Correspondence

Reply to Gazzola et al

To the Editor—We were interested to read about additional experience with use of the FRAX score among adults with human immunodeficiency virus (HIV) infection. Gazzola et al [1] demonstrated that the FRAX score computed on the basis of only classical risk factors had poor sensitivity (22%) for identifying patients with low bone mineral density (BMD; defined as a T score of <-1 and Z score of <-1). The sensitivity was only modestly improved (37%) when HIV infection was included in the FRAX score as a secondary cause of osteoporosis.

In our article [2], we demonstrated that the FRAX score computed without BMD was not able to discriminate adequately between HIV-infected adults with osteopenia and those without osteopenia, because the fracture risk level provided by the FRAX score for patients with osteopenia was similar to that provided for patients without osteopenia.

We reanalyzed our cohort of 153 adults (150 [98%] were male, 67 [44%] were receiving tenofovir, and 81 [53%] were receiving a ritonavir-boosted protease inhibitor; median age, 48 years) to assess the role of HIV disease. When HIV infection was included in the FRAX score as a secondary cause of osteoporosis, the FRAX score was not able to discriminate between patients with osteopenia and those without osteopenia (data not shown).

In addition, we performed new analyses on the sensitivity and the specificity of adding HIV infection as a secondary cause of osteoporosis to the FRAX score computed without BMD, in predicting the risk for a major osteoporotic fracture; any risk of major osteoporotic fracture above a threshold of 7.5% [3] or 20% [4] at 10 years would warrant bisphosphonate treatment (intervention threshold). Second, we also chose a threshold that would warrant BMD assessment (assessment threshold) when the risk of major osteoporotic fracture would exceed 5% at 10 years [5].

Of the 65 patients with a low BMD, the FRAX score computed without HIV infection included as a secondary cause of osteoporosis identified only 11 patients (sensitivity, 17%) for whom bisphosphonate treatment would be appropriate (intervention threshold, 7.5%). When HIV infection was included in the FRAX score, the sensitivity increased to 35%. Choosing an intervention threshold of 20% dramatically decreased the sensitivity (3% with and 1.5% without HIV infection as a secondary cause; data not shown). We found a similar difference in sensitivity when the threshold was lowered to 5% in order to identify patients who need a BMD assessment: the sensitivity increased from 39% to 51% after the inclusion of HIV infection as a secondary cause of osteoporosis (Table 1).

Therefore, the FRAX score appears to be an imperfect tool for BMD screening among HIV-infected adults who are receiving antiretroviral therapy: even when HIV infection is included as a secondary cause of osteoporosis, the score conservatively assumes that the risk is exclusively mediated by low BMD, which reflects the data available for rheumatoid arthritis. Indeed, when BMD is entered into the FRAX equation, no weight is accorded to these secondary causes, which may increase bone fragility independently of BMD losses. In addition, biochemical markers for bone turnover are not incorporated into assessment algorithms, but we and others [6] have shown that patients receiving tenofovir were likely to have increased bone turnover. Thus, the FRAX tool is mainly limited, because it does not recognize HIV infection as a possible cause of bone fragility and because HIV infection may only be considered to have an effect on fracture risk through an effect on BMD loss. A model that would help predict who could benefit from dual-energy x-ray absorptiometry assessment, and therefore who would be eligible for a preventive therapeutic approach, is lacking.

Table 1. Sensitivity and Specificity of the FRAX Algorithm to Predict Fracture Risks, Computed With or Without Human Immunodeficiency Virus (HIV) Infection Considered as a Secondary Cause of Osteoporosis

	No. of patients with risk levels above assessment threshold				No. of patients with risk levels above intervention threshold			
	Fracture risk without HIV		Fracture risk with HIV		Fracture risk without HIV		Fracture risk with HIV	
Patients' BMD	⩾5%	<5%	⩾5%	<5%	⩾7.5%	<7.5%	⩾7.5%	<7.5%
Low (n = 65)	25	40	33	32	11	54	23	42
Normal (n = 74)	34	40	38	36	8	66	27	47
Sensitivity or specificity, %[a]	39	54	51	49	17	89	35	64

NOTE. The assessment threshold is defined as a risk of major osteoporotic fracture of ⩾5%. The intervention threshold is defined as a risk of major osteoporotic fracture of ⩾7.5%. BMD, bone mineral density.

[a] Sensitivity for patients with risk levels at or above the threshold, and specificity for patients with risk levels below the threshold.

We do recognize, however, that routine BMD assessment of all HIV-infected adults by means of dual-energy x-ray absorptiometry may be impractical in many settings.

In conclusion, no adequate tool is validated to guide the clinicians in when to perform a BMD assessment. If the FRAX score is used to prompt the decision to assess BMD, we suggest that HIV infection be included as a secondary cause of osteoporosis but that clinicians keep in mind that only 50% of the patients with low BMD will be identified. Our data are in line with those of Gazzola et al [1], and we urge the development of a model for fracture prediction that can be applied for younger patients who are affected by chronic diseases that are not included as classical risk factors in the FRAX tool. Alternatively, the guidelines recently issued by the European AIDS Clinical Society [7] recommend considering BMD measurements for postmenopausal women, men >50 years of age, and patients with hypogonadism, prolonged glucocorticoid use, or a history of low-impact fracture or a high risk of falls. Again, these risk factors only identify a minority of the patients with osteopenia.

Alexandra Calmy,[1,2,3] Christoph A. Fux,[4] Cécile Delhumeau,[3] and Andrew Carr[1,2]

[1]HIV, Immunology, and Infectious Diseases Unit and [2]Centre for Applied Medical Research, St Vincent's Hospital, Sydney, Australia; [3]HIV Unit, Geneva University Hospital, Geneva, and [4]University Clinic for Infectious Diseases and University of Berne, Berne, Switzerland

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Reprints or correspondence: Dr Alexandra Calmy, HIV Unit, Geneva University Hospital, 4 rue Gabrielle Perret-Gentil, 1205 Geneva, Switzerland (acalmy@gmail.com).

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