Which HIV patients should be screened for osteoporosis: an international perspective

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Purpose of review
This review provides international insights into the real-world clinical approach to screening for bone mineral density (BMD) and osteoporosis in people living with HIV (PLWH) using opinions from HIV physicians from key regions around the world.

Recent findings
Although a significant proportion of PLWH are aged over 50, the relative importance of low BMD to clinical care differs significantly between countries and regions, based on factors such as the population at risk, access to adequate screening resources, and physicians' knowledge. Generally, management of osteoporosis in PLWH follows similar principals as for the general population, with risk factors for fracture combined with measurement of BMD by dual energy X-ray absorptiometry in algorithms such as Fracture Risk Assessment Tool, designed to provide an overall risk estimation. Although in most regions age is considered among the most important factors contributing to low BMD and fractures, considerable country and region-specific factors become apparent, such as malnutrition, inactivity and impact of comorbidities, substance abuse, and increasing use of tenofovir disoproxil fumarate.

Summary
These opinions highlight the diversity that still exists in the approach to the long-term management of PLWH and highlight challenges facing development of consensus guidelines that can be effectively implemented worldwide.

Keywords
bone mineral density, fracture, HIV, osteoporosis screening

INTRODUCTION

Widespread use of antiretroviral therapy (ART) has significantly impacted the global HIV epidemic. With longer lifespans, many people living with HIV (PLWH) now experience medical conditions that commonly accompany ageing [1], including decreased bone mineral density (BMD) and osteoporosis, both of which occur at higher rates in PLWH

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Curr Opin HIV AIDS 2016, 11:000–000
DOI:10.1097/COH.0000000000000269

KEY POINTS

- Evaluation of low BMD and osteoporosis in PLWH generally follow the same principals as for the general population and vary according to country-specific guidelines.
- In clinical practice, approaches to screening of low BMD in PLWH might vary because of different characteristics of patients under care and access to the necessary resources required for screening and treatment.
- The lack of HIV-specific guidelines is identified as a limitation to screening in both resource-rich and resource-limited settings, with lack of physician awareness also reported as a limitation in several countries.

[2–4]. The overall clinical consequence of low BMD is increased risk of fracture, with higher fracture rates reported, even in younger PLWH [5–7].

These high rates of osteoporosis may reflect overrepresentation of traditional risk factors such as smoking, alcohol use, and low BMI in this population coupled with effects of long-term HIV infection, continued immune dysfunction, and ART-induced toxicities. HIV likely contributes to low BMD through a combination of viral, immune, and treatment-related effects on bone metabolism [3].

Evaluation and management of low BMD and osteoporosis in PLWH generally follow the same principles as for the general population and vary according to country-specific guidelines. Most guidelines in the general population recommend formal fracture risk assessment using FRAX in all postmenopausal women and men at least 50 years of age, with screening using dual energy X-ray absorptiometry (DXA) recommended in women at least 65 years of age, and men at least 70 years of age regardless of clinical risk factors [8], whereas the Infectious Diseases Society of America and the European AIDS Clinical Society (EACS) both recommending DXA screening in PLWH who are postmenopausal women or men aged at least 50 years [9,10]. It has also recently been suggested to include HIV infection as a secondary cause of osteoporosis in FRAX fracture risk assessments [9,11▪▪]. In addition to screening, guidelines also recommend approaches to reduce fractures in PLWH, including ensuring sufficient dietary calcium and vitamin D intake, use of bisphosphonates in osteoporotic postmenopausal women and men more than 50 years old and strategies to optimise ART to preserve or improve BMD [9,10,11▪▪].

Despite these guidelines, in clinical practice, approaches to screening and management of low BMD in PLWH might vary because of different characteristics of patients under care and access to the necessary resources required for screening and treatment. To explore this, we invited international perspectives on real-world practice approaches for screening of bone disease in PLWH obtained through answers provided by expert clinicians in the field.

METHODS

HIV and bone disease experts from 11 countries worldwide were asked to provide opinions on their approach to determining fracture risk in clinical practice based on answers to the following questions:

- The proportion of PLWH aged over 50 and postmenopausal women in their treatment population
- How important a priority is low BMD and osteoporosis to patient care
- What, if any, is their personal experience of low BMD/fractures in their patients
- The approach to screening for low BMD within their population
- Which guidelines (if any) they follow for screening
- Access to DXA scanning or limitations to performing DXA screening

In addition, contributors were asked to rank nine risk factors proposed to contribute to fracture risk, including age, low BMI, low vitamin D, malnutrition, other chronic diseases/medications (including corticosteroid exposure), substance abuse (alcohol/drug use other than smoking), inactivity (sedentary lifestyle), ART, and advanced HIV disease (low $CD4^+$ cell count/high HIV RNA/AIDS illnesses). A 'word cloud' map was generated using country-specific rankings (Tagul.com) providing regional clustering of words, with those factors considered most important appearing larger compared with those ranked less important.

RESULTS

Estimated proportion of study participants meeting recommended criteria for BMD screening

According to national surveys and local cohort studies, the estimated proportions of PLWH under care aged over 50 years was higher in North America,

Table 1. Population characteristics and screening practices according to responses provided by HIV and bone expert clinicians from 11 countries

	Global data		ID clinic-personal perspective				
Region	**HIV population characteristics**	**Data source**	**Study participants over 50 (%)**	**Postmenopausal women (%)**	**Data source**	**Guidelines for screening**	**Access to DXA scan**
North America							
United States	1218400 PLWH prevalence 0.5%; 21% over 50	CDC Division of HIV/AIDS and Prevention [12]	56	53	Johns Hopkins HIV/ AIDS Service	IDSA [10]; US Preventive Service Task Force guidelines [13]	Yes (insurance coverage for DXAs scans)
Canada	75500 PLWH prevalence 0.2%; 12% over 50	Public Health Agency of Canada [14]	47	7	HIV Clinic; Toronto General Hospital	Canadian Osteoporosis Guidelines [15]	Yes
South America							
Argentina	110000 PLWH; prevalence 0.2%	UNAIDS report 2014 [16]	40	5.5	HIV Cohort; Hospital Italiano de Buenos Aires	Argentinian HIV management and treatment guidelines [17]	Limited
Europe							
Spain	150000 PLWH; prevalence 0.3%; 36% over 50	UNAIDS report 2014 [18]	48	16	HIV Centre; Hospital Clinic – IDIBAPS	Spanish Metabolic Diseases Guidelines [19]; EACS guidelines [9]	Yes
Germany	67000 PLWH; prevalence 0.08%; 36% over 50	Robert Koch Institute Epidemiology Report [20]	36*	30	ID Centre in Hamburg	German Osteoporosis Guidelines [21]	Yes (reimbursement restrictions)
Ireland	8000 PLWH; prevalence 0.3%; 8.5% over 50	Health protection Surveillance Centre [22], UNAIDS report 2014 [23]	18.8	24	ID Clinics; Mater Misericordiae University Hospital	EACS guidelines [9]	Yes
Eurasia							
Turkey	11500 PLWH; prevalence 0.015%	UNAIDS report 2014 [24]	17	1.7	HIV Cohort; Hacettepe University	Turkish Endocrinology and Metabolism Society Guidelines [25]	Yes
Russia	717691 PLWH; prevalence 0.5%	UNAIDS report 2014 [26]	11	6	Moscow Regional AIDS Centre	National Osteoporosis Foundation Guidelines, Washington, DC USA [8]	Yes
Asia							
China	501000 PLWH; prevalence 0.03%	UNAIDS report 2014 [27]	22	16.6	National Free AIDS treatment Program	No official national guidelines. IDSA [10] and OSTA [34] sometimes used	Limited

Table 1 (*Continued*)

Region	Global data		ID clinic-personal perspective				
	HIV population characteristics	Data source	Study participants over 50 (%)	Postmenopausal women (%)	Data source	Guidelines for screening	Access to DXA scan
Pacific							
Australia	27 150 PLWH; prevalence 0.1%	The Kirby Institute Annual Surveillance Report 2015 [28]	35	1	HIV Cohort; Kirby Institute, USNW Medicine	EACS guidelines [9]; Osteo Renal Exchange program [11▪▪]	Yes (reimbursement restrictions)
Africa							
Uganda	1 600 000 PLWH; prevalence 7.3%	UNAIDS report 2014 [29]	15.2	7.3	ID Institute HIV Outpatient Clinic Mulago Hospital	No national guidelines	No (only research)

CDC, Centers for Disease Control and Prevention; DXA, dual-X-ray absorptiometry scan; EACS, European AIDS Clinical Society; ID, infectious disease; IDSA, Infectious Diseases Society of America; OSTA, Osteoporosis Self-assessment Tool for Asians; PLWH, people living with HIV; UNAIDS, the Joint United Nations Programme on HIV/AIDS; USNW, University of New South Wales.

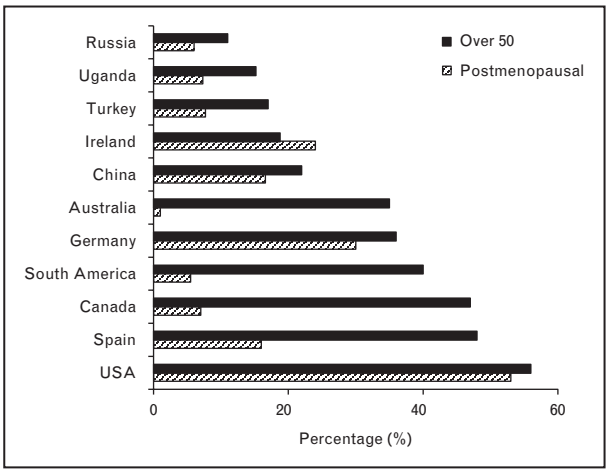

FIGURE 1. Geographical distribution of HIV patients over the age of 50 and postmenopausal women based on HIV cohort data provided by HIV and bone expert clinicians from 11 countries.

South America, Europe, and Australia compared with Asia and Africa, with numbers ranging from 35 to 56% and 11 to 17%, respectively (Table 1, Fig. 1) [9,12–29]. Similarly, data on the proportion of women with HIV either over 50 or postmenopausal was highest in the United States (53%) followed by Germany (30%) and Ireland (24%), and much lower in other countries, ranging from 1 to 16% (Table 1, Fig. 1) [9,12–29].

Country-specific experiences in patient management

North America

United States

Source: The Johns Hopkins HIV/AIDS Service.

Johns Hopkins is one of the largest HIV providers in the state of Maryland, with approximately 3600 PLWH in care, of whom 56% are men over 50 years old and 53% postmenopausal women. The patient population is diverse, with approximately 75% African-American, 35% women, and 40% with a history of injection drug use. Osteoporosis screening practices vary widely according to 19 physicians who contributed information on practice, ranked a 'very important' medical priority by four of 19 (21%) and 'somewhat important' by the other 15 (79%). The estimated median (interquartile range) percentage of men aged 50–69 years and postmenopausal women screened for osteoporosis was 20% (10–40%), with higher rates [55% (10–80%)] for men over 70 and women over 65 years old,

representing approximately 4% of the clinic population. Almost all clinicians had patients with osteoporosis, with six (32%) having more than five patients with osteoporosis and 12 (63%) having patients with fragility fractures. HIV Primary Care guidelines (HIV Medicine Association of the Infectious Diseases Society of America) [9] were followed by eight (42%), five (26%) followed the US Preventive Service Task Force guidelines [13], with the remaining eight (42%) not following any guidelines. Limitations to screening included competing medical/social concerns (89%, 17/19), lack of time in clinic (47%, 9/19), patients lack of follow-up with screening (21%, 4/19), and lack of insurance coverage for DXA (16%, 3/19). Age, low BMI, and substance abuse were the main factors considered to contribute to fracture risk in this population (Fig. 2).

Canada

Source: HIV clinic from the Toronto General Hospital.

This HIV clinic serves 1269 PLWH, of whom 47% are aged over 50, and 7% are postmenopausal women. Despite this, fractures are infrequently seen and mainly associated with presence of traditional risk factors. Therefore, overall screening for low BMD and osteoporosis is considered a lesser priority than screening for other comorbidities such as cardiovascular, liver, and renal diseases. Canadian osteoporosis guidelines recommend screening for low BMD using DXA and two additional fracture risk assessment tools, both validated using Canadian data, Canadian Association of Radiologists and Osteoporosis Canada Risk Assessment Tool 2010 and FRAX [15]. However, despite availability of DXA, lack of specific osteoporosis management guidelines for PLWH (including normal ranges, particularly for younger men) was considered a limitation with screening left to the discretion of the clinician. The main risk factors thought to contribute to fracture risk were presence of other comorbidities, advanced HIV disease, and substance abuse (Fig. 2).

South America

Argentina

Source: HIV cohort from the Infectious Diseases and Clinical Pharmacology Department of the Hospital Italiano de Buenos Aires.

In Argentina, an estimated 30–40% of PLWH who attend major regional clinical sites are over 50 years old and approximately 4–6% are over 70, with the proportion of postmenopausal women under care difficult to estimate. Generally throughout Argentina, osteopenia/osteoporosis is not considered a high clinical priority, with the majority of

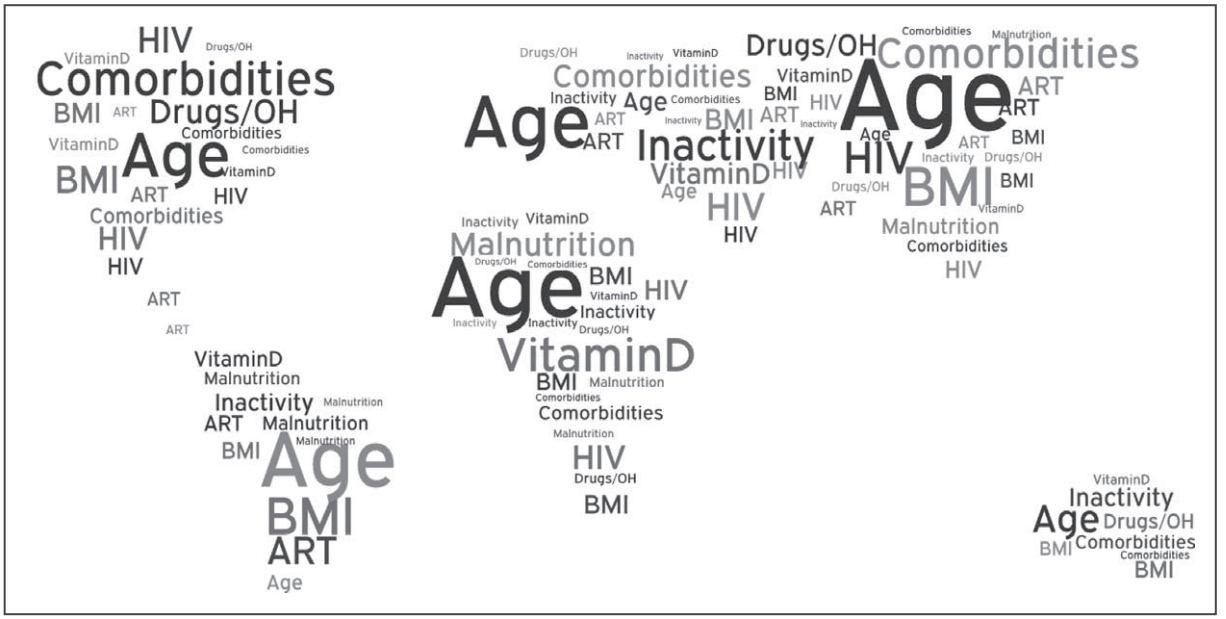

FIGURE 2. Factors that most contribute to fracture risk in different populations according to HIV experts consulted from 11 countries. Risk factors ranked 1–3, with 1 being the most important contributing factor for each country, appear larger compared with those ranked less important (background words). For simplicity low BMI is displayed as 'BMI' in the word cloud map, low vitamin D as 'VitaminD', other chronic diseases/medications (including corticosteroid exposure) as 'Comorbidites', substance abuse (alcohol/drug use other than smoking) as 'Drugs/OH', and advanced HIV disease (low $CD4^+$ cell count/high HIV RNA/AIDS illnesses) as 'HIV' (word cloud map created with Tagul.com).

PLWH unlikely to have undergone formal osteoporosis screening. However, in some centres, such as the Hospital Italiano de Buenos Aires (serving 800 PLWH), where 5.5% of women are over 50 and 6.5% of PLWH are aged over 70, BMD evaluation is an important component of initial patient work up with DXA performed routinely at first presentation and periodically thereafter. Although estimated prevalence of osteopenia and osteoporosis was 35 and 5%, respectively, pathological fractures are not considered a significant problem. The Argentinian HIV Management and Treatment Guidelines recommend DXA screening for all PLWH aged over 50 regardless of other risk factors, and for patients under 50 with other risk factors for fracture [17]. Limitations to screening include access to DXA (not available in many hospitals and care centres) and physician education on the need for osteoporosis screening as part of routine clinical assessment. Factors considered to most contribute to fracture risk include older age, low BMI, and exposure to ART (Fig. 2).

Central Europe

Spain

Source: Day Care HIV Centre in Barcelona (IDIBAPS).

In this HIV population, comprising 48% aged over 50 and 16% postmenopausal women, low BMD is considered very important and approaches to screening follow Spanish HIV guidelines for managing bone disease and EACS guidelines [9,19]. Screening includes risk factor assessment at first presentation, repeated when the patient reaches the age of 50, with additional DXA screening in those over 50 years old. In addition, lateral lumbar spine X-ray is also performed to assess for vertebral fractures in any patient with chronic back pain. The major limitation to screening is access to DXA for the number of patients requiring screening. Age, poor mobility, and substance abuse were identified as the main factors contributing to increased fracture risk in this population (Fig. 2).

Germany

Source: Infectious Disease Centre in Hamburg.

It is estimated that approximately 36% of PLWH in Germany are aged over 50, 18% of whom are women with an estimated 30% of those attending Infectious Disease Centre in Hamburg being postmenopausal women. Although DXA scanners are widely available, access to BMD screening is limited because of restrictions on reimbursement through public health insurance, with a highly suspected probability of osteoporosis and/or intention to treat necessary criteria to assess DXA. German HIV treatment guidelines do not list criteria for BMD screening in PLWH [30]. Non-HIV German osteoporosis guidelines are used where appropriate (men from the age of 60 and in postmenopausal women) [21]. Reimbursement criteria are fulfilled in only a small minority of patients [31]. Although the prevalence of low BMD is approximately 30%, fractures in the absence of trauma, are considered relatively rare, with age, presence of comorbidities, and ART considered the main factors contributing to fracture risk in this population (Fig. 2).

Ireland

Source: Infectious Disease Clinics, Mater Misericordiae University Hospital.

The Mater Misericordiae University Hospital clinical service provides care to approximately 1100 PLWH, with 18.8% aged over 50. Although data on postmenopausal status is lacking, of those over 50, 24% are women. The clinic follows the EACS guidelines for comorbidity screening [9], including BMD assessment by DXA in those at risk. The main limitation to screening is patient engagement. Most fractures observed arise from trauma with use of illicit drugs, alcohol abuse, and frailty considered to be the main contributing factors (Fig. 2).

Eurasia

Turkey

Source: HIV cohort of study participants from the Hacettepe University in Ankara.

The HIV cohort of the Hacettepe University attends 440 PLWH of whom approximately 17% are aged over 50 and 1.7% are postmenopausal women. Nearly 15% of the overall treatment cohort are women, with approximately half adhering to faith-led clothing practices that involve covering almost the entire body, greatly reducing overall sun exposure. Although almost half of those newly diagnosed with HIV have low BMD, only a handful of fractures have been observed, most in those with advanced HIV or older age. Although there are no HIV-specific Turkish guidelines for management of low BMD in HIV, the Turkish Endocrinology and Metabolism Society issue general guidelines [25]. Screening is by DXA, with reevaluation after 2 years in postmenopausal women, with an estimated 90% patients completing screening. As costs are covered by general health insurance with good access to DXA, principal limitations to screening include lack of both physician knowledge and robust clinical protocols. In addition to reduced sunlight exposure

and resulting vitamin D deficiency, other identified risks for low BMD and fracture include sedentary lifestyle, smoking (nearly half of the population smokes), advanced HIV disease, and poor intake of dairy products, particularly milk, because of the high prevalence of lactose intolerance in the Turkish population (Fig. 2).

Russia

Source: Moscow Regional AIDS Centre.

Of 30 774 PLWH attending the Moscow Regional AIDS Centre, 11% are aged over 50, with an estimated 6% postmenopausal women. Although low BMD and osteoporosis are considered increasingly important as the population ages, fractures have been mainly limited to those with severe comorbidities. Management of low BMD and osteoporosis is based on recommendations from the National Osteoporosis Foundation (USA) [8]. Screening for low BMD by DXA is applied according to indications including advanced age, long-term exposure to ART, and presence of comorbidities, particularly endocrine diseases and previous fractures. The main risk factors contributing to fracture risk include older age, presence of comorbidities, and substance abuse (Fig. 2).

Asia and the pacific

China

Source: Department of Infectious Diseases at Peking Union Medical College.

Based upon data from the Chinese National Free AIDS Treatment Program, 22% of 41 862 adult PLWH started on ART in 2012 were aged over 50 and approximately one-third were women [32], although data on menopausal status are lacking. Antiretroviral regimens containing tenofovir disoproxil fumarate (TDF) are used first line, raising concerns about long-term effects on both bone turnover and BMD [33▪]. There are no formal Chinese guidelines for screening of osteoporosis in PLWH and there is a perceived lack of awareness of the problem among treating HIV clinicians. A few physicians based in major cities may screen individuals aged over 50 based upon international guidelines [10]. FRAX is not generally used because of uncertainty about its accuracy within a Chinese population and the Osteoporosis Self-assessment Tool for Asians [34], which is used in the general Chinese population to estimate osteoporosis risk, is sometimes used as preliminary screening to identify those in need of DXA. Screening is limited by both access to DXA and specialists in osteoporosis. Experience of fractures in PLWH is limited as the population is still relatively young. One multicentre survey of 263 Chinese PLWH did identify 10.7% PLWH reporting a history of fracture, although the majority of these were linked to trauma [35]. In those with HIV, age, low BMI, and advanced HIV infection were considered the main factors contributing to fracture risk (Fig. 2).

Australia

Source: Kirby Institute, USNW Medicine, Sydney.

In this population, approximately 35% of PLWH are aged over 50 with only 1% postmenopausal women. Low BMD is not considered a high priority as fractures are not common. Fracture risk comprises FRAX risk assessment (without BMD) in those over the age of 40, with further screening by DXA limited by insurance reimbursement; patients must have either established low BMD, be aged over 70, or have clinically suspected low BMD. International guidelines used in management include EACS and Osteo Renal Exchange Programme guidelines [9,11▪▪]. The main factors contributing to fracture risk in this population are older age, inactivity, and substance abuse (Fig. 2).

Africa

Uganda

Source: Infectious Diseases Institute, HIV outpatient clinic at Mulago Hospital Complex, Makerere University College of Health Sciences.

This HIV clinic serves 7894 HIV-infected study participants of whom 15.2% are over 50, and 7.3% are postmenopausal women. Prevalence of osteoporosis is high; in those initiating second-line ART, an estimated 53.7 and 28.9% had low BMD and 8 and 1.1% osteoporosis at the lumbar spine and hip, respectively [36▪]. Despite this, low BMD and osteoporosis are not considered a high priority in Uganda, experience of fractures is limited and there are no HIV-specific national guidelines for screening. However, with increased use of TDF in first-line ART regimens, low BMD and osteoporosis is becoming more important. Owing to the lack of access to DXA (only available through research), diagnosis is principally based on clinical suspicion and plain radiographs. In this population, age, vitamin D deficiency, and malnutrition are considered important factors contributing to fracture risk (Fig. 2).

DISCUSSION

The opinions provided highlight the diversity of not only the approach to screening for low BMD and fractures in different regions internationally but also

to physicians' experience of fractures in PLWH. Although centres reported significant numbers of PLWH aged over 50 (Table 1), overall most centres report only a limited experience of fractures, with only one centre (USA) reporting significant fragility fractures. It is notable, however, that this clinic population also has one of the highest proportions of both older patients (56% over 50 years old) and postmenopausal women (53%) of any of the centres contributing perspectives.

Factors considered important contributors to fracture risk also varied according to the population treated (Fig. 2). Although all centres identified age as an important factor, several centres from countries with significant HIV epidemics among intravenous drug users, such as North America, Ireland, Spain, and Russia, reported drug and alcohol abuse as important factors contributing to risk of fracture. In contrast, in countries such as China and Uganda, the more recent introduction of TDF for first-line ART was specifically identified as a potential concern. In addition, country-specific factors such as the impact of faith-based practices on vitamin D deficiency, and lactose intolerance on calcium intake in Turkey highlights the great diversity between populations of PLWH.

Although most centres have identified guidelines to assist in screening and treatment, lack of HIV-specific guidelines is identified as a limitation to screening in both resource-rich and resource-limited settings, with lack of physician awareness also reported as a limitation in several countries. In addition, lack of access to DXA (Africa, China, and Spain) or restrictions on DXA reimbursement (Australia and Germany) were cited as major barriers to screening. These data would point to the need for development of robust, international guidelines that could not only be used for education but also to enable access to screening where needed within this vulnerable population.

CONCLUSION

Although these perspectives are limited by their reliance on both expert opinion and data, several key limitations in approaches to screening of bone health PLWH were identified that could be addressed through international consensus guidelines. Such guidelines could provide the basis for policies to preserve bone health in PLWH.

Acknowledgements

We would like to thank Dr Marisa L. Sanchez (Servicio de Clinica Medica, Hospital Italiano de Buenos Aires, Argentina), Nursel Calik Basaran, MD (Internal Medicine Department, Hacettepe University, Ankara, Turkey), Dr Taisheng Li (Department of Infectious Diseases, Peking Union Medical College Hospital, Beijing, China), Jeanne Keruly, NP (Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, United States), for their assistance in providing data for this study.

Financial support and sponsorship

P.W.G.M. is supported in part by the Irish Health Research Board (award HRA-DI-2014–701). T.T.B. is supported in part by NIH (NIAID) K24AI120834.

Conflicts of interest

M.A.B. reports grants and personal fees from AbbVie, Gilead Sciences, and Merck, personal fees from AbbVie, Bristol Myers Squibb, Boehringer Ingelheim, Gilead Sciences, Janssen Cilag, Merck, and ViiV Healthcare. A.K. has served on advisory boards, speaking engagements, meetings, workshops, symposiums, and clinical trials for AbbVie and Merck. E.M. is currently receiving grants to his institution and honoraria MSD. H.J.S. has served on advisory boards and speaking engagements for AbbVie, Bristol Myers Squibb, and ViiV Healthcare and serves on speakers bureaus for Gilead Sciences, Janssen Cilag, and Merck. S.W. reports grants from Merck, ViiV Healthcare, Gilead Sciences, Abbott, GlaxoSmithKline, and Janssen Cilag and has served on advisory boards, speaking engagements, meetings, workshops, symposiums, and clinical trials for Merck, ViiV Healthcare, Gilead Sciences, Abbott, GlaxoSmithKline, and Janssen Cilag. T.T.B. is currently serving on advisory boards at Merck and Gilead Sciences and is serving as a consultant for Gilead Sciences, AbbVie, EMD-Serono, and Theratechnologies. P.W.G.M. is currently receiving a grant to his institution from GlaxoSmithKline (Ireland) and Gilead Sciences, is serving on advisory boards and speaking engagements for Gilead Sciences, Bristol Myers Squibb, and Janssen Cilag, receives honoraria from Gilead Sciences, and has received honoraria from Gilead Sciences, Bristol Myers Squibb, Janssen Cilag, and MSD. The remaining authors have no conflicts of interest.

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