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SUPPLEMENT ARTICLE

Cognitive Health in Persons With Human Immunodeficiency Virus: The Impact of Early Treatment, Comorbidities, and Aging

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With the advent of virally suppressive antiretroviral therapy (ART), life expectancy for persons with human immunodeficiency virus (HIV) with access to ART now approaches that of the general population. As persons with HIV age, noninfectious comorbidities occur more frequently compared with persons without HIV. Such comorbidities are likely to affect cognitive health, which may also be affected by lifestyle factors that may differ in persons with HIV.

At the National Institutes of Health–supported meeting on Biotypes of Central Nervous System (CNS) Complications in persons with HIV, a session was devoted to early HIV treatment, noninfectious comorbidities, and aging as each pertains to cognitive health. Areas of consideration included acute and early HIV infection (presentation by Phillip Chan), drugs of abuse (Scott Letendre), stroke and cerebrovascular disease (Felicia Chow), mental health (John Joska), and aging (Julian Falutz).

These presentations were followed by a discussion session led by Woody Lin, Jose A. Muñoz-Moreno, Paola Cinque, and Jeff Taylor. Alan Winston and Bruce Brew chaired the meeting with Jasmini Alagaratnam and Htein Linn Aung acting as rapporteurs.

Here we present the main topics covered in the presentations, and the associated discussions highlighting knowledge gaps and future directions.

IMPACT OF ART WITHIN THE FIRST YEAR OF HIV INFECTION

Cognitive disorders remain prevalent among persons with HIV with viral suppression in the ART era. It is well described that a longer duration of untreated HIV, lower nadir $CD4^+$ T-lymphocyte count, and previous AIDS-defining illnesses are associated with cognitive impairment in persons with HIV [1]. The time of onset of CNS injury following HIV acquisition and its reversibility after early initiation of ART remain unclear. The extent to which early ART protects the CNS remains a major question in the field [2, 3].

Recent studies assessing the CNS impact of acute HIV infection (AHI) [4] or primary HIV infection (PHI, here defined as the first 12 months following HIV infection) have provided insight into some of these questions. The RV254 Thai AHI cohort characterizes the very earliest effects of HIV on the CNS. HIV RNA is detectable in the cerebrospinal fluid (CSF) within days of HIV acquisition, with more than 90% of individuals having detectable CSF HIV RNA by the end of AHI [5]. Although slowed hand movements [6], peripheral neuropathy [6], depressed mood [7, 8], impaired cognition [9] and elevated CSF inflammatory and immune activation markers [10] are common during untreated AHI, the timing of CNS HIV compartmentalization and onset of neuronal damage remain elusive. Recent work suggests that these events may occur as early as the first year of HIV infection. CSF neurofilament light chain protein, a biomarker of axonal injury, is elevated in up to 40% (PHI) and 75% (chronic HIV infection) of individuals, but rarely during AHI [11, 12]. Evidence of compartmentalized HIV replication within the CSF was demonstrated in up to 30% of individuals during PHI [13–15]. Conversely, a recent deep sequencing study revealed that only a limited number of persons with AHI had evidence of compartmentalized HIV in CSF, exclusively among those who acquired multiple transmitted or founder (T/F) viruses [16].

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While evidence supporting HIV compartmentalization and neuronal injury during AHI is lacking, initiation of ART during AHI points toward favorable neurological outcomes [10, 11, 17, 18]. The frequency of CSF viral escape was 1% in RV254 participants who commenced ART during AHI [18], compared with up to 5%–10% in individuals who commenced ART during chronic infection. Additionally, the cognitive test performance and mood symptoms of RV254 cohort participants improved with immediate ART and remained stable up to 288 weeks of follow-up [17]. RV254 participants also normalized inflammatory and immune activation biomarkers in CSF but not in plasma after 96 weeks of ART [10]. Biomarker studies focusing on later time points are needed to determine the long-term benefit of early ART in the CNS.

To date, the cohorts investigating early HIV infection on the CNS have predominantly enrolled young men and therefore results may not generalize to other populations with differing demographic factors and comorbidities, including age, sex, coinfections, infection with multiple T/F viruses, and substance use, each of which may alter the degree of HIV transmigration between blood and CSF. Furthermore, cohorts assessing the early effects of HIV on the brain have been undertaken in settings with the infrastructure to identify early HIV infection; this may not be achievable in all healthcare settings.

There are differences in compartmentalization and degree of neuroinvasion of HIV into the CNS, though the factors that drive such differences are unclear. Similarly, the reasons for higher CD4/CD8 ratios and larger differences between plasma and CSF HIV RNA in people with AHI need further study.

Given that macrophage activation markers are strongly associated with cognitive decline, it would be important to investigate whether these markers normalize in the blood compartment over the longer term (>10 years of follow-up) and whether associations with cognitive impairment persist.

In people who initiated early ART, cognitive function remains stable, though whether this remains true in the longer term requires longer follow-up. Participants with the poorest cognitive performance at baseline had the greatest improvements over 6 years of follow-up. This is in contrast with what is seen in people with chronic HIV infection, who are at higher risk of further deterioration in cognitive function [19, 20].

DRUGS OF ABUSE AND BRAIN HEALTH

The prevalence of HIV infection is high in people who inject addictive drugs. A systematic review estimated that the prevalence of HIV among people who inject drugs globally is 17.8% (10.8%–24.8%) [21]. Drug use is also common among people with HIV; for instance, the United States (US) Centers for Disease Control and Prevention reported that about 12% of persons with HIV have ever injected an addictive drug [22] and about 40% have used a noninjection drug in the past 12 months in the US [23].

HIV infection and drug use have synergistic effects on the CNS [24, 25]. For example, both HIV infection and drug use alter dopamine uptake and release by dysregulating the dopamine transporter and subsequently lead to increased extracellular dopamine level in the CNS [26]. This, in turn, could have adverse effects because extracellular dopamine can affect lymphoid, myeloid, and glial cell function [26]. For example, dopamine can increase the migration of $CD14^{+}CD16^{+}$ monocytes across blood-brain barrier models, which is important as in people with HIV, these cells harbor higher HIV DNA content and have been linked to cognitive impairment [27, 28].

HIV infection and drug use also affect the vascular system, which may manifest as white matter abnormalities in the brain. A recent study reported that both HIV infection and methamphetamine use increased fractional anisotropy in diffuse tensor imaging, which reflects disruption of white matter tracts and is associated with poorer cognitive outcome [29]. The combined effects of HIV infection and drug use on cerebral blood flow and functional blood flow are also evident [30].

Understanding the effects of different patterns of addictive drugs on the brain is important. Drug use pattern can vary based on sites, regions, and countries; the use of standardized data collection across studies will allow assessment of geographical variation of drug use, along with additional information, such as the route, quantity (both current and over the lifetime), and age of first drug use. Syndemic social and structural factors should also be considered when managing drug use and HIV. Poor socioeconomic status and childhood adversity often coexist with drug use and also have an adverse impact on engagement in healthcare [31, 32]. Thus, data on social and structural factors, along with drug use patterns, are important.

Genetic and epigenetic factors also play a role in how HIV and addictive drug use affect the CNS. For instance, the effects of methamphetamine on cognition may differ based on genotypic variation in catechol-O-methyltransferase (which is involved in the metabolism of dopamine and other neurotransmitters) [33] and cytochrome P450-2D6 enzyme, which metabolizes methamphetamine [34]. A postmortem study of brain tissues reported the synergistic effects of HIV and drug use on the increase in global DNA methylation, which is associated with neuropsychiatric disorders [35]. Interventions that could address these epigenetic changes may decrease the legacy effects of drug use.

The concept of molecular networks, which identifies HIV transmission networks through viral genetics, also require consideration [36]. These transmission networks can be mapped geographically, to examine where transmissions occur, where they are concentrated, how networks interact with each other, and where high-transmission events occur [37]. Using this information, targeted interventions could be provided to "high transmitters" to encourage drug use cessation and use of safer

practices [38]. Clinical trials of new drugs to treat drug dependency (eg, naltrexone or bupropion for methamphetamine dependence) have had encouraging results and could be used in these interventions [39]. Other factors to consider include the stressful effects of drug use withdrawal on HIV disease and mental health, and the nonlinear effects of some drugs on the brain. For example, even though heavy use of cannabis is detrimental, mild to moderate use may be beneficial in persons with HIV, possibly related to the anti-inflammatory effects of cannabis counterbalancing the adverse effects of chronic dopaminergic stimulation [40, 41].

Key gaps exist in multiple areas of how drug use affects CNS biotypes. As summarized in NIH RFA-DA-22-040 (https://grants.nih.gov/grants/guide/rfa-files/RFA-DA-22-040.html) and other sources, these can be categorized as those that relate to (1) cognition, psychiatry, and behavior; (2) pathogenesis; (3) prevention and therapeutics; and (4) modeling. With regard to cognition, psychiatry, and behavior, key gaps include (1) identifying the influence of psychiatric comorbidities on drug use/effects in persons with HIV and (2) determining strategies and interventions to reduce stigma and address social and structural issues that affect persons with HIV. With regard to pathogenesis, key gaps include identifying (1) the influence of infectious diseases on prevention and treatment of drug use disorders in persons with HIV and (2) the influence of drug use on the molecular mechanisms of HIV latency in the CNS. Examples of key gaps in prevention and therapeutics include developing and testing (1) methods to deliver HIV and drug use therapeutics to persons with HIV and (2) approaches to achieve sustained ART-free remission among persons who use drugs and who experience ART interruptions and delays, and relapse in drug use. Continuing work in modeling of HIV and drug use includes using spatial genomics and other state-of-the art strategies to address questions at the intersection of HIV and drug use disorders.

STROKE, CEREBROVASCULAR DISEASE, AND HIV-ASSOCIATED COGNITIVE IMPAIRMENT

Both large vessel stroke and cerebral small vessel disease (CSVD) contribute to vascular cognitive impairment. The prevalence of stroke is higher among persons with HIV than the general population [42]. A meta-analysis of prospective observational studies reported that the risk of ischemic stroke and hemorrhagic stroke are 1.3 times and 2.2 times higher among persons with HIV than persons without HIV [43]. Furthermore, in high-HIV-prevalence areas of the world, HIV is a primary risk factor for stroke. In a study conducted in Malawi, HIV infection was the second leading risk factor for stroke after hypertension [44].

Despite the robust evidence of a higher burden of stroke among persons with HIV than persons without HIV, findings from previous studies on the risk for CSVD among persons with HIV are mixed. Several studies have demonstrated a higher risk of CSVD, measured by the burden of white matter hyperintensities (WMH), among persons with HIV. One study found the risk of CSVD was 2.3-fold higher among 456 treated persons with HIV under viral suppression compared with 154 persons without HIV [45]. In another study, 203 treated persons with HIV (viral load <200 copies/mL) had a 3.7-fold greater risk of WMH than 58 persons without HIV [46]. However, not all studies have identified a higher burden of CSVD in persons with HIV [47]. For instance, a study conducted among 119 treated and virally suppressed persons with HIV and 55 persons without HIV reported no difference in WMHs between the groups [48]. Several factors may explain these disparate findings, including differences in the age and sex distribution of participants, the degree of viral suppression of persons with HIV, and the quality of matching of persons with HIV and persons without HIV.

While the risk of stroke and possibly of CSVD is higher among persons with HIV, differences in the effect of aging on cerebrovascular pathology among persons with HIV compared with persons without HIV has not been shown. Several studies suggest that the effect of age on brain pathology including WMHs is worse among persons with HIV than persons without HIV [49, 50]. However, the Comorbidity in Relation to AIDS (COBRA) study, which recruited persons without HIV who were well-matched to HIV-infected participants in terms of vascular risk factors, did not find accelerated brain pathology among persons with HIV [51].

Both HIV-specific variables (eg, viral load, immunosuppression, and possibly immune reconstitution, inflammatory markers, and antiretroviral drugs) and non-HIV-related vascular risk factors (eg, older age, smoking, and hypertension) contribute to cerebrovascular pathology among persons with HIV [52–56]. However, in most studies, traditional vascular risk factors appear to be the primary drivers of CSVD in persons with HIV [46].

As in the general population, CSVD and cardiovascular risk factors (eg, diabetes and hypercholesterolemia) are associated with poorer cognition among persons with HIV [57–60]. Few studies have evaluated the association between clinical stroke events and cognitive impairment among persons with HIV. In studies that have identified an association between CSVD and cognition, the effect of CSVD on poorer cognition was independent and not synergistic with HIV infection [48, 57].

Sex may moderate the effect of cerebrovascular disease on cognition. Previous studies have found a higher risk of stroke associated with HIV for women compared with men [55, 61, 62]. A US-based study conducted by Chow et al [55] among 4308 persons with HIV (73% with viral load <400 copies/mL) and 32 423 persons without HIV identified that the hazard of developing ischemic stroke was 76% higher among women compared with men. In addition, studies have observed sex differences in the association between cardiovascular risk factors

and cognition in persons with HIV, with a significant association present only among women and not men [55]. Hence, future studies should be balanced for sex and conduct stratified analyses based on sex to identify the drivers of risk differences between women and men with HIV.

Stress and depression, which are highly prevalent among persons with HIV, may modify the association between cerebrovascular disease and cognition. Stress and depression are established risk factors for stroke [63–66] and cognitive dysfunction [67–69] among both persons with HIV and the general population. Inflammation may be a shared mechanism through which stress contributes to and aggravates the risk of stroke and cognitive impairment in persons with HIV [70].

Critical knowledge gaps in the field include whether targeting cardiovascular risk factors will decrease the risk of cognitive impairment or prevent cognitive decline among persons with HIV; whether the impact of stroke and CSVD on cognition is similar in low- and middle-income countries as in the high-income settings where most of these studies have been done; if race/ethnicity alters the relationship between cerebrovascular disease on cognition; and, finally, which biomarkers identify those at higher risk of vascular-related cognitive impairment and those who may respond best to interventions.

MENTAL HEALTH AND COGNITIVE DISORDERS IN PERSONS WITH HIV

Mental health disorders are common among persons with HIV, and median depression prevalence in the combination ART era is estimated to be 24% [71], ranging from 11% to 53% [72]. Notably, mental health disorders are at least 20%–100% more common among persons with HIV than the general population [73]. For instance, lifetime posttraumatic stress disorder is about 4 to 8 times more prevalent and current depression is 3 times more common among persons with HIV than the general population, albeit with wide confidence intervals.

Depression has a complex association with cognitive impairment. Previous cross-sectional and longitudinal studies conducted among persons with HIV reported that depression is associated with cognitive impairment and decline to symptomatic cognitive disorders [71]. However, the association between depression and cognitive disorders is not greater among persons with HIV than the general population, indicating that there is no interaction effect between HIV infection and depression on cognition [71]. The association between depression and cognition may depend on the severity of the depression and whether it is current, recurrent, or lifetime [71, 74]. In addition, aging may also mediate the effect of depression on cognition, and older people may be more vulnerable to the effect of depression on cognitive disorders.

Depression may be related to peripheral inflammation. In a study conducted among persons without HIV [75], antidepressants improved inflammatory biomarkers such as CCR5 and CCL5 among those who responded to the treatment, and interleukin 6 in all the participants irrespective of response to antidepressants. In another study conducted among 143 persons with HIV (79% with undetectable viral load), increased C-reactive protein, an inflammatory biomarker, was associated with cognitive impairment, but only among those with severe depression [76].

Another important finding is that antidepressants may improve cognition. In a preclinical study by Steiner et al [77], paroxetine had a protective effect on hippocampal neurons among rats. Another phase 1/2 double-blinded randomized controlled trial conducted by the same group among 45 persons with HIV on stable ART showed that paroxetine improved performance in some cognitive domains after 24 weeks [78].

In terms of depression assessment tools, currently available brief screening tools that are commonly used and assumed to be gold-standard tests have limitations when used globally. First, they were developed in high-income settings and not validated in low- and middle-income countries. Second, these tools do not consider local aspects of distress. Third, they emphasize current symptoms rather than lifetime depression.

Mental health problems need to be assessed in a life-course approach. All life events including childhood trauma, poverty, lower education, deprivation, food insecurity, and unstable relationships need to be considered in the diagnostic assessment. These conditions increase the risk for traumatic stress, depression, and alcohol and drug use disorders, which are related to cognitive disorders [79–81].

Research Domain Criteria (RDoC) is a research framework, which unlike traditional symptom-based diagnostic approaches, classifies mental disorders biologically based on neuroscience, genetics, and behavioral science [82, 83]. While RDoC is increasingly recommended to identify the influences on neurological manifestations in persons with HIV, integrating features of RDoC into research and clinical practice could be challenging [82, 83]. Important questions to be addressed are whether current diagnostic or screening tools can be translated into RDoC measures or if RDoC is needed alongside traditional measures, and whether clinician researchers can invest sufficient time and resources to apply all the aspects of RDoC.

There are numerous limitations in the existing research such as small sample sizes, dominance of cross-sectional study designs, paucity of studies with female participants, and heterogeneities in measures used and sample characteristics. Therefore, the following points should be considered for future research: which tools are to be commonly used for mental health screening (a single or a set of tools); if it is possible to recruit a large cohort and collect both retrospective and life-course data, which is always challenging; whether these data can be integrated across different cohorts for innovative big-data analysis; and how cost-effective trials can be conducted in resource-limited settings.

AGING CONSIDERATIONS

The impact of selected geriatric syndromes on cognitive function in treated persons with HIV is a current topic that interlinks with frailty, sensory impairment, and mobility impairment. Preliminary data suggest that persons with HIV on virologically suppressive ART continue to be at increased risk of common geriatric syndromes compared to persons without HIV [84]. However, the impact of unmeasured confounders driving these differences is unclear.

Frailty is a state of increased vulnerability to biological and environmental stressors, which leads to increased risk of comorbidities, disabilities, and mortality. Frailty is related to the inability to maintain homeostasis in multiple organ systems and is due in part to decreased physiological reserve [85]. Frailty is associated with aging, and an association is increasingly recognized between frailty and chronic inflammation [86], which may also contribute to other common age-related conditions. The consequences of frailty include the development of new comorbidities, increased risk of hospitalization, malnutrition, loss of independence, cognitive impairment, and increased mortality.

A novel concept is that of cognitive frailty, which is a heterogenous condition that is characterized by the concurrent presence of both cognitive impairment, without dementia, and physical frailty [87]. In this context, the cognitive impairment may be mild, related to the underlying physical condition, and importantly, has the potential for reversibility. However, unresolved controversies include the precise diagnostic criteria, the distinction from mild cognitive impairment, its relationship with cognitive reserve, and whether it is a precursor for dementia [88].

Low gait speed is reported to be associated with poorer cognitive performance in multiple domains, both in the general population [89] and in persons with HIV [90]. Sarcopenia may link impaired mobility with the pathogenesis of cognitive decline [91]. With regard to sensory impairment and cognition, visual and hearing impairment in the general population are associated with increased risk of dementia [92]. While these associations have not been specifically investigated in persons with HIV, they are at increased risk of macular degeneration [93], as well as both high- and low-frequency pure tone hearing impairment, which can lead to communication difficulties [94]. Early data suggest that in the general population, smell impairment may be an early marker of Alzheimer disease [95]. Preliminary data from 2 US-based studies suggest that persons with HIV who are at high risk for amnestic mild cognitive impairment have poorer ability to detect smells in objective tasks, compared with people considered to be at low risk [96]. In the general population, the presence of multiple sensory impairment increases the risk of developing dementia compared with single sensory impairments [97]. Persons with HIV with multisensory impairments may have at least a similar increased risk of dementia but this remains to be determined.

In summary, these data surrounding geriatric syndromes in persons with HIV remain preliminary and descriptive, and important knowledge gaps exist with regard to the relationship between geriatric syndromes and the impact on cognition. The presence of multiple geriatric syndromes may increase the risk of cognitive impairment in the general population, with evidence to suggest that this is also the case in persons with HIV. Cognitive frailty is still a novel and evolving concept, with several controversial facets that need defining and investigating before it can be accepted as a true entity and incorporated into clinical and research criteria. In persons with HIV, this also currently remains an unknown but potentially important condition to be investigated. Certain geriatric syndromes may be manageable and potentially reversible. Thus, a major area of future research will be on interventions to prevent, mitigate, or reverse cognitive disorders associated with geriatric syndromes, and thereby to potentially improve the overall health span of persons with HIV.

The interactions between frailty and sarcopenia remain under investigation, as does the contribution of sarcopenia to mobility impairment, thereby affecting functional status with downstream consequences for cognition. Further studies of the impact of various sensory deficits on cognition are warranted. Cognitive frailty is still an evolving construct, with several aspects that need defining and clarification before it can be incorporated into clinical and research protocols. Its potential for reversal increases the interest into better insight into this condition.

CONCLUSIONS

Herein we have outlined the potential contribution of the initiation of ART within the first year of HIV acquisition, drug abuse, cerebrovascular health, mental health, and aging to cognitive health in persons with HIV. The contribution of these factors, and some other factors not discussed in this report, are summarized in Figure 1. While current thinking and data point to an additive rather than synergistic role for the effect of comorbidities on cognitive health in persons with HIV, the exact contribution the presence of comorbidities has on cognitive health remains unclear. Indeed, questions remain around possible increased susceptibility to some comorbidities (even in the presence of traditional risk factors) and whether there is increased severity or altered phenotype of such comorbidities (eg, noncalcified atheromatous plaque appears to be more clinically important in persons with HIV).

Several important considerations have been highlighted. First, evolving data suggest that the very early initiation of ART may partly, or even entirely, mitigate the CNS effects of HIV infection, the so-called legacy effects of untreated HIV. However, these findings need to be validated in other settings,

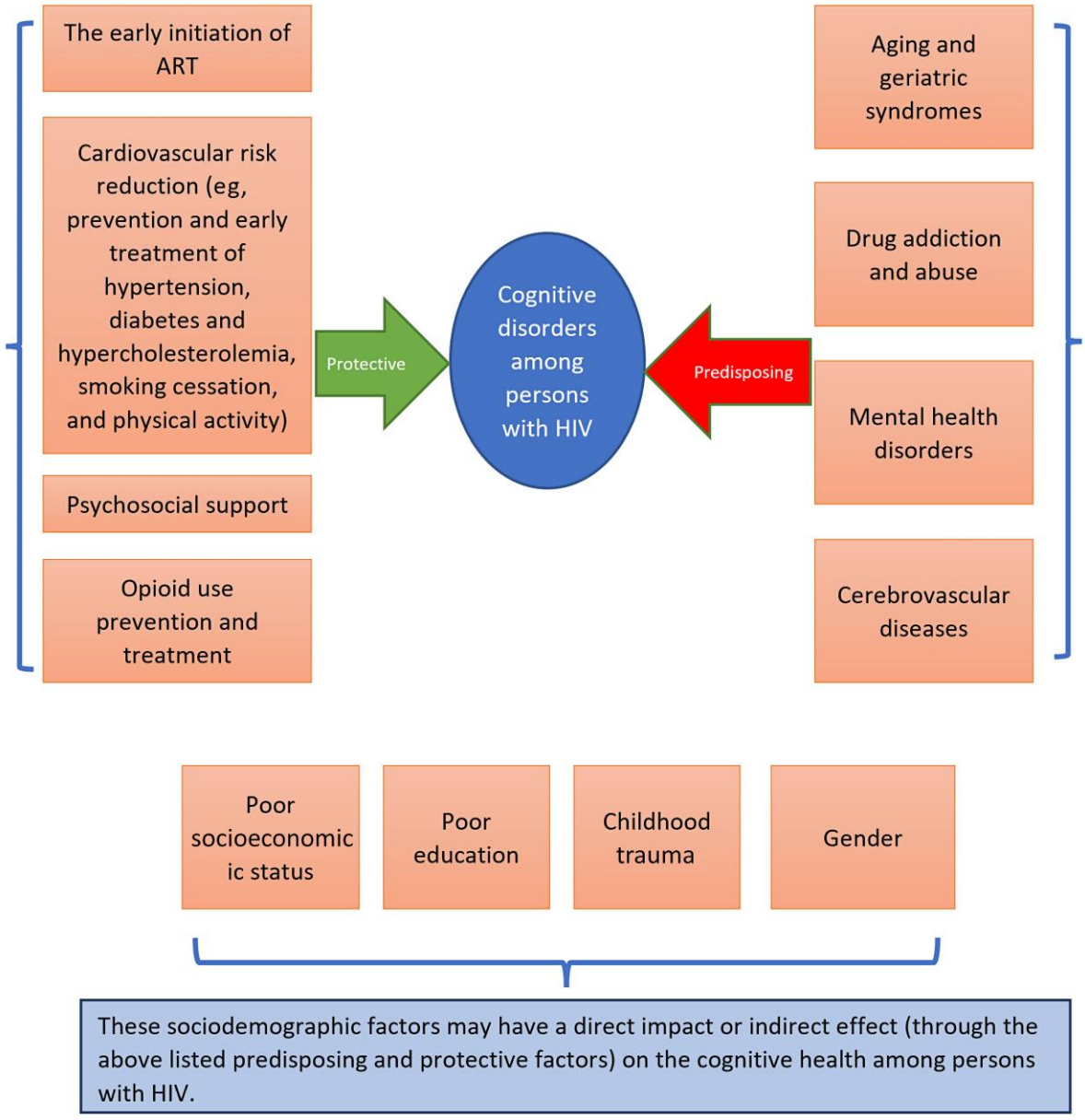

Figure 1. Effects of early treatment, comorbidities, and aging on cognition among persons with human immunodeficiency virus. Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus.

have a longer duration of follow-up, and include other sensitive modalities to assess CNS health. Nonetheless, consideration must be given to the rapid initiation of ART in individuals with newly acquired HIV infection. Most healthcare settings worldwide are unable to undertake frequent HIV testing and ensure that HIV care is offered rapidly to those with newly acquired HIV. To facilitate this, early detection and treatment clinical pathways are urgently needed across all healthcare settings.

Second, the impact of comorbidities, drug abuse, aging, frailty, and mental health on cognitive health in persons with HIV are likely highly significant, as outlined in the above sections of this manuscript. However, the true impact each of these factors has on cognitive health in persons with HIV is challenging to ascertain. Longitudinal studies are required with a long enough duration to observe the effects of such factors. Funding for longitudinal studies of sufficient duration is always challenging, but awareness of this challenge should be highlighted to national and international funding bodies, citing the profound success of other cohorts such as Framingham [98]. Determining the impact of these complex social, medical, and psychological factors across different healthcare settings and different economic settings is needed. Consensus on the optimal metrics is urgently required while being mindful that such metrics have to be

acceptable and achievably measured across diverse cultural and healthcare settings.

Notes

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References

1. Smail RC, Brew BJ. HIV-associated neurocognitive disorder. In: Brew BJ, ed. Handb Clin Neurol **2018**; 152:75–97.
2. Ellis RJ, Badiee J, Vaida F, et al. CD4 nadir is a predictor of HIV neurocognitive impairment in the era of combination antiretroviral therapy. AIDS **2011**; 25:1747–51.
3. Muñoz-Moreno JA, Fumaz CR, Ferrer MJ, et al. Nadir CD4 cell count predicts neurocognitive impairment in HIV-infected patients. AIDS Res Hum Retroviruses **2008**; 24:1301–7.
4. Fiebig EW, Wright DJ, Rawal BD, et al. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. AIDS **2003**; 17:1871–9.
5. Chan P, Patel P, Hellmuth J, et al. Distribution of HIV RNA in CSF and blood is linked to CD4/CD8 ratio during acute HIV. J Infect Dis **2018**; 218:937–45.
6. Hellmuth J, Fletcher JL, Valcour V, et al. Neurologic signs and symptoms frequently manifest in acute HIV infection. Neurology **2016**; 87:148–54.
7. Hellmuth J, Colby D, Valcour V, et al. Depression and anxiety are common in acute HIV infection and associate with plasma immune activation. AIDS Behav **2017**; 21:3238–46.
8. Prats A, Martínez-Zalacaín I, Mothe B, et al. Effects of integrase inhibitor–based antiretroviral therapy on brain outcomes according to time since acquisition of HIV-1 infection. Sci Rep **2021**; 11:1–9.
9. Kore I, Ananworanich J, Valcour V, et al. Neuropsychological impairment in acute HIV and the effect of immediate antiretroviral therapy. J Acquir Immune Defic Syndr **2015**; 70: 393–9.
10. Hellmuth J, Slike BM, Sacdalan C, et al. Very early initiation of antiretroviral therapy during acute HIV infection is associated with normalized levels of immune activation markers in cerebrospinal fluid but not in plasma. J Infect Dis **2019**; 220:1885–91.
11. Peluso MJ, Valcour V, Ananworanich J, et al. Absence of cerebrospinal fluid signs of neuronal injury before and after immediate antiretroviral therapy in acute HIV infection. J Infect Dis **2015**; 212:1759–67.
12. Peluso MJ, Meyerhoff DJ, Price RW, et al. Cerebrospinal fluid and neuroimaging biomarker abnormalities suggest early neurological injury in a subset of individuals during primary HIV infection. J Infect Dis **2013**; 207:1703–12.
13. Sturdevant CB, Joseph SB, Schnell G, Price RW, Swanstrom R, Spudich S. Compartmentalized replication of R5 T cell-tropic HIV-1 in the central nervous system early in the course of infection. PLoS Pathog **2015**; 11:e1004720.
14. Gega A, Kozal MJ, Chiarella J, et al. Deep sequencing of HIV-1 variants from paired plasma and cerebrospinal fluid during primary HIV infection. J Virus Erad **2015**; 1:264–8.
15. Schnell G, Price RW, Swanstrom R, Spudich S. Compartmentalization and clonal amplification of HIV-1 variants in the cerebrospinal fluid during primary infection. J Virol **2010**; 84:2395–407.
16. Tovanabutra S, Sirijatuphat R, Pham PT, et al. Deep sequencing reveals central nervous system compartmentalization in multiple transmitted/founder virus acute HIV-1 infection. Cells **2019**; 8:902.

17. Chan P, Kerr SJ, Kroon E, et al. Cognitive trajectories after treatment in acute HIV infection. AIDS **2021**; 35:883–8.
18. Handoko R, Chan P, Jagodzinski L, et al. Minimal detection of cerebrospinal fluid escape after initiation of antiretroviral therapy in acute HIV-1 infection. AIDS **2021**; 35: 777–82.
19. Gott C, Gates T, Dermody N, Brew BJ, Cysique LA. Cognitive change trajectories in virally suppressed HIV-infected individuals indicate high prevalence of disease activity. PLoS One **2017**; 12:e0171887.
20. Brouillette M-J, Yuen T, Fellows LK, Cysique LA, Heaton RK, Mayo NE. Identifying neurocognitive decline at 36 months among HIV-positive participants in the CHARTER cohort using group-based trajectory analysis. PLoS One **2016**; 11:e0155766.
21. Degenhardt L, Peacock A, Colledge S, et al. Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic review. Lancet Glob Health **2017**; 5:e1192–207.
22. Centers for Disease Control and Prevention (CDC). HIV surveillance report, 2018 (updated). Vol. 31. Atlanta, GA: CDC, **2020**.
23. Centers for Disease Control and Prevention (CDC). HIV infection risk, prevention, and testing behaviors among persons who inject drugs—national HIV behavioral surveillance: injection drug use, 23 U.S. cities, 2018. HIV surveillance special report. Atlanta, GA: CDC, **2020**.
24. Hauser KF, El-Hage N, Stiene-Martin A, et al. HIV-1 neuropathogenesis: glial mechanisms revealed through substance abuse. J Neurochem **2007**; 100:567–86.
25. Ferris MJ, Mactutus CF, Booze RM. Neurotoxic profiles of HIV, psychostimulant drugs of abuse, and their concerted effect on the brain: current status of dopamine system vulnerability in neuroAIDS. Neurosci Biobehav Rev **2008**; 32: 883–909.
26. Gaskill PJ, Calderon TM, Coley JS, Berman JW. Drug induced increases in CNS dopamine alter monocyte, macrophage and T cell functions: implications for HAND. J Neuroimmune Pharmacol **2013**; 8:621–42.
27. Valcour V, Shiramizu B, Sithinamsuwan P, et al. HIV DNA and cognition in a Thai longitudinal HAART initiation cohort: the SEARCH 001 Cohort Study. Neurology **2009**; 72: 992–8.
28. Calderon TM, Williams DW, Lopez L, et al. Dopamine increases $CD14^{+}CD16^{+}$ monocyte transmigration across the blood brain barrier: implications for substance abuse and HIV neuropathogenesis. J Neuroimmune Pharmacol **2017**; 12:353.
29. McKenna BS, Brown GG, Archibald S, et al. Microstructural changes to the brain of mice after methamphetamine exposure as identified with diffusion tensor imaging. Psychiatry Res **2016**; 249:27–37.
30. Ances BM, Vaida F, Cherner M, et al. HIV and chronic methamphetamine dependence affect cerebral blood flow. J Neuroimmune Pharmacol **2011**; 6:409–19.
31. Krüsi A, Wood E, Montaner J, Kerr T. Social and structural determinants of HAART access and adherence among injection drug users. Int J Drug Policy **2010**; 21:4–9.
32. Milloy M-J, Marshall B, Kerr T, et al. Social and structural factors associated with HIV disease progression among illicit drug users: a systematic review. AIDS **2012**; 26:1049.
33. Bousman C, Cherner M, Atkinson J, et al. COMT Val158met polymorphism, executive dysfunction, and sexual risk behavior in the context of HIV infection and methamphetamine dependence. Interdiscip Perspect Infect Dis **2010**; 2010:678648.
34. Cherner M, Bousman C, Everall I, et al. Cytochrome P450-2D6 extensive metabolizers are more vulnerable to methamphetamine-associated neurocognitive impairment: preliminary findings. J Int Neuropsychol Soc **2010**; 16:890–901.
35. Desplats P, Dumaop W, Cronin P, et al. Epigenetic alterations in the brain associated with HIV-1 infection and methamphetamine dependence. PLoS One **2014**; 9: e102555.
36. Mazrouee S, Little SJ, Wertheim JO. Incorporating metadata in HIV transmission network reconstruction: a machine learning feasibility assessment. PLoS Comput Biol **2021**; 17:e1009336.
37. Campbell EM, Jia H, Shankar A, et al. Detailed transmission network analysis of a large opiate-driven outbreak of HIV infection in the United States. J Infect Dis **2017**; 216:1053–62.
38. Wang X, Wu Y, Mao L, et al. Targeting HIV prevention based on molecular epidemiology among deeply sampled subnetworks of men who have sex with men. Clin Infect Dis **2015**; 61:1462–8.
39. Trivedi MH, Walker R, Ling W, et al. Bupropion and naltrexone in methamphetamine use disorder. N Engl J Med **2021**; 384:140–53.
40. Lake S, Kerr T, Werb D, et al. Guidelines for public health and safety metrics to evaluate the potential harms and benefits of cannabis regulation in Canada. Drug Alcohol Rev **2019**; 38:606–21.
41. Datta S, Ramamurthy PC, Anand U, et al. Wonder or evil? Multifaceted health hazards and health benefits of *Cannabis sativa* and its phytochemicals. Saudi J Biol Sci **2021**; 28:7290–313.
42. Rasmussen LD, Engsig FN, Christensen H, Gerstoft J, Kronborg G, Obel N. Risk of cerebrovascular events in persons with and without HIV: a Danish nationwide population-based cohort study. AIDS **2011**; 25:1637–46.

43. Gutierrez J, Albuquerque ALA, Falzon L. HIV infection as vascular risk: a systematic review of the literature and meta-analysis. PLoS One **2017**; 12:e0176686.
44. Benjamin LA, Corbett EL, Connor MD, et al. HIV, antiretroviral treatment, hypertension, and stroke in Malawian adults: a case-control study. Neurology **2016**; 86:324–33.
45. Moulignier A, Savatovsky J, Assoumou L, et al. 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 **2018**; 66:1762–9.
46. Mina Y, Wu T, Hsieh H-C, et al. Association of white matter hyperintensities with HIV status and vascular risk factors. Neurology **2021**; 96:e1823–34.
47. Haddow LJ, Sudre CH, Sokolska M, et al. Magnetic resonance imaging of cerebral small vessel disease in men living with HIV and HIV-negative men aged 50 and above. AIDS Res Hum Retroviruses **2019**; 35:453–60.
48. Sanford R, Strain J, Dadar M, et al. HIV infection and cerebral small vessel disease are independently associated with brain atrophy and cognitive impairment. AIDS **2019**; 33:1197.
49. Clifford KM, Samboju V, Cobigo Y, et al. Progressive brain atrophy despite persistent viral suppression in HIV patients older than 60 years. J Acquir Immune Defic Syndr **2017**; 76:289.
50. Seider TR, Gongvatana A, Woods AJ, et al. Age exacerbates HIV-associated white matter abnormalities. J Neurovirol **2016**; 22:201–12.
51. Cole JH, Caan MW, Underwood J, et al. 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 **2018**; 66:1899–909.
52. Benjamin LA, Allain TJ, Mzinganjira H, et al. The role of human immunodeficiency virus–associated vasculopathy in the etiology of stroke. J Infect Dis **2017**; 216:545–53.
53. Vinikoor MJ, Napravnik S, Floris-Moore M, Wilson S, Huang DY, Eron JJ. Incidence and clinical features of cerebrovascular disease among HIV-infected adults in the southeastern United States. AIDS Res Hum Retroviruses **2013**; 29:1068–74.
54. Chow FC, He W, Bacchetti P, et al. Elevated rates of intracerebral hemorrhage in individuals from a US clinical care HIV cohort. Neurology **2014**; 83:1705–11.
55. Chow FC, Regan S, Feske S, Meigs JB, Grinspoon SK, Triant VA. Comparison of ischemic stroke incidence in HIV-infected and non-HIV-infected patients in a US health care system. J Acquir Immune Defic Syndr **2012**; 60:351–8.
56. Johnson T, Nath A. Neurological complications of immune reconstitution in HIV-infected populations. Ann N Y Acad Sci **2010**; 1184:106–20.
57. Watson C, Busovaca E, Foley JM, et al. White matter hyperintensities correlate to cognition and fiber tract integrity in older adults with HIV. J Neurovirol **2017**; 23:422–9.
58. Valcour VG, Sacktor NC, Paul RH, et al. Insulin resistance is associated with cognition among HIV-1-infected patients: the Hawaii Aging With HIV cohort. J Acquir Immune Defic Syndr **2006**; 43:405–10.
59. Mukerji SS, Locascio JJ, Misra V, et al. Lipid profiles and APOE4 allele impact midlife cognitive decline in HIV-infected men on antiretroviral therapy. Clin Infect Dis **2016**; 63:1130–9.
60. Su T, Wit FW, Caan MW, et al. White matter hyperintensities in relation to cognition in HIV-infected men with sustained suppressed viral load on combination antiretroviral therapy. AIDS **2016**; 30:2329–39.
61. Tirschwell D, Chow F, Becker K, et al. Incidence of stroke in the US Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) Cohort (S51.008). Neurology **2017**; 88 (16 Supplement) S51.008.
62. Chow FC, Wilson MR, Kunling W, Ellis RJ, Bosch RJ, Linas BP. Stroke incidence is highest in women and non-Hispanic Blacks living with HIV in the ALLRT cohort. AIDS **2018**; 32:1125.
63. O'Donnell MJ, Chin SL, Rangarajan S, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. Lancet **2016**; 388:761–75.
64. Feigin VL, Roth GA, Naghavi M, et al. Global burden of stroke and risk factors in 188 countries, during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet Neurol **2016**; 15:913–24.
65. Levy ME, Anastos K, Levine SR, et al. Depression and psychosocial stress are associated with subclinical carotid atherosclerosis among women living with HIV. J Am Heart Assoc **2020**; 9:e016425.
66. Zifodya JS, Duncan MS, So-Armah KA, et al. Community-acquired pneumonia and risk of cardiovascular events in people living with HIV. J Am Heart Assoc **2020**; 9: e017645.
67. Rubin LH, Cook JA, Weber KM, et al. The association of perceived stress and verbal memory is greater in HIV-infected versus HIV-uninfected women. J Neurovirol **2015**; 21:422–32.
68. Rubin LH, Wu M, Sundermann EE, et al. Elevated stress is associated with prefrontal cortex dysfunction during a verbal memory task in women with HIV. J Neurovirol **2016**; 22: 840–51.
69. Rubin LH, Pyra M, Cook JA, et al. Post-traumatic stress is associated with verbal learning, memory, and psychomotor speed in HIV-infected and HIV-uninfected women. J Neurovirol **2016**; 22:159–69.

70. Tawakol A, Ishai A, Takx RA, et al. Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study. Lancet **2017**; 389:834–45.
71. Rubin LH, Maki PM. HIV, depression, and cognitive impairment in the era of effective antiretroviral therapy. Curr HIV/AIDS Rep **2019**; 16:82–95.
72. Akena D, Joska J, Obuku EA, Amos T, Musisi S, Stein DJ. Comparing the accuracy of brief versus long depression screening instruments which have been validated in low and middle income countries: a systematic review. BMC Psychiatry **2012**; 12:1–7.
73. Remien RH, Stirratt MJ, Nguyen N, Robbins RN, Pala AN, Mellins CA. Mental health and HIV/AIDS: the need for an integrated response. AIDS **2019**; 33:1411.
74. Safren SA, O'Cleirigh C, Andersen LS, et al. Treating depression and improving adherence in HIV care with task-shared cognitive behavioural therapy in Khayelitsha, South Africa: a randomized controlled trial. J Int AIDS Soc **2021**; 24:e25823.
75. Bauer O, Milenkovic VM, Hilbert S, et al. Association of chemokine (CC motif) receptor 5 and ligand 5 with recovery from major depressive disorder and related neurocognitive impairment. Neuroimmunomodulation **2020**; 27:152–62.
76. Saloner R, Paolillo EW, Heaton RK, et al. Chronically elevated depressive symptoms interact with acute increases in inflammation to predict worse neurocognition among people with HIV. J Neurovirol **2021**; 27:160–7.
77. Steiner JP, Bachani M, Wolfson-Stofko B, et al. Interaction of paroxetine with mitochondrial proteins mediates neuroprotection. Neurotherapeutics **2015**; 12:200–16.
78. Sacktor N, Skolasky RL, Moxley R, et al. Paroxetine and fluconazole therapy for HIV-associated neurocognitive impairment: results from a double-blind, placebo-controlled trial. J Neurovirol **2018**; 24:16–27.
79. Chibanda D, Benjamin L, Weiss HA, Abas M. Mental, neurological, and substance use disorders in people living with HIV/AIDS in low-and middle-income countries. J Acquir Immune Defic Syndr **2014**; 67:S54–67.
80. Spies G, Ahmed-Leitao F, Fennema-Notestine C, Cherner M, Seedat S. Effects of HIV and childhood trauma on brain morphometry and neurocognitive function. J Neurovirol **2016**; 22:149–58.
81. Muñoz-Moreno JA, Cysique LA, Rourke SB. Neuropsychiatric disorders, emotional disturbances, and their associations with HIV-associated neurocognitive disorder. Curr Top Behav Neurosci **2021**; 50:347–66.
82. Insel T, Cuthbert B, Garvey M, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry **2010**; 167:748–51.
83. Kozak MJ, Cuthbert BN. The NIMH research domain criteria initiative: background, issues, and pragmatics. Psychophysiology **2016**; 53:286–97.
84. Hosaka KR, Greene M, Premeaux TA, et al. Geriatric syndromes in older adults living with HIV and cognitive impairment. J Am Geriatr Soc **2019**; 67:1913–6.
85. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet **2013**; 381:752–62.
86. Soysal P, Stubbs B, Lucato P, et al. Inflammation and frailty in the elderly: a systematic review and meta-analysis. Ageing Res Rev **2016**; 31:1–8.
87. Kelaiditi E, Cesari M, Canevelli M, et al. Cognitive frailty: rational and definition from an (IANA/IAGG) international consensus group. J Nutr Health Aging **2013**; 17:726–34.
88. Cesari M, Sloane PD, Zimmerman S. The controversial condition of cognitive frailty: what it is, what it should be. J Am Med Dir Assoc **2020**; 21:146–8.
89. Grande G, Triolo F, Nuara A, Welmer AK, Fratiglioni L, Vetrano DL. Measuring gait speed to better identify prodromal dementia. Exp Gerontol **2019**; 124:110625.
90. Derry HM, Johnston CD, Burchett CO, Siegler EL, Glesby MJ. Gait speed is associated with cognitive function among older adults with HIV. J Aging Health **2020**; 32:1510–5.
91. Cipolli GC, Yassuda MS, Aprahamian I. Sarcopenia is associated with cognitive impairment in older adults: a systematic review and meta-analysis. J Nutr Health Aging **2019**; 23:525–31.
92. Whitson HE, Cronin-Golomb A, Cruickshanks KJ, et al. American Geriatrics Society and National Institute on Aging Bench-to-Bedside Conference: sensory impairment and cognitive decline in older adults. J Am Geriatr Soc **2018**; 66:2052–8.
93. Jabs DA, Van Natta ML, Pak JW, Danis RP, Hunt PW. Incidence of intermediate-stage age-related macular degeneration in patients with acquired immunodeficiency syndrome. Am J Ophthalmol **2017**; 179:151–8.
94. Torre P, Hoffman HJ, Springer G, et al. Hearing loss among HIV-seropositive and HIV-seronegative men and women. Otolaryngol Head Neck Surg **2015**; 141:202–10.
95. Murphy C. Olfactory and other sensory impairments in Alzheimer disease. Nat Rev Neurol **2019**; 15:11–24.
96. Sundermann EE, Fields A, Saloner R, et al. The utility of olfactory function in distinguishing early-stage Alzheimer's disease from HIV-associated neurocognitive disorders. AIDS **2021**; 35:429–37.
97. Brenowitz WD, Kaup AR, Lin FR, Yaffe K. Multiple sensory impairment is associated with increased risk of dementia among black and white older adults. J Gerontol A Biol Sci Med Sci **2019**; 74:890–6.
98. Mahmood SS, Levy D, Vasan RS, Wang TJ. The Framingham Heart Study and the epidemiology of cardiovascular disease: a historical perspective. Lancet **2014**; 383:999–1008.