(NRTIs).[26] In a ranking system based on several variables, including CSF levels, most PIs had low penetration on the three-level stratification, but ritonavir-boosted indinavir, amprenavir, lopinavir and darunavir demonstrated high penetration.[27-28] In the NRTI class, tenofovir and didanosine had the lowest ranked penetration, while abacavir and zidovudine were among those with the highest penetration.

The premise that reduced viral levels in the CSF will reduce the production of neurotoxic proteins to prevent or slow cognitive loss is compelling, but not yet well established in prospective trials. Antiretroviral regimens containing agents predicted to have poor penetration are associated with higher CSF levels of HIV RNA than regimens predicted to have good penetration,[27] but few prospective studies have demonstrated a difference in cognitive outcome from high penetration agents. In an twelve-week trial, abacavir was not more effective than placebo in improving cognitive function when either was added to a stable background regimen, but this trial was of relatively short duration and only one agent, as opposed to several, was added to the regimen.[29] Overall, the data associating poorer CSF penetration with increased HIV replication in the CSF do support further definitive randomized clinical trials comparing antiretroviral regimens with variable effects on CSF for impact on neurocognitive outcomes.[27, 30]

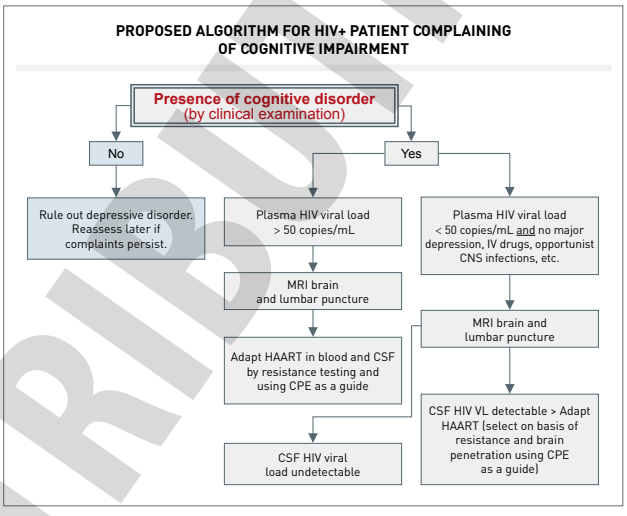
HIV-related frailty is a relatively recently reported phenomenon that may reflect accelerated aging across physiologic systems, including CNS function.[31] In a study comparing individuals initiating antiretroviral therapy over the age of 50 years, the risk of cardiovascular, metabolic or neurologic disorders was more than six times greater (P<0.0001) when compared to a younger cohort even though the antiretroviral regimens were similarly well tolerated.[32] This may be a related independent mechanism of accelerated CNS pathology in aging HIV-infected individuals.

Diagnosis and Monitoring

Based on the high rates of cognitive impairment in individuals with HIV, it is appropriate to perform periodic cognitive testing in all individuals with this infection. Even in relatively young patients, baseline measures permit subsequent changes in cognitive function to be documented. The American Academy of Neurology (AAN) first defined HIV-associated cognitive impairment in 1991,[33] but the significance of cognitive loss in the post-HAART era has evolved. Before HIV viremia could be controlled, the onset of dementia was frequently a signal of advanced immunologic deterioration that predicted the end stages of disease. In the post-HAART era, early and subtle signs of cognitive loss do not necessarily signal imminent and clinically significant morbidity but represent an opportunity for early intervention.

When slowly progressive, cognitive functional loss can be difficult to detect. Moreover, formal assessment of cognition can be time consuming. Therefore, a staged approach is suggested with three levels; the first involves a very brief screen that takes only 2-3 minutes. This could take the form of a screening algorithm as developed by Cysique et al., or by paying close attention to "red flags," as illustrated in Figure 1.

FIGURE 1 | Screening Algorithm for Cognitive Functional Loss



Adapted from Du Pasquier, R et al. *Rev Med Suisse*. 2009 Apr 29;5(201):955-6, 958-61.

If either of these is positive then the patient would be asked to return in another week or so for a longer screen. At this second level of assessment, the HIV dementia scale, CogState, or more detailed and focused questions could be used. This level of assessment would take approximately 10-15 minutes. If one of these was positive then the patient would be asked to return in another week or so for a formal evaluation of cognition.[34]

Although serial monitoring to detect cognitive changes may be useful for detection of dysfunction in early stages, it is important to consider a differential diagnosis that includes a variety of etiologies other than HAND. This includes depression and other psychological issues, metabolic disorders and opportunistic complications where relevant. It also includes the neurodegenerative diseases, such as Alzheimer's and vascular cognitive impairment that may or may not be exacerbated by HIV infection.

Management

One of the most significant clinical issues is whether antiretroviral agents differ for their ability to prevent, reverse, or control HAND. To the degree that HAND is a direct consequence of neurotoxins generated by viral replication in the CNS, the major determinant of relative protection from antiretroviral therapies is likely to stem from their ability to penetrate the blood-brain barrier. Several studies have attempted to quantify this penetration using different techniques, such as quantifying drug levels in the CSF

and evaluating on-treatment HIV suppression in the CSF.[27] Antiretroviral agents with good penetration of the CSF produce lower CSF levels of viremia than agents with less penetration even when plasma viral load suppression is similar.[35] A recently published study with more than 2600 patients associated antiretroviral regimens with good penetration with better neurocognitive function when this variable was assessed in a multivariate regression analysis.[36]

The optimal management of HAND is evolving. The primary focus should be viral suppression in both the blood and the CSF. Adjunctive therapies thus far have not been proven effective with the possible exception of memantine, which has had a modest degree of benefit.[37-38] The presumed pathophysiology of cognitive loss makes control of HIV replication in the CSF an attractive theoretical target. There is support for this approach, even in those with undetectable viral load in the plasma, as approximately 10% of such patients will have detectable HIV replication in the CSF using standard assays.[39] An even higher proportion will have detectable HIV RNA when single copy assays are used, but these are not in general use at present. In addition to a previously cited study in which antiretroviral therapy with good CSF penetration was associated with a reduction in CSF viral loads,[27] another study associated a highly CSF-penetrating regimen with a reduction in cognitive deficit over a median 15-week follow-up relative to those receiving a less penetrative regimen.[30]

The substitution of antiretroviral agents with relatively poor penetration, such as tenofovir, with agents that have good CSF penetration, such as abacavir, is an attractive strategy in patients experiencing cognitive loss. However, in those who are aviraemic in the plasma but detectable in the CSF, ARV resistance should be checked to guide therapy. In such cases, it may be better to add more highly-penetrating antiretrovirals than to substitute. The number of antiretrovirals to add is not known precisely but can be guided by the approach to HIV escape in the blood in HAART-treated patients where two new antiretrovirals are required. In HAND patients who are aviraemic in both the plasma and the CSF, optimal management is unknown. Intuitively, it would seem reasonable to add two highly-penetrating antiretrovirals to the existing regimen, but an evidence base for this is not available at present. The relative ability of this approach to reverse or preserve cognitive impairment may be dependent on the timing of the change in therapy, a specific reduction in HIV viral load in the CSF, or other variables.

Additionally, non-drug related strategies may be helpful for slowing cognitive decline regardless of the pathophysiology. Mental and physical activity have demonstrated benefits in non-HIV patient groups, such as those with Alzheimer's disease,[40] and may be reasonable in the treatment of patients with HAND. Educating patients about the potential for cognitive decline and providing motivation to preserve cognitive function should not be overlooked as a potential intervention.

Conclusion

HAND has been a significant complication of HIV infection from the beginning of the epidemic. Although dementia is a risk factor for poor survival in patients with advanced HIV infection, cognitive impairment in patients whose plasma viremia is well controlled may represent a more subtle but still serious threat to long-term wellbeing. Due to the increasing proportion of HIV-infected individuals in many countries, including Canada, who are at risk for cognitive impairment due to long-term infection, advancing age, or both, the challenge of managing neurocognitive impairment in HIV care is expected to increase. While diseases associated with neurocognitive loss, such as Alzheimer's, increase in incidence and prevalence among older individuals, HIV replication in the CSF appears to increase or accelerate neurocognitive loss. As a result, cognitive loss is encountered earlier and with greater frequency. Anticipation of these problems may be the first step toward improved management.●

Screening and Treatment of Cognitive Function in the Aging HIV Patient

1. Cognitive assessment should begin at an early age. A three-tiered approach may be appropriate:
   - Tier 1: Three-minute brief evaluation tool that provides an ability to detect change over time;
   - Tier 2: 10-15 minute screening tool, such as the HIV dementia scale (minimal training, low cost), in patients with risk factors or suspected of cognitive decline;
   - Tier 3: Formal assessment with specialist referral.

2. Red Flags for Cognitive Loss:
   a. Age > 45 years
   b. Impaired glucose tolerance
   c. Current CD4 count < 350 cells/mm^3
   d. History of CD4 count < 200 cells/mm^3
   e. Lack of antiretroviral agents with good CNS penetration
   f. Anemia

3. In patients with cognitive loss probably related to HIV infection:
   a. Consider switching to regimens with better CSF penetration;
   b. Consider counselling with the potential to help individuals compensate for memory deficits;
   c. Consider neurology referral in patients with rapidly advancing symptoms.

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the AGING HIV PATIENT

osteoporosis

The accelerated loss of bone density in patients with HIV infection threatens a significant health crisis in Canada and other countries with aging HIV-infected populations. There appears to be an important interaction between traditional osteoporosis risk factors and bone loss related specifically to HIV and its therapies. Consistent with accelerated aging across other organ systems, HIV-related loss of bone mineral density is a progressive condition detected soon after infection. It may persist independent of HIV suppression, and it can be exacerbated by some antiretroviral drugs. Strategies to diminish the impact of bone mineral loss depend on early screening and aggressive efforts at preventing or modifying the underlying processes. The rising rates of fracture in aging individuals with HIV infection have intensified attention on this complication, but the scope of this complication is expected to enlarge with the demographic shift that is increasing the proportion of HIV-infected individuals in the age range of vulnerability.

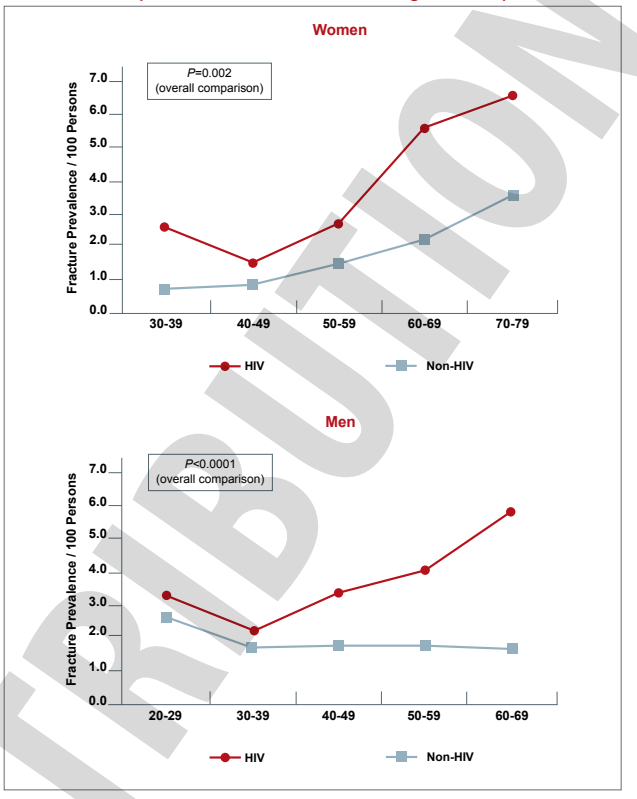
Osteoporosis in HIV: Epidemiology

Osteoporosis is a significant public health problem independent of HIV infection. Although the prevalence is higher in postmenopausal women, the rates of bone loss are similar in women and men after about age 60.[1] In Canada, where the population is aging,[2] it is estimated that one in four women and one in eight men have osteopenia that poses and increased risk of bone fracture.[3-4] Data from the United States suggest that 50% of individuals have developed osteoporosis by the time they reach the age of 80 years.[5] In patients with HIV, the incidence of osteoporosis appears to begin at a much earlier age and the prevalence climbs more steeply.[6] Although it was initially hypothesized that osteoporosis might primarily be a complication of antiretroviral therapy,[7] HIV infection is now recognized as an independent risk factor for bone disease.[8] While specific antiretroviral therapies do appear to accelerate the process, osteopenia begins to develop early in the infection and in the absence of therapy.[6,9] Within two years of HIV infection, bone density declines by as much as 6%,[10] which is similar to that observed among women within the first two years of menopause.[11]

The definition of osteopenia in individuals greater than 50 years of age is more than 1.0 but less than 2.5 standard deviations below the average bone mineral density (BMD) of adults between the ages of 25 and 35, according to the World Health Organization (WHO).[12] This is typically referred to as a T score. The definition of osteoporosis is 2.5 standard deviations below average. Both osteopenia and osteoporosis can also be defined by Z scores, which evaluate standard deviations related to sex- and ethnicity-matched populations of the same age. More commonly used in younger individuals, including those infected with HIV, an abnormal Z score is considered to be 2.0 standard deviations below the benchmark.[13] There is a steep increase in fracture rate with each standard deviation below the mean.[14]

The risk for fracture among individuals with HIV varies based on numerous risk factors, but population-based studies suggest that the overall increase in risk is large. In one study that compared fracture rates among 8525 HIV-infected and 2,208,792 non-infected individuals, the fracture prevalence calculated per 100 persons was 2.87 for those with HIV vs. 1.77 among the comparator group.[15] This 62.1% increase in rate was highly statistically significant (P<0.0001). Although the increased risk of specific fractures was not evenly distributed by site (for example, vertebral facture rates were nearly twice as great in women with HIV, but hip fractures were not significantly different), the overall increase in fracture prevalence among HIV-infected males was even greater (68.3%; P<0.0001) than in females (44.7%; P=0.002) (Figure 1).

FIGURE 1 | Comparison of Fracture Prevalence in HIV-infected vs. non-HIV-infected patients: Gender and Age Group



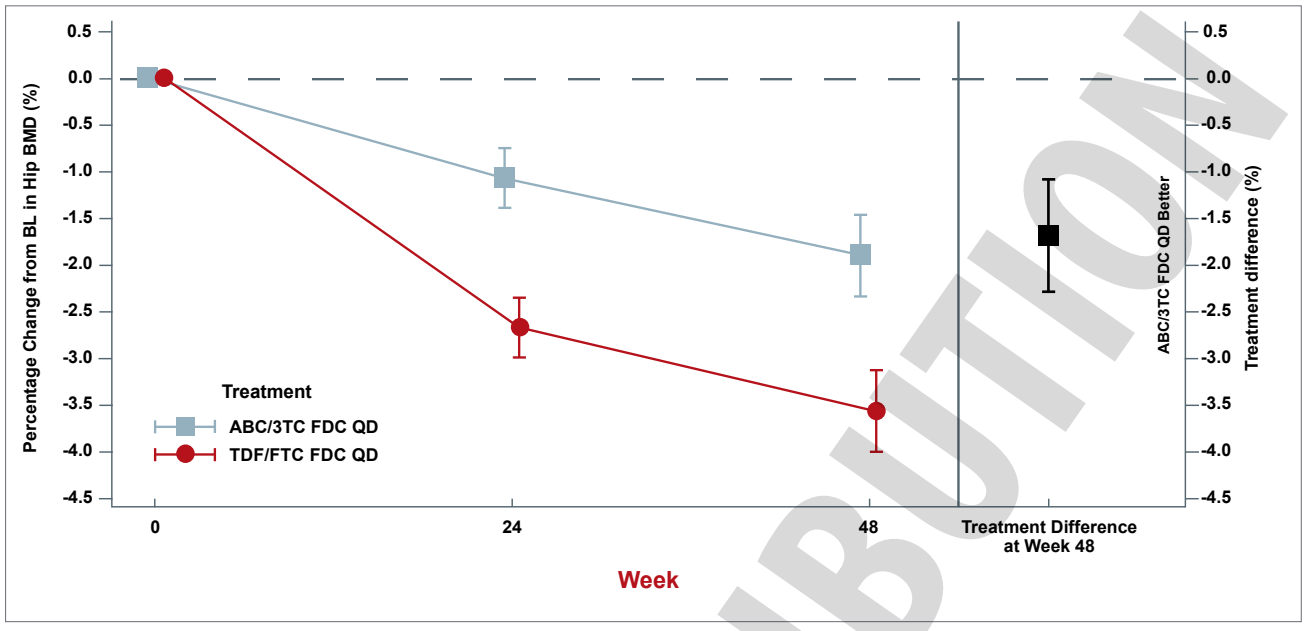
Adapted from Triant VA et al. *J Clin Endocrinol Metab* 2008;93(9):3499-504

Specific antiretroviral agents have been shown to exacerbate the BMD loss associated with HIV. In a substudy of the ANRS 121 study, which randomized HIV-infected individuals to a regimen that included a ritonavir-boosted protease inhibitor (PI/r), a non-nucleoside reverse transcriptase inhibitor (NNRTI) or both, the mean reduction in bone density in the lumbar spine was significantly more on the PI/r arm (-5.8%; P=0.007) and the PI/r and NNRTI combination arm (-4.4%; P=0.001) than on the NNRTI only arm (-1.5%).[16]

The strongest association between antiretroviral therapy and risk of accelerated BMD loss has been with tenofovir (TDF). In a multicenter 385-patient, 96-week study comparing TDF in combination with emtricitabine (FTC) to abacavir (ABC) in combination with lamivudine (3TC), the mean change from baseline was 1.9% in the group receiving ABC/3TC and -3.6% in those receiving TDF/FTC (Figure 2).[17] This 89.4% decrease was highly statistically significant (P<0.001). Moreover, when bone loss greater than 6% was compared at specific sites, many showed loss that was three or four times greater in patients receiving the TDF-containing regimen rather than the combination with ABC. This included the hip (13% vs. 3%) and the spine (15% vs. 5%). Previous controlled studies have also associated TDF exposure with increased risk of bone density loss.[18-19]

The aging of the HIV population predicts rising rates of fractures, but the consequences of BMD loss

FIGURE 2 | Antiretroviral Therapies and Accelerated Bone Mineral Density Loss



ABC, abacavir; FDC, fixed drug combination; FTC, emtricitabine; QD, once daily; TDF, tenofovir; 3TC, lamivudine.
Adapted from Stellbrink HJ, et al. *Clin Infect Dis* 2010;51(8):963-72.

are progressive, suggesting that early prevention may modify clinical risks. While the rising rates of fracture in individuals with long-term HIV infection demonstrate that BMD loss is an important challenge, the complications of osteoporosis have the potential to reduce survival in aging HIV-infected individuals.

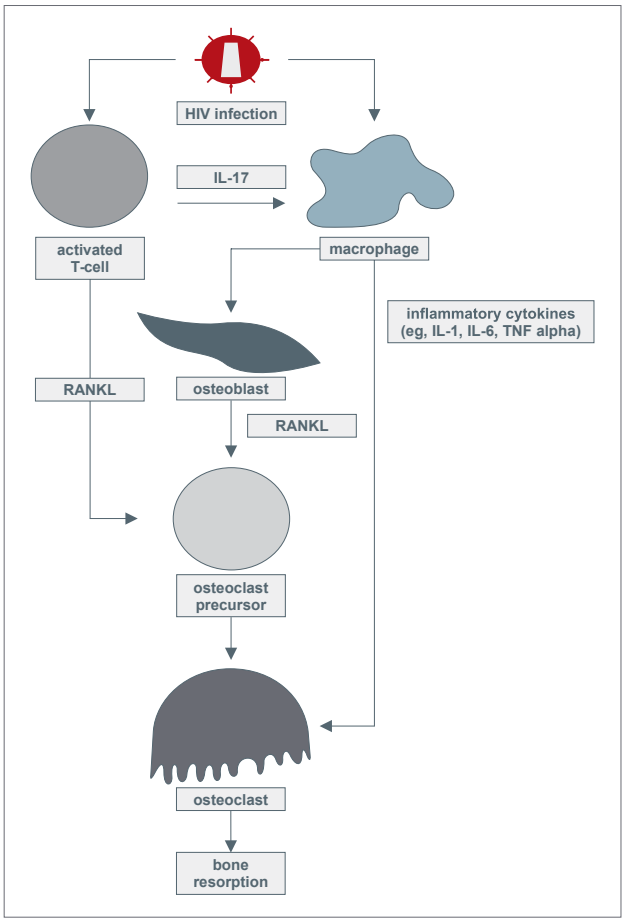
Pathogenesis

Bone metabolism is a dynamic process of bone remodeling in which stable bone density is dependent on a balance between the bone resorption provided by osteoclasts and bone formation by osteoblasts.[20] Although low accumulation of peak bone mass, which is reached in late adolescence or early adulthood,[21] can be a susceptibility factor for osteopenia later in life, the pace of BMD loss over the course of adulthood is influenced by a broad array of factors, including nutrition, exercise, hormone levels, and factors that influence bone metabolism signaling.[22]

While HIV-infected patients are susceptible to the same risks for osteoporosis as those without HIV, including poor nutrition and genetic susceptibility, HIV and its therapies have unique effects on bone metabolism. Perhaps most importantly, HIV proteins have been shown to promote osteoblast apoptosis, inhibiting bone formation,[23] while both HIV proteins and inflammatory cytokines associated with HIV, infection, such as tumor necrosis factor alpha (TNF-α), have been associated with increased osteoclast activity and bone resorption (Figure 3).[23] These activities are consistent with the evidence that significant bone loss begins soon after infection irrespective of the type of therapy or whether therapy is initiated.[10]

In experimental studies, antiretroviral therapies have demonstrated a variety of potential adverse effects on bone metabolism. For example, efavirenz, an NNRTI, has been associated with an impairment of hepatic enzymes important to vitamin D metabolism, while some PIs, such as nelfinavir and ritonavir, increase gene expression of selected pro-inflammatory cytokines, such as interleukin-8 (IL-8), that adversely affect osteoblasts. However, the association of these

FIGURE 3 | HIV Infection and its Association with Bone Mineral Density Loss



Adapted from Mansky KC. *Clin Interv Aging.* 2010; 5:285-92.

agents and exacerbation of bone loss beyond that produced by HIV has been inconsistent.[24-25]

The association of TDF and bone loss, demonstrated in a prospective, randomized controlled trial,[17] has been far more consistent. Several mechanisms may be involved, including alterations in gene expression that control osteoblast and osteoclast activity.[26] TDF, a phosphonate with the potential to be taken up by osteoclasts, may also induce stress that alters reciprocal signaling important to osteoblast activity.[27] In addition, TDF is associated with impairment of renal function,[28] which is a risk factor for osteoporosis.[29] The interaction of TDF with conventional risk factors for osteoporosis deserves further study.

In addition, osteoporosis in patients with HIV may be understood as a consequence of an accelerated aging phenomenon related to immunosenescence.[30] The premise of immunosenescence is that progressive functional impairment in the immunoregulatory system associated with age is the basis for a broad array of diseases that become more common in aging adults, including cancer, atherosclerosis, and osteoporosis.[31] Due to the stress placed on the immune system by HIV infection, this age-related process appears to begin earlier and progress more rapidly.[32]

Diagnosis and Monitoring

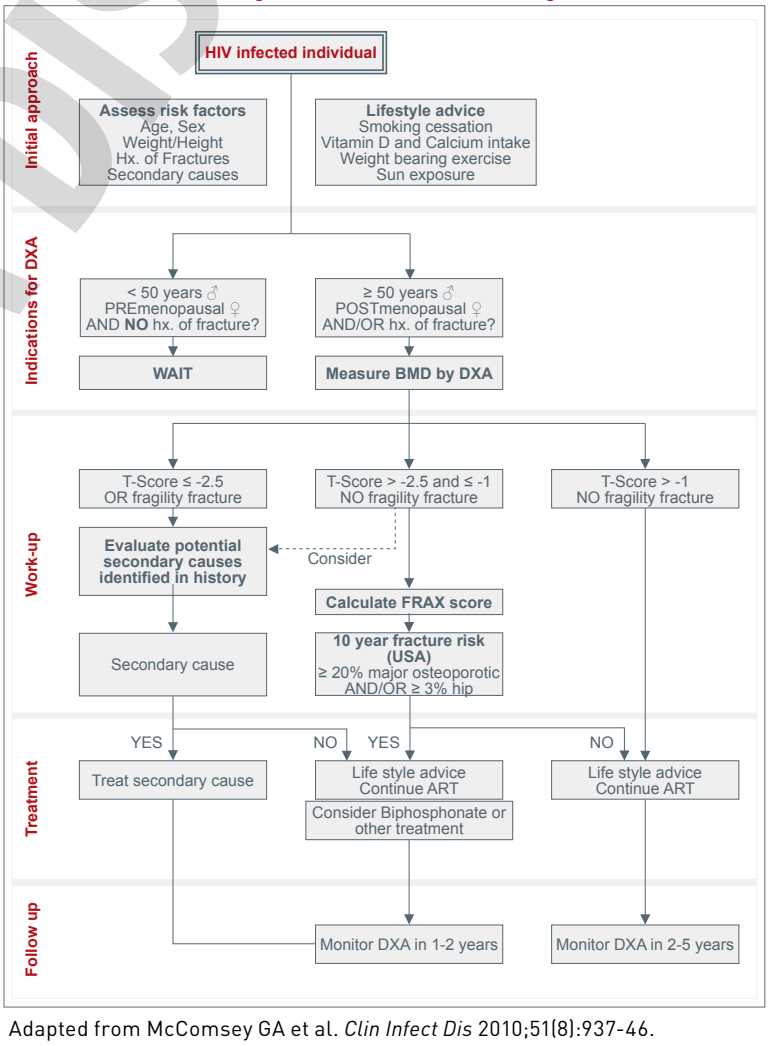
Due to the broadly shared risk of osteoporosis in aging individuals, screening for BMD is recommended in all Canadians 65 years of age or older.[33] The age for screening is lowered to 50 years for both men and menopausal women with risk factors. These risk factors include a fragility fracture after the age of 40, a family history of osteoporosis, current smoking, high alcohol intake, a low body weight, or disorders associated with osteoporosis, such as rheumatoid arthritis, type 1 diabetes, or chronic inflammation. Screening is recommended in younger adults who have had a fragility fracture, prolonged use of glucocorticoids, or diseases associated with osteoporosis, such as hyperparathyroidism. Screening is performed with BMD evaluations typically conducted with dual x-ray absorptiometry (DEXA).

The Osteoporosis Canada guidelines do not specifically identify HIV as a risk factor, but other organizations, such as the Infectious Diseases Society of American (IDSA) have, advocating DEXA scans in all HIV patients with risk factors beginning at 50 years.[34] However, in a more recently published multinational collaborative review, scanning at the age of 50 years was recommended in all patients with HIV regardless of risk factors.[8] This group, comprised largely of clinicians and researchers active in the field of HIV, recommended repeating the test every two to five years. Although screening earlier than age 50 is not routinely recommended, any history of fragility fractures, whether or not patients have HIV, is an indication for a DEXA scan.

Management

In patients with clinically significant bone density loss as defined by T or Z scores, a complete evaluation to determine risk factors is essential to develop an appropriate management plan (Figure 4). While alcoholism, glucocorticoid exposure, and hypogonadism are common risk factors for osteoporosis in general,[35] risk factors for osteoporosis that have been specifically identified to be common in patients with HIV include low body weight, insulin resistance, and hyperlactatemia.[36-37] A thorough examination to identify secondary causes of osteoporosis should include routine blood chemistry tests, renal function tests, serum hydroxyvitamin D level determinations, and appropriate hormone level tests by gender.

FIGURE 4 | HIV Management Plans: Evaluating Risk Factors



Adapted from McComsey GA et al. *Clin Infect Dis* 2010;51(8):937-46.

While secondary causes of osteoporosis should be addressed directly, acute or chronic nutritional and pharmacologic therapies are appropriate to improve bone metabolism. It is reasonable to employ the same treatments in patients with HIV as in those who do not have HIV, although the data demonstrating benefit in the setting of HIV is generally more limited. In addition to ensuring adequate levels of calcium and vitamin D intake, sun exposure, and exercise, this can include bisphosphonates, which have been shown to reduce the risk of fracture in individuals without HIV.[38] In patients with HIV, bone density has improved in patients in a placebo-controlled trial of the bisphosphonate zoledronate, although follow-up was not sufficient to demonstrate an effect on fracture risk.[39]

Selecting an antiretroviral therapy with minimal influence on bone metabolism may also be appropriate. Although sustained suppression of HIV is the single most important priority for preventing life-threatening complications of HIV, there is now strong evidence that TDF increases the risk of BMD loss. Although the evidence that TDF increases the risk of fracture is weaker, it may be appropriate to institute closer monitoring of HIV-infected patients with risk factors for osteoporosis who are taking a regimen that contains TDF or to consider alternatives in those who already have osteoporosis.

Prevention of osteoporosis in patients with HIV has not been well explored. However, due to the high risk of this complication, it is reasonable to consider prophylactic strategies, such as adequate exercise and intake of nutrients important to bone metabolism, even in young adults. Such lifestyle modifications should be implemented immediately in those individuals with osteopenia even if pharmacologic therapies are not yet indicated. In patients with osteoporosis, DEXA scans should be considered one to two years after initiating a treatment program so that pharmacologic therapies, which are not without adverse effects or costs,[40] can be stopped if adequate bone density has been restored.

Conclusion

Osteoporosis is a major health threat in aging individuals with HIV infection. BMD loss and clinical complications of osteoporosis can be observed a decade or more earlier in individuals with HIV than in the general population. The HIV infection appears to impose direct adverse effects on bone metabolism, but the increased rate of osteoporosis is multifactorial and may be part of a syndrome of frailty in individuals with HIV driven by accelerated immunosenescence. Osteoporosis in patients with HIV does appear to be modifiable by addressing risk factors, employing pharmacologic therapies that increase bone density, and reducing exposure to antiretroviral agents that exacerbate bone loss. Greater attention to this problem may be essential to efforts to extend survival in HIV-infected patients who are otherwise well controlled on their antiretroviral therapies. ●

Screening and Treatment of Osteoporosis in the Aging HIV Patient

1. Strategies to promote healthy bone should begin at an early age:
   a. Consider adequate dietary intake of calcium and vitamin D.
2. Screening for osteoporosis should begin no later than age 50:
   a. DEXA scans, yielding T or Z scores, are the preferred screening method.
3. In patients with osteoporosis:
   a. Consider risk factors and secondary causes;
   b. Verify adequate calcium and vitamin D in diet;
   c. Employ bisphosphonates acutely or chronically to restore bone mineral density to target levels.

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