COLLEGE OF MEDICINE

Reduced bone mineral density among people living with HIV and receiving anti-retroviral therapy in Blantyre, Malawi: Pharmacological challenges, prevalence and the role of exercise

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ABBREVIATIONS

1RM	One repetition Maximum
ART	Antiretroviral Therapy
BMD	Bone Mineral Density
BMI	Body mass index
CG	Control group
DEXA	Dual Energy X-ray Absorptiometry
HIV	Human Immunodeficiency Syndrome
HR	Heart rate
MST	Maximal Strength Training
PA	Physical activity
PLWHIV	People living with HIV
QCT	Quantitative Computed Tomography
QECH	Queen Elizabeth Central Hospital
QUS	Quantitative Ultrasound
RLS	Resource limited settings
RRS	Resource rich settings
TDF	Tenofovir
TG	Training group
VO2max	Maximum Oxygen Uptake
WHO	World Health Organisation

ABSTRACT

Reduced bone mineral density (BMD) is common among people living with HIV (PLWHIV) following the use of tenofovir (TDF) based antiretroviral therapy (ART) drugs. Although pharmacological therapies used to manage reduced BMD are associated with adverse effects, non-pharmacological strategies to manage reduced BMD resulting from ART drugs in PLWHIV have not been investigated. Despite evidence that exercise is effective in increasing BMD, there has been minimum effort to investigate effects of exercise on low BMD resulting from ART drugs in PLWHIV. The purpose of the research project was to investigate the prevalence of reduced BMD with its associated factors and the role of exercise in increasing bone mineral density among people living with HIV and receiving antiretroviral therapy in Blantyre, Malawi. This was a cross sectional and randomised controlled study involving HIV-positive adults receiving TDF based ART recruited from Blantyre, Malawi. Data on prevalence of BMD and physical activity (PA) was collected using the Dual Energy X-ray Absorptiometry (DEXA) and a global PA questionnaire. Eligible and willing participants with reduced BMD were then randomised into either maximal strength training group (TG) or control group (CG). Variables of BMD, Peak Oxygen Uptake (VO2max), Peak Heartrate (HRpeak) and One repetition maximum (1 RM) were obtained and analysed at base line and after the exercise intervention in both the TG and CG. Data were analysed using IBM Statistical Package for the Social Sciences (SPSS) version 21. Descriptive statistics using mean and standard deviation (SD) were used to characterize demographic variables. Student T – tests were used to analyse the differences between TG and CG. Out of 282 participants, 55 (20%) had low BMD while 227 (80%) had their BMD within the expected ranges for age. Most participants (40%) had low PA levels, followed by those who were moderately physically active (36%) while a smaller number of participants (24%) had high PA levels. Participants with low PA level (OR 1.23, $p = 0.6$) were more likely to have reduced BMD than those with high PA level. Data of 24 participants with reduced BMD randomised into TG (14) and CG (10) were analysed. After the intervention, there were significant improvements in lumbar BMD ($p < 0.001$) and resting heart rate ($p = 0.03$) in the TG compared to the CG. There were significant improvements in 1 RM in both the TG ($p < 0.001$) and the CG ($p = 0.01$). Prevalence of reduced BMD is high among PLWHIV in Malawi especially male Malawian adults. Most PLWHIV and receiving ART in the sample had low PA levels. The occurrence of reduced BMD was more likely among participants with low PA level. Maximal strength training improves lumbar BMD, resting herat rate and strength in PLWHIV receiving ART in Blantyre, Malawi.

1. INTRODUCTION

1.1 Background

Despite benefits of increased survival, use of tenofovir based anti-retroviral therapy (ART) regimens in Human Immunodeficiency Syndrome (HIV) patients is associated with low bone mineral density (BMD)(1). Low bone mineral density is characterised by osteopaenia and osteoporosis which predispose people living with HIV to fragility and future fall related fractures(2) thereby increasing the risk for morbidity and mortality. Fractures resulting from reduced bone mass in people living with HIV (PLWHIV) and receiving ART has been documented in a number of studies(3). Higher fracture rates among people living with HIV have been reported in the first 2 years after ART initiation relative to subsequent years(4). It has also been suggested that younger HIV infected adults between the ages of 25 – 54 years are at an increased risk of bone fractures due to ART use(5) yet there are no clear directions on effective strategies to prevent and manage reduced bone mineral density among this patient population. Although evidence exists that exercise is effective in increasing bone mineral density(6,7), effects of exercise on low bone mineral density resulting from antiretroviral therapy drugs in HIV infected individuals has not been fully explored.

There is a paucity of data on the prevalence of low BMD among people living with HIV in Malawi. The prevalence of osteoporosis and osteopenia in people living with HIV and receiving ART is estimated to be over three times higher than that in HIV uninfected individuals(8). In high income countries, about 50% to 60% of people living with HIV are osteopenic with an additional 15% being osteoporotic(9). A prevalence of 47% to 67% in low BMD, osteopenia and osteoporosis were also found in low income areas of Nigeria and India(10,11). This could

suggest that low bone mineral density is generally higher among HIV infected individuals in resource limited settings compared with resource rich settings. Despite evidence that tenofovir significantly contributes to loss of bone mass (1,4,12,13), most first line ART treatment regimens recommended by World Health Organisation (WHO) in resource-limited settings, contain tenofovir (14,15). This makes reduced bone mineral density highly likely among people living with HIV in most resource-limited settings such as Malawi. However despite the advent of tenofovir based antiretroviral therapy regimen in 2011(16), there has been minimum effort to investigate the prevalence of low BMD in Malawians living with HIV and receiving ART.

Treatment strategies for low bone mineral density resulting from anti-retroviral therapy have no clear directions. Strategies to manage reduced BMD, osteopenia and osteoporosis resulting from ART include providing vitamin D and calcium supplements as well as pharmacological therapies such as bisphosphonates, teriparatide and denosumab(9). However, beneficial effects of denosumab, Vitamin D and calcium supplements in managing low BMD are not clear and remains to be further investigated(9). Although, Bisphosphonates are available in low income countries, they induce atypical femoral fractures and may not be used for more than 5 years(17). On the other hand, Teriparatide has a rare risk for osteosarcoma(9), which may limit its recommendation for use among people living with HIV. Compliance and adherence issues have also been associated with pharmacological therapies(18) with some studies showing that half of patients treated with bisphosphates discontinue treatment after 4 months(19,20). Over and above, these pharmacological strategies increase the pill burden for people living with HIV who are already on ART. Since pharmacological therapies are associated with a number of side effects

and adherence problems which may limit their use among HIV infected individuals on ART(17–24), non-pharmacological based interventions could be an attractive alternative.

There is growing evidence that exercise increases bone mineral density(6,7). Thus exercise may be used as a strategy to increase bone mineral density in PLWHIV and receiving ART. Despite evidence that exercise is effective in increasing bone mineral density in men and women(6,7), knowledge on the effects of exercise on low BMD among people living with HIV and receiving ART is scarce. Exercise has been proven to be a safe(25), inexpensive and practical way of treating some chronic diseases(26) and improving the quality of life(27,28). In view of declining rates of mortality and morbidity among people living with HIV due to increased accessibility of ART in resource limited settings, exercise may be a cost effective non pharmacological strategy in preventing and increasing BMD thereby reducing osteoporosis and fall related fractures resulting from reduced bone mineral density. Therefore, this thesis highlights challenges in strategies used to manage reduced bone mineral density among people living with HIV, presents the prevalence and associated factors of reduced bone mineral density among Malawian adults living with HIV and present the role of exercise in increasing bone mineral density among people living with HIV and receiving antiretroviral therapies in Malawi. Specifically, the following research questions have been addressed in the thesis:

1) What are the effective strategies used to manage reduced bone mineral density resulting from antiretroviral therapies?
2) What is the prevalence of low bone mineral density among people living with HIV and receiving antireroviral therapy in Blantyre, Malawi?

3) What factors are associated with reduced bone mineral density among people living with HIV and receiving antiretroviral therapy in Blantyre, Malawi?
4) What are the physical activity levels of people living with HIV and receiving antireroviral therapy in Blantyre, Malawi?
5) Does maximal strength exercise training increase bone mineral density among people living with HIV and receiving antiretroviral therapy in Blantyre, Malawi?

1.2 Study aim and objectives

1.2.1 Overall aim

The overall aim of this thesis work was to investigate the prevalence of reduced BMD with its associated factors and the role of exercise in increasing bone mineral density among people living with HIV and receiving antiretroviral therapy in Blantyre, Malawi.

1.2.2. Specific objectives

The specific study objectives are presented in the form of papers, published or submited for publication.

Paper I:

The aim of paper I was to highlight literature gaps in the strategies used to manage reduced bone mineral density resulting from antiretroviral therapies. Furthermore the paper aimed to highlight adherence problems of pharmacological therapies used to manage reduced bone mineral density among people living with HIVand focus on exercise as an alternative or adjuvant strategy.

Paper II:

The aim of paper II was to invesitigate the prevalence of low bone mineral density among people living with HIV and receiving antiretroviral therapy in Blantyre, Malawi. Furthermore, it aimed

at determining factors associated with reduced BMD and the association between femoral neck and lumbar spine bone mineral density among the participants.

Paper III:

The aim of paper III was to determine levels of physical activity among people living with HIV and receiving ART in Blantyre Malawi. In addition, the paper also aimed at identifying the contribution of gender in the levels of physical activity among people living with HIV in Malawi.

Paper IV:

The aim of paper IV was to investigate the effects of progressive resistance exercises on bone mineral density in people living with HIV and receiving antiretroviral therapy in Blantyre, Malawi. The paper also aimed at determining the effects of progressive resistance exercises on maximum oxygen uptake and muscle strength in the participants. The paper speicifically focused on maximal strength training as a form of progressive resistance exercise that can be used in increasing BMD among people living with HIV.

1.2.3 Structure of the thesis

The thesis is based on the following published papers:

I. Chisati EM, Constantinou D, Lampiao F. Management of Reduced Bone Mineral Density in HIV: Pharmacological Challenges and the Role of Exercise. *Front Physiol.* 2018; 9:1074. https://www.frontiersin.org/article/10.3389/fphys.2018.01074.

II. Chisati, EM, Constantinou D, Lampiao F. Reduced bone mineral density among HIV infected patients on anti-retroviral therapy in Blantyre, Malawi: Prevalence and

associated factors. *PLOS ONE*. 2020; 15(1): 1–12: e0227893. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0227893

III. Chisati EM, Munthali F, Constantinou D, Lampiao F. Physical activity levels among Malawian adults living with HIV and receiving anti-retroviral therapy. *Malawi Med J.* 2020;32(March):8–12. ttps://www.ajol.info/index.php/mmj/article/view/194902

IV. Chisati EM, Constantinou D, Lampiao F. Effects of maximal strength training on bone mineral density in people living with HIV and reciving antiretroviral therapy: a pilot study. *BMC Sports Sci Med Rehabil.* 2020;12(67):1 – 7. https://doi.org/10.1186/s13102-020-00216-6

The thesis is divided into eight sections focussing on different areas of the research project. These sections are introduction, literature review, materials and methods, summary of results, discussion, conclusion, recommendations and published original papers.

The first section which is the introduction provides a concise background to the research problem and its potential impact on public health. A brief discussion on the research gap is also provided in this section. The section also highlights the objective of the research project followed by the research questions. The section concludes with a description of the main aim of the study and specific objectives for the thesis work.

After the introduction, the following section is the literature review. This section highlights the knowledge gaps in strategies used in the management of reduced bone mineral density. The sections begin by demonstrating the research gap and goes on to provide concepts and a concept map. Furthermore, this section provides a review of data on the prevalence of bone mineral density resulting from ART among people living with HIV, challenges of pharmacological

therapies used in treating reduced bone mineral density as well as the role of exercise in managing reduced bone mineral density.

Methods and materials is the third section to be presented in this thesis. This section will provide a discussion of the methods that were used to collect data for the research project. Information on study population, data collection, ethical considerations, study design and data variables will be presented under this section. In addition, the section will also present information on how data was analysed using statistical methods.

Following the methods and materials section is the summary of results section. An overview of the research findings will be provided based on the published papers. A summary of most results will be presented in form of tables and figures.

Section five will present a discussion of the results of the research project. This section provides an interpretation of the results also based on the research findings as presented in section four. A summary of the study limitations will also be provided in this section.

After the discussion section, a conclusion will be presented. The conclusion will provide a summary of the main findings of the research project. The conclusion will also guide the choice of recommendations and directions for future investigations.

Section seven will provide study implications and recommendations based on the research findings. This section will provide directions for future investigations based on the conclusion. Information on acknowledgements will follow the recommendations section.

The last section of the thesis is an index of all published and submitted papers. All published and submitted papers emanating from the research project are attached in this section.

2. LITERATURE REVIEW

2.1 Introduction

Despite high prevalence rates, strategies to manage reduce bone mineral density in people living with HIV have not been fully explored. Low bone mineral density (BMD) is becoming more common among people living with HIV (PLWHIV) following the use of current antiretroviral therapy (ART) drugs such as tenofovir (TDF)(1,29–32). Although pharmacological therapies used to treat low BMD(21,22,33) are associated with adverse effects(21–23) and may increase the pill burden in PLWHIV who are already burdened by ART, non-pharmacological strategies to prevent and treat reduced bone mineral density resulting from ART in PLWHIV have not been fully explored. Despite evidence that exercise is effective in increasing BMD(6,7), effects of exercise on low bone mineral density resulting from ART in HIV infected individuals are still unknown.

This literature review chapter will highlight knowledge gaps in strategies to manage bone loss resulting from ART. The review will focus on concepts and conceptual map, the prevalence of bone mineral density resulting from ART, strategies used in treating reduced bone mineral density, effects of exercises on bone mineral density, progressive resistance exercises and bone mineral density in HIV and methodological issues among studies investigating the effects of exercise in increasing bone mineral density. Concepts such as physiology of the bone, assessment of bone mineral density and exercise will be described. Evidence on the prevalence of reduced bone mineral density resulting from ART among people living with HIV in resource rich and resource limited settings will be presented. The review will also assess the effects of both pharmacological and non-pharmacological therapies in treating reduced bone mineral density with emphasis on people living with HIV and receiving ART. An assessment of the types

and designs of exercises that impact bone mineral density increases will as well be discussed. In addition, effects of progressive resistance exercise on bone mineral density in people living with HIV and receiving ART will be discussed. Further the review will highlight main methodological issues among studies investigating the effects of exercise in increasing bone mineral density.

From April to September 2017, online databases such as EMBASE, Google Scholar, MEDLINE, PubMed, Scopus and The Cochrane Library were searched with no period restriction using key words: bone mineral density, antiretroviral therapy, exercise, people living with HIV and progressive resistance exercise. Published articles with potentially relevant titles and abstracts were retrieved. Articles were included in the review if they were investigating (i) the prevalence of low bone mineral density in people living with HIV and receiving ART or (ii) examining strategies that are used to treat reduced bone mineral density or (iii) investigating the effects of exercise on bone mineral density. A total of 143 articles met the inclusion criteria and were included in the review.

2.2 Research gap

Prevalence of low bone mineral density in people living with HIV and receiving ART especially in resource limited settings is not extensively studied. Data on bone mineral density among HIV infected individuals on ART in resource limited settings are currently scanty and subject to methodological concerns such as lack of appropriate control groups, and local BMD reference data(1,11,34). For example, a review by Matovu et al on bone health in resource limited settings, reveal that most studies investigating bone loss in HIV infected individuals on ART did not use local noninfected controls for comparison but instead used the United States National Health and Nutrition Examination Survey reference data for comparisons(1). In addition, data

were not adjusted for differences in body composition and size(35,36). Although data from resource limited settings and resource rich settings show varying and overlapping prevalence of low BMD in people living with HIV on ART(1), a generally higher prevalence rate of reduced bone mineral density was observed in resource limited settings with some studies reporting prevalence of up to 85%(37). Despite the introduction of ART treatment regimens containing tenofovir in the resource limited setting of Malawi in 2011(16), data on the prevalence of low bone mineral density in people living with HIV and receiving ART is lacking.

The wide spread use of tenofovir among people living with HIV receiving ART coupled with high burden of HIV(38) makes reduced BMD inevitable. McComsey and colleagues compared the effects of tenofovir versus other ART regimens on bone mass in a population of 269 people living with HIV. They observed greater decreases in spine and hip bone mineral density in participants treated with tenofovir(13) than those treated with other regimens. Although tenofovir has been shown to significantly contribute to loss of bone mass(22) most first line ART treatment regimens for adults and children above 15 years recommended by World Health Organisation (WHO) in resource limited settings, contain tenofovir(14,15). However, unlike in rich resource settings where medications such as efavirenz are no longer preferred, and alternatives to tenofovir with less bone toxicity are likely to be more frequently used, strategies to minimize bone loss among people living with HIV on ART in resource limited settings are currently lacking(1).

Effective strategies to prevent and treat reduced bone mineral density in PLWHIV and receiving ART remains an area that lacks direction. Pharmacological strategies to manage reduced BMD resulting from ART include medications such as bisphosphonates, teriparatide and denosumab as well as providing vitamin D and calcium supplements(21). However these pharmacological

therapies(21,22,33) are associated with adverse effects such as tumors, infection, nasopharyngitis, osteosarcoma as well as bronchitis(21–23) which limit their recommendation for use in HIV infected individuals(22)**.** In addition, the current cost of treating bone loss using pharmacological therapies such as bisphosphonates is prohibitive(1). Further, pharmacological therapies may increase the pill burden in people living with HIV who are already burdened by ART. Physical activities such as jogging, walking, dancing and weight lifting are also recommended as non-pharmacological strategies for preventing and treating bone loss(39), but the effectiveness of physical activity in increasing bone mass resulting from ART in people living with HIV has not been fully elucidated.

Although there is growing evidence that physical activity and exercise increases bone mineral density in both adult men and women(6,7,40), effects of exercise on loss of bone mass resulting from antiretroviral drugs in PLWHIV must still be investigated(41). Exercise programmes differ in terms of frequency, intensity, duration and type. Among many studies, there is heterogeneity in the type, intensity, frequency and duration of exercise interventions to increase bone mineral density(42) with most trials conducted in either women or adult men(6,39,43) despite evidence of increases in bone loss among young men as well(44). Although reduced bone mineral density is common among PLWHIV following the use of antiretroviral drugs such as tenofovir (1,31) knowledge on effects of progressive resistance exercises on bone mineral density in this patient group is still lacking(41,45).

In order to approach this question, we first need to examine the concepts underlying bone mineral density. Methods used to assess bone mineral density will also be described under the concepts section. In addition, the concepts section will outline possible beneficial role of exercise on bone physiology.

2.3 Concepts and concept map

2.3.1 Physiology of bone mineral density

Bone is a connective tissue in which the matrix is made up of collagen fibres and minerals. Collagen is a protein that provides the bone's flexible framework(46). The minerals, also called bone mineral density or bone mineral content, gives the bone its strength and hardness. Collagen allow bones to bend in order to withstand stress while bone mineral density give bones strength to support the body's other tissues(46). Bone mineral density in the matrix contributes to the support and protection functions of the skeleton. As such, bone mineral density is a surrogate for bone strength and is used to predict fracture risk in an individual. Reduced bone mineral density is characterised by osteopaenia and osteoporosis and can predispose an individual to future fall related fractures.

Bone grows through modeling (construction) and remodeling (reconstruction) processes(46,47). The modeling process involves bone cells called osteoblasts that perform bone formation by laying down new bone(46). On the other hand, remodeling is a continuous process which involves bone resorption. In resorption, bone cells called osteoclasts are attracted to areas needing repair and move in to remove damaged bone(46,48) thus little bone tissues are added along one surface and a little reabsorbed along another surface (figure 1). The remodeling process occurs throughout one's life. It is estimated that 5 – 7% of bone mass is remodeled every week and approximately half gram of calcium is formed or reabsorbed by the adult skeleton every day(47). Any imbalances between modeling and remodeling lead to reduced load bearing capacity as well as loss of bone mineral density which in turn increase the risk for fractures(46). Therefore, increased bone mineral density may reduce the incidence of fractures.

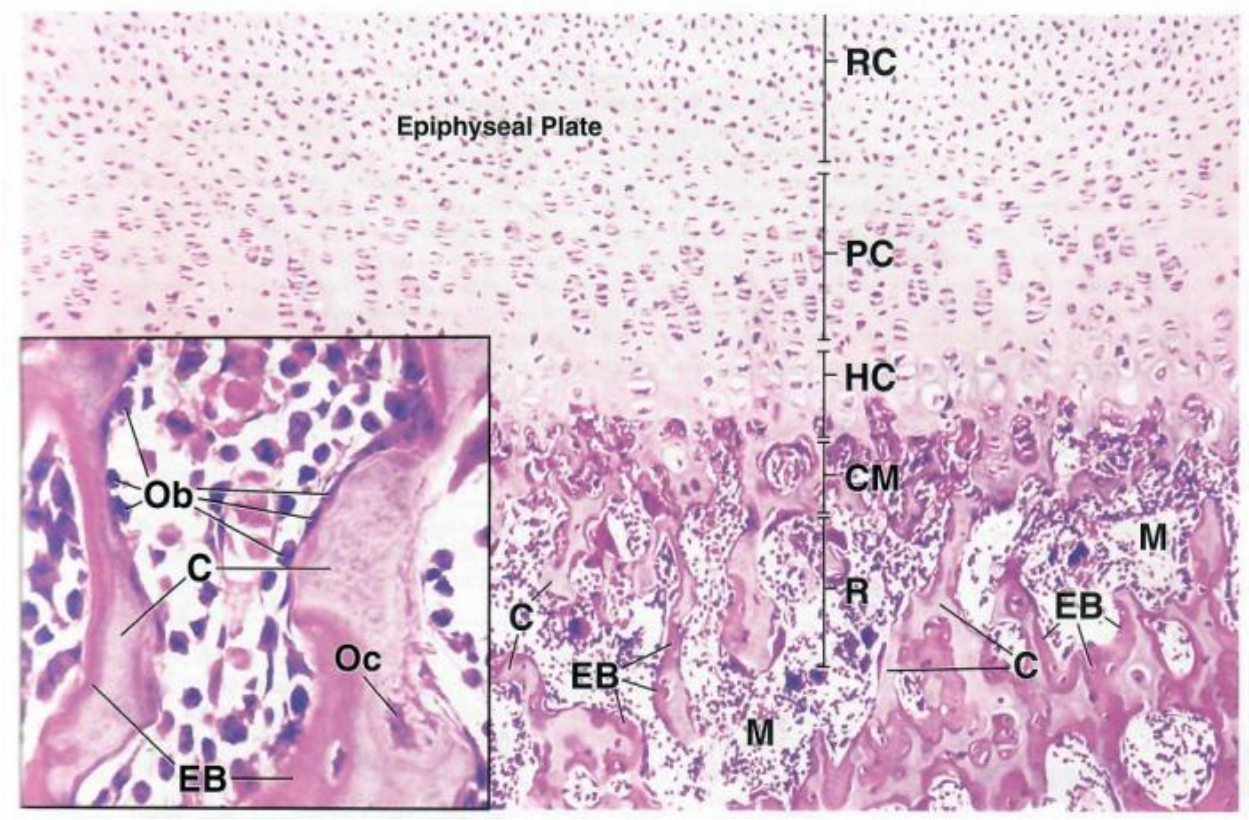

Figure 1: Bone modeling and remodeling. (Source; *Ross MH and Pawlina W, 2011*(49)). ***RC** = Zone of reserve cartilage; **PC** = Zone of proliferating cartilage; **HC** = Zone of hypertrophic cartilage; **HC** = Zone of calcified matrix; **R** = Zone of resorption.*

Bone mass formation (modeling) is normally more than reabsorption (remodeling) with increasing age and peaks between ages 25 and 30: there after bone mass starts to decrease leading to lower bone mineral density(48). The purpose of bone modeling and remodeling is to establish peak bone mass so as to maintain bone strength in adulthood(48). During childhood, a period referred to as growth spurt, bone mineral density accumulates with the bone growing both in size and strength(50). After the growth spurt, usually during the pre and post adolescent period, bone formation continues until a peak bone mass is reached between ages 25 to 30. The age of attainment of peak bone mineral density is site specific with gains of about 5 – 12% in bone mineral density observed after 30 yrs old in other individuals(51). After the third decade,

bone mineral density is maintained for about 10 years before it starts to decline at a rate of about 0.3 – 0.5% per year in both males and females(50,52). At ages between 45 years to 55 years, women loose more bone mineral than men after which the rate of bone loss is gradual and the same in both sexes (figure 2). A rapid loss of bone mineral density in women between ages 45 years to 55 years is possibly due to decreases in oestrogen production as the menstrual cycle ceases during this period(50).

Although bone remodeling is a normal and natural process, some factors are thought to disrupt the remodeling process(50) and thereby reduce or increase bone mineral density than envisaged. Factors such as; physical inactivity, low body weight, nutritional deficiencies especially of calcium and vitamin D, depression, smoking, heavy alcohol use and more recently some antiretroviral drugs(1,29) are associated with reduced bone mineral density. Although some factors such as sex and body size are difficult to modify, physical activity can be changed to stimulate greater accumulation of peak bone mass(50). Since bone modeling and remodeling depends, in part, on mechanical stress, bone strength is enhanced or reduced in response to increased or reduced mechanical loading. Hence an individual's physical activity life style can play a role in either increasing or reducing bone mineral density.

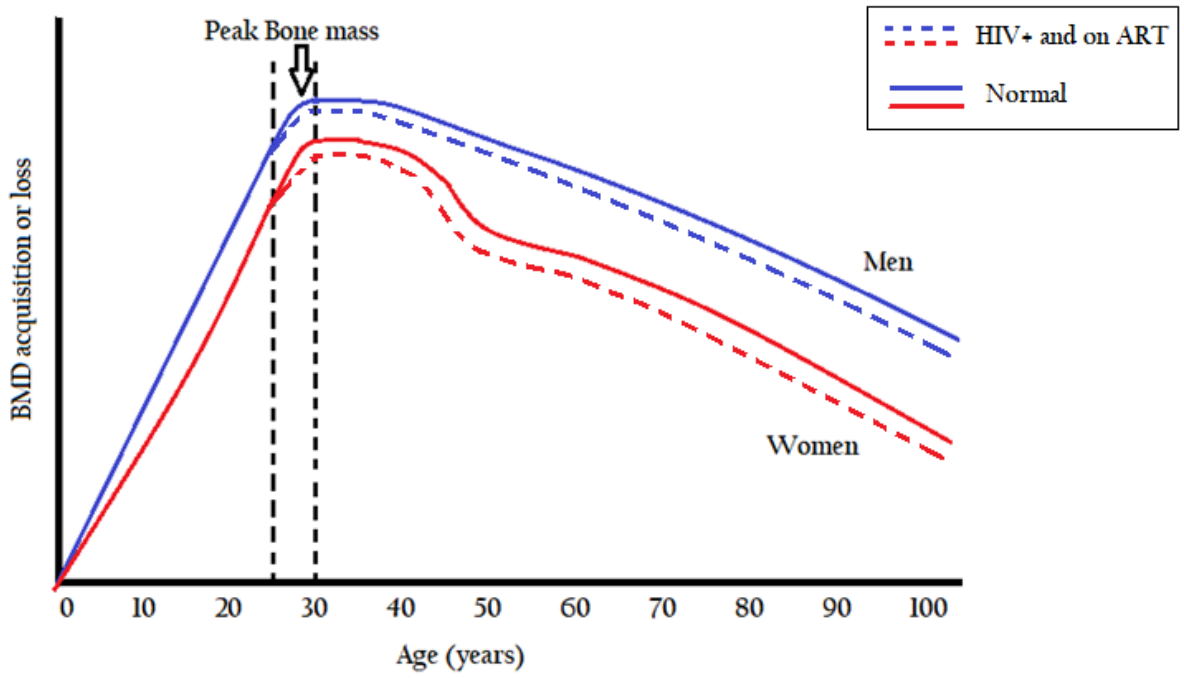

Figure 2: Normal bone mass growth. (Source; *Chisati E, Constantinou D and Lampiao F, 2018*(53))

2.3.2 Assessment of bone mineral density

Bone mass is assessed non-invasively by measuring bone mineral density usually with an aim of diagnosing osteoporosis or predicting an individual's risk for fracture. Common techniques used for measuring bone mineral density include quantitative computed tomography (QCT), quantitative ultrasound (QUS), and dual energy X-ray absorptiometry (DEXA)(50,54). These techniques are generally based on either differential absorption of the ionizing radiation (QCT, DEXA) or modification of sound waves (QUS)(54) Although they may all be appropriate for use, each technique pose limitations for use in clinical practice as discussed below.

Quantitative computed tomography is a bone imaging technique that provides three-dimensional measures of the bone(50). As opposed to other bone measuring techniques, QCT has the ability

to measure the true volumetric density of the bone expressed in grams per cubic centimeter (gm/cm^3)(55). In addition, QCT can independently measure specific compartments such as trabecular and cortical bone in the lumbar spine separately(50). However, apart from long scanning time, QCT has a higher radiation dose compared to other techniques such as DEXA(50). Further, QCT permits less precision as it requires skill to interpret results(50). This makes the use of QCT in clinical practice difficult. As such, it is recommended that quantitative computed tomography be used in conjunction with DEXA for better prediction of osteoporosis and fracture risk(50).

In contrast to QCT and DEXA techniques that use radiation, Quantitative ultrasound uses sound waves to determine bone mineral density. QUS is based on the notion that the rate of sound waves passing through the bone depends on the structural characteristic of the bone(55). Hence modification of the sound waves is influenced by bone mineral density. Although it is less expensive, portable and has no radiation hazards, QUS requires a trained technician to interpret the results obtained(50). In addition, QUS has poorer precision than DEXA since measurements of bone mineral density appear to decrease with age(55). Since there are many QUS devices with variations in technology, measurement site, data acquisition etc, there is currently no consensus on how results from various QUS devices should be interpreted in order to diagnose low bone mineral density(55). This limits the use of QUS as a reliable tool for measuring bone mineral density in clinical practice.

Dual energy X-ray absorptiometry is globally accepted as a standard technique for measuring bone mineral density(50,54–56). On top of having a low radiation dose, DEXA yields a high precision and enables fast scanning(50,55). In addition, DEXA has the capability to evaluate body composition(55), which makes its use desirable from the clinical point of view. Despite

being considered the gold standard for measuring bone mineral density, DEXA is influenced by bone size(50). Thus, the larger the bone, the greater the bone mineral density irrespective of volume. Nonetheless, interpretation of low bone mineral density by World health Organisation (WHO) uses DEXA T - scores which is not possible with QCT and QUS measurements(56). Further, DEXA T- score must be used as a reference standard to compare and validate other bone mineral modalities obtained with other imaging tools(50). This makes DEXA a method of preference for determining reduced bone mineral density.

2.3.3 Exercise

The term exercise is mostly used interchangeably with physical activity. Despite having common elements, exercise is not synonymous with physical activity. Physical activity refers to any bodily movements produced by muscles that expend energy more than the resting metabolic rate(57). On the other hand, exercise is a sub class of physical activity which involves planned, structured and repetitive activities aimed at improving or maintaining one or more components of physical fitness(57). Physical fitness entails the ability of the body to meet the demands of the environment. As is the case with delivery forms, and frequencies when prescribing medications, a degree of precision should be applied when prescribing exercise(58).

Prescription of exercise as a dose centres around modifying the design of an exercise. An exercise design is comprised of frequency, intensity, duration and type of the exercise. Frequency entails how often an individual engages in an exercise(58,59). Frequency of an exercise is usually indicated by how many times or days per week an individual engages in the exercise. Intensity refers to the levels of exertion an individual experience during an exercise or how hard the exercise is(58,59). The effect of an exercise to induce physiological adaptations in an individual primarily depends on the intensity of the exercise(60). Duration refers to the time

taken for an exercise session to be completed(59). Duration entails how long an exercise session will take and it partly depends on the intensity and the goal of the exercise. Type of exercise also referred to as exercise mode is the activity performed during the exercise session such as cycling, jogging, walking and swimming(59).

Any mode of exercise can either be aerobic exercise or resistance exercise. Aerobic exercises are those that focus on improving the aerobic energy system. Activities such as cycling, jogging, walking running and swimming are aerobic type of exercises. On the other hand, resistance exercises focus on improving the musculoskeletal system and the nervous system. Activities such as weight lifting comprise resistance type of exercises. Both aerobic and resistance exercises have been recognised as therapy for most chronic conditions(61). Exercise among people living with HIV has been associated with benefits such as increases in strength, improvements in body composition improvements in cardiovascular fitness and physical function as well as psychological status(41,59,62–64). However, with recent reports of increasing bone loss among people living with HIV due to ART drugs(1,31), the impact of exercise on bone mineral density has not been fully promoted.

2.3.4 Concept map

The concept map (figure 3) shows the three main phases of the study aimed at determining the effects of exercise on bone mineral density among people living with HIV and receiving ART in Blantyre Malawi. The first phase involved identifying the problem which is low bone mineral density in PLWHIV in Malawi through a cross sectional study. This phase involved determining the prevalence of low bone mass and its associated factors in PLWHIV in Malawi. In order to generate valid and reliable data regarding prevalence of low bone mineral density in Malawian individuals living with HIV and receiving ART, methodological challenges common among

many studies such as lack of adjustments to body composition(1) were addressed. The first phase also explored the justification for choosing non-pharmacological strategies as a possible solution to the problem compared to pharmacological strategies. Some challenges with using pharmacological strategies to treat low bone mineral density in individuals living with HIV and receiving ART include the side effects of the drugs used, expensiveness of the drugs especially in resource limited settings like Malawi and the pill burden since PLWHIV are already burdened by antiretroviral drugs.

The second phase involved the formulation of a possible solution to the problem. This phase identified exercise, which is a non-pharmacological strategy for treating low BMD, as the main intervention that was proposed in the study. Exercise is a behavioural change intervention. Behavioural change interventions are defined as coordinated sets of activities designed to change the pattern of a specific behaviour(65). It is well known that adherence to the recommended exercise was key to the success of the intervention. Therefore, an exercise intervention was developed on a thorough understanding of barriers and facilitators for adhering to exercise regimens. The choice of the exercise to be used in this study was based on the COM – B model which is a well-established framework for adherence(65).

The third phase shows execution of the selected intervention. This is the phase in which a randomised control trial was conducted. The type of the exercise intervention selected was maximal strength training exercise. Maximal strength training is a type of progressive resistance exercise. The choice of the maximal strength training exercise design was considered following the medical research council principles for developing and evaluating complex interventions(66–68). Effects of maximal strength training exercise on BMD in other populations have been reported(6,43), but its effects on bone mineral density in PLWHIV have not been explored.

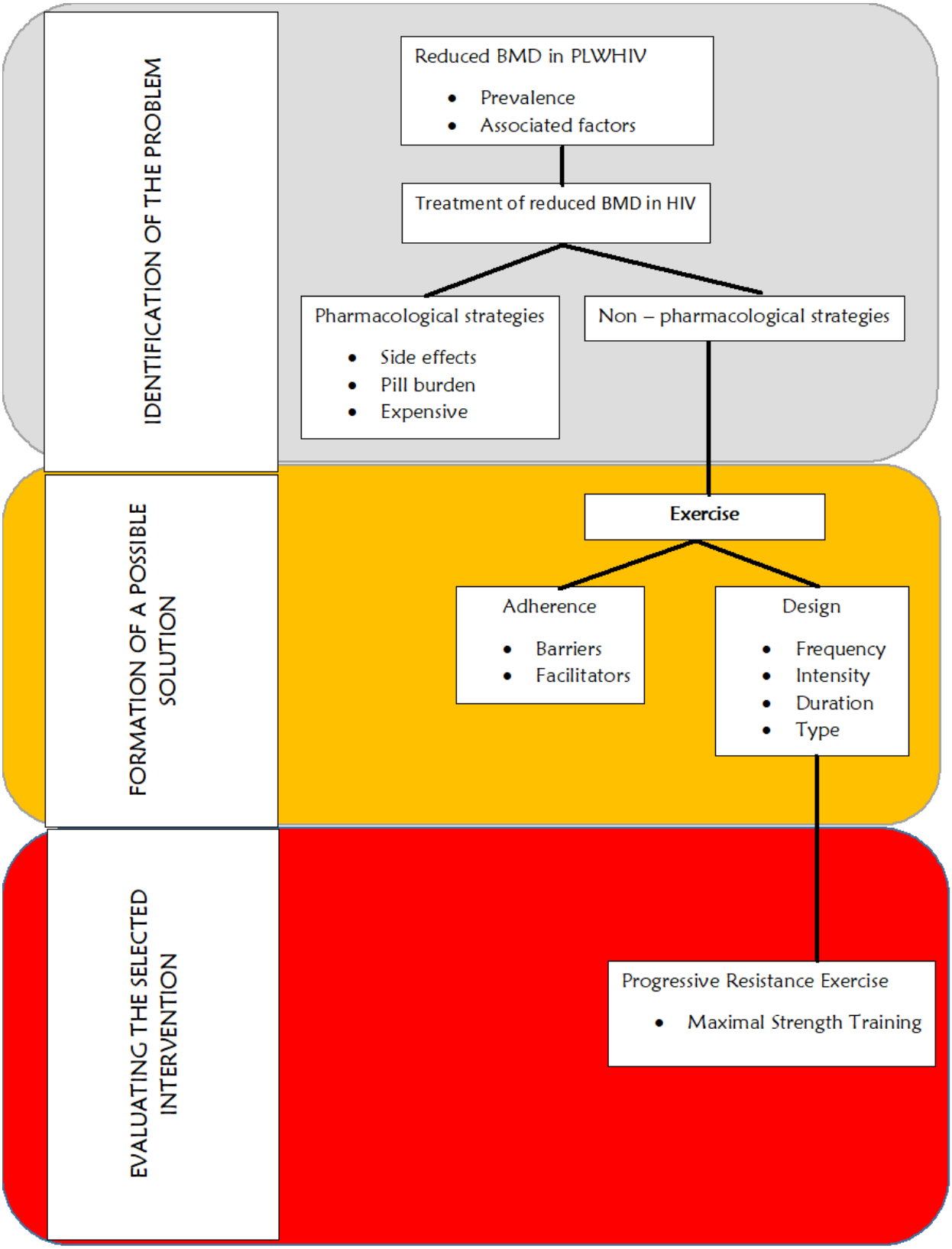

Figure 3: Concept map

2.4 Bone mineral density in HIV

2.4.1 Bone mineral density and ART

Antiretroviral therapy has brought a significant increase in the survival of HIV patients worldwide. Despite benefits of increased survival, ART has been shown to significantly contribute to loss of bone mass(1,29,31). Consequently, medical comorbidities such as osteoporosis and fragility fractures resulting from low bone mineral density are on the rise(3). Emerging evidence indicate that HIV infection is strongly associated with a fivefold increased risk for hip fractures independent of age, gender and comorbidities(69). This could increase the risk for mortality and morbidity in people living with HIV. Initiation of antiretroviral therapy has been shown to increase bone loss in people living with HIV irrespective of regimen(1). Reports show a decrease of about 2 – 6% in bone mineral density in the first two years of ART initiation regardless of the regimen(70).

While decreases in bone mineral density occur at initiation of ART irrespective of regimen, more bone loss is associated with tenofovir containing regimens than other regimens(1,4,12,13). Tenofovir leads to approximately 1 – 3% greater bone mineral loss compared to non tenofovir containing regimens(4). McComsey and colleagues(13) compared the effects of tenofovir versus other ART regimens on bone mass in PLWHIV. They observed greater decreases in spine and hip BMD in participants treated with tenofovir than those treated with other regimens (13). This could suggest that tenofovir has an independent effect on bone regardless of host, viral and immunological factors. Despite evidence that tenofovir significantly contribute to loss of bone mass(1,4,12,13), most first line ART treatment regimens recommended by World Health Organisation (WHO) in resource limited settings, contain tenofovir. (14,15). This makes reduced bone mineral density highly likely among people living with HIV in most resource limited

settings yet strategies to minimize bone loss in PLWHIV in these settings are currently lacking(1).

Although ART contributes to bone loss in people living with HIV, other factors may play a role as well. Traditional factors such as physical inactivity, lower body mass index, female sex, older age, nutritional deficiencies of calcium and vitamin D, depression, smoking and alcohol use are believed to contribute to loss of bone mass in the general population(3). While there is a controversy on traditional risk factors contributing to reduced bone mineral density in PLWHIV(71), other authors have demonstrated that risk factors for reduced bone mineral density in HIV are similar to other populations(72). Other reports indicate that poverty may also contribute to low bone mineral density(73) suggesting that PLWHIV in resource limited settings could be at a higher risk for loss of bone mineral mass.

Evidence is emerging that HIV severity also contributes to reduced bone mineral density in HIV infected individuals receiving ART(74–76). A study by Grant et al demonstrated that with ART initiation, HIV infected individuals with a low DC4 cell count (< 50 cells/mm^3) had greater bone loss than those with a higher CD4 cell count (> 500 cells/mm^3)(77). This indicates that chronic inflammation induced by HIV may impact bone metabolism. Although mechanisms leading to bone loss resulting from ART are unclear, current data suggests that higher levels of C-C chemokine receptor 5 (CCR5) may affect the functional regulation of osteoclasts thereby leading to bone loss(78). However, despite regional increases in HIV inflammation(79,80), data on prevalence of bone mineral density from limited resource settings of sub Saharan Africa is still scarce.

2.4.2 Prevalence of low bone mineral density in HIV

Available data on prevalence of low BMD among people living with HIV from resource limited settings is not consistent and subject to methodological concerns. Studies investigating reduced bone mineral density among PLWHIV reveal variations in the prevalence of low BMD. Alonge and colleagues(11), used a cross sectional study to determine the prevalence of low bone mineral density in 1005 HIV positive males and females in Nigeria. They reported a prevalence of about 47% of low BMD among Nigerians living with HIV. In contrast, a cross sectional study by Dravid et al(34), reported a higher prevalence rate of 67% among 536 HIV infected individuals in the resource limited settings of India. Varying levels of between 47% to 85% in the prevalence of reduced BMD in people living with HIV from resource limited settings have also been reported(11,29,34,35). The disparity in the prevalence of low bone mineral density could be due to methodological variations among the studies. The study by Alonge et al lacked an appropriate control group and did not use local bone mineral density reference data for comparison(11). Dravid et al(34) demonstrated a higher prevalence rate in BMD although their study also lacked a control group and local reference data. However, variations could as well be a result of differences in sample size between the two studies. Alonge and colleagues used a larger sample of 1005 people living with HIV compared to 536 people living with HIV in the study by Dravid et al. Despite evidence that body composition and male gender affect BMD(81), there was no adjustment for differences in body composition and size in both studies. Therefore, cross sectional investigations on prevalence of bone mineral density among PLWHIV in limited resource settings should consider using local non-infected controls for comparison and adjusting for differences in body composition and size.

The prevalence of low BMD among people living with HIV is generally higher in resource limited settings compared to resource rich settings. Higher prevalence rates of up to 85% in low bone mineral density among PLWHIV in resource limited settings have been reported by a number of studies(11,29,34,35,81,82). Differences in prevalence rates between resource limited and resource rich settings could be due to differences in risk factors causing low BMD among people living with HIV. Although most of the risk factors are similar in resource limited and resource rich settings(72), some risk factors such as malnutrition, low body mass index and longer duration since the diagnosis of HIV are more common among PLWHIV in resource limited settings(1). These factors along with the wide spread use of tenofovir among HIV infected individuals on ART in resource limited settings(14,15,38) makes high prevalence rates of reduced bone mineral density unavoidable. Despite the advent of the current ARV regimen in 2011(16), data on the prevalence of low BMD in Malawians living with HIV and receiving ART is still scarce.

2.5 Treatment of reduced bone mineral density

2.5.1 Pharmacological therapies

Treatment of reduced bone mineral density remains an area of controversy. Pharmacological strategies to manage bone loss resulting from antiretroviral therapy include providing vitamin D and calcium supplements as well as pharmacological therapies such as Bisphosphonates, Teriparatide and Denosumab(21). This section will discuss limitations of pharmacological therapies in treating reduced bone mineral density in people living with HIV.

Although vitamin D deficiency has been implicated in the pathogenesis of bone loss in people living with HIV(22), there are no clear recommendations for vitamin D and calcium supplements to treat low bone mineral density in this population(83). A study by Dao reported a 70.3%

vitamin D deficiency in a cohort of 672 HIV infected participants(84). Factors such as African American race and exposure to ART drugs were found to be associated with increased risk to vitamin D deficiency(84). This could suggest that vitamin D deficiencies could be higher among the African American race and moreover it is in Africa where the use of ART is becoming common as a result of high prevalence rates of HIV. A review by Harris recommends higher doses of vitamin D in people living with HIV exhibiting bone loss to maintain targeted levels of bone mass(22). However, due to their small effect on fracture risk reduction, vitamin D and calcium supplements are best used as additional therapies with other osteoporotic drugs(33) and their sole use is not advised.

Among osteoporotic drug treatments, beneficial effects of Denosumab in managing reduced bone mineral density in people living with HIV are not clear(21). Denosumab is a long acting monoclonal antibody that blocks bone resorption(21). Denosumab decreases osteoclastogenesis and is recommended for use in persons with a history of osteoporotic fractures or those who are intolerant to other osteoporotic therapies(22). However, long term use of denosumab in treating bone loss leads to atypical fractures(24). Although seemingly effective, use of Denosumab brings adverse effects such as, tumors, infection, nasopharyngitis, back pain, bronchitis and arthralgia(22,23). These adverse effects are of particular concern to people living with HIV considering that they are already at an increased risk for infection.

Although available in resource limited settings and could be an alternative to denosumab for treating bone loss, bisphosphonates have a number of side effects which are a cause of concern in people living with HIV. Bisphosphonates, available as alendronate, ibandronate, risedronate, and zoledronic acid are said to decrease fracture risks in some parts of the body by between 25% – 50% in the general populations(85–88). However, despite improvements in bone mineral

density among HIV infected individuals following use of alendronate and zoledronic acid, side effects such as difficulty swallowing, esophageal inflammation, dyspepsia, and gastric ulcer are also observed(22). In addition, bisphosphonates induce atypical femoral fractures and may not be used for more than 5 years(17,21). This raises concerns of the long term effects of using bisphosphonates for managing reduced bone mineral density in HIV infected individuals who are currently living longer as a result of ART.

While teriparatide is recommended in individuals where bisphosphates have failed, its recommendation for use to treat bone loss in people living with HIV is still controversial. Some reports indicate that teriparatide has a rare risk for osteosarcoma(21) which may limit its recommendation for use in HIV infected individuals. Additionally, a review by Harris and Brown concluded that data on safety and efficacy of teriparatide in people living with HIV is lacking and requires further investigation(22).

Apart from the many challenges associated with pharmacological therapies in treating bone loss in HIV infected individuals, compliance and adherence issues have also been associated with pharmacological therapies(18). A retrospective study by Fan and colleagues which assessed the level of compliance with drugs prescribed for bone loss for seven years concluded that most patients do not continue to take the medication as prescribed(19). It has also been observed that half of patients treated with bisphosphates discontinue with treatment after 4 months(19,20). Since pharmacological therapies are associated with a number of side effects and adherence problems which may limit their use among HIV infected individuals on ART(17–24), exercise based interventions could be an attractive alternative.

2.5.2 Non pharmacological therapies

Guidelines for good bone health include physical activity and exercise as a major component in preventing bone loss(46,89–91). Physical activity has been suggested as a non-pharmacological strategy that can be used to increase bone mineral density even in people living with HIV(46,91). Among others, physical activities such as jogging, walking, dancing and weight lifting are shown to be beneficial in preventing and treating low bone mineral density(39). However, evidence that physical activity is related to higher bone mass is often inappropriately interpreted as evidence that any activity will improve bone mass(92).

Contrary to reports that all physical activity could be important in increasing bone mineral density(90), weight bearing physical activities with high force, yield a notable increase in bone mineral density(39). This could suggest that the type and intensity of the physical activity has an additive effect on bone density. Although weight bearing physical activities are recommended to improve BMD, appropriate parameters for frequency, intensity, duration and type of physical activity to increase bone mineral density especially among HIV infected individuals have not been fully explored(40,89,93).

2.6 Exercise and bone mineral density

2.6.1 Type and design of exercises

There is growing evidence that exercise increases bone mineral density(6,7,94,95). The effect of exercise on bone mineral density vary from – 0. 7 to 4%. However, not all types of exercises provide notable stimulus to bone(96,97). Aerobic exercises such as swimming, moderate intensity walking, cycling provide insignificant improvement to bone mineral density(98–100). Simply prescribing these exercises in isolation is insufficient to optimise bone health. Bone responds positively to impact activities and high intensity progressive resistance training

(92,101). For example, a Cochrane review(39) on the effects of exercise on bone mineral density in postmenopausal women reported that exercises such as jumping, jogging or dancing results in a between group difference in favour of exercise at the hip (1.55%) but not at the lumbar spine (–1.22%). Similarly, exercises such as moderate intensity walking showed between group improvement with exercise at the lumbar spine (0.85%) but not at the femoral neck (–1.20%)(39). Yet progressive resistance exercises resulted in significant between group differences in favour of exercise at both the femoral neck (1.03%) and lumbar spine (0.86%)(39). Results from this review suggest that progressive resistance exercises may be effective in increasing bone mineral density.

Although progressive resistance exercises have been shown to increase bone mass in the general population(6,7,43,44,61,94,95,102–117), there is heterogeneity in the type, intensity, frequency and duration of exercise interventions to increase bone mineral density among many studies(42). In a longitudinal randomised trial, Allison et al(103) investigated the influence of 12 months high impact exercises on bone mineral density in 50 men. Results of the study reveal an increase of about 1.2% in bone mineral density. Similarly, Bailey et al(104) demonstrated a significant increase in BMD after 6 months of exercise in 65 women compared to 20 non-exercising women. However, in both studies, there was an increase in dropout rates with increasing number of exercise days indicating that long exercise durations could lead to exercise adherence problems.

2.6.2 Adherence to exercises

Adherence to the recommended exercise regimen is key to the success of any exercise intervention. The World Health Organisation defines adherence as "the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes –

corresponds with agreed recommendations from health care provider"(118). In exercise, adherence refers to complying with an exercise design for a specified period of time. It involves maintaining the frequency, intensity, duration and type of a given or prescribed exercise. There are reports that adherence to exercise falls below the desirable level(119,120) including among people living with HIV(121). Poor adherence is manifested through high dropout rates due to less information provided to participants on frequency, intensity and duration of the exercise(122), lack of supervision by qualified professional(119,123,124), lack of time(125,126) and long exercise durations(127). Despite these challenges, exercise yield higher adherence rates compared to pharmacological therapies in treating low bone mineral density(127).

Among the different types of exercise interventions, compliance is higher with progressive resistance exercises than aerobic exercises(128) with an adherence rate of over 80% in randomised controlled trials(129). Reports also indicate that facility based exercises with shorter durations(127) such as maximal strength exercises(6,43) have increased adherence. In addition, adherence is increased in exercise programmes that are individualised and supervised by qualified professionals(119,123,124). It is important therefore to design shorter, supervised, individualised and facility based progressive resistant exercise programmes targeting BMD in order to increase adherence.

2.7 Progressive resistance exercises and bone mineral density in HIV

Although the benefits of progressive resistance exercise such as improvements in strength, cardiovascular fitness and body composition in people living with HIV(62), effects of such exercises on bone mineral density in this population are not fully evaluated(41). Only one study by Santos et al investigating effects of progressive resistance exercise on BMD in PLWHIV was identified from the literature(130). In this study, Santos et al, demonstrated that a shorter exercise

duration of 12 weeks was appropriate to impact significant bone increases in 20 individuals living with HIV. The effectiveness of a 12 weeks' exercise duration to improve BMD is supported by evidence from studies by Mosti et al, who demonstrated the effects of a 12 weeks progressive resistance exercises in increasing BMD in young women and postmenopausal women(6,43). This evidence indicate that shorter exercise durations could as well impact bone metabolism, thereby minimising exercise adherence problems.

However, the study by Santos et al has some methodological shortcomings. The exercise design used by Santos et al, lacked other basic elements of an appropriate exercise programme to elicit improvements(131). The trial neither used non HIV infected controls nor local reference data for BMD for comparison. The Borg Scale used as a measure of exercise intensity in the study is may be biased since it is a subjective measure of exercise intensity. In addition, different types of exercises were used raising concerns of which of the exercises had a greater impact on bone mineral density. Progressive resistance exercises have been proven to be safe and beneficial in improving metabolic outcomes among PLWHIV(41,63,132,133). However, there is still lack of knowledge on the optimal mode of frequency, duration and intensity of progressive resistance exercise on BMD in people living with HIV(59,132) which requires investigation.

2.8 Methodological issues

Progressive resistance exercises have been shown to increase bone mineral density in the general population(6,7,43,44,61,94,95,102–117). However, among many studies, there is heterogeneity in the methods used to determine the effects of exercise on bone mineral density(6,7,43,44,61,94,95,102–117) with most trials conducted in either women or adult men(6,43,107). This section will discuss research designs such as randomised parallel

interventions, randomised control trial, non randomised experimental and cross sectional that have been used in most studies(94,103,109,111,130).

2.8.1 Randomised trials

Most randomised studies evaluating the effects of exercise on bone mineral density are characterised by a high rate of participants' dropout. Hinton et al(109) used a 12 months randomised parallel intervention to examine the effects of either resistance training or jump training on BMD in 75 healthy men aged between 25 to 60 years. However, the study design by Hinton and colleagues lacked other appropriate features of a well-designed randomised trial(134,135). Although results showed a significant increase in BMD in both groups the study design did not include a control group to account for unknown confounders. Out of 75 eligible participants only 58 participated in the intervention with only 36 participants completing the 12 months' period assigned for the intervention representing a 37% dropout rate.

Longer periods of exercise interventions have been implicated as leading to high dropout rates among many exercise studies(122,127). Apart from long exercise periods, factors such as less information provided to participants on frequency, intensity and duration of the exercise(122), lack of supervision by qualified professionals(119,123,124) and lack of time(125,126) also lead to poor adherence among studies examining effects of exercise on BMD. Some evidence indicate that adherence to exercise is lower than desired(119,120) even among people living with HIV(121). To effectively examine the effects of exercise on bone mineral density in PLWHIV, it is important to adopt appropriate research designs that minimize dropout rate and include a control group.

Inappropriate use of control group also affects the interpretation of accrued effects of exercise on bone mineral density. Allison et al(103) used a longitudinal randomised trial to investigate the

influence of a 12 months high impact unilateral exercise intervention on femoral neck BMD in healthy older men aged between 65 to 80 years. Unilateral exercises are defined as exercises that use one limb or body part at a time(104). In the unilateral exercise intervention, Allison and colleagues did not include a control group but used the non-exercising limb as a control. Although unilateral exercise designs are thought to minimize group confounders arising from individual differences and lifestyle modifications(104,136), the control limb may be affected by cross over effects of the exercise which may underestimate the actual effects of the intervention. Some evidence show that both unilateral and bilateral exercise are equally effective(137,138) with bilateral exercises even better among some patient groups(139). Since balance and stability is essential for exercise, bilateral exercises allow for more stability compared to unilateral exercises and could be appropriate for patient groups such as people living with HIV.

2.8.2 Cross sectional studies

Lack of an appropriate control group, small sample size and high dropout rates have been observed in most cross sectional studies investigating effects of resistance exercises on bone mineral density. Ryan and colleagues(94) determined the effects of 6 months whole-body resistive training on total and regional BMD in 17 younger men and women aged between 20 to 29 years old as well as in 20 older men and women aged 65 to 74 years old. Their results reveal an increase in femoral BMD after 6 months of resistance training. However, this study did not use age matched controls for comparison despite evidence that body composition and gender affect BMD(81). In addition, the study used a small sample size which limits appropriate generalization of the results. There was also a high dropout rate in the study partly due to lack of exercise supervision and long exercise period of 6 months. Evidence from other studies indicate that unsupervised exercises and long exercise periods lead to higher dropout rates(119,123–127).

2.8.3 Non randomised trials

Basic elements of an appropriate exercise design have been overlooked in most studies examining the effects of exercise on bone mineral density. Santos et al(130) used a non randomised experimental trial to evaluate the impact of strength training on BMD in individuals living with HIV in Brazil. To determine changes in BMD, Santos and colleagues used 12 weeks of strength training in 4 women and 16 men with reduced bone mineral density. The study demonstrated that a short period of 12 weeks may be enough to impact BMD increases in PLWHIV which could reduce adherence problem observed from longer exercise durations. However, the trial neither used non HIV infected controls nor local reference data for BMD for comparison. Although the study show increases in BMD using strength training, the exercise design used lacked other basic elements of an appropriate exercise programme as recommended by Slade et al(131). For example, the Borg Scale of Perceived Exertion, which is a subjective measure of exercise intensity, was used raising issues of biasness. In addition, different types of exercises were used raising concerns of which of the exercises had a greater impact on bone mineral density.

2.8.4 Randomised controlled trials

Appropriately designed randomised controlled studies with basic elements of an exercise design may be effective in determining the effects of exercise on BMD. Kemmler et al(111) was able to demonstrate that an appropriately designed randomised controlled trial to evaluate the effects of exercise on BMD can improve adherence and compliance among participants. Kemmler and colleagues monitored bone mineral density in 67 early postmenopausal women for 16 years(111). Their study included a control group with a clear description of exercise type, duration, frequency and intensity. Despite high adherence rate to exercise observed in this study,

the long exercise (duration) with freedom for the participants to join any arm of the study may reduce the evidence level of the trial. Although some increases in BMD were observed among participants in the exercising group, it might be difficult to detect confounders on observed BMD changes due to the long period of the exercise.

Since adherence to the recommended exercise is key to the success of the exercise intervention, it is important to develop exercise designs that minimize dropout and maximize compliance. Compliance shows to be higher with progressive resistance exercises than aerobic exercises(128). In addition, progressive resistance randomised controlled trials have a higher rate of adherence of over 80%(129). Facility based exercises with shorter durations(127) such as maximal strength exercises(6,43) have been shown to increase exercise adherence. Additionally, individualised exercise programmes that are supervised by qualified professionals increase adherence(119,123,124). It is also recommended that studies investigating effects of exercise should clearly describe the type, intensity, frequency and duration of the exercise design used(59,131). Therefore, the proposed study will adopt a randomised controlled trial to determine the effects of exercise on BMD in PLWHIV. A supervised, individualised and facility based maximal strength training exercise programme targeting BMD in people living with HIV was used. The exercise was executed three times per week for 12 weeks using 4 sets of 3–5 repetitions at an intensity of 85–90% of an individual's one repetition maximum (1 RM).

2.9 Conclusion

Most pharmacological strategies used to treat bone loss are associated with a number of adverse effects which limit their recommendation for use in PLWHIV. In addition, compliance and adherence issues associated with pharmacological strategies in treating bone loss may limit their use among PLWHIV who are already burdened by ART. Exercise based interventions such as

progressive resistance exercises seem to be an attractive safe and effective alternative strategy that could be used to manage bone loss resulting from ART in PLWHIV. Although progressive resistance exercises are effective in increasing BMD, there is lack of knowledge on the optimal frequency, intensity and duration of the exercise to impact bone which need further investigations. In addition, effects of progressive resistance exercises in increasing BMD in PLWHIV have not been fully investigated. Only one study examining the effects of progressive resistance exercise in increasing BMD among PLWHIV and receiving ART was identified from the literature. Future studies investigating the effects of progressive resistance exercises in increasing BMD in PLWHIV should adopt trial designs with clear descriptions of exercise frequency, intensity and duration.

3. METHODS

This section will present methods that were used to collect data for the study. The section provides information on study setting, study design, study population, data collection, data variables and ethical considerations. In addition, the section presents information on how data was analysed using statistical methods.

3.1 Study design

This was a cross sectional study and randomised controlled trial involving Malawian adults living with HIV and receiving ART from different healthcare facilities in Blantyre, Malawi.

3.2 Cross sectional study

3.2.1 Study setting

This study was conducted at three primary health care facilities (Limbe Health Center, Gateway Health Center and Dream Center) and one tertiary health care facility (Queen Elizabeth Central Hospital, QECH) located within Blantyre city, Malawi. The health facilities are located in four different townships of Limbe, Mandala, Chinyonga and Ginnery Corner in Blantyre (one health facility per township). Limbe Health Center, Gateway Health Center and QECH are public health facilities that run daily ART clinics for PLWHIV from the surrounding areas. Dream Center on the other hand, is a private health care facility that runs ART clinics three days of the week. All four health care facilities provide ART medication refill for PLWHIV on an out-patient basis. Each day the three public health facilities provide ART refills to approximately 50 PLWHIV, whereas Dream Center serves approximately 25 patients. All four health care facilities have medical consultants supported by nurses who provide ART services to the patients.

3.2.2 Study population

The study involved 282 male and female adults aged 18 years to 45 years and receiving ART at the four health facilities. A random sample of four from a list of 10 health facilities in Blantyre city was selected using the RANDBETWEEN function in Microsoft Excel 2016. Using consecutive sampling, a proportional sample was obtained from each facility. Data were collected from February, 2018 to March, 2019.

Patients were invited to participate and after signing informed consent, were included if they were receiving tenofovir based ART regimens for at least 12 months. Participants who had been on ART for at least 12 months were selected as reductions in BMD are more pronounced after

one year(70). Those with a history of diabetes mellitus or impaired glucose tolerance, an active acute opportunistic infection, rheumatoid arthritis, severe diarrhoea, tuberculosis within one month of commencing treatment, glucocorticoid therapy within the past six months, currently pregnant, breast feeding women, contraception medication use or known to be in renal failure, were excluded because such conditions contribute to reduced BMD(81) (Figure 4).

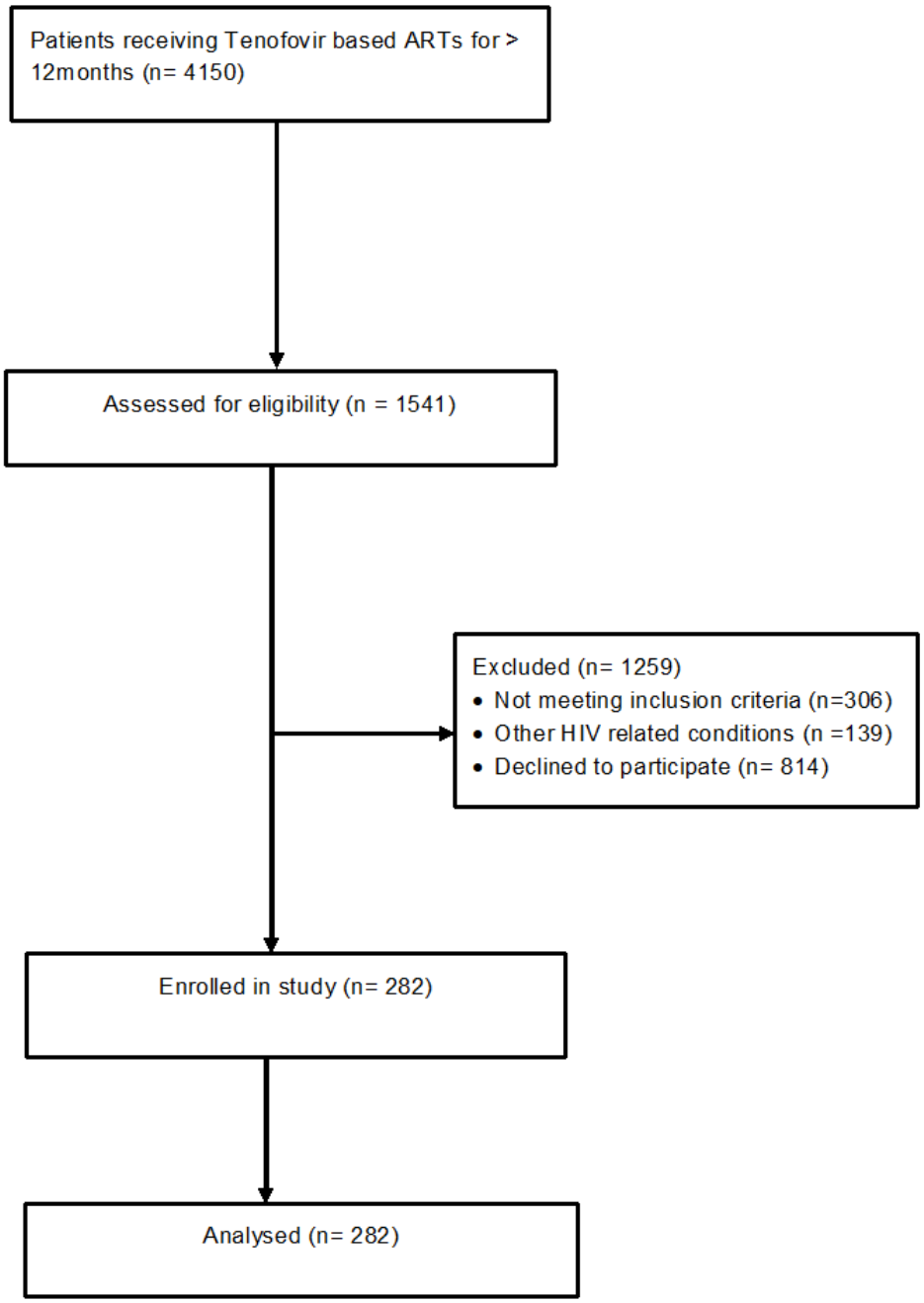

Figure 4: Study flow diagram for the cross section study

3.2.3 Data collection and tools

3.2.3 (i) Demographic data

Trained health workers obtained socio-demographic data from the recruited participants. Data on participants' information on smoking (yes/no), alcohol consumption (yes/no), calcium diet measured as milk intake more than once per week (yes/no) and traditional medication use (yes/no) was obtained using a data collection form. Data on age (years), ART duration and regimen were obtained from participants' clinical records.

3.2.3 (ii) Height and body weight

Body weight (kg) and height (cm) measurements were obtained using a Stadiometer (HS – DBS00361, Model: 1127154) following manufacturer guidelines. Body mass index (BMI) for each participant was calculated by dividing weight measurement by the square of the height measurement in meters (m^2).

3.2.3 (iii) Physical Activity

The International Physical Activity Questionnaire (IPAQ) (Appendix) was used to collect data on PA levels of the participants. The IPAQ comprised questions on frequency, intensity and duration of PA that participants do as part of their everyday life in the previous 7 days. Questions such as "During the last 7 days, on how many days did you do vigorous physical activities like heavy lifting, digging, gardening, aerobics, or fast bicycling?"; "How much time did you usually spend doing vigorous physical activities on one of those days?"; "During the last 7 days, on how many days did you do moderate physical activities like carrying light loads, bicycling at a regular pace, or participating in light sporting events?"; "How much time did you usually spend doing moderate physical activities on one of those days?" etc were asked. To ensure that the questions

in the local language (Chichewa) were conceptually equivalent with the English questions in the IPAQ, forward and backward translation was performed by independent translators. The IPAQ was proven to be a valid and reliable tool for measuring PA among adults aged 18 – 65 years in diverse settings(140).

Variable minutes spent on doing PA were recorded. The minutes were calculated into metabolic equivalents (METs). METs are defined as multiples of the resting metabolic rate ($1\ MET = 3.5ml\ O_2\ kg^{-1}\ min^{-1}$) and MET-minutes were calculated by multiplying the MET score of an activity (an equivalence of kilocalories for a 60 kg person) by the minutes performed(141).

Participants were categorized into low, moderate and high PA levels. Low level PA comprised participants having the lowest PA and did not meet the criteria for moderate or high PA levels. Moderate PA level comprised participants who did 3 or more days of vigorous PA for at least 20 minutes per day. Similarly, participants who performed 5 or more days of walking or moderate intensity PA for at least 30 minutes per day, fell into the moderate PA level category. High PA level comprised participants who performed at least 3 days of vigorous intensity PA accumulating at least 1500 MET minutes per week. Similarly, participants who performed 7 or more days of any combination of vigorous PA, moderate intensity PA or walking achieving a total of at least 3000 MET minutes per week, fell into the high PA level category.

3.2.3 (iv) Bone Mineral Density

All BMD measurements were performed at QECH. Femoral neck and lumbar spine bone mineral density was measured using DEXA [Hologic Discovery-Wi (S/N 84668), software version 13.5.3.2:5, Hologic Bedford Inc., Bedford, MA, USA]. Femoral neck BMD was measured at the left hip. Measurements of unilateral femoral neck BMD minimizes radiation exposure associated

with radiography, time, as well as medical costs(142). Lumbar spine BMD was measured from the first to the fourth lumbar spines.

Z-scores were obtained as an outcome measure of BMD. The World Health Organisation (WHO) recommends the use of Z-scores (defined as an individuals' BMD in comparison to age-matched normal individuals) in reporting BMD for premenopausal women or men less than 50 years of age, and children(143). A Z-score of −2.0 or lower is defined as low BMD for chronological age or below the expected range for age whereas a Z-score above −2.0 is within the expected range for age(89,144,145). Participants were categorised as having low BMD if the femoral neck or total lumbar spine Z-score was – 2 or less.

3.3 Randomised Controlled Trial

3.3.1 Study setting

The randomised controlled study was conducted at the College of Medicine Sports Complex in Blantyre city, Malawi. The Sports Complex houses a gym equipped with a variety of exercise training equipment and accommodates a maximum of about 20 participants per given time. It operates daily from 8.00am to 10.00pm. Different people within Blantyre city patronize the facility to engage in different exercise either for health or sports performance.

3.3.2 Study Population

Participants were recruited from Queen Elizabeth Central Hospital (QECH) in Blantyre Malawi where all BMD measurements were performed. Male and female adults aged 18 – 45 years living with HIV and receiving ART who had reduced BMD were included in the randomised controlled study. Participants with contraindications to exercise (such as serious cardiorespiratory,

neurological or orthopaedic conditions which would limit participation to the exercise regimen) were excluded.

3.3.3 Exercise Protocol

Participants were randomly allocated to either an exercise training group (TG) or control group (CG) (Figure 5). Participants in the TG followed a MST programme for 12 weeks comprising three sessions each week with a total of 36 sessions under the supervision of a qualified physiotherapist. The participants were instructed not to add any leisure exercises that included high impact jumping and lifting heavy loads during the study period. The MST sessions consisted of squat exercises performed on a hack squat machine (Model HLS2000) using the lower extremities. Before the main exercise session, participants performed a warm-up comprising two sets of 8 to 12 repetitions at approximately 50% of the participant's training load. The warm up was followed by the main exercise consisting of four sets of 3 to 5 repetitions at 85 to 90% of one repetition maximum (1RM). A break of 2 to 3 minutes was allowed between the sets. Execution of the exercise started from a straight legs position, down to a 90^{o} angle in the knee joint and up again. Participants' 1RM was re-evaluated every week to guide progression of the intensity of the exercise. Participants in the CG were instructed to keep living their usual lifestyle during the study period.

For effective supervision, each participant was scheduled his or her own time for the exercise. The physiotherapist who was supervising the exercise regimen was blinded from knowing that the participants were in a study and the purpose of the study to obtain reliable results.

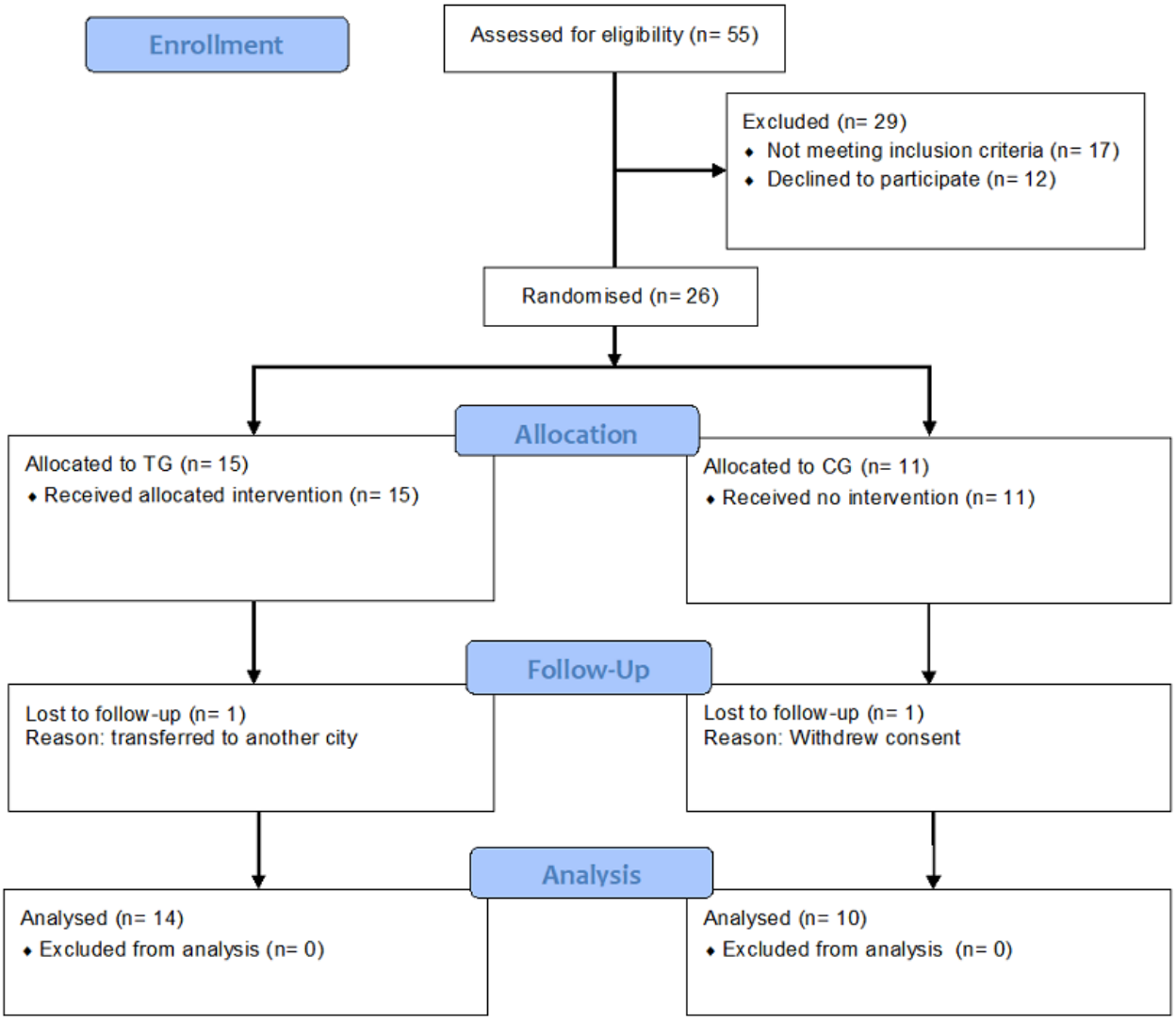

Figure 5: Study flow diagram for the randomised controlled trial

3.3.4 Data collection and equipment

Data was collected from June, 2018 to March, 2019. Variables of BMD ($g.cm^{-2}$), maximal strength, maximal oxygen uptake (VO2max), heart rate, weight, height and body mass index (BMI) were obtained and recorded on a data collection form before and after the exercise programme in the TG and the CG to determine effects of the exercise.

3.3.4 (i) Bone mineral density

Femoral neck and lumbar spine BMD ($g.cm^{-2}$) was measured using dual-energy X-ray absorptiometry (DXA) as indicated in section 3.2. 3 (iv).

3.3.4 (ii) Maximal strength

Maximal strength, obtained as 1RM was measured on the squat machine as described under the exercise protocol section. To determine 1 RM, several lifts were executed with an increasing load of 5 kg for each lift until the highest load lifted was reached.

3.3.4 (iii) Maximum oxygen uptake

Maximum oxygen uptake (VO_2max) was predicted from the Rockport one mile submaximal test(146). The Rockport one mile test procedure was described elsewhere(147).

3.3.4 (iv) Height and body

Data on height and body weight was collected as indicated in section 3.2.3 (ii)

3.3.4 (v) Heart rate

A heart rate monitor (Polar FT4, Model C317T21559445) was used to obtain heart rate measurements before and after each exercise session.

3.4 Data analysis

Data were analysed using IBM Statistical Package for the Social Sciences (SPSS) version 21. Descriptive statistics using mean and standard deviation (SD) were used to characterize age, height, weight and BMI variables. Descriptive statistics revealed that data for continuous variables were normally distributed. Student T – tests were used to analyse the differences between lumbar spine and femoral neck BMD as well as to analyse BMD differences between and within the groups. Chi – Square was used to test associations between categorical variables and BMD. Simple linear regression was used to analyse correlations between lumbar BMD and femoral neck BMD. A logistic regression model was fitted to assess effects of PA, smoking, alcohol, calcium diet and traditional medicine on low BMD. Variables for inclusion into the multivariable models were selected based on biological plausibility and those variables with $p \leq 0.20$ at bivariable level were taken for multivariable analysis. Odds ratios (OR) were obtained to quantify the probability of having low BMD. All statistical tests were two - sided and p values of ≤ 0.05 were considered statistically significant.

3.5 Ethical considerations

As participants came for refilling their ART medication, they were requested to attend a health talk regarding the purpose of the study and requesting their participation. This health talk was conducted by the researchers and the health workers at the clinic. After having their ART refill, willing participants were directed into a separate room where the aim and objectives of the study were again explained and screening for eligibility was done. Consent was obtained from eligible and willing participants. All ethical procedures were followed and privacy and confidentiality were ensured by allocating codes to the participants. The study was approved by the University

of Malawi's College of Medicine Research and Ethics Committee (COMREC) registration number P.06/17/2206. The randomised controlled study was registered with the Pan African Clinical Trial Registry on 22nd December, 2017 with identification number: PACTR201712002889203.

4. SUMMARY OF RESULTS

4.1 Paper I

This is a review paper that highlights literature gaps in strategies used to manage reduced BMD among PLWHIV and receiving ART (first publication). In this paper, evidence that most pharmacological therapies used to manage reduced BMD in PLWHIV are associated with side effects which limit their recommendation for use among PLWHIV and receiving ART is presented. The paper also reveal compliance and adherence problems associated with pharmacological therapies used to treat reduced BMD among PLWHIV. Despite evidence that progressive resistance exercises are effective in increasing BMD. The review highlights lack of knowledge on the optimal frequency, intensity and duration of resistance exercises for increasing BMD.

4.2 Paper II

In this paper, the investigated prevalence of reduced BMD among 282 PLWHIV and ART from within Blantyre, Malawi is presented. The factors associated with reduced BMD among PLWHIV and receiving ART was also analysed (second publication) and an overview of the main results is presented in Tables 1 and 2.

Table 1: Characteristics of participants in terms of age, height, weight, BMI and BMD

	Total n = 282	Male n = 102	Female n = 180	P Value
Age (yrs)	37 ± 6.4	37 ± 6.5	37 ± 6.2	0.49
Weight (kg)	60 ± 11.2	61 ± 10.2	60 ± 12.1	0.84
Height (cm)	160 ± 0.1	165 ± 0.1	158 ± 0.1	< 0.001*
BMI (kg/m^2)	23 ± 4.5	22 ± 3.3	24 ± 4.9	< 0.001*
ART duration (yrs)	5.3±3.5	5.2±3.6	5.4±3.4	0.72
BMD within expected range for age $[n(\%)]$	227 (80)	73 (72)	154 (86)	
BMD below expected range for age $[n(\%)]$	55 (20)	29 (28)	26 (14)	0.04≠

Data are in mean ± SD; BMI = body mass index; = statistically significant; ≠ = Chi-square test*

Table 2: Factors associated with low BMD (PA, Calcium, Smoking, Alcohol and Traditional medicine)

Factor		Adjusted OR	95% CI	P value
PA level				
	High	1(ref)		
	Moderate	0.87	0.41 – 1.85	0.72
	Low	1.23	0.57 – 2.67	0.6
Calcium				
	Yes	1(ref)		
	No	0.38	0.19 – 0.74	0.004
Smoking				
	No	1(ref)		
	Yes	0.57	0.13 – 2.56	0.47
Alcohol				
	No	1(ref)		
	Yes	0.88	0.33 – 2.34	0.8
Traditional Medicine				
	No	1(ref)		
	Yes	0.38	0.11 – 1.36	0.14

(ref) = reference variable

4.3 Paper III

In this paper, PA levels of 213 adult PLWHIV and receiving ART aged 18 to 45 years in Blantyre, Malawi were determined (third publication) and an overview of the main results are presented in Figures 6 and 7.

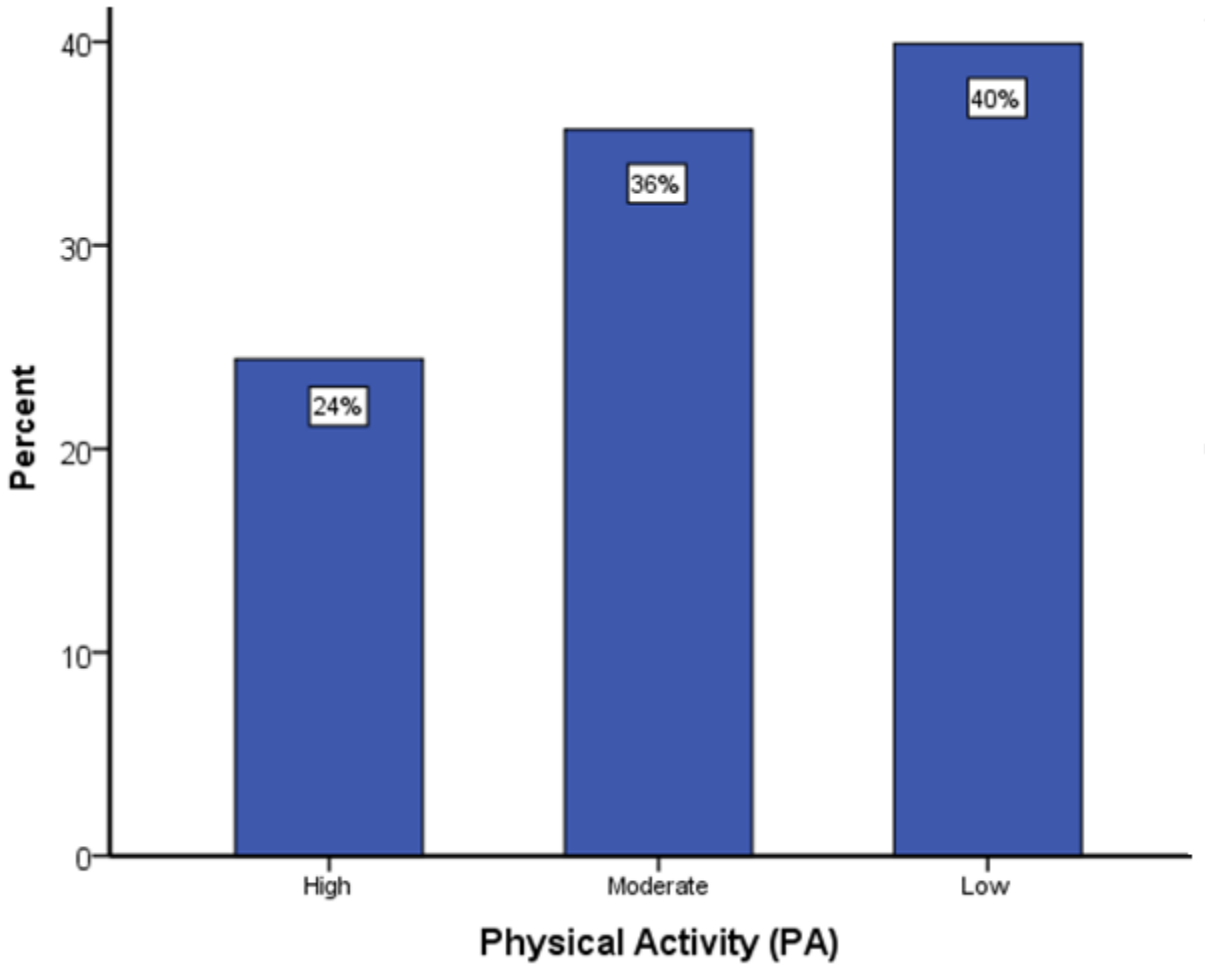

Figure 6: Physical activity (PA) levels of all participants stratified by PA categories.

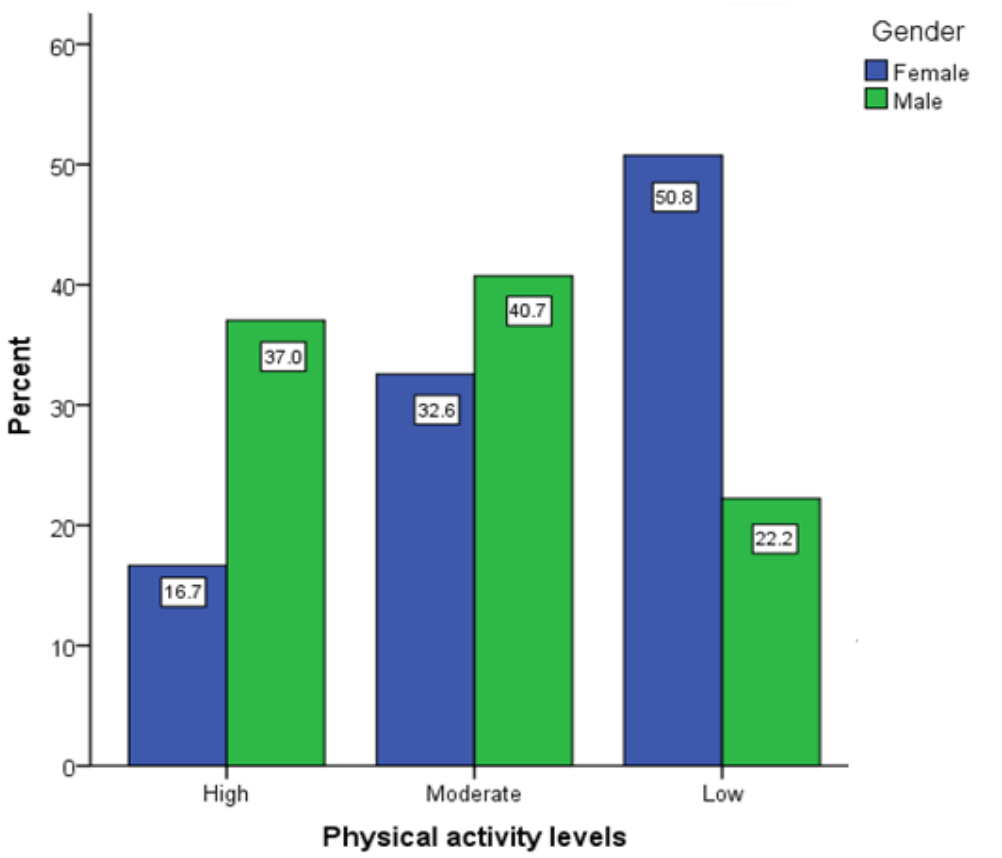

Figure 7: Physical activity (PA) levels of all participants stratified by gender.

4.4 Paper IV

In this paper, the effects of maximal strength training on reduced BMD among 26 PLWHIV and receiving ART in Blantyre, Malawi were analysed (fourth manuscript). An overview of the main results is provided in Table 3.

Table 3: Changes in physiological parameters before and after exercise intervention

	TG (n = 14)		CG (n = 10)	
	Pre-training	Post-training	Pre-training	Post-training
Femoral neck BMD ($g.cm^{-2}$)	0.770 ± 0.109	0.778 ± 0.102	0.772 ± 0.092	0.786 ± 0.098
Lumbar spine BMD ($g.cm^{-2}$)	0.771 ± 0.074	0.804 ± 0.060*	0.774 ± 0.066	0.780 ± 0.068
1 RM (kg)	106.79 ±31.4	222.14 ± 43.2*	110.70 ± 34.8	123.00 ± 33.2
VO_2max ($ml.kg^{-1}min^{-1}$)	45.83 ± 9.7	48.40 ±9.6	40.30 ± 13.1	40.12 ± 9.8
Heart rate (bpm)	87.00 ±16.4	78.86 ± 11.2*	74.30 ± 13.7	76.20 ± 10.3

*Data are presented as mean ± SD, TG = Training group, CG = Control group, bpm = beats per minute, * Significant difference $p<0.05$.*

5. DISCUSSION

This thesis presents the prevalence of reduced BMD as well as factors associated with reduced BMD in people living with HIV and receiving ART in Blantyre, Malawi. The evidence is based on analyses of results from a cross sectional study involving PLWHIV in Blantyre, Malawi. This section also presents evidence on the effects of strength exercises on BMD among people living with HIV. The evidence is based on analyses of a randomised controlled trial of adult Malawians

living with HIV and receiving ART in Blantyre, Malawi. This section will present a discussion of the results of the cross sectional study investigating prevalence and associated factors of reduced BMD in PLWHIV and the randomised controlled trial exploring the effects of MST on BMD in PLWHIV.

5.1 Prevalence and associated factors of reduced bone mineral density

Findings of the cross sectional investigation reveal a high prevalence of reduced BMD among PLWHIV and receiving ART in Malawi. Findings also show that low PA level is associated with reduced BMD. Although higher prevalence rates in reduced BMD among PLWHIV have been reported by some studies(11,29,34,148), a slightly lower prevalence in reduced BMD similar to findings of this study was reported by Cardeal *et al* (2017) among PLWHIV in Brazil(149). Lower prevalence rates in reduced BMD revealed by the current findings could be attributed to the younger age group of study participants which ranged from 18 years to 45 years with an average age of 37 years. Contrary to current findings, studies reporting higher prevalence in reduced BMD among PLWHIV and receiving ART recruited participants older than 45 years whose BMD may have more decreases. The normal bone growth trajectory show that bone mass increases with age and reaches its peak between ages 25 and 30 years after which bone mass starts to decrease (48). Normal decreases in bone mass range from 0.3 to 0.5% for a decade after the age of 30 years in both females and (50,52). However, there are more decreases in BMD between ages 45 to 55 due to effects of menopause and thereafter reduction in BMD is gradual and similar to the bone decreases among males (52). Hence a lower prevalence in reduced BMD revealed in the current findings may be explained by expected bone strength associated with the young age of the participants.

Contrary to bone physiology which indicate that males have stronger bones than females due to the body's response to hormonal changes and variations in skeletal muscles mass (150,151), current results show that more males had reduced BMD than females despite having similar body weights. Most of the reductions were observed at the lumbar spine. Although a study by Erlandson *et al* (2018) has reported reductions in BMD twice as quickly among women living with HIV compared to men living with HIV, their study included female participants who were in menopause thus having more BMD decreases compared to males(152). Evidence on bone physiology reveal that noticeable reductions in BMD among women after menopause is attributed to pronounced decreases in in oestrogen (150). Findings from our study are not in line with those of Erlandson *et al*, since none of the female participants was in menopause. Pronounced reductions in BMD at the lumbar spine in the current study could be attributed to physical activities of most Malawian female adults. Most females in Malawi carry heavy loads on their heads as opposed to males which may likely impact the lumbar spine leading to more bone mass in the lumbar spine. Sexual activities could also have an impact on lumbar bone mass in females as most Malawian cultures encourage females to wriggle their waist during sex which may lead to stronger lumbar bones.

In line with other studies (153,154) the current study reveals a positive and significant correlation between femoral neck and lumbar BMD. This suggests that femoral neck BMD may predict femoral neck BMD among Malawians living with HIV and receiving ART.

Results from the current study show greater decreases in lumbar BMD compared to femoral neck BMD. This is contrary to some investigations among PLWHIV that have reported greater decreases in femoral BMD compared to lumbar BMD (36,148,152). This is likely since studies reporting more bone mass loss in the femoral neck than the lumbar spine were conducted among

the western populations whose PA lifestyles are diferent from those of sub Saharan Africa populations. Bone strength also depends on mechanical loading, hence PA lifestyle of an individual of an individual may either increase or reduce BMD(50). In the current study, more reductions in bone strength in the lumbar spine could be explained by the PA of Malawians such as long distance walking to work places (155) which loads mostly the femoral neck thereby increasing its bone mass.

Results of the current study also reveal a likely occurence of bone loss among participants with low levels of PA. This likelihood is supported by evidence which demonstrates that low PA level has a negative impact on BMD(40). In addition, PA is recommended as an important componemt in the guidelines for good bone health among PLWHIV (91). In line with this recommendation, significant improvements in BMD among 20 PLWHIV were demonstrated by Santo et al (2015) after participants participated in strength exercise for 12 weeks(130). This idicates that PA plays a role in increasing BMD among PLWHIV. Findings from the current study supports evidence that promotes consideration of PA as an intervention for increasing reduced BMD in PLWHIV.

Being the first in Malawi, the current study adds to the body of knowledge on prevalence of reduced BMD among PLWHIV in resource limited settings. The study also provides valuable information on factors affecting bone health among Malawian adults living with HIV and receiving ART. However, due to lack of BMD data on large age related healthy African cohorts that could be used for reference, the study used the United States National Health and Nutrition Examination Survey reference data for comparisons. This may influence interpretation of current BMD data within the sub Saharan Africa region. Therefore, future studies investigating BMD in Malawi should consider using local non-infected controls for comparison.

5.2 Physical activity levels of people living with HIV and receiving ART

Results of the study on levels of PA among PLWHIV and receiving ART from Blantyre, Malawi are contrary to the WHO recommendations for PA (156). Guideline on PA by WHO recommend weekly aerobic PA of 75 minutes of vigorous intensity or 150 minutes of moderate intensity for adults of ages between 18–64 years (156). In addition to aerobic PA, WHO also recommends 2 or more days of strengthening activities that work on all major muscle groups per week (156). Current findings reveal that a considerable proportion of PLWHIV that had low PA levels and fall below the WHO recommendations. Current findings are in agreement with many studies that have shown decreased PA levels among PLWHIV and receiving ART (157–161). Reduced levels of PA among PLWHIV and receiving ART have been attributed to opportunistic infections, depression and body pains by other authors (162). However, in the current study, PLWHIV and receiving ART with opportunistic infections were excluded. Therefore, low levels of PA revealed in the current study may have resulted from depression and body pain. It should be noted nonetheless that depression and body pains were not investigated in this study, hence the foregoing suggestion should be taken with caution.

Aging has also been shown to lead to reduced levels of PA among PLWHIV and receiving ART (157). Nonetheless, the current study recruited young adults aged between 18 and 45 years suggesting that reduced levels of PA in the participants may not be attributed to aging. Our findings are in line with results from a study by Frantz et al who reported found lower levels of PA among most of the younger individuals aged between 15 to 4 years living with HIV and receiving ART in Rwanda (160). Lower levels of PA among a young population is cause of concern owing to the fact that PA levels tend to decrease as one is aging (163,164). In a society, young adults are a productive age group hence having reduced levels of PA negatively impacts

their participation in daily activities thereby lowering their economic contribution to the country and health benefits.

Consistent with other studies (165–167), more male participants had high PA levels compared to female participants in the current study. Higher levels of PA among the male Malawian participants could be explained by the large percentage of males involved in agriculture operations and manual labour. Agricultural operations and manual labour demand considerable physical capacity which lead to high PA levels. In addition, most Malawian males walk long distances to work thereby increasing their PA levels. Further, a majority of Malawian males are employed in industries where their work involves among others pushing heavy levers which in turn impact their physical capacity as well.

Contrary to findings by Frantz et al, who reported low PA levels in participants who were on ART for more than 4 years in Rwanda (160), the current study found similar proportions of participants with low PA levels who were on ART for 1 to 3 years and those on ART for over 3 years. These opposing results could be attributed to differences in the age range of the participants in the two studies. Frantz et al, included participants who were aged between 18 to 75 years in their study while the current study included participants who were in the age group between 18 to 45 years. Therefore, similar proportions of participants with low PA levels in the current study could be due to their young age since lower PA levels are shown to be associated with older age (162).

5.3 Effects of maximal strength training on bone mineral density in people living with HIV and receiving ART

Results of the effects of maximal strength training on BMD reveal improvements in BMD among PLWHIV and receiving ART after 12 weeks of training. Notable improvements in muscle strength among the participants were also observed after 12 weeks of the intervention. Current findings are consistent with findings from a study by Santos et al (2015), who demonstrated that progressive exercise programmes performed for 12 weeks are appropriate in improving BMD among PLWHIV and receiving ART (168). Although some evidence indicate that all physical activity is appropriate in improving BMD (90), weight bearing physical activities that use high load yield notable improvements in BMD (39). The use of high load weight bearing exercise to improve BMD is supported by evidence which indicate that high mechanical loading stimulate bone response by acting on muscles and ground reaction forces which lead to osteogenic differentiation of mesenchymal stem cells to osteoblasts (169). High loads of weight bearing such as those used in MST are more likely to lead to an osteogenic response which triggers a higher mechanostat thresholds (170). Evidence from the current study suggests that MST promote improvements in BMD among PLWHIV on ART and could therefore be used to avert the risk for osteoporosis among this patient population.

Concurrent with previous investigations (94,109,111), the current study has demonstrated significant increases in BMD after 12 weeks of MST. Such significant improvement could be attributed to the high intensity of load bearing and emphasis on progressive loading identical of MST. Re-evaluation of the training was done every week throughout the 12 weeks' intervention period to ensure progressive loading. Progressive loading enhances mechanical stress in the bones and regulates remodeling via osteoblasts (169). Furthermore, reports indicate that exercise

interventions done for over three months lead to increased dropout rates (122,127) suggesting that shorter exercise durations may be effective. In the current study, adherence rate was 93% in the TG and 90% in the CG whereas there was 100% compliance rate in both the TG and CG with all participants reaching the study end line. Therefore, MST which uses a short exercise duration of 12 weeks could be an attractive and alternative management intervention for reduced BMD among PLWHIV.

In line with previous findings (6,43), the current study has revealed significant increases in muscle strength after 12 weeks of MST. As opposed to conventional ways of strength training that emphasies low loads and more receptions, MST uses high loads and few repetitions which focus on increased acceleration in the concentric phase which in turn leads to increased late of force development thereby increasing muscle strength (43). However, while significant improvements in strength were observed in the TG only in the study by Mosti et al (2013)(43), findings of the current study reveal significant improvements in strength in both the TG and CG as observed by increases in 1RM. Although both groups showed significant strength improvements, more improvements were exhibited by participants in the TG. Noteworthy increases in strength in the CG as well in the present study could be explained by occupational activities of most Malawian adults or other undetermined reasons which the current study may not have explored. A reasonable explanation to significant improvements in strength in both groups could be due to the period of data collection or other undetermined reasons. Data for the study was collected between the months of June 2018 and March 2019 which is the farming period in Malawi. Most Malawians are involved in farming during the said data collection period. Hence farming activities such as land preparation, planting and harvesting demand a considerable physical capacity.

Concurrent with other studies(63), notable improvements in heart rate were observed in the current study. O'Brien et al (2008) reported a reduction in heart rate of – 13.2 bpm for participants in the TG in a meta-analysis of randomised controlled trials. The current study has revealed an almost similar reduction in heart rate (– 8.14 bpm) suggesting that MST has an impact on some cardiopulmonary parameters among PLWHIV.

To the best of our knowledge, this is the first randomised controlled trial that has evaluated the effects of MST exercises with focus on BMD as the main outcome in PLWHIV. A supervised, individualised and facility based MST exercise programme targeting BMD with clear descriptions of exercise type, frequency, intensity and duration was adopted. This study provides preliminary data that allows potential for larger prospective studies on effective exercise strategies used to manage reduced BMD among PLWHIV. A limitation of the study was a relatively low sample size. However, based on results from previous studies(43,168), the number of participants in the current study was appropriate to determine effectiveness of a MST programme on bone and strength parameters as revealed in the findings. Another limitation of the study was the lack of a longer follow up after the three months' intervention to determine how long the exercise benefits on BMD would last. Therefore, future studies should consider following up participants to assess whether the BMD increases obtained after the three months' intervention are maintained.

6. CONCLUSIONS AND RECOMMENDATIONS

Reduced BMD is prevalent among Malawian adults living with HIV and receiving ART in Blantyre, Malawi. Among those with reduced BMD, males have more bone loss than females with most of the bone loss observed at the lumbar spine. These results suggest that adult Malawian males living with HIV and receiving tenofovir based ART are at a higher risk for stress and osteoporotic fractures than females living with HIV and receiving tenofovir based ART. The occurrence of reduced BMD was more likely in those PLWHIV who had low PA level. A larger number of people living with HIV and receiving ART within Blantyre, Malawi have low PA levels. A similar proportion of PLWHIV to those with low PA levels is moderately physically active. Furthermore, a larger number of females living with HIV in Blantyre, Malawi have low PA levels compared to males. There is need therefore for health care providers to routinely monitor BMD and PA level of PLWHIV.

A twelve-week exercise programme of MST improves BMD, muscle strength and some cardiorespiratory parameters measured by heart rate in PLWHIV on ART with reduced BMD in Blantyre, Malawi. Results from the current research project suggest that MST has the potential in treating reduced BMD among PLWHIV on ART. Therefore, MST seems to be a cost effective non pharmacological alternative therapy for the management of osteopaenia and osteoporosis among PLWHIV. Future studies should consider using a larger sample size and including a long following up for participants to assess whether the BMD increases obtained after MST are maintained.

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8. REFERENCES

1. Matovu FK, Wattanachanya L, Beksinsk M, Pettifor JM, Ruxrungtham K. Bone health and HIV in resource-limited settings: a scoping review. Curr Opin HIV AIDS [Internet]. 2016;11(3):306–25. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27023284
2. Linda A, Young B, Overton E. Bone, Fractures, Antiretroviral Therapy and HIV. Curr Infect Dis Repos. 2015;16(2):1–10.
3. Pramukti I, Lindayani L, Chen Y, Yeh C, Tai T, Susan F, et al. Bone fracture among people living with HIV : A systematic review and meta-regression of prevalence , incidence , and risk factors. PLoS One [Internet]. 2020;9:1–14. Available from: http://dx.doi.org/10.1371/journal.pone.0233501
4. Grant PM, Cotter AG. Tenofovir and bone health. Curr Opin HIV AIDS. 2016;11(3):326–32.
5. Young B, Dao CN, Buchacz K, Baker R, Brooks JT. Increased rates of bone fracture among HIV-infected persons in the HIV outpatient study (HOPS) compared with the US general population, 2000-2006. Clin Infect Dis. 2011;52(8):1061–8.
6. Mosti M, Carlsen T, Aas E, Hoff J, Stunes A, Syversen U. Maximal Strength Training Improves Bone Mineral Density and Neuromuscular Performance in Young Adult Women. J Strength Cond Res. 2014;28(10):2935–45.
7. Multanen J, Nieminen MT, Häkkinen A, Kujala UM, Jämsä T, Kautiainen H, et al. Effects of High - Impact Training on Bone and Articular Cartilage: 12 - Month Randomised Controlled Quantitative MRI Study. J Bone Miner Res. 2015;29(1):192–201.
8. Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. AIDS [Internet]. 2006;20(17):2165–74. Available

from: http://www.ncbi.nlm.nih.gov/pubmed/17086056

9. Ali MK, Magee MJ, Dave JA, Ofotokun I, Tungsiripat M, Jones TK, et al. HIV and Metabolic , Body , and Bone Disorders : What We Know From Low- and Middle-Income Countries. J Acquir Immune Defic Syndr. 2014;67(Supp 1: September):27–39.

10. Ameet D, Milind K, B A, Sachin D. Prevalence of low bone mineral density among HIV patients on long-term suppressive antiretroviral therapy in resource limited setting of western India. J Int AIDS Soc. 2014;17(November):17–8.

11. Alonge T, Okoje-Adesomoju V, Atalabi O, Obamuyide H, Olaleye D, Adewole I. Prevalence of abnormal bone mineral density in HIV-positive patients in ibadan, Nigeria. J West African Coll Surg. 2013;3(4):1–14.

12. Brown TT, Moser C, Currier JS, Ribaudo HJ, Rothenberg J, Kelesidis T, et al. Changes in bone mineral density after initiation of antiretroviral treatment with Tenofovir Disoproxil Fumarate/Emtricitabine Plus Atazanavir/Ritonavir, Darunavir/Ritonavir, or Raltegravir. J Infect Dis. 2015;212(8):1241–9.

13. McComsey GA, Kitch D, Daar ES, Tierney C, Jahed NC, Tebas P, et al. Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: AIDS Clinical Trials Group A5224s, a substudy of ACTG. J Infect Dis. 2011;203(12):1791–801.

14. World Health Organisation. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. In: Guidelines. 2013. p. 1–269.

15. World Health Organisation. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: What's New. In: Policy Brief. 2015. p. 1–16.

16. Malawi Government. Global AIDS Response Progress Report (GARPR): Malawi Progress Report for 2013. 2014.

17. Fleming B, Greenfield S, Engelgau M, Pogach L, Clauser S, Parrot M. The Diabetes Quality Improvement Project. Diabetes Care. 2001;24(10):1815–20.

18. Brown TT. Challenges in the Management of Osteoporosis and Vitamin D Deficiency in HIV Infection. Top Antivir Med. 2013;21(3):115–8.

19. Fan T, Zhang Q, Sen SS. Persistence with weekly and monthly bisphosphonates among postmenopausal women: Analysis of a US pharmacy claims administrative database. Clin Econ Outcomes Res. 2013;5(1):589–95.

20. Solomon DH, Avorn J, Katz JN, Finkelstein JS, Arnold M, Polinski JM, et al. Compliance With Osteoporosis Medications. Arch Intern Med [Internet]. 2005;165(20):2414–9. Available from: http://archinte.ama-assn.org/cgi/content/abstract/165/20/2414

21. Ali MK, Magee MJ, Dave JA, Ofotokun I, Tungsiripat M, Jones TK, et al. HIV and Metabolic, Body, and Bone Disorders: What We Know From Low- and Middle-Income Countries. J Acquir Immune Defic Syndr [Internet]. 2014;67(Supp 1):S27-39. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25117959

22. Harris V, Brown. T. Bone loss in the HIV-infected patient: Evidence, clinical implications, and treatment strategies. J Infect Dis. 2012;205(SUPPL. 3):391–8.

23. Kendler DL, Roux C, Benhamou CL, Brown JP, Lillestol M, Siddhanti S, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women transitioning from alendronate therapy. J Bone Miner Res. 2010;25(1):72–81.

24. Sellmeyer DE. Atypical Fractures as a Potential Complication of Long-term Bisphosphonate Therapy. JAMA. 2010;304(13):1480–4.

25. Brien KO, Tynan A, Nixon S, Glazier RH, Tynan A, Nixon S, et al. Effects of progressive resistive exercise in adults living with HIV / AIDS : systematic review and meta- analysis of randomized trials. AIDS Care. 2015;20(6):631–53.

26. Batty, D & Lee M. Physical activity and coronary heart disease. Br Med J. 2004;328:1089–90.

27. Powell, K & Pratt C. Physical activity and health: Avoiding the short and miserable life. Br Med J. 1996;313(JuLY):126–7.

28. Ramírez-marrero FA, Smith BA, Meléndez-brau N, Santana-bagur JL. Physical and Leisure Activity , Body Composition , and Life Satisfaction in HIV-Positive Hispanics in Puerto Rico. JANAC. 2004;15(4):68–77.

29. Chitu-Tisu CE, Barbu EC, Lazar M, Ion DA, Badarau IA. Low bone mineral density and associated risk factors in HIV-infected patients. GERMS [Internet]. 2016;6(2):50–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27482514

30. Escota G V, Mondy K, Bush T, Conley L, Brooks JT, Nur O, et al. High Prevalence of Low Bone Mineral Density and Substantial Bone Loss over 4 Years Among HIV-Infected Persons in the Era of Modern Antiretroviral Therapy. AIDS Res Hum Retroviruses. 2016;32(1):59–67.

31. Hamill MM, Pettifor JM, Ward KA, Norris SA, Prentice A. Changes in Bone Mineral Density , Body Composition , HIV-Positive South African Women Over 12 Months. J Bone Miner Res. 2017;32(8):1615–24.

32. Mirembe BG, Kelly CW, Mgodi N, Greenspan S, Dai JY, Mayo A, et al. Bone Mineral Density Changes Among Young, Healthy African Women Receiving Oral Tenofovir for HIV Preexposure Prophylaxis. J Acquir Immune Defic Syndr [Internet]. 2016;71(3):287–

94. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00126334-201603010-00007

33. Gallagher JC, Sai AJ. Vitamin D Insufficiency , Deficiency , and Bone Health. J Clin Endocrinol Metab. 2010;95(June):2630–3.

34. Dravid A;, Kulkarni M, Borkar A, Dhande, Sachin. Prevalence of low bone mineral density among HIV patients on longterm suppressive antiretroviral therapy in resource limited setting of western India. J Int AIDS Soc. 2014;17(November):17–8.

35. Masyeni S, Utama S, Somia A, Widiana R, Merati TP. Factors influencing bone mineral density in ARV-naive patients at Sanglah Hospital, Bali. Indones J Intern Med [Internet]. 2013;45(3):175–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24045386

36. Zhang L, Su Y, Hsieh E, Xia W, Xie J, Han Y, et al. Bone turnover and bone mineral density in HIV-1 infected Chinese taking highly active antiretroviral therapy -a prospective observational study. BMC Musculoskelet Disord. 2013;14:224.

37. Shahar E, Segal E, Rozen GS, Shen-Orr Z, Hassoun G, Kedem E, et al. Vitamin D status in young HIV infected women of various ethnic origins: Incidence of vitamin D deficiency and possible impact on bone density. Clin Nutr [Internet]. 2013 Feb;32(1):83–7. Available from: http://www.sciencedirect.com/science/article/pii/S0261561412001227

38. World Health Organisation. Global Health Sector Response To HIV , 2000 – 2015: Focus on Innovations. Progress report. 2015.

39. Howe TE, Shea B, Dawson LJ, Downie F, Murray A, Ross C, et al. Exercise for preventing and treating osteoporosis in postmenopausal women. Cochrane Database Syst Rev. 2011;(7):1–112.

40. Perazzo JD, Webel AR, Alam SMK. Relationships Between Physical Activity and Bone Density in People Living with HIV : Results from the SATURN-HIV Study', Journal of the Association of Nurses in AIDS Care. J Assoc Nurses AIDS Care [Internet]. 2018;29(4):528–37. Available from: https://doi.org/10.1016/j.jana.2018.03.004

41. Grace JM, Semple SJ, Combrink S. Exercise therapy for human immunodeficiency virus/AIDS patients: Guidelines for clinical exercise therapists. J Exerc Sci Fit [Internet]. 2015;13(1):49–56. Available from: http://dx.doi.org/10.1016/j.jesf.2014.10.003

42. Bolam KA, Van Uffelen JGZ, Taaffe DR. The effect of physical exercise on bone density in middle-aged and older men: a systematic review. Osteoporos Int. 2013;24(11):2749–62.

43. Mosti M, Nils K, Stunes A, Hoff J, Syversen U. Maximal Strength Training in Postmenopausal Women with Osteoporosis or Osteopenia. J Strength Cond Res. 2013;27(10):2879–86.

44. Watts NB, Adler RA, Bilezikian JP, Drake MT, Eastell R, Orwoll ES FJ, Watts NB, Adler RA, Bilezikian JP, Drake MT, Eastell R, et al. Osteoporosis in men: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab [Internet]. 2012;97(6):1802–22. Available from: http://dx.doi.org/10.1210/jc.2011-3045

45. McComsey GA, Tebas P, Shane E, Yin MT, Overton ET, Huang JS, et al. Bone Disease in HIV Infection: A Practical Review and Recommendations for HIV Care Providers. Clin Infect Dis [Internet]. 2010;51(8):937–46. Available from: https://academic.oup.com/cid/article-lookup/doi/10.1086/656412

46. Sharp M. HIV and bone health. BETA [Internet]. 2011;23:28–37. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L364820538

47. Marieb EN, Hoehn K. Human Anatomy & Physiology. 7th ed. Pearson; 2007. 175-201 p.

48. Seeman E, Delmas PD. Bone quality--the material and structural basis of bone strength and fragility. N Engl J Med. 2006;354(21):2250–61.

49. Ross MH, Wojciech P. Histology: A text and Atlas. 6th ed. London: Lippincott Williams and Wilkins; 2011. 250-251 p.

50. Kruger MJ, Nell TA. Bone mineral density in people living with HIV: a narrative review of the literature. AIDS Res Ther [Internet]. 2017;14(35):1–17. Available from: http://aidsrestherapy.biomedcentral.com/articles/10.1186/s12981-017-0162-y

51. Lorentzon M, Mellstrom D, Ohlsson C. Age of attainment of peak bone mass is site specific in Swedish men--The GOOD study. J Bone Miner Res. 2005;20(7):1223–7.

52. Baxter-Jones ADG, Faulkner RA, Forwood MR, Mirwald RL, Bailey DA. Bone mineral accrual from 8 to 30 years of age: An estimation of peak bone mass. J Bone Miner Res. 2011;26(8):1729–39.

53. Chisati EM, Constantinou D, Lampiao F. Management of reduced bone mineral density in HIV: Pharmacological challenges and the role of exercise. Front Physiol. 2018;9(AUG).

54. Dimai HP. Use of dual-energy X-ray absorptiometry (DXA) for diagnosis and fracture risk assessment; WHO-criteria, T- and Z-score, and reference databases. Bone [Internet]. 2016;1–5. Available from: http://dx.doi.org/10.1016/j.bone.2016.12.016

55. Stepan JJ. Techniques for measuring bone mineral density. Int Congr Ser 1229. 2002;1229:63 – 68.

56. Blake GM, Fogelman I. The clinical role of dual energy X-ray absorptiometry. Eur J Radiol. 2009;71(3):406–14.

57. Caspersen CJ, Powell KE, Christenson GM. Physical Activity , Exercise , and Physical

Fitness : Definitions and Distinctions for Health-Related Research. Public Health Rep. 1985;100(2):126–31.

58. Oberg E. Physical activity prescription: our best medicine. Integr Med. 2007;6(5):18–22.

59. Grace JM. Exercise Therapy for Acquired Immune Deficiency Syndrome (AIDS) Patients. In: Fitness Medicine. 2016. p. 129–45.

60. McArdle W, Katch F K V. Exercise physiology: Nutrition, energy, and human performance. 8th Edition. Philadelphia: Lippincott Williams & Wilkins. 2015. 477 p.

61. Ciccolo JT, Carr LJ, Krupel KL, Longval JL. The Role of Resistance Training in the Prevention and Treatment of Chronic Disease. Am J Lifestyle Med [Internet]. 2010;4(4):293–308. Available from: http://ajl.sagepub.com/cgi/content/abstract/1559827609354034v1

62. O'Brien KK, Tynan A, Nixon SA, Glazier RH. Effectiveness of Progressive Resistive Exercise (PRE) in the context of HIV: systematic review and meta-analysis using the Cochrane Collaboration protocol. BMC Infect Dis [Internet]. 2017;17(268):1–23. Available from: http://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-016-1478-2

63. O'Brien K, Tynan A-M, Nixon S, Glazier RH. Effects of progressive resistive exercise in adults living with HIV/AIDS: systematic review and meta-analysis of randomized trials. AIDS Care [Internet]. 2008;20(6):631–53. Available from: http://www.tandfonline.com/doi/full/10.1080/09540120701661708

64. O'Brien K. K, Tynan A-M, Nixon SA, Glazier RH. Effectiveness of aerobic exercise for adults living with HIV: systematic review and meta- analysis using the Cochrane Collaboration protocol. Vol. 16, BMC infectious diseases. BMC Infectious Diseases;

2016. 182 p.

65. Michie S, Stralen MM Van, West R. The behaviour change wheel : A new method for characterising and designing behaviour change interventions. Implement Sci. 2011;6(42):1–11.

66. De Silva MJ, Breuer E, Lee L, Asher L, Chowdhary N, Lund C, et al. Theory of Change: a theory-driven approach to enhance the Medical Research Council ’s framework for complex interventions. BioMed Cent Trials. 2014;15(267):1–12.

67. Craig P, Dieppe P, Macintyre S, Mitchie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions : the new Medical Research Council guidance. BMJ. 2008;337(October):979–83.

68. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions : The new Medical Research Council guidance. Int J Nurs Stud [Internet]. 2013;50(5):587–92. Available from: http://dx.doi.org/10.1016/j.ijnurstu.2012.09.010

69. Güerri-Fernandez R, Vestergaard P, Carbonell C, Knobel H, Avilés FF, Castro AS, et al. HIV Infection Is Strongly Associated With Hip Fracture Risk, Independently of Age, Gender, and Comorbidities: A Population-Based Cohort Study. J Bone Miner Res. 2013;28(6):1259–63.

70. Duvivier C, Kolta S, Assoumou L, Ghosn J, Rozenberg S, Murphy RL, et al. Greater decrease in bone mineral density with protease inhibitor regimens compared with nonnucleoside reverse transcriptase inhibitor regimens in HIV-1 infected naive patients. AIDS. 2009;23(7):817–24.

71. Chew NS, Mcconkey S, Lambert J, Sheehan G, Powderly WG. Traditional risk factors do

not predict osteoporosis in HIV patients. J Int AIDS Soc. 2008;11(Suppl 1):109.

72. Bonjoch A, Figueras M, Estany C, Perez-Alvarez N, Rosales J, del Rio L, et al. High prevalence of and progression to low bone mineral density in HIV-infected patients: a longitudinal cohort study. AIDS [Internet]. 2010;24(18):2827–33. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00002030-201011270-00009

73. Navarro MC, Sosa M, Saavedra P, Lainez P, Marrero M, Torres M, et al. Poverty is a risk factor for osteoporotic fractures. Osteoporos Int [Internet]. 2009;20(3):393–8. Available from: http://dx.doi.org/10.1007/s00198-008-0697-9

74. Ofotokun I, Titanji K, Vunnava A, Roser-Page S, Vikulina T, Villinger F, et al. Antiretroviral therapy induces a rapid increase in bone resorption that is positively associated with the magnitude of immune reconstitution in HIV infection. AIDS. 2016;30(3):405–14.

75. Ofotokun I, McIntosh E, Weitzmann MN. HIV: Inflammation and Bone. Curr HIV/AIDS Rep [Internet]. 2012;9(1):16–25. Available from: http://dx.doi.org/10.1007/s11904-011-0099-z

76. Battalora L, Young B, Overton E. Bone, Fractures, Antiretroviral Therapy and HIV. Curr Infect Dis Rep. 2014;16(2):1–10.

77. Grant PM, Kitch D, McComsey GA, Dube MP, Haubrich R, Huang J, et al. Low baseline CD4+ count is associated with greater bone mineral density loss after antiretroviral therapy initiation. Clin Infect Dis. 2013;57(10):1483–8.

78. Lee J, Hoshino A, Inoue K, Saitou T, Uehara S, Kobayashi Y, et al. The HIV co-receptor CCR5 regulates osteoclast function. Nat Commun [Internet]. 2017;8(2226):1–16.

Available from: http://dx.doi.org/10.1038/s41467-017-02368-5

79. Kaul R, Prodger J, Joag V, Shannon B, Yegorov S, Galiwango R, et al. Inflammation and HIV Transmission in Sub-Saharan Africa. Curr HIV/AIDS Rep. 2015;12(2):216–22.

80. Kaul R, Cohen CR, Chege D, Yi TJ, Tharao W, McKinnon LR, et al. Biological Factors that May Contribute to Regional and Racial Disparities in HIV Prevalence. Am J Reprod Immunol. 2011;65(3):317–24.

81. Pinto Neto LFS, Ragi-Eis S, Vieira NFR, Soprani M, Neves MB, Ribeiro-Rodrigues R, et al. Low Bone Mass Prevalence, Therapy Type, and Clinical Risk Factors in an HIV-Infected Brazilian Population. J Clin Densitom. 2011;14(4):434–9.

82. Aydin OA, Karaosmanoglu HK, Karahasanoglu R, Tahmaz M, Nazlican O. Prevalence and risk factors of osteopenia/osteoporosis in Turkish HIV/AIDS patients. Brazilian J Infect Dis [Internet]. 2013;17(6):707–11. Available from: http://dx.doi.org/10.1016/j.bjid.2013.05.009

83. Lima AL, de Oliveira PR, Palpler PG, Marcolino FMD, Meirelles E, Sugawara A, et al. Osteopenia and osteoporosis in people living with HIV : multiprofessional approach. HIV/AIDS - Res Palliat Care. 2011;3(December):117–24.

84. Dao CN, Patel P, Overton ET, Rhame F, Pals SL, Johnson C, et al. Low vitamin D among HIV-infected adults: Prevalence of and risk factors for low vitamin D levels in a cohort of HIV-infected adults and comparison to prevalence among adults in the us general population. Clin Infect Dis. 2011;52(3):396–405.

85. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-Yearly Zoledronic Acid for treatment of Postmenopausal Osteoporosis. N Engl J Med. 2007;356(18):1809–22.

86. Dennis M, Steven R, David B, Jane A. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet. 1996;348(December):1535–41.

87. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, et al. Reduction of Vertebral Fracture Risk in Postmenopausal Women With Osteoporosis Treated With Raloxifene. JAMA. 1999;282(7):637–45.

88. Harris ST, Watts NB, McKeever CD, Hangartner T, Keller M, Brown J, et al. Effects of Risedronate Treatment on Vertebral and Nonvertebral Fractures in Women With Postmenopausal Osteoporosis: A Randomized Controlled Trial. JAMA [Internet]. 1999;282(14):1344–52. Available from: http://jama.jamanetwork.com/article.aspx?articleid=191987

89. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, et al. Clinician ' s Guide to Prevention and Treatment of Osteoporosis. Osteoporos Int. 2014;25:2359–81.

90. Body JJ, Bergmann P, Boonen S, Boutsen Y, Bruyere O, Devogelaer JP, et al. Non-pharmacological management of osteoporosis: A consensus of the Belgian Bone Club. Osteoporos Int. 2011;22(11):2769–88.

91. Borderi M, Pierluigi V. How to monitor bone disease in HIV infection. HAART, HIV Correl Pathol other Infect. 2013;182–9.

92. Beck BR, Daly RM, Fiatarone MA, Taaffe DR. Exercise and Sports Science Australia (ESSA) position statement on exercise prescription for the prevention and management of osteoporosis. J Sci Med Sport. 2016;1403:1–8.

93. Perazzo JD, Webel AR, Fichtenbaum CJ, Mccomsey GA. Bone Health in People Living With HIV : The Role of Exercise and Directions for Future Research. J Assoc Nurses

AIDS Care [Internet]. 2018;29(2):330–7. Available from: https://doi.org/10.1016/j.jana.2017.09.012

94. Ryan AS, Ivey FM, Hurlbut DE, Martel GF, Lemmer JT, Sorkin JD, et al. Regional bone mineral density after resistive training in young and older men and women. Scand J Med Sci Sport. 2004;14:16–23.

95. Cheung AM, Giangregorio L. Mechanical stimuli and bone health : what is the evidence ? Curr Opin Rheumatol. 2012;24:561–6.

96. Guadalupe-Grau A, Fuentes T, Guerra B, Calbet JA. Exercise and bone mass in adults. Sport Med [Internet]. 2009;39(6):439–68. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19453205

97. Xu J, Lombardi G, Jiao W, Banfi G. Effects of Exercise on Bone Status in Female Subjects, from Young Girls to Postmenopausal Women: An Overview of Systematic Reviews and Meta-Analyses. Sport Med. 2016;46(8):1165–82.

98. Ma D, Wu L, He Z. Effects of walking on the preservation of bone mineral density in perimenopausal and postmenopausal women: a systematic review and meta-analysis. Menopause [Internet]. 2013;20(11):1216–26. Available from: http://journals.lww.com/menopausejournal/Fulltext/2013/11000/Effects_of_walking_on_the_preservation_of_bone.19.aspx

99. Martyn-St James M, Carroll S. Meta-analysis of walking for preservation of bone mineral density in postmenopausal women. Bone [Internet]. 2008 Sep 11;43(3):521–31. Available from: http://dx.doi.org/10.1016/j.bone.2008.05.012

100. Rector RS, Rogers R, Ruebel M, Hinton PS. Participation in road cycling vs running is

associated with lower bone mineral density in men. Metabolism [Internet]. 2008 Sep 11;57(2):226–32. Available from: http://dx.doi.org/10.1016/j.metabol.2007.09.005

101. Bolam KA, Skinner TL, Jenkins DG, Galvão DA, Taaffe DR. The osteogenic effect of impact-loading and resistance exercise on bone mineral density in middle-aged and older men: A pilot study. Gerontology. 2016;62(1):22–32.

102. Ahola R, Korpelainen R, Vainionpää A, Leppäluoto J, Jämsä T. Time - course changes of exercise and its association with 12 month bone changes. BMC Musculoskelet Disord. 2009;10(138):8–15.

103. Allison SJ, Folland JP, Rennie WJ, Summers GD, Brooke-Wavell K. High impact exercise increased femoral neck bone mineral density in older men: A randomised unilateral intervention. Bone [Internet]. 2013;53(2):321–8. Available from: http://dx.doi.org/10.1016/j.bone.2012.12.045

104. Bailey CA, Brooke-Wavell K. Optimum frequency of exercise for bone health: Randomised controlled trial of a high-impact unilateral intervention. Bone [Internet]. 2010;46(4):1043–9. Available from: http://dx.doi.org/10.1016/j.bone.2009.12.001

105. Behringer M, Gruetzner S, McCourt M, Mester J. Effects of weight-bearing activities on bone mineral content and density in children and adolescents: A meta-analysis. J Bone Miner Res. 2014;29(2):467–78.

106. Fairfield WP, Finkelstein JS, Klibanski A, Grinspoon SK. Osteopenia in eugonadal men with acquired immune deficiency syndrome wasting syndrome. J Clin Endocrinol Metab. 2001;86(5):2020–6.

107. Howe T, Shea B, Dawson L, Downie F, Murray A, Ross C, et al. Exercise for preventing and treating osteoporosis in postmenopausal women. Cochrane Database Syst Rev.

2011;(7):1–112.

108. Hui SS-C, Xie YJ, Woo J, Kwok TC-Y. Effects of Tai Chi and Walking Exercises on Weight Loss, Metabolic Syndrome Parameters, and Bone Mineral Density: A Cluster Randomized Controlled Trial. Evidence-Based Complement Altern Med [Internet]. 2015;2015:1–10. Available from: http://www.hindawi.com/journals/ecam/2015/976123/

109. Hinton PS, Nigh P, Thyfault J. Effectiveness of resistance training or jumping-exercise to increase bone mineral density in men with low bone mass: A 12-month randomized, clinical trial. Bone [Internet]. 2015;79:203–12. Available from: http://dx.doi.org/10.1016/j.bone.2015.06.008

110. Kemmler W, von Stengel S. Dose-response effect of exercise frequency on bone mineral density in post-menopausal, osteopenic women. Scand J Med Sci Sport. 2014;24(3):526–34.

111. Kemmler W, Engelke K, von Stengel S. Long-Term Exercise and Bone Mineral Density Changes in Postmenopausal Women-Are There Periods of Reduced Effectiveness? J Bone Miner Res [Internet]. 2016;31(1):215–22. Available from: http://doi.wiley.com/10.1002/jbmr.2608

112. Kelley GA, Kelley KS, Kohrt WM. Exercise and bone mineral density in men: A meta-analysis of randomized controlled trials. Bone [Internet]. 2013;53(1):103–11. Available from: http://dx.doi.org/10.1016/j.bone.2012.11.031

113. Kelley GA, Kelley KS, Kohrt WM. Exercise and bone mineral density in premenopausal women: A meta-analysis of randomized controlled trials. Int J Endocrinol [Internet]. 2013;2013:1–16. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L36827

2310%5Cnhttp://dx.doi.org/10.1155/2013/741639

114. Kukuljan S, Nowson CA, Sanders KM, Nicholson GC, Seibel MJ, Salmon J, et al. Independent and combined effects of calcium-vitamin D3 and exercise on bone structure and strength in older men: An 18-month factorial design randomized controlled trial. J Clin Endocrinol Metab. 2011;96(4):955–63.

115. Langsetmo L, Hitchcock C, Kingwell E, Davison K, Berger C, Forsmo S, et al. Physical Activity, Body Mass Index and Bone Mineral Density— Associations in a Prospective Population-based Cohort of Women and Men: The Canadian Multicentre Osteoporosis Study (CaMos). Bone. 2012;50(1):401–8.

116. Marques EA, Wanderley F, Machado L, Sousa F, Viana JL, Moreira-Gonçalves D, et al. Effects of resistance and aerobic exercise on physical function, bone mineral density, OPG and RANKL in older women. Exp Gerontol [Internet]. 2011;46(7):524–32. Available from: http://dx.doi.org/10.1016/j.exger.2011.02.005

117. Morseth B, Emaus N, Wilsgaard T, Jacobsen BK, Jørgensen L. Leisure time physical activity in adulthood is positively associated with bone mineral density 22 years later. the Tromso study. Eur J Epidemiol. 2010;25(5):325–31.

118. World Health Organisation. Adherence to Long-term Therapies: Evidence for action [Internet]. World Health Organisation. 2003 [cited 2017 Jul 28]. 3 p. Available from: https://books.google.mw/books?hl=en&lr=&id=kcYUTH8rPiwC&oi=fnd&pg=PR5&dq=World+Health+Organisation+Adherence+to+long-term+therapies:+evidence+for+action.+2003+ISBN+92+4+154599+2.&ots=tB-Jgq4jtX&sig=dKD7Z065AfrocLjJTX1uHK11-c4&redir_esc=y#v=onepage&q&f=fal

119. Tønnesen R, Schwarz P, Hovind PH. Physical exercise associated with improved BMD

independently of sex and vitamin D levels in young adults. Eur J Appl Physiol. 2016;116(7):1297–304.

120. Pavey T, Taylor A, Hillsdon M, Fox K, Campbell J, Foster C, et al. Levels and predictors of exercise referral scheme uptake and adherence: a systematic review. J Epidemiol Community Health. 2012;66:737–44.

121. Petróczi A, Hawkins K, Jones G, Naughton DP, Bank W, Thomas S, et al. HIV Patient Characteristics that Affect Adherence to Exercise Programmes : An Observational Study. Open AIDS J. 2010;44(0):148–55.

122. Horne M, Tierney S. What are the barriers and facilitators to exercise and physical activity uptake and adherence among South Asian older adults: A systematic review of qualitative studies. Prev Med (Baltim) [Internet]. 2012;55(4):276–84. Available from: http://dx.doi.org/10.1016/j.ypmed.2012.07.016

123. Hong S-Y, Hughes S, Prohaska T. Factors affecting exercise attendance and completion in sedentary older adults: a meta-analytic approach. J Phys Act Health [Internet]. 2008 May;5(3):385–97. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=18579917&site=ehost-live

124. Jordan J, Holden M, Mason E, Foster N. Interventions to improve adherence to exercise for chronic musculoskeletal pain in adults (Review). Cochrane Database Syst Rev. 2010;(1):1–62.

125. Ley C, Barrio MR, Leach L. Social-Ecological, Motivational and Volitional Factors for Initiating and Maintaining Physical Activity in the Context of HIV. open AIDS Jouranal. 2015;9(Supp 1: M6):96–103.

126. Rodrigues IB, Armstrong JJ, Adachi JD, MacDermid JC. Facilitators and barriers to exercise adherence in patients with osteopenia and osteoporosis: a systematic review. Osteoporos Int [Internet]. 2017;28(3):735–45. Available from: http://dx.doi.org/10.1007/s00198-016-3793-2

127. Kelley GA, Kelley KS. Dropouts and compliance in exercise interventions targeting bone mineral density in adults: A meta-analysis of randomized controlled trials. J Osteoporos [Internet]. 2013;2013:1–19. Available from: http://www.scopus.com/inward/record.url?eid=2-s2.0-84879376408&partnerID=40&md5=726cb0f292e9e3b94b6dc2f6cc331c4e

128. Vancampfort D, Mugisha J, Richards J, De Hert M, Lazzarotto AR, Schuch FB, et al. Dropout from physical activity interventions in people living with HIV: a systematic review and meta-analysis. AIDS Care [Internet]. 2017;29(5):636–43. Available from: http://dx.doi.org/10.1080/09540121.2016.1248347

129. Aitken D, Buchbinder R, Jones G, Winzenberg T. Interventions to improve adherence to exercise for chronic musculoskeletal pain in adults. In: Australian Family Physician. 2015. p. 39–42.

130. Santos WR, Santos WR, Paes PP, Ferreira - Silva IA, Santos AP, Vercese N, et al. Impact of strength training on bone mineral density in patients infected with HIV exhibiting lipodystrophy. J Strength Cond Res. 2015;29(12):3466–71.

131. Slade SC, Keating JL, Slade SC. Exercise prescription : a case for standardised reporting. Br J Sports Med. 2011;1–7.

132. Fillipas S, Cherry CL, Cicuttini F, Smirneos L, Holland AE. The effects of exercise training on metabolic and morphological outcomes for people living with HIV: a

systematic review of randomised controlled trials. HIV Clin Trials. 2010;11(5):270–82.

133. Neto MG, Conceico CS, Carvalho VO, Brites C. Effects of combined aerobic and resistance exercise on exercise capacity, muscle strength and quality of life in HIV-infected patients: A systematic review and meta-analysis. PLoS One [Internet]. 2015;10(9):1–14. Available from: http://dx.doi.org/10.1371/journal.pone.0138066

134. Kendal J. Designing a research project: randomised controlled trials and their principles. Emerg Med J. 2003;20(April):164–9.

135. Spieth PM, Kubasch AS, Penzlin AI, Illigens BM-W, Barlinn K, Siepmann T. Randomized controlled trials - a matter of design. Neuropsychiatr Dis Treat [Internet]. 2016;12:1341–9. Available from: https://www.dovepress.com/randomized-controlled-trials-nbspa-matter-of-design-peer-reviewed-article-NDT

136. Howe, L., Goodwin, J., Blagrove R. The integration of unilateral strength training for the lower extremity within an athletic performance programme. Prof Strength Cond J. 2014;33(33):19–24.

137. McCurdy KW, Langfprd GA, Doscher MW, Wiley LP, Mallard KG. The effects of short term unilateral and bilateral lower body resistance training on measures of strength and power. J Strength Cond Res. 2005;19(1):9–15.

138. Speirs DE, Bennett M, Finn C V., Turner AP. Unilateral vs Bilateral Squat training for Strength, Sprints and Agility in Academy Rugby Players. J Strength Cond Res [Internet]. 2015;30(2):386–92. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00124278-900000000-96829

139. Stoykov ME, Lewis GN, Corcos DM. Comparison of bilateral and unilateral training for

upper extremity hemiparesis in stroke. Neurorehabil Neural Repair. 2009;23(9):945–53.

140. Bassett DR. International physical activity questionnaire: 12-Country reliability and validity. Med Sci Sports Exerc. 2003;35(8):1396.

141. IPAQ Research Committee. Guidelines for Data Processing and Analysis of the International Physical Activity Questionnaire (IPAQ) – Short and Long Forms. Ipaq. 2005.

142. Lessig HJ, Meltzer MS, Siegel JA. The symmetry of hip bone mineral density. A dual photon absorptiometry approach. Clin Nucl Med. 1987;12(10):811–2.

143. World Health Organisation. Scientific group on the assessment of osteoporosis at primary health care level. In: Summary Meeting Report. 2004. p. 1–13.

144. International Society for Clinical Densitometry. 2013 Official Positions - Adult. http://www.iscd.org/official-positions/2013-iscd-official-positions-adult/. 2013.

145. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. Lancet. 2002;359(June 1):1929–36.

146. Kline GM, Porcari JP, Hintermeister R, Freedson PS, Ward A, Mccarron JR, et al. Rockport 1 mile test.pdf. Med Sci Sports Exerc. 1987;19(3):253–250.

147. Chisati EM, Vasseljen O. Aerobic endurance in HIV-positive young adults and HIV-negative controls in Malawi. Malawi Med J. 2015;27(1):5–9.

148. Escota G V., Mondy K, Bush T, Conley L, Brooks JT, Önen N, et al. High Prevalence of Low Bone Mineral Density and Substantial Bone Loss over 4 Years Among HIV-Infected Persons in the Era of Modern Antiretroviral Therapy. AIDS Res Hum Retroviruses [Internet]. 2016;31(1):59–67. Available from: http://online.liebertpub.com/doi/10.1089/aid.2015.0158%5Cnhttp://www.ncbi.nlm.nih.go

v/pubmed/26366785

149. Cardeal D, Soares LR, Pereira RMR, Rutherford GW, Assone T, Takayama L, et al. Low bone mineral density among HIV infected patients in Brazil. J Sao Paulo Inst Trop Med. 2017;59(e89):1–5.

150. Lang TF. The Bone-Muscle Relationship in Men and Women. J Osteoporos. 2011;2011:1–4.

151. Nieves JW, Formica C, Ruffing J, Zion M, Garrett P, Lindsay R, et al. Males Have Larger Skeletal Size and Bone Mass Than Females, Despite Comparable Body Size. J Bone Miner Res. 2005;20(3):529–35.

152. Erlandson KM, Lake JE, Sim M, Falutz J, Prado CM, Domingues R, et al. Bone Mineral Density Declines Twice as Quickly Among HIV-Infected Women Compared With Men. J Acquir Immune Defic Syndr. 2018;77(3):288–94.

153. Choe HS, Lee JH, Min DK, Shin SH. Comparison of vertebral and femoral bone mineral density in adult females. J Phys Ther Sci. 2016;28:1928–31.

154. Namwongprom S, Ekmahachai M. Bone Mineral Density : Correlation between the Lumbar Spine , Proximal Femur and Radius in Northern Thai Women. J Med Assoc Thail. 2011;94(6):725–31.

155. Guthold R, Louazani SA, Riley LM, Cowan MJ, Bovet P, Damasceno A, et al. Physical Activity in 22 African Countries: Results from the World Health Organization STEPwise Approach to Chronic Disease Risk Factor Surveillance. Am J Prev Med. 2011;41(1):52–60.

156. World Health Organisation. Global recommendations on Physical Activity for Health. 2010.

157. Vancampfort D, Mugisha J, Hert M De, Probst M, Gorczynski P, Stubbs B, et al. Global physical activity levels among people living with HIV : a systematic review and meta-analysis. Disabil Rehabil [Internet]. 2017;0(0):000. Available from: http://dx.doi.org/10.1080/09638288.2016.1260645

158. Gomes Neto M, Conceição CS, Ogalha C, Brites C. Aerobic capacity and health-related quality of life in adults HIV-infected patients with and without lipodystrophy. Braz J Infect Dis [Internet]. 2015;20(1):76–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26707972

159. Fillipas S, Bowtell-harris CA, Oldmeadow LB, Cicuttini F, Holland AE, Cherry CL. Physical activity uptake in patients with HIV: who does how much? Int J STD AIDS. 2008;19:514–8.

160. Frantz JM, Murenzi A. The physical activity levels among people living with human immunodeficiency virus/acquired immunodeficiency syndrome receiving high active antiretroviral therapy in Rwanda. J Soc Asp HIV/AIDS [Internet]. 2014;10(3–4):113–8. Available from: http://dx.doi.org/10.1080/17290376.2014.886081

161. Smit E, Crespo CJ, Semba RD, Jaworowicz D, Vlahov D, Tang AM, et al. Physical activity in a cohort of HIV-positive and HIV-negative injection drug users. AIDS Care. 2006;18(8):1040–5.

162. Vancampfort D, Mugisha J, Richards J, De Hert M, Probst M, Stubbs B. Physical activity correlates in people living with HIV/AIDS: a systematic review of 45 studies. Disabil Rehabil. 2017;1–12.

163. Milanovic Z, Pantelic S, Trajkovic N, Sporis G, Kostic R, James N. Age-related decrease in physical activity and functional fitness among elderly men and women. Clin Interv

Aging. 2013;8:549–56.

164. Sagatun Å, Kolle E, Anderssen SA, Thoresen M, Søgaard AJ. Three-year follow-up of physical activity in Norwegian youth from two ethnic groups : associations with socio-demographic factors. BMC Public Health. 2008;8(419):1–9.

165. Azevedo MR, Luiza C, Araújo P, Reichert FF, Siqueira FV, Cozzensa M, et al. Gender differences in leisure-time physical activity. Int J Public Health. 2007;52(2007):8–15.

166. Martinez-gonzalez MA, Varo JJ, Santos JL, Irala JDE, Gibney M, Kearney J, et al. Prevalence of physical activity during leisure time in the European Union. Med Sci Sport Exerc. 2001;0195–913(3307):1142–53.

167. Monteiro CA, Conde WL, Matsudo SM, Matsudo VR, Bonseñor IM, Lotufo PA. A descriptive epidemiology of leisure-time physical activity in Brazil , 1996 – 1997. Pan Am J Public Heal. 2003;14(4):1996–7.

168. Santos W, Santos W, Paes P, Ferreira-Silva I, Santos A, Vercese N, et al. Impact of Strength Training on Bone Mineral Density in Patients Infected with HIV exhibiting Lipodystrophy. J Strength Cond Res. 2015;29(12):3466–71.

169. Yuan Y, Chen X, Zhang L, Wu J, Guo J, Zou D, et al. The roles of exercise in bone remodeling and in prevention and treatment of osteoporosis. Prog Biophys Mol Biol [Internet]. 2016;122(2):122–30. Available from: http://dx.doi.org/10.1016/j.pbiomolbio.2015.11.005

170. Frost HM. Bone's Mechanostat: A 2003 Update. Anat Rec Adv Intergrative Anat Evol Biol. 2003;275(2):1081–101.

9. PUBLICATIONS AND APPENDICES

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REVIEW
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Management of Reduced Bone Mineral Density in HIV: Pharmacological Challenges and the Role of Exercise

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Low bone mineral density is becoming more common among people living with HIV following the use of current antiretroviral therapy drugs such as tenofovir. Although pharmacological therapies used to treat low bone mineral density are associated with adverse effects and may increase the pill burden in people living with HIV who are already burdened by antiretroviral therapy drugs, non-pharmacological strategies to prevent and treat reduced bone mineral density resulting from antiretroviral therapy drugs in people living with HIV have not been fully explored. Despite evidence that exercise is effective in increasing bone mineral density, effects of exercise on low bone mineral density resulting from antiretroviral therapy drugs in HIV infected individuals are still unknown. This review highlights gaps in the strategies used to manage reduced bone mineral density resulting from antiretroviral therapy drugs and focuses on exercise as an alternative or adjunctive strategy.

Keywords: bone mineral density (BMD), antiretroviral therapy (ART), people living with HIV (PLWHIV), exercise, progressive resistance exercise (PRE), osteopenia, osteoporosis

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INTRODUCTION

Despite benefits of increased survival, use of the current antiretroviral therapy (ART) drugs in HIV patients are associated with reduced bone mineral density(BMD) (Purdy et al., 2008; Haskelberg et al., 2012; Alonge et al., 2013; Dave et al., 2015; Escota et al., 2015; Chitu-Tisu et al., 2016; Matovu et al., 2016; Mirembe et al., 2016). Reduced BMD is characterized by osteopaenia and osteoporosis which predispose people living with HIV(PLWHIV) to future fall related fractures thereby increasing the risk for morbidity and mortality. The prevalence of osteoporosis and osteopenia in people living with HIV and receiving ART is estimated to be over three times higher than that in HIV uninfected individuals (Brown and Qaqish, 2006). However, despite the widespread use of ART drugs among people living with HIV (World Health Organisation, 2015a), there is no consensus on effective strategies to manage reduced bone mineral density resulting from ART (Matovu et al., 2016).

Effective strategies to prevent and treat reduced bone mineral density in PLWHIV and receiving ART have no clear directions. Pharmacological strategies to manage reduced BMD resulting from ART include medications such as bisphosphonates, teriparatide and denosumab as well as providing vitamin D and calcium supplements (Ali et al., 2014). However these pharmacological

therapies (Gallagher and Sai, 2010; Harris and Brown, 2012; Ali et al., 2014) are associated with adverse effects such as tumors, infection, nasopharyngitis, osteosarcoma as well as bronchitis (Kendler et al., 2010; Harris and Brown, 2012; Ali et al., 2014) which limit their recommendation for use in HIV infected individuals (Harris and Brown, 2012). In addition, the current cost of treating bone loss using pharmacological therapies such as bisphosphonates is prohibitive (Matovu et al., 2016). Further, pharmacological therapies may increase the pill burden in people living with HIV who are already burdened by ART. Physical activities such as jogging, walking, dancing and weight lifting are also recommended as non-pharmacological strategies for preventing and treating bone loss (Howe et al., 2011), but the effectiveness of physical activity in increasing bone mass resulting from ART in people living with HIV has not been fully elucidated.

Although there is growing evidence that physical activity and exercise increases bone mineral density in both adult men and women (Ryan et al., 2004; Cheung and Giangregorio, 2012; Mosti et al., 2014; Multanen et al., 2015), the effects of exercise on loss of bone mass resulting from antiretroviral drugs in PLWHIV remains unexplored (Grace et al., 2015). Exercise programmes differ in terms of frequency, intensity, duration and type. Among many studies, there is heterogeneity in the type, intensity, frequency and duration of exercise interventions to increase bone mineral density (Bolam et al., 2013) with most trials conducted in either women or adult men (Howe et al., 2011; Mosti et al., 2013, 2014) despite evidence of increases in bone loss among young men as well (Watts et al., 2012). Although reduced bone mineral density is common among PLWHIV following the use of antiretroviral drugs (Purdy et al., 2008; Haskelberg et al., 2012; Alonge et al., 2013; Dave et al., 2015; Escota et al., 2015; Chitu-Tisu et al., 2016; Matovu et al., 2016; Mirembe et al., 2016) knowledge on effects of exercises in increasing bone mineral density in this patient group is still lacking.

This review will highlight knowledge gaps in strategies to manage bone loss resulting from ART. The review will focus on challenges of pharmacological strategies used in treating reduced bone mineral density resulting from ART and the effects of exercises in increasing bone mineral density.

METHODS

From April to September 2017, online databases such as EMBASE, Google Scholar, MEDLINE, PubMed, Scopus and The Cochrane Library were searched with no period restriction using key words: bone mineral density, antiretroviral therapy, exercise, people living with HIV and progressive resistance exercise. Published articles with potentially relevant titles and abstracts were retrieved. Articles were included in the review if they were (i) investigating the prevalence of low bone mineral density resulting from ART; (ii) examining strategies that are used to treat reduced bone mineral density or (iii) investigating the effects of exercise in increasing bone mineral density. A total of 109 articles met the inclusion criteria and were included in the review. All included publications were reviewed in their entirety.

PHYSIOLOGY OF BONE MINERAL DENSITY

Bone is a connective tissue in which the matrix is made up of collagen fibers and minerals. Collagen is a protein that provides the bone's flexible framework (Sharp, 2011). The minerals contribute to the bone mineral density or bone mineral content and give the bone its strength and hardness. Collagen allows bones to bend in order to withstand stress while bone mineral density give bones strength to support the body's other tissues (Sharp, 2011). Bone mineral density in the matrix contributes to the support and protection functions of the skeleton. As such, bone mineral density is a surrogate for bone strength and is used to predict fracture risk in an individual. Reduced bone mineral density is characterized by osteopenia and osteoporosis and can predispose an individual to future fall related fractures.

Bone grows through modeling and remodeling processes (Creager, 1992; Harada and Rodan, 2003; Seeman and Delmas, 2006; Marieb and Hoehn, 2007; Pavy-Le Traon et al., 2007; Guadalupe-Grau et al., 2009; Sharp, 2011; Kruger and Nell, 2017). The modeling process involves osteoblast cells that perform bone formation by laying down new bone (Sharp, 2011). On the other hand, remodeling is a continuous process which involves bone resorption. In resorption osteoclasts are attracted to areas needing repair and move in to remove damaged bone (Seeman and Delmas, 2006; Sharp, 2011) thus some bone tissue is added along one surface while reabsorption occurs at another surface. The remodeling process occurs throughout one's life. It is estimated that 5–7% of bone mass is remodeled every week and approximately 0.5 gram of calcium is deposited or reabsorbed by the adult skeleton daily (Marieb and Hoehn, 2007). Any imbalances between modeling and remodeling lead to reduced load bearing capacity as well as loss of bone mineral density which in turn increase the risk for fractures (Sharp, 2011). Therefore, increased bone mineral density may reduce the incidence of fractures.

Bone mass formation is normally in excess of reabsorption with increasing age and peaks between ages 25 and 30 years, and thereafter bone mass starts to decrease leading to lower bone mineral density (Seeman and Delmas, 2006). Modeling and remodeling processes during growth are aimed at establishing peak bone mass so as to maintain bone strength in adulthood (Seeman and Delmas, 2006). During childhood growth spurt, bone mineral density accumulates with the bone growing both in size and strength (Kruger and Nell, 2017). After the growth spurt, usually during the pre- and post-adolescent period, bone formation continues until a peak bone mass is reached between ages 25 and 30 years. The age of attainment of peak bone mineral density is site-specific with gains of about 5–12% in bone mineral density observed after 30 years old in other individuals (Lorentzon et al., 2005). After the third decade, bone mineral density is maintained for about 10 years before it starts to decline at a rate of about 0.3–0.5% per year in both males and females (Baxter-Jones et al., 2011; Kruger and Nell, 2017). At ages between 45 and 55 women lose more bone mineral than men after which the rate of bone loss is gradual and the same in both sexes (**Figure 1**). A rapid loss of bone mineral density in

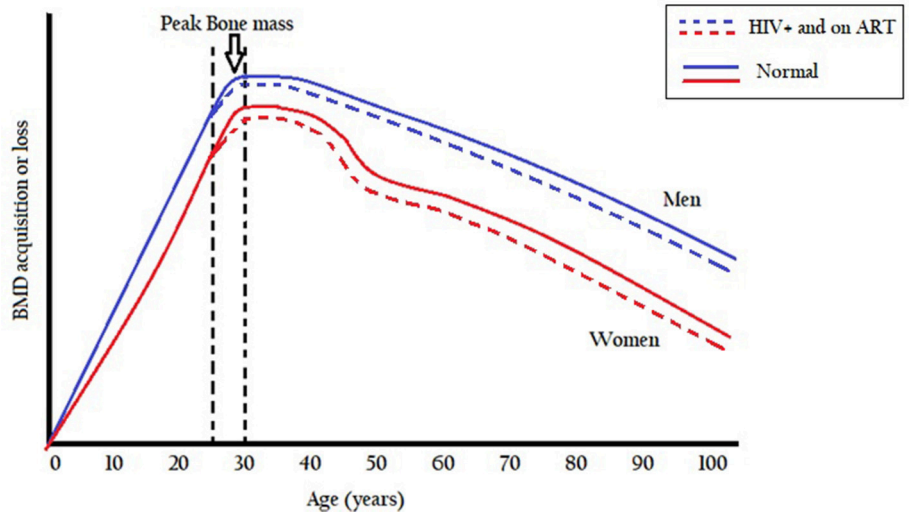

FIGURE 1 | Bone mass growth.

women between ages 45 and 55 years is possibly due to a decrease in estrogen production as the menstrual cycle ceases during this period (Kruger and Nell, 2017).

Although bone remodeling is a normal and natural process, some factors are thought to disrupt the remodeling process (Kruger and Nell, 2017) and thereby reduce or increase the rate of bone mineral density. Factors such as; physical inactivity, low body weight, nutritional deficiencies especially of calcium and vitamin D, depression, smoking, heavy alcohol use, corticoids and other medications, including more recently some antiretroviral drugs (Purdy et al., 2008; Harris and Brown, 2012; Haskelberg et al., 2012; Alonge et al., 2013; Ameet et al., 2014; Dave et al., 2015; Escota et al., 2015; Chitu-Tisu et al., 2016; Matovu et al., 2016; Mirembe et al., 2016) are associated with reduced bone mineral density. Although some factors are not modifiable, physical activity can be changed to stimulate greater accumulation of peak bone mass (Michelson et al., 1996; Guadalupe-Grau et al., 2009; Welz et al., 2010; Pinto Neto et al., 2011; Mdodo et al., 2015; Kruger and Nell, 2017). Since bone modeling and remodeling depends, in part, on mechanical stress, bone strength is enhanced or reduced in response to increased or reduced mechanical loading. Hence an individual's physical activity lifestyle can play a role in either increasing or reducing bone mineral density.

BONE MINERAL DENSITY AND ART

Despite benefits of increased survival, anti-retroviral therapy has been shown to significantly contribute to loss of bone mass (Purdy et al., 2008; Harris and Brown, 2012; Haskelberg et al., 2012; Alonge et al., 2013; Ameet et al., 2014; Dave et al., 2015; Escota et al., 2015; Chitu-Tisu et al., 2016; Matovu et al., 2016; Mirembe et al., 2016). Consequently, medical comorbidities such as osteoporosis and fragility fractures resulting from low bone mineral density are on the rise (Battalora et al., 2014). Emerging evidence indicates that HIV infection is strongly associated with a fivefold increased risk for hip fractures independent of age, gender and comorbidities (Güerri-Fernandez et al., 2013). Güerri-Fernandez et al. reported an increased risk for hip fractures (hazard ratio, 6.2) among HIV infected patients compared to a non-HIV infected general population (Güerri-Fernandez et al., 2013). This risk is higher compared to the risk of lung cancer (hazard ratio, 3.6) and a combined risk of cardiovascular and pulmonary diseases (odds ratio, 1.58) among people living with HIV (Kirk et al., 2007; Schouten et al., 2014). Therefore, the increased risk for hip fractures could consequently increase the risk for mortality and morbidity in people living with HIV.

Initiation of antiretroviral therapy has been shown to increase bone loss in people living with HIV irrespective of regimen (Yin and Overton, 2011; Grant and Cotter, 2016). Reports show a decrease of about 2–6% in bone mineral density in the first two years of ART initiation regardless of the regimen (Duvivier et al., 2009). Although mechanisms underlying bone loss resulting from ART are unclear, it has been suggested by Duvivier (Duvivier et al., 2009) and Borderi (Borderi and Pierluigi, 2013) that HIV infection of osteoblasts may be related to a negative balance of bone remodeling thereby leading to a reduction in bone mineral density in people living with HIV (Duvivier et al., 2009; Borderi and Pierluigi, 2013). Despite suggestions that the likelihood of HIV infection of osteoblasts is very low due to low expression of CD4 (Nachera et al., 2001; Borderi et al., 2009), recent evidence suggests that higher levels of C-C chemokine receptor 5 (CCR5) may affect the functional regulation of osteoclasts thereby leading to bone loss (Lee et al., 2017).

While decreases in bone mineral density occur at initiation of ART irrespective of regimen, more bone loss is associated with tenofovir-containing regimens than other regimens (McComsey et al., 2011; Brown et al., 2015; Grant and Cotter, 2016; Matovu

et al., 2016). Tenofovir leads to approximately 1–3% greater bone mineral loss compared to non tenofovir-containing regimens (Grant and Cotter, 2016). McComsey et al. (2011) compared the effects of tenofovir vs. other ART regimens on bone mass in PLWHIV. They observed greater decreases in spine and hip BMD in participants treated with tenofovir than those treated with other regimens (McComsey et al., 2011). This could suggest that tenofovir has an independent effect on bone regardless of host, viral and immunological factors. Despite evidence that tenofovir significantly contributes to loss of bone mass (McComsey et al., 2011; Brown et al., 2015; Grant and Cotter, 2016; Matovu et al., 2016), most first line ART treatment regimens recommended by World Health Organization (WHO) in resource-limited settings, contain tenofovir (World Health Organisation, 2013, 2015b). This makes reduced bone mineral density highly likely among people living with HIV in most resource-limited settings yet strategies to minimize bone loss in PLWHIV in these settings are currently lacking (Matovu et al., 2016).

Although ART contributes to bone loss in people living with HIV, other factors may play a role as well. Traditional factors such as physical activity, lower body mass index, female sex, older age, nutritional deficiencies of calcium and vitamin D, depression, smoking and alcohol use are believed to contribute to loss of bone mass in the general population (Michelson et al., 1996; Guadalupe-Grau et al., 2009; Welz et al., 2010; Pinto Neto et al., 2011; Mdodo et al., 2015). While there is a controversy on traditional risk factors contributing to reduced bone mineral density in PLWHIV(Michelson et al., 1996), other authors have demonstrated that risk factors for reduced bone mineral density in HIV are similar to other populations (Bonjoch et al., 2010). Other reports indicate that poverty may also contribute to low bone mineral density (Navarro et al., 2009) suggesting that PLWHIV in resource-limited settings could be at a higher risk for loss of bone mineral mass, often the setting of highest HIV burden.

Evidence is emerging that HIV severity also contributes to reduced bone mineral density in HIV infected individuals receiving ART (Ofotokun et al., 2012, 2016; Battalora et al., 2014). A study by Grant et al. demonstrated that with ART initiation, HIV infected individuals with a low CD4 cell count ($<$50 cells/mm^3) had greater bone loss than those with a higher CD4 cell count ($>$500 cells/mm^3) (Grant et al., 2013). This indicates that chronic inflammation induced by HIV may impact bone metabolism. However, despite regional increases in HIV inflammation (Kaul et al., 2011, 2015), data on effective strategies to manage bone loss in people living with HIV lack clear guidelines.

MANAGEMENT OF BONE LOSS RESULTING FROM ART

Pharmacological Therapies

Treatment strategies for reduced bone mineral density resulting from anti-retroviral therapy have no clear directions. Pharmacological strategies to manage bone loss resulting from antiretroviral therapy include providing vitamin D and calcium supplements as well as pharmacological therapies such as Bisphosphonates, Teriparatide and Denosumab (Ali et al., 2014). This section will discuss limitations of vitamin D and calcium supplements as well as pharmacological therapies in treating reduced bone mineral density in people living with HIV.

Although vitamin D deficiency has been implicated in the pathogenesis of bone loss in people living with HIV (Harris and Brown, 2012), there are no clear recommendations for vitamin D and calcium supplements to treat low bone mineral density in this population (Lima et al., 2011). A study by Dao reported a 70.3% vitamin D deficiency in a cohort of 672 HIV infected participants (Dao et al., 2011). Factors such as African American race and exposure to ART drugs were found to be associated with increased risk to vitamin D deficiency (Dao et al., 2011). This could suggest that vitamin D deficiencies could be higher among the Afro American race, moreover it is in Africa where the use of ART is becoming common as a result of high prevalence rates of HIV. A review by Harris and Brown (2012) recommends higher doses of vitamin D in people living with HIV exhibiting bone loss to maintain targeted levels of bone mass (Harris and Brown, 2012). However, due to their small effect on fracture risk reduction, vitamin D and calcium supplements are best used as additional therapies with other osteoporotic drugs (Gallagher and Sai, 2010) and their sole use is not advised.

Among osteoporotic drug treatments, beneficial effects of Denosumab in managing reduced bone mineral density in people living with HIV are not clear (Ali et al., 2014). Denosumab is a long acting monoclonal antibody that blocks bone resorption (Ali et al., 2014). Denosumab decreases osteoclastogenesis and is recommended for use in persons with a history of osteoporotic fractures or those who are intolerant to other osteoporotic therapies (Harris and Brown, 2012). However, long term use of denosumab in treating bone loss leads to atypical fractures (Sellmeyer, 2010). Although seemingly effective, use of Denosumab brings adverse effects such as, tumors, infection, nasopharyngitis, back pain, bronchitis and arthralgia (Kendler et al., 2010; Harris and Brown, 2012). These adverse effects are of particular concern to people living with HIV considering that they are already at an increased risk for infection.

Although available in resource limited settings and could be an alternative to denosumab for treating bone loss, bisphosphonates have a number of side effects which are a cause of concern in people living with HIV. Bisphosphonates, available as alendronate, ibandronate, risedronate, and zoledronic acid are said to decrease fracture risks in some parts of the body by between 25 and 50% in the general populations (Dennis et al., 1996; Ettinger et al., 1999; Harris et al., 1999; Black et al., 2007). However, despite improvements in bone mineral density among HIV infected individuals following use of alendronate and zoledronic acid, side effects such as difficulty swallowing, esophageal inflammation, dyspepsia, and gastric ulcer are also observed (Harris and Brown, 2012). In addition, bisphosphonates induce atypical femoral fractures and may not be used for more than 5 years (Fleming et al., 2001; Ali et al., 2014). This raises concerns of the long term effects of using bisphosphonates for managing reduced bone mineral density in HIV infected

individuals who are currently living longer as a result of ART.

While teriparatide is recommended in individuals where bisphosphates have failed, its recommendation for use to treat bone loss in people living with HIV is still controversial. Some reports indicate that teriparatide has a risk for osteosarcoma (Ali et al., 2014), albeit rare, which may limit its recommendation for use in HIV infected individuals. Additionally, a review by Harris and Brown (2012) concluded that data on safety and efficacy of teriparatide in people living with HIV is lacking and requires further investigation (Harris and Brown, 2012).

Apart from the many challenges associated with pharmacological therapies in treating bone loss in HIV infected individuals, compliance and adherence issues have also been associated with pharmacological therapies (Brown, 2013). A retrospective study by Fan et al. (2013) which assessed the level of compliance with drugs prescribed for bone loss for seven years concluded that most patients do not continue to take the medication as prescribed (Fan et al., 2013). It has also been observed that half of patients treated with bisphosphates discontinue with treatment after 4 months (Solomon et al., 2005; Fan et al., 2013). Since pharmacological therapies are associated with a number of side effects and adherence problems which may limit their use among HIV infected individuals on ART (Fleming et al., 2001; Solomon et al., 2005; Kendler et al., 2010; Sellmeyer, 2010; Harris and Brown, 2012; Brown, 2013; Fan et al., 2013; Ali et al., 2014), exercise based interventions could be an attractive alternative.

Physical Activity

Guidelines for good bone health include physical activity and exercise as a major component in preventing bone loss (Body et al., 2011; Sharp, 2011; Borderi and Pierluigi, 2013; Cosman et al., 2014). Physical activity has been suggested as a non-pharmacological strategy that can be used to increase bone mineral density even in people living with HIV (Sharp, 2011; Borderi and Pierluigi, 2013). Among others, physical activities such as jogging, walking, dancing and weight lifting are shown to be beneficial in preventing and treating low bone mineral density (Howe et al., 2011). However, evidence that physical activity is related to higher bone mass is often inappropriately interpreted as evidence that any activity will improve bone mass (Beck et al., 2016).

Contrary to reports that all physical activity could be important in increasing bone mineral density (Body et al., 2011), weight bearing physical activities with high force, yield a notable increase in bone mineral density (Howe et al., 2011). This could suggest that the type and intensity of the physical activity has an additive effect on bone density. Although weight bearing physical activities are recommended to improve BMD, appropriate parameters for frequency, intensity, duration and type of physical activity to increase bone mineral density especially among HIV infected individuals has not been fully explored (Schambelan et al., 2002; Cosman et al., 2014).

EXERCISE AND BONE MINERAL DENSITY

Type and Design of Exercises

There is growing evidence that exercise increases bone mineral density (Ryan et al., 2004; Cheung and Giangregorio, 2012; Mosti et al., 2014; Multanen et al., 2015). However, not all types of exercises provide notable stimulus to bone (Guadalupe-Grau et al., 2009; Xu et al., 2016). Aerobic exercises such as swimming, walking and cycling provide insignificant improvement to bone mineral density (Martyn-St James and Carroll, 2008; Rector et al., 2008; Ma et al., 2013). Simply prescribing these exercises in isolation is insufficient to optimize bone health. Bone respond positively to impact activities and high intensity progressive resistance training (Beck et al., 2016; Bolam et al., 2016). For example, a Cochrane review (Howe et al., 2011) on the effects of exercise on bone mineral density in postmenopausal women reported that exercises such as jumping, jogging, or dancing results in a between group difference in favor of exercise at the hip (1.55%) but not at the lumbar spine (−1.22%). Similarly, exercises such as walking showed between group improvement with exercise at the lumbar spine (0.85%) but not at the femoral neck (−1.20%) (Howe et al., 2011). Yet progressive resistance exercises resulted in significant between group differences in favor of exercise at both the femoral neck (1.03%) and lumbar spine (0.86%) (Howe et al., 2011). Results from this review suggest that progressive resistance exercises may be effective in increasing bone mineral density. However, despite reports of increases in bone loss due to ART (Yin and Overton, 2011; Grant and Cotter, 2016), the impact of progressive resistance exercise in increasing bone mineral density in PLWHIV has not been fully investigated nor promoted.

Although progressive resistance exercises have been shown to increase bone mass in the general population (Fairfield et al., 2001; Ryan et al., 2004; Ahola et al., 2009; Bailey and Brooke-Wavell, 2010; Ciccolo et al., 2010; Morseth et al., 2010; Howe et al., 2011; Kukuljan et al., 2011; Marques et al., 2011; Cheung and Giangregorio, 2012; Langsetmo et al., 2012; Watts et al., 2012; Allison et al., 2013; Kelley et al., 2013a,b; Mosti et al., 2013, 2014; Behringer et al., 2014; Kemmler and von Stengel, 2014; Hinton et al., 2015; Hui et al., 2015; Multanen et al., 2015; Kemmler et al., 2016), there is heterogeneity in the type, intensity, frequency and duration of exercise interventions to increase bone mineral density among many studies (Bolam et al., 2013). In a longitudinal randomized trial, Allison et al. (2013) investigated the influence of 12 months high impact exercises on bone mineral density in 50 men. Results of the study revealed an increase of 1.2% in bone mineral density. Similarly, Bailey and Brooke-Wavell (2010) demonstrated a significant increase in BMD after 6 months of exercise in 65 women compared to 20 non-exercising women. However, in both studies, there was an increase in dropout rates with increasing number of exercise days indicating that long exercise durations could lead to exercise adherence problems.

Adherence to the recommended exercise regimen is key to the success of any exercise intervention. The World Health Organization defines adherence as "the extent to which a person's behavior—taking medication, following a diet, and/or executing

lifestyle changes—corresponds with agreed recommendations from health care provider" (World Health Organisation, 2003). In exercise, adherence refers to complying with an exercise design for a specified period of time. It involves maintaining the frequency, intensity, duration and type of a given or prescribed exercise. There are reports that adherence to exercise falls below the desirable level among people living with HIV (Petróczi et al., 2010). However, reports indicate that exercise interventions yield higher adherence rates compared to pharmacological interventions in treating low bone mineral density (Kelley and Kelley, 2013).

Among the different types of exercise interventions, compliance is higher with progressive resistance exercises than aerobic exercises(Vancampfort et al., 2017) with an adherence rate of over 80% in randomized controlled trials (Aitken et al., 2015). Reports also indicate that facility based exercises with shorter durations (Kelley and Kelley, 2013) such as maximal strength exercises (Mosti et al., 2013, 2014) have increased adherence. In addition, adherence is increased in exercise programmes that are individualized and supervised by qualified professionals (Hong et al., 2008; Jordan et al., 2010; Tønnesen et al., 2016). It is important therefore to design shorter, supervised, individualized and facility based progressive resistant exercise programmes targeting BMD in order to increase adherence.

Progressive Resistance Exercises

Progressive resistance exercises have proven to be beneficial among people living with HIV. A systematic review by O'Brien et al, found no significant differences in CD4 count and viral load in HIV infected individuals before and after participating in progressive resistance exercises for at least three times per week for at least 6 weeks demonstrating that exercises are safe for people living with HIV (O'Brien et al., 2017). Significant improvements in cardiorespiratory fitness, strength, body composition and body weight following participation in progressive resistance exercises have also been reported among people living with HIV (O'Brien et al., 2008, 2017; Neto et al., 2015). Although the benefits of progressive resistance exercise in people living with HIV are wide, effects of such exercises on bone mineral density in this population have not been fully evaluated (Grace et al., 2015). Only one study by Santos et al. (2015) investigating effects of progressive resistance exercise on BMD in PLWHIV was identified from the literature. In this study, Santos et al. (2015), demonstrated that a shorter exercise duration of 12 weeks was appropriate to impact significant bone increases in 20 individuals living with HIV.

However, the study by Santos et al. (2015) has some methodological shortcomings. The exercise design used lacked other basic elements of an appropriate exercise programme to elicit improvements (Slade and Keating, 2011). The trial neither used non HIV infected controls nor local reference data for BMD for comparison. In addition, different types of exercises were used raising concerns of which of the exercises had a greater impact on bone mineral density. The effectiveness of a 12 weeks' exercise duration to improve BMD is supported by evidence from studies by Mosti et al. (2013, 2014), who demonstrated the effects of a 12 weeks progressive resistance exercises in increasing BMD in young women and postmenopausal women (Mosti et al., 2013, 2014). This evidence indicate that shorter exercise durations could as well impact bone metabolism, thereby minimizing exercise adherence problems.

Progressive resistance exercises have been proven to be safe and beneficial in improving metabolic outcomes among PLWHIV (O'Brien et al., 2008; Fillipas et al., 2010; Grace et al., 2015; Neto et al., 2015). However, there is still lack of knowledge on the optimal mode of frequency, duration and intensity of progressive resistance exercise on BMD in people living with HIV (Fillipas et al., 2010; Grace, 2016) which requires investigation.

CONCLUSION

Most pharmacological strategies used to treat bone loss are associated with a number of adverse effects which limit their recommendation for use in PLWHIV. In addition, compliance and adherence issues associated with pharmacological strategies in treating bone loss may limit their use among PLWHIV who are already burdened by ART. Exercise based interventions such as progressive resistance exercises seem to be an attractive safe and effective alternative strategy that could be used to manage bone loss resulting from ART in PLWHIV. Although progressive resistance exercises are effective in increasing BMD, there is lack of knowledge on the optimal frequency, intensity and duration of the exercise to impact bone which need further investigations. In addition, effects of progressive resistance exercises in increasing BMD in PLWHIV have not been fully investigated. Only one study examining the effects of progressive resistance exercise in increasing BMD among PLWHIV and receiving ART was identified from the literature. Future studies investigating the effects of progressive resistance exercises in increasing BMD in PLWHIV should adopt trial designs with clear descriptions of exercise frequency, intensity and duration.

AUTHOR CONTRIBUTIONS

EC, DC, and FL made significant contributions to the conception and design of the work. EC drafted the work. DC and FL critically revised the work for important intellectual content. All authors had final approval of the version to be published, and are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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REFERENCES

Ahola, R., Korpelainen, R., Vainionpää, A., Leppäluoto, J., and Jämsä, T. (2009). Time - course changes of exercise and its association with 12 month bone changes. *BMC Musculoskelet. Disord.* 10:138. doi: 10.1186/1471-2474-10-138

Aitken, D., Buchbinder, R., Jones, G., and Winzenberg, T. (2015). Interventions to improve adherence to exercise for chronic musculoskeletal pain in adults. *Aust. Fam. Physic.* 44, 39–42. Available online at: https://search.informit.com.au/documentSummary;dn=905348623633626;res=IELHEA

Ali, M. K., Magee, M. J., Dave, J. A., Ofotokun, I., Tungsiripat, M., Jones, T. K., et al. (2014). HIV and metabolic, body, and bone disorders: what we know from low- and middle-income countries. *J. Acquir. Immune Defic. Syndr.* 67, S27–S39. doi: 10.1097/QAI.0000000000000256

Allison, S. J., Folland, J. P., Rennie, W. J., Summers, G. D., and Brooke-Wavell, K. (2013). High impact exercise increased femoral neck bone mineral density in older men: a randomised unilateral intervention. *Bone* 53, 321–328. doi: 10.1016/j.bone.2012.12.045

Alonge, T., Okoje-Adesomoju, V., Atalabi, O., Obamuyide, H., Olaleye, D., and Adewole, I. (2013). Prevalence of abnormal bone mineral density in HIV-positive patients in ibadan, Nigeria. *J. West Afr. Coll. Surg.* 3, 1–14.

Ameet, D., Milind, K., and B. A., Sachin, D. (2014). Prevalence of low bone mineral density among HIV patients on long-term suppressive antiretroviral therapy in resource limited setting of western India. *J. Int. AIDS Soc.* 17:19567. doi: 10.7448/IAS.17.4.19567

Bailey, C. A., and Brooke-Wavell, K. (2010). Optimum frequency of exercise for bone health: randomised controlled trial of a high-impact unilateral intervention. *Bone* 46, 1043–1049. doi: 10.1016/j.bone.2009.12.001

Battalora, L., Young, B., and Overton, E. (2014). Bone, fractures, antiretroviral therapy and HIV. *Curr. Infect. Dis. Rep.* 16, 1–10. doi: 10.1007/s11908-014-0393-1

Baxter-Jones, A. D. G., Faulkner, R. A., Forwood, M. R., Mirwald, R. L., and Bailey, D. A. (2011). Bone mineral accrual from 8 to 30 years of age: an estimation of peak bone mass. *J. Bone Miner. Res.* 26, 1729–1739. doi: 10.1002/jbmr.412

Beck, B. R., Daly, R. M., Fiatarone, M. A., and Taaffe, D. R. (2016). Exercise and sports science australia (ESSA) position statement on exercise prescription for the prevention and management of osteoporosis. *J. Sci. Med. Sport* 1403, 1–8. doi: 10.1016/j.jsams.2016.10.001

Behringer, M., Gruetzner, S., McCourt, M., and Mester, J. (2014). Effects of weight-bearing activities on bone mineral content and density in children and adolescents: a meta-analysis. *J. Bone Miner. Res.* 29, 467–478. doi: 10.1002/jbmr.2036

Black, D. M., Delmas, P. D., Eastell, R., Reid, I. R., Boonen, S., Cauley, J. A., et al. (2007). Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N. Engl. J. Med.* 356, 1809–1822. doi: 10.1056/NEJMoa067312

Body, J. J., Bergmann, P., Boonen, S., Boutsen, Y., Bruyere, O., Devogelaer, J. P., et al. (2011). Non-pharmacological management of osteoporosis: a consensus of the Belgian bone club. *Osteoporos. Int.*22, 2769–2788. doi: 10.1007/s00198-011-1545-x

Bolam, K. A., Skinner, T. L., Jenkins, D. G., Galvão, D. A., and Taaffe, D. R. (2016). The osteogenic effect of impact-loading and resistance exercise on bone mineral density in middle-aged and older men: a pilot study. *Gerontology* 62, 22–32. doi: 10.1159/000435837

Bolam, K. A., Van Uffelen, J. G. Z., and Taaffe, D. R. (2013). The effect of physical exercise on bone density in middle-aged and older men: a systematic review. *Osteoporos. Int.* 24, 2749–2762. doi: 10.1007/s00198-013-2346-1

Bonjoch, A., Figueras, M., Estany, C., Perez-Alvarez, N., Rosales, J., del Rio, L., et al. (2010). High prevalence of and progression to low bone mineral density in HIV-infected patients: a longitudinal cohort study. *AIDS* 24, 2827–2833. doi: 10.1097/QAD.0b013e328340a28d

Borderi, M., Gibellini, D., Vescini, F., Crignis, E., Cimatti, D, and Biagetti, C., et al. (2009). Metabolic bone disease in HIV infection. *AIDS* 23, 1297–1310. doi: 10.1097/QAD.0b013e32832ce85a

Borderi, M., and Pierluigi, V. (2013). How to monitor bone disease in HIV infection. *HAART HIV Correl. Pathol. Other Infect.* 182–189. Available online at: http://www.mnlpublimed.com/public/HA18-A04.pdf

Brown, T. T. (2013). Challenges in the management of osteoporosis and vitamin D deficiency in HIV infection. *Top. Antivir. Med.* 21, 115–118. Available online at: https://europepmc.org/abstract/MED/23981599

Brown, T. T., Moser, C., Currier, J. S., Ribaudo, H. J., Rothenberg, J., Kelesidis, T., et al. (2015). Changes in bone mineral density after initiation of antiretroviral treatment with Tenofovir Disoproxil Fumarate/Emtricitabine Plus Atazanavir/Ritonavir, Darunavir/Ritonavir, or Raltegravir. *J. Infect. Dis.* 212, 1241–1249. doi: 10.1093/infdis/jiv194

Brown, T. T., and Qaqish, R. B. (2006). Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. *AIDS* 20, 2165–2174. doi: 10.1097/QAD.0b013e32801022eb

Cheung, A. M., and Giangregorio, L. (2012). Mechanical stimuli and bone health : what is the evidence ? *Curr. Opin. Rheumatol.* 24, 561–566. doi: 10.1097/BOR.0b013e3283570238

Chitu-Tisu, C. E., Barbu, E. C., Lazar, M., Ion, D. A., and Badarau, I. A. (2016). Low bone mineral density and associated risk factors in HIV-infected patients. *GERMS* 6, 50–59. doi: 10.11599/germs.2016.1089

Ciccolo, J. T., Carr, L. J., Krupel, K. L., and Longval, J. L. (2010). The role of resistance training in the prevention and treatment of chronic disease. *Am. J. Lifestyle Med.* 4, 293–308. doi: 10.1177/1559827609354034

Cosman, F., de Beur, S. J., LeBoff, M. S., Lewiecki, E. M., Tanner, B., Randall, S., et al. (2014). Clinician's guide to prevention and treatment of osteoporosis. *Osteoporos. Int.* 25, 2359–2381. doi: 10.1007/s00198-014-2794-2

Creager, J. A. (1992). *Human Anatomy and Physiology* (Iowa: Wm. C. Brown), 139–153.

Dao, C. N., Patel, P., Overton, E. T., Rhame, F., Pals, S. L., Johnson, C., et al. (2011). Low vitamin D among HIV-infected adults: prevalence of and risk factors for low vitamin D levels in a cohort of HIV-infected adults and comparison to prevalence among adults in the us general population. *Clin. Infect. Dis.* 52, 396–405. doi: 10.1093/cid/ciq158

Dave, J. A., Cohen, K., Micklesfield, L. K., Maartens, G., and Levitt, N. S. (2015). Antiretroviral therapy, especially efavirenz, is associated with low bone mineral density in HIV-infected South Africans. *PLoS ONE* 10:e0144286. doi: 10.1371/journal.pone.0144286

Dennis, M., Steven, R., David, B., and Jane, A. (1996). Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet* 348, 1535–1541.

Duvivier, C., Kolta, S., Assoumou, L., Ghosn, J., Rozenberg, S., Murphy, R. L., et al. (2009). Greater decrease in bone mineral density with protease inhibitor regimens compared with nonnucleoside reverse transcriptase inhibitor regimens in HIV-1 infected naive patients. *AIDS* 23, 817–824. doi: 10.1097/QAD.0b013e328328f789

Escota, G. V., Mondy, K., Bush, T., Conley, L., and Brooks, J. T., Önen, N., et al. (2015). High prevalence of low bone mineral density and substantial bone loss over 4 years among HIV-infected persons in the era of modern antiretroviral therapy. *AIDS Res. Hum. Retroviruses* 31, 59–67. doi: 10.1089/aid.2015.0158

Ettinger, B., Black, D. M., Mitlak, B. H., Knickerbocker, R. K., Nickelsen, T., Genant, H. K., et al. (1999). Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with Raloxifene. *JAMA* 282, 637–645. doi: 10.1001/jama.282.7.637

Fairfield, W. P., Finkelstein, J. S., Klibanski, A., and Grinspoon, S. K. (2001). Osteopenia in eugonadal men with acquired immune deficiency syndrome wasting syndrome. *J. Clin. Endocrinol. Metab.* 86, 2020–2026. doi: 10.1210/jc.86.5.2020

Fan, T., Zhang, Q., and Sen, S. S. (2013). Persistence with weekly and monthly bisphosphonates among postmenopausal women: analysis of a US pharmacy claims administrative database. *Clinicoecon. Outcomes Res.* 5, 589–595. doi: 10.2147/CEOR.S39076

Fillipas, S., Cherry, C. L., Cicuttini, F., Smirneos, L., and Holland, A. E. (2010). The effects of exercise training on metabolic and morphological outcomes for people living with HIV: a systematic review of randomised controlled trials. *HIV Clin. Trials* 11, 270–282. doi: 10.1310/hct1105-270

Fleming, B., Greenfield, S., Engelgau, M., Pogach, L., Clauser, S., and Parrot, M. (2001). The diabetes quality improvement project. *Diab. Care* 24, 1815–1820. doi: 10.2337/diacare.24.10.1815

Gallagher, J. C., and Sai, A. J. (2010). Vitamin D insufficiency, deficiency, and bone health. *J. Clin. Endocrinol. Metab.* 95, 2630–2633. doi: 10.1210/jc.2010-0918

Grace, J. M. (2016). "Exercise therapy for acquired immune deficiency syndrome (AIDS) patients," in *Fitness Medicine* (London, UK: InTechOpen), 129–45.

Grace, J. M., Semple, S. J., and Combrink, S. (2015). Exercise therapy for human immunodeficiency virus/AIDS patients: guidelines for clinical exercise therapists. *J. Exerc. Sci. Fit.* 13, 49–56. doi: 10.1016/j.jesf.2014.10.003

Grant, P. M., and Cotter, A. G. (2016). Tenofovir and bone health. *Curr. Opin. HIV AIDS* 11, 326–332. doi: 10.1097/COH.0000000000000248

Grant, P. M., Kitch, D., McComsey, G. A., Dube, M. P., Haubrich, R., Huang, J., et al. (2013). Low baseline CD4+ count is associated with greater bone mineral density loss after antiretroviral therapy initiation. *Clin. Infect. Dis.* 57, 1483–1488. doi: 10.1093/cid/cit538

Guadalupe-Grau, A., Fuentes, T., Guerra, B., and Calbet, J. A. (2009). Exercise and bone mass in adults. *Sport Med.* 39, 439–468. doi: 10.2165/00007256-200939060-00002

Güerri-Fernandez, R., Vestergaard, P., Carbonell, C., Knobel, H., Avilés, F. F., Castro, A. S., et al. (2013). HIV infection is strongly associated with hip fracture risk, independently of age, gender, and comorbidities: a population-based cohort study. *J. Bone Miner. Res.* 28, 1259–1263. doi: 10.1002/jbmr.1874

Harada, S., and Rodan, G. A. (2003). Control of osteoblast function and regulation of bone mass. *Nature* 423, 349–355. doi: 10.1038/nature01660

Harris, S. T., Watts, N. B., McKeever, C. D., Hangartner, T., Keller, M., Brown, J., et al. (1999). Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. *JAMA* 282, 1344–1352. doi: 10.1001/jama.282.14.1344

Harris, V., and Brown, T. (2012). Bone loss in the HIV-infected patient: evidence, clinical implications, and treatment strategies*J. Infect. Dis.* 205, 391–398. doi: 10.1093/infdis/jis199

Haskelberg, H., Hoy, J. F., Amin, J., Ebeling, P. R., Emery, S., Carr, A., et al. (2012). Changes in bone turnover and bone loss in HIV-infected patients changing treatment to tenofovir-emtricitabine or abacavir-lamivudine. *PLoS ONE* 7, 1–9. doi: 10.1371/journal.pone.0038377

Hinton, P. S., Nigh, P., and Thyfault, J. (2015). Effectiveness of resistance training or jumping-exercise to increase bone mineral density in men with low bone mass: a 12-month randomized, clinical trial. *Bone* 79, 203–212. doi: 10.1016/j.bone.2015.06.008

Hong, S.-Y., Hughes, S., and Prohaska, T. (2008). Factors affecting exercise attendance and completion in sedentary older adults: a meta-analytic approach. *J. Phys. Act. Health* 5, 385–397. doi: 10.1123/jpah.5.3.385

Howe, T. E., Shea, B., Dawson, L. J., Downie, F., Murray, A., Ross, C., et al. (2011). Exercise for preventing and treating osteoporosis in postmenopausal women. *Cochrane Database Syst. Rev.* 2011:CD000333. doi: 10.1002/14651858.CD000333.pub2

Hui, S. S.-C., Xie, Y. J., Woo, J., and Kwok, T. C.-Y. (2015). Effects of tai chi and walking exercises on weight loss, metabolic syndrome parameters, and bone mineral density: a cluster randomized controlled trial. *Evid. Based Complement. Alternat. Med.* 2015:976123. doi: 10.1155/2015/976123

Jordan, J., Holden, M., Mason, E., and Foster, N. (2010). Interventions to improve adherence to exercise for chronic musculoskeletal pain in adults (Review). *Cochrane Database Syst. Rev.* 2010:CD005956. doi: 10.1002/14651858.CD005956.pub2

Kaul, R., Cohen, C. R., Chege, D., Yi, T. J., Tharao, W., McKinnon, L. R., et al. (2011). Biological factors that may contribute to regional and racial disparities in HIV prevalence. *Am. J. Reprod. Immunol.* 65, 317–324. doi: 10.1111/j.1600-0897.2010.00962.x

Kaul, R., Prodger, J., Joag, V., Shannon, B., Yegorov, S., Galiwango, R., et al. (2015). Inflammation and HIV Transmission in Sub-Saharan Africa. *Curr. HIV/AIDS Rep.* 12, 216–222. doi: 10.1007/s11904-015-0269-5

Kelley, G. A., and Kelley, K. S. (2013). Dropouts and compliance in exercise interventions targeting bone mineral density in adults: a meta-analysis of randomized controlled trials. *J. Osteoporos.* 2013:250423. doi: 10.1155/2013/250423

Kelley, G. A., Kelley, K. S., and Kohrt, W. M. (2013a). Exercise and bone mineral density in men: a meta-analysis of randomized controlled trials. *Bone* 53, 103–111. doi: 10.1016/j.bone.2012.11.031

Kelley, G. A., Kelley, K. S., and Kohrt, W. M. (2013b). Exercise and bone mineral density in premenopausal women: a meta-analysis of randomized controlled trials. *Int. J. Endocrinol.* 2013:741639. doi: 10.1155/2013/741639

Kemmler, W., Engelke, K., and von Stengel, S. (2016). Long-term exercise and bone mineral density changes in postmenopausal women-are there periods of reduced effectiveness? *J. Bone Miner. Res.* 31, 215–222. doi: 10.1002/jbmr.2608

Kemmler, W., and von Stengel, S. (2014). Dose-response effect of exercise frequency on bone mineral density in post-menopausal, osteopenic women. *Scand. J. Med. Sci. Sports* 24, 526–534. doi: 10.1111/sms.12024

Kendler, D. L., Roux, C., Benhamou, C. L., Brown, J. P., Lillestol, M., Siddhanti, S., et al. (2010). Effects of denosumab on bone mineral density and bone turnover in postmenopausal women transitioning from alendronate therapy. *J. Bone Miner. Res.* 25, 72–81. doi: 10.1359/jbmr.090716

Kirk, G. D., Merlo, C., Driscoll, P. O., Mehta, S. H., Galai, N., Vlahov, D., et al. (2007). HIV infection is associated with an increased risk for lung cancer, independent of smoking. *Clin. Infect. Dis.* 45, 103–110. doi: 10.1086/518606

Kruger, M. J., and Nell, T. A. (2017). Bone mineral density in people living with HIV: a narrative review of the literature. *AIDS Res. Ther.* 14, 1–17. doi: 10.1186/s12981-017-0162-y

Kukuljan, S., Nowson, C. A., Sanders, K. M., Nicholson, G. C., Seibel, M. J., Salmon, J., et al. (2011). Independent and combined effects of calcium-vitamin D3 and exercise on bone structure and strength in older men: an 18-month factorial design randomized controlled trial. *J. Clin. Endocrinol. Metab.* 96, 955–963. doi: 10.1210/jc.2010-2284

Langsetmo, L., Hitchcock, C., Kingwell, E., Davison, K., Berger, C., Forsmo, S., et al. (2012). Physical activity, body mass index and bone mineral density—associations in a prospective population-based cohort of women and men: the canadian multicentre osteoporosis study (CaMos). *Bone* 50, 401–408. doi: 10.1016/j.bone.2011.11.009

Lee, J., Hoshino, A., Inoue, K., Saitou, T., Uehara, S., Kobayashi, Y., et al. (2017). The HIV co-receptor CCR5 regulates osteoclast function. *Nat. Commun.* 8:2226. doi: 10.1038/s41467-017-02368-5

Lima, A. L., de Oliveira, P. R., Palpler, P. G., Marcolino, F. M. D., Meirelles, E., Sugawara, A., et al. (2011). Osteopenia and osteoporosis in people living with HIV : multiprofessional approach. *HIV/AIDS (Auckl)* 3, 117–124. doi: 10.2147/HIV.S6617

Lorentzon, M., Mellstrom, D., and Ohlsson, C. (2005). Age of attainment of peak bone mass is site specific in Swedish men–the GOOD study. *J. Bone Miner. Res.* 20, 1223–1227. doi: 10.1359/JBMR.050306

Ma, D., Wu, L., and He, Z. (2013). Effects of walking on the preservation of bone mineral density in perimenopausal and postmenopausal women: a systematic review and meta-analysis. *Menopause* 20, 1216–1226. doi: 10.1097/GME.0000000000000100

Marieb, E. N., and Hoehn, K. (2007). *Human Anatomy & Physiology* (San Francisco, CA: Pearson Benjamin Cummings), 175–201.

Marques, E. A., Wanderley, F., Machado, L., Sousa, F., Viana, J. L., Moreira-Gonçalves, D., et al. (2011). Effects of resistance and aerobic exercise on physical function, bone mineral density, OPG and RANKL in older women. *Exp. Gerontol.* 46, 524–532. doi: 10.1016/j.exger.2011.02.005

Martyn-St James, M., and Carroll, S. (2008). Meta-analysis of walking for preservation of bone mineral density in postmenopausal women. *Bone* 1143, 521–531. doi: 10.1016/j.bone.2008.05.012

Matovu, F. K., Wattanachanya, L., Beksinsk, M., Pettifor, J. M., and Ruxrungtham, K. (2016). Bone health and HIV in resource-limited settings: a scoping review. *Curr. Opin. HIV AIDS* 11, 306–325. doi: 10.1097/COH.0000000000000274

McComsey, G. A., Kitch, D., Daar, E. S., Tierney, C., Jahed, N. C., Tebas, P., et al. (2011). Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: AIDS clinical trials group A5224s, a substudy of ACTG. *J. Infect. Dis.* 203, 1791–1801. doi: 10.1093/infdis/jir188

Mdodo, R., Frazier, E. L., Dube, S. R., Mattson, C. L., Sutton, M. Y., Brooks, J. T., et al. (2015). Cigarette smoking prevalence among adults with HIV compared with the general adult population in the United States: cross-sectional surveys. *Ann. Intern. Med.* 162, 335–344. doi: 10.7326/M14-0954

Michelson, D., Stratakis, C., Hill, L., Reynolds, J., Galliven, E., Chrousos, G., et al. (1996). Bone mineral density in women with depression. *N. Engl. J. Med.* 335, 1176–1181. doi: 10.1056/NEJM199610173351602

Mirembe, B. G., Kelly, C. W., Mgodi, N., Greenspan, S., Dai, J. Y., Mayo, A., et al. (2016). Bone mineral density changes among young, healthy African women receiving oral tenofovir for HIV preexposure prophylaxis. *J. Acquir. Immune Defic. Syndr.* 71, 287–294. doi: 10.1097/QAI.0000000000000858

Morseth, B., Emaus, N., Wilsgaard, T., Jacobsen, B. K., and Jørgensen, L. (2010). Leisure time physical activity in adulthood is positively associated with bone

mineral density 22 years later. The Tromso study. *Eur. J. Epidemiol.* 25, 325–331. doi: 10.1007/s10654-010-9450-8

Mosti, M., Carlsen, T., Aas, E., Hoff, J., Stunes, A., and Syversen, U. (2014). Maximal strength training improves bone mineral density and neuromuscular performance in young adult women. *J. Strength Cond. Res.* 28, 2935–2945. doi: 10.1519/JSC.0000000000000493

Mosti, M., Nils, K., Stunes, A., Hoff, J., and Syversen, U. (2013). Maximal strength training in postmenopausal women with osteoporosis or osteopenia. *J. Strength Cond. Res.* 27, 2879–2886. doi: 10.1519/JSC.0b013e318280d4e2

Multanen, J., Nieminen, M. T., Häkkinen, A., Kujala, U. M., Jäms,ä, T., Kautiainen, H., et al. (2015). Effects of high - impact training on bone and articular cartilage: 12 - month randomised controlled quantitative MRI study. *J. Bone Miner. Res.* 29, 192–201. doi: 10.1002/jbmr.2015

Nachera, M., Serrano, S., Gonza, A., Marin, M. L., Vilella, R., Hinarejos, P., et al. (2001). Osteoblasts in HIV-infected patients : HIV-1 infection and cell function. *AIDS* 15, 2239–2243. doi: 10.1097/00002030-200111230-00004

Navarro, M. C., Sosa, M., Saavedra, P., Lainez, P., Marrero, M., Torres, M., et al. (2009). Poverty is a risk factor for osteoporotic fractures. *Osteoporos. Int.* 20, 393–398. doi: 10.1007/s00198-008-0697-9

Neto, M. G., Conceico, C. S., Carvalho, V. O., and Brites, C. (2015). Effects of combined aerobic and resistance exercise on exercise capacity, muscle strength and quality of life in HIV-infected patients: a systematic review and meta-analysis. *PLoS ONE* 10:e0138066. doi: 10.1371/journal.pone.0138066

O'Brien, K. K., Tynan, A., Nixon, S. A., and Glazier, R. H. (2017). Effectiveness of progressive resistive exercise (PRE) in the context of HIV: systematic review and meta-analysis using the Cochrane Collaboration protocol. *BMC Infect. Dis.* 17:268. doi: 10.1186/s12879-017-2342-8

O'Brien, K., Tynan, A.-M., Nixon, S., and Glazier, R. H. (2008). Effects of progressive resistive exercise in adults living with HIV/AIDS: systematic review and meta-analysis of randomized trials. *AIDS Care* 20, 631–653. doi: 10.1080/09540120701661708

Ofotokun, I., McIntosh, E., and Weitzmann, M. N. (2012). HIV: inflammation and bone. *Curr. HIV/AIDS Rep.* 9, 16–25. doi: 10.1007/s11904-011-0099-z

Ofotokun, I., Titanji, K., Vunnava, A., Roser-Page, S., Vikulina, T., Villinger, F., et al. (2016). Antiretroviral therapy induces a rapid increase in bone resorption that is positively associated with the magnitude of immune reconstitution in HIV infection. *AIDS* 30, 405–414. doi: 10.1097/QAD.0000000000000918

Pavy-Le Traon, A., Heer, M., Narici, M. V., Rittweger, J., and Vernikos, J. (2007). From space to earth: advances in human physiology from 20 years of bed rest studies (1986-2006). *Eur. J. Appl. Physiol.* 101, 143–194. doi: 10.1007/s00421-007-0474-z

Petróczi, A., Hawkins, K., Jones, G., Naughton, D. P., Bank, W., Thomas, S., et al. (2010). HIV patient characteristics that affect adherence to exercise programmes: an observational study. *Open AIDS J.* 44, 148–155. doi: 10.2174/1874613601004010148

Pinto Neto, L. F. S., Ragi-Eis, S., Vieira, N. F. R., Soprani, M., Neves, M. B., Ribeiro-Rodrigues, R., et al. (2011). Low bone mass prevalence, therapy type, and clinical risk factors in an HIV-infected brazilian population. *J. Clin. Densitom.* 14, 434–439. doi: 10.1016/j.jocd.2011.06.004

Purdy, J., Gafni, R., Reynolds, J., Zeichner, S., and Hazra, R. (2008). Decreased bone mineral density with off - label use of Tenofovir in HIV - infected children and adolescents. *J. Pediatr.* 152, 582–584. doi: 10.1016/j.jpeds.2007.12.020

Rector, R. S., Rogers, R., Ruebel, M., and Hinton, P. S. (2008). Participation in road cycling vs running is associated with lower bone mineral density in men. *Metabolism* 1157, 226–232. doi: 10.1016/j.metabol.2007.09.005

Ryan, A. S., Ivey, F. M., Hurlbut, D. E., Martel, G. F., Lemmer, J. T., Sorkin, J. D., et al. (2004). Regional bone mineral density after resistive training in young and older men and women. *Scand. J. Med. Sci. Sport* 14, 16–23. doi: 10.1111/j.1600-0838.2003.00328.x

Santos, W. R., Paes, P. P., Ferreira - Silva, I. A., Santos, A. P., Vercese, N., et al. (2015). Impact of strength training on bone mineral density in patients infected with HIV exhibiting lipodystrophy. *J. Strength. Cond. Res.* 29, 3466–3471. doi: 10.1519/JSC.0000000000001001

Schambelan, M., Benson, C. A., Carr, A., Currier, J. S., Dubé, M. P., Gerber, J. G., et al. (2002). Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: recommendations of an international AIDS society – USA panel. *AIDS J. Acquir. Immune Defic. Syndr.* 31, 257–275. doi: 10.1097/00126334-200211010-00001

Schouten, J., Wit, F. W., Stolte, I. G., Kootstra, N. A., Van Der Valk, M., Geerlings, S. E., et al. (2014). Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between hiv-infected and uninfected individuals: the age H IV cohort study. *Clin. Infect. Dis.* 59, 1787–1797. doi: 10.1093/cid/ciu701

Seeman, E., and Delmas, P. D. (2006). Bone quality–the material and structural basis of bone strength and fragility. *N. Engl. J. Med.* 354, 2250–2261. doi: 10.1056/NEJMra053077

Sellmeyer, D. E. (2010). Atypical fractures as a potential complication of long-term bisphosphonate therapy. *JAMA* 304, 1480–1484. doi: 10.1001/jama.2010.1360

Sharp, M. (2011). HIV and bone health. *BETA* 23, 28–37. Available online at: http://sfaf.org/hiv-info/hot-topics/beta/2011-beta-winterspring-bone-health.pdf

Slade, S. C., and Keating, J. L. (2011). Exercise prescription: a case for standardised reporting. *Br. J. Sports Med.* 46, 1110–1113. doi: 10.1136/bjsports-2011-090290

Solomon, D. H., Avorn, J., Katz, J. N., Finkelstein, J. S., Arnold, M., Polinski, J. M., et al. (2005). Compliance with osteoporosis medications. *Arch. Intern. Med.* 165, 2414–2419. doi: 10.1001/archinte.165.20.2414

Tønnesen, R., Schwarz, P., and Hovind, P. H. (2016). Physical exercise associated with improved BMD independently of sex and vitamin D levels in young adults. *Eur. J. Appl. Physiol.* 116, 1297–1304. doi: 10.1007/s00421-016-3383-1

Vancampfort, D., Mugisha, J., Richards, J., De Hert, M., Lazzarotto, A. R., Schuch, F. B., et al. (2017). Dropout from physical activity interventions in people living with HIV: a systematic review and meta-analysis. *AIDS Care* 29, 636–643. doi: 10.1080/09540121.2016.1248347

Watts, N. B., Adler, R. A., Bilezikian, J. P., Drake, M. T., Eastell, R., Orwoll, E. S. F. J., et al. (2012). Osteoporosis in men: an endocrine society clinical practice guideline. *J. Clin. Endocrinol. Metab.* 97, 1802–1822. doi: 10.1210/jc.2011-3045

Welz, T., Childs, K., Ibrahim, F., Poulton, M., Taylor, C. B., Moniz, C. F., et al. (2010). Efavirenz is associated with severe vitamin D deficiency and increased alkaline phosphatase. *AIDS* 24, 1923–1928. doi: 10.1097/QAD.0b013e32833c3281

World Health Organisation (2015a). *Global Health Sector Response To HIV , 2000 – 2015: Focus on Innovations.* Progress Report.

World Health Organisation (2003). *Adherence to Long-Term Therapies: Evidence for Action*. World Health Organisation.

World Health Organisation (2013). *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection. Guidelines*, 1–269.

World Health Organisation (2015b). *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: What's New in Policy Brief*, 1–16.

Xu, J., Lombardi, G., Jiao, W., and Banfi, G. (2016). Effects of exercise on bone status in female subjects, from young girls to postmenopausal women: an overview of systematic reviews and meta-analyses. *Sport Med.* 46, 1165–1182. doi: 10.1007/s40279-016-0494-0

Yin, M. T., and Overton, E. T. (2011). Increasing clarity on bone loss associated with antiretroviral initiation. *J. Infect. Dis.* 203, 1705–1707. doi: 10.1093/infdis/jir184

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PLOS ONE

RESEARCH ARTICLE

Reduced bone mineral density among HIV infected patients on anti-retroviral therapy in Blantyre, Malawi: Prevalence and associated factors

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Abstract

Introduction

Use of tenofovir based anti-retroviral therapy (ART) in HIV patients is associated with low bone mineral density (BMD). Low BMD predisposes people living with HIV (PLWHIV) to fractures thereby increasing morbidity and mortality. Since the introduction of tenofovir based ARV regimens in 2011, information on the prevalence of low BMD in PLWHIV and receiving ART is still scarce in Malawi. This study aimed to determine the prevalence and associated factors of low BMD among adults living with HIV and receiving ART in Blantyre, Malawi.

Methodology

This was a cross sectional study involving 282 HIV-positive adults of whom 102 (36%) were males. The participants aged 18–45 years were recruited from three primary and one tertiary health care facilities. Patients with no other comorbidities or conditions associated with low BMD and on ART >12 months were included. Data on BMD (femoral neck and lumbar spine) were collected using Dual–Energy X-ray Absorptiometry (DEXA). The International Physical Activity Questionnaire (IPAQ) was used to assess the physical activity (PA) levels. Participants' body weight (kg) and height (m) were also measured. Descriptive statistics, Chi–Square test and multivariable logistic regression were used to analyse data.

Results

Mean age of participants was 37(± 6.4) years, mean duration on ART was 5(± 3.5) years and mean body mass index (BMI) was 23(± 4.5) kg/m^2. Twenty percent (55) had reduced BMD. More males (28%) had reduced BMD than females (14%) ($p = 0.04$). There was a significant association between lumbar BMD and femoral neck BMD ($r = 0.66$,$p<0.001$).

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However, on average, lumbar BMD (g/cm^2) was significantly lower than the femoral BMD ($p < 0.001$). Participants with low PA level (*OR* 1.23,$p = 0.6$) had higher odds of having reduced BMD compared to those with high PA level.

Conclusions and recommendation

Prevalence of reduced BMD is high among PLWHIV in Malawi especially male Malawian adults. Occurrence of low BMD is associated with low PA level. There is need for health care providers to routinely monitor BMD and PA levels of this population.

Introduction

Bone mineral density (BMD) is a measure of bone strength as reflected by mineral content. Dual energy X-ray absorptiometry (DEXA) is globally accepted as a standard technique for measuring BMD performed typically at the lumbar spine and femoral neck[1]. BMD is assessed mostly to diagnose osteoporosis or osteopaenia which can predispose an individual to fractures thereby complicating morbidity and increasing the risk for mortality.[2].

Regardless of beneficial increases in survival, use of anti-retroviral therapy (ART) in people living with HIV (PLWHIV) is associated with low BMD[3–6]. An increased risk for hip fractures (hazard ratio, 6.2) among HIV infected patients compared to a non-HIV infected general population has been reported[7]. Compared to the risk of lung cancer (hazard ratio, 3.6) and a combined risk of cardiovascular and pulmonary diseases (odds ratio, 1.58), the risk for hip fractures is higher among people living with HIV [8,9]. Consequently, risk for mortality and morbidity in PLWHIV and receiving ART could increase due to the increasing risk for hip fractures.

Initiation of ART, irrespective of regimen, leads to increases in bone loss in PLWHIV [10,11]. A decrease of about 2–6% in BMD in the first two years after initiation of ART regardless of the regimen has been reported [12]. Although reductions in BMD occur at initiation of ART irrespective of regimen, tenofovir-based regimens are associated with more bone loss than other regimens [10,13–15]. Compared to other regimens, tenofovir leads to approximately 1–3% greater loss in BMD [10]. After comparing the effects of tenofovir and other ART regimens on BMD in PLWHIV, McComsey and colleagues observed greater decreases in BMD in patients receiving tenofovir-containing regimens than those receiving other regimens [15]. This could be suggestive of an independent effect of tenofovir on bone demineralisation regardless of host, viral and immunological factors. Although tenofovir has been shown to significantly contributes to reductions in bone mass [10,13–15], the World Health Organisation (WHO) recommends tenofovir-containing ART as first line treatment regimens in low income settings. [16,17]. This could therefore make reduced BMD highly likely among PLWHIV in low income settings [13].

Higher prevalence rates of up to 85% of low BMD among PLWHIV in low and middle income countries have been reported by a number of studies[18–22]. Apart from ART, factors such as lack of physical activity (PA), lower body mass index (BMI), female sex, older age, nutritional deficiencies of calcium and vitamin D, depression, contraception use, smoking and alcohol use are believed to contribute to high prevalence of low BMD among PLWHIV[22–25]. Although most of the risk factors are similar in low income and high income settings[26], some risk factors such as malnutrition, low BMI and longer duration without ART treatment after the diagnosis of HIV are more common among PLWHIV in low and middle income

settings[13]. These factors could make high prevalence rates of reduced BMD unavoidable among PLWHIV in low and middle income countries.

Malawi's HIV prevalence is one of the highest in the world and accounts for 4% of the total number of PLWHIV in sub-Sahara Africa[27]. About 9.2% of the adult population aged between 15 and 49 are living with HIV in Malawi[27]. In line with WHO recommendations [16], Malawi introduced tenofovir based ARTs in 2011 as first line treatment regimen for PLWHIV[28]. Despite this, there has been minimum effort to investigate the burden of low BMD in such patients in Malawi. In view of the foregoing, this study aimed to determine the prevalence and associated factors of low BMD among PLWHIV on ART in Blantyre, Malawi.

Methods

Study setting

This study was conducted at three primary health care facilities (Limbe Health Center, Gateway Health Center and Dream Center) and one tertiary health care facility (Queen Elizabeth Central Hospital, QECH) located within Blantyre city, Malawi. The health facilities are located in four different townships of Limbe, Mandala, Chinyonga and Ginnery Corner in Blantyre (one health facility per township). Limbe Health Center, Gateway Health Center and QECH are public health facilities that run daily ART clinics for PLWHIV from the surrounding areas. Dream Center on the other hand, is a private health care facility that runs ART clinics three days of the week. All four health care facilities provide ART medication refill for PLWHIV on an out-patient basis. Each day the three public health facilities provide ART refills to approximately 50 PLWHIV, whereas Dream Center serves approximately 25 patients. All four health care facilities have medical consultants supported by nurses who provide ART services to the patients.

Study design and population

This was a cross sectional study involving 282 male and female adults aged 18 years to 45 years and receiving ART at the four health facilities. A random sample of four from a list of 10 health facilities in Blantyre city was selected using the RANDBETWEEN function in Microsoft Excel 2016. Using consecutive sampling, a proportional sample was obtained from each facility. Data were collected from February, 2018 to March, 2019.

Patients were invited to participate and after signing informed consent, were included if they were receiving tenofovir based ART regimens for at least 12 months. Participants who had been on ART for at least 12 months were selected as reductions in BMD are more pronounced after one year[12]. Those with a history of diabetes mellitus or impaired glucose tolerance, an active acute opportunistic infection, rheumatoid arthritis, severe diarrhoea, tuberculosis within one month of commencing treatment, glucocorticoid therapy within the past six months, currently pregnant, breast feeding women, contraception medication use or known to be in renal failure, were excluded because such conditions contribute to reduced BMD[22] (Fig 1).

Data collection and tools

Demographic data. Trained health workers obtained socio-demographic data from the recruited participants. Data on participants' information on smoking (yes/no), alcohol (yes/no), calcium diet measured as milk intake more than once per week (yes/no) and traditional medication use (yes/no) was obtained using a data collection form. Data on age (years), ART duration and regimen were obtained from participants' clinical records.

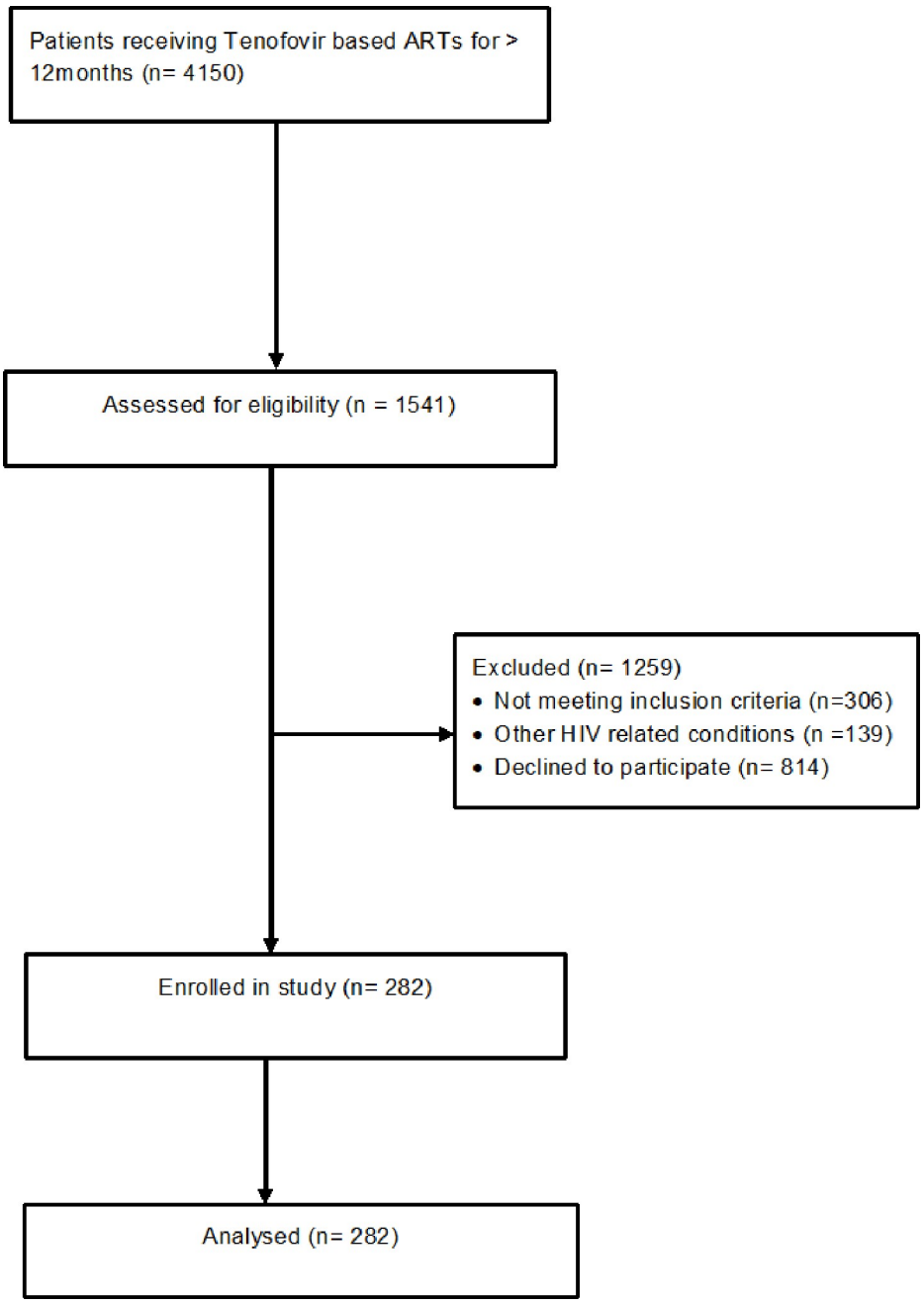

Fig 1. Study flow diagram.

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Height and body weight. Body weight (kg) and height (cm) measurements were obtained using a Stadiometer (HS–DBS00361, Model: 1127154) following manufacturer guidelines. Body mass index (BMI) for each participant was calculated by dividing weight measurement by the square of the height measurement in meters (m^2).

Physical activity. The International Physical Activity Questionnaire (IPAQ) was used to collect data on PA levels of the participants. The IPAQ comprised questions on frequency, intensity and duration of PA that participants do as part of their everyday life in the previous 7

days. Questions such as "During the last 7 days, on how many days did you do vigorous physical activities like heavy lifting, digging, gardening, aerobics, or fast bicycling?"; "How much time did you usually spend doing vigorous physical activities on one of those days?"; "During the last 7 days, on how many days did you do moderate physical activities like carrying light loads, bicycling at a regular pace, or participating in light sporting events?"; "How much time did you usually spend doing moderate physical activities on one of those days?" etc were asked. To ensure that the questions in the local language (Chichewa) were conceptually equivalent with the English questions in the IPAQ, forward and backward translation was performed by independent translators. The IPAQ was proven to be a valid and reliable tool for measuring PA among adults aged 18–65 years in diverse settings[29].

Variable minutes spent on doing PA were recorded. The minutes were calculated into metabolic equivalents (METs). METs are defined as multiples of the resting metabolic rate (1 $MET = 3.5ml\ O_2\ kg^{-1}\ min^{-1}$) and MET-minutes were calculated by multiplying the MET score of an activity (an equivalence of kilocalories for a 60 kg person) by the minutes performed[30].

Participants were categorized into low, moderate and high PA levels. Low level PA comprised participants having the lowest PA and did not meet the criteria for moderate or high PA levels. Moderate PA level comprised participants who did 3 or more days of vigorous PA for at least 20 minutes per day. Similarly, participants who performed 5 or more days of walking or moderate intensity PA for at least 30 minutes per day, fell into the moderate PA level category. High PA level comprised participants who performed at least 3 days of vigorous intensity PA accumulating at least 1500 MET minutes per week. Similarly, participants who performed 7 or more days of any combination of vigorous PA, moderate intensity PA or walking achieving a total of at least 3000 MET minutes per week, fell into the high PA level category.

Bone mineral density. All BMD measurements were performed at QECH. Femoral neck and lumbar spine bone mineral density was measured using DEXA [Hologic Discovery-Wi (S/N 84668), software version 13.5.3.2:5, Hologic Bedford Inc., Bedford, MA, USA]. Femoral neck BMD was measured at the left hip. Measurements of unilateral femoral neck BMD minimizes radiation exposure associated with radiography, time, as well as medical costs[31]. Lumbar spine BMD was measured from the first to the fourth lumbar spines.

Z-scores were obtained as an outcome measure of BMD. The World Health Organisation (WHO) recommends the use of Z-scores (defined as an individuals' BMD in comparison to age-matched normal individuals) in reporting BMD for premenopausal women or men less than 50 years of age, and children[2]. A Z-score of −2.0 or lower is defined as low BMD for chronological age or below the expected range for age whereas a Z-score above −2.0 is within the expected range for age[32–34]. Participants were categorised as having low BMD if the femoral neck or total lumbar spine Z-score was– 2 or less.

Data analysis

Data were analysed using IBM Statistical Package for the Social Sciences (SPSS) version 21. Descriptive statistics using mean and standard deviation (SD) were used to characterize age, height, weight and BMI variables. Data for continuous variables were normally distributed. Student T–tests were used to analyse the differences between lumbar spine and femoral neck BMD. Chi–Square was used to test associations between categorical variables and BMD. Simple linear regression was used to analyse correlations between lumbar BMD and femoral neck BMD. A logistic regression model was fitted to assess effects of PA, smoking, alcohol, calcium diet and traditional medicine on low BMD. Variables for inclusion into the multivariable models were selected based on biological plausibility and those variables with $p \leq 0.20$ at bivariable level were taken for multivariable analysis. Odds ratios (OR) were obtained to quantify the

probability of having low BMD. All statistical tests were two—sided and p values of ≤ 0.05 were considered statistically significant.

Ethical considerations

As participants came for refilling their ART medication, they were requested to attend a health talk regarding the purpose of the study and requesting their participation. This health talk was conducted by the researchers and the health workers at the clinic. After having their ART refill, willing participants were directed into a separate room where the aim and objectives of the study were again explained and screening for eligibility was done. Consent was obtained from eligible and willing participants. All ethical procedures were followed and privacy and confidentiality were ensured by allocating codes to the participants. The study was approved by the University of Malawi's College of Medicine Research and Ethics Committee (COMREC) registration number P.06/17/2206.

Results

A total of 282 adult people living with HIV and receiving tenofovir based ART were included in the study. Height was significantly higher in males than females whereas BMI was significantly higher in females than males (P = < 0.001, two sample T–test) (Table 1). Out of 282 participants, 55 (20%) had low BMD while 227 (80%) had their BMD within the expected ranges for age. More males (28%) had reduced BMD than females (14%) with most of the reduced BMD observed in the lumbar spine. The proportion of participants with reduced BMD was significantly higher among males compared to females (28% vs 14%, P = 0.04, Chi–Square test) (Table 1).

There was a significant positive association between lumbar BMD and femoral neck BMD ($r = 0.66$, $P<0.001$). Fourty three percent of participants had reduced BMD in both the lumbar spine and femoral neck ($R^2 = 0.43$) (Fig 2).

On average, lumbar BMD (g/cm^2) was significantly lower compared to femoral BMD among all participants (mean difference– 0.08, $P < 0.001$, Paired T–test) (Table 2).

Participants with low PA level (OR 1.23, p = 0.6) were more likely to have reduced BMD than those with high PA level. Participants who were not consuming a calcium diet were less likely to have reduced BMD despite a significant association between no calcium diet and low BMD (OR 0.38, p = 0.004) (Table 3). Smoking, alcohol and traditional medicine use were not significantly associated with the occurrence of low BMD.

Table 1. Characteristics of participants.

	Total n = 282	Male n = 102	Female n = 180	P Value
Age (yrs)	37 ± 6.4	37 ± 6.5	37 ± 6.2	0.49
Weight (kg)	60 ± 11.2	61 ± 10.2	60 ± 12.1	0.84
Height (cm)	160 ± 0.1	165 ± 0.1	158 ± 0.1	< 0.001*
BMI (kg/m^2)	23 ± 4.5	22 ± 3.3	24 ± 4.9	< 0.001*
ART duration (yrs)	5.3±3.5	5.2±3.6	5.4±3.4	0.72
BMD within expected range for age [*n*(%)]	227 (80)	73 (72)	154 (86)	
BMD below expected range for age [*n*(%)]	55 (20)	29 (28)	26 (14)	0.04≠

Data are in mean ± SD; BMI = body mass index

* = statistically significant

≠ = Chi-square test

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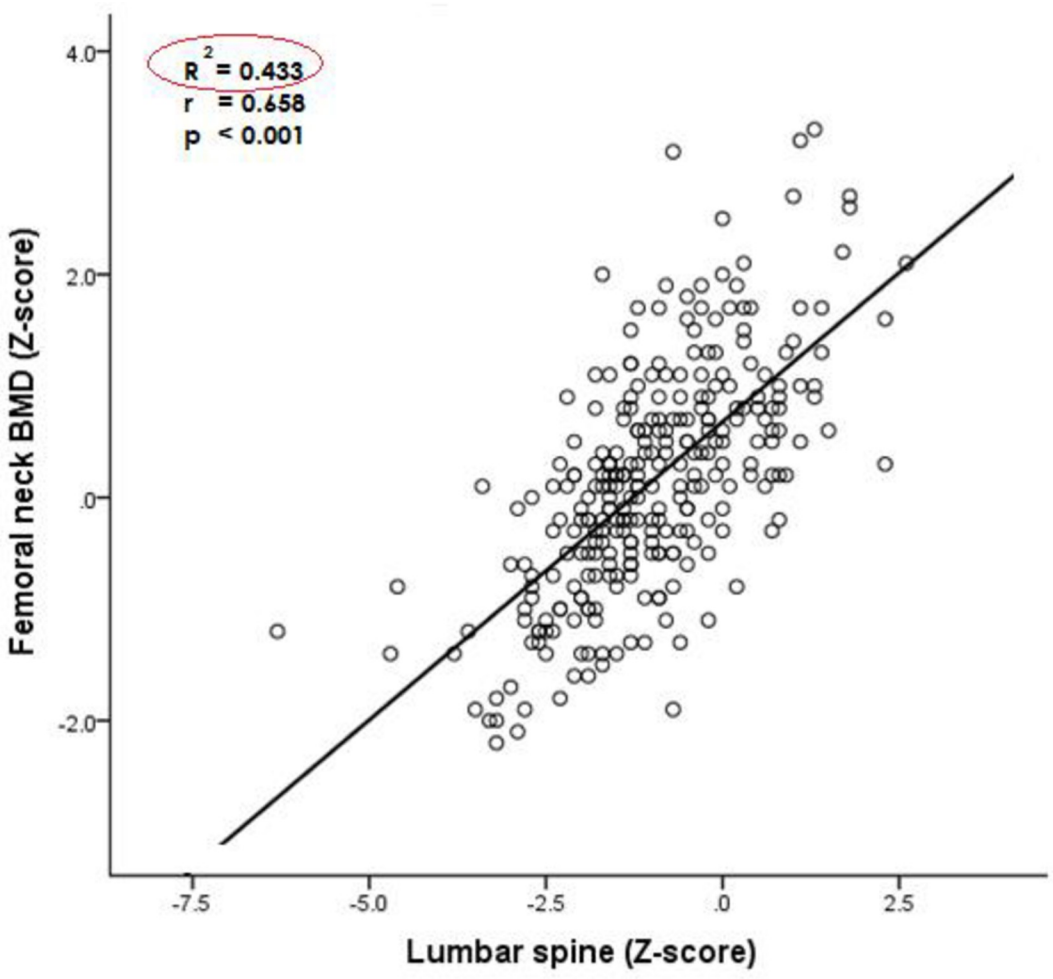

Fig 2. Association between femoral neck and lumbar bone mineral density.

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Discussion

The main purpose of the study was to investigate the prevalence of reduced BMD and associated factors among Malawian adults living with HIV and receiving tenofovir based ART. Findings of the study reveal a high prevalence of reduced BMD among PLWHIV and receiving ART in Malawi. Findings also show that the occurrence of reduced BMD is associated with low PA level.

A comparable prevalence in reduced BMD (23%) was found by Cardeal *et al* (2017) among 108 individuals living with HIV in Brazil[23]. However, some studies have reported higher prevalence rates of reduced BMD ranging from 37% to 80% among PLWHIV [18–20,35]. A slightly lower prevalence in reduced BMD revealed in this study could be due to the age group of participants. The current study recruited adults living with HIV between 18 years and 45 years with a mean age of 37 years. Studies that reported higher prevalence in reduced BMD included participants older than 55 years whose bone mass may have already started decreasing due to ageing. Bone mass increases with age and peaks between ages 25 and 30 years, thereafter bone mass starts to decrease leading to low BMD[36]. After 30 years of age, BMD is maintained for about 10 years before it starts to decline at a rate of about 0.3–0.5% per year in both males and females[37,38]. At ages between 45 to 55 women lose more bone mineral than

Table 2. Differences between femoral neck and lumbar bone mineral density.

Bone parameter	Lumbar spine	Femoral neck	Mean difference	95% CI	P–Value
BMD (g/cm^2)	0.93	0.86	– 0.08	– 0. 09 to– 0.07	< 0.001*
Z–Score	– 1.01	0.14	1.15	1.03 to 1.26	< 0.001*

* = statistically significant

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men after which the rate of bone loss is gradual and the same in both sexes[38]. A rapid loss of BMD in women between ages 45 to 55 is attributed to decreases in oestrogen production as the menstrual cycle ceases during this period[37]. Therefore, a slightly lower prevalence in reduced BMD among PLWHIV revealed in the current study compared to other studies could be attributed to bone strength associated with younger age of most of the participants.

Notably, more males in the current study had reduced BMD than females with most of the reduced bone mass observed in the lumbar spine. Despite comparable body weight, evidence on bone physiology indicate that males have more bone mass than females due to differences in skeletal muscle mass and the body's response to changes in hormones[39,40]. In line with bone physiology, a recent study by Erlandson *et al* (2018) has reported BMD reduction twice as quickly among HIV infected women compared with men[41]. However, 24% of female participants in the study by Erlandson *et al* were menopausal thus leading to more BMD decline[41]. Pronounced decreases in BMD among women has been attributed to large decreases in oestrogen during menopause[39]. Contrary to findings by Erlandson *et al*, the current study did not include female participants in menopause. Pronounced decreases in BMD at lumbar spine among males found in the current study could be due to lifestyle activities among Malawians. In Malawi most females, as opposed to males, carry loads on their heads which likely impacts the lumbar spine which could in turn lead to high density in lumbar spine bones.

Table 3. Factors associated with low BMD.

Factor		Adjusted OR	95% CI	P value
PA level				
	High	1(ref)		
	Moderate	0.87	0.41–1.85	0.72
	Low	1.23	0.57–2.67	0.6
Calcium				
	Yes	1(ref)		
	No	0.38	0.19–0.74	0.004
Smoking				
	No	1(ref)		
	Yes	0.57	0.13–2.56	0.47
Alcohol				
	No	1(ref)		
	Yes	0.88	0.33–2.34	0.8
Traditional Medicine				
	No	1(ref)		
	Yes	0.38	0.11–1.36	0.14

(ref) = reference variable

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Consistent with other studies[42,43], a significant positive correlation between lumbar spine and femoral neck BMD was revealed in the current study. Closer to half of participants who had reduced BMD in the femoral neck were also likely to have reduced BMD in the lumbar spine. With the significant level of correlation, findings of the current study suggest that lumbar spine BMD could be used to predict femoral neck BMD among PLWHIV and receiving ART in Malawi.

Contrary to the current findings, some studies have reported greater reductions in femoral BMD than lumbar BMD among people living with HIV[35,41,44]. However, these studies reporting more reduced BMD in the femoral neck than the lumbar spine were conducted among western and Asian populations who have different PA lifestyles compared to Sub-Saharan African populations. Since bone strength depends, in part, on mechanical stress or mechanical loading, an individual's physical activity lifestyle can play a role in either increasing or reducing BMD[37]. Lower BMD in the lumbar spine compared to the femoral neck observed in the current study could be due to PA of Malawians such as walking long distances to work [45] which may impact the femoral neck bone thereby increasing BMD.

The likely occurence of reduced BMD among participants with low PA level revealed in this study is supported by growing evidence that demonstrates a negative impact of low PA on BMD[24]. Guidelines for good bone health recommends PA as an important component in preventing bone loss among PLWHIV[46]. As demonstrated by Santo et al (2015), significant improvements in BMD were revealed among 20 PLWHIV after particpating in a 12 weeks strength exercise programme[47]. Suggesting that PA could play a role in mainting BMD among PLWHIV. Current findings supports foundation evidence for considering PA as an intervention for managing reduced BMD in PLWHIV.

Being the first in Malawi, this study adds to the body of knowledge on prevalence of reduced BMD among PLWHIV in resource limited settings. The study also provides valuable information on PA and bone health for Malawian adults living with HIV and receiving ART. On the other hand, the current study used a subjective approach of obtaining PA levels through self-reported questionnaire which may result in reporting bias. In addition, the change of BMD over the period of treament could not be established due to the cross sectional design of this study. In addition, most references in the current study reflect circumstances in western countries due to lack of BMD data on large age related healthy African cohorts that could be used for refernce. Furthermore, the current study did not collect data on viral loads or CD4 cell count to determine ART adherence and the cumulative effect of tenofovir exposure among those with reduced BMD. Longitudinal studies aimed at evaluating BMD dynamics in relation to PA are therefore warranted.

Conclusions and recommendations

Reduced BMD is prevalent among Malawian adults living with HIV and receiving ART. Among those with reduced BMD, males had more bone loss than females which may contribute to more incidences of stress and osteoporotic fractures among adult Malawian males living with HIV. Most of the BMD among males was observed at the lumbar spine. The occurrence of reduced BMD was more likely in those who had low PA level. There is need for health care providers to routinely monitor BMD and PA level of this population. In addition, there is need for further research on the effects of exercise interventions on BMD among PLWHIV.

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References

1. Dimai HP. Use of dual-energy X-ray absorptiometry (DXA) for diagnosis and fracture risk assessment; WHO-criteria, T- and Z-score, and reference databases. Bone [Internet]. 2016;1–5. Available from: http://dx.doi.org/10.1016/j.bone.2016.12.016
2. World Health Organisation. Scientific group on the assessment of osteoporosis at primary health care level. In: Summary Meeting Report. 2004. p. 1–13.
3. Mirembe BG, Kelly CW, Mgodi N, Greenspan S, Dai JY, Mayo A, et al. Bone Mineral Density Changes Among Young, Healthy African Women Receiving Oral Tenofovir for HIV Preexposure Prophylaxis. J Acquir Immune Defic Syndr [Internet]. 2016; 71(3):287–94. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00126334-201603010-00007 https://doi.org/10.1097/QAI.0000000000000858 PMID: 26866954
4. Dave JA, Cohen K, Micklesfield LK, Maartens G, Levitt NS. Antiretroviral Therapy, Especially Efavirenz, Is Associated with Low Bone Mineral Density in HIV-Infected South Africans. PLoS One [Internet]. 2015; 10(12):1–9. Available from: http://dx.doi.org/10.1371/journal.pone.0144286
5. Liu AY, Vittinghoff E, Sellmeyer DE, Irvin R, Mulligan K, Mayer K, et al. Bone mineral density in HIV-negative men participating in a tenofovir pre-exposure prophylaxis randomized clinical trial in San Francisco. PLoS One. 2011; 6(8).
6. Purday J, Gafni R, Reynolds J, Zeichner S, Hazra R. Decreased bone mineral density with off—label use of Tenofovir in HIV—Infected children and adolescents. J Paediatr. 2008; 152(4):582–4.
7. Güerri-Fernandez R, Vestergaard P, Carbonell C, Knobel H, Avilés FF, Castro AS, et al. HIV Infection Is Strongly Associated With Hip Fracture Risk, Independently of Age, Gender, and Comorbidities: A Population-Based Cohort Study. J Bone Miner Res. 2013; 28(6):1259–63. https://doi.org/10.1002/jbmr.1874 PMID: 23362011
8. Kirk GD, Merlo C, Driscoll PO, Mehta SH, Galai N, Vlahov D, et al. HIV Infection Is Associated with an Increased Risk for Lung Cancer, Independent of Smoking. Clin Infect Dis. 2007; 45(1):103–10. https://doi.org/10.1086/518606 PMID: 17554710
9. Schouten J, Wit FW, Stolte IG, Kootstra NA, Van Der Valk M, Geerlings SE, et al. Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between hiv-infected and uninfected individuals: The age H IV cohort study. Clin Infect Dis. 2014; 59(12):1787–97. https://doi.org/10.1093/cid/ciu701 PMID: 25182245
10. Grant PM, Cotter AG. Tenofovir and bone health. Curr Opin HIV AIDS. 2016; 11(3):326–32. https://doi.org/10.1097/COH.0000000000000248 PMID: 26859637
11. Yin MT, Overton ET. Increasing clarity on bone loss associated with antiretroviral initiation. J Infect Dis. 2011; 203(12):1705–7. https://doi.org/10.1093/infdis/jir184 PMID: 21606527
12. Duvivier C, Kolta S, Assoumou L, Ghosn J, Rozenberg S, Murphy RL, et al. Greater decrease in bone mineral density with protease inhibitor regimens compared with nonnucleoside reverse transcriptase inhibitor regimens in HIV-1 infected naive patients. AIDS. 2009; 23(7):817–24. https://doi.org/10.1097/QAD.0b013e328328f789 PMID: 19363330
13. Matovu FK, Wattanachanya L, Beksinsk M, Pettifor JM, Ruxrungtham K. Bone health and HIV in resource-limited settings: a scoping review. Curr Opin HIV AIDS [Internet]. 2016; 11(3):306–25. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27023284 https://doi.org/10.1097/COH.0000000000000274 PMID: 27023284

14. Brown TT, Moser C, Currier JS, Ribaudo HJ, Rothenberg J, Kelesidis T, et al. Changes in bone mineral density after initiation of antiretroviral treatment with Tenofovir Disoproxil Fumarate/Emtricitabine Plus Atazanavir/Ritonavir, Darunavir/Ritonavir, or Raltegravir. J Infect Dis. 2015; 212(8):1241–9. https://doi.org/10.1093/infdis/jiv194 PMID: 25948863

15. McComsey GA, Kitch D, Daar ES, Tierney C, Jahed NC, Tebas P, et al. Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: AIDS Clinical Trials Group A5224s, a substudy of ACTG. J Infect Dis. 2011; 203(12):1791–801. https://doi.org/10.1093/infdis/jir188 PMID: 21606537

16. World Health Organisation. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. In: Guidelines. 2013. p. 1–269.

17. World Health Organisation. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: What ' S New. In: Policy Brief. 2015. p. 1–16.

18. Alonge T, Okoje-Adesomoju V, Atalabi O, Obamuyide H, Olaleye D, Adewole I. Prevalence of abnormal bone mineral density in HIV-positive patients in ibadan, Nigeria. J West African Coll Surg. 2013; 3(4):1–14.

19. Chitu-Tisu CE, Barbu EC, Lazar M, Ion DA, Badarau IA. Low bone mineral density and associated risk factors in HIV-infected patients. GERMS [Internet]. 2016; 6(2):50–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27482514 https://doi.org/10.11599/germs.2016.1089 PMID: 27482514

20. Dravid A;, Kulkarni M, Borkar A, Dhande Sachin. Prevalence of low bone mineral density among HIV patients on longterm suppressive antiretroviral therapy in resource limited setting of western India. J Int AIDS Soc. 2014; 17(November):17–8.

21. Aydin OA, Karaosmanoglu HK, Karahasanoglu R, Tahmaz M, Nazlican O. Prevalence and risk factors of osteopenia/osteoporosis in Turkish HIV/AIDS patients. Brazilian J Infect Dis [Internet]. 2013; 17 (6):707–11. Available from: http://dx.doi.org/10.1016/j.bjid.2013.05.009

22. Pinto Neto LFS, Ragi-Eis S, Vieira NFR, Soprani M, Neves MB, Ribeiro-Rodrigues R, et al. Low Bone Mass Prevalence, Therapy Type, and Clinical Risk Factors in an HIV-Infected Brazilian Population. J Clin Densitom. 2011; 14(4):434–9. https://doi.org/10.1016/j.jocd.2011.06.004 PMID: 22051092

23. Cardeal D, Soares LR, Pereira RMR, Rutherford GW, Assone T, Takayama L, et al. Low bone mineral density among HIV infected patients in Brazil. J Sao Paulo Inst Trop Med. 2017; 59(e89):1–5.

24. Perazzo JD, Webel AR, Alam SMK, Sattar A, McComsey GA. Relationships Between Physical Activity and Bone Density in People Living with HIV: Results from the SATURN-HIV Study. J Assoc Nurses AIDS Care. 2018; 29(4):528–37. https://doi.org/10.1016/j.jana.2018.03.004 PMID: 29735237

25. Welz T, Childs K, Ibrahim F, Poulton M, Taylor CB, Moniz CF, et al. Efavirenz is associated with severe vitamin D deficiency and increased alkaline phosphatase. AIDS [Internet]. 2010; 24(12):1923–8. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20588161 https://doi.org/10.1097/QAD.0b013e32833c3281 PMID: 20588161

26. Bonjoch A, Figueras M, Estany C, Perez-Alvarez N, Rosales J, del Rio L, et al. High prevalence of and progression to low bone mineral density in HIV-infected patients: a longitudinal cohort study. AIDS [Internet]. 2010; 24(18):2827–33. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00002030-201011270-00009 https://doi.org/10.1097/QAD.0b013e328340a28d PMID: 21045635

27. UNIAIDS. Global AIDS Monitoring 2018. 2017.

28. Malawi Government. Global AIDS Response Progress Report (GARPR): Malawi Progress Report for 2013. 2014.

29. Bassett DR. International physical activity questionnaire: 12-Country reliability and validity. Med Sci Sports Exerc. 2003; 35(8):1396. https://doi.org/10.1249/01.MSS.0000078923.96621.1D PMID: 12900695

30. IPAQ Research Committee. Guidelines for Data Processing and Analysis of the International Physical Activity Questionnaire (IPAQ)–Short and Long Forms. Ipaq. 2005.

31. Lessig HJ, Meltzer MS, Siegel JA. The symmetry of hip bone mineral density. A dual photon absorptiometry approach. Clin Nucl Med. 1987; 12(10):811–2. https://doi.org/10.1097/00003072-198710000-00013 PMID: 3677526

32. International Society for Clinical Densitometry. 2013 Official Positions—Adult. http://www.iscd.org/official-positions/2013-iscd-official-positions-adult/. 2013.

33. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, et al. Clinician ' s Guide to Prevention and Treatment of Osteoporosis. Osteoporos Int. 2014; 25:2359–81. https://doi.org/10.1007/s00198-014-2794-2 PMID: 25182228

34. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. Lancet. 2002; 359(June 1):1929–36.

35. Escota G V., Mondy K, Bush T, Conley L, Brooks JT, Önen N, et al. High Prevalence of Low Bone Mineral Density and Substantial Bone Loss over 4 Years Among HIV-Infected Persons in the Era of Modern Antiretroviral Therapy. AIDS Res Hum Retroviruses [Internet]. 2015; 31(1):59–67. Available from: http://online.liebertpub.com/doi/10.1089/aid.2015.0158%5Cnhttp://www.ncbi.nlm.nih.gov/pubmed/26366785

36. Seeman E, Delmas PD. Bone quality—the material and structural basis of bone strength and fragility. N Engl J Med. 2006; 354(21):2250–61. https://doi.org/10.1056/NEJMra053077 PMID: 16723616

37. Kruger MJ, Nell TA. Bone mineral density in people living with HIV: a narrative review of the literature. AIDS Res Ther [Internet]. 2017; 14(35):1–17. Available from: http://aidsrestherapy.biomedcentral.com/articles/10.1186/s12981-017-0162-y

38. Baxter-Jones ADG, Faulkner RA, Forwood MR, Mirwald RL, Bailey DA. Bone mineral accrual from 8 to 30 years of age: An estimation of peak bone mass. J Bone Miner Res. 2011; 26(8):1729–39. https://doi.org/10.1002/jbmr.412 PMID: 21520276

39. Lang TF. The Bone-Muscle Relationship in Men and Women. J Osteoporos. 2011; 2011:1–4.

40. Nieves JW, Formica C, Ruffing J, Zion M, Garrett P, Lindsay R, et al. Males Have Larger Skeletal Size and Bone Mass Than Females, Despite Comparable Body Size. J Bone Miner Res. 2005; 20(3):529–35. https://doi.org/10.1359/JBMR.041005 PMID: 15746999

41. Erlandson KM, Lake JE, Sim M, Falutz J, Prado CM, Domingues R, et al. Bone Mineral Density Declines Twice as Quickly Among HIV-Infected Women Compared With Men. J Acquir Immune Defic Syndr. 2018; 77(3):288–94. https://doi.org/10.1097/QAI.0000000000001591 PMID: 29140875

42. Choe HS, Lee JH, Min DK, Shin SH. Comparison of vertebral and femoral bone mineral density in adult females. J Phys Ther Sci. 2016; 28:1928–31. https://doi.org/10.1589/jpts.28.1928 PMID: 27390449

43. Namwongprom S, Ekmahachai M. Bone Mineral Density: Correlation between the Lumbar Spine, Proximal Femur and Radius in Northern Thai Women. J Med Assoc Thail. 2011; 94(6):725–31.

44. Zhang L, Su Y, Hsieh E, Xia W, Xie J, Han Y, et al. Bone turnover and bone mineral density in HIV-1 infected Chinese taking highly active antiretroviral therapy -a prospective observational study. BMC Musculoskelet Disord. 2013; 14:224. https://doi.org/10.1186/1471-2474-14-224 PMID: 23899016

45. Guthold R, Louazani SA, Riley LM, Cowan MJ, Bovet P, Damasceno A, et al. Physical Activity in 22 African Countries: Results from the World Health Organization STEPwise Approach to Chronic Disease Risk Factor Surveillance. Am J Prev Med. 2011; 41(1):52–60. https://doi.org/10.1016/j.amepre.2011.03.008 PMID: 21665063

46. Borderi M, Pierluigi V. How to monitor bone disease in HIV infection. HAART, HIV Correl Pathol other Infect. 2013;182–9.

47. Santos W, Santos W, Paes P, Ferreira-Silva I, Santos A, Vercese N, et al. Impact of Strength Training on Bone Mineral Density in Patients Infected with HIV exhibiting Lipodystrophy. J Strength Cond Res. 2015; 29(12):3466–71. https://doi.org/10.1519/JSC.0000000000001001 PMID: 25970490

ORIGINAL RESEARCH

Physical activity levels among Malawian adults living with HIV and receiving anti-retroviral therapy

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Abstract

Introduction

Despite increasing life expectancy among people living with HIV (PLWHIV), anti-retroviral therapy (ART) side effects, HIV chronic inflammation and co-morbidities may limit functional abilities and reduced participation in exercises and physical activity (PA). PA improves wellbeing and overall quality of life of PLWHIV. In Malawi, there is paucity of information regarding PA levels among Malawians living with HIV and receiving ART. Therefore, this study aimed at determining PA levels among PLWHIV and receiving ART in Malawi.

Methods

A quantitative cross-sectional design was employed. Eligible participants were male and female adults aged 18–45 years living with HIV receiving ART for at least 1 year. The participants were recruited from Limbe Health Center, Gateway Health Center and Queen Elizabeth Central Hospital (QECH) in Blantyre, Malawi. The International Physical Activity Questionnaire (IPAQ) was used to assess the PA levels. A Stadiometer (HS-DBS00361, Model: 1127154) was used to measure weight (kg) and height (cm) of the participants.

Results

A total of 213 participants were recruited. There were more females than male participants (n=132 females). Overall, the mean age of all participants was 37±6.5 years and they were within normal body weight (BMI=23±4.0). Many participants (n=85, 40%) had low PA levels followed by those who were moderately physically active (n=75, 36%). A larger proportion of the female participants (51%) had low PA levels compared to males (22%). Forty-two percent of participants with 1–3 years of ART had low PA whereas 39% with >3 years ART had low PA.

Conclusion

Most PLWHIV and receiving ART in the sample have low PA levels. The study has also revealed that proportionally more females than males had low PA levels.

Key Words

Physical activity, anti-retroviral therapy (ART), people living with HIV (PLWHIV)

Introduction

It is estimated that over 30 million people are infected with human immunodeficiency virus (HIV) with a majority of them living in sub-Saharan Africa[1]. Infection with HIV is increasingly considered a chronic illness, with the introduction of anti-retroviral therapy (ART) having significantly improved life expectancy among people living with HIV (PLWHIV)[2]. PLWHIV are living longer and aging with comorbidities associated with HIV[3,4]. Prevalent comorbidities such as cardiovascular diseases, chronic obstructive pulmonary disease, cancers, arthritis, osteoporosis and liver disease develop earlier and more frequently in PLWHIV than in individuals who are not infected with HIV[5,6]. Side effects of ART such as peripheral neuropathy, osteopaenia, anaemia and fatigue[7,8] as well as HIV-related chronic inflammation have been implicated as risk factors that increase the incidence of comorbidities[9,10]. Decreases in PA among PLWHIV could be exacerbated by most of the HIV related comorbidities [11].

PA is defined as any bodily movement produced by skeletal muscles that results in energy expenditure[12]. PA and exercise are as effective as pharmacological interventions in preventing cardiovascular diseases and mortality in the general population[13]. The benefits of regular PA in the general population include controlling body weight, boosting immunity, preventing non-communicable diseases, increasing fitness and improving mental health[14]. PA has been recommended as a therapeutic intervention that can promote health and quality of life for PLWHIV[15–20]. Existing evidence shows that regular PA improves fitness, body composition, muscle strength, psychological wellbeing and quality of life among people living with HIV[18–20]. PA reduces central fat and metabolic consequences that result from fat accumulation in PLWHIV[21]. Since higher PA levels are associated with many benefits, including lowering cardiovascular disease risk, the leading cause of mortality in people living with HIV[22,23], understanding PA levels among people living with HIV and receiving ART is critical to improving long-term health

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outcomes.

The World Health Organization (WHO) guidelines on PA for health recommend aerobic PA of either 150 minutes of moderate intensity or 75 minutes of vigorous intensity per week for adults aged 18–64 years[24]. In addition, WHO recommends muscle strengthening activities involving all major muscle groups that are done 2 or more days per week[24]. Although the benefits of regular PA are enormous, most PLWHIV are insufficiently physically active[14,15,25,26]. Factors such as opportunistic infections, side effects of anti-retroviral drugs, depression and body pain have been implicated as barriers towards the engagement of PLWHIV in regular PA[27]. PA levels of people living with HIV in Malawi have not been investigated. Therefore, the aim of this study was to determine levels of PA among people living with HIV and receiving ART in Blantyre, Malawi.

Methods

Study design, study sample and recruitment

This was a quantitative cross-sectional study consisting of 81 male (38%) and 132 female (62%) adults living with HIV and receiving ART recruited using convenience sampling. Participants were recruited from Limbe Health Centre, Gateway Health Center and Queen Elizabeth Central Hospital (QECH) in Blantyre, Malawi. As the participants came for refilling their ART medication, they were requested to attend a health talk regarding the purpose of the study and requesting their participation. This health talk was conducted by the researchers and the health workers at the clinic. After getting their ART refill, willing participants were directed into a separate room where the aim and objectives of the study were again explained and screening for eligibility was done. Consent was obtained from eligible and willing participants. All ethical procedures were followed and privacy and confidentiality were ensured by allocating codes to the participants. The study was approved by the University of Malawi's College of Medicine Research and Ethics Committee (COMREC) and is in conformity with the laws of Malawi and the Declaration of Helsinki.

Study period

Data for the study was collected from 28 February 2018 to 30 January, 2019. During this period all eligible people living with HIV and receiving ART from Queen Elizabeth Central Hospital, Limbe Health Center and Gateway Health Center were requested to participate in the study.

Selection criteria

Male and female adults aged 18–45 years living with HIV who were receiving ART for at least 1 year and were adhering to ART treatment were included. Participants who had been on ART for more than 1 year were selected because ART side effects that may affect PA levels tend to manifest after 1 year[28,29]. Pregnant mothers, subjects hospitalized in the previous 2 weeks and all subjects with well-known neurological, cardiorespiratory, orthopaedic or haematological conditions, opportunistic infections and cancers were excluded from the study since such conditions may affect individuals' participation in PA.

Equipment

A Stadiometer (HS-DBS00361, Model: 1127154, Supplied by Taida, Blantyre, Malawi) was used to obtain the weight (kg) and height (cm) of subjects. A health passport was used to cross check the day the subject started ART and the default rate. The International Physical Activity Questionnaire (IPAQ) was used to collect data on PA levels of the participants. Guidelines for data processing of the IPAQ were used to categorize data into levels of PA for each participant.

Variables

Body weight and height

Body weight (kg) and height measurements were obtained using a Stadiometer (HS-DBS00361, Model: 1127154) following manufacturer guidelines.

Body mass index

Body mass index (BMI) for each participant was calculated by dividing weight measurement (kg) by the square of the height measurement (m^2).

Physical activity level

PA levels were obtained using the self-administered short version of the IPAQ. The IPAQ comprised questions on frequency, intensity and duration of PA that participants do as part of their everyday life in the previous 7 days. Questions were asked such as "During the last 7 days, on how many days did you do vigorous physical activities like heavy lifting, digging, gardening, aerobics, or fast bicycling?"; "How much time did you usually spend doing vigorous physical activities on one of those days?"; "During the last 7 days, on how many days did you do moderate physical activities like carrying light loads, bicycling at a regular pace, or participating in light sporting events?"; "How much time did you usually spend doing moderate physical activities on one of those days?" and so on. To ensure that the questions in the local language (Chichewa) were conceptually equivalent with the English questions in the IPAQ, forward and backward translation was performed by independent translators. The IPAQ was proven to be a valid and reliable tool for measuring PA among adults aged 18–65 in diverse settings[30].

Variable minutes spent on doing PAs were recorded. The minutes were calculated into metabolic equivalents (METs). METs are defined as multiples of the resting metabolic rate (1 MET = 3.5 ml O_2 kg^{-1} min^{-1}) and MET-minutes were calculated by multiplying the MET score of an activity (an equivalence of kilocalories for a 60-kg person) by the minutes performed[31].

Participants were categorized into low, moderate and high PA levels. Low level PA comprised participants having the lowest PA and did not meet the criteria for moderate or high PA levels. Moderate level PA comprised participants who did 3 or more days of vigorous PA for at least 20 minutes per day. Similarly, participants who performed 5 or more days of walking or moderate intensity PA for at least 30 minutes per day, fell into the moderate-level PA category. High level PA comprised participants who performed at least 3 days of vigorous intensity PA accumulating at least 1500 MET minutes per week. Similarly, participants who performed 7 or more days of any combination of vigorous PA, moderate intensity PA or walking achieving a total of at least 3000 MET minutes per week fell into the high-level PA category.

Duration on anti-retroviral therapy

The period on ART was obtained through asking the participants and cross-checking in the health passport. Participants were included if the period they have been

receiving ART was 1 year or more. The duration was divided into categories of 1–3 years and above 3 years because side effects of ART that could affect PA become more pronounced after 3 years[28,29].

Data analysis

Data was entered into Microsoft Excel 2016 after which METs for each participant's PA level were computed using guidelines for data processing of the IPAQ[31]. Participants were categorized into low PA, moderate PA and high PA levels. Statistical Package for the Social Science (IBM SPSS statistics for Windows, Version 20.0. Armonk, New York) was used to analyse the data. Descriptive statistics with mean and standard deviation were used to characterize the data variables. All data assumed normal distribution.

Results

The study investigated a sample of 213 adult Malawians aged between 18 and 45 living with HIV and receiving ART from Limbe Health Center, Gateway Health Center and QECH in Blantyre. Overall, the mean age of all participants was 37±6.5 years and they were within normal body weight (BMI=23±4.0). There were more female than male participants (*n*=132 female) with mean age of 36±6.3 years.

Baseline characteristics of participants are presented in Table 1. Most participants (40%) had low PA levels, followed by those who were moderately physically active (36%) while a smaller number of participants (24%) had high PA levels (Figure 1). A larger number of females (51%) had low PA levels compared to males (22%) (Figure 2).

Out of all 77 participants with 1–3 years of ART, 32 (42%) had low PA levels and 53 (39%) out of 136 participants with >3 years ART had low PA levels (Table 2).

Table 1. Baseline characteristics of participants

	Male	Female	Total
	n=81	n=132	n=213
Age (years)	37±6.7	36±6.3	37±6.5
Weight (kg)	59±8.9	59±10.5	59±9.9
Height (cm)	164±0.8	158±0.8	160±0.8
BMI (kg/m^2)	22±3.1	24±4.4	23±4.0

All data are in mean ± standard deviation.

BMI, body mass index.

Table 2. Proportions of PA levels of participants by ART duration

	ART duration	
	1–3 years	>3 years
Low PA	32 (42%)	53 (39%)
Moderate PA	25 (32%)	51 (38%)
High PA	20 (26%)	32 (23%)
Total	77 (100%)	136 (100%)

All data are *n* (%).

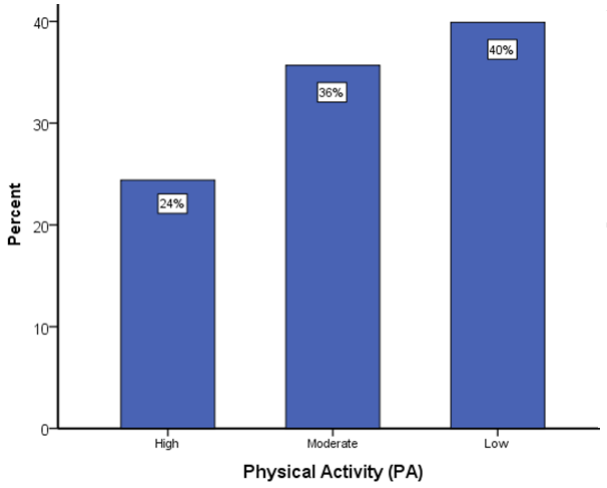

Figure 1: Physical activity (PA) levels of all participants.

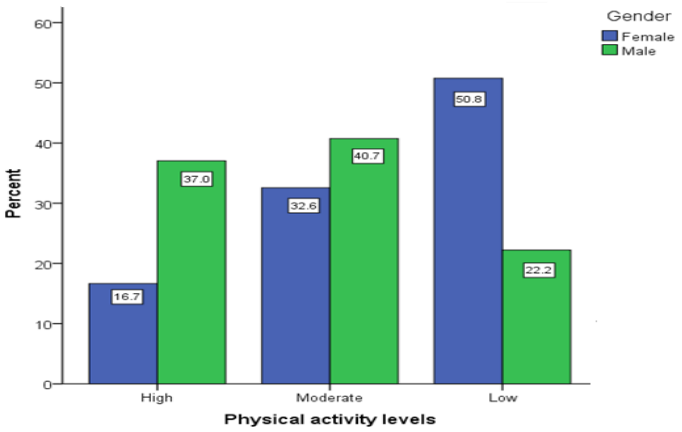

Figure 2: Physical activity (PA) levels of all participants stratified by gender.

Discussion

The study was conducted to determine the levels of PA in a sample of people living with HIV in Blantyre, Malawi. Contrary to WHO recommendations for PA[24], current findings show that a considerable proportion of PLWHIV and receiving ART in Blantyre, Malawi are insufficiently physically active. Our results are consistent with other studies that have shown low levels of PA among people living with HIV and receiving ART[14,15,26,32,33]. Other reports have suggested that lower levels of PA among PLWHIV could be due to lower educational levels, presence of lipodystrophy, body pains, depression and opportunistic infections[27]. It should be noted that some of the indicated factors leading to reduced levels of PA among people living with HIV may be interrelated. For example, presence of lipodystrophy which contributes to reduced PA levels of PLWHIV is a known side effect of stavudine-based ART, which the WHO recommended to be phased out[34]. In our study, none of the participants was taking stavudine-based ART as it was phased out in 2011[35]. In addition, those with opportunistic infections were excluded from the study. Therefore, the presence of lipodystrophy and opportunistic infection may not explain the lower PA levels in our study. Low PA levels among participants in our study could also be due to body pains and depression because these are common among PLWHIV and receiving ART[27]. However, this suggestion should be considered with caution since our study did not investigate depression and body pain among the participants. Although older age has also been suggested as leading to low PA among PLWHIV[27], participants in the current study were young adults aged between 18 and 45 years. Frantz et al. also reported lower PA levels among a majority of the younger population (15–34 years) of PLWHIV[32]. This is a cause for concern because PA levels tend to decrease with

aging[36,37]. Younger adults are considered a productive age group in society, hence having low PA levels poses a public health challenge as they will be unable to participate in daily activities and contribute to the economy of the country.

Results of the study also show that a larger number of female participants had low PA levels compared to male participants. Our results are consistent with a number of studies reporting that males are more active than females[38–40]. Higher PA levels among Malawian males could be expected since a large percentage of the male population is involved in manual labour and agricultural operations that demand considerable physical capacity. Lifestyle activities such as walking long distances to work places, industrial activities that involve pushing levers, land preparation and post-harvest processing of farm produce may also increase physical capacity among Malawian males.

Our results also show a similar proportion of participants with low PA levels between those with 1–3 years ART and those with over 3 years ART. Our findings are contrary to results from a study by Frantz et al., which reported lower levels of PA in participants who were on ART for more than 4 years in Rwanda[32]. This could be due to differences in the age range of the study participants. The study done in Rwanda included older participants (age ranged from 18 to 75) while participants in the current study were younger adults aged between 18 to 45. As revealed by evidence from other studies, lower levels of PA are associated with older age[27].

Limitations

The study focused on the active age groups of people living with HIV in Malawi population other than both age extremities. In addition, the current study used a subjective approach of obtaining data through self-reported questionnaire that may result in reporting bias. The study was conducted among urban settlers living within Blantyre who may have different PAs compared to rural settlers. Hence there is need for more studies to be conducted in other rural areas around Malawi.

Conclusion

This study has highlighted that a larger number of people living with HIV and receiving ART within Blantyre, Malawi have low PA levels, with an almost similar percentage being moderately physically active. Furthermore, a larger number of females have low PA levels compared to males.

Authors' contributions

EC made substantial contributions to the conception, design of the work and drafted the work. FM collected and assisted in analysing data for the study while DC and FL revised the work critically for important intellectual content. All authors are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data availability statement

Data for the study cannot be shared publicly because the data contains potentially identifying information. The restriction has been imposed by the College of Medicine Ethics Committee (COMREC), an IRB that approved the study. Data are available from COMREC (Email: comrec@medcol.mw) for researchers who meet the criteria for access to confidential data.

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Competing interests

The authors state no conflicts of interest in this research or for the development of the article.

References

1. World Health Organization. Global AIDS Update 2016. Geneva: WHO; 2016.

2. Murray CJL, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2197–223. doi:http://dx.doi.org/10.1016/S0140-6736(12)61689-4.

3. Morris A, Gingo MR, George MP, Lucht L, Kessinger C, Hillenbrand M, et al. Cardiopulmonary function in individuals with HIV infection in the antiretroviral therapy era. AIDS. 2012;26(6):731–40. doi: 10.1097/QAD.0b013e32835099ae.Cardiopulmonary.

4. Nlooto M. Comorbidities of HIV infection and health care seeking behavior among HIV infected patients attending public sector healthcare facilities in KwaZulu-Natal: A cross sectional study. PLoS One. 2017;12(2):1-15. doi:10.1371/journal.pone.0170983.

5. Deeks SG, Phillips AN. HIV infection, antiretroviral treatment, ageing, and non-AIDS related morbidity. BMJ. 2009;338:288-292. doi:10.1136/bmj.a3172.

6. Schouten J, Wit FW, Stolte IG, Kootstra NA, Valk MV, Geerlings SE. Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals: The AGEhIV cohort study. Clin Infect Dis. 2014;59(12):1787–97. doi:10.1093/cid/ciu701.

7. Khan K, Khan AH, Sulaiman SA, Soo CT, Ahsan R. Adverse effect of highly active anti-retroviral therapy (HAART) in HIV/AIDS patients. Indian J Pharm Pract. 2014;7(3):6–11. doi:10.5530/ijopp.7.3.7.

8. Alonge T, Okoje-Adesomoju V, Atalabi O, Obamuyide H, Olaleye D, Adewole I. Prevalence of abnormal bone mineral density in HIV-positive patients in Ibadan, Nigeria. J West African Coll Surg. 2013;3(4):1–14.

9. Dillon DG, Gurdasani D, Riha J, Ekoru K, Asiki G, Mayanja BN, et al. Association of HIV and ART with cardiometabolic traits in sub-Saharan Africa: A systematic review and meta-analysis. Int J Epidemiol. 2013;42(6):1754–71. doi:10.1093/ije/dyt198.

10. Hearps AC, Martin GE, Rajasuriar R, Crowe SM. Inflammatory

co-morbidities in HIV+ individuals: learning lessons from healthy ageing. Curr HIV/AIDS Rep. 2014;11(1):20–34. doi:10.1007/s11904-013-0190-8.

11. Baranoski AS, Harris A, Michaels D, Miciek R, Storer T, Sebastiani P, et al. Relationship between poor physical function, inflammatory markers and comorbidities in HIV-infected women on antiretroviral therapy. J Women's Health. 2014;23(1):69–76. doi:10.1089/jwh.2013.4367.

12. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 1985;100(2):126–31.

13. Naci H, Ioannidis JPA. Comparative effectiveness of exercise and drug interventions on mortality outcomes : metaepidemiological study. BMJ. 2013;347:1-14. doi:10.1136/bmj.f5577.

14. Vancampfort D, Mugisha J, Hert M De, Probst M, Firth J, Gorczynski P, et al. Global physical activity levels among people living with HIV : a systematic review and meta-analysis. Disabil Rehabil. 2017;40(4):388–97. doi:10.1080/09638288.2016.1260645..

15. Gomes Neto M, Conceição CS, Ogalha C, Brites C. Aerobic capacity and health-related quality of life in adults HIV-infected patients with and without lipodystrophy. Braz J Infect Dis. 2015;20(1):76–80. doi:10.1016/j.bjid.2015.11.001.

16. Gomes-Neto M, Conceição CS, Oliveira Carvalho V, Brites C. A systematic review of the effects of different types of therapeutic exercise on physiologic and functional measurements in patients with HIV/AIDS. Clinics. 2013;68(8):1157–67. doi:10.6061/clinics/2013(08)16.

17. Leach LL, Bassett SH, Smithdorf G, Andrews BS, Travill AL. A systematic review of the effects of exercise interventions on body composition in HIV+ adults. Open AIDS J. 2015;9:66–79. doi:10.2174/1874613601509010066.

18. Neto MG, Conceico CS, Carvalho VO, Brites C. Effects of combined aerobic and resistance exercise on exercise capacity, muscle strength and quality of life in HIV-infected patients: A systematic review and meta-analysis. PLoS One. 2015;10(9):e0138066. doi:10.1371/journal.pone.0138066.

19. O'Brien KK, Tynan A-M, Nixon SA, Glazier RH. Effectiveness of aerobic exercise for adults living with HIV: systematic review and meta- analysis using the Cochrane Collaboration Protocol. BMC Infect Dis. 2016;16:182. doi:10.1186/s12879-016-1478-2.

20. O'Brien K, Tynan A-M, Nixon S, Glazier RH. Effects of progressive resistive exercise in adults living with HIV/AIDS: systematic review and meta-analysis of randomized trials. AIDS Care. 2008;20(6):631–53. doi:10.1080/09540120701661708.

21. Segatto AM, Junior F, Dos Santos V, Cristina K, Alves P, Barbosa DA, et al. Lipodystrophy in HIV/AIDS patients with different levels of physical activity while on antiretroviral therapy. Rev Soc Bras Med Trop. 2011;44(4):420–4.

22. Dirajlal-Fargo S, Webel AR, Longenecker CT, Kinley B, Labbato D, Sattar A, et al. The effect of physical activity on cardiometabolic health and inflammation in treated HIV infection. Antivir Ther. 2016;21(3):237–45. doi:10.3851/IMP2998.

23. Farahani M, Mulinder H, Farahani A, Marlink R. Prevalence and distribution of non-AIDS causes of death among HIV-infected individuals receiving antiretroviral therapy: a systematic review and meta-analysis. Int J STD AIDS. 2017;28(7):636–50. doi:10.1177/0956462416632428.

24. World Health Organization. Global Recommendations on Physical Activity for Health. Geneva: WHO; 2010.

25. Chisati EM, Vasseljen O. Aerobic endurance in HIV-positive young adults and HIV-negative controls in Malawi. Malawi Med J. 2015;27(1):5–9. doi:10.4314/mmj.v27i1.2.

26. Fillipas S, Bowtell-Harris CA, Oldmeadow LB, Cicuttini F, Holland AE, Cherry CL. Physical activity uptake in patients with HIV: who does how much? Int J STD AIDS. 2008;19:514–8.

27. Vancampfort D, Mugisha J, Richards J, De Hert M, Probst M, Stubbs B. Physical activity correlates in people living with HIV/AIDS : a systematic review of 45 studies. Disabil Rehabil. 2018;40(14):1618–29. doi:10.1080/09638288.2017.1306587.

28. Evans SR, Elias RJ, Chen H, Yeh T, Lee AJ, Schifitto G, et al. Peripheral neuropathy in HIV : prevalence and risk factors. AIDS. 2012;25(7):919–28. doi:10.1097/QAD.0b013e328345889d.Peripheral.

29. Duvivier C, Kolta S, Assoumou L, Ghosn J, Rozenberg S, Murphy R, et al. Greater decrease in bone mineral density with protease inhibitor regimens compared with nonnucleoside reverse transcriptase inhibitor regimens in HIV-1 infected naive patients. AIDS. 2009;23(7):817–24. doi:10.1097/QAD.0b013e328328f789.

30. Bassett DR. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc. 2003;35(8):1396. doi:10.1249/01.MSS.0000078923.96621.1D.

31. IPAQ Research Committee. Guidelines for Data Processing and Analysis of the International Physical Activity Questionnaire (IPAQ) – Short and Long Forms. IPAQ; 2005. Available from www.ipaq.ki.se [cited 2019 March 20]

32. Frantz JM, Murenzi A. The physical activity levels among people living with human immunodeficiency virus/acquired immunodeficiency syndrome receiving high active antiretroviral therapy in Rwanda. J Soc Asp HIV/AIDS. 2014;10(3–4):113–8. doi:10.1080/17290376.2014.886081.

33. Smit E, Crespo CJ, Semba RD, Jaworowicz D, Vlahov D, Ricketts EP, et al. Physical activity in a cohort of HIV-positive and HIV-negative injection drug users. AIDS Care. 2006;18(8):1040–5. doi:10.1080/09540120600580926.

34. World Health Organization. Antiretroviral Therapy for HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach-2010 Revision. Geneva: WHO; 2010.

35. Malawi Government. Global AIDS Response Progress Report (GARPR): Malawi Progress Report for 2013. Malawi Government; 2014. https://www.google.com/search?client=firefox-b-d&q=Malawi++Government.+Global+AIDS+Response+Progress+Report+%28GARPR%29%3A+Malawi+Progress+Report+for+2013.+Malawi+Government%3B+2014.

36. Milanovic Z, Pantelic S, Trajkovic N, Sporis G, Kostic R, James N. Age-related decrease in physical activity and functional fitness among elderly men and women. Clin Interv Aging. 2013;8:549–56.

37. Sagatun Å, Kolle E, Anderssen SA, Thoresen M, Søgaard AJ. Three-year follow-up of physical activity in Norwegian youth from two ethnic groups: associations with socio-demographic factors. BMC Public Health. 2008;8:419.:1-9. doi:10.1186/1471-2458-8-419.

38. Azevedo MR, Luiza C, Araújo P, Reichert FF, Siqueira FV, Cozzensa M, et al. Gender differences in leisure-time physical activity. Int J Public Health. 2007;52(2007):8–15. doi:10.1007/s00038-006-5062-1.

39. Martinez-Gonzalez MA, Varo JJ, Santos JL, Irala JDE, Gibney M, Kearney J, et al. Prevalence of physical activity during leisure time in the European Union. Med Sci Sport Exerc. 2001;33(7):1142–6.

40. Monteiro CA, Conde WL, Matsudo SM, Matsudo VR, Bonseñor IM, Lotufo PA. A descriptive epidemiology of leisure-time physical activity in Brazil, 1996–1997. Pan Am J Public Health. 2003;14(4):246–54.

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RESEARCH ARTICLE Open Access

Effects of maximal strength training on bone mineral density in people living with HIV and receiving anti-retroviral therapy: a pilot study

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Abstract

Background: Anti-retroviral therapy (ART) is associated with low bone mineral density (BMD) among people living with HIV (PLWHIV). Although physical activity is recommended for improving bone health in patients with reduced BMD, data on effects of strength exercises on low BMD among PLWHIV is scarce. This study therefore aimed to determine the effects of a 12 weeks maximal strength training (MST) on BMD among PLWHIV in Blantyre, Malawi.

Methods: Twenty-six PLWHIV with reduced BMD were randomised into a training group (TG, $n = 15$) and control group (CG, $n = 11$). The TG underwent 12 weeks of MST consisting of 4 sets of 3 to 5 repetitions at 85–90% of one repetition maximum (1RM) 3 times per week. The CG was advised to maintain their usual lifestyle. Measurements of BMD using dual-energy X-ray absorptiometry, 1RM using a squat machine, heart rate using a heart rate monitor, weight, height and body mass index were obtained before and after the intervention in the TG and CG. Descriptive statistics and student's t - tests were used to analyse data.

Results: The study was conducted for 12 weeks. Data of 24 participants [14 (TG) and 10 (CG)] were analysed. At base line, there were no significant differences in age ($p = 0.34$), height ($p = 0.91$), weight ($p = 0.43$) and body mass index ($p = 0.34$) between participants in the TG and the CG. After the intervention, there were significant improvements in lumbar BMD ($p < 0.001$) and resting heart rate ($p = 0.03$) in the TG compared to the CG. There were significant improvements in muscle strength (1 RM) in both the TG ($p < 0.001$) and the CG ($p = 0.01$).

Conclusions: MST improves lumbar BMD and strength in PLWHIV receiving ART in Blantyre, Malawi. MST with a shorter exercise duration of 12 weeks seem to have the potential in treating reduced BMD in PLWHIV.

Trial registration: PACTR201712002889203. Registered with the Pan African Clinical Trial Registry on 22nd December, 2017 at www. pactr.org

Keywords: Bone mineral density (BMD), Maximal strength training (MST), People living with HIV (PLWHIV), Anti-retroviral therapy (ART), Exercise

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Background

The use of antiretroviral therapy (ART) to treat human immunodeficiency virus (HIV) leads to reduced bone mineral density (BMD) [1–3]. Low BMD categorised as osteopaenia and osteoporosis may increase the incidence of fractures among people living with HIV (PLWHIV) [4] which may escalate the risk for morbidity and increase mortality. In addition to providing calcium supplements and vitamin D, pharmacological approaches through the provision of Teriparatide, Denosumab and Bisphosphate drugs have been proposed as methods of managing bone demineralisation occurring due to ART [5]. Although promoted in the management of reduced BMD, side effects associated with pharmacological approaches and calcium supplements as well as adherence problems may limit the use of such strategies among PLWHIV [6].

Among other recommendations, physical activity and exercises are included in guidelines for preventing bone loss even among PLWHIV [7–9]. Evidence has shown the beneficial effects of some physical activities such as dancing, walking, weight lifting and jogging in preventing and managing bone demineralisation [10]. However, evidence that high bone mineral density is linked to physical activity is mostly misinterpreted as evidence that any physical activity will lead to increased BMD [11]. Despite some evidence that increases in BMD could result from any physical activity [12], high force weight bearing physical activities lead to pronounced increases in bone mineral density [10]. Therefore, the intensity and type of the physical activity has an important impact on BMD.

Increases in BMD following strength exercises has been reported in a number of studies [7–9, 13]. Thus strength exercise may be used as a strategy to increase BMD in PLWHIV and receiving ART [7]. Compared to pharmacological approaches, exercise interventions are associated with higher adherence rates in managing bone demineralisation [14]. Specifically, strength exercises have shown a higher compliance rate [15] with an adherence rate of over 80% in randomised controlled trials [16]. Reports also reveal an increased adherence among participants performing facility based exercises with shorter durations [14] such as maximal strength exercises [17, 18]. Thus shorter and facility based strength exercise programmes targeting BMD may be appropriate in increasing adherence.

Despite evidence that strength exercises are effective in increasing BMD in men and women [18–21], knowledge on the effects of exercise on low BMD among PLWHIV and receiving ART is scarce. Further, strength exercises have been proven to be safe, practical, inexpensive and beneficial in improving metabolic outcomes among PLWHIV [22–25]. In view of declining rates of mortality and morbidity among PLWHIV due to increased accessibility of ART in resource limited settings, exercise may be a cost effective non pharmacological strategy in preventing bone loss thereby reducing osteoporosis and fall related fractures. However, despite reports of increases in bone loss due to ART [26, 27], there is still lack of information on the optimal mode of frequency, duration and intensity of strength exercise on BMD in PLWHIV [22, 28]. The aim of this study therefore was to determine the effects of a 12 weeks maximal strength training (MST) exercise programme on BMD among PLWHIV in Blantyre, Malawi.

Methods

Study design and setting

This was a parallel randomised controlled pilot study conducted at the College of Medicine Sports Complex in Blantyre city, Malawi. The Sports Complex houses a gym quipped with a variety of exercise training equipment and accommodates about 20 participants per day. It operates daily from 8.00 am to 10.00 pm. Different people within Blantyre city patronize the facility to engage in different exercises either for health or sports performance.

Study population

Participants were recruited from Queen Elizabeth Central Hospital (QECH) in Blantyre Malawi. Male and female adults aged 18–45 years living with HIV and receiving ART who had reduced BMD were included in the study. The World Health Organisation (WHO) recommends the use of Z-scores (defined as an individuals' BMD in comparison to age-matched normal individuals) in reporting BMD for premenopausal women or men less than 50 years of age and children [29]. A Z-score of − 2.0 or lower is defined as low BMD for chronological age or below the expected range for age whereas a Z-score above − 2.0 is within the expected range for age [30–32].

Participants were included if they were receiving tenofovir based ART regimens for more than 12 months and had reduced BMD. The more than 12 months duration was chosen because reductions in BMD are more pronounced after this period [33]. Participants with contraindications to exercise (such as serious cardiorespiratory, neurological or orthopaedic conditions which would limit participation to the exercise regimen), and were taking any calcium supplements and pharmacological therapies were excluded.

Exercise protocol

Participants were randomly allocated to either an exercise training group (TG) or control group (CG). Participants in the TG followed a MST programme for 12

weeks comprising three sessions each week with a total of 36 sessions under the supervision of a qualified physiotherapist. The participants were instructed not to add any leisure exercises that included high impact jumping and lifting heavy loads during the study period. The MST sessions consisted of squat exercises performed on a hack squat machine (Model HLS2000) using the lower extremities. Before the main exercise session, participants performed a warm-up comprising two sets of 8 to 12 repetitions at approximately 50% of the participant's training load. The warm up was followed by the main exercise consisting of four sets of 3 to 5 repetitions at 85 to 90% of one repetition maximum (1RM). A break of 2 to 3 min was allowed between the sets. Execution of the exercise started from a straight legs position, down to a 90° angle in the knee joint and up again. Participants' 1RM was re-evaluated every week to guide progression of the intensity of the exercise. Participants in the CG were instructed to keep living their usual lifestyle during the study period.

For effective supervision, each participant was scheduled his or her own time for the exercise. The physiotherapist who was supervising the exercise regimen was blinded from knowing that the participants were in a study and the purpose of the study to obtain reliable results.

Randomisation

To allocate participants to either TG or CG, a random sequence of numbers was generated from the computer using the RANDBETWEEN function in Microsoft Excel, 2016. Treatments were then allocated to participants in sequence using numbered opaque envelopes containing the treatment allocations. The generation of the number sequence and allocation of the envelops to the participants was done by a Physiotherapist who was not involved in data collection and evaluation of the outcomes.

Data collection and equipment

Data was collected from June, 2018 to March, 2019. Variables of BMD ($g.\ cm^{-2}$), maximal strength, heart rate, weight, height and body mass index (BMI) were obtained and recorded on a data collection form before and after the exercise programme in the TG and the CG to determine effects of the exercise.

Bone mineral density

Femoral neck and lumbar spine BMD ($g.\ cm^{-2}$) was measured using dual-energy X-ray absorptiometry (DEXA) (Hologic Discovery-Wi (S/N 84668), software version 13.5.3.2:5, Hologic Bedford Inc., Bedford, MA, USA) at QECH. Femoral neck BMD was measured at the left hip only. Measurement of the lumbar spine BMD was done from the first to fourth lumbar spines and a total BMD value was recorded.

Maximal strength

Maximal strength, obtained as 1RM was measured on the squat machine as described under the exercise protocol section. To determine 1 RM, several lifts were executed with an increasing load of 5 kg for each lift until the highest load lifted was reached.

Body weight, height and heart rate

Body weight (kg) and height (cm) measurements were obtained using a Stadiometer (HS – he DBS00361, Model: 1127154) following the manufacturer's guidelines. A heart rate monitor (Polar FT4, Model C317T21 559445) was used to obtain heart rate measurements before and after the exercise.

Body mass index

BMI for each participant was calculated by dividing weight measurement by the square of the height measurement in meters (m^2).

Sample size

Sample size estimates are based on the effect size, alpha and number of participants in each group. From the results, an increase of 3% in femoral neck BMD and 4% in lumbar BMD after exercise training was obtained. To detect a 3% increase in mean BMD, with an alpha of 0.05 at 80% power using a two - sided test, 15 participants in each group were required. Sample size calculations were done using a G*power 3.1.6 computer software programme.

Data analysis

Statistical Package for the Social Science (SPSS version 25) was used to analyze the data. Descriptive statistics such as mean and standard deviation (SD) were used to characterize the data variables. All data variables were normally distributed. Student's t - test was used to analyse differences between and within the groups. All statistical tests were two - sided and a p value of ≤0.05 was considered statistically significant.

Ethical considerations

As participants came for refilling their ART medication at QECH, they were requested to attend a health talk regarding the purpose of the study and invited to participate. This health talk was conducted by the researchers. Willing participants were directed into a separate room where the aim and objectives of the study were again explained and screening for eligibility was done. Written informed consent was obtained from eligible and willing participants.

All ethical procedures were followed and privacy and confidentiality were ensured by allocating codes to the participants. The study was approved by the University of Malawi's College of Medicine Research and Ethics Committee (COMREC) registration number P.06/17/2206. The study was registered with the Pan African Clinical Trial Registry on 22nd December, 2017 with identification number: PACTR201712002889203.

Results

Out of 55 eligible participants, 29 participants were excluded because they either did not meet the inclusion criteria or they declined to participate. Twenty-six participants were therefore included and randomly allocated to either a TG ($n = 15$) or CG ($n = 11$). Two participants (one from each group) did not finish the training due to transfer and withdrawal of consent (Fig. 1). The study adhered to CONSORT guidelines for conducting randomised controlled trials. The training group completed all the planned training sessions. No significant differences in baseline characteristics were observed between participants in the TG and the CG (Table 1).

On average, there were significant improvements in lumbar spine BMD and 1RM ($p < 0.001$) as well as in resting heart rate ($p = 0.027$) in the TG participants after 12 weeks (paired samples t-test). Only 1RM was significantly higher ($p = 0.013$) after 12 weeks in the CG (Table 2).

Table 1 Characteristics of participants at baseline

	TG ($n = 14$)	CG ($n = 10$)	P – value
Age (years)	35.1 ± 6.7	37.7 ± 6.3	0.34
Height (cm)	160.1 ± 0.1	159 .7 ± 0.1	0.91
Weight (kg)	57.0 ± 7.8	60.1 ± 11.3	0.43
BMI (kg/cm^2)	22.2 ± 2.5	23.7 ± 4.7	0.34

Data are presented as mean ± SD, *TG* Training group, *CG* Control group, *P*-values are based on Independent samples t – test

The changes in mean values for lumbar spine BMD (0.006 $g.\ cm^{-2}$ vs 0.033 $g.\ cm^{-2}$) and heart rate (1.9 bpm vs − 8.14 bpm) were significantly higher within the TG compared to the CG after 12 weeks. Whereas the mean value for 1RM (12.3 kg vs 115.36 kg) was significantly higher in both the TG and CG after 12 weeks (Table 3).

Discussion

The main purpose of this pilot study was to determine the effects of 12 weeks of MST on reduced BMD in HIV infected individuals receiving ART in Blantyre, Malawi. Results reveal that MST performed three times a week for 12 weeks is effective in increasing lumbar spine BMD

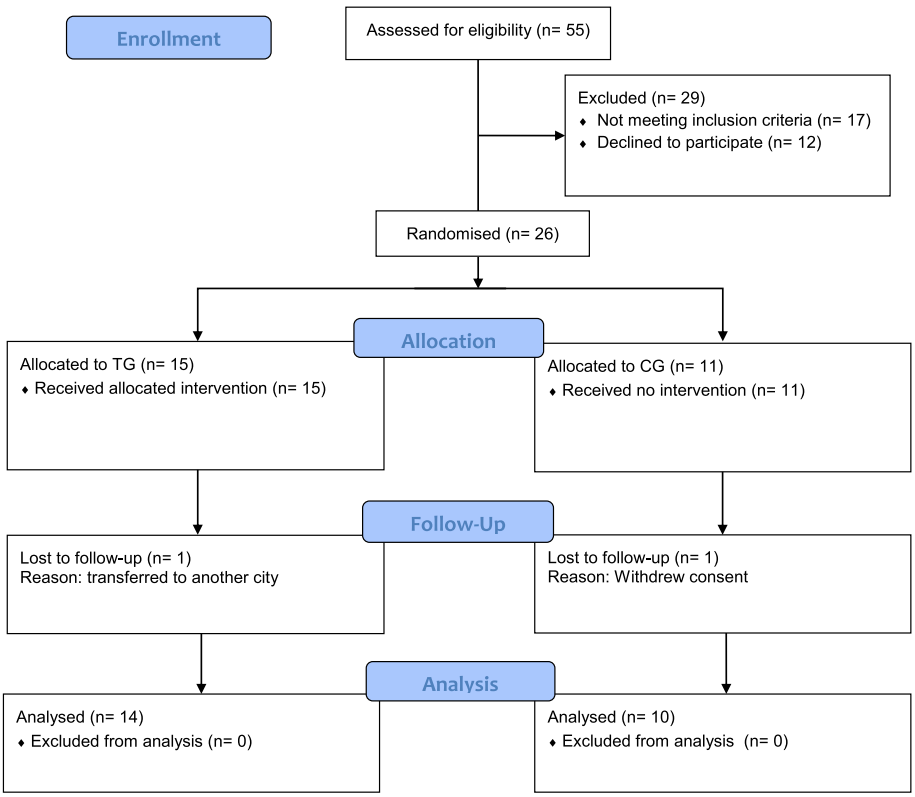

Fig. 1 Study flow diagram showing numbers of participants in the TG and CG

Table 2 Changes in physiological parameters before and after exercise training

	TG (n = 14)		CG (n = 10)	
	Pre-training	**Post-training**	**Pre-training**	**Post-training**
Femoral neck BMD ($g.\ cm^{-2}$)	0.770 ± 0.1	0.778 ± 0.1	0.772 ± 0.1	0.786 ± 0.1
Lumbar spine BMD ($g.\ cm^{-2}$)	0.771 ± 0.1	0.804 ± 0.1*	0.774 ± 0.7	0.780 ± 0.1
1 RM (kg)	106.79 ± 31.4	222.14 ± 43.2*	110.70 ± 34.8	123.00 ± 33.2
Heart rate (bpm)	87.00 ± 16.4	78.86 ± 11.2*	74.30 ± 13.7	76.20 ± 10.3

Data are presented as mean ± SD, *TG* Training group, *CG* Control group, *bpm* beats per minute, * Significant difference $p < 0.05$

among PLWHIV on ART. The MST intervention also caused improvements in muscle strength among the participants.

Current findings are in line with the study by Santos et al. (2015), who demonstrated that a 12 weeks progressive exercise programme was appropriate to impact significant lumbar and femoral neck bone increases in 20 individuals living with HIV[9]. Despite some evidence that all physical activity could be important in increasing BMD [12], weight bearing physical activities with high loads, yield a notable increase in BMD [10]. Although bones respond to small loading stimuli, evidence indicate that high mechanical loading, such as those used in MST, increase BMD by acting on muscle and ground reaction forces which in turn induces mesenchymal stem cells osteogenic differentiation towards osteoblasts [13]. An osteogenic response is more likely with high loads due to the triggering of higher mechanostat thresholds [34]. This could suggest that appropriate load bearing exercises such MST can promote increases in BMD, thereby reducing the risk for osteoporosis among PLWHIV.

Compared to findings of some previous studies [21, 35, 36], significant improvements in BMD were observed after a short strength exercise training programme of 12 weeks in the current study. This could be due to progressive loading and emphasis on intensity monitoring in the MST. In the current study, the training load was re-evaluated every week to ensure progressive loading throughout the intervention which maintains the mechanical stress that regulates bone remodeling through osteoblasts [13]. In addition, it has been reported that longer periods of more than 3 months of exercise interventions lead to high dropout rates [14, 37]. The adherence rate in the current study was 93% in the TG and 90% in the CG. The compliance rate was 100% with all participants completing all planned training sessions. Therefore, MST which promotes shorter exercise durations could be an alternative and attractive intervention for managing reduced BMD in PLWHIV.

Concurrent with previous findings [17, 18], significant improvements in muscle strength following MST were observed in the current study. Contrary to most conventional ways of strength training, MST emphasies on high loads and few repetitions with focus on high acceleration during the concentric phase which leads to high rate of force development as the muscles contaract [17]. However, while significant improvements in strength were observed in the TG only in the study by Mosti et al. (2013) [17], current findings reveal significant strength improvements in both the TG and CG as determined by increases in 1RM. Although both groups exhibited significant strength improvements, there were greater improvements among participants within the TG. Notable increases in strength in the CG in the present study could be attributed to occupational activities of most Malawian adults or other undetermined reasons. Data for the study was collected between June 2018 and March 2019 which falls within the farming period in Malawi. During this period most Malawians are involved in land preparation, planting and harvesting which demand a considerable physical capacity.

In line with other studies [25], significant reductions in heart rate were observed in the current study. A

Table 3 Mean differences in physiological parameters between and within the groups

	Within groups*		Between groups#
	TG (n = 14)	CG (n = 10)	
Femoral neck BMD ($g.\ cm^{-2}$)	0.008 (0.472)	0.014 (0.144)	0.006 (0.675)
Lumbar spine BMD ($g.\ cm^{-2}$)	0.033 (< 0.001)	0.006 (0.568)	0.027 (0.026)
1 RM (kg)	115.36 (< 0.001)	12.30 (0.013)	103.06 (< 0.001)
Heart rate (bpm)	−8 .14 (0.027)	1.90 (0.561)	−10.04 (0.044)

Data are presented as mean difference (*p*-value), *TG* Training group, *CG* Control group, *bpm* beats per minute, *P*-values are based on *Paired samples t-test, #Independent samples t-test

meta-analysis of randomised trials by O'Brien et al. (2008) reported a reduction in heart rate of – 13.2 bpm for participants in the TG. An almost similar reduction in heart rate (– 8.14 bpm) has been shown in the current study suggesting that MST has an effect on some cardiopulmonary parameters among PLWHIV.

To the best of our knowledge, this is the first randomised controlled trial that has evaluated the effects of MST exercises with focus on BMD as the main outcome in PLWHIV. A supervised, individualised and facility based MST exercise programme targeting BMD with clear descriptions of exercise type, frequency, intensity and duration was adopted. This pilot study provides preliminary data that allows potential for larger prospective studies on effective exercise strategies used to manage reduced BMD among PLWHIV. One limitation of the study was a relatively low sample size. However, based on previous studies [9, 17] the number of participants was adequate to assess the effectiveness of a MST programme on bone and strength parameters as revealed in the findings. Considering that gender may be a plausible confounder for bone responses to external loads, another limitation of the study was that analysis for BMD responses within gender were not done due to low sample size. Therefore, larger prospective trials with larger sample size investigating the effects of MST on BMD in PLWHIV are warranted.

Conclusions

The study demonstrates that a 12 weeks' exercise programme of MST improves lumbar BMD, heart rate and muscle strength in PLWHIV on ART exhibiting reduced BMD in Blantyre, Malawi. Data from this pilot study suggest that individualized and supervised MST performed for a shorter duration of 12 weeks seem to have the potential in treating reduced BMD among PLWHIV on ART. Since this was a pilot study, larger randomized controlled trials investigating the effects of 12 weeks MST on reduced BMD among PLWHIV with a larger sample size are merited.

Abbreviations

1RM: One repetition Maximum; ART: Antiretroviral Therapy; BMD: Bone Mineral Density; CG: Control group; DEXA: Dual Energy X-ray Absorptiometry; HIV: Human Immunodeficiency Syndrome; MST: Maximal Strength Training; PLWHIV: People living with HIV; TG: Training group

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Authors' contributions

EC made substantial contributions to the conception, design of the work and drafted the work. DC and FL revised the work critically for important intellectual content. All authors have read and approved the manuscript and are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Availability of data and materials

The data that support the findings of this study are available from the College of Medicine Ethics Committee (COMREC), but restrictions apply to the availability of these data, because the data contains potentially identifying information and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of COMREC an IRB that approved the study.

Ethics approval and consent to participate

The study was approved by the University of Malawi's College of Medicine Research and Ethics Committee (COMREC) with registration number P.06/17/2206. The study was registered with the Pan African Clinical Trial Registry on 22nd December, 2017 with identification number: PACTR201712002889203. Necessary ethical procedures were followed when recruiting participants and privacy as well as confidentiality were ensured by allocating codes to the participants. Written informed consent was obtained from eligible and willing participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. Chisati EM, Demitri C, Lampiao F. Reduced bone mineral density among HIV infected patients on anti-retroviral therapy in Blantyre, Malawi : prevalence and associated factors. PLoS One. 2020;15(1):1–12. https://doi.org/10.1371/journal.pone.0227893.
2. Chitu-Tisu CE, Barbu EC, Lazar M, Ion DA, Badarau IA. Low bone mineral density and associated risk factors in HIV-infected patients. GERMS. 2016; 6(2):50–9. https://doi.org/10.11599/germs.2016.1089\rgerms.2016.1089.
3. Escota GV, Mondy K, Bush T, et al. High prevalence of low bone mineral density and substantial bone loss over 4 years among HIV-infected persons in the era of modern antiretroviral therapy. AIDS Res Hum Retrovir. 2016; 31(1):59–67. https://doi.org/10.1089/aid.2015.0158.
4. Linda A, Young B, Overton E. Bone, fractures, antiretroviral therapy and HIV. Curr Infect Dis Rep. 2015;16(2):1–10. https://doi.org/10.1007/s11908-014-0393-1.Bones.

5. Ali MK, Magee MJ, Dave JA, et al. HIV and metabolic, Body , and bone disorders : what we know from low- and middle-income countries. J Acquir Immune Defic Syndr. 2014;67(Supp 1: September):27–39.
6. Chisati EM, Constantinou D, Lampiao F. Management of reduced bone mineral density in HIV: pharmacological challenges and the role of exercise. Front Physiol. 2018;9:1. https://doi.org/10.3389/fphys.2018.01074.
7. Perazzo JD, Webel AR, Fichtenbaum CJ, Mccomsey GA. Bone health in people living with HIV : the role of exercise and directions for future research. J Assoc Nurses AIDS Care. 2018;29(2):330–7. https://doi.org/10.1016/j.jana.2017.09.012.
8. Perazzo JD, Webel AR, Alam SMK. Relationships between physical activity and bone density in people living with HIV: results from the SATURN-HIV study', journal of the Association of Nurses in AIDS care. J Assoc Nurses AIDS Care. 2018;29(4):528–37. https://doi.org/10.1016/j.jana.2018.03.004.
9. Santos W, Santos W, Paes P, et al. Impact of strength training on bone mineral density in patients infected with HIV exhibiting Lipodystrophy. J Strength Cond Res. 2015;29(12):3466–71.
10. Howe TE, Shea B, Dawson LJ, et al. Exercise for preventing and treating osteoporosis in postmenopausal women. Cochrane Database Syst Rev. 2011;7:1–112. https://doi.org/10.1002/14651858.CD000333.pub2.
11. Beck BR, Daly RM, Fiatarone MA, Taaffe DR. Exercise and sports science Australia (ESSA) position statement on exercise prescription for the prevention and management of osteoporosis. J Sci Med Sport. 2016;1403:1–8.
12. Body JJ, Bergmann P, Boonen S, et al. Non-pharmacological management of osteoporosis: a consensus of the Belgian bone Club. Osteoporos Int. 2011;22(11):2769–88. https://doi.org/10.1007/s00198-011-1545-x.
13. Yuan Y, Chen X, Zhang L, et al. The roles of exercise in bone remodeling and in prevention and treatment of osteoporosis. Prog Biophys Mol Biol. 2016;122(2):122–30. https://doi.org/10.1016/j.pbiomolbio.2015.11.005.
14. Kelley GA, Kelley KS. Dropouts and compliance in exercise interventions targeting bone mineral density in adults: a meta-analysis of randomized controlled trials. J Osteoporos. 2013;2013:1–19. https://doi.org/10.1155/2013/250423.
15. Vancampfort D, Mugisha J, Richards J, et al. Dropout from physical activity interventions in people living with HIV: a systematic review and meta-analysis. AIDS Care. 2017;29(5):636–43. https://doi.org/10.1080/09540121.2016.1248347.
16. Aitken D, Buchbinder R, Jones G, Winzenberg T. Interventions to improve adherence to exercise for chronic musculoskeletal pain in adults. Aust Fam Physician. 2015;44:39–42.
17. Mosti M, Nils K, Stunes A, Hoff J, Syversen U. Maximal strength training in postmenopausal women with osteoporosis or osteopenia. J Strength Cond Res. 2013;27(10):2879–86.
18. Mosti M, Carlsen T, Aas E, Hoff J, Stunes A, Syversen U. Maximal strength training improves bone mineral density and neuromuscular performance in Young adult women. J Strength Cond Res. 2014;28(10):2935–45.
19. Multanen J, Nieminen MT, Häkkinen A, et al. Effects of high impact training on bone and articular. JBMR. 2015;29(1):192–201. https://doi.org/10.1002/jbmr.2015.
20. Cheung AM, Giangregorio L. Mechanical stimuli and bone health : what is the evidence ? Curr Opin Rheumatol. 2012;24:561–6. https://doi.org/10.1097/BOR.0b013e3283570238.
21. Ryan AS, Ivey FM, Hurlbut DE, et al. Regional bone mineral density after resistive training in young and older men and women. Scand J Med Sci Sports. 2004;14:16–23. https://doi.org/10.1046/j.1600-0838.2003.00328.x.
22. Fillipas S, Cherry CL, Cicuttini F, Smirneos L, Holland AE. The effects of exercise training on metabolic and morphological outcomes for people living with HIV: a systematic review of randomised controlled trials. HIV Clin Trials. 2010;11(5):270–82. https://doi.org/10.1310/hct1105-270.
23. Grace JM, Semple SJ, Combrink S. Exercise therapy for human immunodeficiency virus/AIDS patients: guidelines for clinical exercise therapists. J Exerc Sci Fit. 2015;13(1):49–56. https://doi.org/10.1016/j.jesf.2014.10.003.
24. Neto MG, Conceico CS, Carvalho VO, Brites C. Effects of combined aerobic and resistance exercise on exercise capacity, muscle strength and quality of life in HIV-infected patients: a systematic review and meta-analysis. PLoS One. 2015;10(9):1–14. https://doi.org/10.1371/journal.pone.0138066.
25. O'Brien K, Tynan A-M, Nixon S, Glazier RH. Effects of progressive resistive exercise in adults living with HIV/AIDS: systematic review and meta-analysis of randomized trials. AIDS Care. 2008;20(6):631–53. https://doi.org/10.1080/09540120701661708.
26. Grant PM, Cotter AG. Tenofovir and bone health. Curr Opin HIV AIDS. 2016;11(3):326–32. https://doi.org/10.1097/COH.0000000000000248.
27. Yin MT, Overton ET. Increasing clarity on bone loss associated with antiretroviral initiation. J Infect Dis. 2011;203(12):1705–7. https://doi.org/10.1093/infdis/jir184.
28. Grace JM. Exercise therapy for acquired immune deficiency syndrome (AIDS) patients. Fitness Med. 2016;1:129–45.
29. World Health Organisation. Scientific group on the assessment of osteoporosis at primary health care level. Summary Meeting Rep. 2004;1:1–13.
30. International Society for Clinical Densitometry. 2013 Official Positions - Adult. http://www.iscd.org/official-positions/2013-iscd-official-positions-adult/.
31. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician ' s guide to prevention and treatment of osteoporosis. Osteoporos Int. 2014;25:2359–81. https://doi.org/10.1007/s00198-014-2794-2.
32. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. Lancet. 2002;359(June 1):1929–36.
33. Duvivier C, Kolta S, Assoumou L, et al. Greater decrease in bone mineral density with protease inhibitor regimens compared with nonnucleoside reverse transcriptase inhibitor regimens in HIV-1 infected naive patients. AIDS. 2009;23(7):817–24. https://doi.org/10.1097/QAD.0b013e328328f789.
34. Frost HM. Bone's Mechanostat: a 2003 update. Anat Rec Adv Intergrative Anat Evol Biol. 2003;275(2):1081–101. https://doi.org/10.1002/ar.a.10119.
35. Kemmler W, Engelke K, von Stengel S. Long-term exercise and bone mineral density changes in postmenopausal women-are there periods of reduced effectiveness? J Bone Miner Res. 2016;31(1):215–22. https://doi.org/10.1002/jbmr.2608.
36. Hinton PS, Nigh P, Thyfault J. Effectiveness of resistance training or jumping-exercise to increase bone mineral density in men with low bone mass: a 12-month randomized, clinical trial. Bone. 2015;79:203–12. https://doi.org/10.1016/j.bone.2015.06.008.
37. Horne M, Tierney S. What are the barriers and facilitators to exercise and physical activity uptake and adherence among south Asian older adults: a systematic review of qualitative studies. Prev Med (Baltim). 2012;55(4):276–84. https://doi.org/10.1016/j.ypmed.2012.07.016.

Publisher's Note

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

SHORT LAST 7 DAYS SELF-ADMINISTERED FORMAT

FOR USE WITH YOUNG AND MIDDLE-AGED ADULTS (15-69 years)

The International Physical Activity Questionnaires (IPAQ) comprises a set of 4 questionnaires. Long (5 activity domains asked independently) and short (4 generic items) versions for use by either telephone or self-administered methods are available. The purpose of the questionnaires is to provide common instruments that can be used to obtain internationally comparable data on health–related physical activity.

Background on IPAQ

The development of an international measure for physical activity commenced in Geneva in 1998 and was followed by extensive reliability and validity testing undertaken across 12 countries (14 sites) during 2000. The final results suggest that these measures have acceptable measurement properties for use in many settings and in different languages, and are suitable for national population-based prevalence studies of participation in physical activity.

Using IPAQ

Use of the IPAQ instruments for monitoring and research purposes is encouraged. It is recommended that no changes be made to the order or wording of the questions as this will affect the psychometric properties of the instruments.

Translation from English and Cultural Adaptation

Translation from English is supported to facilitate worldwide use of IPAQ. Information on the availability of IPAQ in different languages can be obtained at www.ipaq.ki.se. If a new translation is undertaken we highly recommend using the prescribed back translation methods available on the IPAQ website. If possible please consider making your translated version of

IPAQ available to others by contributing it to the IPAQ website. Further details on translation and cultural adaptation can be downloaded from the website.

Further Developments of IPAQ

International collaboration on IPAQ is on-going and an ***International Physical Activity Prevalence Study*** is in progress. For further information see the IPAQ website.

More Information

More detailed information on the IPAQ process and the research methods used in the development of IPAQ instruments is available at www.ipaq.ki.se and Booth, M.L. (2000). *Assessment of Physical Activity: An International Perspective*. Research Quarterly for Exercise and Sport, 71 (2): s114-20. Other scientific publications and presentations on the use of IPAQ are summarized on the website.

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

   _____ **days per week**

   ☐ No vigorous physical activities → ***Skip to question 3***

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

   _____ **hours per day**
   _____ **minutes per day**

   ☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

_____ **days per week**

☐ No moderate physical activities → ***Skip to question 5***

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

_____ **hours per day**
_____ **minutes per day**

☐ Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you have done solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

_____ **days per week**

☐

No walking → ***Skip to question 7***

6. How much time did you usually spend **walking** on one of those days?

_____ **hours per day**
_____ **minutes per day**

☐ Don't know/Not sure

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

_____ **hours per day**
_____ **minutes per day**

☐ Don't know/Not sure

This is the end of the questionnaire, thank you for participating.