

Original Article



## Fracture Risk with Modified FRAX in Men Living with HIV

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### Abstract

**Background:** Aging of the HIV-infected population and prolonged use of ARTs, produced metabolic alterations, including increased fracture risk. FRAX is a validated, computer-based clinical fracture risk calculator which estimates 10-year risk of major fracture, and hip fracture. However may underestimate risk in HIV-infected individuals. Several experts recommend considering HIV a cause of secondary osteoporosis.

**Methodology:** Were included 52 men living with HIV, classified as high, moderate and low risk using ABRASSO graphic tool.

**Results:** High risk prevalence found for major fracture and hip fracture were both 2 (4.2 %) using FRAX; while 10 (20.8 %) and 14 (29.2 %) using modified FRAX, respectively. Considering bone densitometry, 5 (12.8 %) were high risk for hip fracture and was noticed an increase in high risk major fracture from 4.2 % with FRAX to 5.1 % with FRAX considering bone densitometry. As for the low risk, 19 (39.6 %) for major fracture and 23 (47.9 %) for hip fracture with FRAX. While low risk modified FRAX were 0 (0 %) for major fracture and 8 (16.7 %) for hip fracture. It was also evidenced an association of high risk for major fracture and hip fracture with modified FRAX using Fisher's exact test [ $p=0.0273$  (bilateral)].

**Conclusion:** It was concluded is recommended using modified FRAX for people living with HIV for better control and therapeutic decision-making about osteometabolic alterations provoked for the virus and ARTs.

**Keywords:** Fracture risk; HIV; Modified FRAX.

### Background

Reduced bone mineral density (BMD) is observed in people living with HIV/AIDS (PLWHA), and consequently osteopenia and osteoporosis with an elevated prevalence of fractures compared to the general population.<sup>1</sup> Since the discovery of HIV-1, more than 40 antiretroviral drugs have been developed, which are able to control the infection when used in various combinations, their use is recommended regardless of CD4 count and has been followed by an increase in life expectancy of

PLWHA.<sup>2</sup> However, the greater longevity of PLWHA becomes a challenge due to prolonged exposure to antiretroviral drugs and their possible distress.<sup>3</sup>

PLWHA bone loss is primarily caused by two factors: HIV infection, due to immune dysregulation; and the use of Antiretroviral Therapy (ART), mainly over the first years of treatment.<sup>4,5</sup> Bone homeostasis disruption and BMD reduction are among the most important side effects of ART.<sup>6</sup>

FRAX is a tool that considers clinical factors which can be used to evaluate fracture risk even in the absence of BMD. Its results indicate the 10-year probability of a major fracture (MF) - clinical vertebral, forearm, humerus, and hip fractures (HF), or an isolated hip

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fracture.<sup>7</sup> Minor traumas, equivalent to falling from one's height, can cause a low bone mass fracture and be considered a fragility fracture.<sup>8</sup>

The main clinical risk factors for osteoporosis precise determination, can improve the prediction of fracture risk and promote greater screening of high risk patients, allowing a greater selection of patients for treatment. The biggest challenge is understanding which factors can increase fracture risk and the impact they produce in bone health. It is believed that HIV is underestimated by FRAX, as it is not considered a clinical risk factor.<sup>8</sup>

Fragility fracture risk is around 35 % higher in PLWHA than in uninfected individuals and it increases with age. For this reason, experts recommend considering HIV as a cause of secondary osteoporosis when calculating the FRAX in PLWHA, naming it as modified FRAX. With the increasing life expectancy of PLWHA, identifying individuals at increased risk of fractures is critical for intervention in modifiable risk factors and fracture prevention.<sup>9</sup>

## Methods

This study is a quantitative, cross-sectional analysis, with an analytical-exploratory observational approach, being classified in terms of purpose as applied research. The study was conducted in the city of Belém, state of Pará, Brazil, the participants consisted of male patients living with HIV/AIDS treated at an endocrinology clinic. An interview was carried out to collect data from the patient, their risk factors, and bone densitometry. FRAX and modified FRAX (considering HIV infection as a cause of secondary osteoporosis) were applied. The research protocol collected data such as age, gender, weight, and height for BMI calculation and was dichotomized (yes or no) for previous fracture, history of hip fracture in the parents, smoking, alcoholism (3 or more units of alcohol/day), glucocorticoid use (minimum of 3 months of current or previous exposure to prednisone 5mg/day or more, or equivalent), and presence of rheumatoid arthritis (RA). Other secondary causes of osteoporosis were also investigated, such as diabetes mellitus (DM), hyperthyroidism, disabsorptive intestinal disease, chronic liver disease, chronic kidney disease, and chronic obstructive pulmonary disease (COPD). The FRAX calculation was performed using a tool available on the

internet at <https://www.shef.ac.uk/FRAX/tool.aspx?country=55>. The value found was applied in the graphic tool of ABRASSO (Brazilian Association of Bone and Osteometabolic Evaluation) classifying as low, moderate or high risk, calculating the index with and without the result of bone densitometry.

This study has been approved by the Research Ethics Committee of the Health Science Institute of Federal University of Pará - CEP/ICS-UFGPA - CAAE#39365419.1.0000.0018, Brazil. All participants provided written informed consent prior to enrollment in the study.

## Results

In this study were analyzed data from 52 male patients living with HIV/AIDS, which were classified as high, moderate and low risk by FRAX, modified FRAX, and FRAX with BMD, the values obtained were shown in Table 1. It was not possible to calculate the risk of 3 patients in the FRAX and 12 in the FRAX with BMD, as 3 were aged below 40 years, and 9 did not have results from BMD.

High risk prevalence for major fracture and hip fracture was 2 (4.2 %) in FRAX, but in modified FRAX values found were 10 (20.8 %) and 14 (29.2 %) for major fracture and hip fracture, respectively. When analyzing high risk values with BMD, it was evidenced a hip fractures high risk rise to 5 (12.8 %) and percentage increase in major fractures of 4.2 % with FRAX to 5.1 % with FRAX with BMD, which demonstrates a modification of increased severity and risk for fractures, corroborated by Table 2, which specifically explores high risk values in FRAX and modified FRAX.

Low risk values found in FRAX were 19 (39.6 %) for major fractures and 23 (47.9 %) for hip fractures. Using modified FRAX these values were minimal, 0 (0 %) for major fracture and 8 (16.7 %) for hip fracture, demonstrating a diminished bone health. Percentages with BMD also show a decrease in low risk patients, with values of 13 (33.3 %) for major fractures and a percentage increase in hip fractures of 20 (51.8 %), shown in Table 1.

Table 2 presents the results regarding the high risk for major fracture and hip fracture in the FRAX and modified FRAX in men living with HIV/AIDS.

**Table 1**  
FRAX, modified FRAX and FRAX with BMD of male living with HIV/AIDS

|               | FRAX           |              | Modified FRAX  |              | FRAX with BMD  |              |
|---------------|----------------|--------------|----------------|--------------|----------------|--------------|
|               | Major fracture | Hip fracture | Major fracture | Hip fracture | Major fracture | Hip fracture |
| High risk     | 2 (4.2 %)      | 2 (4.2 %)    | 10 (20.8 %)    | 14 (29.2 %)  | 2 (5.1 %)      | 5 (12.8 %)   |
| Moderate risk | 27 (56.2 %)    | 23 (47.9 %)  | 38 (79.2 %)    | 26 (54.2 %)  | 24 (61.5 %)    | 14 (35.9 %)  |
| Low risk      | 19 (39.6 %)    | 23 (47.9 %)  | -              | 8 (16.7 %)   | 13 (33.3 %)    | 20 (51.3 %)  |

**Table 2**  
Major fracture and Hip fracture high risk with FRAX and modified FRAX

| FRAX                            | Major fracture - High risk |             | Hip fracture - High risk |             |
|---------------------------------|----------------------------|-------------|--------------------------|-------------|
|                                 | Yes N ( %)                 | No N ( %)   | Yes N ( %)               | No N ( %)   |
| Non modified                    | 2 (4.2 %)                  | 46 (95.8 %) | 2 (4.2 %)                | 46 (95.8 %) |
| Modified                        | 10 (20.8 %)                | 38 (79.2 %) | 14 (29.2 %)              | 34 (70.8 %) |
| P (value) - Fisher's Exact Test | 0.0273                     | 0.0018      |                          |             |

Values found in Table 2 using Fisher's exact were  $p=0.0273$  (bilateral) for major fracture and  $p=0.0018$  for hip fracture. Therefore, there was an association of increased risk of major fracture and hip fracture with the modified FRAX. These results reveal that when using the modified FRAX, the high risk increases considerably from 2 (4.2 %) in major fractures and 2 (4.2 %) in hip fractures to 10 (20.8 %) and 14 (29.2 %), respectively.

Table 3 presents the results regarding moderate risk for major fracture and hip fracture in the FRAX and modified FRAX in men living with HIV/AIDS.

The moderate risk of major fracture using FRAX is 27 (56.2 %) and using modified FRAX is 38 (79.2 %), shown in Table 3. Furthermore, the moderate risk of hip fracture with FRAX is 23 (47.9 %), and modified is 26 (54.2 %). For that reason, there is evidence of an increase in the alert values, which suggests the need to request a BMD test. Evaluating hip fracture values using chi-square did not suggest an association. However, in the major fracture, there was an association with the modified FRAX, indicating the need to request a BMD test.

Ultimately, considering values of the lumbar T-score and femoral T-score values of men living with HIV/AIDS under 40 years old, unable to be classified as low, medium, and high risk was evidenced precocious BMD loss. All 3 patients had lumbar T-score less than 0, among them 1 presented -1.3 lumbar T-score, being classified as osteopenia. Those results showed the need for earlier screening to identify BMD reduction in PLWHA.

## Discussion

Our study evaluated the risk of fractures in males living with HIV/AIDS using FRAX and modified FRAX.

PLWHA have reduced BMD and, therefore, have increased risk for fractures.<sup>1-10,11</sup> Our results suggest a risk of fracture underestimated by FRAX in this population. For that reason, it's possible that patients who need treatment are not receiving the attention needed.

Previous research identified greater accuracy of FRAX when adding HIV as a risk factor for secondary osteoporosis.<sup>12</sup> Yin et al reported a 31 % increase in risk for major fracture and 67 % for hip fracture in 10 years.<sup>9</sup> Another study showed a 77 % increase in sensitivity and specificity to identify low BMD in PLWHA.<sup>13</sup> Our study corroborates with data presented in previous studies, demonstrating an increase in the number of patients classified as high risk in the modified FRAX, for major fractures this increase was from 2 (4.2 %) to 10 (20.8 %), and for hip fracture from 2 (4.2 %) to 14 (29.2 %). Fisher's exact test showed values of  $p=0.0273$  and  $p=0.0018$  for high risk of major fracture and hip fracture, demonstrating an association with the modified FRAX.

The study by Tsai et al presented 24.1 % of patients eligible for treatment in FRAX with BMD, while modified FRAX and FRAX identified only 13.3 % and 6.7 %, respectively, with a sensitivity of 79.2 % and a specificity of 100 %.<sup>14</sup> In our study, FRAX with BMD showed a higher number of patients classified as high risk, when compared to FRAX without BMD. For major fractures, it increased from 4.2 % to 5.1 %, and for hip fractures from 4.2 % to 20.5 %. Our study hasn't demonstrated a difference between the modified FRAX and the FRAX with BMD, however, we had a smaller sample and some patients did not have BMD test results.

In a study carried out in Spain with 217 patients, where 98 % had at least one classic factor related to low BMD

**Table 3**  
Major fracture and Hip fracture moderate risk with FRAX and modified FRAX

| FRAX                        | Major fracture - Moderate risk |             | Hip fracture - Moderate risk |             |
|-----------------------------|--------------------------------|-------------|------------------------------|-------------|
|                             | Yes N ( %)                     | No N ( %)   | Yes N ( %)                   | No N ( %)   |
| Non modified                | 27 (56.2 %)                    | 21 (43.8 %) | 23 (47.9 %)                  | 25 (52.1 %) |
| Modified                    | 38 (79.2 %)                    | 10 (20.8 %) | 26 (54.2 %)                  | 22 (45.8 %) |
| P (value) - Chi-square test | 0.0291                         | 0.6830      |                              |             |

or HIV-related, the estimate risk for fracture increased up to 216 % after adding BMD when compared to selecting only the “secondary osteoporosis” option in the tool box.<sup>15</sup> These data demonstrated the FRAX limitations, including the modified version, and point to the need of developing a specific assessment method for this population.

We evaluated the BMD of 3 patients aged less than 40 years old, all of which had lumbar T-scores below 0, demonstrating an early reduction in BMD and, in a 36-year-old patient, osteopenia was identified. Gregson et al recommends FRAX application in all men over the age of 50 and, in case of a medium or high risk score, BMD test should be performed to guide decision-making.<sup>16</sup> However, it's not possible to use the FRAX classification for patients younger than 40 years old. Had we not requested a BMD test for those patients, we would have lost the opportunity to identify this reduction in BMD early in our population, and it wouldn't have been possible to carry out the guidance and adequate follow-up of these individuals. Therefore, requesting a BMD test proves to be essential for screening bone disease in PLWHA, regardless of age.

## Conclusions

Although the use of ART has changed the course of the natural history of disease and increased life expectancy of PLWHA, metabolic alterations caused by its use and by the virus itself were observed, with the risk of fragility fracture being 35 % higher in this population.<sup>9</sup> For this reason, it's necessary to further investigate the effects on BMD, adopt measures for better categorization of high-risk patients and employ preventive actions.

It is supported by the current literature that the FRAX underestimates HIV, since it's not among the clinical risk factors. Considering it as a risk factor for secondary osteoporosis in the modified FRAX brings it closer to more accurate risk values. For that reason, careful determination and validation of the main clinical risk factors for osteoporosis improve the prediction of fractures and promotes a more adequate screening of risk patients, allowing a better selection of patients for treatment.

The data obtained will serve as a subsidy for future research, as well as be used to expand clinical evidence regarding the adequate control of bone parameters in patients living with HIV/AIDS undergoing treatment with antiretroviral therapy. In this context, there is scarce data in literature related to HIV as a clinical risk factor for bone fractures and its application in FRAX. Therefore, the use of the modified FRAX is encouraged. With prevention and proper treatment, morbidity and mortality caused by bone fractures are decreased, and quality of life of PLWHA is increased.

This is an ongoing research, therefore, its limitations lie in the low sample size and low number of patients with BMD test results, making it impossible to perform a more

accurate comparison between FRAX and FRAX with BMD.

## Declaration of Competing Interest

None.

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