THE AGING HIV PATIENT

Aging in HIV: Overview
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overview

Age-related diseases, such as atherosclerosis and osteoporosis, are being observed at a younger age in patients infected with human immunodeficiency virus (HIV) than in those without infection. The apparent acceleration in aging may be related to several causes, including persistent upregulation of the inflammatory response and the adverse effects of antiretroviral therapies. The acceleration of aging processes threaten to shorten the lifespan of patients with HIV even when immune function has been improved and the viremia remains optimally suppressed. The individual risk for specific diseases varies, but it has become important to direct attention toward opportunities to modify or circumvent the potential for irreversible damage to target organs. In general, the average age for symptomatic manifestations of processes common to aging individuals, such as bone mineral loss and neurocognitive decline, appears to be at least one decade earlier when those with HIV infection are compared to those without. In Canada, where the population of HIV-positive individuals over the age of 50 is increasing, strategies for anticipating and modifying these risks are expected to be an increasingly important part of HIV management.

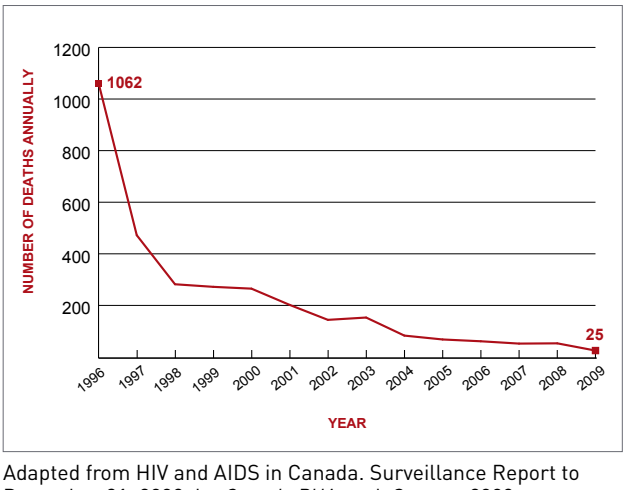
Aging of the HIV Population: Epidemiology

In Canada, like many other countries where antiretroviral agents are readily available, the ability of current therapies to sustain control of human immunodeficiency virus (HIV) has led to a growing number of patients who are 50 years old or older.[1-2] This age stratification, used by the Public Health Agency of Canada for tracking the epidemiology of HIV and acquired immunodeficiency syndrome (AIDS),[3] is a potentially useful threshold because of increasing evidence that HIV may pose unique challenges in aging patients. Older patients have long been over-represented among AIDS cases relative to their total representation among patients with HIV,[1] but there is growing concern that HIV infection may complicate or even accelerate the co-morbidities common to the aging process,[4] such as cardiovascular disease (CVD),[5] renal impairment,[6] osteoporosis,[7] liver disease,[8] and neurocognitive decline.[9]

The aging of the HIV population in Canada can be understood in two different ways. One is the increasing proportion of new infections in patients who are 50 years old or older. Individuals over the age of 50 now represent close to 15% of new infections in Canada, a proportion that has almost doubled since the late 1990s.[3] The other is the prolonged survival made possible with highly active antiretroviral therapies (HAART). While the proportion of HIV-positive patients who are older than age 50 increased very modestly in Canada over the last 10 years because the majority of new infections still occur in younger individuals,[10] the absolute number of older individuals with HIV is increasing along with the increasing estimated number of total infections, which exceeded 70,000 persons by the end of 2010.[1]

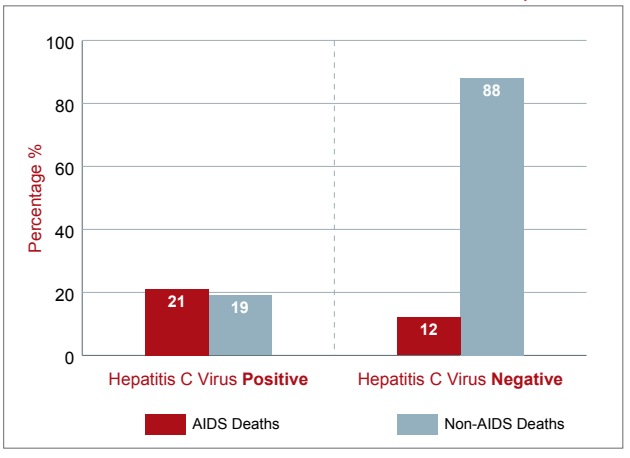
While persistent and sustained suppression of HIV remains critical to the survival of patients with HIV, AIDS deaths are now infrequent in Canada. In 2009, there was a total of 25 deaths attributed to AIDS, which represented an 84% reduction since 2003 despite a substantial increase in the number of individuals living with HIV (Figure 1).[10] Similar reductions have been recently reported in other countries with ready access to antiretroviral therapies, such as Switzerland.[11] In the Swiss HIV Cohort Study (SHCS), less than 20% of all deaths in 2005 through 2009 were due to AIDS. Rather, non-AIDS malignancies followed by CVD were the most common causes of death in patients without hepatitis C virus (HCV) infection. Liver disease, followed by non-AIDS infections were the most common causes of mortality in HIV patients co-infected with HCV. Over this study period, the median age at death climbed from 45 to 49 years while the median CD4 count at time of death increased from 257 to 321 cells/mm^3 (Figure 2).

FIGURE 1 | AIDS Deaths in Canada: 1996 to 2009



Adapted from HIV and AIDS in Canada. Surveillance Report to December 31, 2009. In: *Canada PHAo*, ed. Ottawa; 2009.

FIGURE 2 | 2005 - 2009 Deaths in the HIV Population



Adapted from Ruppick, M et al. As presented during Conference on Retroviruses and Opportunistic Infections; 2011; Boston; 2011. Abs 789.

These data suggest that prolonging survival in patients with HIV is becoming less dependent on developing better therapies for suppressing HIV than controlling disease processes that are exacerbated by the presence of HIV or its treatments. The risks for specific diseases, such as those affecting the cardiovascular (CV) system, the central nervous system (CNS), or the skeleton, may range substantially among HIV-infected individuals due to an array of variables that affect specific risk, including familial susceptibility, lifestyle choices, and medication history, but current data suggest that the treatment of these co-morbid conditions will be increasingly critical to the effort to extend the life span of individuals infected with HIV.

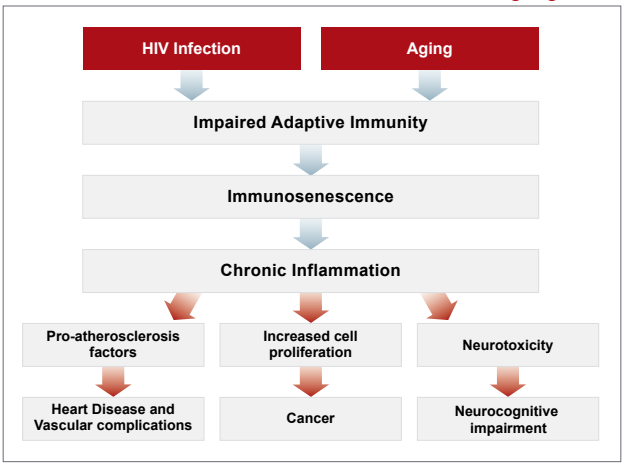
Pathogenesis

The association between HIV infection and an increased risk of CVD, which is well described and one of the first signals that age-related diseases occur earlier in patients with HIV,[12-14] was not initially recognized as a manifestation of accelerated aging. Rather, the initial focus was on the dyslipidemias associated with protease inhibitors (PIs) and the high prevalence of conventional heart disease risk factors, such as smoking, in the HIV-infected population.[15-16] Those factors remain relevant, but numerous other factors appear to be contributing, including a direct influence

of HIV on CV risk, and that this risk may in part be mediated by immunosenescence.[17] The concept of immunosenescence, which is relevant to natural aging, is based on a decline in the adaptive immune system that, among other effects, leads to upregulation of inflammatory mediators.[18] In CVD, it is now believed that inflammation participates in promoting both atherosclerosis and thrombotic events.[19-20]

A similar interplay between an upregulation of the immune system and accelerated senescence may be relevant to other organ systems in patients with HIV.[21] The aging process, which is generally recognized as a progressive cumulative deterioration in normal physiologic molecular and cellular functions resulting in organ damage, has been linked to expression of several specific inflammatory cytokines, such as interleukin-6 (IL-6), in normal as well as HIV-associated aging.[22-23] This has led to the hypothesis that HIV patients are aging more quickly simply because the persistent infection exhausts the immune system at a more rapid pace (Figure 3).[17]

FIGURE 3 | HIV Infection and Accelerated Aging



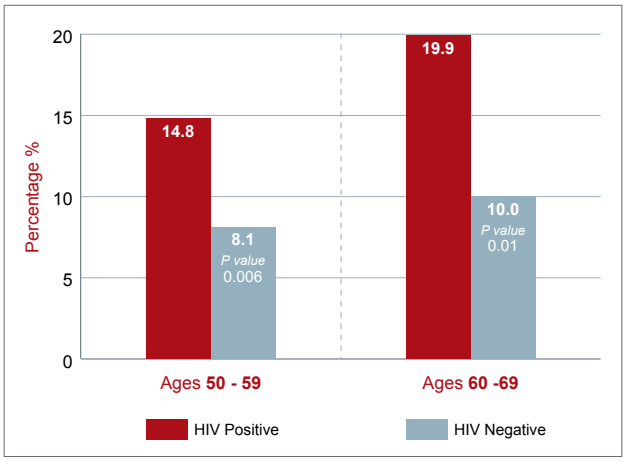
Adapted from Deeks SG. HIV infection, inflammation, immunosenescence, and aging. *Annu Rev Med* 2011;62:141-55.

In normal aging, the rate of impairment in specific organs depends on multiple factors, particularly genetics. Genetic variables that affect risk have been defined for CVD,[24] neurocognitive impairment,[25] osteoporosis,[26] and renal impairment.[27] Although lifestyle choices may have an important influence on the relative risk of all of these processes, suggesting that genetic predisposition can be exacerbated or reduced, the risk of death from any single cause of death appears to vary widely. Current efforts to determine the relative contribution of DNA damage and repair, telomere shortening, and mitochondrial dysfunction may all provide insight on individual differences in the rate of aging in specific organs.[28] All of these factors are likely to be relevant to the relative rate of deterioration in specific organ systems in those who are HIV infected.

Clinical Features

The cumulative effect of the aging process in normal individuals is a generalized frailty, which is also observed in individuals with HIV. As anticipated by an accelerated rate of aging, the increasingly well-defined frailty phenotype occurs at a much younger age in individuals who are HIV positive (Figure 4). In new data from the Multicenter AIDS Cohort Study (MACS), pre-defined frailty characteristics were almost twice as common in men with HIV relative to men without HIV between the ages of 50 and 59 (14.8% vs. 8.1%; *P*=0.006) and 60 and 69 (19.9% vs. 10.0%; *P*=0.01).[29] In this study, individuals were considered to have frailty if they had three or more of the following: low grip strength (20th percentile for age), slow four-meter walk (<20th percentile for age), low physical activity, exhaustion as defined by the Short-Form 36 (SF-36), and unintentional weight loss of >10 pounds.

FIGURE 4 | Frailty Phenotype



Adapted from Margolick J et al. As presented during Conference on Retroviruses and Opportunistic Infections; 2011; Boston; 2011. Abs 794.

Traditionally, the goals of HIV therapy have been to suppress viremia while minimizing the potential for adverse effects from medications. The evidence of accelerated aging suggests a new paradigm that includes attention to target organs at risk.[30] While a specific definition of frailty in the HIV-positive patient may be helpful to better understand this phenomenon, criteria for early recognition of the process is supported by the association of frailty with adverse outcomes in individuals who are HIV-negative.[31]

Diagnosis and Monitoring

The evidence that HIV accelerates aging promotes a proactive approach to patient care. Unlike acute health complaints, age-related deterioration in organ systems can be subtle and insidious. Many of the processes, including CVD and renal impairment, may not elicit direct complaints but remain asymptomatic up until life-threatening complications occur. It is therefore appropriate to consider an organized approach to gathering baseline information about CV risk factors, renal function, cognitive function, and bone mineral density. It is essential to recognize that aging processes in all of these organ systems are multifactorial. For example, while dyslipidemias were

once considered to be the most likely explanation for the relationship between antiretroviral therapy and CVD,[32] exposure to protease inhibitors, nucleoside reverse transcriptase inhibitors (NRTIs) specifically and antiretroviral agents overall have also been associated with increased insulin resistance, an independent risk factor for CVD.[33-34]

HIV-infected individuals face the same health risks as non-infected individuals, but the interrelationship of normal health risks, accelerated aging, and the effects of antiretroviral therapy defines a need to initiate more rigorous monitoring of age-related risks at a much earlier timepoint than would be appropriate in individuals without HIV infection. Due to the multiple pathophysiologic processes at work in HIV-infected individuals, each risk factor may threaten a greater impact than anticipated in an individual without HIV. For example, therapeutic agents designed to reverse the complex effect of HIV infection on visceral fat, insulin resistance, and lipodystrophy, are being pursued for their potential to circumvent a synergy between these risk factors.[17]

Management

Evidence of risk in specific organ systems can be addressed with targeted therapies according to evidence-based guidelines, such as those provided by the Canadian Cardiovascular Society for CV risk factors or the Canadian Society of Nephrology for the management of chronic kidney disease.[35-36] However, the best opportunity for reducing the morbidity and mortality in aging patients with HIV may be to intervene in advance of pathology. Although strategies must be individualized for the individual risk profiles, aggressive interventions at a relatively young age, including lifestyle changes, may have a large impact on subsequent risk.

In this setting, family history, in addition to baseline monitoring, can be helpful for anticipating risks. Although no objective takes precedence over sustained suppression of HIV, the relative safety of antiretroviral agents for lipid metabolism or kidney function may be relevant in patients with elevated risk for CVD or kidney disease, respectively. Recent attention to the relative penetration of antiretroviral agents into the CNS compartment may prove relevant to relative risk reduction for neurocognitive impairment,[37] although more studies are required to understand the potential for neurotoxicity among antiretroviral agents and to confirm the relative clinical value of agents that do or do not have a high CNS penetration effectiveness (CPE) score. Ultimately, strategies for optimal management of age-related diseases are likely to evolve as the growing number of older HIV-positive patients expands the scope of this clinical challenge.

Conclusion

With the identification of numerous effective antiretroviral combinations that provide sustained control of HIV, age-related diseases will increasingly represent the primary obstacle to a normal lifespan among infected individuals. The relative risks of specific organ diseases appear to be patient-specific, but the vulnerability may have a common pathway related to immunosenescence and the persistent upregulation of the inflammatory response induced by the presence of HIV. Strategies for an individualized but proactive approach to slowing decline in susceptible organs are emerging, but this is a dynamic area which is expected to evolve.

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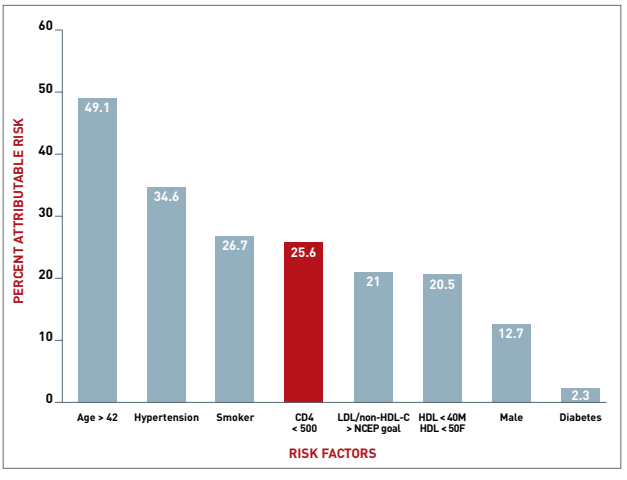
Early death from cardiovascular (CV) complications in aging individuals infected with human immunodeficiency virus (HIV) is a growing challenge in chronic HIV management. There are numerous factors that have converged to increase CV risk in individuals infected with HIV compared to age-matched individuals without infection. These include a greater prevalence of CV risk factors, the adverse effects of several antiretroviral agents that appear to contribute to CV risk, and a direct or indirect effect of HIV itself. In HIV patients with otherwise well controlled viremia, CV disease is expected to become an increasingly important cause of preventable death. The effort to modify the impact of this potential crisis depends on heightened awareness of the risks in HIV patients and aggressive monitoring and intervention for modifiable risk factors. Individualization of therapy will be increasingly important when attempting to reduce CV risks in the context of sustained HIV suppression.

Background

The introduction of combined antiretroviral therapy (cART) was associated with a large reduction in human immunodeficiency virus (HIV)-related deaths, but had a very modest influence on the rate of death from cardiovascular (CV) complications.[1] Prior to cART, dilated cardiomyopathy secondary to infective endocarditis was a major source of CV complications from HIV.[2] Since the introduction of cART, infective endocarditis remains an important source of adverse events, including death, in patients on cART who continue to use illicit intravenous drugs,[3] but suppression of HIV has reduced the risk for the opportunistic infections associated with this complication.[4] Although other types of CV complications were observed in patients with HIV prior to the introduction of cART, such as cardiac Kaposi's sarcoma,[5] CV disease (CVD) was not a major cause of death because of the greater importance of other risks.[6]

The potential for CVD to emerge as a significant cause of death in aging patients with well-controlled HIV can be predicted on the simple basis that CVD is the most important cause of death worldwide overall, particularly in aging individuals.[7] In Canada, vascular diseases account for nearly one third of all deaths and cause only slightly fewer deaths than all malignancies combined.[8] In a recent analysis of attributable risk for CVD among a large cohort of HIV patients, a low CD4 count produced the fourth greatest influence. Age greater than 42 years provided the greatest (Figure 1).[9] Moreover, additional factors may exacerbate the effect of age. Evidence that CVD might be a particular problem in an HIV population on cART therapy was first identified very early after protease inhibitors (PIs) were introduced into the routine management of this infection.[10] Subsequent studies reinforced the specific risk posed by PIs by showing increasing risk of myocardial infarction (MI) with increasing exposure to PIs.[11] The suspected mechanisms included disturbances in serum lipid levels and insulin metabolism,[12] but other effects,

FIGURE 1 | CD4 Count a Major CVD Risk Factor in HIV Patients

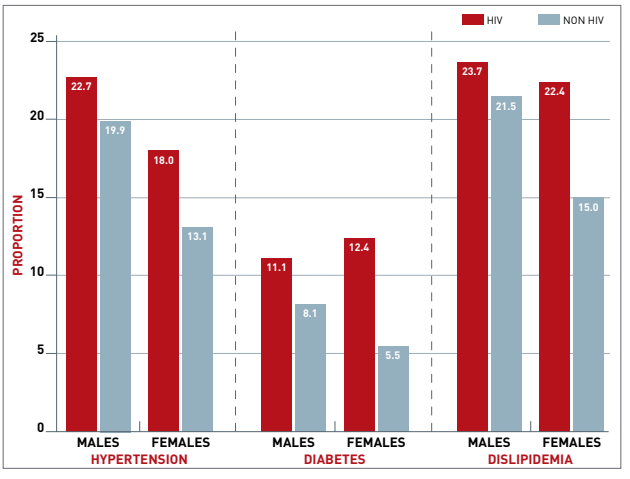


Adapted from Lichtenstein KA et al. *Clin Infect Dis* 2010;51:435-47.

such as elevated fibrinogen levels,[13] have also been identified as potential contributors to this risk. One study calculated a 29% increase in the age-adjusted risk of MI for each year of highly active antiretroviral therapy (HAART) exposure.[14]

However, the increased risk of CVD cannot be wholly attributed to PI exposure or even to antiretroviral therapy overall. Rather, numerous cohort studies have associated HIV infection itself with an increased risk of CVD relative to rates in non-infected individuals,[9,15] including studies that found an increased risk after adjusting for hypertension, diabetes, and dyslipidemia (Figure 2).[16] In a study which compared health claims data in two large hospitals in the United States, the MI rate was almost twice as great in those with HIV as in those without HIV after multiple adjustments, including age (11.13 vs. 6.98 per 1000 patients).[16]

FIGURE 2 | Cardiac Risk Factors in HIV and non-HIV Cohorts



Adapted from Triant VA et al. *J Clin Endocrinol Metab* 2007;92(7):2506-12.

It is important to evaluate the contributors to the increased risk of CVD in HIV patients in order to develop meaningful strategies of treatment, but the demographic shift that is increasing the proportion of HIV-infected individuals in age ranges where CV and other chronic diseases are common are making this an inevitable and increasing challenge in care of the individual with HIV.[17] Although many of the risk factors for CVD, such as dyslipidemia, diabetes, hypertension, and renal impairment, are progressive conditions that generate an increasing and cumulative risk for MI and other CVDs over time, the current evidence indicates that CV events will begin at a substantially earlier age in those with HIV than in those who are not infected.[18-19]

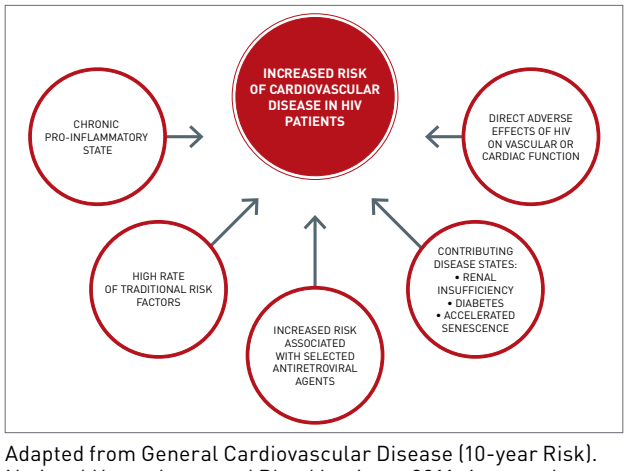
Pathogenesis

The accelerated aging phenotype that includes earlier expression of CVD is not fully understood, but there are numerous and increasingly well supported theories which indicate that systemic immune activation plays a role. While the concept originally centered on immune function alone, producing

the term immunosenescence, the effects of an upregulated immune system has been observed in all aging individuals.[20] However, this process appears to begin at a much younger age in individuals infected with HIV, and the accelerated senescence clearly extends to all or most physiologic systems.[21] The link between aging of the immune system and such organs as the heart could be an inability to suppress inflammation, which is known to contribute to atherosclerosis,[22] but other processes, such as shortening of telomeres on myocytes or other cells important to CV health, may also be involved.[23]

In many patients, including those with a familial susceptibility, CVD is the culmination of pathogenic processes driven by numerous risk factors, such as hypertension, diabetes, hyperlipidemia, renal impairment, and smoking (Figure 3).[24] Several cohort studies have found that all or most of these risk factors are more common in an HIV-infected population.[15,25] However, the acceleration of CVD is greater than that predicted by these risk factors alone. In a study that evaluated subclinical coronary atherosclerosis by measuring coronary artery calcium (CAC) deposits with computed tomography (CT), a validated tool for evaluating CVD progression, an increase in coronary age based on findings was observed in 69% of 233 HIV infected adults.[26] Even though HIV was well controlled in these individuals, who had a median age of 43 years, the risk of increased coronary age was associated with increasing duration of HIV infection, increasing use of antiretroviral therapies, and low CD4+ cell count nadir, along with traditional risk factors. Another study using CAC has also associated HIV with a more advanced vascular age than anticipated in non-HIV infected individuals.[27]

FIGURE 3 | Risk Factors that Lead to CVD



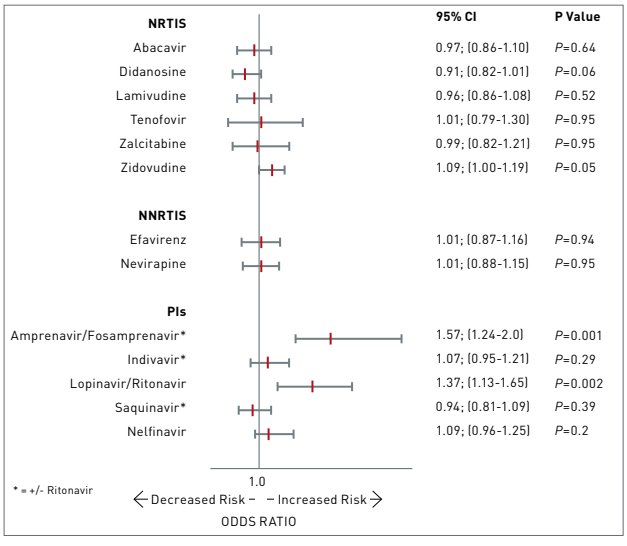
Adapted from General Cardiovascular Disease (10-year Risk). National Heart, Lung, and Blood Institute, 2011. Accessed February 8, 2011, at http://www.framinghamheartstudy.org/risk/gencardio.html.

The ability of aging processes in other organs to advance CVD should not be overlooked. For example, diabetes mellitus, a major risk factor for CVD, is also more prevalent in individuals with HIV than those who are not infected.[28] This spectrum of aging processes has produced what is being termed the HIV-related frailty syndrome.[29] While this deserves its own attention, these aging processes are relevant to the effort to address CVD as a specific endpoint of this phenomenon.

The specific contribution of antiretroviral therapies to CV risk may be relatively modest in the context of the acceleration in CVD and the accompanying risk factors. The initial cohort studies that associated HAART with increased CV risk primarily implicated PI therapy,[30] leading to the theory that this risk was secondary to altered lipid or insulin metabolism caused by this class of antiretroviral agent.[31] However, this association was largely made prior to appreciation of the role of the infection itself in promoting CVD. Moreover, many of the newer PIs, such as atazanavir, have not been associated with abnormalities in lipid metabolism.[32] The reduced risk of lipid abnormalities with newer PIs may minimize the CV risk, but other pro-thrombotic effects, such as elevated levels of fibrinogen, have been associated with agents in this class.[13]

The D:A:D cohort found an association between abacavir and didanosine exposures and the risk of myocardial infarction but not stroke.[33] As abacavir was and remains a commonly used nucleoside reverse transcriptase inhibitor (NRTI), several other groups attempted to reproduce this specific association with inconsistent results.[34] The potential problem of observational studies is limiting the bias and effective adjustment for confounders, such as preferential use of one NRTI over another in individuals with specific risks relevant to CVD, such as renal impairment. Several studies have been unable to associate abacavir with any changes in vascular function consistent with CV risk, such as altered endothelial function, increased inflammation,

FIGURE 4 | Odds Ratios for MI by Antiretroviral Drug Exposure



Adapted from Lang, S et al. *Arch Intern Med* 2010;170(14):1228-38.

or increased coagulation,[35-36] and the clinical significance of this association, if any, remains unclear. In nested case control study employing data from the French Hospital Database on HIV, the only antiretroviral agents that significantly increased the odds ratio of MI were PIs (Figure 4).[19]

The effort to prevent or modify the progression of CVD in aging individuals with HIV is an appropriate target of efforts to prolong life in this population, but this risk must be considered in context. In particular, there may be no goal more important for survival than effective and sustained suppression of HIV. Moreover, individual patients may have more imminent health problems, such as renal impairment or liver disease, which may be more urgent than CV risk management. However, CVD among the most frequent causes of death independent of HIV disease in most industrialized countries, including Canada.[37] In those individuals with HIV, the risk of CVD appears to be magnified.

Diagnosis

CV risk is not evenly distributed even within the HIV population, making individual risk assessments essential. Risk factors for CVD should be considered even in relatively young individuals because of the opportunity early diagnosis offers for early intervention and improved outcome. The modifiable risk factors are the same as those observed in a non-HIV population, including smoking, hypertension, hyperlipidemia, hyperinsulinemia, and renal impairment. However, the age-related risk factors, such as hypertension, are likely to emerge at a younger age in those with HIV. As a result, tighter monitoring and more aggressive control is appropriate.

There are no guidelines for early diagnosis of CVD in HIV patients, but it is reasonable to adapt guidelines recommended for individuals without HIV because the contributing risk factors are similar. For asymptomatic individuals, several risk scoring systems are available, including the Framingham,[38] SCORE,[39] and Reynolds methods.[40] In general, these advise initial assessment of familial risk as well as evaluation of standard risk factors, such as smoking, blood pressure, serum lipid levels, and fasting glucose levels. More sophisticated testing is not generally recommended in individuals with low or intermediate risk, defined as an estimated 10-year risk of a CV event of <5%.

However, such tests as exercise electrocardiography (ECG) or echocardiography is recommended in patients with greater degrees of baseline risk even if asymptomatic. In recommendations from the American Heart Association (AHA), the role of such tests as ECG or echocardiography is generally reserved for individuals over the age of 50,[41] but 26% of HIV patients with a mean age of 41 years had diastolic dysfunction and 40% had left atrial enlargement in one prospective echocardiographic study,[42] suggesting that earlier assessments may be appropriate in this population.[43]

Management

The single most important goal in patients with HIV is to provide sustained suppression of viremia. This is valid even when considering how to manage CV risk, because uncontrolled HIV is likely to pose a far greater immediate threat to survival than CVD even in advanced stages. In patients on PIs, for example, neither elevated lipids nor the presence of CVD is an absolute contraindication even to those PIs that adversely affect lipids. In individuals with elevated serum cholesterol on a PI, statin therapies may be sufficient to reach target reductions. While switching therapies to modify CV risk is reasonable, it should not be performed when the risk includes the potential for loss of HIV suppression.

CV risk factor management in patients with HIV should be directed by goals and treatments recommended in the non-HIV population. This includes the same targets for blood pressure, serum lipids, and blood glucose as recommended in general guidelines. Due to the greater risk of CVD, efforts to control risk factors, including smoking, should be considered urgent even in relatively young patients. Although the acceleration in aging processes has now been postulated in numerous organ systems, the frequency with which CV events are life-threatening should be a particular motivation for clinicians and patients to address CV risks and to adhere to treatment recommendations.

Conclusion

The most important defense against CVD in aging individuals with HIV is greater awareness. Evaluation of risk factors early in life, including the presence of familial susceptibility, will help outline strategies of prevention that may slow the process. While individuals with HIV appear to have more risks for CVD, the biggest threat is the earlier onset of CVD. In addition, increased risk of CVD may be driven in part by other accelerated conditions of age-related pathogenic process, such as hypertension, diabetes, and renal dysfunction. Close monitoring and aggressive treatment of CV risk factors should be immediately incorporated into HIV care.

Screening and Diagnosis of CV Risk in the Aging HIV Patient

1. CV risk assessment should begin at an early age:
    a. Evaluate family history of CVD;
    b. Obtain baseline measures of blood pressure, lipids, and glucose and renal function;
    c. Screen and treat for smoking.

2. In patients with modifiable risk factors, treat aggressively:
    a. Blood pressure, serum lipids, and blood glucose goals should be the same as those defined for a non-HIV population;
    b. Advocate lifestyle changes compatible with CV risk reductions, including exercise.

3. In aging patients (age ›40 years) with high CV risk scores:
    a. Consider sophisticated testing of CV function, even if asymptomatic;
    b. Consider antiretroviral treatment modifications if appropriate;
    c. Consider aggressive therapeutic goals even in advance of a CV event on the premise of accelerated risk.

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Guest Editor

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the AGING HIV PATIENT

renal impairment

Chronic kidney disease (CKD) is a significant threat to the long-term survival of individuals infected with human immunodeficiency virus (HIV). Although the introduction of highly active antiretroviral therapy (HAART) dramatically reduced the risk of end-stage renal disease (ESRD) from HIV-specific causes, as it did many of the other complications of uncontrolled HIV, it attenuated but did not eliminate the development of compromised renal function from causes indirectly related to HIV infection. Until recently, the risk of renal failure as a complication of HIV has been concentrated in African-Americans, who have demonstrated an increased susceptibility to HIV-associated nephropathy, but the incidence of renal impairment in aging individuals with otherwise well-controlled HIV infection is climbing. In the setting of HIV infection, therapies traditionally employed to preserve renal function, such as renin-angiotensin-aldosterone system (RAAS) inhibitors, are appropriate, but other steps should be considered. This may include preferential use of antiretroviral agents with the least potential to exacerbate renal dysfunction. Close monitoring of renal function is appropriate because of variability in the individual risk for renal disease and progression of nephropathy once it is established.

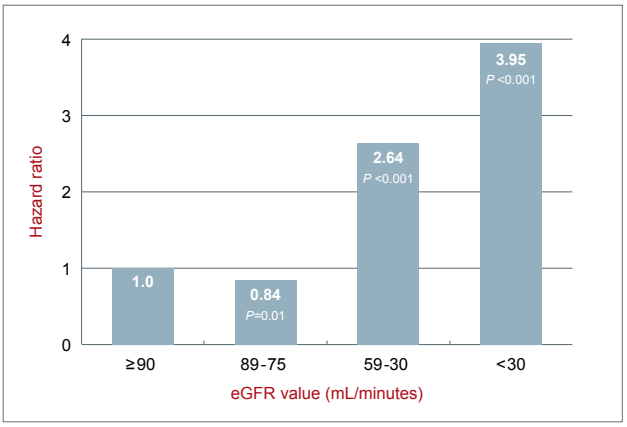
Background

One of the earliest descriptions of human immunodeficiency virus (HIV)-associated nephropathy (HIVAN), published in 1984, described a focal segmental glomerulosclerosis of unclear aetiology.[1] In the subsequent period leading up to the introduction of highly active antiretroviral therapy (HAART), HIVAN was recognized as a major cause of HIV-related mortality, particularly among those of Black race.[2] The condition was frequently accompanied by severe proteinuria, and acute kidney injury (AKI) leading rapidly to end-stage renal disease (ESRD) and death.[3]

In the HAART era, the risk of ESRD in HIV patients has diminished substantially in both Blacks and Whites.[4-5] Individuals of African descent, however, still remain at greater risk for HIVAN and other forms of kidney disease.[6] This is attributed to a large extent to a genetic susceptibility created by variants of the APOL1 gene on chromosome 22,[7] which are uniformly present in those with HIVAN, a histopathological entity distinct from other forms of chronic kidney disease (CKD) that is best confirmed with biopsy. The variants, or polymorphisms, also appear to explain the increased risk of ESRD in HIV-negative Blacks relative to HIV-negative Whites,[8] and may explain the far more rapid deterioration of renal function in HIV-positive Blacks when compared to HIV-positive Whites.[5] There have been no randomized trials to confirm the ability of HAART to prevent HIVAN, but retrospective analyses indicate that HIVAN is an uncommon complication in patients who begin HAART prior to severe immune deficiency and who maintain a HIV viral load <400 copies/mL.[9] HIVAN is now generally confined to patients who reach an advanced stage of immunodeficiency before antiretroviral therapy is initiated, but current treatment strategies, as discussed below, may prevent progression to ESRD. In those evolving to ESRD kidney transplantation may allow a dialysis free, long-term survival.[10]

Despite the diminished likelihood of HIVAN in the HAART era, the risk of renal disease in patients with HIV infection is expected to increase in aging HIV-infected individuals for a number of reasons. The presence of microalbuminuria, a precursor to more severe renal disease, is up to five-times higher than in non-HIV controls after multivariate adjustment.[11] Unlike HIVAN, renal disease in the era of HAART is associated with indolent rather than acute pathological processes, even though, ultimately, it may be no less life-threatening. In the assessment of renal function obtained in 20,132 HIV-infected patients, baseline estimated glomerular filtration rate (eGFR) in the post-HAART era was a strong predictor of mortality (Figure 1).[12] This is not surprising due to the numerous studies in the non-HIV infected showing similar outcomes.

FIGURE 1 | Adjusted Hazard Ratio for Death



Adapted from Ibrahim, F et al. As presented during the 18th Conference on Retroviruses and Opportunistic Infections 2011:Abstract 836.

In the growing literature documenting acceleration of age-related processes, the kidney can be both directly and indirectly affected.[13] For example, type 2 diabetes mellitus, which is a major risk factor for renal impairment, is four times more prevalent in patients with HIV relative to an age-matched population.[14] The prevalence of hypertension, another risk factor for renal impairment, is up to three times higher.[15] Hepatitis C virus (HCV), which can also impair renal function, is far more common in individuals with HIV than in those who are not infected.[16]

In addition, it is now clear that several antiretroviral therapies also increase the risk of chronic kidney disease (CKD). Often, the relative increase in risk is subtle, but antiretroviral therapies must be taken indefinitely, possibly producing risk from a cumulative effect. Although there may be no goal more important in the treatment of HIV than sustaining a low viral load, selecting an agent that poses a low risk of renal impairment may be particularly important to those who already have risk factors for renal disease or established renal impairment.[17]

For the clinician, it is important to recognize the growing problem of CKD in aging individuals with HIV infection and to consider a broad range of presentations and aetiologies.[18] Importantly, many of these aetiologies are the same as those encountered in a non-HIV-infected population but

TABLE 1 | CKD: Risk Factors and Complications

Risk Factor	Non HIV Infected	HIV Infected
Hepatitis C	<1% (particularly among non-IDU)	Common
Diabetes	Common ~5%	Up to four times higher
Antibiotic agents (amphotericin B, gentamicin)	Common	Higher if history of opportunistic infections
Antiretroviral agents (tenofovir, indinavir)	Not applicable	Common
Age-related renal impairment	Common age >65	Common age >50

Adapted from Fine DM, et al. *Drugs* 2008;68:963-80

occur at a younger age with a greater propensity for life-threatening complications over a shorter period of time (Table 1).

The HIVAN of the pre-HAART era and the CKD common to aging individuals with controlled HIV infection are generated by very different pathological events. HIVAN has been attributed to localized HIV infection of renal glomerular and tubular epithelial cells, which produces glomerulosclerosis and tubulointerstitial scarring.[19-20] HIV infection of renal epithelial cells thereby drives impairment of glomerular filtration by directly disturbing cell functions. HIV-specific immune complex glomerulonephritis and HIV-related thrombotic microangiopathy, which do not occur more frequently in Blacks, are less common renal diseases associated HIV.[7]

To understand the recent and ongoing growth of renal disease in individuals with HIV infection, it is important to recognize that CKD is a common condition in the absence of HIV infection, and that overall rates are increasing. Likely to be at least partly due to the growing problem of obesity and its associated pathology, particularly diabetes,[21] the rising rates of CKD may also be attributed to the demographic shift that is increasing the median age in Canada and elsewhere.[22] Similar trends, particularly the aging of individuals with HIV, explain the rising rate of CKD in individuals infected with HIV.

However, the HIV population has additional risks, which not only include a high prevalence of diseases that may adversely affect renal function, such as hepatitis C infection, but a relatively high risk of exposure to nephrotoxic drugs, which includes antiretrovirals, illicit drugs such as cocaine, as well as antibiotics such as gentamicin and amphotericin.[23] Patients with HIV infection may not have any greater risk of exposure to other agents associated with nephrotoxicity, such as non-steroidal anti-inflammatory drugs (NSAIDs), but they may be more likely to develop renal complications, including acute interstitial nephritis, as a result of the large number of drugs to which they are exposed.[24]

Isolated cases of AKI have been reported for essentially all antiretroviral agents, but the two agents most consistently linked with acute and chronic renal effects are the nucleoside reverse transcriptase inhibitor (NRTI) tenofovir and the protease inhibitor (PI) indinavir.[6] Overall, the risk of AKI and CKD is low on tenofovir among young and relatively healthy patients,[25] but this agent may induce proximal renal tubule damage that may pose increasing risk for kidney injury in patients with other risk factors. The risk of damage to the kidney from tenofovir is likely to be increased in those who already have CKD and those with prolonged exposure.[26] In one retrospective analysis of 10,000 patients exposed to tenofovir, nephrotoxicity was identified in only 2% of patients, but the risk of demonstrating a rise in serum creatinine of >0.5 mg/dL (44.2 µmol/L) was increased by an elevated baseline serum creatinine, concomitant use of another nephrotoxic agent, and older age.[27] The risk posed by indinavir, unlike tenofovir, appears to stem from chronic interstitial nephritis,[28] but this protease inhibitor is rarely used in the current era and so does not contribute substantially to current risk (Table 2).

TABLE 2 | Toxicity and Renal Complications with Drug Exposure

Drug		Mechanism
Tenofovir		Tubular Injury
Indinavir Penicillin Sulfa Antibiotics	NSAIDS Fluroquinolones Proton Pump Inhibitors	Acute interstitial nephritis
Amphotericin B	Gentamicin	Acute tubular necrosis
Sulfadiazine Atazanavir	Indinavir	Crystal nephropathy
Cocaine NSAIDS	Radiological contrast agents	Renal ischemia

Adapted from Winston J, et al. *Clin Infect Dis* 2008;47:1449-57

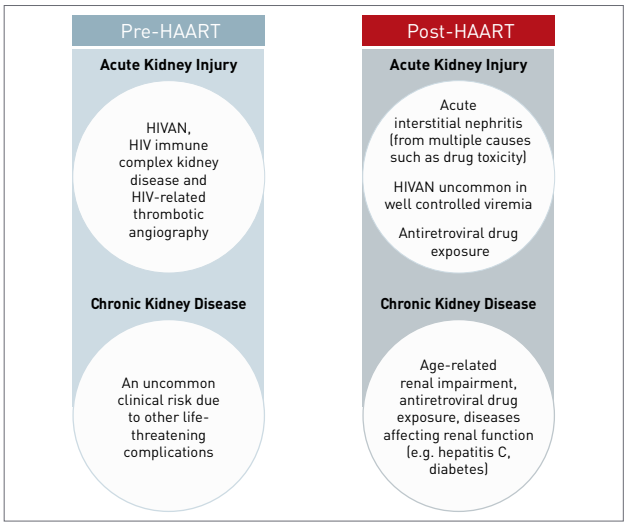
Clinical Features and Evaluation of Renal Disease in HIV Patients

In the post-HAART era, HIVAN should not be overlooked as a potential complication of HIV, particularly in individuals of African descent not virally suppressed on antiretroviral medication. HIVAN typically presents with a high level of proteinuria, which is often but not always nephrotic, and rapidly progressive acute kidney failure.[3] HIVAN, which is not typically associated with hypertension or oedema, is generally observed in HIV-infected patients with acquired immunodeficiency syndrome (AIDS) or who otherwise have a low CD4 count and high viral loads.

However, most renal disease in HIV-infected individuals is now due to aetiologies either indirectly related to HIV infection, such as antiretroviral therapies, or to processes that may be exacerbated but not caused by HIV infection. Many of these aetiologies are generally shared with a non-HIV-infected population, but the onset may be earlier or complicated by concomitant diseases, such as HCV infection. It is helpful when reaching a diagnosis to distinguish between AKI, which represents rapid renal impairment, and CKD, which, although more slowly progressive, is generally irreversible even if further progression can be attenuated (Figure 2).

Whether nephropathy is due to immune-related glomerulonephritis or progressive renal insufficiency due to other pathologic processes, including age-related decline in function or drug-induced renal damage, the early stages are likely to be clinically silent detectable only by laboratory testing. It is therefore appropriate to include renal function

FIGURE 2 | Important Renal Disease Etiologies in the Pre- and Post-HAART era



Adapted from Fine DM, et al. *Drugs* 2008;68:963-80

assessments within routine evaluation of HIV-infected patients, including those who are otherwise well with good infection control.[29]

Proteinuria typically provides the earliest signal of renal disease in those diseases that manifest with proteinuria (generally diseases with glomerular involvement).[30] Up to one-third of patients with HIV will demonstrate abnormal kidney function on the basis of elevated protein in the urine.[31] Although not all have a level that requires therapy, proteinuria is often associated with progressive renal disease, suggesting the need for close observation in such patients. Proteinuria, even in the microalbuminuria range (30 to 300 mg/24 hours) is an adverse prognostic sign, predicting increased health risks, including cardiovascular events. Although a 24-hour urine collection is generally considered the most accurate method for assessing proteinuria, the Infectious Diseases Society of America (IDSA) accepts a urine dipstick as a screening tool in guidelines for monitoring renal function in HIV patients. However, a protein-to-creatinine ratio on a single urine sample, commonly referred to as a spot test, provides a more accurate assessment of proteinuria with reasonable convenience.

Regardless of the degree of proteinuria, an eGFR analysis (with the use of creatinine based formulas) is warranted to evaluate renal function in all patients upon initial presentation. The accepted diagnosis of CKD is eGFR <60 ml/min/173m^2 persisting for at least three months or the presence of another kidney abnormality, such as proteinuria, for more than 3 months regardless of eGFR.[32] The decision regarding how often to perform repeated eGFR assessments should be influenced by the degree of proteinuria and the presence of risk factors for CKD, the presence of diabetes or other co-morbidities, exposure to nephrotoxic drugs, smoking, dyslipidemia, or use of intravenous drugs.[29]

In young, otherwise healthy individuals with good control of HIV infection and no risk factors for renal disease, routine monitoring of renal function can be reserved for periodic health assessments, but the frequency of monitoring and the types of monitoring should be intensified with increasing age and increasing number of risk factors. While dipstick urine measurements of proteinuria may be adequate in low-risk patients, concern about the potential presence of renal disease should prompt additional measures, including protein-to-creatine or albumin-to-creatine assessments and eGFR, when risk is high or the presence of proteinuria suggests a more thorough evaluation.

In HIV-infected patients, renal biopsy may be required for a definitive diagnosis of the aetiology AKI or CKD, including HIVAN. In patients with AKI, particularly those suspected of HIVAN, a kidney biopsy should be conducted promptly because of the rapid deterioration in renal function associated with this condition. One of the most common alternative causes of AKI in patients with HIV is acute interstitial nephritis (AIN), which, like HIVAN, may have characteristic features that facilitate diagnosis on biopsy. In patients with CKD, biopsy may not be necessary if the decline in renal function is consistent with a concomitant disease, such as diabetes. However, biopsy may be useful for evaluating renal involvement in patients with HCV when attempting to identify the best management strategy. In patients with multiple diagnostic possibilities, biopsy is particularly useful in guiding management.

Treatment

In many cases, nephropathy cannot be reversed but the progression can be slowed substantially. The first step is to modify or eliminate potential sources of nephropathy or nephrotoxicity. This may include treating hepatitis C or switching to HAART regimens that do not include tenofovir. Early detection of declining renal function may provide an opportunity to intervene when renal damage is limited, particularly if the aetiology can be identified. With tenofovir use, for example, the immediate risk of clinically significant renal disease appears to be low in the context of slowly declining renal function, but the adverse consequences of long-term treatment may be cumulative or increased in the presence of additional risk factors for CKD.[33]

For patients with HIVAN or HIV immune complex renal disease, who have not yet started antiretroviral therapy, suppression of the viral load is the most important immediate step. Steroids may also be of benefit during the acute presentation of HIVAN. After the acute phase, progression of renal impairment may be attenuated with angiotensin converting enzyme (ACE) inhibitors.[34] Care of HIVAN (or any other kidney disease) that has advanced to ESRD or

has a high likelihood of advancing to ESRD should be directed by nephrologists who can provide dialysis and who have access to sophisticated therapeutic options, such as organ transplant.

In patients with CKD, the same principles for preserving kidney function in individuals who are HIV-negative apply for those with HIV infection. This includes strict blood pressure control and glucose control (in diabetics), control of dyslipidemias, avoidance of nephrotoxic agents, and adequate doses of ACE inhibitors or other inhibitors of the renin-angiotensin system. Avoiding smoking and low levels of alcohol ingestion are also prudent. Due to the association of renal dysfunction with abnormal bone metabolism and anemia, these potential problems should be monitored.

Conclusion

HIV infection has been a risk factor for renal dysfunction and progression to ESRD from the earliest stages of the epidemic. Although the introduction of HAART greatly modified the risk for HIVAN, rates of renal disease are expected to climb faster in an aging HIV population even when their infection is well controlled when compared to individuals of similar age without HIV. There are numerous reasons to anticipate high rates of CKD in aging patients with HIV, including a greater number of risk factors, higher exposure to nephrotoxic drugs, and what appears to be a more rapid aging process in HIV-infected individuals. While screening for renal function should be included in routine health assessments in individuals with HIV as in individuals who are not infected with HIV, more frequent and more rigorous screening is warranted in this population.●

Screening and Diagnosis of Renal Impairment in the Aging HIV Patient

1. At initial visit, assess risk factors for renal impairment, such as hypertension, diabetes, hepatitis C infection, exposure to nephrotoxic drugs, family history of renal disease, advanced immunodeficiency prior to HIV treatment, cocaine exposure, and cigarette smoking. Baseline laboratory screening for proteinuria and serum creatinine concentration (with estimation of GFR) should be performed to detect existing kidney disease and to provide a baseline for subsequent measurements.

2. A protein-to-creatinine ratio or albumin-to-creatinine ratio on a random urine collection should be calculated from a urine sample at the initial visit. This provides an accurate and convenient screening test for underlying kidney problems. Monitoring on a semi-annual basis may be sufficient in patients on stable antiretroviral therapy with consistent viral suppression and risk factors for kidney disease (noted in 1 above). In those without proteinuria and no risk factors, intermittent monitoring should be guided by clinical picture.

3. In cases of microalbuminuria (30 to 300 mg/24 hours or albumin-to-creatinine ratio on microalbuminuria testing of 30-300 mg albumin/g creatinine) on an initial or subsequent evaluation, repeat the test within three months to evaluate rate of progression and then every 6 months.

4. Further evaluation including kidney ultrasound, evaluation by a nephrologist or other specific testing in the following situations:
    a. In patients with overt proteinuria (urinary protein in amounts exceeding 0.3 g in a 24-hour urine collection, spot urine protein to creatinine ratio > 0.3 g protein/g creatinine, or albumin-to-creatinine ratio > 300 mg/g creatinine);
    b. Patients with unexplained decrease in eGFR (increasing creatinine);
    c. Patients with unexplained CKD.

5. In patients on tenofovir therapy:
    a. Monitoring of serum creatinine, phosphate and urine glucose at each routine clinical visit to monitor for kidney failure and/or tubular defects.

6. In patients with CKD, establish treatment plan:
    a. Address causes such as diabetes mellitus or hypertension;
    b. In addition to appropriate blood pressure management, consider ACE inhibitors;
    c. Avoid nephrotoxins with the potential to cause or exacerbate CKD;
    d. Modification of cardiovascular risk factors, such as hypercholesterolemia, obesity and cigarette smoking;
    e. Dietary modifications, such as dietary salt, potassium or phosphate restriction, when appropriate.

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Guest Editor
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the AGING HIV PATIENT
neurocognitive deficit

Cognitive decline is an insidious and frequently progressive complication of human immunodeficiency virus (HIV) infection. While the introduction of highly active antiretroviral therapy (HAART) largely eliminated the dementia associated with end-stage acquired immunodeficiency syndrome (AIDS), cognitive impairment remains a common complication of HIV even in those with well controlled viremia. The incidence and the severity of HIV-associated neurocognitive disorders (HAND) are rising with an aging HIV population – a potential consequence of both increased susceptibility in older individuals and progressive impairment with longer duration of infection. The clinical challenges posed by this complication are substantial. The relative ability of specific antiretroviral therapies to cross the blood brain barrier to reduce central nervous system (CNS) viral load, and the specific, perhaps genetic, susceptibility of individual patients are among factors that may explain the variable risk of cognitive impairment. In addition, HIV-independent variables may also be important in some individuals. Clinical sensitivity to changes in cognitive function through periodic assessments is appropriate in the context of strategies to understand and prevent HAND.

Neurocognitive Loss: Epidemiology

Prior to the introduction of highly active antiretroviral therapy (HAART), dementia was a common acquired immunodeficiency syndrome (AIDS)-defining complication of human immunodeficiency virus (HIV) infection, occurring in at least 15% of patients by the time of death.[1] In this pre-HAART era, the risk of AIDS-dementia complex (ADC) increased with diminishing immune function and appeared to be a direct effect on uncontrolled HIV infection.[2] In the post-HAART era, ADC has been joined by HIV-associated neurocognitive disorders (HAND), the inclusive term that describes the spectrum of HIV-associated decrements in neurologic function from ADC to asymptomatic neurocognitive impairment.[3] Although HAART has significantly reduced the risk of dementia, the rates of HAND appear to be unchanged after adjusting for age, education, gender, race, and CD4 count.[4] The evidence of progressive cognitive deficits observed in patients even with well-controlled viremia suggests an active intracerebral process that persists even when clinical signs of infection have otherwise been eliminated.[5] In a recently completed cross-sectional study, dementia was rare, but HAND was common with 52% of patients having some degree of neuropsychological impairment.[6] Specifically, 33% had asymptomatic cognitive impairment, 12% had mild but symptomatic cognitive impairment, and 2% had dementia, while the remaining had other causes of neuropsychological deficit.

Cognitive loss progresses over time even in patients with HIV that is well controlled on the basis of plasma viremia levels. In one study that evaluated HIV-infected patients with undetectable viremia, up to one third demonstrated a decline in function over 27 months of follow-up.[7] Treatable causes of cognitive loss were ruled out. Age and duration of HIV infection are likely to be risk factors for cognitive loss. In a prospective study comparing one cohort of patients older than age 50 years to a second cohort between the ages of 20 and 39 years, the incidence of cognitive loss was twice as great in the older group (25% vs. 13%; P=0.041).[8] In a large cohort study that looked at multiple risk factors for cognitive impairment in the post-HAART era, both older age at the time of seroconversion and the duration of infection were independent predictors.[9] The potential for an interaction between age, duration of infection, and HIV-independent risk factors for cognitive dysfunction, such as cerebrovascular disease, are potentially important in the aging HIV population.[10]

Although a substantial proportion of HIV-infected patients have not developed detectable cognitive impairment even after long duration of infection, suggesting that some genetic susceptibility factors may be important,[11] there are numerous other variables that appear to influence risk in individuals whose viremia is otherwise well controlled. For example, one study found rates of global cognitive impairment to be almost 50% higher (63% vs. 43%) in patients co-infected with hepatitis C when compared to those with HIV alone.[12] Biomarkers to predict cognitive dysfunction in patients with HIV are actively being pursued.[13] Although it is not clear whether cognitive loss shortens survival, except in advanced HIV,[14] high rates of cognitive loss in aging patients with HIV threaten a major public health crisis.

Pathogenesis

The pathophysiology of HAND is driven by neurotoxic HIV viral proteins generated by infected cells, which include astrocytes and microglia as well as macrophages, and by neurotoxic cytokines, chemokines, and other mediators generated by pro-inflammatory signalling from non-infected cells in the CNS.[15] It is likely that HIV crosses the blood-brain barrier into the CNS through a subset of infected monocytes establishing a CNS reservoir of HIV capable of neurotoxicity sometime after seroconversion, possibly early.[16] Over subsequent years of infection, HIV evolving in the CNS occurs independently of the virus in the periphery.[17]

There are several mechanisms for neuronal and neural damage encompassing synapto-dendritic injury but oxidative stress including excitotoxicity is the most important.[18,19] Autopsy studies reveal dominantly subcortical mononuclear cell infiltrates with microglial nodules, multinucleated giant cells, and gliosis.[20] In HAART-treated patients, there are fewer infiltrates and in some there are overlapping features with Alzheimer's disease, including elevated amyloid deposition.[21]

Cognitive function can be stratified into a wide range of measures, such as speed of information processing, attention, memory storage, and memory access, that involve different processes in different areas of the brain.[22] Due to differences in the types of cognitive losses associated with specific pathologies, a variety of measures are used to document different types of change. In one study, diminished motor skills and verbal fluency were found to be common examples of cognitive loss in the pre-HAART era, whereas loss of memory and executive function have been more common in aging patients with well-controlled viremia.[23] Other studies corroborate the types of cognitive deficits typical in aging adults, such as loss of memory storage and retrieval,[23-25] suggesting that HIV-associated cognitive loss in the HAART era overlays a parallel pathology associated with aging, to produce a compounding of effects.[26]

Importantly, the cerebrospinal fluid (CSF) penetration of antiretroviral agents differs markedly even within drug classes, such as protease inhibitors (PIs) or nucleoside reverse transcriptase inhibitors

(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]

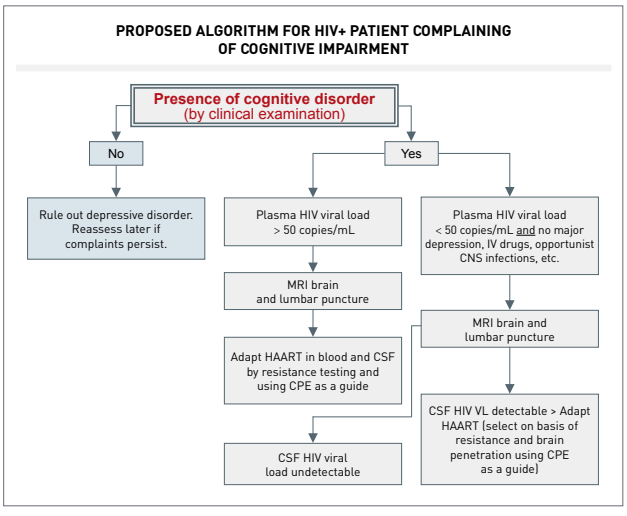
HIV-related frailty is a relatively recently reported phenomenon that may reflect accelerated aging across physiologic systems, including CNS function.[31] In a study comparing individuals initiating antiretroviral therapy over the age of 50 years, the risk of cardiovascular, metabolic or neurologic 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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Guest Editor

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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.

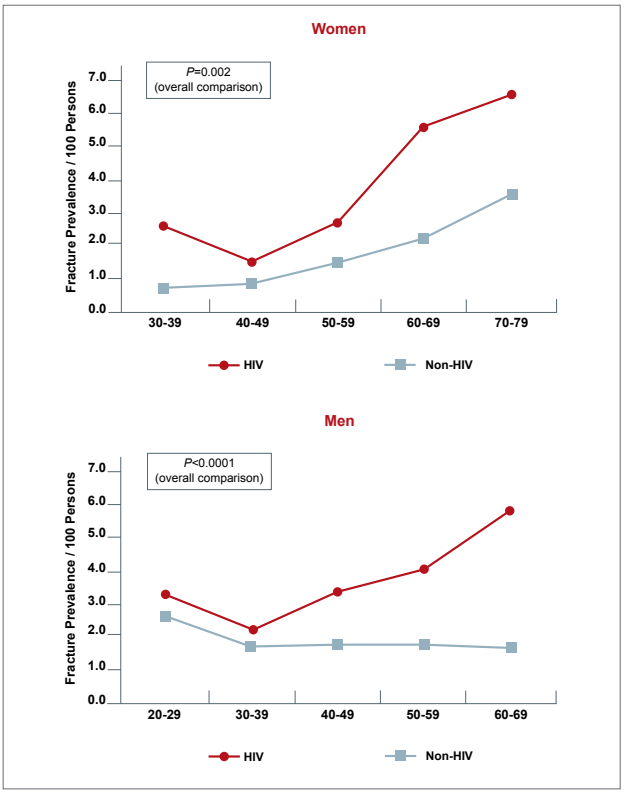
Osteoporosis in HIV: Epidemiology

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



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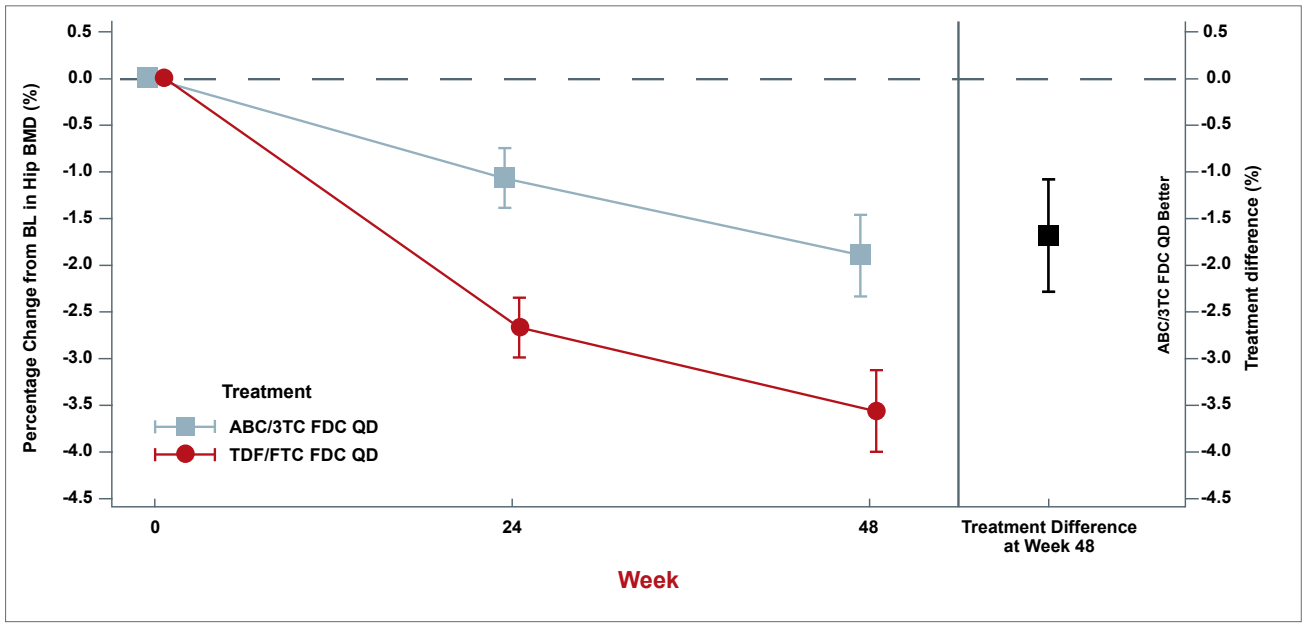
Specific antiretroviral agents have been shown to exacerbate the BMD loss associated with HIV. In a substudy of the ANRS 121 study, which randomized HIV-infected individuals to a regimen that included a ritonavir-boosted protease inhibitor (PI/r), a non-nucleoside reverse transcriptase inhibitor (NNRTI) 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.

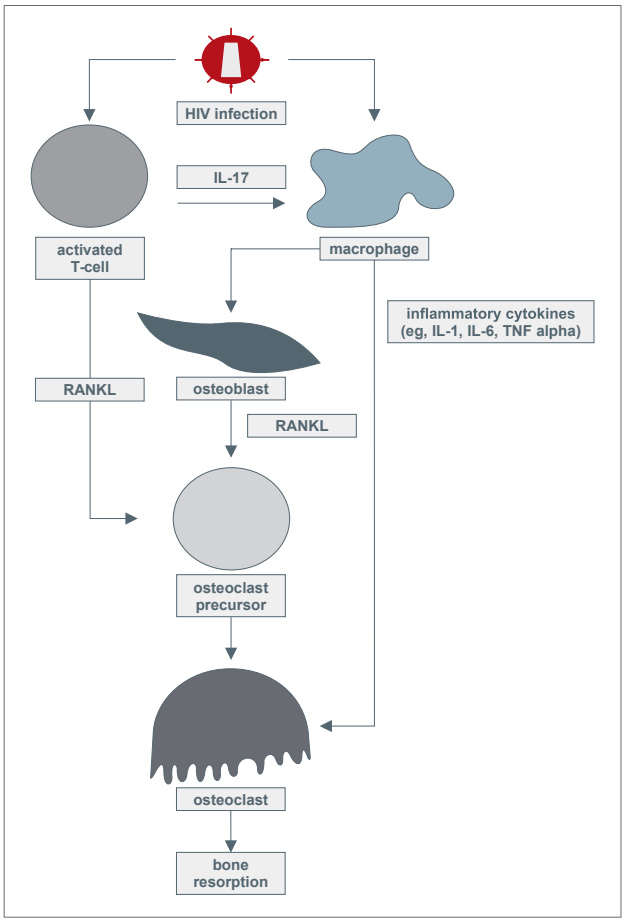
Pathogenesis

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

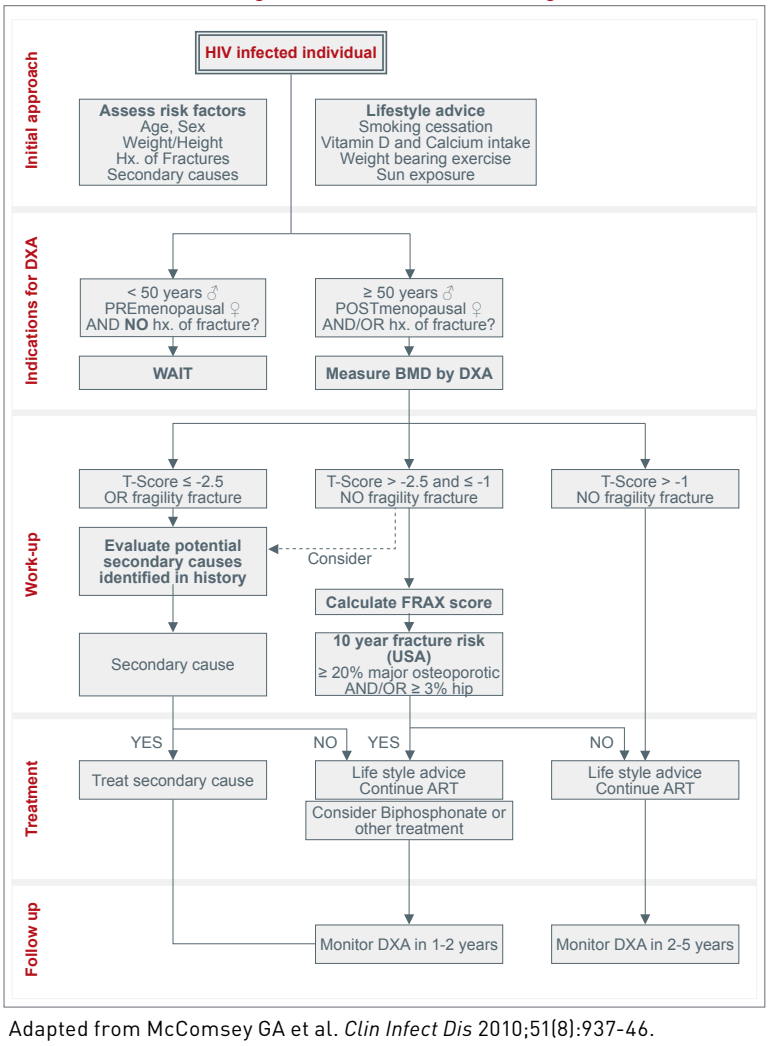
Due to the broadly shared risk of osteoporosis in aging individuals, screening for BMD is recommended in all Canadians 65 years of age or older.[33] The age for screening is lowered to 50 years for both men and menopausal women with risk factors. These risk factors include a fragility fracture after 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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