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High risk and probability of progression to osteoporosis at 10 years in HIV-infected individuals: the role of protease inhibitors

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Abstract

We estimated the risk and probability of progression to osteopenia/osteoporosis by studying our HIV-infected patients who had at least 2 DXA scans (3,726 DXA scans from 875 patients) (1999-2016). Time-nonhomogeneous bidirectional multistate models based on 3 states (normal BMD, osteopenia, osteoporosis) were used to model the progression of BMD as a function of age and to study the association between the risk of bone loss and antiretroviral use.

At the first DXA scan, 52.2% had osteopenia, and 16.7% osteoporosis. The hazard ratios associated with age (>45 vs. ≤45 years) for men and women were: 1) from normal BMD to osteopenia, 0.71 (95%-CI: 0.45-1.11) and 1.06 (95%-CI: 0.55-2.05), respectively; and 2) from osteopenia to osteoporosis, 0.83 (0.51-1.35) and 0.99 (0.38-2.56), respectively. The probability of transition from osteopenia to osteoporosis over 10 years among men aged 30, 40, and 50 years was 14.9% (95% CI: 10.5-20.4%), 17.2% (14-21.3%), and 19% 14.3-24.3%), respectively; for women, 6.9% (3.1-14.4%), 21.1% (14.8-29.5%), and 30.1% (19.8-41.8%), respectively. An increased risk of osteoporosis was observed for PIs and PIs plus TDF; darunavir was associated with a higher risk among men (HR: 3.9; 95% CI: 2-7.5) and women (4.5; 1.4-14.7); atazanavir for women (HR: 4.2; 95% CI: 1.3-14).

Our results highlight the importance of monitoring BMD owing to the high probability of progression to osteopenia/osteoporosis, even at early ages, especially in women. In the coming decade, changes in antiretrovirals other than tenofovir, such as PIs, should be recommended to reduce the risk of fracture.

Keywords: Osteoporosis, DXA scan, Risk of progression, Protease inhibitors, HIV infection.

INTRODUCTION

HIV-infected people have a high risk of osteoporosis owing to multiple factors related not only to the host, but also to the virus, chronic inflammation, and antiretroviral treatment (1-8). Evidence from large cohort studies points to a higher prevalence of low-energy fractures in HIV-infected persons than in the general population (5, 8-14). However, despite the many recently published recommendations on management of bone disease in HIV-infected individuals (15-19), the current low frequency of fracture managed in our daily clinical practice could make physicians less sensitive to evaluate bone health. Consequently, osteoporosis seems to be underdiagnosed and, consequently, undertreated in HIV-infected persons, thus leaving this population vulnerable to early fractures and disability (20). However, in aging persons, the long-term nature of HIV infection, persistent systemic inflammatory status, and prolonged exposure to antiretroviral drugs make the number of bone fractures among this population likely to increase. This is especially true in individuals aged 50 years or older (10,11). Therefore, clinicians should be aware of problems affecting bone and proactively manage bone health.

In this study, we estimate the magnitude of an emerging problem among chronically HIV-infected persons by studying progression to osteopenia/osteoporosis in a large cohort of patients assessed using dual-energy X-ray absorptiometry (DXA) scan.

METHODS

Study design, population, and objective

We performed a retrospective longitudinal observational study of all DXA scans from HIV-infected patients attended in our HIV Unit and who had had at least 2 DXA scans between January 1999 and December 2016.

The analysis included 3,726 DXA scans from 875 patients. The scans were requested as part of the patient's follow-up in clinical practice or in the context of clinical trials. In recent years, DXA scans were requested according to current recommendations for HIV-infected persons as follows: men aged >50 years, menopausal women, persons with a history of bone fractures, or patients using drugs or with diseases associated with a decrease in bone mineral density (BMD) (18,19).

The main objective of the study was to evaluate the risk of progression of bone loss. Patients were classified into 3 groups according to their BMD: normal BMD, osteopenia, and osteoporosis. We estimated the following: 1) the percentage of patients in each group at the first and last DXA scan; 2) the number of transitions from one group to another (normal BMD to osteopenia, osteopenia to osteoporosis, or osteoporosis to osteopenia); 3) the risk of progression of bone loss or bone gain; 4) the probability of progression over time; and 5) the risk of low BMD according to the antiretroviral drugs used during the year before each DXA scan (tenofovir disoproxil fumarate [TDF], protease inhibitors [PI], combination of both [TDF and PI], and the use of lopinavir or atazanavir or darunavir).

The T score for the lumbar spine (L1-L4) and hip (femoral neck, trochanter, and total femur) measured by DXA (Lunar Prodigy, GE Healthcare, Belgium) was collected, and the minimum of the four T scores was considered for patient's classification. Osteopenia and osteoporosis were defined following the criteria of the World Health Organization (WHO),

as follows: normal BMD, minimum T score ≥ –1.0 SD; osteopenia, minimum T score –1.0 SD to –2.5 SD; and osteoporosis, minimum T score < –2.5 SD (21).

Statistical analysis

Categorical variables of interest were described using absolute and relative frequencies; numerical variables were described using the median and interquartile range (IQR).

The BMD history was studied following a multistate model. The model assumes 3 states — normal BMD (State 1), osteopenia (State 2), and osteoporosis (State 3)— and the time scale chosen is based on age at the DXA scan. The 4 possible transitions considered are transitions from State 1 to State 2 and from 2 to 3, corresponding to bone loss, and transitions from State 2 to State 1 and from 3 to 2, corresponding to bone recovery. Each of these 4 transitions can be characterized based on the instantaneous transition intensities (α_{12}, α_{21}, α_{23}, α_{32}) or, equivalently, on the transition probabilities. The model was fitted assuming that the future time course depends only on the present state and not on the previous history (Markov property). In addition, constant transition intensities were assumed before and after the age of 45 years; for example, in the case of the transition from State 1 to State 2, $\alpha_{12}(t) = \alpha_{12}^{a}$ if $t \leq 45$ and $\alpha_{12}(t) = \alpha_{12}^{b}$ if $t \geq 45$. The choice of this cutoff value was based on the data being 45 (years) the average midpoint of the age intervals from the first to the last DXA scan. Based on the estimates of the transition intensities, transition probabilities can be estimated as a function of age (22). This estimation was made first by using separate models without covariates for both women and men. Next, the use of antiretroviral drugs during the year prior to the DXA scan was included as a covariate in the model, in 4 different ways: PI vs. no PI; TDF vs. no TDF; combined use of PI and TDF; and specific PI (atazanavir, darunavir, lopinavir, or other).

The possible effects of these drugs were studied by transition-specific hazard regression models, which provide the hazard ratio as the effect size measure of interest.

All statistical analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria), version 3.3.2, in particular, the msm package, which enables a multistate model to be fitted to panel data, that is, with observations of a continuous-time process at arbitrary times (23).

RESULTS

The analysis included 3,726 DXA scans from 875 patients who had had at least 2 DXA scans. During the 18 years of follow-up, the median number of scans per patient was 3 (range: 2-18), the median time (IQR) from the first to the last DXA scan was 5 years (2.2-9.6), and the median (IQR) time between consecutive DXA scans was 1.1 years (0.6-2.2). Among the 875 patients, 294 (33.6%) had 2 DXA scans, 188 (21.5%) had 3, 118 (13.5%) had 4, and 275 (31.4%) had 5 or more DXA scans.

The median age (IQR) of the cohort at the first DXA scan was 41.7 (36.5-47.8) years, and 75.3% were men. Epidemiological and clinical data at the time of the first DXA scan are summarized in Table 1.

Prevalence and transitions

The overall percentages of patients in the 3 groups at the first DXA scan were as follows: 31.1% for normal BMD, 52.2% for osteopenia, and 16.7% for osteoporosis. At the last DXA these values were 28.1% for normal BMD, 54.5% for osteopenia, and 17.4% for osteoporosis. Figure 1A shows the joint distribution of the states at the first and the last DXA scan.

The total numbers of DXA scans among the 659 men and 216 women were 2828 and 898, respectively. Hence, there were 2169 transitions in subsequent DXA scans (2828-659) in men and 682 transitions (898-216) in women; the corresponding distributions are shown in Figures 1B and 1C. A deterioration in BMD from one DXA scan to the next was observed in 174 transitions (8%) among men (94 from normal BMD to osteopenia and 80 from osteopenia to osteoporosis) and in 75 transitions (11%) among women (46 from normal BMD to osteopenia and 29 from osteopenia to osteoporosis). An improvement was observed in 178 transitions (8.2%) and 37 transitions (5.4%), respectively.

Risk of progression

The risk of progression of bone loss or bone gain was studied as a function of age (>45 vs. ≤45 years). The hazard ratios associated with age for HIV-infected patients were as follows: 1) transition from normal BMD to osteopenia, 0.71 (95% CI: 0.45-1.11) for men and 1.06 (95%-CI: 0.55-2.05) for women; 2) transition from osteopenia to osteoporosis, 0.83 (0.51-1.35) for men and 0.99 (0.38-2.56) for women; 3) transition from osteopenia to normal BMD, 0.41 (0.26-0.65) for men and 0.42 (0.18-0.99) for women; and 4) transition from osteoporosis to osteopenia, 0.67 (0.42-1.05) for men and 0.12 (0.04-0.36) for women. Figure 2 shows the estimated hazard ratios associated with age for both genders.

Probability of progression

Figure 3A shows the estimated probabilities of progression from normal BMD to osteopenia/osteoporosis over 10 years among HIV-infected men and women aged 30, 40, and 50 years. Given a normal BMD at baseline, the probability that a 30-year-old HIV-infected man progresses to either osteopenia or osteoporosis at age 40 is 60.6% (95% CI:

53.9-69.7%) and 51.1% (39-64.5%) for a 30-year-old woman. The corresponding probabilities of progression for men and women aged 40 to 50 years, respectively, are 62.6% (55.8-70.5%) and 59.5% (50.1-70.1%), and for those aged 50 to 60 years, 59.7% (49.2-71.1%) and 62.4% (47.2-77.3%).

With respect to the transition from osteopenia to osteoporosis, the estimated transition probabilities over 10 years are shown in Figure 3B. In HIV-infected men aged 30, 40, and 50 years, the probabilities were 14.9% (95% CI: 10.5-20.4%), 17.2% (14-21.3%), and 19% (14.3-24.3%), respectively. A different probability pattern was obtained for women, with values of 6.9% (3.1-14.4%), 21.1% (14.8-29.5%), and 30.1% (19.8-41.8%), respectively.

Risk of low BMD according to antiretroviral therapy

Information on antiretroviral treatment regimens 1 year before the DXA scans was available for 862 of the 875 patients (98.5%), ie, 3516 of the 3726 DXA scans (94.4%) (Table 1). The estimated hazard ratios (HRs) associated with treatment combinations containing PI/TDF for both deterioration transitions are shown in Figures 4A (men) and 4B (women), respectively. In the cases of HIV-infected women, increased risks for osteoporosis were observed both for use of PIs versus no PI+no TDF (HR: 5.9; 95% CI: 1.2-27.6) and for combined use of PIs plus TDF versus no PI+no TDF (HR: 6.9; 95% CI: 1.4-34.4). The corresponding values among HIV-infected men were 1.8 (95% CI: 0.9-3.4) and 1.2 (95% CI: 0.6-2.6), respectively.

Darunavir was associated with a higher risk of osteoporosis among men (HR: 3.9; 95% CI: 2-7.5) and women (HR: 4.5; 95% CI: 1.4-14.7), as well as with a higher risk of osteopenia among women (HR: 2.8; 95% CI: 1.1-7.1) (Figures 5A and 5B). In addition, atazanavir increased the risk of osteoporosis among women (HR: 4.2; 95% CI: 1.3-14), although this

varied little among men (HR: 1.2; 95% CI: 0.4-3.2). The always larger confidence intervals among HIV-infected women result from the smaller sample size and the small number of transitions.

A sensitivity analysis considering cutoff values other than 45 years (>40 vs. ≤40 years and >50 vs. ≤50 years) was carried out to ensure that the conclusions on the effects of the antiretroviral therapies did not depend on that choice. The models using different cutoffs provided nearly exactly the same estimates of the hazard ratios and confidence intervals of the hazard ratios associated with antiretroviral therapy (data not shown).

Discussion

The prevalence of osteopenia and osteoporosis was high in our cohort. The risk and the probability of progression from osteopenia to osteoporosis over 10 years were higher among women, especially those aged over 40 years; for men, the risk increased progressively, although the increment was more attenuated. Therapy with darunavir and atazanavir was associated with an increased risk of progression to bone loss.

Osteoporosis is a major public health problem owing to the impact of osteoporotic bone fracture, whose health consequences include not only chronic pain, respiratory compromise, reduced mobility, disability, and mortality, but also increased social cost because of lost workdays, increased health and nursing care, and long-term rehabilitation. Consequently, assessment of the risk of fracture should be a high priority among health measures. Since the mid-1990s, the WHO operational definition of osteoporosis has been based on measurement of BMD using DXA in order to identify persons at higher risk of

bone fracture. It is well known that decreases in vertebral and hip BMD predict vertebral fractures (relative risk [RR]: 2.3; 95% CI. 1.9-2.8]) and hip fractures (RR: 2.6; 95% CI: 2.0-3.5), respectively (24).

The rate of osteoporosis appears to be greater in HIV-infected individuals than in the general population and is progressively increasing (6, 25, 26). In our cohort of almost 900 persons, of whom 25% were women, only a third of the population had a normal BMD; half had osteopenia and 17% osteoporosis. These rates are similar to those observed in other cohorts (8,27) and support the relevance of this condition in HIV-infected persons.

Nevertheless, osteoporotic fractures still remain very infrequent in daily clinical practice, and physicians rarely evaluate the risk of fractures. We wanted to assess the magnitude of this problem in the near future by determining the risk and likelihood of progression to osteoporosis in 10 years in a large cohort of chronically HIV-infected persons assessed using DXA scan, with a median of 3 scans per patient (more than 60% had 3 or more scans) and a median of 5 years from the first to the last DXA scan.

First, in order to obtain an overview of progression of bone loss in the DXA scans, we analyzed transitions from one DXA scan to the next. Deterioration of BMD —defined as a change in status from normal BMD to osteopenia or from osteopenia to osteoporosis between 2 consecutive DXA scans— was observed in around 10% of transitions; this rate was considerably high, considering that the median time between consecutive DXA scans was only 1 year. Improvement was observed in 5-8% of transitions, and the difference was similar in men and women.

When the risk of progression was calculated according to age (>45 vs. ≤45 years, >40 vs. ≤40 years and >50 vs. ≤50 years) and gender, the risk of bone loss changed little with age. The low number of patients aged 60 or over included in the study could make it difficult to detect differences in deterioration between age groups. On the other hand, as expected, the risk of recovery (bone gain) was more likely for patients younger than 45 years. This finding supports the assessment of bone health at early ages and suggests that intensive interventions should be implemented, if necessary, at early stages of bone loss to achieve better recovery.

However, when we evaluated the probability of progression over time, it is noteworthy that the probability of progression from normal BMD to osteopenia/osteoporosis over 10 years was very high, around 50-60%, and similar between men and women and for persons aged 30, 40, or 50 years. In other words, at the age of 30 years, the probability of progression to osteopenia was as high as 60.6% for men and 51.1% for women at 10 years. In contrast, when we evaluated the probability of progression from osteopenia to osteoporosis, larger differences between age and gender were obtained; the estimated risks of progression were 14.9%, 17.2%, and 19% for men at age 30, 40, and 50 years, respectively, and 6.9%, 21.1%, and 30.1% for women. These data indicate that with respect to a 30-year-old woman, the risk of progressing to osteoporosis is 3-fold higher in a 40-year-old woman, and almost 5-fold higher in a 50-year-old woman, whereas in a man, the risk of progression is much lower. Data assessing the BMD decline over time according to the HIV status have been recently published with controversial results (25,26). Unfortunately, our study cannot elucidate this question because HIV-uninfected controls were not included.

As for antiretroviral therapy, besides evidence for TDF, there is solid evidence about the potential negative effect of PIs on BMD (5,6,27,28). In Japanese HIV-infected patients, the duration of treatment with a PI correlated significantly with bone loss, while discontinuation of the PI enabled bone recovery, especially in the lumbar spine (27). However, data from other studies did not found association between BMD decline and the use of PIs (25,26). Our results confirm the impact of PIs on bone loss, which was notable among women taking PIs and PIs+TDF. In men, a trend towards the risk of osteoporosis was seen with the use of PIs; however, it is unknown whether this is a class effect of all PIs or whether it is an adverse effect of a specific PI. To our knowledge, there are no firm data about the specific role of each individual PI in bone loss. Our large sample size made it possible to evaluate the individual impact of the most commonly used PIs (atazanavir, lopinavir, and darunavir). Having a closer look at the specific PIs, darunavir was associated with risk of bone loss among men and women, whereas atazanavir was only associated with this risk in women. These results, together with data from studies in which the PI is replaced or interrupted (27,29), support the recommendation to avoid or change PIs, if possible, in the case of osteoporosis (18). However, this finding should be interpreted with caution because only the antiretroviral combination received during the year before the DXA scan was analyzed. The retrospective nature of the study prevents us from evaluating the cumulative and continuous effect of each antiretroviral agent. In addition, the effect of other secondary risk factors on bone loss, such as menopausia, or the use of treatment for osteoporosis on bone gain was not assessed.

In conclusion, given the increased prevalence of osteoporosis and risk of bone fractures in HIV-infected individuals, osteoporosis and other factors leading to fracture, such as

sarcopenia, should be regularly assessed in clinical practice. DXA scan or fracture prediction algorithms such as the FRAX® equation (30) help to identify individuals at risk. Our results highlight the need for monitoring of BMD owing to the high probability of progression to osteopenia, even at early ages, in both genders, and to osteoporosis, especially in women aged ≥40 years. In addition, changes in antiretroviral drugs other than tenofovir (eg, PIs), changes in lifestyle, and non-pharmacological and pharmacological interventions should be recommended to reduce the risk of recurrence of fracture in the coming decade among individuals at high risk.

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Transparency Declarations

All authors have not conflicts of interests in this work

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Table 1. Epidemiological and clinical data at the first DXA scan.

	875 patients
Gender, men, n (%)	659 (75.3%)
Age, years	41.7 (36.1-47.8)
DXA scans per patient, number	3 (2-18)
Patients and DXA scans, n (%)	
Two DXA scans	294 (33.6%)
Three DXA scans	188 (21.5%)
Four DXA scans	118 (13.5%)
Five or more DXA scans	275 (31.4%)
Time from the first to the last DXA scan, years	5 (2.2-9.6)
Time between consecutive DXA scans, years	1.1 (0.6-2.2)
Antiretroviral therapy during the year before DXA, number	

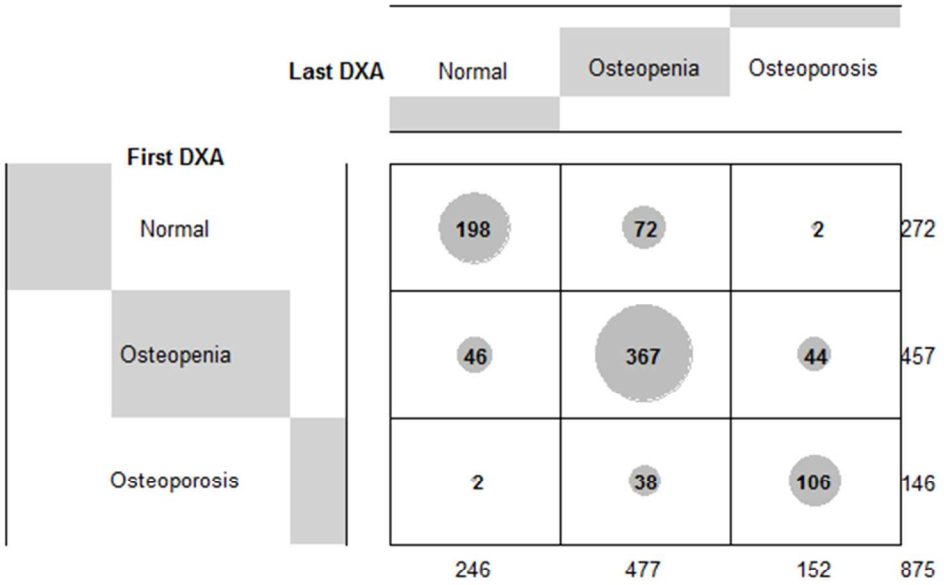
of DXA scans (%) *	
PI + TDF	567 (16.1)
Only PI	1290 (36.7)
Only TDF	734 (20.9)
Neither PI nor TDF	925 (26.3)
DXA scans in patients receiving a PI, n (%)	
Darunavir	519 (27.9)
Lopinavir	616 (33.2)
Atazanavir	253 (13.6)
Other PIs	469 (25.3)

Values are expressed as median (IQR) or number (%).

PI, protease inhibitor; TDF, tenofovir disoproxil fumarate.

*Information on the antiretroviral treatment regimens 1 year before the DXA scans was available for 862 of the 875 patients (98.5%), ie, 3516 of the 3726 DXA scans (94.4%).

392
393 **Figure 1A.**



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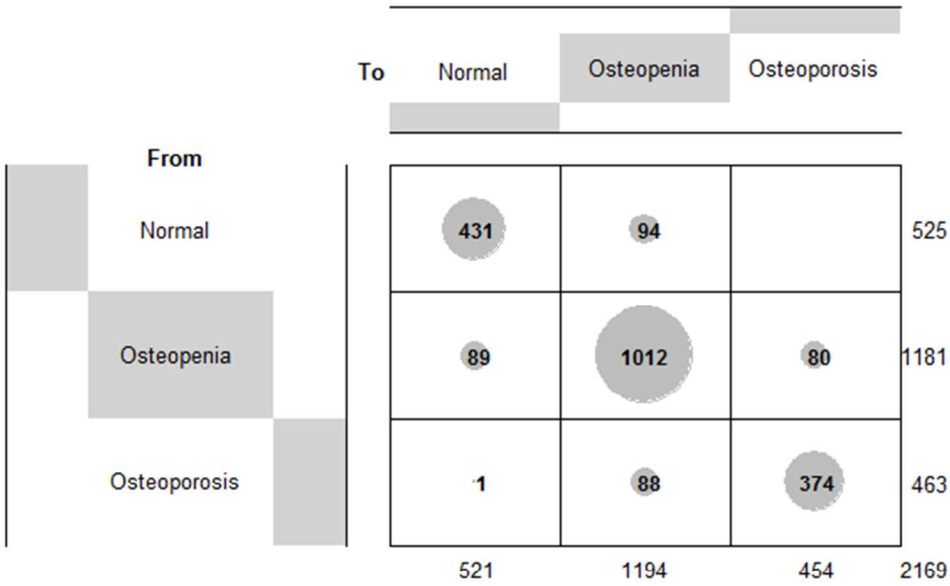
396 **Figure 1B.**



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399 **Figure 1C.**

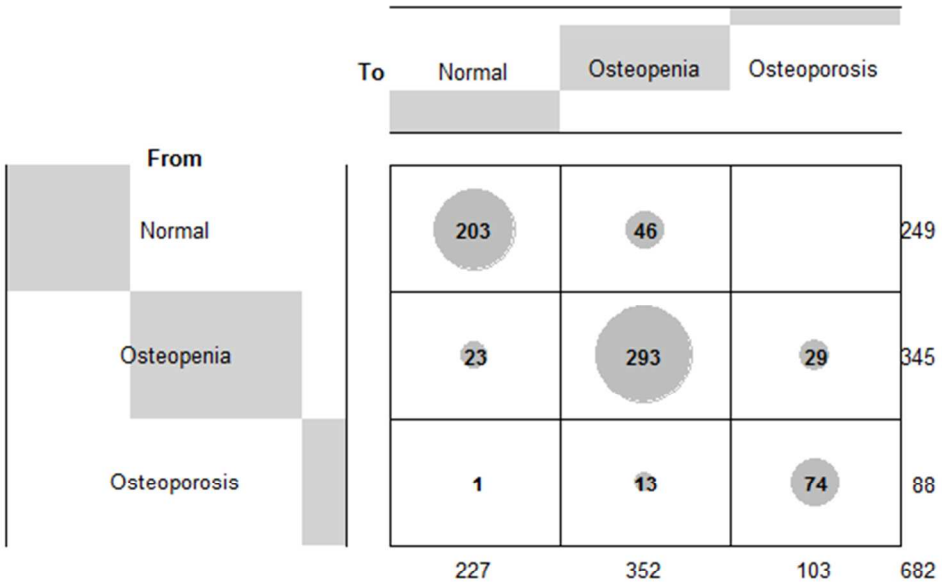

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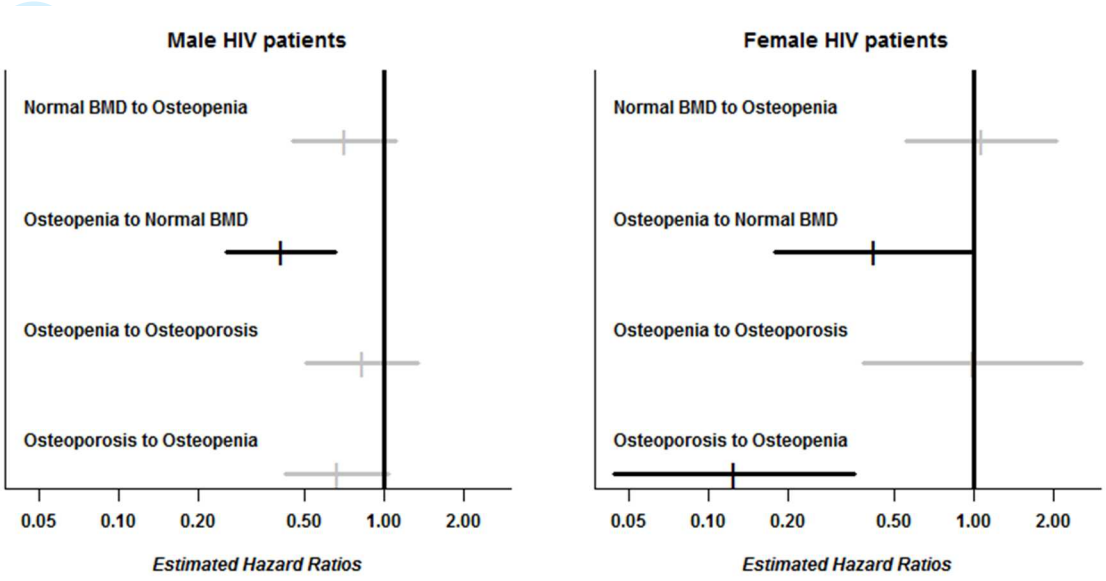
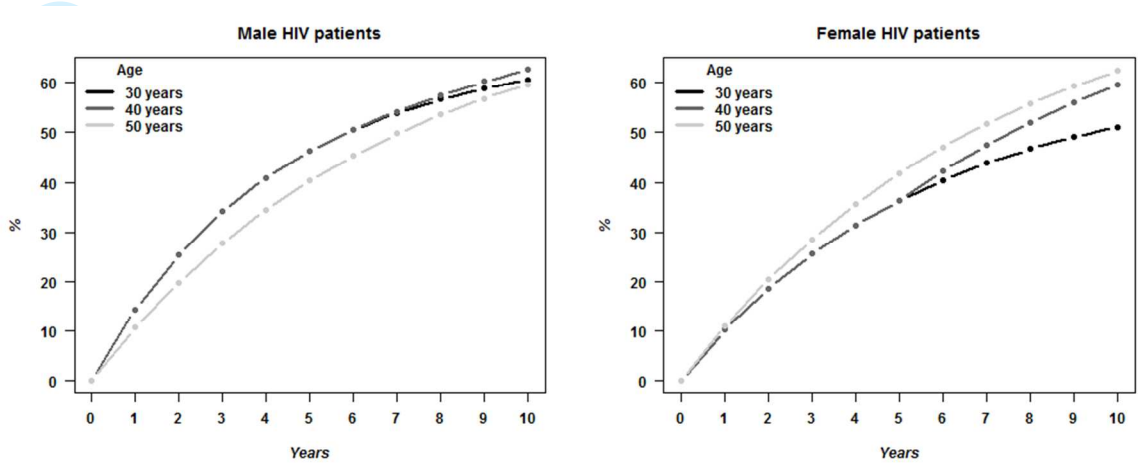
Figure 2.



406 **Figure 3A**.

407



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410 **Figure 3B**.

411

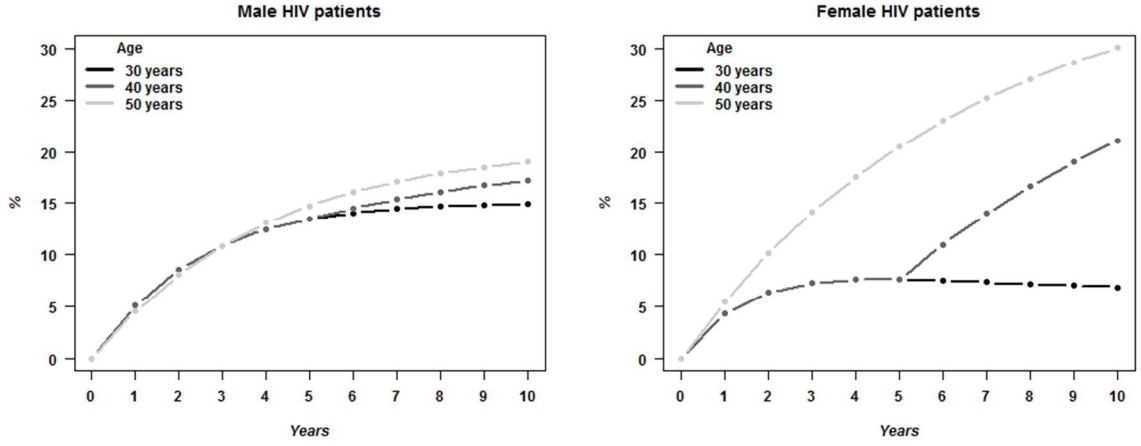

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Figure 4A.

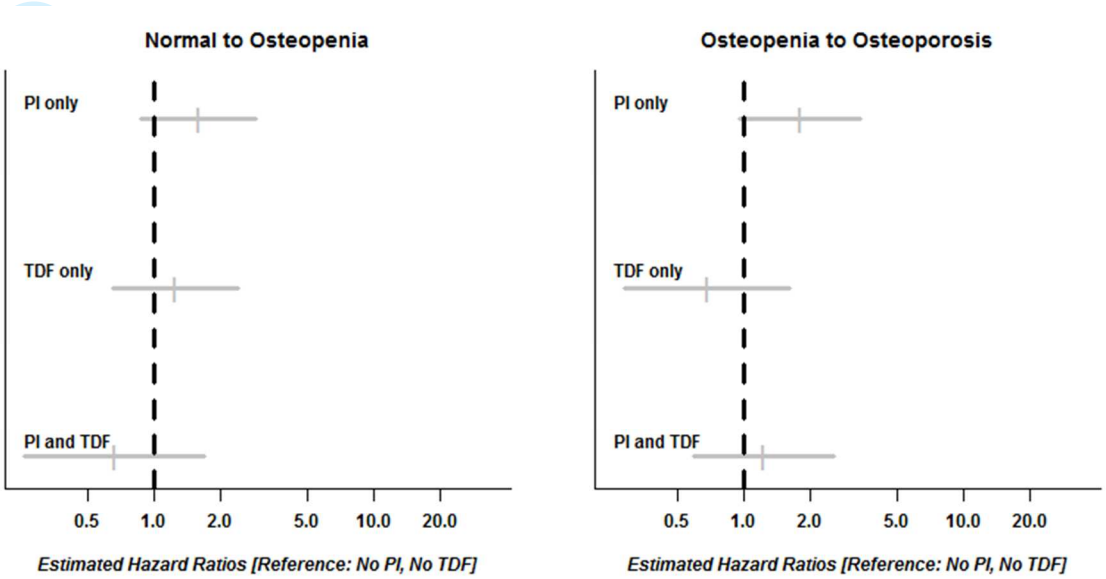

Figure 4B.

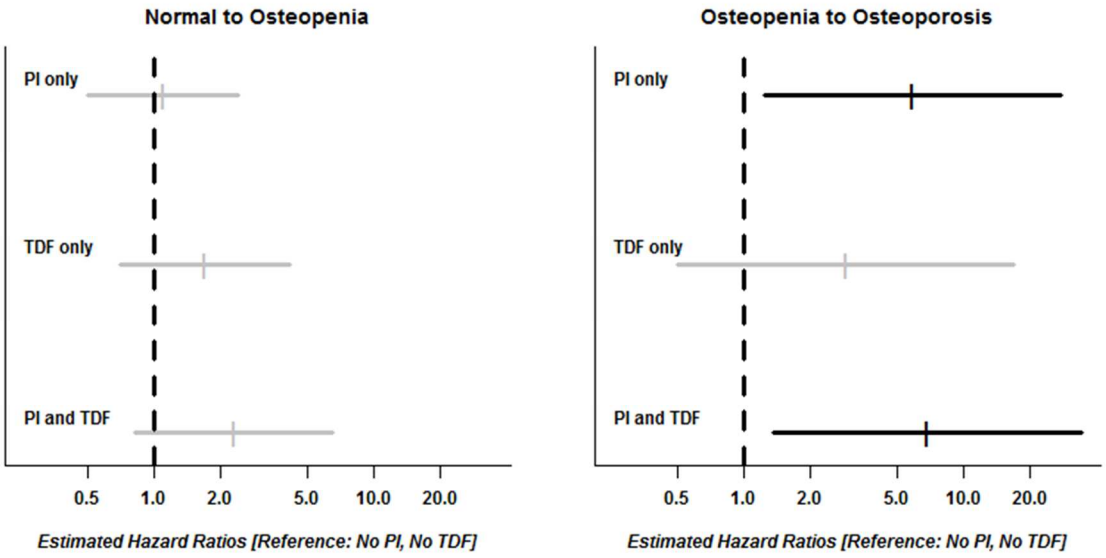

Figure 5A.

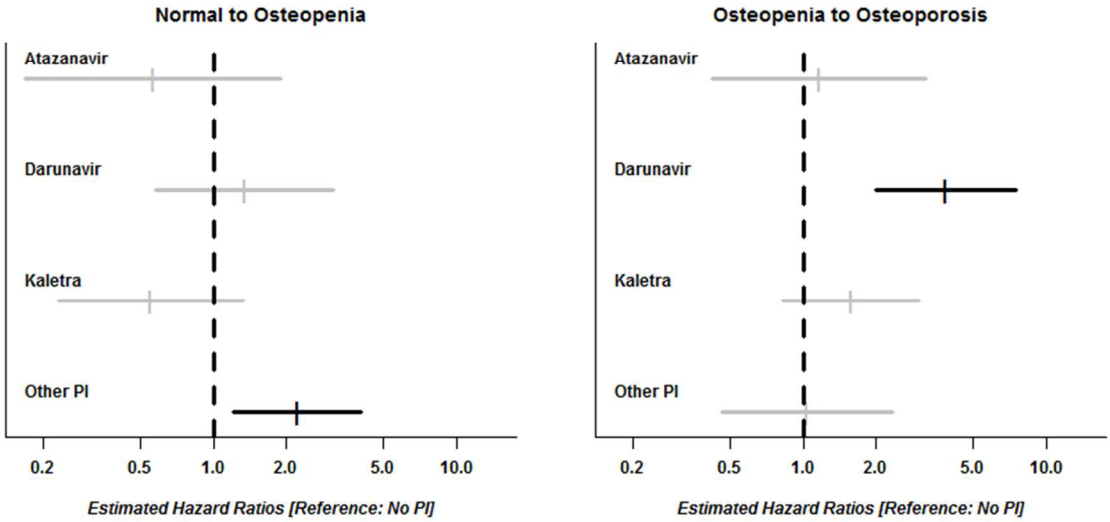

Figure 5B.

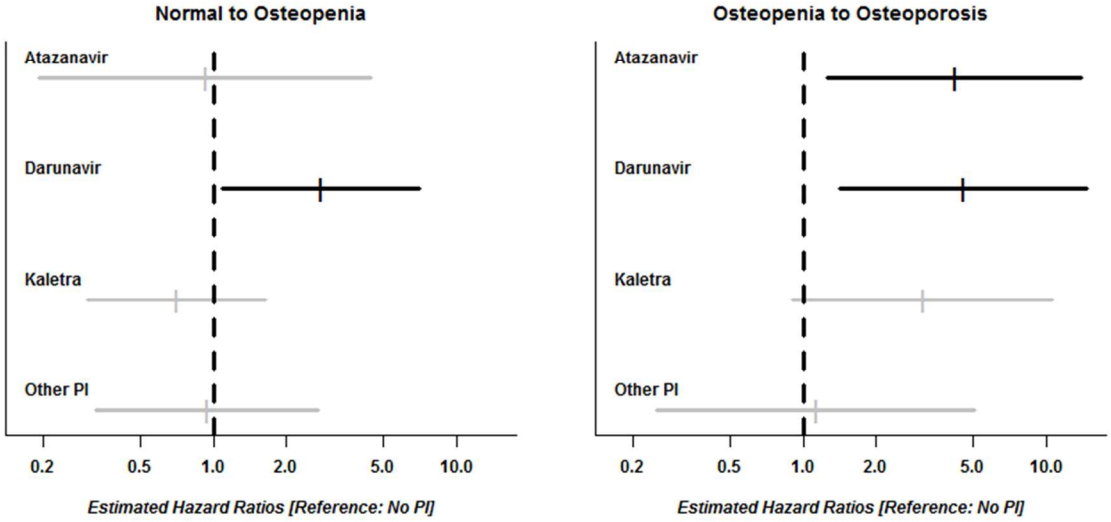

Figure Legends

Figure 1A: Joint distribution of the BMD status at the first and last DXA scans.

Figure 1B: Total number of transitions among men.

Figure 1C: Total number of transitions among women.

Figure 2: Estimated hazard ratios and 95% confidence intervals associated with age (>45 years vs. ≤45 years) for model transitions. Lines in black indicate a greater likelihood of recovery from bone loss among younger HIV-infected patients.

Figure 3A: Estimated probabilities of transition from normal bone mineral density to osteopenia/osteoporosis over 10 years for HIV-infected patients aged 30, 40, and 50 years.

Figure 3B: Estimated probabilities of transition from osteopenia to osteoporosis over 10 years for HIV-infected patients aged 30, 40, and 50 years.

Figure 4A: Estimated hazard ratios and 95% confidence intervals associated with PIs and TDF in monotherapy and combined among HIV-infected men. Left panel: Transition from normal bone mineral density to osteopenia; right panel: transition from osteopenia to osteoporosis.

Figure 4B: Estimated hazard ratios and 95% confidence intervals associated with PIs and TDF in monotherapy and combined among HIV-infected women. Left panel: transition from normal bone mineral density to osteopenia; right panel: transition from osteopenia to osteoporosis.

Figure 5A: Estimated hazard ratios and 95% confidence intervals associated with specific PIs among HIV-infected men. Left panel: transition from normal bone mineral density to osteopenia; right panel: transition from osteopenia to osteoporosis.

456 **Figure 5B**: Estimated hazard ratios and 95% confidence intervals associated with specific
457 PIs among HIV-infected women. Left panel: Transition from normal bone mineral density
458 to osteopenia; right panel: transition from osteopenia to osteoporosis.