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Review

Understanding mechanisms to promote successful aging in persons living with HIV

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ABSTRACT

The mortality rate associated with HIV infection plummeted after the introduction of effective antiretroviral therapy pioneered two decades ago. As a result, HIV-infected people now have life expectancies comparable to that of HIV-uninfected individuals. Despite this, increased rates of osteoporosis, chronic liver disease, and in particular cardiovascular disease have been reported among people living with HIV infection. With the aging HIV-infected population, the burden of these comorbid illnesses may continue to accrue over time. In this paper, we present an overview of the aging HIV-infected population, its epidemiology and the many challenges faced. How to define and measure successful aging will also be reviewed. Finally, opportunities that may help mitigate the challenges identified and ensure successful aging among people living with HIV infection will be examined.

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Introduction

The introduction of potent antiretroviral therapy (ART) has significantly improved survival among people living with HIV infection (PLWH), with life expectancy now close to that of the HIV-negative population (Lohse et al., 2007). Globally, the proportion of PLWH receiving ART increased in the 5 years from 2010 to 2015, leading to significant reductions in AIDS-related deaths and increased life-expectancy (Centers for Disease Control and Prevention, 2016). The Centers for Disease Control and Prevention (CDC) estimated that by 2017, more than half of PLWH in the USA would be older than 50 years (Justice, 2010). Successful aging may be more difficult among PLWH because of their increased vulnerability to the development of multiple comorbidities over time compared to the general population (Guaraldi et al., 2011).

Epidemiology of the aging population

In the USA, the proportion of PLWH aged at least 50 years increased by over 100% from 2001 to 2014 (Centers for Disease Control and Prevention, 2009; Centers for Disease Control and Prevention, 2015). Currently, persons aged over 50 years comprise 42% of all PLWH (Centers for Disease Control and Prevention, 2009). Some regions of the country already have the majority of their HIV-positive patients over 50 years (San Francisco Department of Public Healh., 2013). By the end of 2014, 58% of PLWH in San Francisco were over 50 years of age.

HIV-infected persons over the age of 50 years in the USA comprise two groups: the majority are persons infected with HIV at a younger age who are aging due to the success of ART; the others comprise persons who are newly infected or newly diagnosed with HIV, who make up 17% of all persons with a new diagnosis of HIV (Centers for Disease Control and Prevention, 2016).

The proportion of PLWH over 50 years of age is also increasing in other parts of the world. The prevalence rate of older PLWH has increased consistently in all regions at varying rates since 2007, with Western/Central Europe and North America having the highest proportions of PLWH over 50 years (30%) and the lowest rates in regions of Sub-Saharan Africa (7.6%) (Centers for Disease Control and Prevention, 2016; United Nations AIDS Report, 2013).

Challenges faced by the aging population

As a result of the demographic changes discussed above, caring for PLWH now comes with the additional complexity of managing diseases commonly associated with aging. Increased rates of osteoporosis, frailty, diabetes, malignancy, chronic liver disease, chronic kidney disease, and in particular, cardiovascular diseases have been reported in PLWH when compared to the general population (Palella et al., 2006; Guerri-Fernandez et al., 2013; Clifford, 2017; Janssen et al., 1992). Data from the Veterans Aging Cohort Study (VACS) compared the rates of comorbidities experienced by over 30 000 HIV-positive veterans to those of their HIV-negative counterparts and demonstrated increased rates of individual age-related comorbidities, as well as multimorbidity, in the HIV-positive group. However, it should be noted that HIV-positive and negative populations were not completely matched; for example, the HIV-positive group had higher rates of drug dependency and lower socioeconomic status (Goulet et al., 2007). This study raises two important questions. Firstly, are PLWH aging in an accelerated or accentuated fashion as a result of increased comorbidities (Pathai et al., 2014)? Secondly, are these comorbidities attributable to the HIV infection itself or to the increased rates of traditional risk factors associated with lower socioeconomic status and increased rates of substance abuse seen in PLWH, as suggested by the VACS cohort, or to ART toxicities?

Cardiovascular disease

Cardiovascular disease (CVD) is a leading cause of death in PLWH on effective ART (Rodger et al., 2013). Although the overall mortality in those living with HIV in the USA halved between 1999 and 2013, deaths from CVD increased two-fold despite a decrease in CVD-related mortality in the general population (Feinstein et al., 2016). Multiple factors have been attributed to the increased CVD risk observed in PLWH, including the HIV infection itself, ART toxicity, and increased rates of traditional risk factors including smoking, diabetes mellitus, hypertension, and dyslipidemia (Triant et al., 2007; Saves et al., 2003). Although of unclear mechanism, individuals who reported recent use of abacavir were shown to have a 90% greater risk of acute myocardial infarction compared to those who had not used abacavir (Sabin et al., 2008). Even after correcting for channeling bias (i.e., patients who have higher CVD risk are preferentially prescribed abacavir), a follow-up study still demonstrated an excess risk of CVD with abacavir use (Sabin et al., 2016). At present, this association remains debatable, as several other large studies have not shown an association between abacavir and CVD (Brothers et al., 2009; Ribaudo et al., 2011).

Higher myocardial infarction rates were consistently observed across three age categories of HIV-positive veterans in the VACS cohort compared to HIV-negative controls. This persisted after adjustment for Framingham risk factors, substance abuse, and geographic location, which would at least in part take socioeconomic factors into account. There was an increased risk of incident acute myocardial infarction of 48% (hazard ratio (HR) 1.48, 95% confidence interval (CI) 1.27–1.72) amongst HIV-positive veterans (Armah et al., 2014). In the absence of major CVD risk factors, HIV-positive veterans had a two-fold increased risk of myocardial infarction compared to HIV-negative veterans (HR 2.0, 95% CI 1.0–3.9; $p = 0.044$), suggesting that at least for myocardial infarction, the increased rates seen in PLWH are not entirely explained by an over-representation of traditional CVD risk factors (Paisible et al., 2015).

A more recent study from the VACS cohort also demonstrated an association between HIV infection and heart failure with preserved and reduced ejection fractions. Although socioeconomic status was not accounted for in the overall analysis, the association between heart failure and HIV persisted after adjustment for multiple traditional risk factors and remained unchanged even after restricting the analysis to participants without hypertension, substance use, or smoking history (Freiberg et al., 2017).

Osteoporosis and fracture

PLWH are six times more likely to have low bone mineral density and almost four times more likely to have osteoporosis compared to the general population (Brown and Qaqish, 2006). In a large cohort study, HIV infection was shown to be independently associated with low bone mineral density, an association that remained despite adjustment for traditional risk factors such as age, sex, and smoking status, as well as educational level (Cotter et al., 2014). Higher rates of hip fracture (four times higher risk), non-hip fracture (63% increased risk), and all clinical fractures (75% higher risk) have also been demonstrated in PLWH, although it should be noted that in the latter study, which examined fractures in PLWH, data on drug use and socioeconomic status were not included (Guerri-Fernandez et al., 2013).

Malignancy

Although the rates of AIDS-defining malignancy (Kaposi sarcoma, cervical cancer, and non-Hodgkin lymphoma) have declined over time with ART, the rates of non-AIDS-defining cancer continue to increase (Bedimo et al., 2009; Shiels et al., 2009). In particular, infection-related cancers (i.e., anal cancer, Hodgkin lymphoma, and liver cancer) and cancers highly associated with smoking (i.e., lung and laryngeal cancer) have higher incidence rates in HIV-infected individuals than in the general population (Shiels et al., 2009). Rather than attributing the latter to the direct effect of HIV, it is more likely that the increased rates of smoking in PLWH may be responsible. Tobacco smoking rates amongst PLWH reportedly range from 40% to 70%, equating to two to three times higher than the general population (Petoumenos et al., 2011). A number of studies have demonstrated increased rates of lung cancer after adjustment for smoking status in PLWH, although these have been limited by a lack of data on cumulative smoking exposure (Engels et al., 2006; Kirk and Vlahov, 2007). The underlying mechanism for increased rates of infection-related malignancies in PLWH is also not entirely clear, but may be related to either increased exposure to oncogenic viruses or persistent infection related to HIV-induced immune suppression (Shiels et al., 2009).

Chronic liver disease and kidney disease

Arising from shared modes of acquisition, the prevalence of co-infection with hepatitis B and C viruses amongst PLWH is approximately 25 times higher than in the general population (8% versus 0.3% for hepatitis B virus (HBV), and 30% versus 1.3% for hepatitis C virus (HCV)) (Kellerman et al., 2003; Staples et al., 1999; Denniston et al., 2014). Co-infection with HIV accelerates the progression of liver fibrosis among HBV- and HCV-infected patients, leading to higher rates of cirrhosis and hepatocellular carcinoma (Castellares et al., 2008; Silverberg et al., 2015).

HIV-associated nephropathy (HIVAN) used to be the most common cause of end-stage renal disease (ESRD) requiring hemodialysis among HIV-infected persons (Winston et al., 1998). In the era of ART, the incidence of HIVAN has declined, but the overall rates of chronic kidney disease (CKD) have remained stable (Eggers and Kimmel, 2004). The prevalence of a glomerular filtration rate $<$60 ml/min among HIV-infected persons ranges from 5% to 10% (Campos et al., 2016). HIV-infected persons are particularly at risk of developing CKD because of several risk factors, including exposure to specific antiretrovirals such as tenofovir disoproxil fumarate, as well as increased rates of other comorbidities including hypertension and diabetes.

HIV neurocognitive disease

The prevalence of HIV-associated dementia was estimated at 10–15% before the era of ART. The prevalence dropped dramatically after the introduction of ART to approximately 2% (Heaton et al., 2010). Despite this, some studies have shown that even at younger ages and with well-controlled HIV infection, more than half of PLWH have varying degrees of neurocognitive dysfunction (Clifford, 2017; Heaton et al., 2010). It is important to note that this finding is driven primarily by asymptomatic and mild neurocognitive dysfunction, the relevance of which is unclear. Additionally, neurocognitive testing may be significantly impacted by socioeconomic status, test bias, and contextual factors (Arentoft et al., 2015).

Frailty and other aging-related conditions

Defined as an aging-related syndrome that predisposes an individual to an increased risk of multi-morbidity and mortality, frailty is estimated to occur in 5–19% of PLWH. Data from a study that examined frailty in HIV-positive and negative intravenous drug users (IVDU) demonstrated that although frailty was strongly associated with advanced HIV, the prevalence of frailty in IVDU with well-controlled HIV was similar to that in HIV-negative IVDU, suggesting that untreated HIV infection contributes to the development of frailty (Piggott et al., 2013).

Other geriatric conditions have also been reported at increased rates in PLWH. Data from a cohort of 155 HIV-infected patients aged at least 50 years and receiving ART for at least 3 years, demonstrated that more than half of participants had at least two geriatric syndromes. The most common were pre-frailty (56%), difficulty with activities of daily living (46%), cognitive impairment (46%), depression (40%), visual impairment (35%), falls (26%), and urinary incontinence (25%). Although there was no HIV-negative control group in the study, when compared to other studies in the literature, these prevalence rates were equivalent to cohorts in the general population who were 65 years and older (Greene et al., 2015). Of note, 23% of subjects in this cohort were current smokers, and IVDU was the mode of HIV acquisition in 12% of the study population, with 5% reporting ongoing use of intravenous drugs. Seventy-four percent of subjects had exposure to older-generation ART such as didanosine, zalcitabine, stavudine, and zidovudine, although unexpectedly this was associated with decreased rates of geriatric syndromes, potentially resulting from survival bias, but overall making it difficult to apply the findings to contemporary cohorts.

Mechanisms behind the increased burden of chronic illnesses in HIV infection

The observation that PLWH are experiencing more chronic illnesses over time may simply be a reflection of the aging population with the success of ART. Hence, this perceived higher risk of developing these comorbid diseases among HIV-positive individuals may represent a cohort effect. However, the occurrence of these comorbid illnesses at younger ages and at frequencies comparable to much older individuals in the general population, as well as the over-representation of risk factors for these chronic diseases among PLWH, argue for mechanisms beyond a cohort effect.

It is clear that the increased rates of comorbid illness observed in PLWH cannot be entirely attributed to HIV infection alone and are likely to represent a complex interplay of factors, including differing demographics and socioeconomic status, higher rates of traditional risk factors, co-infections and opportunistic infections and associated inflammation, and exposure to ART, along with the direct effect of the HIV infection itself (Burch et al., 2016).

As previously discussed, traditional risk factors for developing chronic diseases are found in excess in PLWH. For example, increased rates of smoking, a strong risk factor for malignancy, cardiovascular, bone, chronic kidney, and liver diseases, as well as neurocognitive dysfunction and frailty, have repeatedly been reported across a number of HIV acquisition risk groups (Niaura et al., 2000).

Substance abuse, including alcohol and intravenous drug use, is also highly prevalent in PLWH and has been linked to CVD, geriatric syndromes, and increased all-cause mortality (Chander et al., 2006). Co-infections with HBV and HCV, as mentioned previously, lead to a higher burden of hepatocellular carcinoma, and HCV infection is also an independent risk factor for osteopenia and osteoporosis (Bedimo et al., 2016). Other traditional risk factors for the development of chronic diseases, including hypertension, diabetes, dyslipidemia, and obesity, are all seen at increased rates in PLWH.

Along with traditional risk factors, exposure to certain antiretroviral agents has also been shown to contribute to the development of some comorbid illnesses. For example, tenofovir disoproxil fumarate is associated with osteoporosis and kidney disease (Cooper et al., 2010). As discussed previously, abacavir has been linked to acute myocardial infarction (Sabin et al., 2008), and older-generation nucleoside reverse transcriptase inhibitors (NRTI) such as zidovudine, stavudine, and didanosine, as well as protease inhibitors, have been associated with anemia, dyslipidemia, and insulin resistance.

Untreated HIV has been associated with increased levels of immune activation and inflammation, as well as endothelial dysfunction, altered coagulation, platelet dysfunction, and gut microbial translocation, all of which are factors known to contribute to the development of chronic diseases such as CVD. Likewise, co-infection with cytomegalovirus and HCV contributes to immune activation. Elevated levels of systemic inflammatory markers (e.g., soluble CD14, tumor necrosis factor (TNF)), which represent a hallmark of HIV infection, have been shown to predict not only mortality, but also the development of several of the comorbid illnesses discussed previously. The maintenance of viral suppression through the use of ART reduces but does not fully normalize this level of inflammation (Hearps et al., 2012). However, in patients on effective ART, the residual effect of HIV infection itself on the development of comorbidities and on mortality remains controversial, with further research required in this area.

Successful aging

Successful aging in the general population

Although of critical importance to the general population, there is no consistent definition of successful aging that has been accepted by the research community. Successful aging, when compared to usual aging, occurs when extrinsic factors such as diet, exercise, and psychosocial factors play a neutral or positive role instead of intensifying the effects of aging (Rowe and Kahn, 1987). To date, there are over 25 unique definitions of successful aging, leading to a wide range of prevalence rates (1–94%, median 35%) (Depp et al., 2010). Current definitions stem from the classical definition by Rowe and Kahn, which states that successful aging comprises three major criteria: avoidance of disease and disease-related disability (including risk factors for developing them), high cognitive and physical functional capacity (i.e., sustaining physical, mental, and emotional aptitude for performing activities), and active engagement with life (i.e., maintaining productivity and keeping valuable interpersonal relations) (Rowe and Kahn, 1997). Of these criteria, physical and/functional disability is the one included as a component of more than half of the definitions of successful aging.

However, these definitions are not necessarily in keeping with the opinions of older persons with regard to aging. In one study, half of participants considered themselves successful agers based on a self-rated scale, while only 18% met the successful aging criteria of Rowe (Strawbridge et al., 2002). In another study, 92% of older community-dwelling adults rated themselves as successfully aging despite having chronic illnesses or physical disability (Montross et al., 2006). In these studies, older adults emphasized independence, resilience, coping mechanisms, and overall well-being as the more important components of successful aging.

Successful aging in the HIV-infected population

HIV infection poses unique obstacles to achieving successful aging. Apart from being predisposed to multi-morbidity and polypharmacy, PLWH are more vulnerable to developing cognitive and psychiatric impairments that contribute to a loss of personal control, life satisfaction, and productivity (Vance et al., 2011). Successful aging has not been studied well in the context of HIV infection and thus predictors of successful aging among PLWH are not known.

The definition of successful aging in HIV has been based on the achievement of certain quality-of-life outcomes, which include attaining a well-adapted affective state (i.e., absence of depression and maintenance of high morale), finding meaning in life despite chronic illness, and sustaining valued activities and relationships, rather than on the attainment of physical health (Kahana and Kahana, 2001). Data from one study that used a self-rated successful aging scale employed in the general population, found that two-thirds of HIV-positive participants had high scores on the self-rated scale, although their scores remained lower than HIV-negative participants matched by age, sex, race, and educational attainment (Moore et al., 2013). They further demonstrated that although HIV-positive participants had lower physical and mental functioning and experienced greater psychosocial stressors compared to their HIV-uninfected counterparts, HIV-positive individuals had similar levels of optimism, personal mastery, and social support. Thus, they concluded that even if PLWH had physical impairment or disability, the achievement of successful psychosocial aging was possible.

The HIV landscape is dominated by health disparity. HIV disproportionately affects economically disadvantaged individuals (i.e., those who are below the poverty threshold, disabled, and unemployed), men who have sex with men (MSM), and blacks. These vulnerable groups already carry an excessive burden of morbidity and mortality even in the absence of HIV infection (Stringhini et al., 2017; Emlet, 2016; Harper et al., 2007). Furthermore, these population groups are not mutually exclusive, which further impacts health outcomes. The health disparities also widen with aging as more disabilities and chronic illnesses accumulate. In the USA, the overwhelming majority of HIV-infected individuals are male, of whom the majority are MSM. As a group, MSM are vulnerable to social stigma, discrimination, social isolation, and victimization, which persist throughout life and bear lifelong negative physical, social, and psychological consequences; these ultimately lead to poor health outcomes (Emlet, 2016). These additional stressors pose a considerable challenge to successful aging. Furthermore, substance abuse, which is also linked with adverse health outcomes, is intricately tied not only to these social stressors but also to low socioeconomic status and racial disparity.

Path to successful aging in the HIV-infected population (Figure 1)

Initiation of ART regardless of CD4+ T-cell count

CD4+ T-cell counts of $<$500 cells/μl have been linked to higher mortality from both AIDS-defining and non-AIDS defining malignancies, death from liver disease, and risk for incident CVD, CKD, and fragility fractures (Collaboration of Observational HIVEREiE et al., 2012; Lichtenstein et al., 2010; Yong et al., 2011; Weber et al., 2006; Monforte et al., 2008; Ganesan et al., 2013). Early initiation of ART at higher CD4+ T-cell counts is more likely to result in patients achieving and maintaining CD4+ T-cell counts $>$500 cells/μl. In a study of 655 patients who initiated ART, only patients with a baseline CD4+ T-cell count $>$350 cells/μl experienced a full immunological recovery after 6 years of viral suppression (Moore and Keruly, 2007).

The benefit of early initiation of ART also extends beyond CD4+ T-cell normalization. In the Strategic Timing of Antiretroviral Treatment (START) study, a randomized controlled trial involving

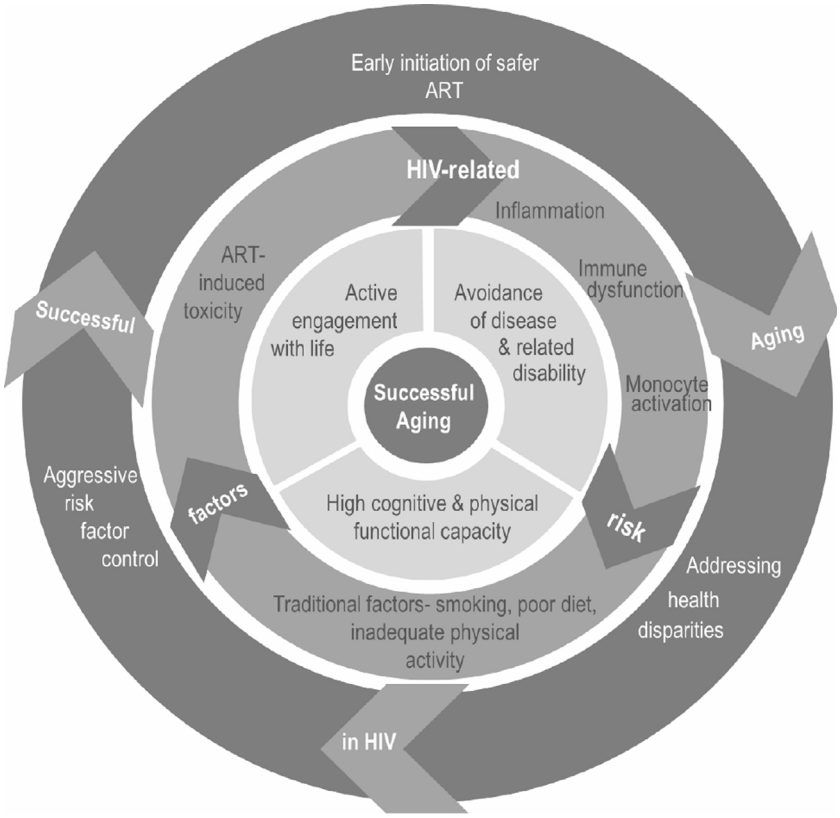

Figure 1. Factors associated with successful aging in HIV.

more than 4500 patients with CD4+ T-cell counts >500 cells/μl who were randomized to initiate ART immediately or to have ART deferred until their CD4+ T-cell count decreased to <350 cells/μl or until the development of AIDS, it was found that immediate initiation of ART not only led to fewer serious AIDS-related events (HR 0.28; $p < 0.001$), but also resulted in fewer serious non-AIDS-related events, including myocardial infarction, stroke, coronary revascularization, ESRD, liver disease, non-AIDS-defining cancer, and death from these comorbidities (HR 0.61; $p < 0.04$) (Group ISS et al., 2015). In both the immediate and deferred arms of the trial, the mean CD4+ T-cell count remained >500 cells/μl at every time point over 5 years. This led to a paradigm shift in the treatment of HIV infection. At present, ART initiation is recommended for all HIV-infected patients regardless of CD4+ cell count (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2016).

Use of safer ART

Although the net benefit of viral suppression and immune recovery with the use of ART among PLWH is an improvement in the lipid profile (i.e., lowering the total cholesterol to high density lipoprotein ratio) (Riddler et al., 2003), older-generation protease inhibitors (e.g., indinavir, lopinavir, fosamprenavir) and thymidine NRTI (e.g., stavudine, didanosine, zidovudine) have been linked to the development of dyslipidemia and insulin resistance by inhibiting several important molecular pathways in lipid metabolism and insulin signaling (Non et al., 2017a). Older protease inhibitors have also been associated with an increased cardiovascular risk because of their effects on lipid metabolism (Group DADS et al., 2007). On the other hand, until recently it was thought that newer protease inhibitors (e.g., atazanavir and darunavir) did not confer these risks (Overton et al., 2012; Kamara et al., 2016; Noor et al., 2006; Yan and Hruz, 2005; Aberg et al., 2012; Monforte et al., 2013). However, recent data from the D:A:D cohort showed that darunavir was independently associated with a 59% higher risk of CVD per 5 years of exposure, while atazanavir was protective (Ryom et al., 2017). However, these data need to be corroborated in other large observational cohorts.

Integrase inhibitors are the newest class of antiretroviral agents. Most experience has been with the use of raltegravir, which has been on the market for 10 years now. It has not been associated with dyslipidemia, insulin resistance, or lipodystrophy. Likewise, it has not been linked to cardiovascular, bone, or kidney disease. Current guidelines in the USA (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2016) and Europe (European AIDS Clinical Society, 2016) reflect the important shift to using safer antiretroviral medications. Because of their potency and favorable long-term safety profiles, integrase inhibitor-based therapy is now the recommended first-line therapy for treatment-naïve patients.

Newer treatment options are also being investigated that promise to provide safer regimens for the treatment of HIV infection, including new drug formulations and combination therapies (Gallant et al., 2016; Mills et al., 2016; Sax et al., 2017; Llibre et al., 2017; Joly et al., 2017; Cahn et al., 2016).

Application of primary prevention and screening guidelines and aggressive control of risk factors

A recent study from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) on population attributable fractions (PAFs; proportion of cases avoided if a risk factor was not present, holding all other risk factors constant) showed that 43%, 41%, and 38% of myocardial infarction could have been avoided if HIV-positive individuals had not had elevated total cholesterol, hypertension, or smoking, respectively (Althoff et al.,

2017). It also showed that the PAFs for these three risk factors were considerably higher compared to having uncontrolled viremia (6%) and a lower CD4 count (10%). This study emphasizes the importance of screening for and aggressively controlling traditional risk factors that contribute to CVD.

Smoking leads to almost all comorbidities seen with increasing incidence in the aging HIV-infected population. The high PAF associated with smoking is consistent in all studies (Althoff et al., 2017). It is estimated that HIV-positive smokers lose 140% more life-years compared to non-smokers (Helleberg et al., 2013). A recent modeling study demonstrated that HIV-infected smokers aged 40 years lose >6 years of life expectancy from smoking, potentially a greater loss of life expectancy than that resulting from the HIV infection itself (Reddy et al., 2016). Smoking likely contributes to higher rates of inflammation among PLWH as well. Compared to non-smokers, PLWH who smoke have higher levels of inflammatory markers, including soluble CD14 and expression of HLA-DR on both CD8+ and CD4+ T-cells (Cioe et al., 2015). Because of the considerably high smoking rates among PLWH, smoking cessation should be an integral part of routine HIV care.

Annual screening for diabetes and dyslipidemia, and frequent blood work to monitor liver and kidney toxicity from prescribed antiretroviral drugs are recommended for all HIV-positive patients. In addition, it is recommended that co-infection with HCV and HBV is also screened for at clinic entry and regularly thereafter, depending on additional risk factors for acquiring viral hepatitis. It is recommended that screening for osteoporosis is started at age 50 years for all PLWH, a cut-off that is much younger than that applied in the general population, given the higher rates of osteoporosis and fracture among PLWH. The recommendations for cancer screening are not different from those for the general population. However, aggressive screening for lung cancer for high-risk patients should be emphasized given the high prevalence of smoking among PLWH.

The most recent 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines on the management of cholesterol in the general population, expanded the indication for statin use for the primary and secondary prevention of atherosclerotic CVD (Stone et al., 2014). These new guidelines introduce a new method for calculating cardiovascular risk called the pooled cohort equation (PCE). Individuals with a PCE score of ≥7.5%, even in the absence of diabetes, dyslipidemia, or prior history of a CVD, are recommended to use statins for the primary prevention of CVD. Validation studies in the general population have shown that the PCE overestimates the true risk of CVD by as much as 150% (Ridker and Cook, 2013). In contrast, studies in the HIV-positive population have shown that the PCE underestimates cardiovascular risk among PLWH (Thompson-Paul et al., 2016; Regan et al., 2015). Despite this discrepancy, the use of CVD risk assessment tools is still strongly advocated, especially in the aging HIV-infected population (Grinspoon et al., 2008).

Statins are underutilized among PLWH. In a cohort of HIV-positive patients who were older than 40 years at the Washington University Virology Clinic, two-thirds were not prescribed statins despite a strong indication for their use based on the new ACC/AHA guidelines (Non et al., 2017b). Prescriber-related factors may serve as a major driver for the underutilization of statins. A survey was conducted of all physicians who take care of HIV patients at Washington University and it was found that most providers had some awareness of the 2013 ACC/AHA guidelines, but few routinely used the PCE calculator in their practice (Non et al., 2017c). The top three barriers to prescribing statins identified were concerns for drug–drug interaction, polypharmacy, and poor medication adherence.

Addressing health disparity

As the population ages, the health disparities based on sexual orientation, ethnicity, socioeconomic status, and disability widen. Thus, successful aging is fundamentally allied to narrowing the gap in health outcomes between different population groups. This requires a concerted effort from the patient (i.e., personal responsibility for his/her health), the physician (i.e., cultural sensitivity, non-discrimination policy, delivery of excellent, cost-effective, and evidence-based care), the healthcare system (i.e., improvements in access to medical care, provision of universal insurance coverage), and the government (i.e., national leadership, consistent and bipartisan efforts, promotion of medical and social research). In addition, a targeted intervention to promote social engagement among HIV-infected MSM is necessary to address longstanding social stigma and social isolation. Social support and social network size have been shown to be positively associated with physical and mental health in older MSM (Fredriksen-Goldsen et al., 2015). Together with health-promoting behaviors (i.e., physical activity, avoidance of smoking, avoidance of alcohol/substance use), social support contributes to resilience, i.e., the ability to adapt well in the face of adverse circumstances (e.g., disability, chronic illnesses). In the general population, resilience despite physical and cognitive impairments has been associated with successful aging (Jeste et al., 2013).

Ongoing research on chronic inflammation

Like all cellular components of the body, the immune system undergoes age-associated remodeling. Considered a hallmark of aging, these changes are characterized by alterations in T-cell subtypes and T-cell function ('immunosenescence') and increased levels of inflammatory cytokines and markers of immune activation ('inflammaging') (Lopez-Otin et al., 2013). These changes manifest as poor response to vaccination, increased susceptibility to infection, and higher risk of cancer, CVD, and death in the elderly. These changes that occur in the immune system with normal aging show similarities with processes that occur in HIV infection (Deeks, 2011).

The increased levels of inflammation prior to ART contribute to immune suppression and mortality among HIV-positive individuals (Kalayjian et al., 2010; Ledwaba et al., 2012). ART effectively suppresses HIV to undetectable levels in the blood but fails to eradicate infection. Studies have shown that despite suppressive ART, the level of HIV-associated inflammation decreases but remains elevated compared to individuals without HIV. The contribution of this residual inflammation among patients receiving fully suppressive ART to the development of non-AIDS-defining illnesses and mortality remains unclear. Some studies have shown that among individuals with fully suppressed HIV, markers of inflammation, coagulation, and gut microbial translocation remain significantly associated with all-cause mortality after adjusting for traditional risk factors (Tien et al., 2010; Tenorio et al., 2014; Hunt et al., 2014). Another study demonstrated that markers of TNF-α activation were significantly associated with incident type 2 diabetes (Brown et al., 2010). However, these studies are limited because of residual confounding. For example, important variables such as family history of premature CVD, smoking, composite Framingham risk, and more importantly, socioeconomic status, are not always included in the regression models used in these studies. The latter, like age, is a powerful predictor of morbidity and mortality (Stringhini et al., 2017; Tobias, 2017). However, large databases of HIV-positive individuals used for research often fail to or under-represent this important variable.

Whether decreasing residual inflammation further after the achievement of full virological suppression and/or robust immunological recovery (CD4+ T-cell count >500 cell/ml) with ART will lead to a further reduction in mortality and morbidity among PLWH remains unknown. Statins have emerged as the leading candidate drugs in potentially curbing the effects of inflammation. Studies in the general population have shown that statin therapy decreases chronic inflammation and reduces all-cause mortality by 14% (Taylor et al., 2013). In PLWH, statins have been shown to modestly reduce chronic inflammation and immune activation among individuals who are treatment-naïve (Ganesan et al., 2011). Among individuals receiving stable ART, the data are mixed. Data from Stopping Atherosclerosis and Treating Unhealthy Bone with Rosuvastatin in HIV (SATURN-HIV) showed a significant reduction in inflammation after 48 weeks of rosuvastatin in individuals receiving ART (Funderburg et al., 2015). However, in that study, 22% of the participants were not virologically suppressed. In a study that restricted enrolment to patients with full virological suppression on stable ART, atorvastatin did not lead to further reductions in the levels of inflammation, although it resulted in significant changes in lipid profile over the study period (Nixon et al., 2017).

In retrospective studies, statins have been shown to reduce all-cause mortality, decrease malignancy risk, and lower cirrhosis risk among HIV/HCV-co-infected patients (Lang et al., 2015; Moore et al., 2011; Overton et al., 2013; Chao et al., 2011; Galli et al., 2014; Oliver et al., 2016). It must be noted, however, that other studies have not shown a mortality benefit with statin use (Overton et al., 2013; Krsak et al., 2015; Rasmussen et al., 2013). Statin therapy has also not been shown to reduce bone loss in a randomized trial of HIV-positive subjects receiving suppressive ART (Erlandson et al., 2016). Of note, retrospective studies have not shown a benefit of statin therapy for CVD risk reduction (e.g., myocardial infarction, stroke) among individuals on stable ART (Overton et al., 2013; Krsak et al., 2015). However, statin use has been shown in randomized controlled trials to improve surrogate markers of CVD among individuals with mostly suppressed viremia (e.g., carotid intima media thickness, arterial inflammation) (Lo et al., 2015; Longenecker et al., 2016). The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE), the first randomized controlled trial designed to determine whether statin therapy would reduce cardiovascular events among HIV-infected individuals, is currently ongoing. Results from this multicenter study will provide more insights into the benefits of statin use in the primary prevention of CVD among HIV-infected persons.

Future directions

Future studies that aim to understand the pathophysiology and contribution of the residual inflammation among HIV-infected individuals on fully suppressive ART should be pursued. It remains unknown whether age-associated inflammation will aggravate residual HIV-associated inflammation in these patients over time. These studies, together with HIV cure research, represent significant challenges in the path towards successful aging. Future research should also take advantage of the low-hanging fruit in this path towards successful aging. These include improving the cascade of HIV care and addressing health disparity, increasing the proportion of HIV-infected persons who are receiving suppressive ART and maintained in care, using safer antiretroviral medications, and improving the uptake of primary care preventative guidelines among HIV-infected persons including statin therapy, lifestyle modification, smoking cessation, and the treatment of risk factors.

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Conflict of interest

The authors do not have any conflicts of interest.

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