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Original Article

Cost-effective osteoporosis treatment thresholds for people living with HIV infection in Greece

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Abstract

Objectives: We aimed to specifically define the FRAX-based cost-effective treatment thresholds for osteoporosis among people living with HIV (PLWHIV) in Greece and to compare them with those of the general population. **Methods:** A previously described state transition Markov cohort model was used in order to estimate the cost-effective intervention thresholds for osteoporotic therapy among Greek PLWHIV employing the FRAX® tool. The model-derived relative risk at which an incremental cost-effectiveness ratio of 30,000€/QALY gained was observed for treatment versus no intervention was multiplied by the average Greek FRAX-based 10-year probabilities for both major osteoporotic and hip fractures. **Results:** There exists no significant difference in the cost-effective FRAX® based thresholds between PLWHIV and general population. The absolute 10-year probabilities of 2.5 and 10% for hip and major osteoporotic fractures, respectively, could be used for the initiation of treatment for PLWHIV of both genders under the age of 75; for older subjects the proposed intervention threshold is raised to 5 and 15% 10-year probability for hip and major osteoporotic fracture, respectively. **Conclusions:** Our study confirms the general recommendation for the use of country specific FRAX® thresholds when managing bone fragility within PLWHIV. In any case, clinical judgment and appropriate screening are mandatory and irreplaceable.

Keywords: Osteoporosis, FRAX, HIV, 10-year Fracture Probability, Greece

Introduction

The increase in life-expectancy of people living with HIV (PLWHIV) was a major success over the course of the last 20 years, bringing forward issues related to ageing with the HIV infection, the ageing process itself and the need for continuous use of antiretrovirals. Non-AIDS related comorbidities, such as osteoporosis, represent a major part of HIV care, with a special focus on prevention of major complications like fractures. Among both PLWHIV and the general population osteoporosis is frequently underdiagnosed and undertreated, and even patients with major vertebral and non-vertebral fractures receive treatment at a rate of <10-20% within the first year following the event[1,2].

HIV is independently associated with lower BMD[2]. HIV-infected individuals have a 6.4-fold increased risk of low bone mineral density (BMD) and a 3.7-fold increased risk of osteoporosis in comparison with HIV-uninfected individuals[3]. Prevalence of fractures of the spine, hip, and wrist, sites commonly associated with osteoporosis can be 60% higher in HIV-infected individuals compared with the uninfected ones[4]. For HIV-infected individuals, there is a nearly 5 times increased risk in hip fracture incidence commonly associated with osteoporosis, independent of sex, age, and smoking[5]. Additionally, younger patients between 20-30 years old, still developing peak bone mass, will be adversely affected by BMD-lowering HIV treatments[6].

Guidelines for bone disease in HIV recommend a screening/risk evaluation process guided by age and classical risk factors, followed by the implementation of BMD and/or FRAX® algorithm accordingly[7,8]. Current

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Table 1. Cost-effective 10-year probabilities for hip and major osteoporotic fractures, according to gender and age, in people living with HIV (PLWHIV) in Greece.

Age	Women			Men		
	RR	"cost effective" Major fracture	"cost effective" Hip fracture	RR	"cost effective" Major fracture	"cost effective" Hip fracture
50	4.32	13.8	1.7	7	17.5	1.4
55	1.39	6.2	1	1.88	6	0.75
60	1.26	8.3	1.6	1.45	6.2	1.2
65	1	9.3	2.5	1.37	7.7	2.0
70	1	13	4.5	1.04	7.6	2.8
75	1	18	8.1	1.06	10.3	5
80	1	23	12	1	12	7.2
85	1	23	13	1	13	8.2

Major: 10-year probability for major osteoporotic fractures; Hip:10-year probability for hip fracture; RR: Relative Risk.

guidelines recommend the use of country-specific, general population FRAX® risk thresholds into the decision algorithm for fracture risk-mitigating interventions[8]. For the general population, Greece appears within the high-risk countries for osteoporotic fractures. Cost-effective osteoporosis treatment may be facilitated in Greece if the FRAX® algorithm is used to identify subjects with 10-year probabilities for hip and major osteoporotic fractures of 2.5 and 10%, under the age of 75, while for older patients, the relevant thresholds are 5 and 15%, respectively[9,10].

In this study we aimed to specifically define the FRAX-based cost-effective treatment thresholds for osteoporosis among PLWHIV in Greece. Given the particular pattern of HIV-related bone disease, the secondary endpoint of this study was the comparison of the cost-effective treatment thresholds for osteoporosis between PLWHIV and the general Greek population.

Materials and methods

Model structure

FRAX® integrates significant clinical risk factors and optionally hip bone mineral density (BMD) in order to calculate fracture risk for each individual patient[11]. In this study we used a previously described state transition Markov cohort model[10] to estimate the cost-effective intervention thresholds of osteoporotic therapy among Greek PLWHIV employing the FRAX® tool. Model inputs included treatment efficacy, incidence of fractures, mortality, quality of life and costs.

The specific model can calculate the relative risk (RR) that should be multiplied with the baseline risk of fractures (hip, vertebral, forearm) for the treatment to become cost-effective in every defined population. However, we herein present intervention thresholds on the basis of absolute 10-year hip and major fracture risk in order to allow direct comparison with published national reports. The FRAX® cost effective intervention threshold was calculated by multiplying the derived, by the Markov model, RR with the corresponding average 10-year hip and major fracture risk at each age group, as previously described[10,12]. As an example, in our analysis a RR of 1.88 must be applied to the baseline risk of each fracture type (hip, vertebral, forearm) in order for the treatment to become cost-effective for the 55-year old male Greek PLWHIV (Table 1). Given that the "secondary cause" box should always be checked whenever using the FRAX® calculator tool among PLWHIV[8], the same population without any other risk factors with a BMI of 25 kg/m^2, has an average FRAX® 10-year fracture risk of 3.2% for major osteoporotic fractures and 0.4% for hip fractures. These results translate into absolute 10-year probabilities of 6.0% for major osteoporotic fractures (3.2% multiplied by relative risk of 1.88) and 0.75% for hip fractures (0.4% multiplied by relative risk of 1.88) as cost-effective treatment intervention thresholds (Table 1). In this calculation there exists the apparent assumption of no prevalent FRAX risk factors and this assumption might underestimates the 10-year fracture probability compared to reality as many patients smoke, drink alcohol or even have prevalent fractures. It is also assumed that a BMD measurement is not available.

A validation procedure was performed, as previously described under the general principles for model transparency and validation by the International Society for Pharmacoeconomics and Outcomes Research and the Society for Medical Decision Making (ISPOR-SMDM) Modeling Good Research Practices Task Force[13]. The authors and external experts reviewed and approved the face validity of the model. Finally, validation for external consistency followed the cross-validation methodology, using the Zethreus et al.[14] model as the basis for comparisons; both models provided corresponding results when applied on similar baseline populations.

Treatment efficacy

In our model a bisphosphonate-like intervention for 5 years is used as in previous similar studies[12,15] assuming

full persistence and a treatment-induced reduction of 35% (R.R=0.65) in the risk of all fractures for any individual therapeutic modality and in each considered population group during the treatment period. The remaining effect wanes linearly for the next 5 years following discontinuation of treatment until fully offset[14]. The intervention is compared with standard treatment (solely calcium and vitamin D).

Incidence of fractures

Data on the incidence of fractures for HIV-patients in Greece were indispensable in order to populate the model and calculate the cost-effective intervention thresholds. Due to the lack of local data regarding specific incidence rates, the international literature was used in order to adjust the fracture incidence of the general population, available from our previously published study[10], and reflect the respective rates of the HIV population. Therefore, incidence rates were adjusted from a study published by Triant VA et al.[4], for both PLWHIV and HIV uninfected individuals. The fracture rates of the HIV-uninfected population provided by Triant VA et al. were compared to those derived from Makras et al.[10] for the general Greek population as mentioned above; this comparison resulted into ratios according to which the incidence of fractures for the HIV-population described by Triant VA et al.[4] were modified in order to reflect the incidence of fractures of the Greek HIV-population. Thus, for male individuals the incidence ratios were estimated as follows: for vertebral fractures: 2.10, for hip fractures: 1.755, for wrist fractures: 1.4747, for other fractures: 1.683. For female individuals the respective ratios were: for vertebral fractures: 1.8, for hip fractures: 0.839, for wrist fractures: 1.5783, for other fractures: 1.4476.

Mortality

The age-specific incidence rates of deaths related to fractures were also adjusted following the same methodology and using as reference a study published by Marcus JL et al.[16] for PLWHIV and HIV-uninfected, male and female individuals. According to the study, the crude mortality rates were 381 and 1,054 per 100,000 person-years for HIV-uninfected and PLWHIV respectively. As a result a ratio estimated at 2.7664, reflecting the difference regarding mortality between HIV and non-HIV populations, was multiplied by the respective Greek general population's mortality rates resulted in mortality rates of the HIV population. The incidence of causally related deaths in Greece within the first year after fracture was calculated per 100,000.

Costs

In order to have comparable results with our previous study[10] we kept the input of costs at the exactly same level. Therefore, the first year cost of hip fracture was assumed at 12,550€, of clinical vertebral fracture at 2,776€, while the cost of other fractures was computed at 6,624€. The annual nursing home costs, constituting long-term disability costs, were estimated at 13,271€[17]; the annual cost of a BMD measurement (60€) and a physician visit (10€) were also included in the cost assumptions. Finally, annual medication cost was estimated at 733.7€ in the base case analysis as previously described[10] while indirect costs such as fracture-related productivity losses were not included.

Cost-effectiveness analysis

According to our previous analysis[10] and in order to have comparable results, we intended to determine the fracture probability at which intervention becomes cost-effective from a third-party payer perspective and assuming a willingness to pay (WTP) an incremental cost-effectiveness ratio (ICER) of 30,000€ per each gained quality-adjusted year of life (QALY).

With a BMI set at 25 kg/m^2 and for each sex and age group (50-85 years, in 5-years steps) cost-effective intervention thresholds were calculated by multiplying the average FRAX 10-year fracture risk of major and hip fracture of each age group with the relevant RR of the model that yielded a 30,000€ cost per QALY. All possible combinations of model's RR between 1 and 20.0 were tested in 0.01 steps.

Statistical analysis

Continuous data are presented as mean ± standard error of the mean (SEM). Kolmogorov-Smirnov test was used to check the normality of distributions of continuous variables. Paired samples T-test were used for between group comparisons, in cases of two groups of continuous variables. Analysis of variance (ANOVA) or Kruskal-Wallis test were used for between group comparisons, in cases of more than two groups of continuous variables. In case of significant differences, Bonferroni post-hoc correction was used for multiple pairwise comparisons. In all the above mentioned tests, $p<0.05$ was considered statistically significant. Statistical analysis was performed with SPSS 21.0 for Macintosh (IBM Corp., Armonk, NY).

Results

10-year probability of a major osteoporotic fracture

The cost-effective 10-year major osteoporotic fracture probability exhibited a gradual increasing trend with age, in both sexes and with a fair relationship with the ICER throughout the age range (Table 1). In general, minor age-variations were noticed, except for the age-range of 50-54 because of the low incidence of fractures at this particular age group resulting in high FRAX® thresholds. In specific, drug intervention was calculated as cost-effective at or below 13.8% (range: 6.9%-13.8%) for women and 17.5% (range: 7.1%-17.5%) for men aged from 50 to 54 years. The respective thresholds between 55 and 65 years were estimated between 6.2%-9.3% for women and 6.0%-7.7% for men. When considering women and men aged older than 65 years and up to 75 years old the cost-effective thresholds

Table 2. Cost-effective 10-year probabilities for hip and major osteoporotic fractures, according to gender and age, in HIV-uninfected Greek population.

Age	Women			Men		
	RR	"cost effective" Major fracture	"cost effective" Hip fracture	RR	"cost effective" Major fracture	"cost effective" Hip fracture
50	8.5	20.4	1.7	18	34.2	1.8
55	2.38	7.8	0.95	4	9.6	0.8
60	1.93	9.1	1.5	3	9.3	1.5
65	1.33	8.7	1.8	2.5	10	2.25
70	1	9.2	2.6	1.75	8.9	2.4
75	1	13	4.7	1.6	10.56	4.48
80	1	16	7.1	1.4	11.2	5.9
85	1	16	7.8	1.37	11.23	6.57

Major: 10-year probability for major osteoporotic fractures; Hip:10-year probability for hip fracture; RR: Relative Risk.

Table 3. Cost-effective intervention thresholds in relation to WTP cut-offs of 30,000€,15,000€, 22,500€ per QALY, in people living with HIV (PLWHIV) in Greece.

Age	Women									Men								
	30,000€			22,500€			15,000€			30,000€			22,500€			15,000€		
	RR	Major	Hip	RR	Major	Hip	RR	Major	Hip	RR	Major	Hip	RR	Major	Hip	RR	Major	Hip
50	4.32	13.8	1.7	5.75	18.5	2.3	8.6	27.5	3.4	7	17.5	1.4	9.8	24.5	2.0	15.8	39.5	3.2
55	1.39	6.2	1	1.8	8.1	1.3	2.5	11.3	1.7	1.88	6	0.75	2.44	7.8	1.0	3.48	11.1	1.4
60	1.26	8.3	1.6	1.6	10.6	2.1	2.3	15.2	3.0	1.45	6.2	1.2	1.88	8.0	1.5	2.65	11.4	2.1
65	1	9.3	2.5	1.25	11.6	3.1	1.75	16.3	4.4	1.37	7.7	2.0	1.77	9.9	2.7	2.45	13.7	3.7
70	1	13	4.5	1	13.0	4.5	1.3	16.9	5.8	1.04	7.6	2.8	1.31	9.6	3.5	1.78	13.0	4.8
75	1	18	8.1	1.1	19.8	8.9	1.45	26.1	11.7	1.06	10.3	5	1.31	12.7	6.3	1.71	16.6	8.2
80	1	23	12	1.15	26.4	13.8	1.45	33.3	17.5	1	12	7.2	1.21	14.5	8.7	1.52	18.2	10.9
85	1	23	13	1.22	28.0	15.9	1.47	33.8	19.1	1	13	8.2	1.11	14.4	9.1	1.34	17.4	11.0

WTP: willingness to pay; Major: 10-year probability for major osteoporotic fractures; Hip:10-year probability for hip fracture; RR: Relative Risk; QALY: quality-adjusted year of life.

were computed between 13%-18% for women and 7.6%-10.3% for men, respectively. Finally, for women and men over 75 years old the cost-effective intervention thresholds were calculated at 23.0% for women and between 12.0% and 13% for men. No difference were found between the cost effective 10-year major osteoporotic fracture probabilities of PLWHIV and uninfected population both within females [14.32±2.28 (HIV +) Vs. 12.52±1.61 (HIV -), p=0.32] and males [10.03±1.40 (HIV +) Vs. 13.12±3.02 (HIV -), p=0.17].

10-year probability of a hip fracture

Similarly with major osteoporotic fractures, the cost-effective 10-year probability rates exhibited an increase with age at both sexes when considering hip fractures. For similar reasons with the major osteoporotic fractures, minor age-variations were noticed in the age group of 50-54 years, and a 10-year probability for a hip fracture at 1.7% (range: 0.98%-1.7%) for women and 1.4% (range: 0.9%-1.5%) for men was found to be cost-effective. Regarding the 55-65 years age group a 10-year probability between 1.0% and 2.5% for women and 0.75%-2.0% for men was calculated. For the next age group up to 75 years old the threshold was calculated between 4.5% and 8.1% for women and 2.8%-5% for men. Finally, taking into consideration women and men aged older than 75 years, the cost-effective 10-year probability for a hip fracture was computed at 12.0% -13% and 7.2%-8.2% for women and men, respectively. No differences were found between the cost effective 10-year hip fracture probabilities of HIV infected and uninfected male population [3.56±1.01 (HIV +) Vs. 3.21±0.76 (HIV -), p=0.23]. However, the cost effective 10-year hip fracture probabilities of HIV infected females were significantly higher than those of the uninfected population (Table 2): [5.55±1.71 (HIV +) Vs. 3.51±0.94 (HIV -), p=0.03]; this difference is attributed to the higher cost-effective thresholds of females ≥70-years old [9.4±1.94 (HIV +) Vs. 5.55±1.18 (HIV -), p=0.01], while for the younger population no significant differences were found [1.7 ± 0.3 (HIV +) Vs. 1.5 ± 0.18 (HIV -), p=0.28].

Sensitivity analysis

The cost-effective intervention thresholds in relation to WTP of 30,000€, 22,500€, and 15,000€ are presented in Table 3. As expected, the cost-effective intervention thresholds proportionally increase with decreasing WTP.

Discussion

With the exception of 10-year probabilities for hip fracture among ≥70-years old HIV infected females, the findings of our study indicate that there exists no difference in the cost-effective FRAX® based thresholds between the PLWHIV and HIV-uninfected individuals. Therefore, for Greece we suggest that the absolute 10-year probabilities of 2.5 and 10% for hip and major osteoporotic fractures, respectively, could be used for the initiation of treatment for PLWHIV of both genders under the age of 75; for older subjects the proposed intervention threshold is raised to 5 and 15% 10-year probability for hip and major osteoporotic fracture, respectively.

The cause of bone loss in HIV is multifactorial including the traditional risk factors, some of which disproportionately affect PLWHIV, the alterations in bone metabolism due to antiretroviral therapy exposure, HIV infection *per se*, and the underlying chronic inflammation beyond successful long-term viral suppression. Commonly used antiretrovirals, such as Tenofovir Disoproxil Fumarate (TDF) or boosted protease inhibitors, have shown more significant BMD loss vs other currently available treatment options[18]. New treatment modalities such as Tenofovir Alafenamide (TAF), the novel prodrug of tenofovir, is related to significant less impact on BMD in naïve patients and BMD increases in virologically suppressed patients switching from a TDF- to a TAF-based regimen[19,20]. However, the impact of these observations in general recommendations is yet to be defined. Bisphosphonates are the most frequently used medication against osteoporosis among PLWIV. However, the long-term effects of these agents on clinically important outcomes such as fracture remain to be determined and there is currently no study adequately powered study to demonstrate an effect on fracture in this specific population. Yet, bisphosphonates have been shown to improve BMD in HIV-infected men and women[21,22]. Alendronate or zoledronate or risedronate should be considered to enhance BMD and possibly consequently decrease fracture incidence in HIV-infected patients at high risk for fragility fractures[21]. In a meta-analysis of the effects of bisphosphonates in HIV-infected patients with low BMD, a significant increase in bone mineral density at the lumbar spine was observed in the bisphosphonates group at 48 weeks (MD: 2.84%; 95% CI: 2.11-3.57) and 96 weeks (MD: 6.76%; 95% CI: 4.98-8.54); analogously, bisphosphonates were associated with an increase in total hip bone mineral density at 48 weeks (MD: 2.12%; 95% CI: 1.43-2.81) and 96 weeks (MD: 3.2%; 95% CI: 1.52-4.88)[23].

It has been suggested that FRAX® algorithm underestimates the fracture risk among PLWHIV, even when modified to include HIV as a secondary cause[24-26]. Given that the "secondary osteoporosis" box should always be checked when calculating the FRAX-based 10-years fracture probabilities[8] and especially when BMD is not available, one can suggest that the proposed thresholds of our study could be easily attained within the PLWHIV population, which has a relatively high proportion of smokers and alcohol consumers[27,28]. However, this is not probably the case as for example a 55-years old HIV-infected male with a BMI of 25 kg/m^2, who smokes and drinks ≥3 alcohol units per day, has a FRAX® score of only 4.3 and 1.0% for major osteoporotic and hip fractures, respectively. The same case of a female individual has a FRAX® score of 6.1 and 1.6% for major osteoporotic and hip fractures, respectively. Both cases are not considered eligible for osteoporosis treatment according to our analysis. In addition, Greek guidelines suggest a dual energy X-Ray absorptiometry (DXA) measurement of BMD in all subjects <50-years old with a pathologic condition related to bone loss and fractures such as HIV infection[29]. Therefore, DXA hip measurements will definitely make the estimation of FRAX® probabilities more accurate among this population. In addition, the cost-effective RR in our study is 1.0 for females ≥65-years old and males ≥70-years old. This may appear as suggesting osteoporosis treatment in every HIV infected individual within the above age limits. However, this is also not the case in a country as Greece with the second largest number of DXA machines in the European Union[30] and with guidelines supporting the BMD measurements in this population[29]. As an example a 65-year old HIV infected female with a BMI of 25 kg/m^2 and no other clinical risk factors would be marginally eligible for initiation of osteoporosis treatment according to our analysis only if exhibiting a T-score ≤-2.3 while for a male subject the relevant T-score should be ≤-1.8.

The relatively increased cost-effective 10-year probabilities for hip fracture between HIV infected females ≥70 years is probably due to the decreased estimated ratio of 0.839 for hip fractures. According to our adjustment, the only relatively decreased (≤1.0) incidence ratio was that for hip fractures among the female population, while all the other incidence ratios were between 1.4476 and 2.1 for both genders as expected. This calculation seems initially peculiar; however, it is probably derived from the age distribution of hip fractures, which exhibits some differences between males and females. In specific, the incidence of hip fractures presents a particular pattern as it is gradually increased after the age of 65 among females while this is the case approximately 5-10 years later within the male population[31]. The life expectancy of PLWHIV may significantly vary reaching the estimations for the general population[32]. With an approximate mean decrease of 7-10 years in life expectancy of HIV subjects, mortality competes with the probability of fractures in elderly people thus increasing the intervention thresholds among these older subjects. This is possibly more evident among women in whom the steep increase in hip fracture incidence is more significantly blunted by the decrease in life expectancy than men. However, we do not believe that there exists a crucial reason to change the cost-effective

intervention thresholds for hip fractures in this specific age group within the Greek health care setting. Except from the confusing message to the health care providers, we do not feel that a higher threshold will result in significant savings for the healthcare system.

The major limitation of our study is the current lack of Greek specific data regarding the real incidence of fractures and mortality rates of PLWHIV. Other limitations are similar to the previous analysis of the whole Greek population including the assumption of a 35% efficacy in reduction of all fracture types with anti-osteoporotic treatment, and the restriction in a single WTP threshold of 30,000€[10]. However, it was purposefully decided to use the same model applied to the general Greek population and in order for the results of this analysis to remain comparable with the outcomes of our analysis of the general patient population, we also assumed that patients were fully persistent to treatment, as in the original model. Nevertheless, optimal persistence is not the case in the real world and, in this context, this should be acknowledged as another major limitation of this analysis. Finally, our results are limited at ages of 40 years and older as FRAX® is only applicable at this age range which unfortunately leaves out a significant proportion of PLWHIV.

In conclusion, although PLWHIV in Greece may exhibit higher FRAX® scores than HIV-uninfected individuals, there is no difference in the cost-effective FRAX® based thresholds for the initiation of osteoporosis treatment between the PLWHIV and HIV-uninfected individuals. Therefore we suggest that there exists an indication for osteoporosis treatment for PLWHIV in Greece at similar with the Greek general population FRAX® thresholds. In every case, clinical judgment and appropriate screening are mandatory and cannot be replaced by any health economic modeling result.

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