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Association between Bone Mass Density and Highly Active Anti-Retroviral
Therapy: A Systematic Review and Meta - Analysis

TESIS

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To our parents for their unconditional support

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ABSTRACT

Objectives

Quality of life in HIV positive patients can be deteriorated by diseases like osteoporosis or osteopenia. Multiple studies have investigated the causes of reduced bone mineral density in HIV patients. The objective of our study was to perform a systematic review and meta-analysis to determine the association between the use of HAART (Highly Active Antiretroviral Therapy) and low bone mass density in HIV infected patients.

Methods

We searched several data bases to identify cross sectional, case controls, cohorts and randomized clinical trials. Two independent researchers reviewed the databases and a third investigator was involved in case of discrepancies. We identified eight cross-sectional studies and one cohort that reported the association between bone mineral density in patients with HIV in HAART versus patients with HIV naïve treatment.

Results

Eight cross sectional studies and one cohort reporting the association between low bone mass density in HIV treated patients versus non-treated were retrieved; the majority with low quality. A meta-analysis was performed and the following results were obtained. The odds of osteopenia and osteoporosis in HIV-infected patients receiving HAART compared with naïve patients was OR 1.03 CI 95%: 0.69-1.55; I²: 17% and OR 1.27 CI 95%: 0.67-2.38; I²: 5% respectively.

Conclusion

Our results show that evidence is not strong enough to determine that HAART has an effect on BMD. Statistical significance was not found, nevertheless low quality studies jeopardize the conclusions. Further research is needed with larger cohorts with longer follow-up and adjusted to anthropometric and infection related data.

Keywords: Bone Mineral Density; HAART; HIV

RESUMEN

Objetivos

La calidad de vida en pacientes VIH positivo puede verse afectada por enfermedades como la osteoporosis u osteopenia. Múltiples estudios han investigado las causas de la disminución de densidad mineral ósea en esta población. El objetivo fue realizar una revisión sistemática y meta análisis para determinar la asociación entre el uso de TARGA (Tratamiento Antirretroviral de Gran Actividad) y la baja densidad mineral ósea en pacientes infectados.

Métodos

Se realizó una búsqueda en diversas bases de datos para identificar estudios transversales, casos y controles, cohortes y ensayos clínicos aleatorizados. Dos investigadores independientemente revisaron las bases de datos y un tercero intervino en caso de discrepancias. Se identificaron ocho estudios transversales y una cohorte que reportan la asociación entre la densidad mineral ósea en pacientes con VIH en TARGA versus paciente con VIH sin tratamiento.

Resultados

Ocho estudios transversales y una cohorte que reportan la asociación entre baja densidad mineral ósea y VIH en pacientes tratados versus pacientes sin tratamiento fueron obtenidos; la mayoría de baja calidad. Se realizó un meta análisis y los siguientes resultados fueron obtenidos. Los odds de osteopenia y osteoporosis en pacientes con VIH recibiendo TARGA versus pacientes sin tratamiento fue OR 1.03 CI 95%: 0.69-1.55; I²: 17% y OR 1.27 CI 95%: 0.67-2.38; I²: 5% respectivamente.

Conclusión

Nuestros resultados muestran que la evidencia no es suficientemente fuerte para determinar si el TARGA tiene un efecto verdadero sobre la DMO. Los resultados no fueron estadísticamente significativos, sin embargo la baja calidad de los estudios puede alterar las conclusiones. Se requirieren mayores estudios como cohortes con seguimiento a largo plazo y ajustados a datos antropométricos y propios de la enfermedad.

Palabras clave: Densidad Mineral Ósea; TARGA; VIH

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1 INTRODUCTION

The human immunodeficiency virus (HIV) has affected more than 70 million people since its discovery (1); according to UNAIDS, by 2015 there were 36.7 million people globally living with HIV, of whom, 17 million are on treatment (2, 3). Since 1996 when HAART (Highly Active Antiretroviral Treatment) was introduced, mortality rates decreased in HIV patients, transforming this condition into a chronic infectious disease (4, 5). Currently, basic first line treatment consists of three drugs that can vary along the way according to the level of adherence the patient exhibits and resistance pertaining the virus (6, 7). Despite this evident reduction of morbidity and mortality, prolonged use of HAART has been associated with numerous metabolic complications such as hyperlipidemia, lipodystrophy and osteoporosis (8, 9, 10). Nevertheless, the direct association between HAART and the reduction of bone mass density is still a controversial topic (11).

Several mechanisms have been described through which HAART can cause an impact on bone mineral density, directly, they generate an inhibitory response in osteoblastic activity and activation of osteoclasts (11, 12, 13). Indirectly, they are associated to renal losses of phosphate, vitamin D alterations or changes in the parathyroid hormone metabolism (11, 12, 13). Furthermore, studies have linked HAART caused immune reconstitution to bone demineralization (11, 12, 13).

Loss of bone mineral density has also been associated directly with HIV infection and/or the pro-inflammatory state related to immune activation (11). Several studies indicate that bone homeostasis is affected by osteogenic cells infected by the virus and by cytokines such as TNF-Alpha, which are increased in patients with high viral load (10, 11, 14, 15, 16). Furthermore, other studies suggest that viral proteins (mainly gp120) interfere with osteoblastic and osteoclastic cellular activity resulting in bone mineral loss (11, 12, 15, 17). These issues, in addition to a variety of factors related to bone fracture in general population such as alcohol abuse, smoking, opiate use, low body mass index, and malnutrition are frequently present in HIV positive patients contributing to bone fragility (13, 15, 18).

Elevated levels of inflammatory and coagulation markers have been associated to HIV and aging. These markers also remain elevated in patients on HAART and are associated to an

increase in mortality (19), therefore, these patients are showing signs of early aging and it's important to maintain continuous monitoring (20).

Several studies show there are multiple HIV directed factors associated with low BMD such as duration of infection, HIV viral burden, and a more advanced HIV disease (21, 22). It is believed that all HAART regimens may have a negative impact in bone mineral density, regardless of the regimen type, since bone loss appears as a general phenomenon after HAART initiation (21). Likewise, there is also evidence which shows that specific drugs can affect bone mineral density, such as Protease Inhibitors (PIs) and Tenofovir (TDF) (21), nevertheless this information is inconclusive and contradictory.

We hypothesize that HAART is indeed associated with low bone mass density. Some studies support our hypothesis in that HAART is the main cause of reduced bone mineral density (8, 23, 24) others have evidence against it (9, 10, 16, 25, 26, 27) and some are inconclusive (28, 29, 30). This systematic review will allow us to have a better understanding of the real causes.

2 OBJECTIVES

To conduct a systematic review and meta-analysis in which our primary objective is to determine the association between HAART and low Bone Mass Density in HIV infected patients by measuring the pooled odds ratio, following the Cochrane guidelines. The population being all HIV infected patients, the exposure factor being HAART, the comparison group: HIV infected patients naïve to treatment, and the outcome measured would be the diminution of bone mass density. The secondary objectives include determining the prevalence of osteopenia and osteoporosis in HIV infected patients on HAART vs Naïve and determining the prevalence of low BMD in HIV infected patients on HAART vs Naïve.

3 METHODS

The protocol was registered in PROSPERO with record number #42016048234.

3.1 Data sources and searches:

Studies included in the analysis were identified by searching MEDLINE/Pubmed, Cochrane central register of controlled trials, EMBASE and Global Health Library without time restriction until 2016. Additionally, we searched for grey literature on Grey Literature Report, Web of Science, SCOPUS and International AIDS Society (IAS) conference's abstract books (2015 and 2016). The terms used for the search are annexed (Appendix 1). We combined the results obtained from the strategy above to generate a pool of preliminary studies. We searched the references of the previously selected articles for other potential studies and further explored the frequently mentioned authors for more references.

Potentially included articles were cross-sectional, case-controls, cohorts and randomized clinical trials; nevertheless, eight cross sectional studies and one cohort were retrieved. Case reports, congress summaries/letter to the editor and other systematic reviews were excluded. All participants had to be HIV positive either taking HAART or not. We did not disregard participants according to the duration, frequency or type of medications taken. Studies in which patients had any bone related diseases were excluded (including osteopenia and osteoporosis at baseline).

3.2 Study selection and data extraction:

Two reviewers (AA, DR), independently, reviewed titles and abstracts of the pool of preliminary studies to evaluate if they meet the inclusion and exclusion criteria. Any discrepancies were discussed between investigators and if a unanimous decision was not achieved, the third reviewer (CU-G) would intervene to make a final decision. The same methodology was employed for the full text review in which we further analyzed the articles to ensure the population, exposure, comparison and outcome were adequate for our research.

We proceeded to contact authors via email about potentially eligible studies, identified in the full text search, to request more information for its inclusion. If the author could not be reached or additional information were not provided in 3 weeks, we excluded them and used only the published data.

3.3 Outcome measures:

From each publication obtained, relevant information was extracted. Information such as demographic, anthropometric and other variables were attained, as well as bone mass density (BMD), the main outcome. To measure bone mass density dual-energy x-ray absorptiometry (DEXA) is used. This method uses a small dose of ionizing radiation to measure bone loss and results are interpreted using standard deviations. The World Health Organization (WHO) criteria defines osteoporosis and osteopenia according to the T-score on postmenopausal women and men aged 50 years or more; T-score between -1 and -2.5 Standard Deviations is classified as osteopenia, and T-score $\leq$ -2.5 Standard Deviations is classified as osteoporosis (31). Z-scores are preferred in females prior to menopause and in males younger than age 50. A z-score of $\leq$ -2.0 is defined as “below the expected range for age”, and a z-score above -2.0 is “within the expected range for age” (32). Furthermore, we categorized the outcome as normal or reduced BMD, including in the later one all patients that met the criteria for osteopenia and osteoporosis according to WHO (31).

3.4 Evaluation of study quality:

The quality of the included studies was assessed independently by two authors (AA) (DR), using the New-Castle-Ottawa Scale, as recommended by the Cochrane Collaboration (Appendix 2). For any discrepancies, the third reviewer (CU-G) made a final determination.

The Funnel plot to evaluate publication bias, was not performed since only 9 articles were used on the meta-analysis; at least 10 are needed to accomplish a funnel plot.

3.5 Data synthesis and analysis:

This systematic review and meta-analysis was based on the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) collaboration (33). To calculate the pooled odds ratio and 95% confidence intervals we used a random – effects model and the inverse variance method which indicates the proportion of the total variation that is attributable to heterogeneity (34). The I^2 test was used to evaluate heterogeneity, values up to 25% would be considered low heterogeneity, from 25% to 50% moderate heterogeneity and up to 75% high heterogeneity. Also Chi^2 test was used, in which a p-value of <0.05 would indicate statistical heterogeneity. We used Review Manager 5 to evaluate all statistical analyses.

4 RESULTS:

6832 citations were retrieved, from which 78 remained and were further analyzed in full text (Figure 1). Seven of these met the inclusion criteria (23, 25, 27, 35, 36, 37, 38) and were included in the qualitative synthesis. Additionally, we included two more articles (26, 39) to develop a meta-analysis that only evaluated bone mass density as normal or reduced. In total, nine articles were used in this systematic review. The general characteristics of the primary studies extracted for our systematic review are shown in Table 1 and specific characteristics concerning bone mass density measurements in Table 2. Most of the articles retrieved used T-scores to classify osteopenia and osteoporosis regardless of age. These studies involved 1467 HIV patients, from which 1210 were on HAART and 257 were naïve to treatment. Some studies were performed in Europe (Spain=2, Slovenia=1, Belgium=1), others in Asia (China=2, Taiwan=1), and the remaining two were done in USA, and Brazil. 8/9 studies (23, 25, 26, 27, 35, 37, 38, 39) were cross sectional. The remaining study (36) is a cohort.

According to the New Castle Ottawa Scale most of the studies, with the exception of the cohort, had low quality. The cohort study scored seven stars according to the scale. Regarding heterogeneity, I^2 values and p scores showed low heterogeneity on osteopenia ($p=0.30$, I^2 17%) and osteoporosis ($p=0.38$, I^2 5%) Forrest Plots. Contrariwise, high heterogeneity was found on the reduced bone mass density Forrest Plot ($p=0.02$, I^2 57%).

For the analysis of osteopenia and osteoporosis in HIV patients (naïve versus HAART) seven articles were used (Table 3). These involved 1229 HIV patients, from which 1050 were on HAART and 179 were naïve. Osteopenia and osteoporosis were not associated with HAART. The odds of osteopenia and osteoporosis in HIV-infected patients receiving HAART compared with naïve patients was OR 1.03 CI 95%: 0.69-1.55; I^2 : 17% (figure 2) and OR 1.27 CI 95%: 0.67-2.38; I^2 : 5% (figure 3) respectively.

Afterwards, a meta-analysis was conducted to evaluate bone mass density; nine articles were used (Table 4), showing no association. The odds of reduced bone mass density in HIV infected patients receiving HAART compared with naïve patients was OR 1.27 CI 95%: 0.74-2.20; I^2 : 57% (figure 4).

With the information retrieved, amongst the population used for the meta-analysis, prevalence of osteopenia was 51% (range:17 – 57%) on HIV infected naïve patients, and 47% (range:37 –

72%) on HIV infected patients on HAART. Prevalence of osteoporosis was also calculated, being 8% (range:0 – 13%) on naïve patients and 9% (range:0 – 26%) on HAART patients. Concerning low bone mass density, the prevalence was 48% (range:12 - 69%) on naïve patients and 52% (range:31 – 98%) on HAART patients.

On the other hand, the only cohort we found that met our criteria, not only measured BMD at baseline (SUN) but also compared its results with a population of non-HIV patients (NHANES) (35). The prevalence of osteopenia was 45% (SUN) vs. 28% (NHANES) and osteoporosis was 3.5% (SUN) and 0.9% (NHANES). Moreover, 170 patients virologically suppressed, with 2-year treatment prior to study, were followed 4 years. Results showed, 35% (femoral neck), 49% (total hip) and 29% (lumbar spine) maintained a stable BMD. Contrariwise, 31% (at any site) showed a >5% decrease of BMD.

5 DISCUSSION:

Our main objective was to determine the association between the use of HAART and low bone mass density on HIV infected patients. Regarding the results, there was no association between the use of HAART and low bone mass density. Nevertheless, the only cohort retrieved, showed a significant reduction of BMD (>5%) on a 4 year follow up, despite antiretroviral treatment. Most of the articles didn't adjust their results for anthropometric traits or infection related data such as viral load, CD4 count, HIV infection duration and HAART duration that could jeopardize this association.

There is evidence that supports that premature aging occurs in HIV patients (40). There are numerous common pathways between HIV infection and normal aging that lead to chronic illness such as immune activation, senescence inflammation, hyper coagulation and body composition (40, 41). Related to bone mineral density, several references indicate that in naïve patients, direct viral and inflammatory effects of HIV lead to an unsuccessful homeostasis between bone resorption and bone formation (10, 11, 14, 17). Osteoblastic activity is reduced and apoptosis is increased, on the contrary, osteoclastic activity is increased (11, 13, 15, 17).

Contrariwise, several studies indicate that PI use results in increased bone turnover, accelerated bone loss and lower bone mass density (42, 43, 44, 45) whilst other have contradictory information (9, 10, 46, 47). On the other hand, there is evidence that shows that Tenofovir-based treatment has a clear impact on low BMD (48, 49). Nevertheless, some cohort studies have showed no impact of tenofovir on BMD (50, 51). In a study by Duvivier et al., BMD diminution occurred with a combination of PIs and NNRTIs (Non-nucleoside reverse transcriptase inhibitors), and also when used independently (43). Therefore, not undergoing HAART could have a toll on bone mass density.

On the other hand, there is solid evidence that shows HIV affects other body structures, for instance, cardiovascular system. Premature atherosclerosis (including stroke and myocardial infarction), cardiomyopathies, and clinical heart failure are associated to HIV infection, regardless of HAART (52). On to the metabolic system, HIV infection per se can also cause lipid perturbations, such as increase of triglycerides and reduction of HDL cholesterol (53). Based on recent information it's been shown that metabolic syndrome is associated with HIV disease (53).

Moreover, there is information which indicates that HAART also has a roll in the development of this comorbidities (54). Mitochondrial toxicity caused by HAART is strongly correlated to premature and accelerated aging (54). Chronic use of antiretroviral therapy has been repeatedly associated with a variety of metabolic syndromes such as dyslipidemia, fat redistribution, high blood pressure and insulin resistance (55). Likewise, two prospective studies show an increase risk in cardiovascular disease in long term HIV infected population (56, 57).

There are quite a few limitations to this study. Regarding bone mass density measurement, DEXA does have some limitations. Results are influenced by bone size, which could have false negative results, since a greater BMD is seen in larger bones irrespective of its volume (35). This stances a possible problem since men have bigger bones and could display higher BMD in comparison to women; our meta-analysis does not exclude studies by sex. Also, DEXA can be applied in different body sites or get a total body measurement (58). Most instruments will measure the most important sites such as spine, hip and forearm; whereas more specialized systems also perform whole body scans to determine BMD in whole body and in sub regions such as arm, legs and trunk. As is showed in Figure 2, the articles included measure BMD in different locations. Only two articles (23, 36) measured BMD at total body and other specific sites, while the rest only measured at local anatomic sites (59). Site specific measurements can underestimate or overestimate the results since the same cutoff points are being used, which could alter the outcomes when comparing the studies. Furthermore, the commercial manufacturers of DEXA instruments can influence T-score or Z-score value due to differences in calibration, bone edge detection, and other factors (38). Most of the studies use the same manufacturer, nevertheless others don't. Therefore, when merging the articles, the overall findings could be jeopardized.

Naïve and HAART patients involved in our study had a mean age of 36.4 and 40 years respectively, while some studies did not report age (table 1). Following ISCD guidelines BMD in females prior to menopause and males younger than age 50 should be reported using Z score, nevertheless most of the articles included use of T score to classify patients as osteopenic or osteoporotic (32). To have a more accurate representation of bone mass density in HIV infected patients, studies should follow international guidelines to report their outcome. Achieving this would consequently improve studies quality.

Regarding the cohort study (36), they compared HIV patients on HAART (from the SUN study) with non-HIV patients (from the NHANES database) by matching 1:1 according to age, sex, race and BMI; and analyzing the bone mass density. This showed there is indeed a higher prevalence of osteopenia and osteoporosis in the HIV population. Afterwards, the study followed 170 patients from the SUN study to evaluate the percentage that would lose more than 5% of BMD; showing a considerable number of patients in this group (31%). This data confirms that there is a significant number of persons on HAART with suppressed viremia that continue to experience bone loss. Studies like this allow us to have a better understanding of the effect on long term of the antiretroviral drugs.

Longitudinal studies (cohort) would be the best way to evaluate the association between HAART and BMD in HIV patients receiving or initiating ART. Our research was aimed to find these types of studies nevertheless the ones we found didn't meet the inclusion criteria since the control group were not naïve patients. This could be explained by the fact that CDC guidelines specify that every patient diagnosed with HIV must initiate HAART regardless of the HIV viral load.

As seen on the results, there is a large proportion of the population that shows an altered bone density regardless of the treatment. However, only 9% of patients developed osteoporosis. The low quality studies don't allow us to have an exact representation of reality, therefore the importance of bone mass density controls in HIV patients, regardless of treatment, may be underestimated.

6 CONCLUSION:

The results of our systematic review show that evidence is not strong enough to determine that HAART influences BMD. Statistical significance was not found. This is not necessarily an actual representation of reality due to several limitations we have encountered. However, the only cohort study found, showed a diminution of BMD (of >5%) in a 4 year follow up in HIV patients on HAART. This continues to be a matter of importance amongst the HIV community, due to the high prevalence of reduced bone mass density and the repercussion osteoporosis and osteopenia has on the quality of life. Further research must be done preferably with longitudinal studies and larger population databases weighing in the limitations (specifically confounders and biases) that could jeopardize the outcomes.

More studies like such, will allow to determine when screening and prompt treatment is required. Consequently, decreasing amount of complications associated to low bone mass density in HIV patients.

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Figure 1: Flowchart shows the process of identification, screening, selection and extraction of the articles included in the systematic review.

Figure 2: Odds of Osteopenia (T-score between -1 and -2.5) in HIV-infected patients receiving HAART compared with Naïve patients

HAART, Highly active antiretroviral treatment

Figure 3: Odds of Osteoporosis (T-score <-2.5) in HIV-infected patients receiving HAART compared with Naïve patients

HAART, Highly active antiretroviral treatment

Figure 4: Odds of reduced Bone Mass Density T-score <-1 in HIV infected patients receiving HAART compared with Naïve patients

HAART, Highly active antiretroviral treatment

Table1

Studies comparing BMD in HIV infected patients receiving HAART vs. Naïve Patients

Study, year	Location	Study groups	N	Male (%)	Age (years; SD)	Race	BMI (SD)	CD4+ count	Viral Load	HIV infection duration	HAART Duration	% Use of Pls
Knobel et al. , 2001	Spain	ART +	54	NR	42.63 (11.37)	NR	23 (2.3)	NR	NR	NR	NR	31
		ART -	26	NR	36 (10)	NR	22 (4)	NR	NR	NR	NA	NA
García Aparicio et al. , 2006	Spain	ART +	17	100%	41 (8.6)	NR	22.7 (2.0)	536.52 (391.08) (cells/mm3)	345 (886.76) (copies/ml)	9.26 y(4.6)	NR (at least 2 years)	100
		ART -	13	100%	35 (4.4)	NR	24.1 (3.1)	554.30 (178.86)	7853.92 (7498.33)	8.15 y(4.04)	NA	NA
Tomazic et al. , 2007	Slovenia	ART +	72	100%	44.6	NR	25.4	496.1 (cells/mm3)	<20 (copies/ml)	11.3y	5.3 y	48.6
		ART -	24	100%	39.6 (10.3)	NR	24.3 (2.6)	398.7 (188)	48314 (82939)	3.7 (4.7) y	NA	NA
Libois. ,2009	Belgium	ART +	52	0%	37	Caucasian=13 African=39	24.5	411(cells count/ul)	NR	2.04y	3.4y	51.9
		ART -	37	0%	36.5	Caucasian=2 African=35	25.7	517.9	NR	6.4y	NA	NA
Fu Ping et al. , 2010	China	ART +	50	NR	NR	NR	NR	NR	NR	NR	NR	NR
		ART -	12	NR	NR	NR	NR	NR	NR	NR	NA	NA
Su et al. , 2012	China	ART +	108	NR	NR	NR	NR	NR	NR	NR	NR	NR
		ART -	41	NR	NR	NR	NR	NR	NR	NR	NA	NA
Tsai et al. ,2012	Taiwan	ART +	302	NR	NR	NR	NR	NR	NR	NR	NR	NR
		ART -	18	NR	NR	NR	NR	NR	NR	NR	NA	NA
De Menezes Barbosa et al. , 2013	Brazil	ART +	40	100%	40.5	NR	23.1	508.6	NR	98.1 m	68.6 m	50
		ART -	10	100%	30.8	NR	20.4	521.9 (82.6)	NR	34.8 m (20.7)	NA	NA
Escota et al. , 2016	USA	ART +	515	NR	NR	NR	NR	NR	NR	NR	NR	NR
		ART -	76	NR	NR	NR	NR	NR	NR	NR	NA	NA

Note: ART, Antiretroviral Treatment; N, Number of patients; Y, Years; M, months; SD, Standard Deviation; BMI, Bone Mass Index; NR, Not reported; NA, Not applicable

Table 2

DEXA sites and commercial manufacturer for studies comparing BMD in HIV infected patients receiving HAART vs. Naïve

Study, year	DXA: Sites reported					Commercial Manufacturer		
	TB	FN	TH	SP	OTHER	Lunar	Hologic	Norland
Knobel et al. , 2001		X		X	X		X	
García Aparicio et al. , 2006		X	X	X		X		
Tomazic et al. , 2007		X	X	X			X	
Libois. , 2009		X	X	X			X	
Fu Ping et al., 2010	X	X			X	X		
Su et al., 2012		X	X			X		
Tsai et al. ,2012				X		X		
De Menezes Barbosa et al. , 2013	X			X	X		X	
Escota et al. , 2016	X	X	X	X	X	X	X	

Note: TB, Total Body; FN, Femoral Neck; TH, Total Hip; SP, lumbar spine

Table 3

Results of individual studies included in the systematic review comparing osteopenia and osteoporosis

Study	Type of study	Year	Total Naïve	Total HAART	Naïve with osteopenia	HAART with osteopenia	Naïve with osteoporosis	HAART with osteoporosis
Knobel, et al.	Cross - sectional	2001	26	54	15	39	3	14
Garcia Aparicio, et al	Cross - sectional	2006	13	17	8	9	1	2
Tomazic, et al.	Cross - sectional	2007	24	72	13	32	3	9
Fu Ping, et al.	Cross - sectional	2010	12	50	6	19	2	1
Tsai, et al.	Cross - sectional	2012	18	302	3	111	0	12
De Menezes Barbosa, et al.	Cross - sectional	2013	10	40	4	22	0	0
Escota, et al	Cohort	2016	76	515	42	259	6	53

Note: HAART, Highly active antiretroviral treatment

Table 4

Results of individual studies included in the systematic review comparing reduced bone mass density

Study	Type of study	Year	Total Naïve	Total HAART	Naïve with reduced BMD	HAART with reduced BMD
Knobel, et al.	Cross - sectional	2001	26	54	18	53
Garcia Aparicio, et al	Cross - sectional	2006	13	17	9	11
Tomazic, et al.	Cross - sectional	2007	24	72	16	41
Libois , et al.	Cross - sectional	2009	37	52	9	19
Fu Ping, et al.	Cross - sectional	2010	12	50	8	20
Su, et al.	Cross - sectional	2012	41	108	5	34
Tsai, et al.	Cross - sectional	2012	18	302	7	119
De Menezes Barbosa, et al.	Cross - sectional	2013	10	40	4	22
Escota, et al	Cohort	2016	76	515	48	312

Note: HAART, Highly active antiretroviral treatment

APPENDIX 1

Pubmed Search

HIV

Search (((hiv infection[MeSH Terms]) OR HIV[MeSH Terms]) OR HIV infection) OR human immunodeficiency virus

AND/OR

Search (((((((agents, antiretroviral[MeSH Terms]) OR antiretroviral therapy, highly active[MeSH Terms]) OR Antiretroviral*) OR ARV) OR antiretroviral therap*) OR anti-retroviral therap*) OR HAART

AND

BONE MINERAL DENSITY

("bone densities"[MeSH Terms] OR "density, bone"[All Fields] OR "bone mineral density"[All Fields] OR "bone mineral densities"[All Fields] OR "density, bone mineral"[All Fields] OR "bone mineral content"[All Fields] OR "bone mineral contents"[All Fields]

OR

"bone diseases, metabolic"[MeSH Terms] OR osteopenia[Text Word]

OR

"osteoporosis, postmenopausal"[MeSH Terms] OR "osteoporosis"[MeSH Terms] OR osteoporosis[Text Word]

EMBASE search

1) 'hiv'/exp OR hiv OR 'aids'/exp OR aids OR 'human immunodeficiency virus'/exp OR 'human immunodeficiency virus' OR 'acquired immune deficiency syndrome'/exp OR 'acquired immune deficiency syndrome' AND ('osteopenia' OR 'osteoporosis' OR 'bone density'/exp OR 'bone density' OR 'osteoporosis'/exp OR osteoporosis OR 'osteopenia'/exp OR osteopenia)

2)(hiv OR aids OR 'human immunodeficiency virus'/exp OR 'acquired immune deficiency syndrome'/exp) AND ('haart'/exp OR 'haart' OR 'antiretroviral therapy, highly active' OR 'highly active antiretroviral therapy') AND ('bone density'/exp OR 'osteopenia'/exp OR 'osteoporosis'/exp OR 'bone density' OR osteoporosis OR osteopenia)

Global Index Medicus search

((ALL ("HIV") OR ALL("AIDS") OR ALL("Human Immunodeficiency Virus")) AND (ALL("HAART") OR ALL("antiretroviral")) AND (ALL ("bone density") OR ALL("osteopenia") OR ALL("osteoporosis")) AND (LIMIT-TO(EXACTKEYWORD,"Human") OR LIMIT-TO(EXACTKEYWORD,"Humans")))

APPENDIX 2

	SELECTION				COMPARABILITY	OUTCOME		NCOS QUALITY SCORE
Study ID	Representativeness of the sample	Sample size	Non- respondents	Ascertainment of the exposure	The subjects in different outcome groups are comparable, based on the study design or analysis.	Assessment of the outcome	Statistical test	(number of stars)
Knobel, et al.	-	-	-	*	*	*	*	4
Garcia Aparicio, et al.	-	-	-	*	-	*	-	2
Tomazic, et al.	-	-	-	*	*	*	-	3
Libois, et al.	-	-	-	*	*	*	*	4
Fu Ping, et al.	-	-	-	*	-	*	-	2
Su, et al.	-	-	-	*	-	*	-	2
Tsai, et al.	-	-	-	*	*	*	*	4
De Menezes Barbosa, et al.	-	-	-	*	*	*	*	4

New-Castle-Ottawa scale for cross sectional studies

	SELECTION				COMPARABILITY	OUTCOME			NCOS QUALITY SCORE
Study ID	Representativeness of the exposed cohort	Selection of the none exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at baseline	Comparability of the cohorts on the basis of the design analysis	Assessment of the outcome	Adequate length of follow up	Adequacy of follow up of cohorts	(number of stars)
Escota et al	*	-	*	*	*	*	*	*	7

New-Castle-Ottawa scale for cohort study

CHARACTERISTICS OF STUDIES

Garcia Aparicio 2006

Methods	Cross Sectional
Participants	Two different subject groups with the same demographic characteristics were enrolled: 13 HIV-asymptomatic-infected patients without treatment, and 17 HIV asymptomatic-infected patients receiving HAART over the last 2 years. Exclusion criteria: women, patients with any known factor associated to osteopenia, patients receiving medications that could affect bone metabolism
Exposure	In the HAART receiving group, patients where con protease inhibitors (PI) mainly due to viral load for at least two years.
Results	Osteopenia was present in 8 out of 13 from the naïve group and 9 out of 17 from the PI group.
Conclusions	In the present study, no relationship was found between osteopenia or osteoporosis and PI-containing HAART.

Methods	Cross Sectional
Participants	Adult male patients enrolled from January to February 2006 at the department of infectious diseases of Slovenia. Treated and not treated but infected with HIV patients were considered. 133 men fulfilled the criteria but only 96 took part on the study.
Exposure	They were divided in three groups Group A: 24 HIV infected patients, naïve to treatment Group B1: 37 HIV infected patients treated with two nucleoside analogs and efavirenz (no PI's) and HIV infected patients treated with PI Group B2: HIV infected patients that had been treated with lopinavir/ritonavir during the previous 12 months but some of them had received different PI regimens in their previous ART.
Results	Group A: 54% had osteopenia and 12% had osteoporosis Group B1: 41% had osteopenia and 16% had osteoporosis Group B2: 46% had osteopenia and 9% had osteoporosis BMD was lower in group A than in the other two groups
Conclusions	A very high prevalence of bone mass reduction in HIV-infected male patients was found. Absence of ART was confirmed as an independent predictor of osteopenia/osteoporosis. No difference among different drug regimens was found.

Libois 2009

Methods	Cross Sectional
Participants	Pre-menopausal HIV-infected women were divided in 3 groups. Group 1: 37 women never treated Group 2: 25 women treated without PI Group 3: 27 women treated with PI Exclusion criteria: post-menopausal women, women with AIDS or taking any medication that could alter bone metabolism, and women whose treatment had been modified 3 months before the study
Exposure	Group 2, were exposed to treatment for at least 1 year with NRTI and NNRTI and had never received PI's. Group 3, were women treated with regimens containing PI for at least one year.
Results	There was no difference in BMD between the three groups. In total, 28/89 women had osteopenia or osteoporosis. Group 1: 9 out of 37 had reduced bone mass density Group 2: 8 out of 25 had reduced bone mass density Group 3: 11 out of 27 had reduced bone mass density
Conclusions	In this group of HIV-infected pre-menopausal women, osteopenia and osteoporosis was not associated with HAART (containing PI or not) but was associated with a low BMI.

Fu Ping 2010

Methods	Cross sectional
Participants	Clinical data from 2007 - 2008 was analyzed and 82 patients were included in the study. From which 20 were healthy patients (control group), and 62 HIV infected patients.
Exposure	Out of the HIV infected patients, 50 were treated with HAART and 12 patients were naïve to antiretroviral therapy.
Results	Osteopenia and osteoporosis in HIV treated patients was 38% and 2% respectively. In HIV, naïve group the prevalence of osteopenia and osteoporosis was 50% and 16.7%.
Conclusions	HIV infected patients have a lower bone mass density rate.

Methods	Cross sectional
Participants	80 HIV infected patients were considered in the study, of whom 26 were naïve to treatment.
Exposure	From the 54 patients on HAART, 37 were on regimens containing PI's and 17 were on HAART without PI's (two nucleoside reverse transcriptase inhibitors plus one non-nucleoside reverse transcriptase inhibitor).
Results	On the naïve to treatment group 58% and 11% patients had osteopenia and osteoporosis respectively. On the PI treatment group 70% and 30% patients had osteopenia and osteoporosis respectively. On the remaining group 76% and 18% patients had osteopenia and osteoporosis respectively
Conclusions	No differences in BMD were found in HIV-infected patients, irrespective of the treatment or type of treatment; however, the HIV-infected patients have lower BMD compared with healthy adults. BMD was not correlated with HIV categories, viral load, CD4 cell count, duration of therapy, or the presence of lipodystrophy, and was correlated with weight and body mass index.

Methods	Cross sectional
Participants	149 HIV positive patients and 20 HIV negative patients were included in the study.
Exposure	HIV positive patients were divided into 3 groups: untreated group with 41 patients; HAART for 1—2 years group with 60 patients; HAART over 5 years group with 48 patients
Results	The incidence of low bone mineral density in patients receiving HAART for 1-2 years group was 31.7% and receiving HAART over 5 years group was 31.3% The incidence of naïve group was 12.2%.
Conclusions	BMD of right hip and right femur neck were significantly lower in HAART over 5 years group. The incidence of low bone mineral density was significantly higher in patients receiving HAART. BMD was correlated negatively with HAART duration

Methods	Cross sectional
Participants	During the 4-year study period, 320 patients participated in the survey. 302 (94.4%) were receiving cART. Exclusion criteria: patients that had received growth hormone, testosterone, bisphosphonates, immunosuppressants, chemotherapy, or steroids; were pregnant; or had a history of hospitalization or immobilization within the previous three months.
Exposure	CART was defined as a combination of at least 3 antiretroviral agents that contained 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus 1 or 2 protease inhibitors or 1 non-nucleoside reverse transcriptase inhibitor (NNRTI) or triple NRTIs.
Results	79 HAART patients and 5 naïve had normal bone mineral density. 111 HAART patients and 3 naïve had osteopenia 12 HAART patients and 0 naïve had osteoporosis.
Conclusions	Prevalence of reduced BMD is high in HIV-infected patients in Taiwan, and is associated with increased age, time on antiretroviral treatment and being underweight.

Methods	Cross sectional
Participants	50 HIV positive adult men treated or not treated with ART where included in the study.
Exposure	Group A: 10 treatment-naïve subjects Group B: ART use for >2 years, subdivided into: Group B1: 10 subjects treated with protease inhibitors (PIs) and NRTIs and Group B2: 10 subjects treated with NRTIs and NNRTIs Group C: subjects treated with ART <2 years, subdivided into: Group C1: 10 subjects treated with PIs and NRTIs and Group C2: 10 subjects treated with NRTIs and NNRTIs
Results	40% of HAART treated patients and 55% of naïve patients had osteopenia. None of the patients had osteoporosis. Patients using NRTIs and NNRTIs for an average time of 118 months showed a greater reduction of BMD compared to the remaining groups.
Conclusions	There is an increase in the bone reabsorption marker, indicating high bone tissue reabsorptive activity in HIV-infected patients on ART. Patients with longer use of ART found greater bone loss compared with the treatment-naïve group of antiretroviral.

Methods	Cohort
Participants	Data from patients on the SUN study was taken, which included HIV infected patients enrolled from 2004 to June 2006; at baseline 653 patients were used (median age: 41). Then 462 SUN participants were compared to data from NHANES. NHANES is a survey that represents a sample of non-HIV infected patients, of approximately 5,000 people across the US. Information from 2007 – 2008 cycle was used.
Exposure	SUN study participants on HAART were followed for 4 years to evaluate the decrease of BMD (n=170).
Results	<p>At baseline 61% had evidence of low BMD (osteopenia 51% and osteoporosis 10%)</p> <p>After comparison was made between SUN and NHANES, results showed lower BMD at femoral neck on SUN subjects (47% vs 29%) ($p<0.001$). Osteopenia and osteoporosis was also more prevalent in the SUN group, 45% and 3.5% vs. 28% and 0.9% respectively.</p> <p>The results of longitudinal change of BMD, showed that 31% of participants had a decrease of >5% of BMD after the 4 year follow up.</p>
Conclusions	Most subjects remained in the same WHO BMD classification after 4 years and the prevalence of WHO-defined osteopenia or osteoporosis also remained stable over time. The prevalence of osteopenia or osteoporosis was high (61%) in this cohort of HIV-infected persons with mostly well-controlled viremia and high CD4+ cell counts. A significant number of persons on HAART continue to experience bone loss despite suppressed viremia.