]

HAART has also made it possible to achieve sustained HIV suppression, eliminating the risk of HIV transmission.[73,74,71,75,76,77]

This study found that only 40.8% of PLWH on ART achieved viral suppression, which is far below the third of the UNAIDS target of "90-90-90" by 2020.[78]

The probability of achieving viral suppression for HIV patients on ART who were between the ages of 18 to 28 years old was 73% less than that of HIV patients who were older than 48 years old (aOR = 0.27, 95% Cl= 0.13-0.60, P-value=0.001), while for those between the ages of 29 and 48 years old was 39% less than that of HIV patients who were older than 48 years (aOR = 0.61, 95% Cl= 0.39-0.95, P-value=0.028). These show that viral suppression is higher amongst the older age groups, similar to a study by Hess and Hall in 2018.[79] The lower chances of achieving viral suppression in younger patients may be due to lower adherence to antiretroviral medications by

younger patients compared to older patients. This could possibly be due to younger persons' awareness that HIV infection is no longer a 'death sentence'. However, this possible attitude could lead to drug resistance which is a public health concern. Another reason may be that older patients are more concerned about their health, overcome stigma easily, stay at home more, which results in better adherence to their medication hence higher rate of viral suppression.

The finding relating to their level of education has shown that patients who had primary school education were 57% less likely to achieve viral suppression than those who had tertiary level education (aOR = 0.43, 95% Cl= 0.22-0.83, P-value=0.012), whilst patients with high school education were 50% less likely to achieve viral suppression than those who had tertiary level education (AOR = 0.50, 95% Cl=0.28-0.87. P-value=0.014). This is expected, as higher level of education could make an individual understand instructions and counselling better, be able to seek for further clarification from health professionals and trained counsellors, they could also read written materials that are meant to enlighten patients and the general public about HIV, its management and outcomes. Another possible reason for this difference in viral suppression outcomes may be that the higher the education an individual has, the better the chance of being employed which assists them financially in managing their condition.

HIV patients on ART, who had encouragement from family members to adhere to their medications were about 4 times likely to achieve viral suppression than those who did not receive family encouragement (aOR = 3.74, 95% Cl= 1.30-10.70, P-value= 0.014.) This finding is similar to another study conducted in South Africa which indicated an improved viral suppression among patients on ART who received community-based adherence support.[80] The effect of encouragement from family is mediated through a variety of mechanisms such as greater disclosure, reduction in stigma, decrease in psychological problems, which in turn are likely to

increase adherence to medications.[81,82] These, most likely were responsible for the desired outcome of viral suppression seen in these patients.

Furthermore, patients on ART that had baseline CD4 counts <200 cells/µL were 53% less likely to achieve viral suppression compared to those who had ≥200 cell/µL (aOR = 0.47, 95% Cl= 0.31-0.70, P-value= 0.000), that is, virological failure is higher with patient who initiated ART at a lower baseline CD4 cell count (<200 cells/µL). This finding supports the WHO recommendation that ART should be initiated in everyone who tests positive for HIV irrespective of CD4 cell count.[83]

Patient factors and immunologic recovery

CD4 count is an important guide for the commencement and stoppage of primary and secondary prophylaxis against opportunistic infections such as Pneumocystic jirovecii, Cytomegalovirus and other opportunistic pathogens during antiretroviral therapy (ART) in patients with HIV infection. Prophylaxis against opportunistic infections can be stopped safely, the moment CD4 count increases above 500 cells/µL.[85,84]

In this study when patient specific factors were investigated it was found that, the higher the baseline CD4 cells count at the commencement of antiretroviral therapy was, the higher the percentage increase in CD4 cell count towards the reference range of 500 – 2000 cells/µL, leading to better chances of achieving full immunologic recovery. This corresponds with a study by Adewumi et al., in 2015 [87].

The prevalence of immunologic failure (CD4<200 cells/µL) among PLWH on ART was 8.6% in this study. There is scarcity of data in South Africa on prevalence of immunologic failure among PLWH on ART. However, studies have shown that there is a pattern of decrease in CD4 cells after some years on ART.[88,89,90]

Patient's age, stopping medication after being adherent for a long time (2 to 3 years) and baseline CD4 cells count of PLWH on ART were significantly associated with immunologic response (current CD4 cell count).

After adjusting for confounders, the predictors to immunologic recovery of PLWH on ART were baseline CD4 cell counts, duration on treatment (ART) and non-adherence to ART (forgetting to take HIV medicines sometimes).

The probability of immunologic failure for PLWH on ART who had baseline CD4 cells count <200 cells/μL was more than 8 folds higher that those who had baseline CD4 cells count ≥200 cells/μL (AOR = 8.03, 95% Cl= 3.28-19.67, P-value = 0.000). This strongly supports the current recommendation of 'Treat all', rather than allowing CD4 cells count to drop before treatment commences.[86]

There was significant association between immunologic failure and patient's stopping medications after a long time (2 to 3 years) of being adherent. The probability of immunologic failure for PLWH on ART who did not strictly adhere to treatment (sometimes forget to take their medicines) was more than 3 folds higher than those who strictly adhered to their medications (aOR = 3.06, 95% Cl=1.28-7.33, P-value = 0.012). This shows that poor adherence to ART, either occasional forgetfulness or a break after a long period of adherence**,** results in immunologic failure. This finding is similar to an earlier study.[91] and further underscores the necessity of strict adherence to antiretroviral therapy by PLWH to prevent immunologic failure, achieve and maintain immunologic recovery as well as prevent resistance to ART, which could be a public health threat, as affirmed by other studies.[92,91] Poor adherence has been a major cause of treatment failure, it is therefore extremely essential to formulate effective strategies to combat it in order to achieve optimum treatment outcomes in PLWH on ART.

Prevalence and predictors of diabetes mellitus among PLWH

In this study the prevalence and predictors of diabetes among PLWH on ART in the eThekwini municipality of KZN was assessed.

It was important to understand the magnitude of the problem as proper management is essential, not only for the prevention of diabetic complications, mortalities due to the complications or for the improvement of quality of life but also to prevent possible negative impact on the outcomes of managing HIV.

The prevalence of diabetes among PLWH on ART in KZN was 9%, this was consistent with findings by other studies.[94,95,96,93] , this was higher than the prevalence of diabetes among the general population which was 5.4%.[97] However, a study by Diabetes Focus eMag[98] indicated that prevalence of diabetes among PLWH is similar to that among the general population. This difference in findings from different studies may be due to differences in the prevalence of diabetes amongst different populations**.**

There was higher prevalence of diabetes among females PLWH (9.5%) than that of males (7.4%), similar to a study by Hernandez-Ronieu et al, in 2017.[99] where it was shown that the prevalence of diabetes is higher in females among the general population. This also confirms our finding that female gender is a predictor to diabetes in PLWH, as males living with HIV were 65% less likely to have diabetes than females (aOR = 0.35, 95% Cl= 0.15-0.82, P-value=0.016) in this study. This finding is similar to other studies which indicated that females who are HIV positive are more likely to have non-communicable diseases (NDC) co-morbidity.[100,101] Hence, all persons who test positive for HIV, particularly females, should be screened for diabetes and should be repeatedly tested at close interval while they are on ART, in order to detect diabetes early and manage them

accordingly, so as to avoid diabetic complications which could further increase pill burden and worsen morbidity and mortality due to both conditions.

Over 60% of the PLWH were diagnosed with diabetes after the commencement of ART, however, there was no statistically significant association between commencement of ART and the incidence of diabetes mellitus. Earlier studies vary in their findings with regards to the association between ART and diabetes, with some studies showing similar results to this study,[98] whilst other studies found association between ART and diabetes.[102,94,95,96] While the question whether ART actually predisposes PLWH to diabetes or not remains debatable, people who test positive for HIV should be tested for diabetes before the commencement of ART and periodically thereafter.

Almost half (47.1%) of the PLWH with diabetes in this study had uncontrolled blood sugar (Mean FBS of 11.7 mmol/L). This is particularly concerning, as this predisposes them to diabetic complications such as retinopathy, neuropathy, nephropathy among others. There is need to involve specialists in the management of patients with HIV and diabetes comorbidity for the attainment and maintenance of glycemic control

Older age is the other predictor for diabetes among PLWH. The likelihood of diabetes for those older than 48 years of age was 88% compared to those that were younger than 48 years of age (aOR = 0.12, 95% Cl= 0.06-0.26, P-value=0.000). This is in line with other studies which showed that old age is a risk factor to chronic co-morbidities in PLWH.[100,101] As ART increases the life span of PLWH, predisposing them to chronic medical conditions such as diabetes, clinicians should give adequate attention to diabetes in PLWH as they do to other co-morbidities.

Limitation of the study

Data for 291 patients from one of the hospitals was incomplete, due to researcher not being given access to some of the data, despite obtaining written permission from the authorities concerned. However, during the analysis such missing data were accounted for by ensuring that all analysis that required those missing data were done by excluding that specific hospital analysis in order to ensure the integrity of the results.

Conclusion and recommendations

Though clinicians adhered to the treatment guidelines, a significant percentage of PLWH from 2013 till 2018 were initiated late on ART (baseline CD4 count <200 cells/µL). Steps should be taken to ensure that those who test positive to HIV are initiated immediately on ART as long as possible.

Female gender and late initiation of ART were the predictors of ART regimen change. It is therefore essential to develop strategies to increase the durability of initial regimens in order to avoid exhausting the available treatment options which would be detrimental not only to the patients concerned but could also be a public health challenge.

The percentage of viral suppression was low (40.8%). Predictors to viral suppression in PLWH on ART were older age, higher level of education, family support and baseline CD4 count higher than 200 cells/µL.

Predictors to immunologic failure were poor adherence to ART and lower baseline CD4 count (CD4 cell count <200 cells/µL).

Further research is recommended to determine the reason(s) for late initiations of ART in South Africa. This late initiation contributes substantially to the less-than-desired outcomes. This continues to occur despite the recommendation by the DoH to initiate ART, immediately, a person tests positive for HIV.

Prevalence of diabetes among PLWH was higher than that of the general population with 47.1% of them having uncontrolled blood sugar (mean FBS of 11.7 mmol/L). There is need to give particular attention to diabetes in PLWH as done with other comorbidities.

Female gender and older age were predictors to diabetes among PLWH on ART. Screening for diabetes should be intensified among PLWH on ART. Policy makers should consider diabetes as a comorbidity of interest in PLWH , by making the screening of diabetes a requirement for all those who test positive for HIV . Screening should be done before the initiation of ART and at regular intervals while on ART as well as manage those patients that are found to be diabetic.

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101. Palellaa FJ, Hartb R, Armonb C, Tedaldic E, Yangcod B, Novake R, et al. for the HIV Outpatient Study (HOPS), Non-AIDS comorbidity burden differs by sex, race, and insurance type in aging adults in HIV care, AIDS 2019; 33:2327–2335)

102. Paengsai N, Jourdain G, Chaiwarith R, Tantraworasin A, Bowonwatanuwong C, Bhakeecheep S, et al. Incidence and clinical outcomes of diabetes mellitus in HIV-infected adults in Thailand: a retrospective cohort study, BMC Public Health, 2018; 18(1079) Available at: https://doi.org/10.1186/s12889-018-5967-7.

ANNEXURE 1: ETHICS APPROVAL

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

26 September 2018

Mr M Umar (217075064)
School of Health Sciences
College of Health Sciences
217075064@stu.ukzn.ac.za

Protocol: Evaluation of the management of HIV/AIDS with diabetes as a co-morbid condition in public health facilities in eThekwini Metro of KwaZulu-Natal. Defining contributory factors to patients outcomes.
Degree: PhD

BREC Ref No: BE314/18

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 14 May 2018.

The study was provisionally approved pending appropriate responses to queries raised. Your response received on 10 September 2018 to BREC letter dated 19 June 2018 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full **ethics approval** and may begin as from 26 September 2018. Please ensure that site permissions are obtained and forwarded to BREC for approval before commencing research at a site.

This approval is valid for one year from **26 September 2018.** 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 **09 October 2018.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Prof V Rambiritch
Chair: Biomedical Research Ethics Committee

cc (postgraduate administrator):
Supervisor:

Biomedical Research Ethics Committee
Professor V Rambiritch (Chair)
Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban 4000
Telephone: +27 (0) 31 260 2486 **Facsimile:** +27 (0) 31 260 4609 **Email:** brec@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

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100 YEARS OF ACADEMIC EXCELLENCE

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ANNEXURE 2: PATIENT INFORMED CONSENT FORM

UKZN BIOMEDICAL RESEARCH ETHICS COMMITTEE

Information Sheet and Consent to Participate in Research

Date: ……..

Dear Sir/Madam,

My name is ……, from Discipline of Pharmaceutical Sciences, University of Kwazulu-Natal, Westville Campus, Durban. 0670842890, 217075064@stu.ukzn.ac.za , myresearchmail2017@gmail.com .

You are being invited to consider participating in a study that involves research on 'Evaluation of the management of HIV/AIDS with diabetes as a comorbid condition in public health facilities in the eThekwini metro of Kwazulu-natal. Defining contributory factors to patient outcomes'. The aim and purpose of this research is to find out how HIV patients are treated, to find out if some of them have diabetes and how the diabetes is treated, to find the things that patients do that affect their treatment. The study is expected to enroll at least 249 participants in each ARV clinic, that is a total of 996 participants in 4 ARV clinics in eThekwini metro of Kwazulu-natal. It will involve the following procedures, collection of data from people living with HIV using a questionnaire as well as collecting data from patient chart that is in the hospital. Then use the data collected to find out how patients are managed and what the outcomes are. The duration of your participation if you choose to enroll and remain in the study is expected to be just today. The study is funded by the college of health sciences, University of Kwazulu-natal.

The study will provide no direct benefits to you. This study is hoped to show how best to manage HIV to achieve better outcomes.

This study has been ethically reviewed and approved by the UKZN Biomedical research Ethics Committee (approval number_____).

In the event of any problems or concerns/questions you may contact the researcher at the Discipline of Pharmaceutical Sciences, University of Kwazulu-Natal, Westville Campus, Durban. 0670842890, 0608225125, 217075064@stu.ukzn.ac.za , pharmumar73@gmail.com) or the UKZN Biomedical Research Ethics Committee, contact details as follows:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION

Research Office, Westville Campus

Govan Mbeki Building

Private Bag X 54001
Durban
4000

KwaZulu-Natal, SOUTH AFRICA

Tel: 27 31 2604769 - Fax: 27 31 2604609

Email: BREC@ukzn.ac.za

Participation in this research is voluntary and you may withdraw participation at any point, in the event you refuse to participate or withdraw from participation after you have started, you will not incur any penalty or loss your treatment. If you choose to withdraw from the study at any point while filling the questionnaire, you can notify the researcher and return the questionnaire to him. The researcher will terminate your participantion from the study if he discovers that you are below 18years of age.

You will not incur any cost because of your participation in this study. There are no incentives or reimbursements for your participation in this study.

Only information that is necessary to enable the researcher to carry out this study will be collected from you or your chart. Your identity will not be disclosed to any one during or after this study. Your data will be converted into a format that will not reveal your identity and then analyzed in group to arrive at a conclusion. All hard copy documents such as the questionnaire and tabulated data will be kept in a secure locker and will be destroyed when relevant information is entered into statistical software for analyses.

CONSENT

I……
have been informed about the study titled 'Evaluation of the management of HIV/AIDS with diabetes as a comorbid condition in public health facilities in the eThekwini metro of KwaZulu-Natal. Defining contributory factors to patient outcomes by David Mohammed Umar.

I understand the purpose and procedures of the study.

I have been given an opportunity to answer questions about the study and have had answers to my satisfaction.

I declare that my participation in this study is entirely voluntary and that I may withdraw at any time without affecting any treatment or care that I would usually be entitled to. If I have any further questions/concerns or queries related to the study I understand that I may contact the researcher at the Discipline of Pharmaceutical Sciences, University of Kwazulu-Natal, Westville Campus, Durban. 0670842890, 217075064@stu.ukzn.ac.za , pharmumar73@gmail.com.

If I have any questions or concerns about my rights as a study participant, or if I am concerned about an aspect of the study or the researcher then I may contact

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION

Research Office, Westville Campus

Govan Mbeki Building

Private Bag X 54001
Durban
4000

KwaZulu-Natal, SOUTH AFRICA

Tel: 27 31 2604769 - Fax: 27 31 2604609

Email: BREC@ukzn.ac.za

_____ _____

Signature of Participant **Date**

_____ _____

Signature of Witness **Date**

(Where applicable)

_____ _____

Signature of Translator **Date**

(Where applicable)

ANNEXURE 3: PATIENT INFORMATION SHEET

PATIENT INFORMATION SHEET

S/N	Doctor's Code	Patient Code	Sex	Age	Date ARVs Started	Date of Last Visit	Initial CD4 Count	Current CD4 Count	Initial Viral Load	Current Viral Load	Opportunistic Infections	HIV Associated Comorbidities	Initial Weight (Kg)	Current Weight (Kg)

Initial Clinical Stage	Current Clinical Stage	ARV Regimen	Date	Changes in ARV Regimen	Date	Reasons for the Changes	Initial Blood Sugar Level (mMol/L)	Date	Current Blood Sugar Level (mMol/L)	Date	Diabetic Complications	Diabetes Medications

ANNEXURE 4: QUESTIONNAIRE

Dear Participant,

Thank you for agreeing to participate in this study.

You indicated you are taking medication for your HIV. Some individuals have identified many issues concerning their medicine-taking behavior and we are interested in your experiences. There is no right or wrong answer. Please answer each question based on your personal experience with your HIV medication.

Please TICK the appropriate box

1. Gender

Male	Female	Transgender

2. How old are you (In years)?

18-23	24-28	29-33	34-38	39-43	44-48	49-53	54-58	59-63	64-68	Above 68 Years

3. What is your educational level?

Primary school	High school	Tertiary level	No formal education

4. Are you employed?

Yes	No

5. When do you usually take your HIV medicine (s) every day?

In the morning	In the afternoon	In the evening	At night

6. Do you sometimes forget to take your medicine for HIV?

Yes	No

7. Thinking over the past 2 weeks, were there any days when you did not take your HIV medicine(s)?

Yes	No

8. If yes, what was the reason(s) for not taking your HIV medicine(s)?

I forgot	Too many people around	I got tired of taking it	Was too busy	Others (Please specify)

9. Thinking over the past 1 month, were there any days when you did not take your HIV medicine(s)?

Yes	No

10. If yes what was the reason(s) for not taking your HIV medicine(s)?

I forgot	Too many people around	I got tired of taking it	Was too busy	Others (Please specify)

11. Have you ever cut back or stopped taking your HIV medicine(s) without telling your doctor/nurse because you felt worse when you took it?

Yes	No

12. What do you mean by feeling worse?

Felt nauseous	Had diarrhea	Had Headache	Others (Please specify)

13. Did you visit the doctor/nurse thereafter?

Yes	No

14. If Yes, what did the doctor/nurse do?

Treated me but did not change the medicines	Treated me and changed the medicines	Others (Please specify)

15. When you travel or leave home, do you sometimes forget to take along your HIV medicine(s)?

Yes	No

16. Did you take all your HIV medicines yesterday?

Yes	No

17. When you feel like your symptoms are under control, do you sometimes stop taking your HIV medicine(s)?

Yes	No

17. If yes, when do you start taking your medicines again?

The next day	After 2 days	After 5 days	After 1 week	After 1 month	Others (Please specify)

18. Taking HIV medicine(s) every day is a real inconvenience for some people. Do you ever feel inconvenienced about sticking to your treatment plan?

Yes	No

19. How often do you have difficulty remembering to take all your HIV medicines?

Never	Once in a while	Sometimes	Usually	All the time

20. Do you take alcohol?

Yes	No

21. If yes, how often do you take alcohol?

Occasionally	Sometimes	Usually	Everyday

22. When do you usually take alcohol?

In the morning	In the afternoon	In the evening	Anytime

23. Do you take herbal/traditional medicines?

Yes	No

24. If yes, have you told your doctor/nurse that you take herbal/traditional medicine?

Yes	No

25. If no, why have you not told the doctor/nurse?

Afraid to tell them	Did not think it necessary to tell them	My traditional healer asked me not to tell the doctor or nurse.	Others [please specify]

26. Do you take your herbal/traditional medicines and your HIV medicines at the same time?

Yes	No

27. Do you take supplements?

Yes	No

28. Do you take your supplements and your HIV medicines at the same time?

Yes	No

29. Do you think it is necessary you take your HIV medicines every day?

Yes	No

30. Do you think the HIV medicines you take can really keep you healthy?

Yes	No

31. Did you ever stop taking your HIV medicines after taking it for a long time, like 2 to 3 years?

Yes	No

32. Did you tell any of your family members your HIV status?

Yes	No

33. If yes, do your family members encourage you to always take your HIV medicines?

Yes	No

34. Whenever you fall sick do you receive enough care and assistance from your family?

Yes	No

35. Do you get financial assistance from your family when you need it to transport yourself to the clinic?

Yes	No

36. Do you experience any form of discrimination from your family or friends?

Yes	No

37. If your answer to the above question is yes, please specify the kind of discrimination you experience?

They don't share cutleries with me	They don't like interacting with me	Others (Please specify)

38. Do you have diabetes?

Yes	No

39. When were you diagnosed with diabetes?

Before I was diagnosed with HIV	About the same time I was diagnosed with HIV	About 6 months after I started taking medicines for HIV	Longer than 6 months after I started taking medicines for HIV

40. Are you receiving medicines for diabetes?

Yes	No

41. Are you receiving your medicines for diabetes in this hospital?

Yes	No

42. After starting your diabetic treatment do you feel better than before?

Yes	No

43. After starting your diabetic treatment do you feel worse than before?

Yes	No

44. Do you sometimes not take your medicines for diabetes?

Yes	No

45. Do they usually check your blood sugar in the hospital?

Yes	No

46. How often do the check your blood sugar in the hospital?

Every visit	After some visit	Rarely	Never

47. When they check your blood sugar how often is your blood sugar high?

Never	Rarely	Sometimes	Most times	Always	I don't know

48. Are there some food or drinks you were asked not to eat or drink much?

Yes	No

49. If your answer to the above question (number 50) is YES, do you obey the instruction? Yes No

ANNEXURE 5: APPROVAL FROM PROVINCIAL DEPARTMENT OF HEALTH

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Physical Address: 330 Langalibalele Street, Pietermaritburg
Postal Address: Private Bag X9051
Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782
Email:
www.kznhealth.gov.za

DIRECTORATE:
Health Research & Knowledge Management

HRKM Ref: 290/18
NHRD Ref: KZ_201807_032

Dear Mr M. Umar
UKZN

Approval of research

1. The research proposal titled **'Evaluation of the management of HIV/AIDS with diabetes as a co-morbid condition in public health facilities in the eThekwini metro of KZN. Defining contributory factors to patient outcomes'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at King Edward VIII, Wentworth, RK Khan and Prince Mshiyeni Memorial Hospital.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. 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 Mr X. Xaba on 033-395 2805.

Yours Sincerely

Clutpe

Dr E Lutge
Chairperson, Health Research Committee
Date: 14/08/18

ANNEXURE 6: FACILITIES APPROVALS

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

OFFICE OF THE HOSPITAL CEO
KING EDWARD VIII HOSPITAL

Private Bag X02, CONGELLA, 4013
Corner of Rick Turner (Francois Road) & Sydney Road
Tel: 031-3603853, Fax:031-2061457, Email: [illegible]
www.kznhealth.gov.za

Ref.: KE 2/7/1/(32/2018
Enq.: Mrs. R. Sibiya
Research Programming

26 June 2018

Mr. M. Umar
School of Laboratory Medicine and Medical Sciences
Nelson Mandela - School of Medicine
UNIVERSITY OF KWAZULU-NATAL

Dear Mr. Umar

Protocol: "Evaluation of the management of HIV/AIDS with diabetes as a co-morbid condition Public Health Facilities in eThekwini Metro of KwaZulu-Natal. Defining contributory factors to patients' outcomes". Degree-PhD; BREC REF. NO. BE314/18

Permission to conduct research at King Edward VIII Hospital is provisionally granted, pending approval by the Provincial Health Research Committee, KZN Department of Health.

Kindly note the following:-

- The research will only commence once confirmation from the Provincial Health Research Committee in the KZN Department of Health has been received.
- Signing of an indemnity form at Room 8, CEO Complex before commencement with your study.
- King Edward VIII Hospital received full acknowledgment in the study on all Publications and reports and also kindly present a copy of the publication or report on completion.

The Management of King Edward VIII Hospital reserves the right to terminate the permission for the study should circumstances so dictate.

Yours faithfully

SUPPORTED/~~NOT SUPPORTED~~

28/06/2018

DR. SA MOODLEY
ACTING SENIOR MEDICAL MANAGER

DATE

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Physical Address : R.K. Khan Circle
Physical Address : CHATSWORTH
Tel: [031] 4596001 Fax:[031] 4011247 Email:Sharon.gounden@kznhealth.gov.za
www.kznhealth.gov.za

DIRECTORATE:
R.K. KHAN HOSPITAL
OFFICE OF THE CEO

17 July 2018

Mr M. Umar [217075064]
School of Health Sciences
College of Health Sciences
University of Kwazulu-Natal

RE: PERMISSION TO CONDUCT RESEARCH: EVALUATION OF THE MANAGEMENT OF HIV/AIDS WITH DIABETES AS A CO-MORBID CONDITION IN PUBLIC HEALTH FACILITIES IN ETHEKWINI METRO OF KWAZULU-NATAL DEFINING CONTRIBUTORY FACTORS TO PATIENTS OUTCOMES

Permission is granted to conduct the study at this institution.

Please note the following:

1. Please ensure that you adhere to all the policies, procedures protocols and guidelines of the Institution with regards to this research.

2. Please ensure this office is informed before you commence your research and your University's Ethics approval must be attached.

3. You will be expected to provide feedback on your findings to this institution.

4. You will be liaising with : Dr J. Brijkumar
HOD : ARV
Tel: [031 – 4596428]

Yours faithfully

CHIEF EXECUTIVE OFFICER

R K KHAN HOSPITAL
HOSPITAL / HOSPITAAL
2018 -07- 17
PRIVATE BAG X004
CHATSWORTH
4030

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE: Senior Medical Manager

Mangosuthu Highway, Private Bag X 07
MOBENI
Tel: 031 907 8317/8304 Fax: 031 906 1044 Email:myint.aung@kznhealth.gov.za
www.kznhealth.gov.za

Prince Mshiyeni Memorial
Hospital

Enquiry: Dr M AUNG
Ref No: 37/RESH/2018
Date: 02/07/2018

TO: David Mohammed Umar

RE: LETTER OF SUPPORT TO CONDUCT RESEARCH AT PMMH

Dear researcher;

I have pleasure to inform you that PMMH has considered your application to conduct research on **"EVALUATION OF THE MANAGEMENT OF HIV/AIDS WITH DIABETES AS A CO-MORBID CONDITION IN PUBLIC HEALTH FACILITIES IN THE ETHEKWINI METRO OF KWAZULU-NATAL. DEFINING CONTRIBUTORY FACTORS TO PATIENT OUTCOMES"** in our institution.

Please note the following:

1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Please ensure this office is informed before you commence your research.
4. The institution will not provide any resources for this research.
5. You will be expected to provide feedback on you finding to the institution.

Should the following requirements be fulfilled, a Permission/ Approval letter will follow.

- Full research protocol, including questionnaires and consent forms if applicable.
- Ethical approval from a recognized Ethic committee in South Africa

Thank you.

MYINT AUNG
Senior Medical Manager & specialist in Family Medicine
MBBS, DO(SA), PGDip in HIV (Natal), M.Med.Fam.Med (natal), PhD
Tel: 031 9078317
Fax: 031 906 1044
myint.aung@kznhealth.gov.za

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

1 Boston Road, Jacobs 4025
Private Bag, Jacobs 4025
Tel: 031-460 5000 Fax: 031-4689654
www.kznhealth.gov.za

DIRECTORATE:
WENTWORTH HOSPITAL
PRIVATE BAG
JACOBS 4026

Reference : Research Protocol
Enquiries: Dr. S. Zulu
Telephone: 031- 460 5006/7

E Mail: Sizwe.Zulu3@kznhealth.gov.za

Date: 18TH JULY 2018

Mr. Umar
School of Health Sciences
University of KwaZulu-Natal
Private Bag X54001
Durban
4000

Pharmunmar2011@gmail.com

Dear Mr. Umar

RE: Evaluation of the management of HIV/AIDS with diabetes as a co-morbid condition in public health facilities in the EThekwini Metro of Kwazulu-Natal. Defining contributory factors to Patient outcomes.

I have pleasure informing you that permission has been granted to you to conduct the above research.

Kindly take note of the following information before you continue:-

1. Please adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the Kwazulu Natal Department of Health.
3. Kindly ensure that this office is informed before you commence your research.
4. The hospital will not provide any resources for this research.
5. You will be expected to provide feedback once your research is complete to the Chief Executive Officer.

Yours faithfully

DR. S. ZULU
MEDICAL MANAGER

ANNEXURE 7: ETHICS CERTIFICATE

Zertifikat
Certificat
Certificado
Certificate

Promouvoir les plus hauts standards de ethique dans la protection des participants à la recherche biomedicale
Promoting the highest ethical standards in the protection of biomedical research participants

Clinical Trials Centre
The University of Hong Kong

Certificat de formation - Training Certificate

Ce document atteste que - this document certifies that

David Mohammed Umar

a complété avec succès - has successfully completed

Introduction to Research Ethics

du programme de formation TRREE en évaluation éthique de la recherche
of the TRREE training programme in research ethics evaluation

August 5, 2017

Professeur Dominique Sprumont
Coordinateur TRREE Coordinator

FMH

FPH

Ce programme est soutenu par - This program is supported by:

Zertifikat
Certificat
Certificado
Certificate

Promouvoir les plus hauts standards de ethique dans la protection des participants à la recherche biomedicale
Promoting the highest ethical standards in the protection of biomedical research participants

Clinical Trials Centre
The University of Hong Kong

Certificat de formation - Training Certificate

Ce document atteste que - this document certifies that

David Mohammed Umar

a complété avec succès - has successfully completed

Informed Consent

du programme de formation TRREE en évaluation éthique de la recherche
of the TRREE training programme in research ethics evaluation

August 8, 2017

Professeur Dominique Sprumont
Coordinateur TRREE Coordinator

FMH

FPH

Ce programme est soutenu par - This program is supported by:


TRREE
Zertifikat
Certificat
Certificado
Certificate
Promouvoir les plus hauts standards éthiques dans la protection des participants à la recherche biomédicale
Promoting the highest ethical standards in the protection of biomedical research participants
Clinical Trials Centre
The University of Hong Kong
Certificat de formation - Training Certificate
Ce document atteste que - this document certifies that
David Mohammed Umar
a complété avec succès - has successfully completed
Public Health Research Ethics
du programme de formation TRREE en évaluation éthique de la recherche
of the TRREE training programme in research ethics evaluation
August 7, 2017
Professeur Dominique Sprumont
Coordinateur TRREE Coordinator
FMH
FPH
Ce programme est soutenu par - This program is supported by :

ANNEXURE 8: PAPER 1 EVIDENCE OF SUBMISSION TO JOURNAL

Gmail

Mohammed Umar <pharmumar73@gmail.com>

Confirmation of your submission to BMC Infectious Diseases - INFD-D-20-02033

1 message

BMC Infectious Diseases Editorial Office <em@editorialmanager.com> Thu, Jun 11, 2020 at 9:24 AM
Reply-To: BMC Infectious Diseases Editorial Office <marielette.costoy@springer.com>
To: DAVID MOHAMMED UMAR <pharmumar73@gmail.com>

INFD-D-20-02033
ADHERENCE TO HIV TREATMENT PROTOCOLS BY PUBLIC SECTOR CLINICIANS IN THE ETHEKWINI METRO OF KWAZULU NATAL: A RETROSPECTIVE STUDY
DAVID MOHAMMED UMAR, M.Sc; PANJASARAM NAIDOO, PhD
BMC Infectious Diseases

Dear Mr UMAR,

Thank you for submitting your manuscript 'ADHERENCE TO HIV TREATMENT PROTOCOLS BY PUBLIC SECTOR CLINICIANS IN THE ETHEKWINI METRO OF KWAZULU NATAL: A RETROSPECTIVE STUDY' to BMC Infectious Diseases.

The submission id is: INFD-D-20-02033

Please refer to this number in any future correspondence.

During the review process, you can keep track of the status of your manuscript by accessing the following website:

https://www.editorialmanager.com/infd/

If you have forgotten your password, please use the 'Send Login Details' link on the login page at https://www.editorialmanager.com/infd/. For security reasons, your password will be reset.

Best wishes,

Editorial Office
BMC Infectious Diseases
https://bmcinfectdis.biomedcentral.com/

As a result of the significant disruption that is being caused by the COVID-19 pandemic we are very aware that many researchers will have difficulty in meeting the timelines associated with our peer review process during normal times. Please do let us know if you need additional time. Our systems will continue to remind you of the original timelines but we intend to be highly flexible at this time.

This letter contains confidential information, is for your own use, and should not be forwarded to third parties.

Recipients of this email are registered users within the Editorial Manager database for this journal. We will keep your information on file to use in the process of submitting, evaluating and publishing a manuscript. For more information on how we use your personal details please see our privacy policy at https://www.springernature.com/production-privacy-policy. If you no longer wish to receive messages from this journal or you have questions regarding database management, please contact the Publication Office at the link below.

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: https://www.editorialmanager.com/infd/login.asp?a=r). Please contact the publication office if you have any questions.

ANNEXURE 9: PAPER 2 EVIDENCE OF SUBMISSION TO JOURNAL (MANUSCRIPT UNDER REVIEW)

Gmail

M.D. Umar <pharmumar2011@gmail.com>

AIDS Care - Manuscript ID AC-2019-12-1164

1 message

AIDS Care - Psychology, Health & Medicine - Vulnerable Children and Youth Studies <onbehalfof@manuscriptcentral.com>
Reply-To: k.roberts@ucl.ac.uk
To: pharmumar2011@gmail.com

Sun, Jan 12, 2020 at 12:33 AM

11-Jan-2020

Dear Mr. Umar,

Your manuscript entitled "PATIENT FACTORS AND VIRAL SUPPRESSION IN HIV MANAGEMENT" has been successfully submitted online and is presently being given full consideration for publication in AIDS Care.

Your manuscript ID is AC-2019-12-1164.

Please mention the above manuscript ID in all future correspondence or when calling the office for questions. If there are any changes in your street address or e-mail address, please log in to Manuscript Central at https://mc.manuscriptcentral.com/ac-phm-vcy and edit your user information as appropriate.

You can also view the status of your manuscript at any time by checking your Author Centre after logging in to https://mc.manuscriptcentral.com/ac-phm-vcy.

Thank you for submitting your manuscript to AIDS Care.

Yours Sincerely,
AIDS Care Editorial Office

ANNEXURE 10: PAPER 3 JOURNAL ACCEPTANCE LETTER

PONTE
Since 1905 Florence, Italy
Multidisciplinary Journal of Sciences & Research
Via L.Manara, 10/12, FLORENCE, ITALY

PJ-1MCWS
21 May 2020

ACCEPTANCE LETTER

Dear Author(s),

We are pleased to inform you that your paper,
Entitle: '**Patient factors and immunologic recovery in HIV management**'
Author(s): **DAVID MOHAMMED UMAR,Panjasaram Naidoo**
has been accepted for publication in **PONTE Journal** after the peer-review process. It will be published in an upcoming issue (**Vol. 76, Issue 5**) and available on the PONTE Journal website.
Also the DOI link of your paper is: http://dx.doi.org/10.21506/j.ponte.2020.5.7
Thank you for submitting your paper to this journal.

Sincerely yours,

Dr. Maria E. Boschi
Editor-in-Chief
PONTE International Scientific Journal

ANNEXURE 11: PAPER 4 EVIDENCE OF SUBMISSION OF REVISED MANUSCRIPT TO JOURNAL

Gmail M.D. Umar <pharmumar2011@gmail.com>

Confirmation of revised submission to BMC Public Health - PUBH-D-20-03462R1

1 message

BMC Public Health Editorial Office <em@editorialmanager.com> Fri, Jul 17, 2020 at 1:11 AM
Reply-To: BMC Public Health Editorial Office <victorino.silvestre@biomedcentral.com>
To: DAVID MOHAMMED UMAR <pharmumar2011@gmail.com>

PUBH-D-20-03462R1
PREVALENCE AND PREDICTORS OF DIABETES MELLITUS AMONG PERSONS LIVING WITH HIV (PLWHIV)
DAVID MOHAMMED UMAR, M.Sc; PANJASARAM NAIDOO
BMC Public Health

Dear Mr UMAR,

Thank you for the revised version of your manuscript 'PREVALENCE AND PREDICTORS OF DIABETES MELLITUS AMONG PERSONS LIVING WITH HIV (PLWHIV)' submitted to BMC Public Health.

You may check the status of your manuscript at any time by accessing the following website:

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Best wishes,

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Our flexible approach during the COVID-19 pandemic

If you need more time at any stage of the peer-review process, please do let us know. While our systems will continue to remind you of the original timelines, we aim to be as flexible as possible during the current pandemic.

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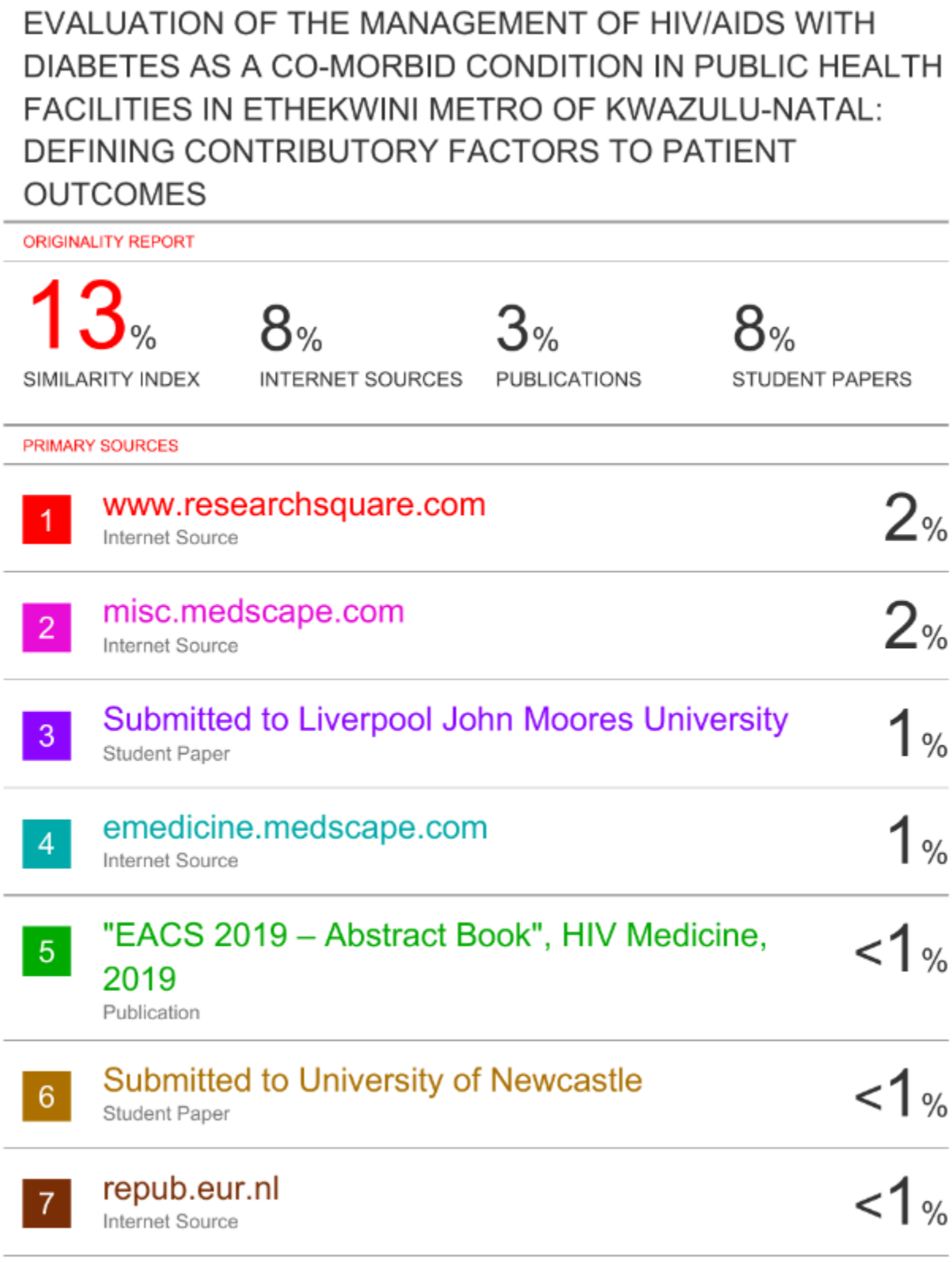
ANNEXURE 12: TURNITIN REPORT



EVALUATION OF THE MANAGEMENT OF HIV/AIDS WITH DIABETES AS A CO-MORBID CONDITION IN PUBLIC HEALTH FACILITIES IN ETHEKWINI METRO OF KWAZULU-NATAL: DEFINING CONTRIBUTORY FACTORS TO PATIENT OUTCOMES

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