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Aging, Health, and Quality of Life for Older People Living With HIV in Sub-Saharan Africa: A Review and Proposed Conceptual Framework

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Abstract

Objective—The number of people living with HIV (PLWH) over 50 years old in sub-Saharan Africa is predicted to triple in the coming decades, to 6-10 million. Yet, there is a paucity of data on the determinants of health and quality of life for older PLWH in the region.

Methods—A review was undertaken to describe the impact of HIV infection on aging for PLWH in sub-Saharan Africa.

Results—We (a) summarize the pathophysiology and epidemiology of aging with HIV in resource-rich settings, and (b) describe how these relationships might differ in sub-Saharan Africa, (c) propose a conceptual framework to describe determinants of quality of life for older PLWH, and (d) suggest priority research areas needed to ensure long-term gains in quality of life for PLWH in the region.

Conclusions—Differences in traditional, lifestyle, and envirnomental risk factors, as well as unique features of HIV epidemiology and care delivery appear to substantially alter the contribution of HIV to aging in sub-Saharan Africa. Meanwhile, unique preferences and conceptualizations of quality of life will require novel measurement and intervention tools. An expanded research and public health infrastructure is needed to ensure that gains made in HIV prevention and treamtent are translated into long-term benefits in this region.

Keywords

HIV/AIDS; sub-Saharan Africa; aging; gerontology; inflammation; noncommunicable diseases

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The Aging of People Living With HIV (PLWH) in Sub-Saharan Africa

HIV is a CD4+ T-cell tropic virus that, if untreated, results in an accelerated acquired immunodeficiency and death for the vast majority of those infected. However, the advent of combination of antiretroviral therapy (ART), which inhibits HIV viral replication and enables repopulation of target immune cells, can convert the disease from a routinely fatal infection to a treatable, chronic disease (Hammer et al., 1997; Palella et al., 1998).

At the turn of the 21st century, ART access was largely restricted to research-rich settings. However, over the past 15 years, massive global investments have been made into HIV care programs in sub-Saharan Africa (Bendavid, Holmes, Bhattacharya, & Miller, 2012; El-Sadr et al., 2012), where more than 25 million people are infected and the adult prevalence of HIV reaches more than 20% in multiple countries. (UNAIDS Global AIDS Epidemic Update) These investments, which have enabled more than 12 million people in the region gain access to ART, have resulted in significant reductions in AIDS-related mortality (Bor, Herbst, Newell, & Barnighausen, 2013; Mills et al., 2011; Nsanzimana et al., 2015; Reniers et al., 2017). Some of the best evidence for this benefit comes from South Africa, which is home to more than 7 million PLWH and the world's largest HIV epidemic. A demographic and health survey following nearly 100,000 individuals in the KwaZulu-Natal Province has demonstrated that, in the 8 years after implementation of large-scale ART distribution, the *general* population life expectancy increased from 49 to 61 years, and these gains were fully accounted for by increases in life span among PLWH (Bor et al., 2013). Similar improvements in life expectancy have been reported in Uganda and Rwanda among PLWH (Mills et al., 2011; Nsanzimana et al., 2015); and life expectancies in the region for PLWH who access ART are now approaching those of uninfected individuals (Johnson et al., 2013; Mills et al., 2011).

Consequently, the number of PLWH in sub-Saharan Africa above 50 years old is predicted to triple in the coming decades; to up to 10 million by 2040 (Hontelez et al., 2012). Despite these gains, and multiple calls for research and public health programs aimed at enhancing quality of life for older aged PLWH (Green, 2016; High et al., 2012; Mills, Barnighausen, & Negin, 2012; Negin, Barnighausen, Lundgren, & Mills, 2012), there is a paucity of data on the determinants of health and quality of life for older PLWH in the region. This review will summarize what is known about the pathophysiology and epidemiology of aging with HIV in developed settings, how these relationships might differ in sub-Saharan Africa, and discuss priority research areas to ensure that the benefits realized by providing ART to PLWH in sub-Saharan Africa are translated into long-term gains in health and quality of life.

Pathophysiology of Aging With HIV in Developed Settings

Heightened Risk of Noncommunicable Disease With HIV in Developed Settings

In resource-rich settings, the discovery that combination ART improves survival (Hammer et al., 1997; Mocroft et al., 1998; Palella et al., 1998) was followed by the realization that PLWH were at higher risk of non-AIDS-related comorbidities, including cardiovascular disease (D:A:D Study Group et al., 2008; Friis-Moller et al., 2007; Obel et al., 2007; Triant, Lee, Hadigan, & Grinspoon, 2007), cancer (Engels et al., 2006; Smith et al., 2014), and

geriatric syndromes such as frailty and decreased physical functioning (Desquilbet et al., 2007; Greene et al., 2015; Greene, Justice, Lampiris, & Valcour, 2013; Gustafson et al., 2016; Pathai, Gilbert, et al., 2013; Piggott et al., 2013). Traditional risk factors only partially account for the increased risk of many of these comorbidities among PLWH (Justice & Braithwaite, 2012; Rodriguez-Penney et al., 2013). ART regimen toxicities were once thought to also be the major cause (Friis-Moller et al., 2007; Sabin et al., 2016); however, this hypothesis has been convincingly rejected, because ART-mediated virologic suppression has been subsequently demonstrated to significantly decrease the incidence of most chronic comorbidities and mortality among PLWH (El-Sadr et al., 2006; The INSIGHT START Study Group et al., 2015).

Chronic Inflammation and Noncommunicable Disease Risk With HIV in Developed Settings

Instead, immune activation caused by direct HIV infection of end-organ tissues (Dube et al., 2008; Eugenin et al., 2008) and coinfections (Hunt et al., 2008; Sylwester et al., 2005; Wilson et al., 2014) is thought to precipitate chronic activation of both innate and adaptive immunologic pathways (Boasso & Shearer, 2008; Esser et al., 2001; Hardy, Graham, Shearer, & Herbeuval, 2007; Martin et al., 2013). This phenomenon persists despite suppressive ART (French, King, Tschampa, da Silva, & Landay, 2009; Hearps et al., 2012; Hunt et al., 2003). Moreover, HIV infection promotes the so-called senescence-associated secretory phenotype (Coppe, Desprez, Krtolica, & Campisi, 2010), characterized by proliferation of $CD8^{+}CD57^{+}CD28^{-}$ T-lymphocytes, which have been implicated in increased cytokine production (Macaulay, Akbar, & Henson, 2013), decreased naïve T-cell precursor populations, diminished humoral immunity, and attenuated vaccine responses (Xie & McElhaney, 2007). For example, virologically suppressed PLWH have higher relative populations of $CD8^{+}CD57^{+}CD28^{-}$ T-lymphocytes as HIV-uninfected individuals of the same age and similar levels to those decades older (Desai & Landay, 2010; Serrano-Villar et al., 2014).

The resulting inflammatory state as well as markers of immune senescence have been correlated with frailty, neurocognitive dysfunction, functional impairment, and mortality in older aged PLWH (Brothers & Rockwood, 2014; Deeks, 2011; Erlandson et al., 2013; Hsu et al., 2016; Knudsen et al., 2016; S. A. Lee et al., 2014; Lyons et al., 2011; Piggott et al., 2015; Tien et al., 2010). The association of HIV infection with the frailty phenotype has been consistently reported across HIV cohorts. In the Women's Interagency HIV Study, women with low CD4 counts had 2 to 3 times the odds of frailty (as measured by the Fried Frailty Phenotype Criteria; Fried et al., 2001) compared with HIV-uninfected women independent of age (Gustafson et al., 2016). The Multicenter AIDS Cohort Study (MACS) also reported increased odds of the frailty phenotype, as measured by an adapted Fried scale that removed the grip strength criterion and substituted self-reported measures for gait speed, among men living with HIV with greater duration of HIV infection (adjusted odds ratio [AOR] 3.4 for HIV duration <4 years, AOR > 12 for HIV duration >4 years; Desquilbet et al., 2007). Intriguingly, in the Veterans Aging Cohort Study (>95% male), which used a similar adapted version of the Fried criteria to the MACS investigators, frailty also appeared to be more common in PLWH with active viremia than HIV-uninfected comparators but less common among PLWH with a suppressed viral load (Akgun et al., 2014). Physical

functioning, measured by both self-report (Oursler et al., 2011) and using the Short Physical Functioning Battery (Greene et al., 2014), has also been consistently shown to be impaired in PLWH versus age-matched HIV-uninfected counterparts. Importantly, decreased physical function and a frailty phenotype appear to be both of greater severity and develop at younger ages among PLWH in developed settings (Desquilbet et al., 2007; Gustafson et al., 2016; Oursler et al., 2011), leading some to consider HIV a cause of both accelerated and accentuated aging (Pathai, Bajillan, Landay, & High, 2014). For example, in the MACS cohort, the prevalence of a frailty phenotype was similar in recently infected PLWH less than 55 years old as in HIV-uninfected men greater than 65 years (Desquilbet et al., 2007).

Chronic Comorbidities and Inflammation With HIV in Sub-Saharan Africa

Traditional Chronic Disease Risk Factors Vary in Sub-Saharan Africa

Yet, extrapolation of these data to the sub-Saharan African region, where more than two thirds of PLWH reside, should be done cautiously. Differences in genetics, the social-environmental milieu, timing of ART initiation, commonly used ART regimens, and prevalence of coinfections in sub-Saharan Africa will almost certainly alter the risk profile and morbidity phenotypes among PLWH. For example, rates of smoking and alcohol use, diet and physical activity patterns (Amare et al., 2012; Guthold et al., 2011; Steyn, Nel, Parker, Ayah, & Mbithe, 2011), the epidemiology of HIV coinfections (Appay et al., 2011; Borkow & Bentwich, 2004; Cannon, Schmid, & Hyde, 2010; de Mast et al., 2015; Elliott, Summers, & Weinstock, 2007; Hochman & Kim, 2009; Hsue et al., 2006; Turner et al., 2003), nadir CD4 counts (M. J. Siedner, Ng, et al., 2015), and recommended first- and second-line regimens (World Health Organization, 2016) are markedly different in sub-Saharan Africa than in the United States and Europe.

Such differences have been particularly apparent in studies measuring prevalence of chronic comorbidities and their traditional risk factors among PLWH in sub-Saharan Africa. In the Ugandan Non-Communicable Diseases and Aging Cohort Study (Clinicaltrials.gov registration number: NCT 02445079), a population-based cohort study in rural Uganda which includes both PLWH on suppressive ART and age and gender-matched HIV-negative comparators (Siedner et al., 2016, #443), more than 70% of PLWH meet World Health Organization (WHO) criteria for high physical activity, less than 10% are current smokers, and less than 5% have a fasting low-density lipoprotein greater than 130 mg/dL (Feinstein et al., 2017). In stark contrast to cohort studies from the United States, PLWH were less likely to be active smokers, and had better blood pressure and diabetes control. Studies from elsewhere in the African region have also generally demonstrated a lower prevalence of obesity and hypertension among PLWH compared with HIV-uninfected comparators (Gaziano et al., 2017; Kwarisiima et al., 2016; Malaza, Mossong, Barnighausen, & Newell, 2012).

Although reductions in hypertension prevalence might be partially attenuated after ART initiation (Okello et al., 2016; Okello et al., 2015; Peck et al., 2014), a growing body of literature argues that the HIV care infrastructure in sub-Saharan Africa might offer secondary benefits through primary care delivery and improved chronic disease risk factor management (Gupta & Bukhman, 2015; Manne-Goehler et al., 2017). Yet, whereas many of

the traditional cardiovascular disease risk factors appear to be decreased in HIV infection in sub-Saharan Africa, arterial stiffness (Siedner et al., 2016, stroke (Benjamin et al., 2015), and cancer (Dryden-Peterson et al., 2015) preliminarily appear to be associated with HIV infection in the region. Taken together, these results highlight the need to collect data on regional risk factors for chronic comorbidities among older PLWH, which are likely to alter the disease profile of the population (Figure 1; Alwan et al., 2010; Riha et al., 2014).

Chronic Inflammation With HIV in Sub-Saharan Africa

There is likewise compelling evidence for altered inflammatory pathways among PLWH in rural Africa (Anthony, Rutitzky, Urban, Stadecker, & Gause, 2007; Banerjee, Mondal, Das, & Ray, 2012; de Mast et al., 2015; Dutta, Ray, & Banerjee, 2012; Geffken et al., 2001), compared with the United States and Europe. For example, the Ugandan AIDS Rural Cohort Study has demonstrated novel elevations in indoleamine 2,3-dioxygenase (IDO) activity among PLWH in Uganda, resulting in increased tryptophan metabolism and an increased kynurenine:tryptophan ratio (K:T). This alteration in tryptophan metabolism, which has since been additionally reported elsewhere in the region, including urban areas of South Africa (Bipath, Levay, & Viljoen, 2015), has been associated with an increased risk of atherosclerosis, depression, AIDS-related cancer, and all-cause mortality (Byakwaga et al., 2015; S. Lee et al., 2017; Martinez et al., 2014; M. J. Siedner, Kim et al., 2015).

Multiple groups in the region have also demonstrated key differences in inflammatory marker profiles in sub-Saharan Africa compared with U.S.-based cohorts. Three such markers—sCD14, a biomarker of innate immune activation; IL-6, a generalized marker of systemic inflammation; and sCD163, a specific marker of macrophage activation—have been systematically demonstrated to be elevated among PLWH compared with HIV-uninfected comparators in the United States and Europe, and independently associated with cardiovascular events, the frailty phenotype, and mortality, despite suppressive ART (Duprez et al., 2012; Hsu et al., 2016; Knudsen et al., 2016; Kuller et al., 2008; S. A. Lee et al., 2014; Leng, Chaves, Koenig, & Walston, 2002; Lien et al., 1998; Longenecker et al., 2014; Mendez-Lagares et al., 2013; Sandler et al., 2011; Wada et al., 2015). In Uganda, however, although we have found significantly increased levels of sCD14 in PLWH versus community-based, HIV-uninfected comparators ($p < .001$), we found no differences by serostatus in IL-6 or sCD163 ($p > .40$ for both, unpublished data). Other cohort studies from South Africa and Uganda comparing HIV-uninfected individuals with PLWH on and off ART have also failed to detect significant differences in IL-6 by HIV serostatus (Fourie, Schutte, Smith, Kruger, & van Rooyen, 2015; Olwenyi et al., 2016).

Although markers of systemic inflammation and immune activation might be muted in sub-Saharan Africa, the single study that has assessed molecular aging among PLWH in sub-Saharan Africa did demonstrate evidence of accelerated aging. Shorter telomeres and greater CD2NKA leukocyte expression, which is inversely related to cellular replicative capacity, were found in PLWH compared with age- and sex-matched HIV-uninfected comparators, and low CD4 counts predicted accelerated biological aging (Pathai, Lawn, et al., 2013).

Nontraditional Chronic Disease Risk Factors in Sub-Saharan Africa

While the mechanisms that drive these putatively unique inflammatory pathways require further study, early evidence points to genetic, environmental, and coinfection exposures. For example, a polymorphism has been identified that might predispose populations in Uganda to increased IDO activity, resulting in increased K:T ratio (S. A. Lee et al., 2016). Biomass cooking fuel exposure, which is a another distinctively regional risk factor (Brook et al., 2010; Salvi & Barnes, 2009), is independently associated with carotid atherosclerosis (Painschab et al., 2013), cardiovascular disease events (Brook et al., 2010; M. S. Lee et al., 2012), and chronic obstructive pulmonary disease (Salvi & Barnes, 2009), and shares pathways of systemic inflammation, immune activation, oxidative stress, and pulmonary epithelial barrier dysfunction with HIV infection (Ghio & Devlin, 2001; Hajat et al., 2015; Hu et al., 2013; Li, Gilmour, Donaldson, & MacNee, 1996; Park et al., 2011; Rylance et al., 2015; Sussan et al., 2014). The potential impact of air pollution on health of PLWH is further supported by the fact that nonsmoking exposures account for more than 50% of cardiopulmonary disease (COPD)-associated mortality in males and more than 80% of COPD-associated mortality in females in low- and middle-income countries (Eisner et al., 2010).

Highly prevalent tropical coinfections might similarly differentiate interactions between HIV, inflammation, and chronic disease risk in resource-poor settings. For example, malaria immunity and susceptibility are reduced in HIV infection (Finney et al., 2013; Hochman & Kim, 2009), and malaria infection triggers HIV viral replication (Hoffman et al., 1999). Subclinical malaria has been associated with elevated markers of immune activation in adults (de Mast et al., 2015), and malaria infection has recently been shown to induce a chronic proinflammatory response among HIV-infected apes (Trott, Richardson, Hudgens, & Abel, 2013). Soil-transmitted helminth infections are also highly endemic in much of sub-Saharan Africa, (Kabatereine et al., 2005; Karagiannis-Voules et al., 2015), induce complex effects on gut and systemic immunity, and unlike HIV, cytomegalovirus (CMV) and malaria, activate Th2 immune responses (Anthony et al., 2007; Salgame, Yap, & Gause, 2013). Whereas prior studies have investigated relationships between CD4 count trajectories and helminthic infection and HIV treatment (Lankowski et al., 2014; Walson et al., 2012), less is known about how these intestinal infections alter gut immunity, microbial translocation, and chronic immune activation among PLWH in the region.

Contributions of HIV to Geriatric Syndromes in Sub-Saharan Africa

Whereas chronic morbidity prevalence estimates in sub-Saharan Africa abound, much less has been described on multifactorial geriatric syndromes, functioning, and disability among older aged PLWH in the region. Such syndromes are more predictive of self-reported health, healthcare utilization, and mortality than classical medical syndromes in developed settings (Koroukian et al., 2016; Wang, Shamliyan, Talley, Ramakrishnan, & Kane, 2013). Consequently, defining their epidemiology might illustrate more global determinants of well-being for older PLWH in the region. To date, data have been contrasting about relationships between HIV and geriatric syndromes in sub-Saharan Africa. A cross-sectional study from South Africa including clinic-based PLWH in care and community-based

controls found more than twice the odds of frailty among PLWH, defined using an adapted version of the Fried Frailty Scale (Pathai, Gilbert, et al., 2013). This finding is in keeping with similar estimates about HIV and a frailty phenotype from the United States as described above. In contrast, baseline data from the large community-based, Health and Aging in Africa Longitudinal Study in South Africa (HAALSI) have demonstrated a similar occurrence of age-adjusted, self-reported disability and functioning between relatively old age PLWH (greater than 40 years) and HIV-uninfected comparators, and faster gait speeds among PLWH (Payne, Gomez-Olive, Kahn, & Berkman, 2017). Similarly, a study comparing functioning, disability, and chronic comorbidities between older PLWH (>50 years) and age-matched HIV-affected individuals (family member with HIV or loss of family member to HIV) in Uganda found generally similar rates of disability and comorbidity between groups (Scholten et al., 2011). Given these contrasting findings, a clear priority for the region is to better classify both the locally relevant syndromes which comprise health and functioning for older PLWH in the region, and expand data collection to comprehensively describe their prevalence and determinants.

The epidemiology of cognitive deficits with HIV infection in sub-Saharan Africa, as well as contributions from inflammation and local risk factors, also remains poorly defined. In the pre-ART era in the United States and Europe, HIV was associated with frank dementia at early age (Sacktor et al., 1996). This syndrome has become rare after widespread ART availability, replaced with more subtle HIV-associated neurocognitive deficits (McArthur, Steiner, Sacktor, & Nath, 2010; McCutchan et al., 2007). Chronic immune activation of central nervous system macrophages is hypothesized to mediate this condition (Saylor et al., 2016). In sub-Saharan Africa, advanced HIV is most strongly associated with neurocognitive deficits, and ART similarly mitigates the prevalence and severity of these deficits (Habib et al., 2013). However, there are few data on the pathophysiologic processes responsible. Moreover, whether the heightened risk of central nervous system infections (e.g., cryptococcal meningitis, childhood cerebral malaria, tuberculous meningitis) as well as nutritional and metabolic factors that are considerably more common in sub-Saharan Africa affect these relationships remains an important, but an unexplored, area of study.

Quality of Life for Older PLWH in Sub-Saharan Africa

Importantly, significant work also remains in bridging the gap between medical conceptualizations of health and more global elements of well-being among PLWH in sub-Saharan Africa. To date, the lion's share of research on quality of life among PLWH in the sub-Saharan African region has focused on the impact of ART on health-related quality of life. Not surprisingly, these studies have identified strong and rapid gains in quality of life after ART initiation (Louwagie et al., 2007; Pitt, Myer, & Wood, 2009; Wouters, Meulemans, Van Rensburg, Heunis, & Mortelmans, 2007). Most of these studies have relied on structured scales with a specific focus on health-related quality of life, such as EuroQOL (EuroQol, 1990), which have been validated in sub-Saharan African populations for this purpose (Jelsma & Ferguson, 2004; Jelsma, Mkoka, Amosun, & Nieuwveldt, 2004), including among PLWH (Jelsma, Maclean, Hughes, Tinise, & Darder, 2005). In addition to expected gains in quality of life after ART initiation, these data help shed light on other health system factors that might contribute to the quality of life for PLWH in sub-Saharan

Africa. For example, accessing additional HIV/AIDS-related services, being visited by community health workers, and having HIV treatment supporters were associated with increasing health and/or emotional quality of life, and speak to the ability of the formal healthcare and public health institutions to affect well-being for PLWH in the region (Booysen Fle, Van Rensburg, Bachmann, Louwagie, & Fairall, 2007).

A limitation of many of the studies that describe quality of life among PLWH is the narrow focus on physical and health-related quality of life at the exclusion of more global elements of well-being, particularly in aging populations (Higgs, Hyde, Wiggins, & Blane, 2003). Qualitative work in the United States on psychosocial determinants of healthy aging and coping mechanisms for older aged PLWH has often identified coping domains related to self-reliance, drug use, and accessing support from networks of other PLWH (DeGrezia & Scrandis, 2015; Emlet, Tozay, & Raveis, 2011; Psaros et al., 2015).

In contrast, definitions and expectations of health and aging in sub-Saharan Africa tend to focus more on obligations to family and social networks (Mudege & Ezeh, 2009). Indeed, available formative data suggest that quality of life in older aged groups is defined as a capacity to meet expectations related to family roles and responsibilities (Ogunmefun, Gilbert, & Schatz, 2011; Schatz, 2007; Schatz & Gilbert, 2014; Ssengonzi, 2009). Moreover, the pervasiveness of the HIV epidemic and its high mortality in young adults early in the epidemic have frequently altered these roles, and in many cases increased obligations of (and burdens on) older aged family members (Kautz, Bendavid, Bhattacharya, & Miller, 2010; Madhavan & Schatz, 2007; Mudege & Ezeh, 2009; Muga & Onyango-Ouma, 2009). Specifically, the classic role of the younger generation family member as the caregiver and income generator for both young and elderly adults has often been reversed (Schatz, 2007; Schatz & Gilbert, 2014), and may be of particular relevance for female-headed households (Schatz, Madhavan, & Williams, 2011). Critical areas of future reserach include studies to better estimate how PLWH alters the risk of chronic diseases among older-individuals, and how the regional public health system will help relieve any additional burden on familial caregivers Bendavid, Ford, & Mills, 2012; de-Graft Aikins et al., 2010; Kautz et al., 2010).

Thus, developing a conceptual framework to better describe contributors and barriers to quality of life for older aged PLWH in sub-Saharan Africa will be a critical addition to the field, and necessary to design future studies and interventions to improve health in these populations. Recently, preliminary work has begun to accomplish this goal by establishing the consistency and validity of more global quality of life measures in PLWH in Eastern Africa. The Functional Assessment of HIV Infection Score intends to more broadly consider domains of physical, emotional, functional/global, social and cognitive well-being (Cella, McCain, Peterman, Mo, & Wolen, 1996; O'Brien et al., 2010). It has recently been evaluated and adapted in Kenya with reasonable internal consistency and preliminary evidence of external validity (Nyongesa et al., 2017). Of interest in this study was the relatively low factor loadings and low correlation observed between social and cognitive functioning subscores and external functional measures, compared with the physical and emotional functioning subscores, suggesting that global conceptualizations of well-being for aging PLWH are likely to differ in ways that will require novel frameworks, data collection tools, and interventions that focus on unique domains of aging.

A Conceptual Framework for Aging With HIV in Sub-Saharan Africa

Proposed here is a conceptual framework that incorporates the relevant data from the field as summarized above to describe determinants of health-related quality of life for older aged PLWH in rural sub-Saharan Africa (Figure 2). The framework incorporates a syndromic approach to gerontology (Fried et al., 2001; Mitnitsky, Mogilner, & Rockwood, 2001) to include domains of physical, cognitive, and social functioning (Rubtsova et al., 2017; Thurn & Gustafson, 2017). It includes key determinants of these domains derived from prior work on HIV and aging in the United States, which have demonstrated independent effects of HIV-related inflammation on domains of physical and neurocognitive functioning (Erlandson et al., 2013; Lyons et al., 2011; Scully et al., 2016). It also adds locally relevant elements described in qualitative studies among older aged PLWH in Kenya and South Africa, which demonstrate the importance of familial deaths, and their impact on caregiving and household responsibility structures (Madhavan & Schatz, 2007; Mudege & Ezeh, 2009; Muga & Onyango-Ouma, 2009), as well as the importance of HIV stigma, which disrupts access to social support mechanisms in this population (Takada et al., 2014; Tsai et al., 2013). The framework intends to serve as a launching point for future work both to validate and to alter these conceptualizations, and further priority public health and research domains for older PLWH in the sub-Saharan African region.

Knowledge Gaps and Future Research Priorities

Notwithstanding over two decades of research on the HIV epidemic in sub-Saharan Africa that have revealed the devastation of the early epidemic, identified priority interventions to improve health, and documented extraordinary gains with implementation of ART programs, there remains a paucity of data on the determinants of well-being among older PLWH in sub-Saharan Africa. Critical to this process will be formative work that considers relevant domains to geriatric health, such as independence, functioning, and social well-being more broadly, and accounts for locally adapted features of quality of life. Such information will be required to ensure that data collection platforms and public health responses are targeted to locally established preferences for health and quality of life, and not transplanted conceptions of these domains that might be relevant to other regions.

Additional quantitative data are needed to specify biomedical, psychosocial, and environmental determinants of health and quality of life, and their relative contributions to both, for the many millions of people who have survived the AIDS epidemic into middle and late life. In the biomedical realm, there are vanishingly little data on priority causes of morbidity in sub-Saha-ran Africa among PLWH above the age of 45, the upper age limit of most demographic and health surveys, which have historically focused on child and maternal health. Because few countries have death registries in the region, most estimates on causes of death are derived from verbal autopsy, or modeling studies that predict disease burden based on general population prevalent morbidities assessed by the WHO Sage and 10/66 Dementia surveys (Kowal et al., 2010; Prince et al., 2007; Prince et al., 2015). However, few of these studies are powered to make conclusions by HIV serostatus, and they tend to focus on a handful of countries in sub-Saharan Africa—most notably South Africa—which is one of only six middle-income countries in the region.

Multicenter, longitudinal cohorts of PLWH and/or demographic health surveys that enroll sufficient PLWH and HIV-uninfected comparators could serve such a purpose. They must include both traditional and regionally relevant risk factor data, as well as incident morbidity, and mortality data to better discern health priorities for older PLWH. For example, the most compelling evidence that HIV infection is associated with non-AIDS conditions, including geriatric syndromes such as frailty and decreased physical functioning, has come from longitudinal studies in the United States and Europe, such as the MACS, the Women's Interagency Health Study, and the Veterans' Aging Cohort Study, which study both HIV-infected and uninfected populations (Currier et al., 2003; Freiberg et al., 2013; Hadigan et al., 2001; Kaplan et al., 2008; Kingsley et al., 2008; Klein et al., 2015; Seaberg et al., 2010). Plausible estimation of associations between HIV infection and chronic disease risk requires a well-matched comparator group, ideally enrolled from the community to minimize selection bias.

Finally, interventional studies, targeted at the individual, health center, and community level, will be needed to translate observational findings into improvements in health for older PLWH in sub-Saharan Africa. While many traditional interventions that focus on known determinants of health and quality of life (e.g., smoking cessation, exercise) may play a role, it is also highly likely that entirely new interventions will be necessary to improve health in the local context. This is due to both the unique risk factors and health determinants in the region (e.g., cooking fuel exposure, loss of familial caregivers in the HIV epidemic) and the profoundly different structure and capacity of healthcare delivery in the sub-Saharan African region.

An Actionable Public Health Response

The infrastructure supported by HIV care programs has built an ideal platform through which to evaluate and deliver sustainable interventions to address non-HIV-related health needs (Gupta & Bukhman, 2015). Currently, this HIV care system supports millions of individuals across the region to receive routine medical care through multiple annual visits with clinicians, pharmacists, counselors, and other ancillary staff with a primary goal of sustaining health. Thus, a foundation is in place to deliver interventions if priority targets and cost-effective approaches can be identified. Innumerable potential solutions could be envisioned that meet these criteria. As one example, if familial HIV-related deaths and their deleterious effects on social support and caregiver provision meaningfully undermine quality of life for older PLWH in the region, clinic-based solutions that target caregiver support have been found to be highly effective in such settings (Uebel, Nash, & Avalos, 2007).

Conclusion

To sustain the benefits of global investments in HIV care in sub-Saharan Africa, there is a need for increased research on determinants of health and quality of life for older aged PLWH in sub-Saharan Africa. To date, most studies of aging with HIV in the region have been cross-sectional, have focused on single morbidity domains (e.g., hypertension or obesity), and lack local insight about preferences for quality of life. Available evidence suggests that the determinants of quality of life among older aged PLWH in rural sub-

Saharan Africa differ meaningfully from those in the United States and Europe; and that elucidating these determinants and their relative contributions is essential to developing effective interventions to optimize health. Priority areas for future research on aging among PLWH include (a) developing locally and regionally validated conceptual frameworks to describe determinants of health and quality of life; (b) examining the characteristics and epidemiology of aging-related syndromes in this population; (c) assessing the contributions of genetic, environmental, sociodemographic, and HIV-specific (e.g., inflammatory, ART related) determinants; and (d) leveraging these data to develop and evaluate interventions that can meaningfully improve health and well-being for this population. The well-established HIV care infrastructure in the region affords a ready foundation on which to design such interventions. Failing to accomplish these goals risks squandering the extraordinarily successful investments made to extend the life of PLWH in the region.

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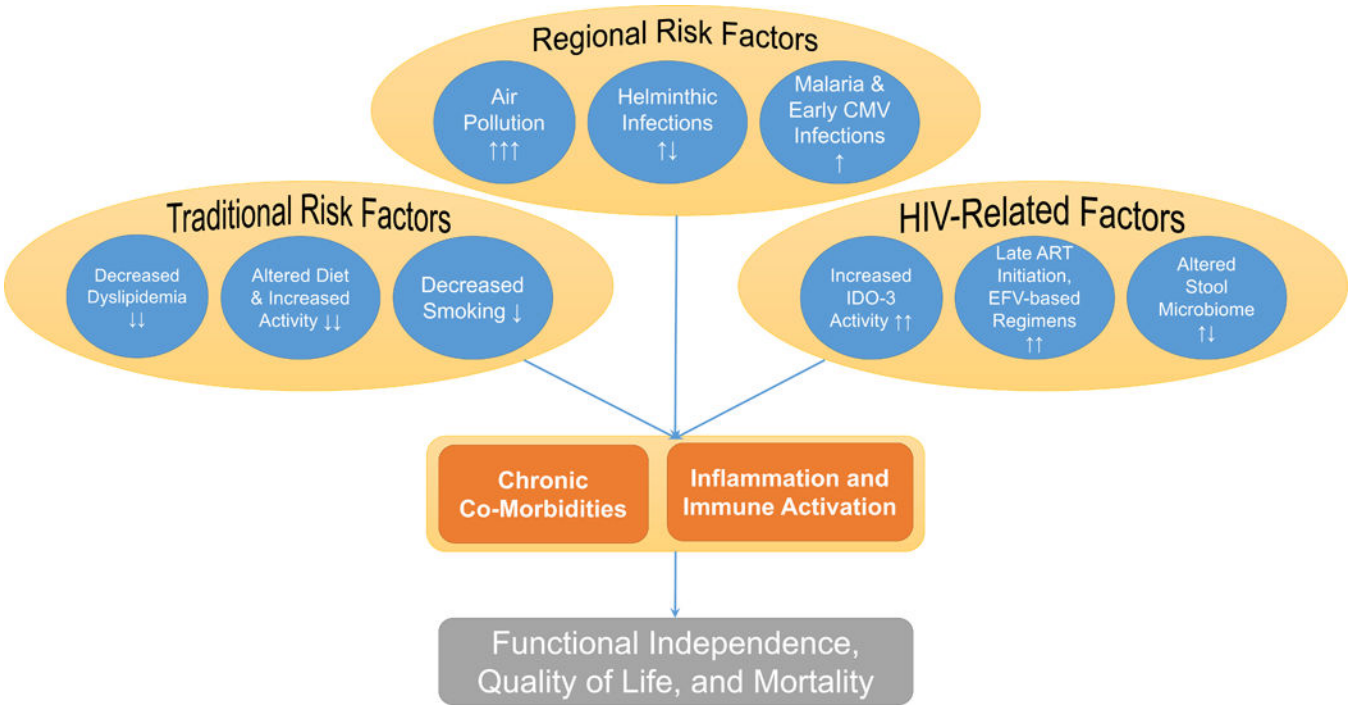

Figure 1.

Altered risk profile for cardiopulmonary disease risk among PLWH in rural sub-Saharan Africa.

Note. PLWH = people living with HIV.

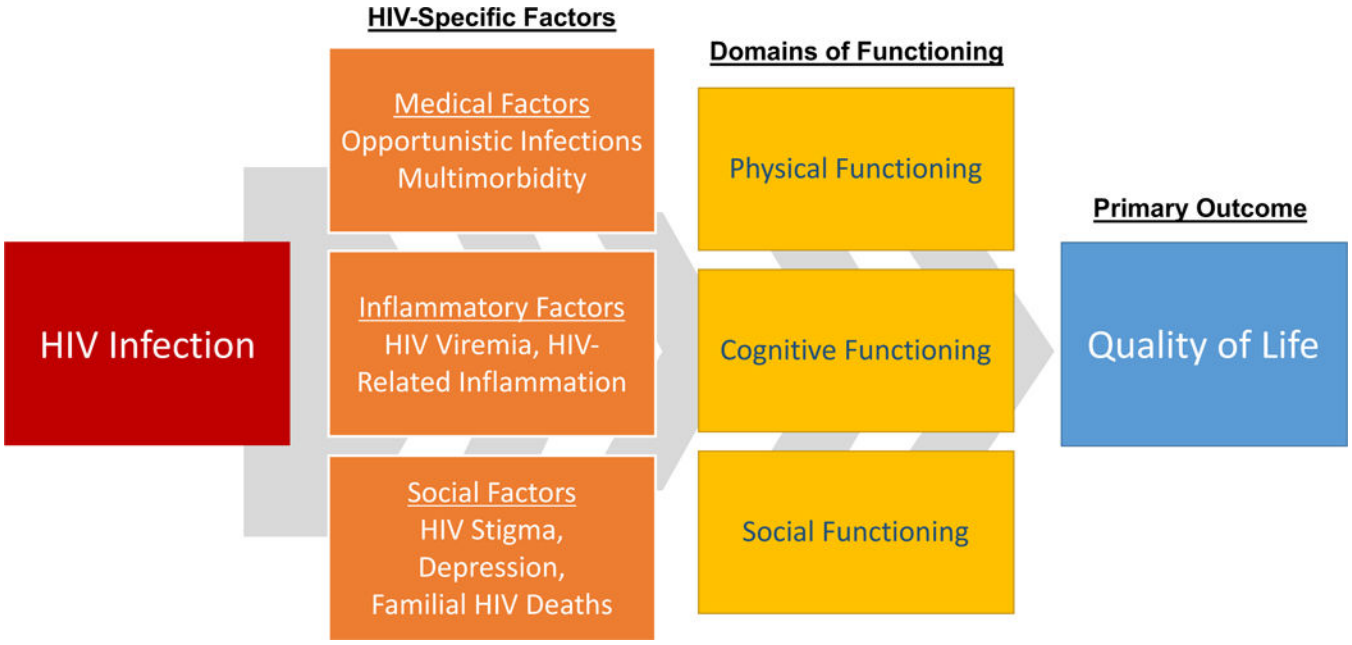

Figure 2.

Proposed conceptual framework to describe health-related quality of life for older aged PLWH in Uganda.

Note. PLWH = people living with HIV.