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Prevalence of osteoporosis in HIV infected patients initiating antiretroviral drugs living in Johannesburg

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Prevalence of osteoporosis in HIV-infected patients initiating anti-retroviral drugs living in Johannesburg



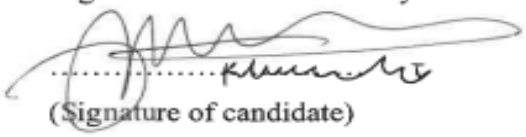
Mzwakhe Khumalo

A research report was submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Medicine

Johannesburg, 2023

Declaration

I, Mzwakhe Khumalo, declare that this research report is my own, unaided work. It is being submitted for the Degree of Master of Medicine in the branch of Orthopaedic Surgery at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



(Signature of candidate)

28 day of February 2023 in Johannesburg

Dedication

This work is dedicated to my parents. To my mother (1965 – 2021) and my father (1962 – 2021), may your souls continue to rest in peace.

Presentations and publications arising from the research project

The data used in this study is derived from the ADVANCE Study, whose primary outcomes were presented by Prof F. Venter at the 10th International AIDS Society Conference on HIV Science held in Mexico City from 21 – 24 July 2019 (Venter WF *et al*.).

Abstract

Background: Low-energy fractures complications are a major public health issue that make osteoporosis even worse. In sub-Saharan Africa, the prevalence of osteoporosis varies from 18.2% to 65.8%. In wealthy nations, it affects one-third of white women over 50. There was no change in bone mineral density (BMD) between HIV-infected and non-HIV-infected women in Sub-Saharan Africa, where human immunodeficiency virus (HIV) is widespread. Other investigations that demonstrated that HIV-infected people had poor BMD both before and after starting anti-retroviral treatment did not consistently show a low BMD finding. Inflammation-mediated bone remodelling has been associated with low BMD in HIV-infected patients. Antiretroviral Therapy (ART) has been demonstrated to exacerbate bone loss in addition to the pre-existing intrinsic risk of developing osteoporosis. Nucleoside reverse transcriptase (Tenofovir) has been shown to cause the most significant bone loss, followed by protease inhibitors (Lopinavir/Ritonavir). On the other hand, integrase inhibitor (Raltegravir) has the least noticeable effects on BMD, despite its pathophysiological causes of decreased BMD in patients on ART being poorly understood.

Research question: Is there loss of bone in HIV-infected patients before initiating ART?

Methodology: The case files of patients who were HIV-positive and enrolled in the ADVANCE research were retrospectively reviewed on a desk. All of the 1053 individuals in the ADVANCE research had a DXA scan performed to evaluate BMD as part of the initial screening and recruitment approach. The ADVANCE research enrolled HIV-positive people and randomly assigned them to three ART arms. The original pre-treatment data points on bone mineral density were used in this study to respond to the research question.

Results: A total of 400 black patients were reviewed. Of these 400 records reviewed, 62.3% were female. The female to male ratio was 1.6:1. Eighty percent of the participants were younger than 40 years old, and only 3% were older than 50 years. Eighty two percent were virally suppressed with less than 50 viral copies. The prevalence of osteopenia was 25.5% and osteoporosis was 2.8%, observed in predominantly African female participants aged between 30 and 39 years.

Conclusion: The findings of this study confirm that there is pre-existing bone loss among HIV-infected ART naïve individuals. Approximately twenty eight percent (28.3%) in our study

had clinically confirmed evidence of bone loss and of these, 2.8% of the entire cohort had osteoporosis. Bone loss was most prevalent in black females who are virologically suppressed.

Acknowledgments

I would like to acknowledge and express my gratitude to head of department (HOD) of Orthopaedic Surgery, Prof Ramokgopa for the opportunity to carry out this study. I would also like to thank my children for their support.

To Prof Venter, thank you for allowing me to use data from the ADVANCE study and Mr Godspower Akpomomie for helping me with Advance Study data collection.

I am particularly grateful to my supervisors Dr Jingo, Prof Bischof, and Prof Magobotha for continued guidance throughout this process.

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Nomenclature

AIDS	: Acquired Immune Deficiency Syndrome
ART	: Antiretroviral Therapy
BMD	: Bone Mineral Density
BMI	: Body Mass Index
DXA	: Dual-Emission X-ray Absorptiometry
EU	: European Union
HAART	: Highly Active Antiretroviral Therapy
HIV	: Human Immunodeficiency Virus
HREC	: Human Resource Ethics Committee
IOF	: International Osteoporosis Foundation
NRTI	: Nucleoside Reverse Transcriptase Inhibitors
NNRTI	: Non-Nucleoside Reverse Transcriptase Inhibitors
PI	: Protease Inhibitor
RANKL	: Receptor Activator of Nuclear Factor Kappa Beta
SA	: South Africa
TAF	: Tenofovir Alafenamide
TDF	: Tenofovir Disoproxil Fumarate
TNF	: Tumour Necrosis Factor
USA	: United States of America
WHO	: World Health Organisation

CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

1.1 Background

Low bone mass and qualitative changes in the macro- and micro-architecture of the skeletal tissue are the two main contributors to osteoporosis (1). It affects 5% of the general population and increases the fragility of bones and fracture risk (1,2). The condition is fatal, causing agony, incapacity, and occasionally death from fractures (1). The risk of fracture dramatically rises as the bones become more porous and brittle; patients typically are not aware they are at danger or even have osteoporosis until a fracture takes place (1). Because the bone loss is gradual and symptomless, there is a lack of awareness (3). Menopause, the use of glucocorticoids, alcohol consumption, smoking, and hypogonadism are all recognised risk factors for osteoporosis (1–3). Human immunodeficiency virus (HIV)-infected individuals with low body mass index (BMI), high resorption biomarkers, and osteoporosis have recently shown a link (1–3). HIV, which is present in over 42 million individuals worldwide, is a significant risk factor for the onset and progression of osteoporosis, particularly in patients who already have other risk factors for bone loss (1–3).

The World Health Organisation (WHO) classifies osteoporosis as having a bone density score between -1 and -2.5, whereas osteopenia is the condition that precedes it. In contrast, a dual-energy x-ray absorptiometry (DXA) test for osteoporosis yields a bone density score of less than -2.5 (1–3). Despite the fact that males with mitochondrial abnormalities are more likely to have osteopenia than osteoporosis, both conditions share the same risk factors (4). Furthermore, compared to the general population, HIV-infected people have higher rates of osteopenia and osteoporosis (2,5). In a study of 221 HIV-positive men, osteoporosis and osteopenia were present at 3% and 22%, respectively (2). Changes in bone mineral density (BMD) were independently linked to high lactate levels and low BMI in the same survey (2). Compared to matched controls, postmenopausal Hispanic and African American Hispanic women with HIV had osteoporosis at rates of 42% and 23%, respectively (2). Sixty seven percent of the participants in a meta-analytical analysis of 20 publications with a sample size of 884 HIV-infected patients had reduced BMD, and 15% of these persons matched the criteria for osteoporosis (2). According to the study cited above, HIV-positive patients had

an osteoporosis prevalence that was three times higher than that of HIV-negative controls (2).

Numerous other investigations found that HIV-infected people had reduced BMD at baseline when compared to matched controls (2,5–7). Up to 42% of HIV-infected people, who were primarily men, had osteopenia (2,5–7). Although osteopenia plateaus after a year of treatment, stratification according to treatment *versus* non-treatment revealed that the prevalence of osteopenia was 49% in the treatment group against 23% in the non-treatment group (2,5–7). Numerous case studies have documented osteomalacia brought on by the use of tenofovir-containing HAART (8). Additionally, a strange case report of two acquired immunodeficiency syndrome (AIDS) patients who had osteoporosis and presented with low stress fractures was published in the literature (9). In other places, 20 – 30% of HIV-infected males have hypogonadism, which is the primary cause of osteoporosis in both HIV-infected and non-HIV-infected males (2,4).

1.2 Burden of osteoporosis

Patients and society pay enormous healthcare costs as a result of bone fractures (1,6). Osteoporosis sufferers experience significant discomfort, severe impairment, and even death, as has already been mentioned. All of these are quite expensive for society (3). Although osteoporosis is regarded as a disease that affects the entire world, its scope is still unknown because of inconsistent methods for diagnosing and raising awareness of the problem (3). Fragility fractures are expected to afflict 1 in 3 women and 1 in 5 men worldwide (3). According to estimates, osteoporosis will afflict 50% of white women in the United States of America (USA) over the age of 50. In comparison, the illness will only affect 6% of white men the same age (10). In 2005, the increased risk of hip fractures and low-trauma fractures cost the US healthcare system $19 billion (10). Osteoporosis was estimated to affect 5.5 million men and 22 million women in Europe in 2010. (10). As a result, 3.5 million new fragility fractures occurred, costing the economy an estimated €37 billion (3).

Additionally, research conducted in Canada found that osteoporotic fractures make up roughly 80% of all fractures that affect postmenopausal women (11). According to statistics gathered between 2000 and 2005, the number of such fractures in Canada is estimated to be higher than 138 000 (11). In Ontario, there were 57 000 osteoporosis-related fractures in 2005 (11). The associated hospitalisation and long-term healthcare expenses came to nearly

$500 million (11). Males have been demonstrated to have a lower fracture risk than females do for the same amount of bone loss, unless they also have other comorbid conditions or Vitamin D deficiencies (4).

1.3 Osteoporosis in Sub-Saharan Africa

Information on osteoporosis in the Sub-Saharan Africa region is scarce. The incidence of osteoporosis in Caucasian, Asian, and coloured groups in Sub-Saharan Africa is comparable to that reported from affluent countries, according to the international osteoporosis foundation (IOF). There is still no information on fractures (12). African Americans have a lower incidence of hip osteoporosis, and similar data were found in the USA (12). In sub-Saharan Africa, the prevalence of osteoporosis ranges from 18.2% to 65.8%. (13). In Egypt, osteoporosis affects both men and women at rates of 21.9% and 28.4%, respectively (13). Twenty six percent and 53.9% respectively were osteopenic in the same population (13). In Morocco and Tunisia, the prevalence of osteoporosis is 21 – 31% and 25%, respectively where as in Algeria, it is reported to be 35.8% (13). The hip fracture rate in black South African women and men is 69.2 per 100 000 and 73.1 per 100 000 respectively (13,14).

1.4 Bone mineral density in HIV infection

Globally, an estimated 40 million persons between the ages of 15 and 49 are HIV positive (2). Antiretroviral therapy (ART) was developed to improve survival, but it has also resulted in the development of long-term problems linked to the condition and its treatment, including lower BMD and an increase in markers of accelerated bone turnover (2,5,7,15). When compared to matched controls, people with HIV who are 40 years old typically have low BMD in the osteopenic and osteoporotic categories (2,5,7). The prevalence of osteoporosis in HIV-infected individuals is 16% compared to 4% in matched controls (HIV negative). Overall, the ranges for osteopenia and osteoporosis are 22 – 50% and 3 – 21%, respectively, in persons living with HIV (2,5,7).

In South Africa (SA), a study of premenopausal women found that the BMD of HIV-positive but ART-naive women and HIV-negative women was the same (16). Studies also shown that premenopausal HIV-positive and HIV-negative women experienced BMD declines at a rate of 0.4% to 0.8% (5,7,17). However, numerous cohort studies have demonstrated that HIV-positive women's BMD is low, which is associated with the weight of HIV-infected people (2,17). Low BMD in HIV-infected individuals also resulted from the interaction of HIV

infection with traditional osteoporosis risk factors (such as smoking, alcohol use, gonadal hormone insufficiency, and drug use), which were exacerbated by the effects of chronic HIV infection (5,18).

Lack of vitamin D significantly contributes to the inadequate mineralisation of bone (16). It has been demonstrated that the prevalence of vitamin D insufficiency is similar in industrialised and developing countries (19). Low cluster of differentiation 4 (CD4) numbers, excessive viremia, and a lack of vitamin D have all been linked, according to research (15,16,19). Compared to the general population, HIV-infected people have a higher risk of vitamin D insufficiency. Between 70.3% and 83.7% of HIV-infected people, have inadequate levels of vitamin D (19). This is consistent with the finding that Vitamin D levels are adversely connected with tumour necrosis factor (TNF)-alpha, which increases the risk of HIV infection (2). Assessment of Vitamin D level and subsequent supplementation are therefore indicated to manage HIV-positive patients (19). It is important to highlight that many scientists did not discover abnormalities of the calcium and phosphate metabolism because the populations they studied were Vitamin D deficient (2). It is hypothesised that TNF-alpha, through preventing the 1-alpha hydroxylation of 25-hydroxyvitamin D, is the main cause of vitamin D insufficiency in HIV-positive individuals (2).

In addition, people who have never used ART have been found to have greater incidences of low BMD. This is believed to be caused by uncontrolled viremia, which starts systemic inflammation and causes bone remodelling as a result (5,16,20). As a result, HIV infection poses a serious risk for osteoporosis. Fixed and changeable factors can be used to classify osteoporosis risk factors into two groups (3,12). Age, gender, family history, previous fracture, ethnicity, menopause, HIV infection, rheumatoid arthritis, and hypogonadism are some of the risk variables that cannot be changed (3,12). Alcohol, smoking, low BMI, poor nutrition, vitamin D deficiency, eating disorders, oestrogen deficit, insufficient exercise, low calcium intake, and a history of falls are among the modifiable risk factors (3,12). Exacerbating factors of bone loss in HIV infection include malnutrition, abnormal calcium-phosphate metabolism, and hypogonadism, which has a 20 – 30% prevalence among men living with HIV (2).

1.5 Biochemical and physiology of bone loss in HIV

In HIV-infected individuals' levels of bone resorption markers (C-telopeptides) increase while bone formation markers (osteocalcin and bone alkaline phosphatase) decrease (2,5,6,15,21). HIV infection results in the upregulation of p55 and p75 TNF receptors that correlate with TNF activation, promoting C-telopeptides and inhibiting osteocalcin (2,5,6,15,21). Once initiation of ARV therapy occurs, protease inhibitors were shown to increase bone resorption markers further while deactivating TNF and improving CD4+ count (2,5,6,15,21). This immune reconstitution leads to the coupling of bone metabolism, which refers to an average balance between bone deposition and bone resorption (2,5,6,15,21).

1.6 Osteoporosis and HIV treatment

It has been demonstrated that antiretroviral therapy accelerates bone loss, which then plateaus after around 2 years from treatment initiation (6,9,22). Due to the activation of pro-inflammatory cytokines such tumour necrosis factor (TNF), interleukin-6 (IL-6), and receptor activator of nuclear factor kb ligand (RANKL), osteoclastic activity has been linked to the reduced BMD seen in HIV-infected patients (6,15,22). When an HIV-infected person is receiving treatment, their nutritional and hormonal status improves, which causes a state of bone resorption that subsequently slows down. Additionally, when ARV therapy in an HIV-positive person is optimised, immunological modulation takes place, which stops the progression of bone loss (6,15,22). Kalyan et al., (2018) described the shortening of telomere length in leucocytes in osteogenic cells of persons affected by HIV, resulting in lower BMD over 20 – 25 years (23).

Treatment for HIV infection has advanced significantly during the past ten or more years (21,22). A fixed-dose combination of at least three antiretroviral medications, often taken as a single pill once daily, is the recommended treatment for HIV (21,22). Nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase inhibitors are all included in the category of ART (21,22). Devastating bone loss has been linked to the start of various ARTs (21,22). It is unclear what causes the bone loss that is a side effect of ART (21,22). Traditional and specific HIV-related risk factors linked to poor BMD and fractures are more common in HIV-infected people (21,22). Utilising ART, having chronic inflammation, and having concomitant conditions are risk factors for HIV infections (21,22).

1.7 ART regimens and bone loss

Studies have shown a bone loss of between 2 – 6% in the hip and spine of HIV-infected people who initiated ART treatment for 1 – 2 years (7,24–26). Protease inhibitors in case-control studies were correlated with osteopenia in 35 – 40% of the patients, where only 30% were affected in the ARV-naive cohort and 8% in non-HIV-infected patients (2,22). Osteoporosis was seen in 15 – 20% of participants treated with a protease inhibitor compared to those who were not (5 – 10%) (2,22). Patients on ARV therapy in a study of 824 HIV positive patients were 2.4 more likely to develop osteoporosis than those not on treatment (2,22). Similarly, a prospective multi-centre cohort study conducted in the Netherlands showed an increase in bone turnover in HIV-infected men on ART (21). In contrast, the untreated HIV-infected men showed decreased BMD of the hip and increased bone turnover (21).

ART regimens that contained tenofovir (a nucleoside reverse transcriptase inhibitor) have been consistently reported to cause the most significant bone loss (18,25–27). Research data shows that protease inhibitors compared to NNRTIs containing regimens were related to devastating bone loss in the spine (28). On the contrary, integrase inhibitors have been shown to reduce bone loss (29). In the study, participants were randomised to lopinavir/ritonavir + raltegravir (an integrase inhibitor) or lopinavir/ritonavir + two or three nucleoside/nucleotide reverse transcriptase inhibitors as second-line therapy, bone loss in the spine and hip (over 48 weeks) was significantly less in those with the treatment arm containing raltegravir (29). Similar results were observed in another prospective study that compared raltegravir's effects with tenofovir/emtricitabine in treatment naïve HIV-infected patients (30). Participants in the raltegravir group were shown to have increased whole-body BMD, while the tenofovir/emtricitabine group had a significant bone loss (30).

1.8 HIV infection and fracture risk

Osteopenia and osteoporosis both increase the risk of low-energy fractures, which have been linked to large health care expenses in this literature review (1). Numerous confounding factors and bias in epidemiological studies estimating the fracture risk in HIV-infected patients have been identified (2). However, a Canadian analytical investigation found that HIV-positive female patients were 1.7 times more likely to experience pathological fractures than HIV-negative female patients (2). In the same cohort, the prevalence of pathological

fractures was 26.1% for HIV-positive women and 17.3% for HIV-negative women (2).

1.9 Treatment of Osteoporosis in HIV infection

There are no specific guidelines for managing osteoporosis in HIV- infection (22). Osteoporosis is underdiagnosed in patients living with HIV and may only be suspected or discovered when low-energy fractures occur (22). Preventative treatment until recently has been calcium and Vitamin D supplementation (16,19). Current literature advocates the addition of alendronate to calcium and Vitamin D supplementation, which has shown increased BMD in different randomised controlled trials (RCT) (31). Alendronate regimens increased BMD by 5.7% compared to 1.3% when only Vitamin D and calcium were supplemented (31). Alendronate and risedronate have been licenced to treat male osteoporosis in France (31). Furthermore, a multi-centre randomised placebo-controlled trial (FOSIVIR) demonstrated a BMD increase of 7.1% in HIV-infected male patients compared to placebo (32).

2.0 Study Aim and Objectives

The study aims to determine the prevalence of osteoporosis in HIV-infected patients initiating ART.

The objectives of this study are:

- To determine the bone stock of HIV-infected patients before taking ART.
- To describe the associated sociodemographic, clinical, and laboratory profile of HIV-infected patients with baseline osteoporosis

CHAPTER 2

METHODOLOGY

2.1 Research Question

Is there a loss of bone stock in HIV-infected patients before initiating ART?

2.2 Research Design

This study was a retrospective review of case files of HIV-infected participants enrolled in the ADVANCE study.

Study population

The ADVANCE study is a 96-week study conducted in Johannesburg that enrolled ART naïve people living with HIV, of which around 60% were female. The study commenced in January 2017, and by May 2018, a total of 1053 participants were recruited. Participants were initiated on the ART therapy and evaluated for the study's outcomes. Participants were randomised into three study arms namely:

Arm 1:
TAF/Emtricitabine/dolutegravir
Arm 2:

TDF / Emtricitabine / Dolutegravir
Arm 3:

TDF / Emtricitabine / Efavirenz

All the ADVANCE study participants had a DXA scan done to assess BMD as part of the initial assessment. This study used the initial bone density assessment data points to answer the research question.

Study site

Desktop review for analysis of retrospective data.

2.3 Methods

2.4 Selection Criteria

Inclusion criteria:

- HIV-infected patients initiating ART.
- Patients aged between 18 and 50 years old.
- Patients with positive DXA scan findings with or without X-rays for osteoporosis.

Exclusion criteria:

- Patients on glucocorticoid therapy.
- Patients with endocrine disorders.
- Patients with primary bone disease or with metastasis to the bones.

2.5 Data Collection

The University of the Witwatersrand's Human Research Ethics Committee (HREC) has granted approval for this study. Permission to use the ADVANCE study data was sought from Prof Francois Venter who is the director of Ezintsha research group at Wits University. Patients' socio-demographic, clinical, laboratory profile and DXA scan data before ART initiation was reviewed. The data collection sheet that was used is shown in Appendix A. Our study calculated a sample size of more than 400 patients.

2.6 Limitations

The sampling technique for this study was not representative of ancestry, age, and gender. The study design also limits the inferences that can be made from the study's findings, such as missing or incomplete records.

CHAPTER 3

RESULTS

A total of 400 black participants were reviewed. Of the 400 records reviewed, 62.3% were female. The female to male ratio was 1.6:1. Eighty percent of the participants were younger than 40 years old, and only 3% were older than 50 years. Eighty two percent of the participants were virally suppressed with less than 50 viral copies. Most records reviewed were of South African citizens (57%), followed by Zimbabwean citizens (36%). A detailed breakdown of the descriptive statistics is shown in Table 3.1.

Table 3.1: Socio-demographic and clinical characteristics

	Frequency	
	n	**(%)**
Age (mean = 32.8 years, SD = 7.5)		
Less than 20 years	2	0.5
20 – 29 years	139	34.7
30 – 39 years	182	45.5
40 – 49 years	69	17.3
50 – 59 years	7	1.7
60 years and older	1	0.3
Gender		
Male	151	37.7
Female	249	62.3
Race		
Black	400	100.0
Marital status		
Single/ unmarried	295	73.7
Married/ domestic partnership	82	20.5
Divorced/ separated	13	3.3
Widowed	10	2.5
Country of origin		

Cameroon	2	0.5
DRC	1	0.3
Lesotho	3	0.7
Malawi	6	1.5
Mozambique	9	2.3
Nigeria	1	0.3
South Africa	228	57.0
Swaziland	6	1.5
Zambia	1	0.3
Zimbabwe	143	35.8
Level of education		
No schooling	1	0.3
Primary	23	5.7
Secondary	355	88.7
Tertiary	21	5.3
Hypertension		
No	324	81.0
Yes	76	19.0
HIV viral load		
Below 50 copies	329	82.2
50 – 999 copies	28	7.0
1000 or more copies	43	10.8

Figure 3.1 below shows an “Age distribution” graph, where most patients were between the ages of 30 and 39 years (45.5%), following by 20 and 29 years group (34.7%) and above the 60-year group was the least with only one participant in the study accounting 0.2%.

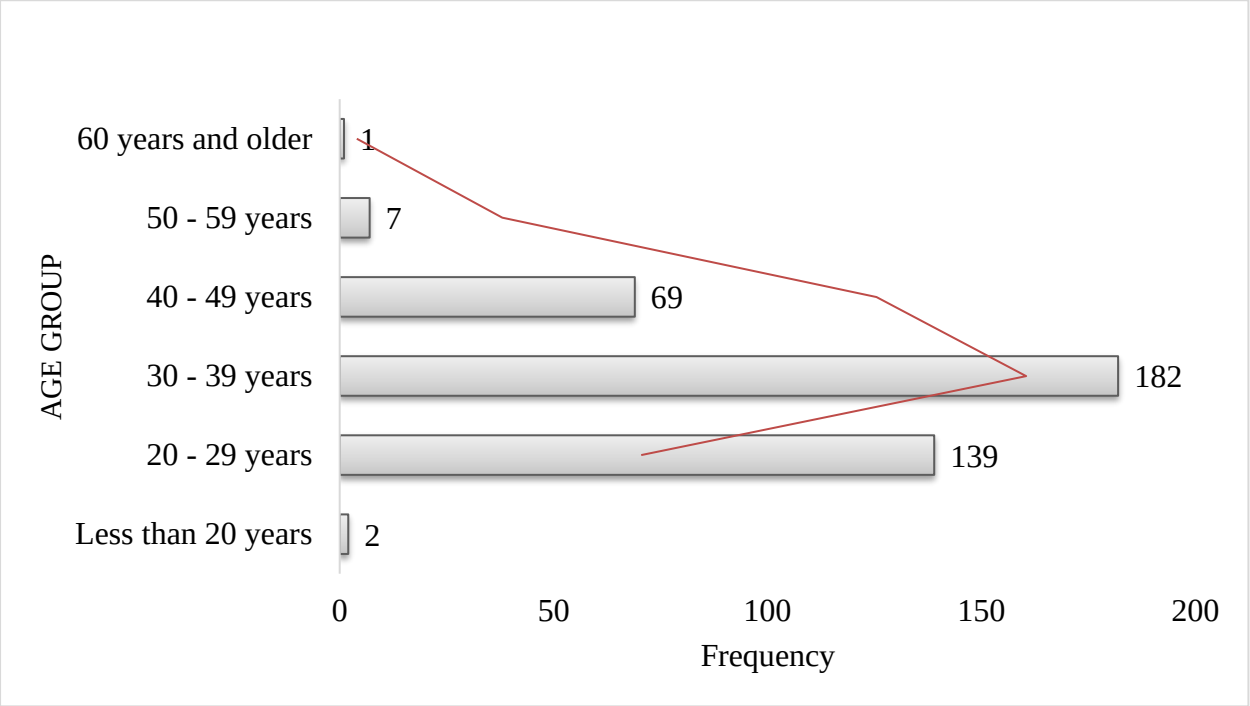


Figure 3.1: Age distribution of patients

Figure 3.2 below shows a “Gender distribution” graph where there were 151 (38%) males and 249 (62%) females, thereby giving the ratio of 1:1.6, respectively.

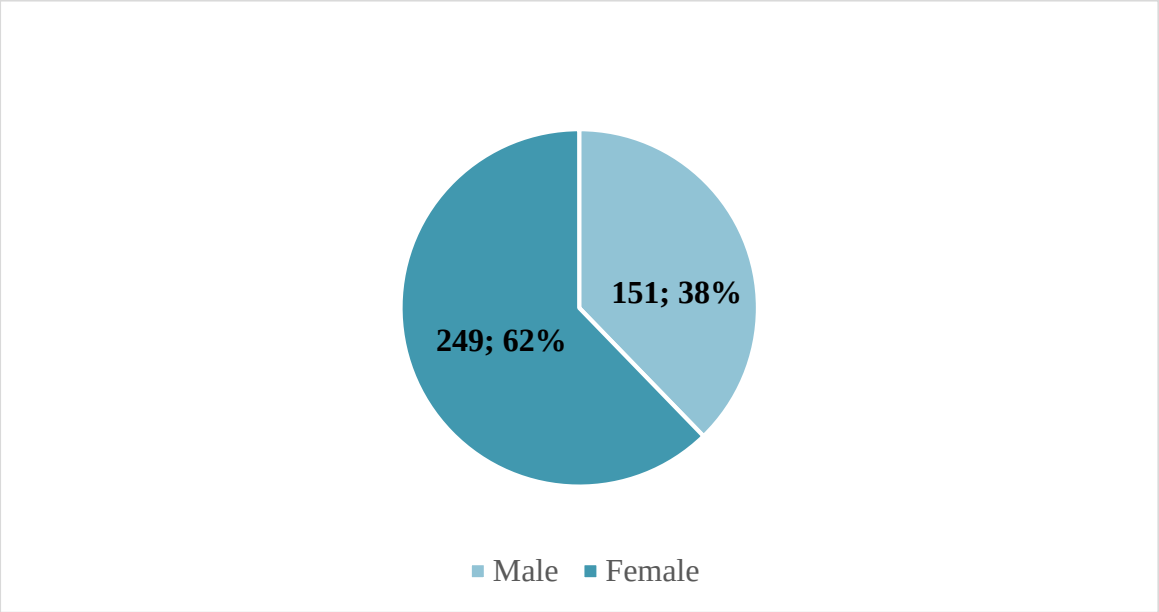


Figure 3.2: Gender distribution of patients

Figure 3.3 below shows the Hypertension status of the participants. Of the 400 participants in the study, 76 (19%) participants had hypertension.

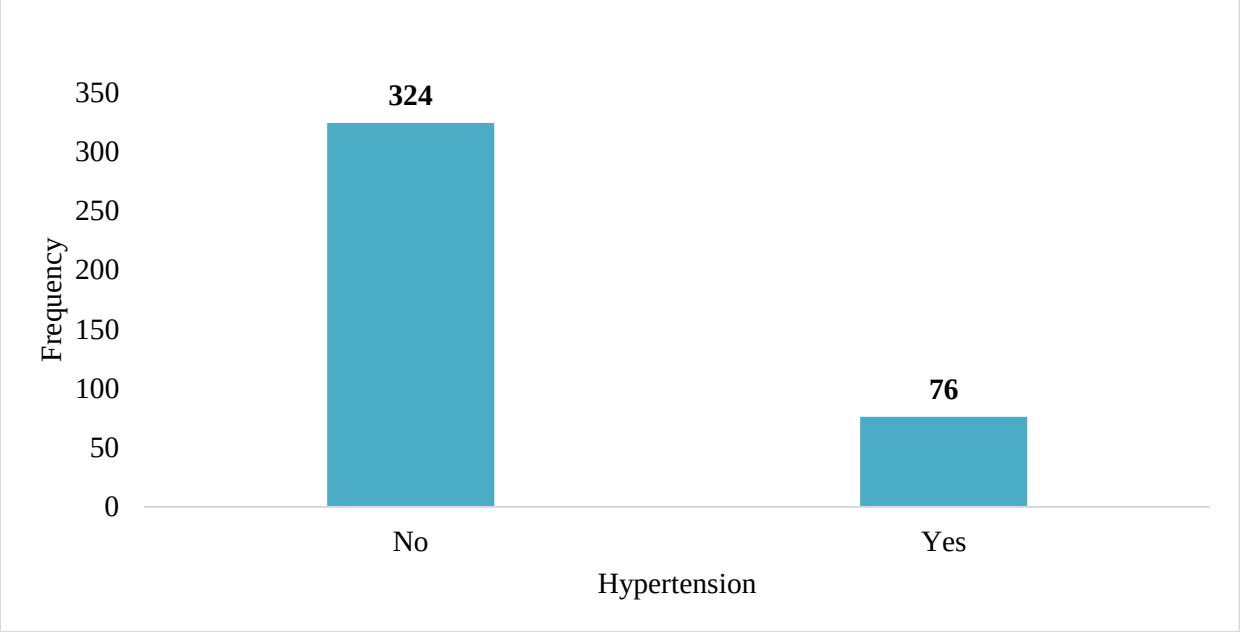


Figure 3.3: Hypertension status of participants

Figure 3.4 below shows the HIV viral load of the participants. The graph shows that 329 (82.2%) participants were virologically suppressed (< 50 copies).

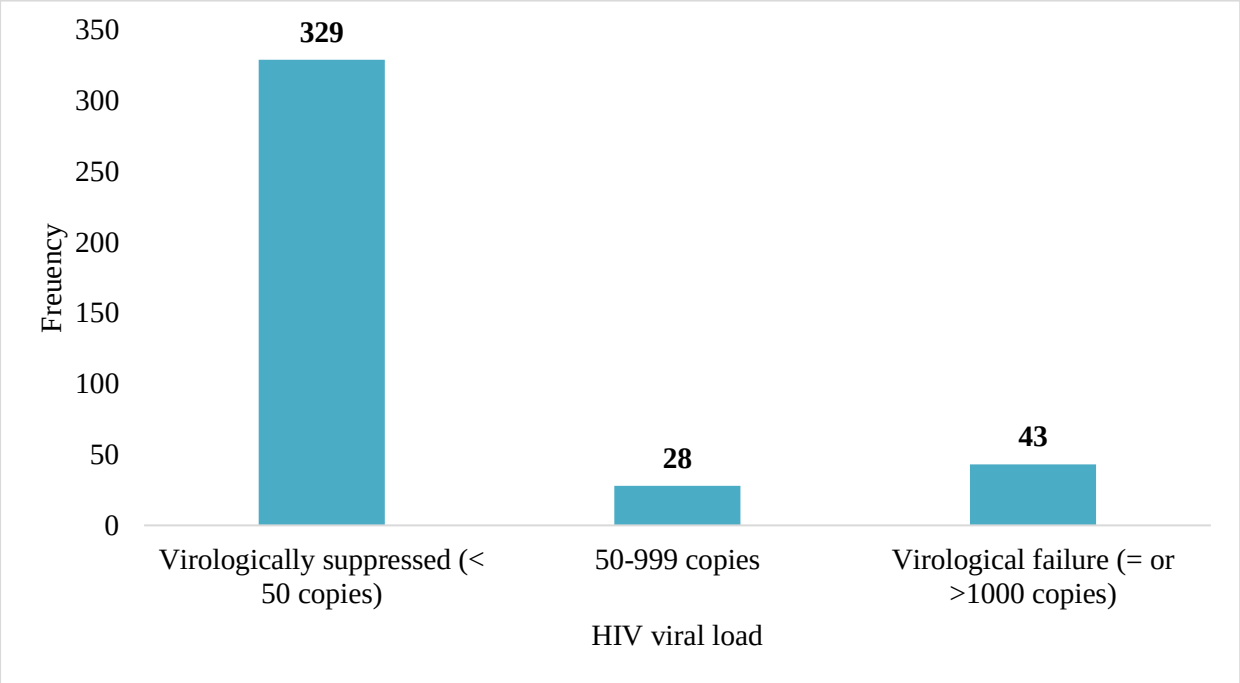


Figure 3.4: HIV viral load of participants

Table 3.2 below shows the distribution of bone stock in patients. Most of the patients (71.7%) had average bone stock. 25.5% of the participants were osteopenic and only 2.8% had osteoporosis.

Table 3.2: Distribution of bone stock of patients

	Frequency	
	n	**(%)**
WHO Hip		
Normal	287	71.7
Osteopenia	102	25.5
Osteoporosis	11	2.8
Z score		
< -2	258	64.5
≥ -2	142	35.5
T score		
-1.1 to -2.4	100	25.0
≤ -2.5	235	58.7
> -1.0	65	16.3

Table 3.3 below shows the distribution of the patients' baseline Osteoporosis. Of the 11 patients who had osteoporosis at baseline, five (45.4%) were aged 30 to 39 years, followed by three patients aged 20 – 29 years. More females (7/11) than males had osteoporosis at baseline. The single patients were the most affected by osteoporosis at baseline (6/11) then the married (4/11).

Table 3.3: Distribution of the patients' baseline osteoporosis by socio-demographic, clinical, and laboratory profiles

	WHO status		
	Average n **(%)**	Osteopenia ***n* (%)**	Osteoporosis ***n* (%)**
Age			
Less than 20 years	1 (0.4)	0 (0.0)	1 (9.1)
20 – 29 years	94 (32.8)	42 (41.2)	3 (27.3)
30 – 39 years	126 (43.9)	51 (50.0)	5 (45.4)
40 – 49 years	59 (20.6)	8 (7.8)	2 (18.2)
50 – 59 years	7 (2.4)	0 (0.0)	0 (0.0)
60 years and older	0 (0.0)	1 (1.0)	0 (0.0)
Gender			
Male	108 (37.6)	39 (38.2)	4 (36.4)
Female	179 (62.4)	63 (61.8)	7 (63.6)
Race			
Black	287(100.0)	102 (100.0)	11 (100.0)
Marital status			
Single/ unmarried	204 (71.1)	85 (83.3)	6 (54.6)
Married/ domestic partnership	63 (22.0)	15 (14.7)	4 (36.4)
Divorced/ separated	11 (3.8)	2 (2.0)	0 (0.0)
Widowed	9 (3.1)	0 (0.0)	1 (9.1)

Country of origin			
Cameroun	2 (0.7)	0 (0.0)	0 (0.0)
Zambia	1 (0.4)	0 (0.0)	0 (0.0)
Zimbabwe	98 (34.2)	43 (42.2)	2 (18.2)
DRC	1 (0.4)	0 (0.0)	0 (0.0)
Lesotho	2 (0.7)	1 (1.0)	0 (0.0)
Malawi	6 (2.1)	0 (0.0)	0 (0.0)
Mozambique	6 (2.1)	2 (2.0)	1 (9.1)
Nigeria	1 (0.4)	0 (0.0)	0 (0.0)
South Africa	166 (57.8)	55 (52.9)	7 (63.6)
Swaziland	4 (1.4)	1 (1.0)	1 (9.1)
Hypertension			
No	231 (80.5)	82 (80.4)	11 (100)
Yes	56 (19.5)	20 (19.6)	0 (0.0)
HIV viral load			
Below 50 copies	241 (84.0)	79 (77.4)	9 (89.8)
50-999 copies	17 (5.9)	11 (10.8)	0 (0.0)
1000 or more copies	29 (10.1)	12 (11.8)	2 (18.2)

None of the hypertensive patients had osteoporosis at baseline. Patients who were virologically suppressed accounted for the most significant proportion of cases of osteoporosis (9/11), and the remaining two had a virological failure.

CHAPTER 4

DISCUSSION

Osteoporosis is a significant public health problem affecting a third of white women above 50 years complicated by low trauma fractures globally (1). The prevalence of osteoporosis in sub-Saharan Africa ranges from 18.2 to 65.8% (13). The hip fractures rate in black South African women and men is 69.2 per 100 000 and 73.1 per 100 000, respectively (13). Overall, the ranges for osteopenia and osteoporosis are 22 – 50% and 3 – 21%, respectively, in persons living with HIV aged 36 to 40 years (2,12,13). In this study, the prevalence of osteopenia and osteoporosis was 25.5% and 2.8% observed in predominantly African female participants aged 30 – 39 years, consistent with other studies. Participants above the age of 50 were not affected. The prevalence of osteoporosis and osteopenia can be attributed to pro-inflammatory states found HIV/AIDS infection may contribute to bone metabolism promoting bone resorption that can quantify ART naïve individuals (2).

Very few inferences can be made on the relevance of race in this study (all the participants were black). However, some authors have reported that osteoporosis is less prevalent among African ancestry in the USA and Africa (12). In addition, one study found in Sub-Saharan Africa, no difference in BMD was observed in HIV-infected women not on treatment compared to non-HIV-infected women (12). Nevertheless, our study seems to support that ARV naive HIV-infected participants experience bone loss. It is important to note that viremia does not appear to play a significant role in the development of osteopenia and osteoporosis in our analysis of results, as 89% and 88% of the patients with osteoporosis and osteopenia, respectively, were virally suppressed.

Other co-morbidities observed in the participants, such as hypertension, did not contribute to low BMD; this is in keeping with the known risk factors of changes in BMD. Of the 11 African countries represented among the participants, those affected by osteoporosis in decreasing order were South Africa, Zimbabwe, Mozambique, and Swaziland. Twenty-five percent of the participants were osteopenic with similar sociodemographic, clinical, and laboratory profiles as those with osteoporosis. This finding brings the prevalence of clinical evidence of bone loss in this cohort of HIV-infected ARV naïve participants to 27.8% in African black patients

younger than 50 years. This supports the hypothesis of the study that there is pre-existing bone loss in HIV-infected ARV-naïve (5,7,17).

These findings are pivotal to consider routinely assessing bone mineralization density in HIV/AIDS antiretroviral treatment guidelines, as ARV treatment may further exacerbate existing bone loss. Other ramifications of our study findings are that we expect to observe more low trauma fractures in HIV-infected individuals pre- and post-initiation on antiretroviral treatment. Furthermore, vitamin D and Calcium supplementation alongside alendronate can be considered in the participants in this study that were osteopenic and osteoporotic (31,32).

4.1 Recommendations

The findings of this study recommend:

- A follow-up study with the current participants to check their BMD after initiation of ARV treatment
- An analytical study comparing BMD of the patient at initiation and different intervals on ARV treatment with three arms. The first group of patients can be on a nucleoside reverse transcriptase-containing regimen; the second, a protease inhibitor-containing regimen and the third, an integrase inhibitor-containing regimen.
- BMD studies as a baseline investigation before initiation of ARV treatment resources permitting
- A cohort study to assess the prevalence of low trauma among HIV/AIDS patients.

CHAPTER 5

CONCLUSION

The findings of this study confirm that there is pre-existing bone loss among HIV-infected ARV naïve individuals. In our study, 27.8% of the participants had clinically confirmed evidence of bone loss on DXA, and of these, 2.8% of the entire cohort had osteoporosis. Bone loss was most prevalent in black females who are virologically suppressed.

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APPENDICES

Appendix A: Data Collection sheet

Study Number	
Age	
Sex	
Race	
Comorbidities	
Osteoporosis diagnosis T-score Z-score	

Appendix B: Definitions

Most low-trauma fractures occur in patients whose bone density is greater than the World Health Organization (WHO) threshold for a densitometric diagnosis of osteoporosis. The threshold is T-score < -2.5 by dual-emission x-ray absorptiometry (DXA). Osteoporosis is a common condition affecting 30% of women and 12% of men at some point in their lifetimes. To further categorise osteoporosis, bone mineral density (BMD) with the DXA technique was based on the definition of two parameters: Z-score and the T-score.

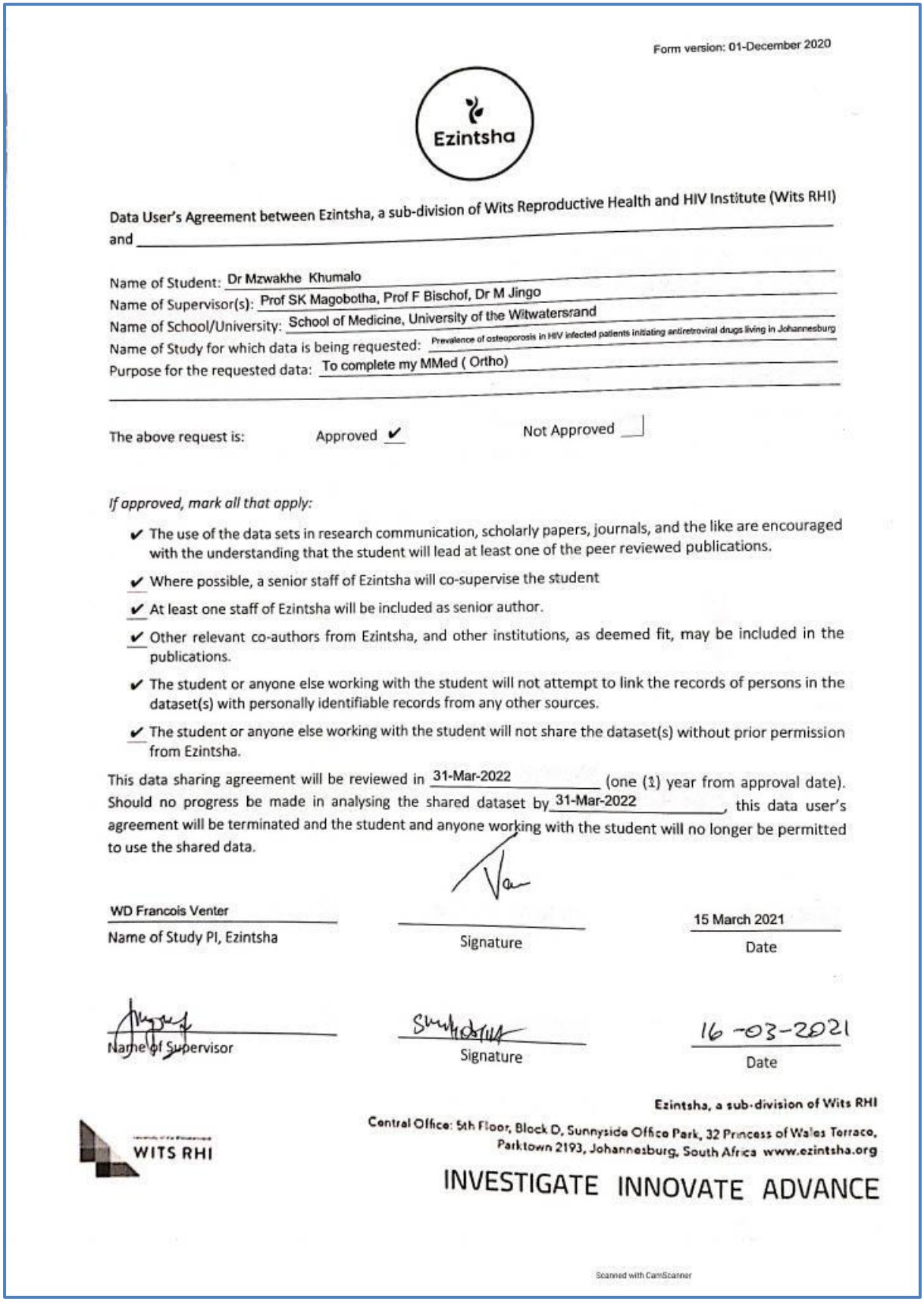
The Z- score evaluates and compares the bone mineral density to the average levels for a person of the same age and gender. According to the Z- score, the score of

- **0**: is in the mean (average)
- **+ 1**: is above the standard deviation
- **- 1**: is below the standard deviation

The T- score is the standard deviation, adjusted for sex and race. According to the T- score value; there are four different groups of patients:

- **Normal:** BMD not more than a standard deviation below the reference value.
- **Osteopenia:** BMD is between 1 and 2.5 standard deviations below the reference value.
- **Osteoporosis:** BMD more than 2.5 standard deviations below the reference value.
- **Severe osteoporosis:** BMD more than 2.5 standard deviations below the reference value with the presence of 1 or more fragility fractures.

Appendix C: Letter of permission from the Wits Rural Health Initiative to access ADVANCE study data



Form version: 01-December 2020

Ezintsha

Data User's Agreement between Ezintsha, a sub-division of Wits Reproductive Health and HIV Institute (Wits RHI) and _____

Name of Student: Dr Mzwakhe Khumalo
Name of Supervisor(s): Prof SK Magobotha, Prof F Bischof, Dr M Jingo
Name of School/University: School of Medicine, University of the Witwatersrand
Name of Study for which data is being requested: Prevalence of osteoporosis in HIV infected patients initiating antiretroviral drugs living in Johannesburg
Purpose for the requested data: To complete my MMed (Ortho)

The above request is: Approved ✔ Not Approved ___

If approved, mark all that apply:

- ✔ The use of the data sets in research communication, scholarly papers, journals, and the like are encouraged with the understanding that the student will lead at least one of the peer reviewed publications.
- ✔ Where possible, a senior staff of Ezintsha will co-supervise the student
- ✔ At least one staff of Ezintsha will be included as senior author.
- ✔ Other relevant co-authors from Ezintsha, and other institutions, as deemed fit, may be included in the publications.
- ✔ The student or anyone else working with the student will not attempt to link the records of persons in the dataset(s) with personally identifiable records from any other sources.
- ✔ The student or anyone else working with the student will not share the dataset(s) without prior permission from Ezintsha.

This data sharing agreement will be reviewed in 31-Mar-2022 (one (1) year from approval date). Should no progress be made in analysing the shared dataset by 31-Mar-2022, this data user's agreement will be terminated and the student and anyone working with the student will no longer be permitted to use the shared data.

WD Francois Venter		15 March 2021
Name of Study PI, Ezintsha	Signature	Date
Name of Supervisor	Signature	16-03-2021 Date

WITS RHI

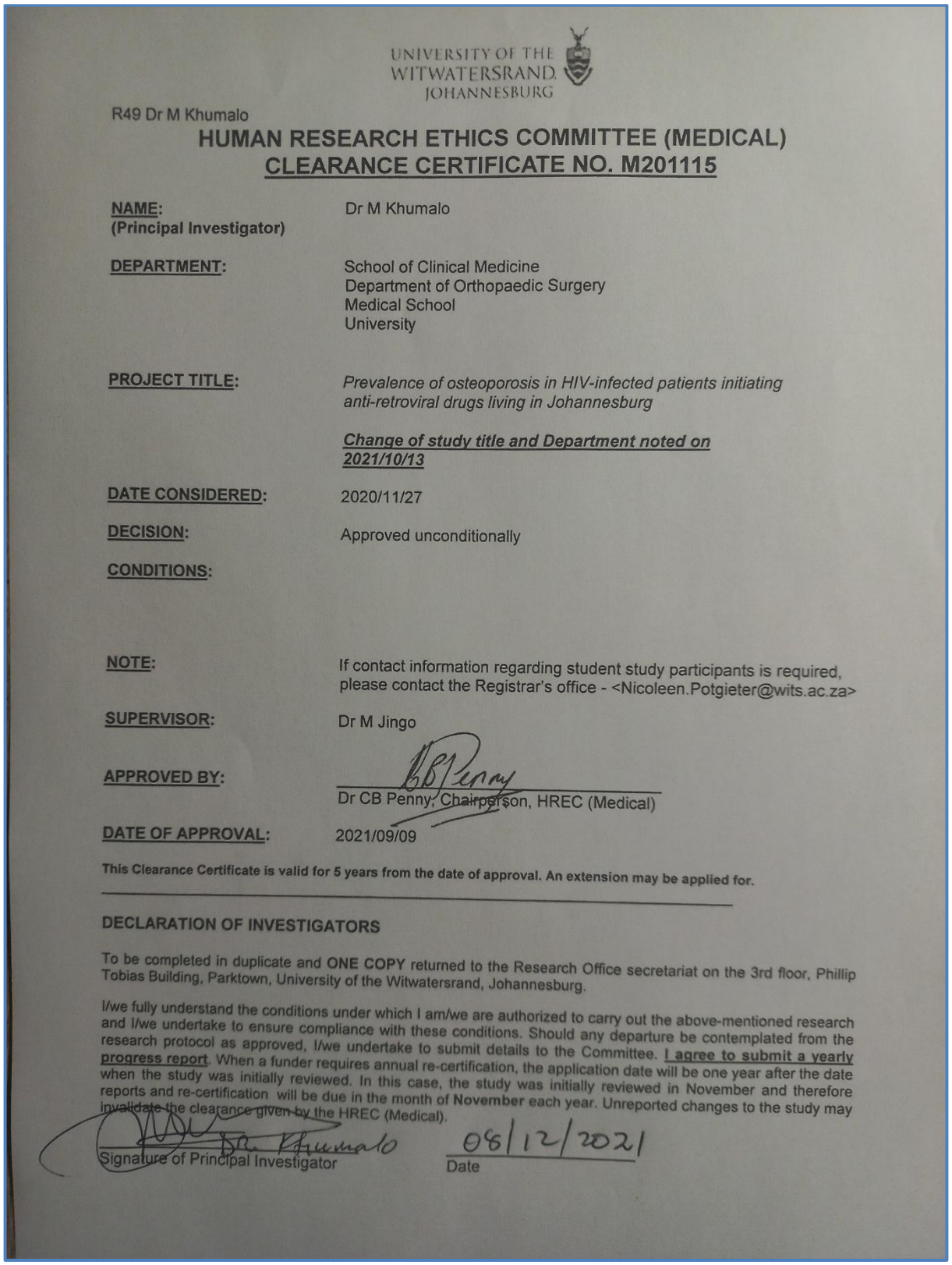
Ezintsha, a sub-division of Wits RHI

Central Office: 5th Floor, Block D, Sunnyside Office Park, 32 Princess of Wales Terrace, Parktown 2193, Johannesburg, South Africa www.ezintsha.org

INVESTIGATE INNOVATE ADVANCE

Scanned with CamScanner

Appendix D: Ethics Clearance Certificate



UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Dr M Khumalo

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M201115

NAME: (Principal Investigator)	Dr M Khumalo
DEPARTMENT:	School of Clinical Medicine Department of Orthopaedic Surgery Medical School University
PROJECT TITLE:	*Prevalence of osteoporosis in HIV-infected patients initiating anti-retroviral drugs living in Johannesburg* ***Change of study title and Department noted on 2021/10/13***
DATE CONSIDERED:	2020/11/27
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Dr M Jingo
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2021/09/09

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

DECLARATION OF INVESTIGATORS

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

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

Signature of Principal Investigator

06/12/2021
Date