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REVIEW

How all-type dementia risk factors and modifiable risk interventions may be relevant to the first-generation aging with HIV infection?

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Abstract

Purpose The purpose of this review is to provide an overview of established risk factors for all-type dementia and results of interventions on dementia modifiable risk factors, all with relevance to aging people living with HIV (PLHIV).

Methods Narrative literature review.

Results Our review identifies a high prevalence of risk factors for dementia in the global HIV population that is entering dementia age range (60+), in relation to both traditional and HIV-specific risk factors. This includes age (HIV-related premature aging and possibly HIV-related accelerated brain aging and cerebrovascular injury), HIV-related and non-HIV-related cardiovascular diseases burden with related-vascular brain damage, HIV-associated neurocognitive disorders, high mental health burden, low educational/socio-economic status, historical immune compromise, and persistent immune activation with consequent augmented immune senescence. Our review highlights that the results of interventions on all-type dementia modifiable factors show discrepancies between positive observational study results and inconclusive clinical trials. The main reasons for such discrepancies relate to the preventative framework that complex interventions' trials have difficulty to emulate and the suboptimal measurement of cognitive change. Multi-domain intervention trials are now advocated to concomitantly tackle complex age-related comorbid profiles.

Conclusions The burden of dementia risk in aging PLHIV is higher than that in the general population, particularly in the most vulnerable clusters. Epidemiological studies are urgently needed to provide accurate estimates. Lessons from interventions trials in all-type dementia on modifiable factors need to be carefully considered for enhancing trials' potential in aging PLHIV. A comprehensive and preventative neurogeriatric healthcare response linked with HIV communities and dementia associations should be urgently put in place.

Keywords HIV/AIDS · Dementia · Risk factors · Aging · HIV-associated neurocognitive disorders · Interventions · Dementia modifiable risk factors

Aging people living with HIV infection (PLHIV)

Globally with increased access to potent antiretroviral therapy (ART), PLHIV live almost as long as the general population [1–3]. For the majority, HIV infection has transformed from a life-threatening illness to a chronic condition that requires long-term treatment and care [4, 5]. UNAIDS [6] estimated that there were 5.8 million PLHIV aged over 50 years in 2015, with 80% living in low and middle income countries. In 2000, only 8% of the global HIV population was over 50 years of age but in 2015 it has doubled to 16%, and is estimated to rise up to 22% by 2020. Smit et al. [7] predicted that the proportion of elders (those over 50 years of age) amongst PLHIV would increase up to 73% in 2030

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based on an HIV cohort in the Netherlands. In some countries such as the US and Brazil, the proportion of elders among PLHIV has already exceeded 50% [8].

The increase in the proportion of elders amongst PLHIV is also driven by an upward trend in acquisition and diagnosis of HIV at an older age [8–13]. As reported by the European Centre for Diseases Control and Prevention [14], HIV diagnoses have been increasing steadily among both males and females aged over 50 years of age between 2007 and 2016 across Europe. This also applies to African nations [15, 16].

Aging does not always mean happy and healthy aging for people with chronic HIV infection [17]. However, this message needs to be explained with nuances to avoid further stigma in the HIV population at large. On the one hand, it is clear that potent ART has led to major health improvements in the health of the HIV population and has reduced the occurrence of the most severe form of HIV-associated neurocognitive impairment, namely HIV-associated dementia (HAD) to a rare diagnosis (2–4% of advanced chronic HIV-infected people, and less in early treated PLWH). On the other hand, it is important to recognize that a life-long treated chronic illness whether it is HIV or for example Type I diabetes [18] carries some added risk for dementia as people age. We should, therefore, advocate for an adapted HIV neurogeriatric response and obtain accurate estimates of dementia as people enter the at-risk dementia ages (60 +). This should not be construed as "fear mongering" but rather as appropriate preparedness. It is now widely recognized that there is a pattern of multi-comorbidities in aging PLHIV, some of which are well-established risk factors for dementia [19]—as we will review.

The comorbidities burden is probably the most relevant question in terms of HIV neurogeriatric care, while it is still important to understand the role of HIV even if suppressed. A modeling study has projected that by 2030, about 85% of elderly PLHIV will have at least one non-AIDS comorbidity [7], many of which are recognized factors for dementia. Over or underestimation of comorbidities burden amongst elderly PLHIV is possible. Survival bias [9] and limited availability of research findings from low and middle income countries where limited resources contribute to a higher ill health burden may lead to under estimation of the age-related disease burden in some older PLHIV. On the other hand, late ART initiation (a prominent risk factor for comorbidities) in the majority of current older HIV cohort [20] could contribute to an over estimation of age-related conditions when compared with people who will eventually age and were treated early.

The aim of this review was to summarize the most robust evidence for all-type-of-dementia risk factors in the general population and then assess them with relevance to the global aging HIV population. We also consider HIV-specific factors that may further contribute to the added dementia burden in aging PLHIV. We also review the dementia prevention/reduction strategy literature and discuss the level of evidence and limitations with relevance to the aging HIV population. We conclude by proposing some directions in the translation of this research to aging PLHIV.

Risk factors for dementia in the general population

Our understanding of the underlying causes of dementia in the general population has advanced greatly over the past 20 years. There is now robust evidence from various longitudinal observational studies supporting the involvement of several risk factors, some of which are non-modifiable (e.g., age, genetics) and others that are modifiable (e.g., lifestyle and medical factors including vascular and psychosocial factors) [21, 22]. Importantly, some estimates suggest that modifiable risk factors account for 30–50% of dementia prevalence [23]. In this section, we provide a summary of the main risk factors of dementia from observational studies, and recent findings from intervention randomized clinical trials (RCTs).

Non-modifiable risk factors

Age

Advanced age is the strongest predictor for developing dementia. There is a clear and significant increase in the percentage of people living with dementia after 65 years of age, with a 2010 US population study reporting that the prevalence of Alzheimer's disease (AD) increases from an estimated 3% of people between ages 65–74 to 17% for ages 75–84 and 32% for those aged 85 + [24]. The same trajectory is seen when considering all-type dementia [25].

Age and HIV

Age as the number one risk factor for dementia should be specifically considered in the aging HIV population. Indeed, data are converging to show that there is evidence of premature systemic aging, but limited evidence of accelerated systemic aging [20, 26]. Similarly, the evidence for premature cognitive and brain aging is stronger than that for accelerated aging [27, 28]. However, this research is based on cohorts where most PLHIV are aged < 60 years old—well before the dementia age range. Furthermore, when looking at specific conditions (i.e., cerebrovascular diseases and stroke), the weight of evidence favors accelerated brain aging [29]. Using the surrogate of biological aging rather than chronological aging probably represents a better marker for the

aging process. For example, the prevalence of geriatric syndromes such as frailty [30–32], multimorbidity [12, 33], polypharmacy and disability [34] is higher amongst older PLHIV than the general population, and the syndromes are observed at a younger age than expected [26, 35–38]. In addition, the decline rate in physical activity is faster among seniors with HIV than without HIV [39]. Biological aging as measured by epigenetic aging shows evidence of both premature and accelerated aging in the HIV population [40] including in children [41, 42]. Overall, even if we only consider the premature age signal and greater age-prevalence of age-related conditions, this represents a major risk factor for dementia that is higher than in the general population. Its exact effect size determination demands large longitudinal studies with at least 50% age 60 + .

Dementia genetics

First-degree relatives of people with AD are at a slightly higher risk of developing AD themselves [43] and the risk increases when more than one first-degree relative is diagnosed [44]. The unique contribution of genes versus epigenetic and environmental factors is unclear. Over 20 genes have been identified that appear to influence a person's risk of developing dementia [45]. The most studied of these is apolipoprotein E (ApoE) which is particularly relevant for AD given its involvement in regulating β-amyloid metabolism, aggregation and deposition along with cerebrovascular functioning [46]. People with the ε4 allele variant are at the highest risk. Having one ε4 allele is sufficient to confer around a 3-times increased risk of developing AD while the risk is around 15 times greater when two copies are present [43]. However, being an ApoE ε4 carrier is not sufficient in and of itself to cause AD, indicating that it is a risk factor. Relevant to the comorbid burden of aging PLHIV, some observational studies have shown that ApoE ε4 carriers are reported to have an increased vulnerability to the harmful effects of smoking, excessive alcohol, physical inactivity and consumption of saturated fats, showing the interactive effects between genetic and lifestyle factors leading to increased dementia risk [47].

Dementia genetics and HIV

Investigations of the link between APOE ε4 genotype and HAND have yielded mixed results [48] because the effect of APOE ε4 may not be apparent until a more advanced age has been reached and may be more prominent when present along with other risk factors for neuronal damage. NeuroHIV studies assessing APOE ε4 effect were composed of > 30% of subjects who were not virally suppressed and whose average age was in their mid-40 s. A single study has shown that PLWH who have individuals with a family history of dementia obtained lower neuropsychological performance [49]. Further replication is needed particularly in older PLHIV.

Gender and ethnicity

Women are at higher risk than men for AD possibly due to the reduced estrogen effect in older age [50]. On the other hand, men are at higher risk of Vascular Dementia (VD) due to a generally higher risk of cardiovascular diseases (CVD) and stroke [50]. In US studies, people of African descent have a higher rate of dementia compared to white people, and those have a higher rate of dementia compared to people of Asian descent [51]. A complex interplay between modifiable factors, educational, social opportunity, in addition to early life trauma and life-span stressors is probably at play in such results [51]. This interpretation is supported by a lower rate of dementia in African Americans who received better education/social opportunity than their older counterparts [52]. Globally, studies comparing dementia prevalence in various countries suffer from major methodological limitations, as there is a lack of cross-culturally valid tools and methods' harmonization [53]. Importantly, efforts for uniform criteria to harmonized data greatly reduced the variation in Mild Cognitive Impairment (MCI) prevalence internationally [54].

Gender and ethnicity and HIV

There is no definitive research that shows that women are more at risk of for HIV-associated neurocognitive disorders (HAND); however, based on the dementia research it is clear that specific research needs to be dedicated to aging Women Living with HIV infection (WLHIV) as they may be at increased risk of all-type dementia due to the interaction between menopausal changes and HIV, in addition to other risk factors for poorer cognitive and mental health that are common in WLHIV [55]. There is also no evidence that some ethnicities are more at risk of HAND per se when using appropriate normative data [56]. However, geographical and regional differences may remain apparent because of the complex interplay between some ethnicities and health disparities, and thus play a role in dementia prevalence across the diverse ethnic groups that composed the HIV population [57]. The NeuroHIV field needs to continue developing cross-culturally valid tools and methods to correctly estimate dementia risk across the diverse HIV population [56].

Modifiable risk factors

Cardiovascular health and risk factors

Cardiovascular risk factors have a large modifiable component and are relevant to all-type dementia [58, 59]. All these

CVD risk factors are highly pertinent to the global aging PLHIV from midlife onward [60].

Hypertension: evidence from observational studies has shown that hypertension in midlife (less than 65 years of age) has a strong positive association with high risk of late-life dementia and AD [21]. The association between hypertension in late-life and dementia is less clear [21]. Antihypertensive treatments are found to have a preventive effect on cognitive decline and dementia. However, the results from RCTs are not conclusive [19]. Methodological issues contribute to the negative RCTs results (e.g., not being able to account for strict placebo-controls, cognition not being the primary outcome, short follow-ups) [61].

Obesity: some observational studies, but not all [62], have shown that obesity in midlife is associated with an increased risk of dementia [22, 63]. However, the evidence for obesity with onset in later life is less consistent with some showing a reduced risk of dementia [22]. Possible reasons include a 'reverse causality' phenomenon, where early pre-clinical effects of dementia may include body weight loss (sarcopenia) and/or reduced physical activity, among other symptoms [62].

Hypercholesterolemia: while hypercholesterolemia in midlife is associated with an increased risk of dementia [64], rapid decline in cholesterol levels during midlife to late-life is a risk factor for dementia and AD [64]. Prospective observational cohort studies show that statin treatment is beneficial at reducing the development of all-type dementia [65]. However, RCTs results have concluded that statins given to individuals in late-life had no beneficial effect and did not prevent dementia or cognitive decline [65]. There is also growing but still controversial evidence for reversible cognitive impairment for a small percentage of the population of statin users [65]. Additional RCTs are required to conclusively determine the global effects of statins on the brain. Such studies should address the pharmacological differences amongst the statins in terms of crossing the blood brain barrier.

Diabetes: the 2014 World Alzheimer's report [63] concludes that diabetes in late-life (and probably in midlife) is strongly associated with an increased risk of dementia, but more studies are needed to confirm this association [63]. Type 2 diabetes has been consistently associated with poor cognitive performance and is associated with a 47% increased risk of dementia [19]. RCTs involving treatment of diabetes with hypoglycemic drugs and insulin have not shown consistent results [66, 67]. In addition, hypoglycemia for both type 1 and 2 diabetes [68] could arise due to complications of diabetes treatment and may be associated with worse cognitive outcomes [68].

Stroke: stroke is another powerful risk factor for all-type dementia. A recent systematic review and meta-analysis showed that a history of stroke increases dementia risk by around 70%, while recent strokes doubled the risk of dementia [69].

Smoking: smoking is a risk factor for dementia and AD [63]. Current smoking increases the risk for incidence of AD and may increase risk for other dementias. This evidence is sufficient to encourage smoking cessation.

Physical activity: physical activity of mild to moderate intensity has been associated with a reduced risk of cognitive decline across several studies (reviewed in [70]). This association is observed when levels of physical activity in midlife are examined, but physical activity is also beneficial if maintained or increased during late life [70]. In contrast to the positive results from observational studies that examined the capacity of physical activity to prevent dementia, evidence from preventative RCTs is inconclusive [19]. These mixed results have stirred controversies and show the needs for more research with improved specifications for exercise types, frequency, duration and intensity [19]. In NeuroHIV, some trials are currently underway.

Diet: regular intake of fish, vegetables, fruits and nuts have shown to have a protective effect on brain functions [19, 70]. RCTs of the Mediterranean diet (MEDI), DASH (Dietary Approaches to Stop Hypertension) and MIND (Mediterranean-DASH Intervention for Neurodegenerative Delay) have promising results on dementia reduction [19]. Relevant to HAND, participants on the DASH diet exhibited greater improvements in psychomotor speed as compared to the usual diet control.

Cardiovascular health and risk factors and HIV

Studies have reported that the CVD risk is 1–2 times higher among older PLHIV than the general population of the same age [71, 72], and in advance of 10 years compared to the normative chronological age [39]. Another study found that HIV itself is associated with atherosclerosis irrespective of viral load, CD4-T cell count levels and ART [71]. Some ART drugs such as Protease Inhibitors (PI) and Abacavir have been shown to contribute to CVD burden amongst some PLHIV [26], although some controversy [73] and complexities [74] remain. Low CD4-T cell count has also been identified as an independent predictor of CVD among aging PLHIV [39]. Traditional risk factors such as smoking and obesity play a prominent role in CVD in the general population, and because they are even more prevalent in aging PLHIV [75], they could have a disproportionate impact on HIV-related CVD prevalence [9, 26, 76]. Metabolic alterations such as insulin resistance and dyslipidemia potentially caused and compounded by HIV and ART drugs also contribute to the high risk of CVD incidence among older PLHIV [76, 77]. In addition, HIV has been reported to be independently associated with hypertension [4], heart failure [78] and diastolic dysfunction [37]. Overall, it is increasingly

recognized that HIV is a CVD risk factor [79]. There is emerging evidence that this is associated with vascular brain damage burden in aging PLHIV [80], so much that HAND may include an increasing mild and moderate (i.e., stroke) Vascular Cognitive Impairment component (see [29] for details). CVD is treatable but tremendous challenges remain [74]. In this regard, international data show vast inequalities in CVD treatment access in PLHIV across the gender and resource setting gaps [60]. Because it is midlife CVD that contributes the most to dementia risk [22], it would be important to link the dementia risk in PLHIV to their CVD health at that particular age and assess to what extent aggressive CVD treatment has a positive impact, especially when considering the controversies on statins, and the persisting CVD abnormalities in some PLHIV despite CVD treatment [60].

Psychiatric, psychological and emotional health, alcohol and substance use

Depression with onset in later-life has been shown to be a clear and consistent risk factor for dementia, with increased risk of up to 90% for AD [81] and 85–100% for all-type dementia [82]. However, it remains controversial as to whether depression has a causal role or is rather a prodromal symptom of dementia. It is less clear whether anxiety is a risk factor, although recent reviews have suggested that midlife anxiety may confer an additional risk [83]. Other psychosocial factors that possibly impact on dementia risk are only starting to be more systematically studied including various markers of well-being such as loneliness and stress. Therefore, their current level of evidence as dementia risk factors is limited and more studies need to be carried out. Alcohol use disorders have been linked to earlier onset of all-type dementia [63, 84]. More specifically, there is evidence from a cohort study that people who abstained from alcohol or consumed more than 14 units of alcohol per week during midlife were at a higher risk of developing dementia [85]. Conversely, studies involving older adults show that light to moderate levels of alcohol per week have a lower risk of dementia as compared to those who do not drink at all [63, 85]. Light to moderate drinking is typically defined as 1-14 standard drinks per week, though it must be noted that there are country variations on the definition of what is a standard drink. Due to the paucity of studies assessing dementia risk in long-term substance users, there is no knowledge on this potential extra risk that is highly relevant to the HIV population [86]. Direct (drug-reward brain pathway damage) and indirect (CVD) substances neurotoxicity may be at play, and in some instances be further compounded by the poorer socio-economic status that is characteristic of PLHIV with a substance use disorder [86].

Psychiatric, psychological and emotional health, alcohol and substance use, and HIV

The mental health burden is high in the global HIV population for multiple reasons [87]. For example, depression, which is often under recognized and treated, is highly prevalent among HIV-infected in general and even more so in elder PLHIV [36, 39, 88, 89]. In the aging PLHIV, the long-term chronic illness and stigmatization may exacerbate psychological symptoms [88, 90]. For many, depression is linked to social isolation [91] which in part is due to the loss of their loved ones to AIDS. Having multiple age-comorbidities and enduring the chronic illness may lead to poor quality of life (QOL) and reduced wellbeing amongst elderly PLHIV [38, 88]. A Dutch study reported that HIV status is independently associated with poor quality of life amongst PLHIV despite treatment and viral control [88]. Although having a greater comorbidity burden was associated with worse physical QOL, it did not change the effect of HIV status on the quality of life, meaning that there can be residual effect of chronic HIV on the QOL even when comorbidities are prevented and treated. Mental health burden especially in its chronic form [92] and traumatic life events (e.g., childhood trauma) are increasingly recognized as major risk factors for dementia [93, 94]. Further adding to the mental health burden is the well-recognized high prevalence of recreational drug use in PLHIV compared to the general population [95], some of which are both cardiotoxic and neurotoxic (methamphetamine) [96]. In other words, a substantial number of PLHIV—at the global level—are likely to be very vulnerable for dementia, in virtue of the high level of psychiatric burden that is often comorbid to the other risk factors we reviewed.

Educational attainment, socio-economic status and mental stimulation

There is cumulative evidence that higher education has a protective effect against development of dementia. Higher levels of education probably confer added direct benefit through enhancing and diversifying brain networks and/or through enhancing opportunities for mental stimulation, such as access to more cognitively demanding jobs [97]. Higher educational attainment also tends to be associated with higher socio-economic status, and in many countries, better awareness of healthy nutrition/diets, access to better medical care and lower incidence of cardiovascular risk factors and disease [97]. A few studies have suggested that having a wider social network and more engagement in socially enriching activities is associated with a reduced risk of dementia [97], although it is difficult to disentangle the relative contributions of cognitive stimulation and physical activity from purely social aspects. Cognitively stimulating

activities should be conceived as a broad concept including work complexity, engagement in cognitively stimulating activities during leisure time like reading, writing and using computers [98]. In terms of cognitive training RCTs, the best evidence for some potential benefit comes from The Advanced Cognitive Training for independent and Vital elderly (ACTIVE) trial, which showed that the intervention group improved their cognitive skills of reasoning and processing speed but did not improve memory function [19]. Meta-analyses of RCTs have shown that cognitive training interventions might improve cognitive abilities in healthy and cognitively impaired participants but with no effect on the incidence of dementia [21].

Educational attainment, socio-economic status and mental stimulation and HIV

There is good evidence that low education and lower socio-economic status are associated with a greater prevalence and incidence of HAND [99]. Conversely, greater cognitive reserve has been associated with lower prevalence of HAND [100]. These results largely mimic those from the dementia literature [101]. However, dementia research has also cumulatively shown that a higher education level is not associated with a slower progression of dementia [102]. This research needs to be also conducted in NeuroHIV. Considering the wide range of educational achievement across the HIV population internationally, but also within each country, it will be important to properly account for education effects in the detection of early dementia in aging PLHIV. The use of optimal normative neuropsychological data could not be more emphasized in this population so as to avoid both under and over diagnosis of dementia. Cognitive training trials in PLHIV are underway.

Specific HIV dementia risks factors

Historical and ongoing HIV brain involvement

A sometimes forgotten finding from the early cART NeuroHIV research is that any form of historical HIV brain involvement that has resolved on treatment remains a risk for cognitive deterioration [103]. It should be noted that at the global population level HAD and CNS opportunistic infections still occur and with treatment access are more likely to survive [104]. This finding confirms results in dementia research showing that previous brain trauma is a risk factor for dementia [97]. The prevalence of HAND has been recently the focus of some debates [56, 105], but even when taking the most conservative estimates, it is undeniable that a non-negligible part of the first generation who are aging with HIV infection has a much higher brain vulnerability burden compared to the general population entering the dementia age range. Furthermore, age is a risk factor for HAND and HAD and it is estimated that once 50 + PLHIV are considered, HAND prevalence goes up by 10% [106]. The mildest forms of HAND are the most common in the cART era. They seem to still have a relapsing/remitting profile, although with greater intervals between episodes, which translate into long-periods of stability [107]. But when studies have long-term endpoints (> 10 years), or in those aged 60 +, progression is detected and even accelerated brain changes [108–110]. This is true to a greater extent in those with multiple comorbidities and unsurprising when referenced against what is established in the dementia literature (e.g., The Cardiovascular Risk Factors, Aging and Dementia (CAIDE) risk score, see [19] for an overview). Yet, it seems that even in some PLHIV with low comorbidities accelerated brain aging can be detected [108]. More studies are needed, especially once PLHIV have reached 60 + because the finding of accelerated brain aging is not consistent [28]—it is, however, consistent for premature brain aging [111]. How HAND and the probable increasing contribution of vascular brain injury in aging PLHIV will play out deserve attention because these are yet again combined risk factors for all-types of dementia and well-established promoters of neurodegeneration.

Remaining stable on cART is still the best treatment to avoid HAND and avoid HAND progression once it has been diagnosed. Once on stable treatment, between 70 and 80% of PLHIV remain cognitively stable across years [56]. There is a good chance that some strategies to reduce HAND occurrence and progression will also be protective against dementia development, although empirical evidence is needed. cART early initiation is now standard recommendation [112]. However, there is no definitive evidence that it protects against dementia because no study could have been designed to assess this question. Early treatment is both beneficial against progression to AIDS and the occurrence of non-AIDS events [112]. Importantly, AIDS is a risk factor for HAND, so that a reduction of the prevalence of HAND will have an impact on the rate of potential dementia in PLHIV who will be aging while having been treated early. The relation of non-AIDS condition (the main one being cancer) to dementia in PLHIV is unknown. The reduction of chronic HIV-related CVD because of early treatment would also have beneficial impact on dementia reduction in the HIV population at large. However, it would be important to follow-up early treated PWHIV to old age to extract accurate estimates. Furthermore, it is unknown if some ARV drugs taken 50 + years may eventually have adverse neurological impact. Finally, by virtue of genetic risk factors, some PLHIV will be destined to develop dementia. In these cases, it is unknown if being treated early, having controlled HIV, having a chronic illness that means routine health monitoring will impact dementia risk in one way or the other.

HIV-related immune compromise, chronic immune activation, immune senescence

There is strong immune and HIV basic science rationale to the parallels between how aging and chronic-treated HIV infection affects the immune system [36, 37, 113, 114]. In chronic PLHIV, premature aging is probably caused through an integrated pathway of aetiologies converging towards chronic immune activation [115], which is worse as a function of HIV-related immune compromise. Beyond the scope of this review, HIV basic science research shows that the mechanisms driving systemic immune activation in chronic HIV infection are multifactorial (i.e., translocation of microbial products from the gastrointestinal tract, low-level detectable virus, persistent viral reservoirs, and co-infections with other highly common viral pathogens such as the human herpes viruses especially cytomegalovirus) [115]. The chronic state of immune activation leads to an inflammatory response characterized by excessive production and/or accumulation of proinflammatory cytokines (TNFα, IL-1β and IL-6), excessive activation of macrophages and monocytes activation markers (CD14, CD163), increased non-specific inflammation (elevated C-reactive protein (CRP) and cystatin C [116]) that further promotes immune activation. And those inflammatory markers are associated with vascular inflammation and coronary atherosclerosis in PLHIV as well as the general population [117]. As individuals grow older, this vicious cycle probably intensifies because of immune senescence [118].

Supporting this rationale are findings relating to the Immune Risk Profile [119] in PLHIV. The Immune Risk Profile distinctly identifies an immunological profile of individuals at increased risk of morbidity and mortality in the general population [119] and not surprisingly this profile has been described in treated HIV+ individuals at significantly younger ages [120] lending credence to the hypothesis of premature and potentially accelerated aging in this population. Importantly, there is evidence that the Immune Risk Profile in resource-limited setting is increased due to higher rates of baseline immune compromise [121], and higher background level of immune activation linked in part to a higher exposure to common human herpes viruses [122]. Finally, with increasing focus on chronic immune dysregulation as a direct contributor to AD [123], and an indirect cause through immune-driven vascular damage [124], there is in addition to non-HIV driven age-comorbidities, a plausible pathophysiological pathway of increased dementia risk even in those PLHIV aging with low comorbidities [125].

ART neurotoxicity

Ethical reasons and the trade-off benefit of being HIV-infected and off therapy have precluded the study of potential ART neurotoxicity in RCTs. Nevertheless, pre-cART studies have demonstrated abnormal neurochemical metabolism in HIV-infected adults on reverse transcriptase inhibitors related to brain mitochondrial toxicity [126] similar to the pathophysiological pathway in the peripheral nervous system leading to peripheral neuropathy. Most of the Nucleoside reverse transcriptase inhibitors (NRTIs) used then are not on the market anymore, but their length of use may have caused some vulnerability to brain damage, nevertheless. One drug that has known adverse neuropsychiatric effects (Efavirenz) [127] has been associated in a least a subset of PLHIV with neurocognitive impairment. Any link to dementia in old age is unknown. In all, it is not impossible that some aging PLHIV may be more vulnerable to dementia in part due to ART neurotoxicity. Recent findings including new types of ART would support this hypothesis [128].

ART-related chronic kidney disease

While the prevalence of HIV-associated nephropathy is low, PLHIV are developing chronic kidney diseases as a result of the higher prevalence of hypertension, Diabetes Mellitus, inflammatory markers and widespread use of Tenofovir DF [129]. A study conducted among veterans in US found out that PLHIV have a higher risk of chronic kidney disease compared to those without HIV and it occurred at a younger age among them compared to the general population [130]. Chronic kidney disease markers have been associated with cognitive decline in PLHIV [131]. This may, therefore, represent an added dementia risk factor as PLHIV age although Tenofovir DF will be increasingly replaced by a less toxic version.

Conclusions and future directions

Specific research attention and funding need to be dedicated to the first generation of aging PLHIV now rather than later. At the global level, and even when accounting for the beneficial effect of ART, this generation shows cumulative comorbid risk for all-type dementia. When considered against the evidence in all-type dementia research, the added level of dementia risk in PLHIV is undeniable. Unfortunately, the interpretation of the research on all-type dementia risk reduction/prevention is not straightforward. It is important to recognize that the level of evidence may change in the future and, at the same time, that observational studies have yielded fair evidence for monitoring and treatment of modifiable factors as a dementia prevention strategy. Besides recognized methodological limitations pertaining to the complexity of risk factors' impact in RCTs (reviewed in [132]), and caveats around the specifics of each intervention (reviewed in [19]), there are specific methodological issues in NeuroHIV

research that need to be anticipated if such RCTs are to be optimally tested in aging PLHIV.

First, how cognitive change is measured needs to be a central focus [133]. PLHIV at risk of HAND or with HAND have a fluctuating cognitive profile. The suboptimal tools for measuring cognitive change that are widely used in dementia research (e.g., MMSE, ADAS-Cog, CDR) need to be avoided at all cost in NeuroHIV studies and trials [134]. These tools were not developed to measure change, but to screen for dementia. They have wide measurement errors if not demographically corrected. Their test–retest reliability is inadequate principally due to their truncated range of values at the upper performance band. They are highly sensitive to practice effect, which in most instances is never accounted for properly [133, 134]. Equivalent tools to avoid in NeuroHIV would be for example the (I)HDS or the MOCA [134]. Screening tools with better psychometric properties to identify cognitive change include screens that are based on a good number of tasks with infinite range of values (e.g., CogState [134], Neuroscreen [135], or selected combinations of standard neuropsychological tests [134]). Although practice effect and norms are still needed to optimally interpret these tools. The importance of measuring cognitive performance optimally is not a trivial issue as it is the primary outcomes of RCTs. It is also needed to capture normal and pathological aging trajectories [136] because not all people have equivalent resilience in the face of the same neurodegenerative burden. This demands a sophisticated approach to the measurement of cognitive change across decades of chronic HIV and the development of longitudinal normative data to truly extract the practice effect. The lack of practice correction and the mixing of people with completely different dementia trajectories may currently mask the potential benefit of some interventions in dementia research.

Second, the dementia field increasingly recognizes that both pharmacological and non-pharmacological interventions should be tested from midlife onwards (i.e., preventative framework). Increasingly, in such longitudinal preventative context where there are obvious ethical limitations [63], some statisticians, clinicians and researchers are now proposing alternatives to RCT which the NeuroHIV community should be aware of [137] (e.g., use of normative longitudinal data and other forms of prior knowledge, adaptive randomization when possible).

Third, the multifactorial aspect of dementia will be even greater in chronic, treated, aging PLHIV. Currently dementia research to tackle this question in interventional RCTs is focusing on multi-domain interventions that target several risk factors at the same time [19]. For example, the recent Finnish Geriatric Intervention study to Prevent Cognitive Impairment and Disability (FINGER trial) has demonstrated that multi-domain lifestyle interventions including diet, exercise, cognitive training and management of vascular risk factors have beneficial effects on cognition [19]. In NeuroHIV it will be key to also include mental health, alcohol and substance use reduction when needed, HIV medicine, and last, but not least, delivery of interventions in safe and non-stigmatizing environments.

Finally, HIV geriatricians [28, 71, 138] have advocated that planning for the care burden associated with both age *plus* HIV is needed to avoid sending PLHIV into mainstream dementia and geriatric care where they will likely experience stigma, and where both HIV and dementia care may be suboptimal. Provision of appropriate care is also important to avoid misdiagnosis, especially when neurological conditions and dementia are considered complex diagnoses, which demand expertise that is not always present at the global HIV population level. There is evidence that PLHIV can be further stigmatized and isolated as they get older [139]—a tardive or poor HIV neurogeriatric response should avoid contributing to this. Lastly, education of the HIV community on Mild Cognitive Impairment (MCI) and dementia is also urgently needed as there is an increase concern among aging PLHIV that these conditions are highly stigmatized in the HIV community [140–142]. Education programs exist in the field of dementia led internationally by several Alzheimer's patients' associations. In this educational framework, the role and support of both formal and informal caregivers are central. Similar efforts should be targeted towards aging PLHIV potentially linking these associations with the HIV neurogeriatric researchers/clinicians and HIV community organizations.

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Compliance with ethical standards

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References

1. Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA et al (1998) Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med 338(13):853–860
2. Teeraananchai S, Kerr S, Amin J, Ruxrungtham K, Law M (2017) Life expectancy of HIV-positive people after starting combination antiretroviral therapy: a meta-analysis. HIV medicine. 18(4):256–266
3. Lima VD, Harrigan R, Bangsberg DR, Hogg RS, Gross R, Yip B et al (2009) The combined effect of modern highly active antiretroviral therapy regimens and adherence on mortality over time. J Acquired Immune Deficiency Synd 50(5):529
4. Deeks SG, Lewin SR, Havlir DV (2013) The end of AIDS: HIV infection as a chronic disease. Lancet 382(9903):1525–1533
5. Mahungu TW, Rodger AJ, Johnson MA (2009) HIV as a chronic disease. Clin Med 9(2):125–128
6. UNAIDS (2017) HIV and Ageing. Switzerland: UNAIDS
7. Smit M, Brinkman K, Geerlings S, Smit C, Thyagarajan K, Sighem A et al (2015) Future challenges for clinical care of an ageing population infected with HIV: a modelling study. Lancet Infect Dis 15(7):810–818
8. Sprague C, Brown SM (2017) Local and global HIV aging demographics and research. Interdisciplinary topics in gerontology and geriatrics 42:1–10
9. Justice AC (2010) HIV and aging: time for a new paradigm. Curr HIV/AIDS Rep 7(2):69–76
10. Tavoschi L, Gomes Dias J, Pharris A (2017) New HIV diagnoses among adults aged 50 years or older in 31 European countries, 2004–15: an analysis of surveillance data. Lancet HIV 4(11):e514–e521
11. Talukdar A, Khanra D, Ray S, Talukdar P, Rana S, Banerjee B et al (2013) HIV among the elderly with special reference to mode of presentation at a tertiary care hospital in Kolkata, India. Tropical doctor 43(3):100–102
12. Allavena C, Hanf M, Rey D, Duvivier C, BaniSadr F, Poizot-Martin I et al (2018) Antiretroviral exposure and comorbidities in an aging HIV-infected population: the challenge of geriatric patients. PLoS One 13(9):e0203895
13. Cornell M, Johnson LF, Schomaker M, Tanser F, Maskew M, Wood R et al (2015) Age in antiretroviral therapy programmes in South Africa: a retrospective, multicentre, observational cohort study. Lancet HIV 2(9):e368–e375
14. Europe ECfDPaCWROf (2017) HIV/AIDS surveillance in Europe 2017–2016 data. Stockholm
15. Mahy M, Autenrieth CS, Stanecki K, Wynd S (2014) Increasing trends in HIV prevalence among people aged 50 years and older: evidence from estimates and survey data. Aids 28(Suppl 4):S453–S459
16. Negin J, Barnighausen T, Lundgren JD, Mills EJ (2012) Aging with HIV in Africa: the challenges of living longer. Aids 26(Suppl 1):S1–S5
17. Brothers TD, Kirkland S, Theou O, Zona S, Malagoli A, Stentarelli C et al (2014) Exploring aging trajectories among people with HIV and a general community-based cohort: transitions in health status and risk of death. Reviews in Antiviral Therapy & Infectious Diseases 7
18. Kuo CL, Lu CL, Chang YH, Li CY (2018) Population-based cohort study on dementia risk in patients with type 1 diabetes mellitus. Neuroepidemiology 50(1–2):57–62
19. Kivipelto M, Mangialasche F, Ngandu T (2018) Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease. Nat Rev Neurol 14(11):653–666
20. Costagliola D (2014) Demographics of HIV and aging. Curr Opin HIV AIDS 9(4):294–301
21. Solomon A, Mangialasche F, Richard E, Andrieu S, Bennett DA, Breteler M et al (2014) Advances in the prevention of Alzheimer's disease and dementia. J Intern Med. 275(3):229–250
22. Deckers K, van Boxtel MP, Schiepers OJ, de Vugt M, Munoz Sanchez JL, Anstey KJ et al (2015) Target risk factors for dementia prevention: a systematic review and Delphi consensus study on the evidence from observational studies. Int J Geriatr Psychiatry. 30(3):234–246
23. Barnes DE, Yaffe K (2011) The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol. 10(9):819–828
24. Hebert LE, Weuve J, Scherr PA, Evans DA (2013) Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. Neurology. 80(19):1778–1783
25. Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, Ofstedal MB et al (2007) Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology. 29(1–2):125–132
26. Wing EJ (2016) HIV and aging. International journal of infectious diseases. 53:61–68
27. Cysique LA, Brew BJ (2014) The effects of HIV and aging on brain functions: proposing a research framework and update on last 3 years' findings. Curr Opin HIV AIDS. 9(4):355–364
28. Milanini B, Valcour V (2017) Differentiating HIV-associated neurocognitive disorders from Alzheimer's Disease: an emerging issue in geriatric NeuroHIV. Curr HIV/AIDS Rep. 14(4):123–132
29. Cysique LA, Brew BJ. Vascular Cognitive Impairment and HIV-Associated Neurocognitive Disorder: A New Paradigm. J Neurovirol. In Press
30. Piggott DA, Erlandson KM, Yarasheski KE (2016) Frailty in HIV: epidemiology, biology, measurement, interventions, and research needs. Curr HIV/AIDS Rep. 13(6):340–348
31. Tassiopoulos K, Abdo M, Wu K, Koletar SL, Palella FJ, Kalayjian R et al (2017) Frailty is strongly associated with increased risk of recurrent falls among older HIV-infected adults. Aids. 31(16):2287–2294
32. Önen NF, Agbebi A, Shacham E, Stamm KE, Önen AR, Overton ET (2009) Frailty among HIV-infected persons in an urban outpatient care setting. J Infect 59(5):346–352
33. Maciel RA, Klück HM, Durand M, Sprinz E (2018) Comorbidity is more common and occurs earlier in persons living with HIV than in HIV-uninfected matched controls, aged 50 years and older: a cross-sectional study. Int J Infect Dis 70:30–35
34. Johs NA, Wu K, Tassiopoulos K, Koletar SL, Kalayjian RC, Ellis RJ et al (2017) Disability among middle-aged and older persons with human immunodeficiency virus infection. Clin Infect Dis. 65(1):83–91
35. Vance DE, Cody SL (2015) Predictions of geriatric HIV in 2030. Lancet Infect Dis. 15(7):753–754
36. Sharp M. The unintended consequences of AIDS survival
37. Pathai S, Bajillan H, Landay AL, High KP (2014) Is HIV a model of accelerated or accentuated aging? J Gerontol Ser A, Biol Sci Med Sci 69(7):833–842
38. Rajasuriar R, Chong ML, Ahmad Bashah NS, Abdul Aziz SA, McStea M, Lee ECY et al (2017) Major health impact of accelerated aging in young HIV-infected individuals on antiretroviral therapy. Aids. 31(10):1393–1403
39. Brooks JT, Buchacz K, Gebo KA, Mermin J (2012) HIV infection and older Americans: the public health perspective. Am J Publ Health 102(8):1516–1526
40. Xu S, Vucic EA, Shaipanich T, Lam S, Lam W, Montaner JS et al (2018) Decreased telomere length in the small airway epithelium suggests accelerated aging in the lungs of persons

living with human immunodeficiency virus (HIV). Respir Res. 19(1):117
41. Gianesin K, Noguera-Julian A, Zanchetta M, Del Bianco P, Petrara MR, Freguja R et al (2016) Premature aging and immune senescence in HIV-infected children. Aids. 30(9):1363–1373
42. McCrary AW, Nduka CU, Stranges S, Bloomfield GS (2017) Features of cardiovascular disease in low-income and middle-income countries in adults and children living with HIV. Curr Opin HIV AIDS. 12(6):579–584
43. Loy CT, Schofield PR, Turner AM, Kwok JB (2014) Genetics of dementia. Lancet. 383(9919):828–840
44. Lautenschlager NT, Cupples LA, Rao VS, Auerbach SA, Becker R, Burke J et al (1996) Risk of dementia among relatives of Alzheimer's disease patients in the MIRAGE study: what is in store for the oldest old? Neurology. 46(3):641–650
45. Paulson HL, Igo I (2011) Genetics of dementia. Semin Neurol. 31(5):449–460
46. Blennow K, Mattsson N, Scholl M, Hansson O, Zetterberg H (2015) Amyloid biomarkers in Alzheimer's disease. Trends Pharmacol Sci. 36(5):297–309
47. Strand BH, Rosness TA, Engedal K, Magnus P, Bergem AL, Schirmer H et al (2015) Interaction of apolipoprotein E genotypes, lifestyle factors and future risk of dementia-related mortality: the cohort of Norway (CONOR). Dement Geriatr Cogn Disord. 40(3–4):137–147
48. Morgan EE, Woods SP, Letendre SL, Franklin DR, Bloss C, Goate A et al (2013) Apolipoprotein E4 genotype does not increase risk of HIV-associated neurocognitive disorders. J Neurovirol. 19(2):150–156
49. Moore DJ, Arce M, Moseley S, McCutchan JA, Marquie-Beck J, Franklin DR et al (2011) Family history of dementia predicts worse neuropsychological functioning among HIV-infected persons. J Neuropsychiatry Clin Neurosci. 23(3):316–323
50. Pike CJ (2017) Sex and the development of Alzheimer's disease. J Neurosci Res. 95(1–2):671–680
51. Mayeda ER, Glymour MM, Quesenberry CP, Whitmer RA (2016) Inequalities in dementia incidence between six racial and ethnic groups over 14 years. Alzheimers Dement. 12(3):216–224
52. Noble JM, Schupf N, Manly JJ, Andrews H, Tang MX, Mayeux R (2017) Secular trends in the incidence of dementia in a multiethnic community. J Alzheimers Dis. 60(3):1065–1075
53. Sachdev PS, Lipnicki DM, Kochan NA, Crawford JD, Rockwood K, Xiao S et al (2013) COSMIC (Cohort Studies of Memory in an International Consortium): an international consortium to identify risk and protective factors and biomarkers of cognitive ageing and dementia in diverse ethnic and sociocultural groups. BMC Neurol. 13(165):165
54. Sachdev PS, Lipnicki DM, Kochan NA, Crawford JD, Thalamuthu A, Andrews G et al (2015) The prevalence of mild cognitive impairment in diverse geographical and ethnocultural regions: The COSMIC Collaboration. PLoS One. 10(11):e0142388
55. Rubin LH, Maki PM, Springer G, Benning L, Anastos K, Gustafson D et al (2017) Cognitive trajectories over 4 years among HIV-infected women with optimal viral suppression. Neurology. 89(15):1594–1603
56. Saloner R, Cysique LA (2017) HIV-Associated neurocognitive disorders: a global perspective. J Int Neuropsychol Soc. 23(9–10):860–869
57. Marquine MJ, Sakamoto M, Dufour C, Rooney A, Fazeli P, Umlauf A et al (2016) The impact of ethnicity/race on the association between the Veterans Aging Cohort Study (VACS) Index and neurocognitive function among HIV-infected persons. J Neurovirol. 22(4):442–454
58. Justin BN, Turek M, Hakim AM (2013) Heart disease as a risk factor for dementia. Clin Epidemiol. 5:135–145
59. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C (2014) Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. Lancet Neurol. 13(8):788–794
60. Holloway CJ, Boccara F (2017) HIV-related cardiovascular disease: closing the gap in mortality. Curr Opin HIV AIDS. 12(6):509–512
61. Hernandorena I, Duron E, Vidal JS, Hanon O (2017) Treatment options and considerations for hypertensive patients to prevent dementia. Expert Opin Pharmacother. 18(10):989–1000
62. Qizilbash N, Gregson J, Johnson ME, Pearce N, Douglas I, Wing K et al (2015) BMI and risk of dementia in two million people over two decades: a retrospective cohort study. Lancet Diabetes Endocrinol. 3(6):431–436
63. Alzheimer's Disease International (2014) World Alzheimer's report: Dementia and risk reduction: an analysis of protective and modifiable factors https://www.alz.co.uk/research/world-report-2014. London: Alzheimer's disease International (AdI)
64. Anstey KJ, Ashby-Mitchell K, Peters R (2017) Updating the evidence on the association between serum cholesterol and risk of late-life dementia: review and meta-analysis. J Alzheimers Dis. 56(1):215–228
65. Schultz BG, Patten DK, Berlau DJ (2018) The role of statins in both cognitive impairment and protection against dementia: a tale of two mechanisms. Transl Neurodegener. 7(5):5
66. Cheng C, Lin CH, Tsai YW, Tsai CJ, Chou PH, Lan TH (2014) Type 2 diabetes and antidiabetic medications in relation to dementia diagnosis. J Gerontol Ser A, Biol Sci Med Sci 69(10):1299–1305
67. Williamson JD, Launer LJ, Bryan RN, Coker LH, Lazar RM, Gerstein HC et al (2014) Cognitive function and brain structure in persons with type 2 diabetes mellitus after intensive lowering of blood pressure and lipid levels: a randomized clinical trial. JAMA Intern Med. 174(3):324–333
68. Meneilly GS, Tessier DM (2016) Diabetes, dementia and hypoglycemia. Can J Diabetes. 40(1):73–76
69. Kuzma E, Lourida I, Moore SF, Levine DA, Ukoumunne OC, Llewellyn DJ (2018) Stroke and dementia risk: a systematic review and meta-analysis. Alzheimers Dement. 14(11):1416–1426
70. Zhao C, Noble JM, Marder K, Hartman JS, Gu Y, Scarmeas N (2018) dietary patterns, physical activity, sleep, and risk for dementia and cognitive decline. Curr Nutr Rep. 7(4):335–345
71. Van Epps P, Kalaylian RC (2017) Human immunodeficiency virus and aging in the era of effective antiretroviral therapy. Infect Dis Clin N Am. 31(4):791–810
72. Post G (2013) HIV infection and the risk of acute myocardial infarction. US News & World Report (versions also appeared in MSN, Health24, MentalHelp, and 12 other publications)
73. Dorjee K, Choden T, Baxi SM, Steinmaus C, Reingold AL (2018) Risk of cardiovascular disease associated with exposure to abacavir among individuals with HIV: a systematic review and meta-analyses of results from 17 epidemiologic studies. Int J Antimicrob Agents 52(5):541–553
74. Maggi P, Di Biagio A, Rusconi S, Cicalini S, D'Abbraccio M, d'Ettorre G et al (2017) Cardiovascular risk and dyslipidemia among persons living with HIV: a review. BMC Infect Dis. 17(1):551
75. Barnes RP, Lacson JC, Bahrami H (2017) HIV infection and risk of cardiovascular diseases beyond coronary artery disease. Curr Atheroscler Rep. 19(5):20
76. Grinspoon SK (2014) Perspective cardiovascular disease in HIV: traditional and nontraditional risk factors. Topics Antiviral Med 22(4):676
77. Bozzette SA (2011) HIV and cardiovascular disease. Oxford University Press, Oxford

78. Freiberg MS, Chang CH, Skanderson M, Patterson OV, DuVall SL, Brandt CA et al (2017) Association between HIV infection and the risk of heart failure with reduced ejection fraction and preserved ejection fraction in the antiretroviral therapy era: results from the veterans aging cohort study. JAMA Cardiol. 2(5):536–546
79. Gutierrez J, Albuquerque ALA, Falzon L (2017) HIV infection as vascular risk: a systematic review of the literature and meta-analysis. PLoS One. 12(5):e0176686
80. Moulignier A, Savatovsky J, Assoumou L, Lescure FX, Lamirel C, Godin O et al (2018) Silent cerebral small-vessel disease is twice as prevalent in middle-aged individuals with well-controlled, combination antiretroviral therapy-treated human immunodeficiency virus (HIV) than in HIV-uninfected individuals. Clin Infect Dis. 66(11):1762–1769
81. Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D (2006) Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. Arch Gen Psychiatry. 63(5):530–538
82. Cherbuin N, Kim S, Anstey KJ (2015) Dementia risk estimates associated with measures of depression: a systematic review and meta-analysis. BMJ Open. 5(12):e008853
83. Gimson A, Schlosser M, Huntley JD, Marchant NL (2018) Support for midlife anxiety diagnosis as an independent risk factor for dementia: a systematic review. BMJ Open. 8(4):e019399
84. Schwarzinger M, Pollock BG, Hasan OSM, Dufouil C, Rehm J (2018) Contribution of alcohol use disorders to the burden of dementia in France 2008–13: a nationwide retrospective cohort study. Lancet Publ Health. 3(3):e124–e132
85. Sabia S, Fayosse A, Dumurgier J, Dugravot A, Akbaraly T, Britton A et al (2018) Alcohol consumption and risk of dementia: 23 year follow-up of Whitehall II cohort study. Bmj. 362:k2927
86. Norman LR, Basso M (2015) An update of the review of neuropsychological consequences of HIV and substance abuse: a literature review and implications for treatment and future research. Curr Drug Abuse Rev. 8(1):50–71
87. Mitchell J, Wight M, Van Heerden A, Rochat TJ (2016) Intimate partner violence, HIV, and mental health: a triple epidemic of global proportions. Int Rev Psychiatry. 28(5):452–463
88. Langebeek N, Kooij KW, Wit FW, Stolte IG, Sprangers MAG, Reiss P et al (2017) Impact of comorbidity and ageing on health-related quality of life in HIV-positive and HIV-negative individuals. Aids. 31(10):1471–1481
89. Milanini B, Catella S, Perkovich B, Esmaeili-Firidouni P, Wendelken L, Paul R et al (2017) Psychiatric symptom burden in older people living with HIV with and without cognitive impairment: the UCSF HIV over 60 cohort study. AIDS Care. 29(9):1178–1185
90. Porter L (2017) Older people with HIV enter uncharted territory (2014+). Nursing Older People. 29(2):14
91. McDonald K, Elliott J, Saugeres L (2013) Ageing with HIV in Victoria: findings from a qualitative study. HIV Aust 11(2):13
92. Cysique LA, Dermody N, Carr A, Brew BJ, Teesson M (2016) The role of depression chronicity and recurrence on neurocognitive dysfunctions in HIV-infected adults. J Neurovirol. 22(1):56–65
93. Ford E, Greenslade N, Paudyal P, Bremner S, Smith HE, Banerjee S et al (2018) Predicting dementia from primary care records: a systematic review and meta-analysis. PLoS One. 13(3):e0194735
94. Radford K, Delbaere K, Draper B, Mack HA, Daylight G, Cumming R et al (2017) Childhood stress and adversity is associated with late-life dementia in aboriginal Australians. Am J Geriatr Psychiatry. 25(10):1097–1106
95. Amin P, Douaihy A (2018) Substance use disorders in people living with human immunodeficiency virus/AIDS. Nurs Clin North Am 53(1):57–65
96. Paratz ED, Cunningham NJ, MacIsaac AI (2016) The cardiac complications of methamphetamines. Heart Lung Circ 25(4):325–332
97. Anstey KJ, Cherbuin N, Herath PM (2013) Development of a new method for assessing global risk of Alzheimer's disease for use in population health approaches to prevention. Prev Sci 14(4):411–421
98. Yates LA, Ziser S, Spector A, Orrell M (2016) Cognitive leisure activities and future risk of cognitive impairment and dementia: systematic review and meta-analysis. Int Psychogeriatr 28(11):1791–1806
99. Morgan EE, Woods SP, Smith C, Weber E, Scott JC, Grant I (2012) Lower cognitive reserve among individuals with syndromic HIV-associated neurocognitive disorders (HAND). AIDS Behav 16(8):2279–2285
100. Cysique LA, Brew BJ (2011) Prevalence of non-confounded HIV-associated neurocognitive impairment in the context of plasma HIV RNA suppression. J Neurovirol 17(2):176–183
101. Lipnicki DM, Crawford JD, Dutta R, Thalamuthu A, Kochan NA, Andrews G et al (2017) Age-related cognitive decline and associations with sex, education and apolipoprotein E genotype across ethnocultural groups and geographic regions: a collaborative cohort study. PLoS Med 14(3):e1002261
102. Meng X, D'Arcy C (2012) Education and dementia in the context of the cognitive reserve hypothesis: a systematic review with meta-analyses and qualitative analyses. PLoS One 7(6):e38268
103. Cysique LA, Maruff P, Brew BJ (2006) Variable benefit in neuropsychological function in HIV-infected HAART-treated patients. Neurology 66(9):1447–1450
104. Vivithanaporn P, Heo G, Gamble J, Krentz HB, Hoke A, Gill MJ et al (2010) Neurologic disease burden in treated HIV/AIDS predicts survival: a population-based study. Neurology 75(13):1150–1158
105. Nightingale S, Winston A, Letendre S, Michael BD, McArthur JC, Khoo S et al (2014) Controversies in HIV-associated neurocognitive disorders. Lancet Neurol 13(11):1139–1151
106. Cysique LA, Heaton RK, Kamminga J, Lane T, Gates TM, Moore DM et al (2014) HIV-associated neurocognitive disorder in Australia: a case of a high-functioning and optimally treated cohort and implications for international neuroHIV research. J Neurovirol. 20(3):258–268
107. Gott C, Gates T, Dermody N, Brew BJ, Cysique LA (2017) Cognitive change trajectories in virally suppressed HIV-infected individuals indicate high prevalence of disease activity. PLoS One. 12(3):e0171887
108. Pfefferbaum A, Zahr NM, Sassoon SA, Kwon D, Pohl KM, Sullivan EV (2018) Accelerated and premature aging characterizing regional cortical volume loss in human immunodeficiency virus infection: contributions from alcohol, substance use, and hepatitis C coinfection. Biol Psychiatry Cogn Neurosci Neuroimaging. 3(10):844–859
109. Clifford KM, Samboju V, Cobigo Y, Milanini B, Marx GA, Hellmuth JM et al (2017) Progressive brain atrophy despite persistent viral suppression in HIV patients older than 60 years. J Acquir Immune Defic Syndr. 76(3):289–297
110. Goodkin K, Miller EN, Cox C, Reynolds S, Becker JT, Martin E et al (2017) Effect of ageing on neurocognitive function by stage of HIV infection: evidence from the multicenter AIDS Cohort Study. Lancet HIV. 4(9):e411–e422
111. Cole JH, Caan MWA, Underwood J, De Francesco D, van Zoest RA, Wit F et al (2018) No evidence for accelerated aging-related brain pathology in treated human immunodeficiency

virus: longitudinal neuroimaging results from the comorbidity in relation to AIDS (COBRA) project. Clin Infect Dis 66(12):1899–1909
112. Lundgren JD, Babiker AG, Gordin F, Emery S, Grund B, Sharma S et al (2015) Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med 373(9):795–807
113. Avelino-Silva VI, Ho YL, Avelino-Silva TJ, Santos Sde S (2011) Aging and HIV infection. Ageing Res Rev. 10(1):163–172
114. Horvath S, Levine AJ (2015) HIV-1 infection accelerates age according to the epigenetic clock. J Infect Dis 212(10):1563–1573
115. Appay V, Sauce D (2008) Immune activation and inflammation in HIV-1 infection: causes and consequences. J Pathol. 214(2):231–241
116. Neuhaus J, Jacobs DR Jr, Baker JV, Calmy A, Duprez D, La Rosa A et al (2010) Markers of inflammation, coagulation, and renal function are elevated in adults with HIV infection. J Infect Dis. 201(12):1788–1795
117. Burdo TH, Lo J, Abbara S, Wei J, DeLelys ME, Preffer F et al (2011) Soluble CD163, a novel marker of activated macrophages, is elevated and associated with noncalcified coronary plaque in HIV-infected patients. J Infect Dis. 204(8):1227–1236
118. Appay V, Kelleher AD (2016) Immune activation and immune aging in HIV infection. Curr Opin HIV AIDS. 11(2):242–249
119. Wikby A, Mansson IA, Johansson B, Strindhall J, Nilsson SE (2008) The immune risk profile is associated with age and gender: findings from three Swedish population studies of individuals 20–100 years of age. Biogerontology. 9(5):299–308
120. Duffau P, Wittkop L, Lazaro E, le Marec F, Cognet C, Blanco P et al (2015) Association of immune-activation and senescence markers with non-AIDS-defining comorbidities in HIV-suppressed patients. Aids. 29(16):2099–2108
121. Petoumenos K, Choi JY, Hoy J, Kiertiburanakul S, Ng OT, Boyd M et al (2017) CD4:CD8 ratio comparison between cohorts of HIV-positive Asians and Caucasians upon commencement of antiretroviral therapy. Antivir Ther. 22(8):659–668
122. Yap SH, Abdullah NK, McStea M, Takayama K, Chong ML, Crisci E et al (2017) HIV/Human herpesvirus co-infections: impact on tryptophan-kynurenine pathway and immune reconstitution. PLoS One. 12(10):e0186000
123. Jevtic S, Sengar AS, Salter MW, McLaurin J (2017) The role of the immune system in Alzheimer disease: etiology and treatment. Ageing Res Rev. 40:84–94
124. van der Flier WM, Skoog I, Schneider JA, Pantoni L, Mok V, Chen CLH et al (2018) Vascular cognitive impairment. Nat Rev Dis Primers. 4(18003):18003
125. Brew BJ, Crowe SM, Landay A, Cysique LA, Guillemin G (2009) Neurodegeneration and ageing in the HAART era. J Neuroimmune Pharmacol. 4(2):163–174
126. Schweinsburg BC, Taylor MJ, Alhassoon OM, Gonzalez R, Brown GG, Ellis RJ et al (2005) Brain mitochondrial injury in human immunodeficiency virus-seropositive (HIV +) individuals taking nucleoside reverse transcriptase inhibitors. J Neurovirol. 11(4):356–364
127. Apostolova N, Funes HA, Blas-Garcia A, Galindo MJ, Alvarez A, Esplugues JV (2015) Efavirenz and the CNS: what we already know and questions that need to be answered. J Antimicrob Chemother. 70(10):2693–2708
128. Soontornniyomkij V, Umlauf A, Soontornniyomkij B, Gouaux B, Ellis RJ, Levine AJ et al (2018) Association of antiretroviral therapy with brain aging changes among HIV-infected adults. Aids. 32(14):2005–2015
129. Lucas GM, Ross MJ, Stock PG, Shlipak MG, Wyatt CM, Gupta SK et al (2014) Clinical practice guideline for the management of chronic kidney disease in patients infected with HIV: 2014 update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis 59(9):e96–e138
130. Althoff KN, McGinnis KA, Wyatt CM, Freiberg MS, Gilbert C, Oursler KK et al (2015) Comparison of risk and age at diagnosis of myocardial infarction, end-stage renal disease, and non-AIDS-defining cancer in HIV-infected versus uninfected adults. Clin Infect Dis. 60(4):627–638
131. Yuen T, Brouillette MJ, Fellows LK, Ellis RJ, Letendre S, Heaton R et al (2017) personalized risk index for neurocognitive decline among people with well-controlled HIV infection. J Acquir Immune Defic Syndr. 76(1):48–54
132. Liyanage SI, Santos C, Weaver DF (2018) The hidden variables problem in Alzheimer's disease clinical trial design. Alzheimers Dement (NY). 4:628–635
133. Gates TM, Cysique LA, Siefried KJ, Chaganti J, Moffat KJ, Brew BJ (2016) Maraviroc-intensified combined antiretroviral therapy improves cognition in virally suppressed HIV-associated neurocognitive disorder. Aids. 30(4):591–600
134. Kamminga J, Lal L, Wright EJ, Bloch M, Brew BJ, Cysique LA (2017) Monitoring HIV-associated neurocognitive disorder using screenings: a critical review including guidelines for clinical and research use. Curr HIV/AIDS Rep. 14(3):83–92
135. Robbins RN, Gouse H, Brown HG, Ehlers A, Scott TM, Leu CS et al (2018) A mobile app to screen for neurocognitive impairment: preliminary validation of NeuroScreen among HIV-infected South African Adults. JMIR Mhealth Uhealth. 6(1):e5
136. Molsberry SA, Lecci F, Kingsley L, Junker B, Reynolds S, Goodkin K et al (2015) Mixed membership trajectory models of cognitive impairment in the multicenter AIDS cohort study. Aids. 29(6):713–721
137. Henry D, Tolan P, Gorman-Smith D, Schoeny M (2017) Alternatives to randomized control trial designs for community-based prevention evaluation. Prev Sci 18(6):671–680
138. Guaraldi G, Palella FJ (2017) Clinical implications of aging with HIV infection: perspectives and the future medical care agenda. Aids 31(Suppl 2):S129–S135
139. Rueda S, Law S, Rourke SB (2014) Psychosocial, mental health, and behavioral issues of aging with HIV. Curr Opin HIV AIDS 9(4):325–331
140. Levin J. Aging of HIV-Infected: a explosive and underestimated phenomena being ignored, needs attention—special support services for patients & clinics needed-lack of federal/state response—HCV too—Commentary by Jules Levin. Community Perspectives: "A call to action: What should our research, care, education and social support priorities be?" http://www.natap.org/2017/HIV/040417_01.htm2018
141. Cummins D, Waters D, Aggar C, Crawford D, Fethney J, O'Connor C (2018) Voices from Australia-concerns about HIV associated neurocognitive disorder. AIDS Care 30(5):609–617
142. Terpstra AR, Worthington C, Ibanez-Carrasco F, O'Brien KK, Yamamoto A, Chan Carusone S et al (2018) I'm Just Forgetting and I Don't Know Why": exploring how people living with HIV-associated neurocognitive disorder view, manage, and obtain support for their cognitive difficulties. Qual Health Res 28(6):859–872