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Review Article

Modern Antiretroviral Therapy and Fracture Risk

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Abstract

Excessive bone loss has been noticed in HIV patients, under no antiretroviral therapy, suggesting that HIV is an independent factor for osteoporosis. However, it is still controversial if bone mineral density reduction and increased fracture risk is related to HIV itself or to antiretroviral therapy, with a contribution from both likely. The purpose of this study is to review the association of modern antiretroviral drugs with fracture risk. A simple literature review was performed in the PubMed database. The final search identified 21 studies (6 prospective randomized studies, 4 prospective cohort studies, 3 cross-sectional studies, 4 case–control studies, and 4 retrospective studies). It appears that the pathogenesis of osteoporotic fractures in AIDS patients is multifactorial. The majority of studies show mixed results regarding the effect of most antiretroviral drugs. Further high-quality research is needed to fully elucidate the role of antiretroviral drugs in the pathogenesis of bone loss, osteoporosis, and osteoporotic fractures in HIV-infected patients.

Keywords: Antiretroviral therapy, Bone mineral density, Fracture risk, HIV, Osteoporosis

Introduction

The Human Immunodeficiency Virus (HIV) is a retrovirus infecting humans and causing Acquired Immunodeficiency Syndrome (AIDS). HIV is transmitted through sexual contact, during pregnancy or childbirth, or from blood transfusion. It infects human immune cells, such as T-lymphocytes, macrophages and dendritic cells, causing their apoptosis. After its entrance to target cells, HIV uses the enzyme reverse transcriptase in order to convert its RNA genome to double-stranded DNA, which enters cell nucleus and integrates with the host DNA. Viral DNA is then transcribed, producing new viral particles and leading to the death of the host cells. When the number of CD4+ lymphocytes falls below a critical level, cell-mediated immunity collapses, leaving the body unable to deal with common bacteria and giving rise to opportunistic infections and cancers, leading to the development of AIDS[1-2].

There are 3 main phases of AIDS[2] At the first stage of AIDS (acute infection phase), which occurs 2 – 4 weeks after HIV infection, patients may be asymptomatic or have unspecific flu-like symptoms. The phase lasts for 1 – 2 weeks and transmissibility is high, as plenty of HIV particles circulate in patients' blood. The second stage of the disease (chronic phase or clinical latency), is an asymptomatic stage, which, if left untreated, may last from 3 to 20 years. HIV is still active but replicates at very low rates. At the end of this stage, the rate of HIV replication increases and the number of CD4+ lymphocytes decreases. As the number of HIV particles increases, patients may experience symptoms such as fever, weight loss and lymphadenopathy. Then, AIDS, the third stage of the disease emerges, being the most severe and infectious phase of HIV infection[2]. A diagnosis of AIDS is made when the number of CD4+ lymphocytes falls below 200 cells per μl or if certain opportunistic infections and cancers develop. Without treatment, AIDS patients usually survive about three years[3].

As no effective cure exists, treatment of AIDS consists of the use of specific antiviral drugs, called antiretroviral

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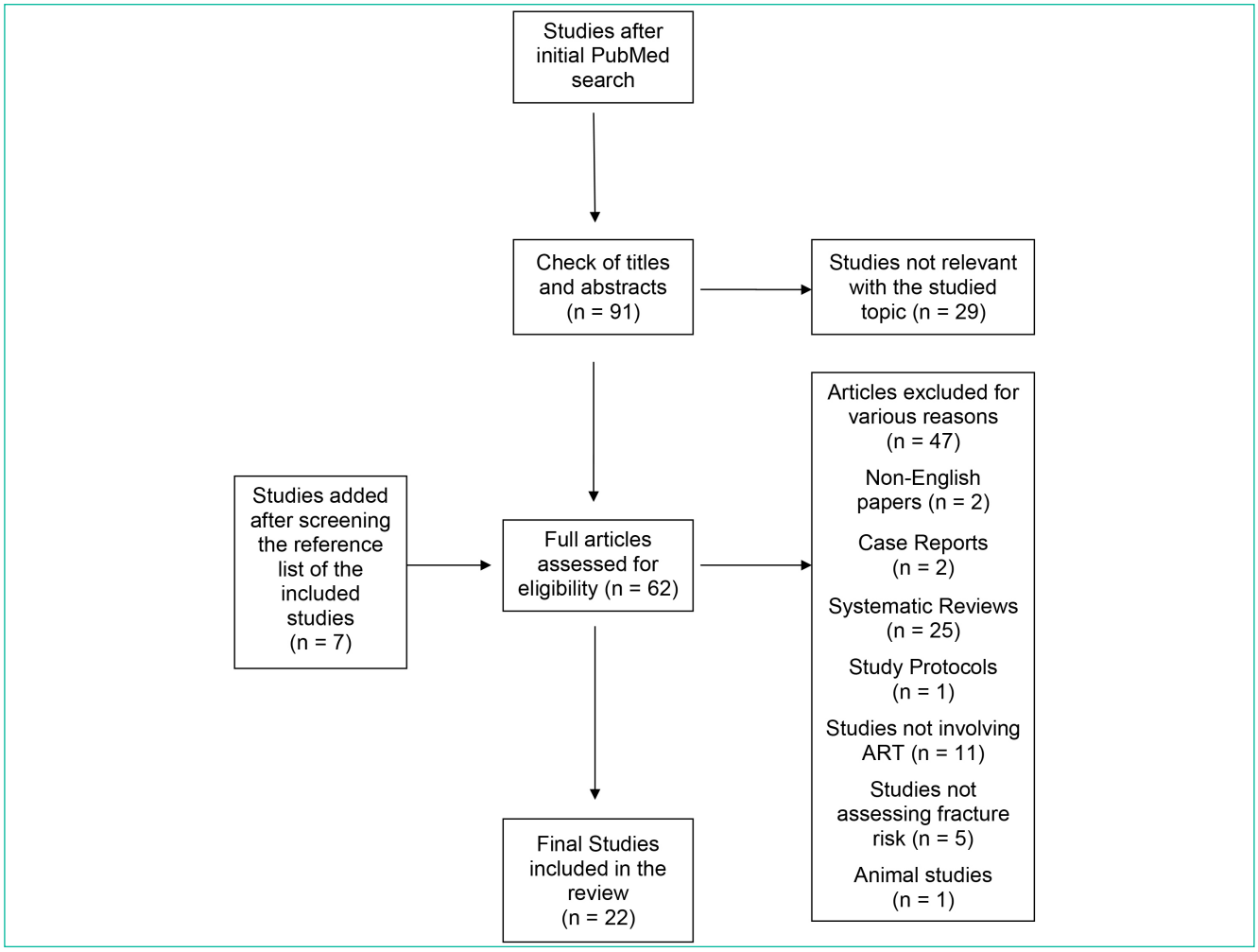

Figure 1. Study FlowChart.

therapy (ART), which aims to slow the progression of the disease. There are few categories of antiretroviral agents that act at different stages of the HIV life cycle. These include nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), or integrase inhibitor. Typical NRTIs include zidovudine, tenofovir, lamivudine or emtricitabine. No single antiretroviral drug has been shown to suppress HIV infection for long. Standard treatment consists of a combination of drugs (often called "highly active antiretroviral therapy" or HAART) that suppress HIV replication. Usual combinations include two NRTIs along with a NNRTI, a PI or an integrase inhibitor[4]. The aim of these drug combinations is the preservation of immune system, the reduction of morbidity and mortality, the prevention and treatment of opportunistic infections, the prevention of HIV transmission by suppressing HIV replication and the overall improvement of quality of life[5-9]. Inappropriate ART use may lead to the emergence of resistant strains, which can very quickly become the dominant genotypes[10]. In contrast, combinational ART prevents the development of resistance, creating multiple barriers to HIV replication, keeping the viral copy number low and reducing the chance of a negative mutation[11].

Osteoporosis, is a musculoskeletal disease consisting of Low bone mineral density (BMD) and deterioration of bone microarchitecture, thus leading to increased risk of fracture In most HIV cohorts, a high rate of osteoporosis is observed in comparison to the general population[12]. It has been reported that fracture risk is greater in HIV patients, in comparison to controls[13]. This increased fracture risk cannot be exclusively attributed to a decrease in BMD, suggesting a direct effect of HIV on bone metabolism, and indirect effects through coexisting risk factors and ART[14]. Coexisting risk

AUTHOR	YEAR	TYPE OF STUDY	n	MAIN FINDING
Peters[28]	2013	RCT	444	ART results in 50% increase of FR
Hoy[26]	2017	RCT	399	Timing of initiation of HAART does not affect FR
Haskelberg[25]	2012	RCT	301	No difference in FR among tenofovir/ emtricitabine and abacavir/ lamivudine
Martin[35]	2009	RCT	357	No difference in FR among tenofovir/ emtricitabine and abacavir/ lamivudine
McComsey[36]	2011	RCT	269	No difference in FR among tenofovir/ emtricitabine and abacavir/ lamivudine combined with efavirenz and atazanavir plus ritonavir
Gallant[34]	2004	RCT	600	No difference in FR among tenofovir and stavudine
Bloch[19]	2014	PCS	37	Substitution of tenofovir with raltegravir in HIV patients receiving rPIs led to a modest decrease in 10-year hip FR
Young[32]	2011	PCS	5826	No association of ART with FR
Borges[33]	2017	PCS	11820	Tenofovir was associated with a 25 – 40% increase of FR
Womack[13]	2011	PCS	119318	Current PIs use was associated with a 41% increase of FR
Taras[29]	2014	CSS	112	The higher the amount of ART consumed, the higher the FR
Abdo[17]	2021	CSS	45	High levels of tenofovir increase FR
Dalla Grana[21]	2019	CSS	83	Tenofovir and PIs were associated with increased FR
Costagliola[20]	2019	Case-Control	630	No association of tenofovir, NRTIs, NNRTIs and PIs with FR
Yong[31]	2011	Case-Control	183	No association of tenofovir, NRTIs, NNRTIs and PIs with FR
Yin[30]	2010	Case-Control	2391	Cumulative use of NNRTIs was associated with a 8% reduction of FR
Mundy[27]	2012	Case-Control	11621	Darunavir, delavirdine, and saquinavir were associated with increased FR. Efavirenz, emtricitabine, lamivudine, tenofovir, and zidovudine were associated with decreased FR. No association of amprenavir, atazanavir, enfuvirtide, fosamprenavir, indinavir, lopinavir, tipranavir and zalcitabine with FR
Bedimo[18]	2012	RCS	56660	Cumulative use of tenofovir was associated with a 12 – 13% increase of FR. Use of PIs was associated with a 9 – 13% increase of FR
Gedmintas[22]	2017	RCS	2663	No association of tenofovir with FR
Hansen[23]	2012	RCS	31836	HAART results in 80% increase of FR
Yin[37]	2012	RCS	8038	No association of ART with FR. Incidence of fracture was higher within the first 2 years after ART initiation
Sutton[38]	2020	RCS	8834	Current use of tenofovir was associated with a 2,3-fold increase of FR.

Table 1. Main findings of the included studies. RCT: Randomized Controlled Trials. PCS: Prospective Cohort Studies. CSS: Cross-Sectional Studies. RCS: Retrospective Comparative Studies. FR: Fracture Risk. ART: Antiretroviral Therapy. HAART: Highly Active Antiretroviral Therapy. n: number of patients.

factors in AIDS and osteoporosis include smoking, alcohol consumption, low body mass index and hypogonadism. AIDS may affect bone metabolism through activation of immune system, increased insulin resistance and lipodystrophy[15-16]. Adverse effects of antiretroviral drugs on bone metabolism were initially observed with the use of tenofovir. Suggested mechanisms of impaired bone metabolism include increased renal phosphate secretion, increased bone resorption, low rate of bone formation and impaired vitamin D metabolism. However, there are numerous studies that have failed to establish this correlation. The purpose of this review is to evaluate the association of modern ART with fracture risk.

Materials and Methods

Through the electronic database PubMed, and with the use of the EndNote 7.0 software, a simple search of the literature was performed with the use of the following keywords: ("antiretroviral" OR "HAART" OR "NRTIs" OR "nucleoside

reverse transcriptase inhibitors" OR "fosamprenavir" OR "indinavir" OR "lopinavir" OR "nelfinavir" OR " ritonavir" OR "saquinavir" OR "tipranavir" OR "abacavir" OR "emtricitabine" OR "lamivudine" OR "stavudine" OR "zidovudine" OR "doravirine" OR "efavirenz" OR "etravirine" OR "nevirapine" OR "rilpivirine") AND ("fracture risk" OR "risk of fracture"). Inclusion criteria were human studies associating modern antiretroviral therapy with fracture risk. Case reports, systematic reviews, study protocols, animal studies, non – English studies and studies not involving antiretroviral treatment were excluded from the review.

Results

The search revealed a total of 91 studies. After screening titles and abstracts, 29 publications were rejected, as irrelevant with the studied topic. Among the 62 studies evaluated, 47 were rejected for various reasons. After screening the reference list of the included studies, 6 more studies were added, leaving 22 studies for the present review (Figure 1), including 6 prospective randomized studies, 4 prospective cohort studies, 3 cross-sectional studies, 4 case–control studies, and 5 retrospective studies[13,17-38]. Table 1 depicts the main features and findings of the included studies.

Prospective randomized studies

A prospective, randomized, study by Peters et al evaluated BMD, fracture history, and fracture risk factors in 222 AIDS patients and matched controls. The majority of patients was under HAART (99% received NRTIs, 78% received tenofovir and 43% received PIs). The fracture prevalence was 3-fold higher in HIV patients in comparison with controls (20.3% vs 7.2%). Osteoporosis was more common in AIDS patients. 10 – year fracture risk was similar to both patients and controls (about 4%). However, remaining lifetime fracture probability was 20% higher in HIV patients in comparison to healthy controls (p-value = 0.003). Moreover, fracture risk was 50% increased in patients under antiretroviral treatment (p-value = 0.03)[28].

The START Bone Mineral Density Substudy was a prospective, randomized study which compared the effect of early initiation of HAART (CD4+ > 500 cells/μL) with late initiation of HAART (at CD4+ < 350 cells/μL) on BMD change and fracture risk. After a mean follow-up of 2.2 years, fracture risk was found to be similar between the 2 groups (p-value = 0.62), suggesting that the timing of initiation of HAART does not affect fragility fracture risk. Researchers attributed the lack of association to the low median age of the studied population (32 years)[26].

In a prospective, randomized trial, Haskelberg et al compared parameters of bone metabolism and fracture risk between 2 groups of HIV patients receiving ART. Group A (n = 147) received tenofovir/emtricitabine, while group B (n = 154) received abacavir/lamivudine. Patients were followed for 96 weeks. While the combination of tenofovir/emtricitabine was associated with lower BMD, no statistically significant difference in fracture risk was observed among the two groups. However, authors stated that the real fracture risk may have been underestimated[24].

The same fixed-dose NRTIs combinations were compared in a randomized, controlled trial, published by Martin et al. Group A (n = 178) received tenofovir/emtricitabine, while group B (n = 179) received abacavir/lamivudine. Patients were followed for 96 weeks. Two fractures occurred at each group during the study period. While the combination of tenofovir/emtricitabine was associated with lower BMD, no statistically significant difference in fracture risk was observed among the two groups[35].

Similar findings were recorded in another randomized, controlled trial by McComsey et al, which included 269 HIV patients randomized to 4 arms: group A receiving efavirenz, tenofovir, emtricitabine (n = 69), group B receiving efavirenz, abacavir, lamivudine (n = 70), group C receiving atazanavir plus ritonavir, tenofovir, emtricitabine (n = 65) and group D receiving atazanavir plus ritonavir, abacavir, lamivudine (n = 65). No statistically significant difference in fracture risk was observed among the 4 groups[36].

Gallant et al prospectively evaluated the efficacy and the adverse events of tenofovir in comparison to stavudine in 600 HIV patients. Patients were randomized to receive either tenofovir, lamivudine and efavirenz (Group A, n = 299) or stavudine, lamivudine and efavirenz (Group B, n = 301). After a follow-up of 144 weeks, no difference in fracture rate was detected among the 2 groups[34].

Prospective non-randomized studies

According to a prospective, non-randomized study by Bloch et al, substitution of tenofovir for raltegravir in 37 AIDS patients (97% male, mean age 49 years) with low BMD receiving ritonavir-boosted PIs was safe and led to a modest decrease in 10-year hip fracture risk after 48 weeks. No significant difference was found in the 10-year risk of major osteoporotic fractures[19].

In a prospective observational cohort study, Young et al used data from the electronic database of HIV Outpatient Study (HOPS) and analyzed 233 fragility fractures in more than 5800 HIV patients during the period 2000-2008. Median age of patients was 40 years and 73% of them received ART. Fracture risk was higher in older patients, drug users, patients with CD4+ cell count < 200 cells/mm^3, bone mass index less than 18.5, hepatitis C co-infection, and diabetes mellitus. The study did not detect any association of fracture risk with antiretroviral treatment (p = 0.01)[32].

Borges et al analyzed data from the EuroSIDA study, an international prospective cohort of more than 20,000 AIDS patients from across Europe, Argentina and Israel. The study population included 11820 seropositive patients with a median age of 41 years. Among them, 619 fractures were recorded. After multivariable analysis, use of tenofovir disoproxil fumarate led to a 25 – 40% increase of fracture

risk. No other ART treatment was associated with fracture risk. In agreement to other studies, age, white race, CD4+ count and HCV co-infection were found to be independent predictors of fracture risk[33].

A prospective, observational study by Womack et al used data from the Veterans Aging Cohort Study Virtual Cohort. About 40.000 AIDS patients were compared with 80.000 uninfected persons. After the examination of a plethora of covariates, only current PIs use was associated with a 41% increase of risk for fragility fracture. However, authors doubt for the validity of this finding, as the use of PIs is a marker for the severity and duration of disease. Therefore, increased fracture risk may be a result of a more advanced stage of the disease[13].

Cross-sectional studies

Using a 18-item questionnaire, a cross-sectional study by Taras et al assessed fracture risk in a population of 112 AIDS patients (89 men – 23 women), with an mean age of 43 years. 25.0% of them were not on ART, 23.2% were on ART for ≤1 year, and 51.8% were on ART for >1 year. Multivariable analysis revealed that the higher the amount of ART consumed, the higher the risk of fracture. Half of the patients agreed to initiate anti-osteoporotic treament[29].

Fracture risk in HIV patients under antiretroviral therapy was indirectly assessed by a recent cross-sectional study which evaluated the association between tenofivir diphosphate levels and aging factors in 45 AIDS patients. 51% of patients were below 35 years of age while 49% were above 60 years old. Higher tenofivir diphosphate concentrations were correlated with lower hip BMD, functional impairment, and greater risk of falls, factors that strongly increase fracture risk[17].

Dalla Grana et al published a cross-sectional study, evaluating alterations of bone metabolism and the prevalence of vertebral fractures in 83 HIV(+), hepatitis B (+) and hepatitis C (+) patients receiving ART. Mean age of patients was 57 years old. Patient group was compared to 40 healthy controls. The majority of patients received tenofovir ± PIs. After logistic regression analysis, authors concluded that ART containing tenofivir and PIs was an important predictor of vertebral fractures[21].

Case-control studies

To evaluate the impact of ART on fragility fracture risk, Costagliola et al conducted a case–control study including 254 HIV patients with a low-energy fracture and 376 HIV patients with no fracture as controls, between 2000 and 2010. 49% of patients had received tenofivir and 82% of patients had received PIs. After multiple regression analysis, no association was found between administration of tenofivir, NRTIs, NNRTIs or PIs and fracture risk[20].

A similar case-control study was published by Yong et al, in 2011. The study population consisted of 61 HIV patients with a low-energy fracture and 122 HIV patients with no fractures. Mean age of patients at the time of fracture was about 50 years old. Multivariable analysis revealed that the only predisposing factors for fragility fractures in HIV patients were CD4+ < 200 cells/μl, administration of steroids and antiepileptics. No significant association was detected between fragility fracture risk and ART use (including tenofovir, NNRTIs and PIs) or duration of ART use[31].

Within Women's Interagency HIV study, a case–control study by Yin et al evaluated predisposing factors for osteoporotic fractures among 1728 HIV (+) premenopausal women and 663 HIV (-) controls. In the study period, the rate of fracture in HIV(+) and controls was 8.6% and 7.1% respectively. Median follow-up was 5.4 years. After multiple regression analysis, the only factors that predicted osteoporotic fracture were older age, white race and cigarette use. The cumulative use of NNRTIs was associated with a modest but statistically significant protective effect in reducing fracture risk of 8% (p-value = 0.033)[30].

Analyzing data from the Ingenix Impact National Benchmark Database (INBD), Mundy et al published a case-control study, including about 2500 HIV(+) patients with fractures and 9000 HIV(+) patients without fractures, in the period 1997-2008. An increased fracture risk was found in patients receiving darunavir, delavirdine, and saquinavir, while a decreased fracture risk was associated with efavirenz, emtricitabine, lamivudine, tenofovir, and zidovudine. Fracture risk was not affected by administration of amprenavir, atazanavir, enfuvirtide, fosamprenavir, indinavir, lopinavir, tipranavir and zalcitabine[27].

Retrospective studies

Bedimo et al conducted a retrospective study assessing the effect of tenofivir and other antiretroviral drugs in the risk of osteoporotic fractures in 56,600 patients with AIDS from the period 1988 – 2009. More than 32.000 patients received HAART. In the studied period, 951 osteoporotic fractures were recorded (13% vertebral, 51% wrist, 36% hip). Multivariate analysis showed that cumulative exposure to tenofivir was associated with 12 – 13 % increase in the risk of osteoporotic fractures. The use of PIs such as the lopinavir/ritonavir combination was associated with a 9% - 13% increase in the risk of osteoporotic fractures. No association was found between use of abacavir, zidovudine/ stavudine and NNRTIs and fracture risk[18].

A retrospective study by Gedmintas et al selected patients from the Research Patient Data Registry, aiming to identify the contribution of tenofovir disoproxil fumarate to fracture risk, in comparison to other antiretroviral drugs. The study included 1,981 AIDS patients who had received tenofovir at some point during treatment and 682 patients who had not, during the period 2001 - 2012. Mean age of patients was 43 years old and mean follow-up was 3 years. 100 fractures were detected in the group receiving tenofovir and 80 fractures were detected in the non-tenofovir users. HCV co-infection was associated with a 60% increased fracture risk.

CD4+ < 200 cells/μl was associated with a 3-fold increase in fracture risk. In multivariate analysis, age > 40 years, white race, previous fracture, steroid use and history of falls were associated with increased fracture risk. However, no association was found between tenofovir administration and fracture risk (p-value = 0.16)[22].

A similar population-based study by Hansen et al selected patients from Danish registries, trying to analyse the impact of HAART on fracture risk. 5300 HIV patients were compared with a control group of 26500 healthy people in the general population, during the period 1995-2009. Median age of patients was 37 years old. HIV seropositivity resulted in a 50% higher fracture risk compared with the general population. Among AIDS patients, HAART treatment led to a 80% increase of fracture risk. This increased risk was also associated with comorbidities and smoking[23].

Yin et al, retrospectively analyzed data from the ACTG Longitudinal-Linked Randomized Trial database. The study population consisted of 4640 HIV(+) patients, receiving ART, with a median age of 39 years. Fracture risk was compared to 3400 HIV(+) patients who did not receive ART. Overall, 116 fractures were reported within 2.3 years of follow-up. Multivariate analysis failed to detect any association between any type of ART and hazard of fracture. Incidence of fracture was higher within the first 2 years after ART initiation, in relation to the following years[37].

Finally, Sutton et al, recently evaluated the association among tenofovir use, kidney dysfunction and osteoporotic fractures. Using the Veterans Affairs Informatics and Computing Infrastructure, researchers compared about 6800 HIV patients receiving tenofovir and 1950 HIV patients who had never received tenofovir. In adjusted models, current use of tenofovir was associated with a 2.3-fold increase of risk of osteoporotic fractures[38].

Discussion

Bone loss, BMD reduction and subsequent increase of fracture risk in patients with AIDS is an established clinical situation. Several studies have detected increased rates of osteopenia, osteoporosis, and fragility fractures in HIV population in comparison with healthy subjects[39-45]. These rates are expected to increase as life expectancy of these patients is prolonging. In 2015, life expectancy of these patients in the United States was more than 50 years old[46].

Several pathophysiological mechanisms have been implicated in the HIV-derived bone loss. The upregulation of inflammatory cytokines, such as interleukins and tumor necrosis factor-a (TNF-a), which is observed in the presence of chronic inflammation in AIDS, stimulates osteoclastic activity[47-48]. Bone demineralization in AIDS patients may be the result of this persistent cytokine dysfunction[49]. In AIDS patients, a plethora of traditional risk factors for osteoporosis coexists, including low bone mass index, malnutrition, steroid use, cigarette use, vitamin D deficiency and HCV co-infection[13,50].

The introduction of ART in the treatment of AIDS has certainly improved the prognosis and the life expectancy of HIV patients by decreasing their mortality and morbidity, but has also revealed several complications associated with the treatment. Excessive bone loss has been noticed in AIDS patients, under no ART, suggesting that HIV is an independent factor for osteoporosis[41,51]. However, it is still controversial if BMD reduction is related to HIV itself or to ART, with a contribution from both being implied by many authors as likely.

Pathogenesis of reduced bone mass in ART-treated HIV patients is multifactorial. Most antiretroviral drugs may affect bone metabolism, but there are certain categories of antiretroviral drugs that have a greater impact on BMD, such as tenofovir and PIs. Brown et al observed a 60% greater loss in BMD in HIV patients receiving PIs, in comparison to HIV patients receiving other types of HAART[12].

HAART has been proposed to decrease vitamin D biosynthesis through the suppression of 25-hydroxylase and 1a-hydroxylase[52]. PIs such as indinavir may attenuate osteoblastogenesis in vitro and enhance osteoclast activity, such as ritonavir, saquinavir, nelfinavir and indinavir[53]. PIs can reduce calcium deposition and ALP expression in osteoblasts, which are both biomarkers of osteoblast differentiation[54]. Some PIs including indinavir, nelfinavir and ritonavir, attenuate vitamin D production, altering phosphate and calcium homeostasis, and increasing PTH levels, causing secondary hyperparathyroidism[52,55]. Experimental studies have shown that PIs and tenofovir act on renal phosphate metabolism, resulting in increased bone resorption[56]. NRTIs augment bone demineralisation and increase calcium hydroxyapatite secretion from osteoid, through lactic acidosis[57]. Tenofovir, a NRTI, has been associated with bone loss in HIV patients, possibly through proximal tubule toxicity leading to excessive phosphate secretion[24]. NNRTIs such as efavirenz may enhance vitamin D catabolism via upregulation of CYP24A1 gene expression[58].

Conclusions

There are several studies that have evaluated the effect of modern ART on fracture risk in HIV-infected patients. It appears that the pathogenesis of osteoporotic fractures in AIDS patients is multifactorial. The majority of studies show mixed results regarding the effect of most antiretroviral drugs. Further high-quality studies are needed to fully elucidate the impact of antiretroviral drugs in the pathogenesis of bone loss, osteoporosis, and osteoporotic fractures in HIV-infected patients.

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