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Vascular cognitive impairment and HIV-associated neurocognitive disorder: a new paradigm

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Abstract

In this review, we propose that vascular cognitive impairment (VCI), with relevance for the global HIV population, is fundamentally and clinically linked to the persistence of mild forms of HIV-associated neurocognitive disorders (HAND) in ageing people living with HIV infection (PLWH). After placing our review within the context of the general literature on HIV and ageing, we review non-VCI risks for dementia in ageing PLWH. We then present the recently updated VCI nomenclature and show that the neuropsychological and neuroimaging phenotypes of VCI and HAND are largely overlapping, suggesting that further research is needed to accurately distinguish them. We further link VCI and HAND at the mechanistic level by advancing the innovative proposal that the neuro-vascular unit (NVU) may represent the primary target of HIV-related brain injury in treated HIV infection. To this, we add the fundamental impact of mild and major VCI on the NVU. Importantly, we show that the potential contribution of vascular damage to overall brain damage in ageing PLWH is probably much higher than currently estimated because of methodological limitations, and because this research is only emerging. Finally, because all VCI risk factors are more prevalent, premature, and sometimes accelerated in the HIV population at large, we conclude that the probable total burden of VCI in the global HIV population is higher than in the general population and would need to be compared to chronic conditions such as type I diabetes and multiple sclerosis to account for the disease chronicity and lifelong treatment effects. Therefore, this review is also a call to action. Indeed, it is fully established that this amount of VCI burden is a major risk factor for dementia at aged 60+.

Keywords HIV-associated neurocognitive disorders · Vascular cognitive impairment · HIV infection · Ageing · Dementia · Stroke · Vascular dementia · Alzheimer's disease · Neurodegenerative diseases

The context of current NeuroHIV research in ageing PLWH

With increased life expectancy on successful combined antiretroviral treatment (cART), people living with HIV infection (PLWH) have almost similar life expectancy to the general population (The Antiretroviral Therapy Cohort Collaboration 2008). Because of this, an increasing body of literature has been dedicated to the question of whether chronic HIV infection may promote premature ageing and/or accelerated ageing. Large sample studies have investigated whether systemic age-related conditions have different age prevalence and age incidence rates compared to the general population (Althoff et al. 2015; Guaraldi et al. 2011; Petoumenos et al. 2014; Rasmussen et al. 2015; Schouten et al. 2014). In the few instances where HIV-related neurological diagnoses were included in these studies, it was only the most severe form (e.g. HIV-associated dementia, HAD), for which prevalence is rare in the cART era (Antinori et al. 2007; Cysique et al. 2014; Heaton et al. 2010). Therefore, the relevance of such studies to brain premature ageing and the potential precipitation of HAD and non-HIV types of dementia in PLWH age 60+ is limited. Nevertheless, there is growing consensus within the HIV and ageing literature that there is *premature ageing* (Guaraldi et al. 2011) in the HIV population

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at large in the form of greater age prevalence of age-related systemic conditions, but no evidence for widespread *accelerated ageing except for one of the most severe forms of cerebrovascular diseases* (i.e. *stroke*) (Benjamin et al. 2016). Importantly, from a modern clinical neuroscience and neurology perspective, even premature ageing remains highly relevant for a potential increased dementia risk as ageing is the number one risk factor for dementia in the general population (Deckers et al. 2015).

There are several other important caveats to be made regarding the relevance of the existing HIV and ageing research to NeuroHIV: (1) while there may not be accelerated systemic ageing in the majority of PLWH in the form of greater age incident rates of mid-life conditions, it is however established that these conditions, including their subclinical forms, are risk factors for dementia (Deckers et al. 2015); (2) the survivor bias was not taken into account in these studies and this is a major limitation particularly in the context of age-related neurological predictions as we will discuss below; and (3) the cumulative aspect of age-related comorbidities (Smit et al. 2015) was not factored in and again, it is well established that cumulative mid-life systemic diseases increase dementia risk (Ford et al. 2018; McHutchison et al. 2017).

In all, how ageing impacts the prevalence and incidence of neurological disorders is not based on a linear impact of systemic age-related conditions, and there is no reason why it should be different in HIV (Brew et al. 2009). With ageing being the number one factor for all types of dementia, the question of whether PLWH are at increased risk of dementia is not rhetorical, but empirical: by definition, ageing PLWH reaching their 60s are entering the dementia risk range by virtue of their chronological age, which is prematurely older at least in some PLWH. Another important concept not adequately captured by the general HIV and ageing research is that the dementia risk pattern is exponential over the age of 60 years (Milanini and Valcour 2017). Currently, not enough studies have been conducted in large samples of PLWH aged 60+ to make any valid predictions (Milanini and Valcour 2017).

In this context, it is important to remember that the majority of *the first generation of ageing PLWH are survivors* of the pre-cART era as they typically have long HIV duration. This impact is far from being accurately identified in ageing HIV studies, and it is even more relevant in NeuroHIV research. Indeed, bias due to selective mortality (Mayeda et al. 2016) is a major concern in dementia research as it dramatically alters dementia prediction risks. This is especially relevant in HIV neurocognitive ageing where there is undeniable evidence that HIV-related neurological complications strongly predict subsequent mortality (Vivithanaporn et al. 2010). This was true in the pre-cART era for HIV-associated dementia, neuropathy (Bouwman et al. 1998), and CNS opportunistic infections (Le and Spudich 2016). Globally, it is still true in places where treatment access is restricted and new HIV infections continue to rise (GBD 2015 HIV Collaborators 2016). This also continues to be true in the cART era including for mild HIV-associated neurocognitive disorders (HAND) (Patel et al. 2018; Vivithanaporn et al. 2010). The exact magnitude of the *neurological survivor bias* in chronic HIV infection is uncertain. It can however be partially estimated from AIDS-related death and non-AIDS death (Cysique et al. 2011), but this has not been routinely done in NeuroHIV research would require very large sample sizes to extract accurate estimates. Such data need accurate information to produce valid trends (Stover et al. 2017). However, HAND is not accurately determined anywhere in a national registry as opposed to HIV cases, which are captured. Survival bias impact is further complicated in the case of chronic HIV, as while those who have survived may be partially resistant to the effect of ageing, they have also experienced many comorbidities including probable toxicities from earlier types of antiretrovirals (Cysique and Brew 2009). In all, survivor bias has many ramifications for the accuracy of dementia detection as it influences representation of dementia genetic/epigenetic/disease risks, the degree of biological resilience, and is further confounded by attrition, some of which is due to old age and more severe or rapidly progressive dementia (Weuve et al. 2015). Without taking this into account, the conclusion, based on studies that have included people in their 40–60s (Milanini and Valcour 2017), that there are no major dementia signals needs to be viewed cautiously. Indeed, there are studies showing some signals, even in those with low comorbidities, of premature genetic and epigenetic ageing (Lagathu et al. 2017), and premature brain ageing (Cole et al. 2017; Cysique et al. 2013; Goodkin et al. 2017; Harezlak et al. 2011; Pfefferbaum et al. 2018).

Another complicating factor is the increasing number of people acquiring HIV infection at age 50+ (GBD 2015 HIV Collaborators 2016). While these often receive early treatment, thereby significantly reducing the rates of AIDS and non-AIDS comorbidities, there is evidence of a higher mortality rate (Tang et al. 2018), a blunted CD4 response, and greater prevalence of cardiovascular diseases (CVD) (Dawood et al. 2018), albeit not in all studies (Wright et al. 2013). Furthermore, it is possible that, with old age, immune senescence will interfere with the long-term control of viral activity with consequent chronic immune activation despite cART (Appay and Sauce 2017)—the latter being a recognised risk factor for dementia (Schwartz and Baruch 2014) Thus, HIV duration *and* age at which HIV was acquired are important factors when assessing the risk of neurocognitive deterioration in chronic ageing PLWH (Cysique and Brew 2014).

Chronic CVD and HIV effects are a "game changer" for HAND and vascular brain health in ageing PLWH

Various systemic conditions have been associated with the risk of dementia, but all research points to one overwhelming

factor: *CVD, particularly in mid-life*. CVD are a recognised risk factor for vascular dementia (VaD), mixed dementia, and Alzheimer's disease (AD) (Panza et al. 2012). While the exact pathophysiology is still the object of intense research, the dementia field has established that clinically relevant and subclinical CVD is a fundamental causal factor for dementia at the molecular, cellular, and system level (Xia et al. 2018). It is also increasingly recognised that ageing and psychiatric multimorbidity (of a bi-directional nature in some instances) is associated with CVD. This is further compounded by the morbid role of socio-economic factors (poverty, health care access) and racial/ethnicity factors (Akinyemi et al. 2018), and lifestyle factors (e.g. smoking, alcohol, and drug use). Crucially, this exact multi-morbidity profile is highly prevalent in the HIV population.

Additionally, the wider dementia field is now giving specific attention to the potential role of chronic viral infection in promoting neurodegeneration. Specifically, the "recent discovery that amyloid-beta peptide (Aβ) is an antimicrobial peptide (AMP) acting against bacteria, fungi, and viruses gives increased credence to an infection hypothesis in the etiology of AD" (Fulop et al. 2018). The authors state that "production of Aβ as an AMP will be beneficial on first microbial challenge but will become progressively detrimental as the infection becomes chronic and reactivates from time to time". This possibility is highly relevant in the context of chronic-treated HIV as immune activation contributes to the pathogenesis of many age-associated diseases (including CVD) (Appay and Sauce 2008). This is of specific relevance to HIV infection if we conceptualise Aβ as a dysregulated antimicrobial peptide that accumulates in the brain, possibly under the chronic pressure of chronic residual (Dahl et al. 2014) or restricted HIV (Bachani et al. 2013). Brain amyloid accumulation is one of the major neurodegenerative pathways. NeuroHIV research may therefore have a crucial role to play in elucidating the AD infection hypothesis, which can "mesh" with the amyloid hypothesis; the two should be seen as interlocking pieces of the puzzle. The mechanisms driving systemic immune activation in chronic HIV infection are multifactorial, such as translocation of microbial products from the gastrointestinal tract, low-level detectable viral RNA, and viral components such as tat, persistent viral sanctuaries and reservoirs, and crucially co-infections with highly common viral pathogens such as the human herpes viruses, especially cytomegalovirus (CMV). These can be reactivated especially in the context of immune senescence (Appay and Sauce 2008). Indeed, CMV antibody levels are associated with neurocognitive impairment despite viral suppression (Brunt et al. 2016; Letendre et al. 2018), worse CVD outcomes (Brunt et al. 2016), and blunted CD4 response to cART (Giuliano et al. 2017).

When considering the multi-layered comorbid dementia risk in the global HIV population (i.e. focusing not only on data relating to men from wealthier economies that has dominated the HIV and ageing literature but also on global data relating to women and minorities in limited resource settings), there is serious pause for concern. Even if mechanistically residual HIV activity may not *directly* promote dementia, from a multi-morbidity and disease burden perspective, it is plausible that chronic immune activation, immune senescence, the CVD component, and associated multiple comorbidities represent major cumulative dementia risks in ageing PLWH.

A new NeuroHIV paradigm: vascular cognitive impairment as a key mechanism and risk factor for HAND and non-HIV types of dementia

The multi-morbid features inherent to old age and accentuated in PLWH are challenging. Guaraldi and Pallela have proposed a new discipline to address this challenge: HIV geriatrics (Guaraldi and Palella Jr. 2017). Taking this beyond the clinical management in which it was first proposed, this framework could also help guide our research questions and study design. Indeed, "multidisciplinary and multidimensional process, designed to evaluate an older person's functional ability, physical health, cognition, overall mental health, and socio-environmental circumstances" could become a standard way of assessing dementia risk in ageing PLWH. By contrast, an infectious disease-centred perspective on HIV residual activity, viral suppression, and immune response, concentrating only on men who are virally suppressed, fundamentally "misses the mark" when it comes to extracting accurate dementia risk estimates in ageing PLWH. It is also an erroneous strategy if we want to determine whether a yet unknown type of dementia (combining vascular cognitive impairment (VCI) and HAND) may occur and progress more rapidly.

Consequently, a multidisciplinary approach for age-related neurological complication risk should aim to propose a unifying mechanism that is relevant to the entire HIV population (men, women, and children globally), involve the role of HIV (even controlled or restricted) along with the role of HIV-specific and non-specific immune activation and immune senescence, account for the high CVD burden in the HIV population, and further reflect the most common regional distribution of brain abnormalities in chronic-treated HIV (striato-frontal/temporal white matter injury, fronto-parietal grey matter and the hippocampus) (Nichols et al. 2018; Pfefferbaum et al. 2018). *We propose that this mechanism is VCI.*

The possibility that VCI represents a unifying pathological mechanism in treated PLWH who are ageing resonates with a recent clinic-neuropathological correlation hypothesis according to which the neurovascular unit (NVU) may represent the primary target of chronic HIV injury (Gelman 2015). Briefly, Gelman proposes that the endothelial cell surface may be

chronically perturbed in virally suppressed HIV-infected persons, leading to chronic alteration of the NVU and disturbed brain microvasculature and blood brain perfusion. This innovative idea is postulated on the basis of results from the National NeuroAIDS Tissue Consortium brain gene array study (Gelman et al. 2012). The study found that HAND without HIV encephalopathy (HIVE being HAND untreated neuropathological substrate) is characterised by abnormal brain gene transcription regulation limited to a network of brain genes expressed by endothelial cells—cells that are functionally dyregulated (Kallianpur et al. 2018). Gelman concludes, "The implication overall is that perturbation of neurovascular biology may be a keystone process in patients who are virally suppressed, whereas in the patients without viral suppression, brain [acute] inflammation is a more prevalent force". Gelman also adds, "Heightened awareness that there are two types of HAND with divergent neurovirological and brain transcriptional patterns was suggested two decades ago before the introduction of effective viral suppression" (Glass et al. 1995). Following this hypothesis, it is possible that cART has made the "NVU-related form of HAND" more prevalent. This would, in any case, fit with the milder clinical profile of HAND in the cART era (Saloner and Cysique 2017; Smail and Brew 2018) where acute brain inflammatory infiltrates are not prevalent anymore, while a form of low-grade chronic immune activation is much more common (Brew 2016; Cysique et al. 2013; Harezlak et al. 2011; Ulfhammer et al. 2018). Furthermore, the HIV-related NVU is likely additionally altered by CVD abnormalities, thereby further contributing to neurodegeneration (Helman and Murphy 2016).

Vascular cognitive impairment and connections to HAND

A group of world experts (van der Flier et al. 2018) has proposed the following definition of VCI: "VCI refers to the entire spectrum of vascular brain pathologies that contribute to any degree of cognitive impairment, ranging from subjective cognitive decline to dementia". VCI is most commonly attributed to direct ischaemic tissue injury. "VCI pathology includes microinfarcts, lacunar infarcts, larger infarcts (of embolic or thrombotic origin), and white matter lesions" (Skrobot et al. 2017). The number, location, and size of infarcts affects the likelihood that they will be associated with cognitive impairment; in general, multiple infarcts, larger infarcts, and infarcts in cortical regions are more likely to be associated with dementia (van der Flier et al. 2018). Yet, single infarcts in specific brain regions can also substantially influence cognitive function (strategic infarcts in the thalamus, the cortical regions of the parietal and temporal lobes, and the genu of the internal capsule). Further, microinfarcts (very small infarcts that are defined in terms of pathology as infarcts that cannot be observed by the eye but that can be observed using microscopy) can be easily missed on MRI brain scans: the highest-resolution MRI for human (7 T) only detects microinfarcts around 1 mm in diameter (van der Flier et al. 2018). This means that neuroimaging studies will systematically underestimate the extent of microinfarct pathology in PLWH as most studies are based on 3-T MRI scanners. Histopathological studies and animal models will therefore be key in delineating the true burden of mild VCI in ageing HIV infection similar to what is proposed for cerebral small vessel disease (CSVD) (Horsburgh et al. 2018).

The Vascular Impairment of Cognition Classification Consensus Study (VICCCS) (Skrobot et al. 2018; Skrobot et al. 2017) has proposed to refer to *mild and major VCI* in order "to achieve a broader consensus on the conceptualisation of impairment in cognition contributed by vascular pathology, for clinical diagnosis and research". Mild and major VCI also account for a large degree of heterogeneity. Probably the primary form of VCI that is most relevant to an increased dementia risk in virally suppressed PLWH is *mild VCI* including its subclinical form: silent cerebral small vessel disease (Moulignier et al. 2018) (Table 1). In this case, the neurocognitive and neuropsychiatric profile of mild VCI is largely overlapping with that of mild HAND, so much so that standard neuropsychological testing as recommended by the Frascati criteria (Antinori et al. 2007) would make them phenotypically indistinguishable (Brew et al. 2009) (see Table 1). Interestingly, the mild VCI cognitive profile is designed for *very early* detection requiring impairment in one cognitive domain only (Table 1). This is very much at odds with recent proposals in NeuroHIV that have called for a revised threshold of impairment that would end up detecting only the moderate to severe form of HAND (Underwood et al. 2018), thereby missing VCI in PLWH. What this shows, as we have written elsewhere, is that NeuroHIV needs to keep evolving along with the wider neuroscientific field, which increasingly aims to detect and intervene early in cognitive impairment (Gates and Cysique 2016).

The neurological profile of major VCI closely resembles the more severe forms of HAND, namely HAD, where abnormal motor signs are more prominent, although these signs can emerge in ageing PLWH (Brew et al. 2009). "Other neurological signs and symptoms [in VCI], including reflex asymmetry, dysarthria, parkinsonism, rigidity or urinary incontinence, often occur (van der Flier et al. 2018)". This neurological profile, however, is consistent with mostly visible vascular infarcts (Kouassi and Doumbia-Ouattara 2017). Importantly, one major issue in the field of VCI is that early pathophysiology is far from being completely described and understood (Horsburgh et al. 2018). This is in part because most studies have been conducted in patients aged 70+. At this age, comorbidities can mask and transform the contribution of CVD to early VCI (Horsburgh et al. 2018). It is only recently that the

Table 1 VICCCS2 (Skrobot et al. 2018) definitions and diagnosis of VCI

Mild VCI: Impairment in at least one cognitive domain and mild to no impairment in instrumental activities of daily living (IADLs)/activities of daily living (ADLs), respectively (independent of the motor/sensory sequelae of the vascular event).
Major VCI (vascular dementia): Clinically significant deficits of sufficient severity in at least one cognitive domain (deficits may be present in multiple domains) and severe disruption to IADLs/ADLs (independent of the motor/sensory sequelae of the vascular event). Clinically significant deficits include moderate severity. Cognitive impairment in mild VCI is differentiated from major (VaD) by not being clinically significant. Major VCI is subcategorized according to the underlying pathology: Poststroke dementia, Dementia due to mixed pathology (for example, VCI–Alzheimer disease), Subcortical ischaemic vascular dementia (incorporates the overlapping clinical entities of Binswanger disease and lacunar state), Multi-infarct dementia. "Probable" and "possible"—terms for the availability of evidence: MRI is a gold standard requirement for a clinical diagnosis of VCI. Possible mild VCI or possible major VCI (VaD) would be appropriate diagnoses if neither MRI nor computed tomography imaging were available.
Those at risk of VCI*: It is recommended that greater consideration for diagnosis be given to people who are at risk of VCI if they present with at least 6 months of sustained impairment (even if very mild), rather than transient impairment, as identified through caregiver reporting and clinical observation. All other potential causes of sustained impairment (e.g., depression or vitamin D deficiency, in addition to the already agreed exclusions from diagnosis) should have been excluded.
Exclusions from diagnosis: Drug/alcohol abuse/dependence within the last 3 months of first recognition of impairment or delirium. NB: Neuropsychological profile of impairment includes deficits in executive function, attention, memory, language and visuospatial function.

*VaD and VCI risk factors include *vascular risks*: hypertension, diabetes mellitus, myocardial infarction, ischaemic heart failure, atrial fibrillation, positive family history, hypercholesterolaemia, mid-life obesity; *lifestyle factors*: smoking-reduced physical activity; *comorbidities*: depression; and *demographic factors*: age, low education, low social class, and genetic factors: APOE (ε 4 allele) and MTHFR variants (Skrobot et al. 2017; van der Flier et al. 2018)

earliest forms of VCI have begun to be studied in younger patients (40–60 years of age). CSVD pathology is heterogeneous and includes subcortical lacunae, microbleeds, white matter hyperintensities (WMH), enlarged perivascular spaces, and silent brain infarctions (Horsburgh et al. 2018; Zwanenburg and van Osch 2017). Recent data (Horsburgh et al. 2018; Zwanenburg and van Osch 2017) show that the aetiologies of early CSVD may be different in the brain grey and white matter. In terms of treatment, it would also be important to better characterise the earliest forms of VCI as they are thought to be reversible, while more severe forms are not (Horsburgh et al. 2018).

Major VCI particularly in the form of various stroke subtypes is also relevant to chronic-treated HIV. First, the risk of all strokes with known aetiologies is heightened in treated PLWH compared to the general population (Chow et al. 2012; Durand et al. 2013; Rasmussen et al. 2011), including in only aviremic cohorts (Sico et al. 2015; Vinikoor et al. 2013). Second, the risk of stroke of undetermined aetiology is also higher in treated PLWH compared with age-comparable uninfected individuals (Chow et al. 2017). The risk factors and pathophysiology of increased strokes in treated HIV are incompletely understood but there is some overlap with VCI and HAND (Barnes et al. 2017). Of note, the majority of the PLWH in these studies are well below 60 years of age, raising the possibility of increased risk for dementia (van der Flier et al. 2018). Among the large cohort studies (Chow et al. 2012; Durand et al. 2013; Rasmussen et al. 2011), there was no definite consistency in the risk factors associated with increased stroke risk except for AIDS and past immune compromise. Some found that comorbidities and lifestyle factors were more explanatory (Durand et al. 2013). This discrepancy may be due to the definition of stroke, the subtype of stroke most represented in a particular cohort, and the types of CVD risk factors and other comorbidities present in that cohort.

Similar to the mild HAND profile, the brain distribution of mild VCI pathology is diffused and primarily across the striato-frontal-parietal-temporal white matter (Biesbroek et al. 2017; Peng et al. 2018). If silent or in the form of microinsults, only high-resolution diffusion imaging and multi-modal MRI (Biesbroek et al. 2017; Peng et al. 2018) will be able to differentiate HIV and VCI pathology (Biesbroek et al. 2017; Cysique et al. 2017). In the non-HIV population, VCI injury is commonly observed in the white matter of older individuals and individuals with vascular risk factors and disease, and is related to an increased likelihood of cognitive impairment (van der Flier et al. 2018). Although not specific to vascular diseases, white matter injuries commonly co-occur with vascular disease (atherosclerosis, diabetes, metabolic syndrome) and are often presumed to be vascular in origin. The exact mechanisms and consequences of white matter injuries are not well understood and are currently the object of intense research (van der Flier et al. 2018). Among the most likely mechanisms are alterations of the blood-brain barrier, altered vascular reactivity, hypoperfusion, and chronic inflammation (van der Flier et al. 2018), mechanisms that are thought to play a major role in chronic HIV-related injury (Smail and Brew 2018).

Similar to chronic and treated HIV in the context of ageing (i.e. 60+), VCI is increasingly perceived not only as the cause of a specific pathogenic process, but also as a contributor to neurodegenerative changes. Indeed, "although vascular pathology is common in elderly individuals with cognitive decline, pure vascular dementia [or VCI] (that is, [VCI] dementia caused solely by vascular pathology) is uncommon. Most patients with [VCI] also have other types of pathology, the most common of which is AD (specifically, the diffuse accumulation of amyloid-β plaques and neurofibrillary tangles composed of tau) (van der Flier et al. 2018)".

Another parallel between mild HAND and mild VCI is that mild VCI is a risk factor for major VCI (i.e. subcortical ischaemic VaD or multi-infarct (cortical) dementia subtype, poststroke dementia). Mild HAND is a risk factor for cognitive decline (Gott et al. 2017; Grant et al. 2014) in the population age 40–60. Furthermore, both mild VCI and major VCI contribute to neurodegeneration (e.g. AD, dementia with Lewy bodies (DLB)) based on mechanisms that remain to be elucidated. Overall, the hypothesis that chronic-treated HIV in age 60+ where HIV + VCI or HIV*VCI adds yet an additional risk factor for more severe VCI and/or neurodegeneration is biologically plausible. If we consider the increased risk of CVD in PLWH (particularly in mid-life while still including the moderating effects of CVD treatment), and the extensive list of multi-morbidities in the ageing PLWH, the hypothesis becomes even more likely (Gutierrez et al. 2018).

At present, the main treatment for VCI is prevention by treating vascular diseases and other risk factors for VCI, such as hypertension and diabetes mellitus. However, van der Flier et al. (2018) propose a more comprehensive management regime in addition to prevention that resembles the HIV geriatric principle developed by Guaraldi and Palella Jr. (2017). van der Flier et al. also provide an excellent review of the ongoing research on pharmaceutical and non-pharmaceutical treatments (van der Flier et al. 2018). Figure 1 summarizes the steps for prevention, management and treatment of VCI. Similar efforts should continue in NeuroHIV with a special focus on boosting the early detection of neurocognitive impairment and brain injury rather than the opposite (Gates and Cysique 2016) and refining assessment of interventions (Cody and Vance 2016) in order to improve quality of life and concerns about potential cognitive deterioration (Cummins et al. 2018; Terpstra et al. 2018).

Risk factors for vascular cognitive impairment in people ageing with HIV infection

HIV-related CVD and HAND share common pathogenic pathways, which include immunosuppression and unsuppressed viral load in untreated or poorly adherent PLWH (Barnes et al. 2017; Gutierrez et al. 2017; Lacson et al. 2017). In treated HIV infection, mild VCI and mild HAND share common pathogenic pathways through persistent subclinical and clinically relevant CVD (HIV as a vascular risk factor; Barnes et al. 2017; Gutierrez et al. 2017; Lacson et al. 2017), chronic immune activation, and immune senescence, some of which probably relates to viral reservoir activity (Gelman 2015; Holloway and Boccara 2017; Hsue et al. 2012; Smail and Brew 2018). Mild VCI and mild HAND share additional potential pathogenic pathways via microbial translocation, and reactivation of common pathogens (CMV, herpes simplex viruses) (Barnes et al. 2017). HIV proteins (trans-activator of transcription (Tat) and

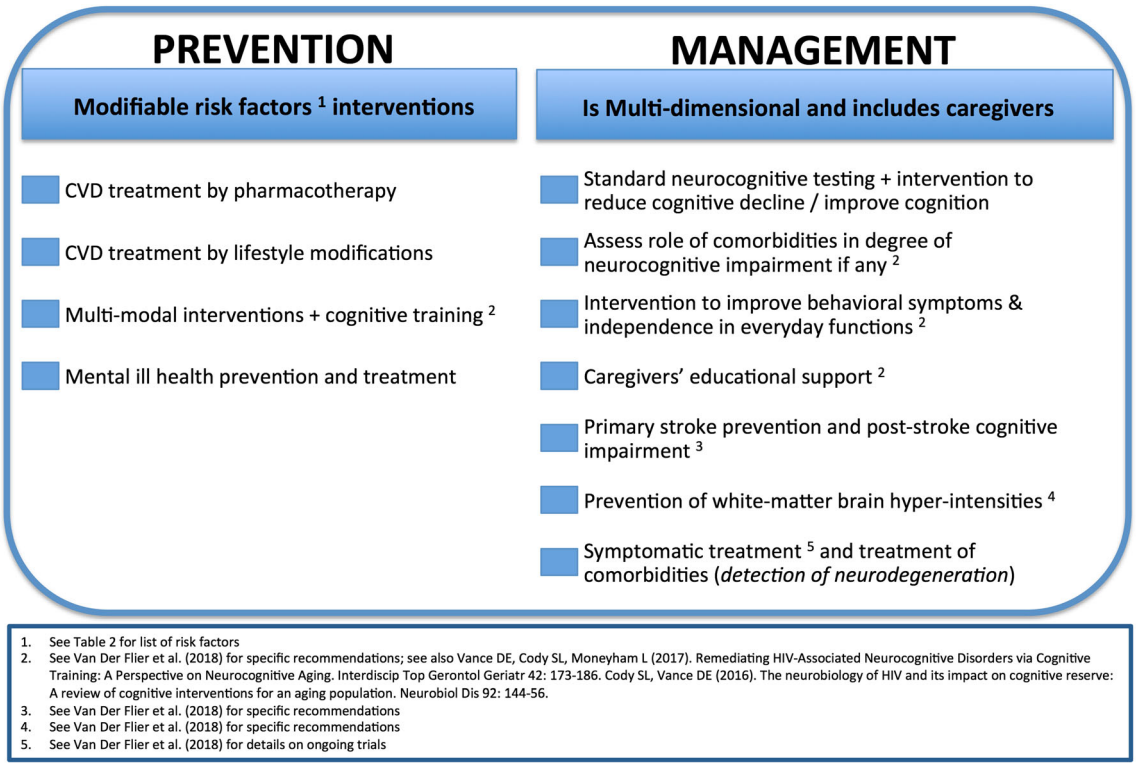

Fig. 1 Summary steps for prevention, management, and treatment for VCI as proposed by van der Flier et al. (2018)

Table 2 Risk factors for vascular cognitive impairment in people ageing with HIV infection

CVD	Viral replication directly or indirectly causes vascular disease (Hsue et al. 2012)
	CVD complications are more common in PLWH on long-term cART than in age-matched uninfected individuals, and this is a worldwide effect in PLWH (Bijker et al. 2017; Gutierrez et al. 2017; Hyle et al. 2017; Rajasuriar et al. 2017).
	CVD burden in PLWH relates to increased hypertension (van Zoest et al. 2017), heart failure (Hsue and Waters 2017), (Lacson et al. 2017), and ischaemic heart disease (Triant and Grinspoon 2017).
	Chronic HIV is a vascular risk factor (Gutierrez et al. 2017).
	Persistence of vascular complications in optimally treated PLWH support the growing body of evidence that chronic inflammation despite cART and potentially through Tat and Nef (Atluri et al. 2015) is directly and causally associated with a higher age prevalence of CVD and the accelerated development of atherosclerosis (Hsue et al. 2012).
	Predicted 10-year CVD disease risk remains relatively low at present in the majority of PLWH; it will increase in relation to the progressive ageing (Friis-Moller et al. 2010).
CVD treatment	Prevention and treatment of CVD is unequal across geographical locations (Gutierrez et al. 2017), gender (women have been less targeted in both clinical practice and research), race/ethnicity, and socio-economic strata (Hatleberg et al. 2017).
Ageing, premature, and accelerated ageing, frailty	Ageing is a risk factor for both CVD and VCI.
	Emerging evidence that mild VCI (i.e. CSVD) is more prevalent in ageing PLWH (Moulignier et al. 2018).
	Brain ageing is accelerated in some PLWH with low comorbidities (Goodkin et al. 2017) and more so PLWH with greater comorbid burden that are risk factors for VCI (Pfefferbaum et al. 2018) and HAND (Clifford et al. 2017).
	Biological age is premature and accelerated in PLWH when defined as telomere shortening, immune ageing, and frailty indexes (Appay and Sauce 2017; Guaraldi et al. 2011; Xu et al. 2018).
	VCI and premature brain ageing have been observed in paediatric HIV (Blokhuis et al. 2017).
Mild HAND long-term persistence	Longitudinal studies clearly show that HAND persists in virally suppressed PLWH with low (Gott et al. 2017) and high comorbidities (Rubin et al. 2017) and that age is a risk factor (Cysique and Brew 2014).
Socio-economic, geographical, racial/ethnicity factors, sex	Increased CVD risk is also present in limited resources setting in both adults and children (McCrary et al. 2017).
	WLHIV in North America and Europe exhibit high CVD incidence rates, which are on par with those of men living with HIV (Stone et al. 2017).
	Racial minorities in Western countries are at higher risk of CVD and VCI and once diagnosed at greater risk of morbid progression (Carnethon et al. 2017; Christopher et al. 2018; Gyaneshwar et al. 2016; Wiemers et al. 2018).
	Low education and low socio-economic class are recognised factors for VaD and HAND as well as all other forms of dementia (Cysique et al. 2014; Lipnicki et al. 2017; Skrobot et al. 2018).
Psychiatric burden (depression, stress, traumatic events, stigma, social isolation)	CVD and depression has demonstrated a bi-directional relation between major depression and CVD, while depression is a risk factor for VCI (van der Flier et al. 2018).
	The HIV population psychiatric burden is 3–5 times higher than the general population (Nedelcovych et al. 2017).
	The experience of stigma, stress, and traumatic events are higher in the HIV population and worsen with ageing due to social isolation (Johnson Shen et al. 2018).
Alcohol, smoking, and recreational drug use	Traditional risk factors for CVD including smoking and alcohol use are highly prevalent in the HIV population (Raposeiras-Roubin et al. 2017).
	Recreational drugs commonly used in PLWH such as methamphetamine and cocaine have a well-established cardiotoxic profile (Paratz et al. 2016).
	There is good evidence that drug use in PLWH is associated with increased risk for cerebrovascular events (Rasmussen et al. 2011).
Antiretrovirals	Some ART agents which were/are prescribed in mid-life are associated with metabolic abnormalities (Friis-Moller et al. 2010); this could represent an added risk for mild VCI, mild HAND, and neurodegeneration in old age (Gorelick et al. 2011).
	Less cardiotoxic ART agents are being prescribed; nevertheless, there are significant international disparities.
	Use of antiretroviral therapy has been found to be an inconsistent risk for cardiac outcomes (Gutierrez et al. 2017; Rasmussen et al. 2011).

negative regulatory factor (Nef) proteins) are not eliminated by cART and both are pro-inflammatory as well as being pro-atherogenic (Atluri et al. 2015). Finally, mild VCI and mild HAND share a vast amount of comorbid burden if one considers the HIV population globally. The overlapping risk factor burden between CVD, VCI, and established risk factors for HIV disease progression and HAND despite cART is striking. In addition to an overlapping burden, most risk factors in PLWH have a higher prevalence and severity of burden than in the general population. Even from the most conservative

perspective, this cumulative profile of risk factors represents one of the worst profiles for dementia in old age in modern clinical neurosciences/neurology. Further studies should be dedicated to comparing dementia risk factor burden and underlying mechanisms in these chronic conditions to account for chronicity and lifelong treatment effects and to provide the needed guidance to patients. Other risk factors are summarised in Table 2.

Evidence for vascular cognitive impairment in people ageing with HIV infection

There is increased recognition that stroke is becoming a complex health problem in long-term-treated PLWH with some studies showing premature occurrence compared to the general population, especially in low-middle-income countries (Barnes et al. 2017). One to five percent of PLWH experience clinical stroke. Ischaemic lesions are seen in 4–34% of brain autopsies, but recent data show that stroke of undetermined aetiology is also common (Chow et al. 2017). However, the HIV research field should also be aware that cerebrovascular disease in HIV does not necessarily equate to stroke (van der Flier et al. 2018).

Indeed, when considering the updated VCI nomenclature briefly presented above, it is clear that stroke in treated HIV likely represents "the tip of the iceberg". As such the prevalence of mild VCI is probably much higher especially if we consider CSVD, microinfarcts, and microbleeds. Mild VCI has been the focus of NeuroHIV research only recently. Unsurprisingly, there is mounting evidence for widespread mild VCI-like injury in long-term-treated and ageing PLWH, and worryingly also in children (Blokhuis et al. 2017; Gutierrez et al. 2018; Moulignier et al. 2018; Su et al. 2017). Importantly, this evidence is only based on fairly "crude" neurocognitive and neuroimaging methods compared to the more advanced methods used in VCI research (de Roos et al. 2017). Finally, the role and nature of mild HAND as a distinct entity in this context is becoming fundamentally unclear.

Conclusions and future directions

In all, it is urgent to link NeuroHIV and VCI research efforts. This is important so that initiatives in developing systemic evidence-based approaches to help appropriately diagnose and classify the subtypes of HIV-related etiologies in ischaemic stroke for example (Benjamin et al. 2016) are not dissociated from the wider understanding of mild/major VCI and dementia risk. It may be needed eventually to update the VCI criteria with HIV as risk factor for VCI with emphasis on PLWH and high comorbidities. Similarly, the current HAND criteria will probably need a specific update to account for the mounting VCI level that has begun to be observed in ageing PLWH, but also in children.

Long-term and large studies need to be carried out internationally to assess the risk of dementia in the HIV population at large, measuring CVD, VCI, and mild HAND optimally, while taking into account the survivor bias. The exclusion of the highest risk groups for both VCI and mild HAND should be systematically avoided, as it will lead to erroneous epidemiological figures and disease burden with consequences for research funding and healthcare policies. Finally, studies investigating the connection and distinction of VCI and HAND at the brain molecular, cellular, and macroscopic levels are needed to determine precise mechanistic pathways and potential therapeutic targets. Most standard imaging techniques in humans are inappropriate or underpowered for distinguishing between VCI and HAND. Liaising with VCI researchers on these matters will be crucial. Neuropathological studies including animal models are necessary, but they will need to be based on the chronic phase of HIV infection and informed by animal models in VCI research (Horsburgh et al. 2018).

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Compliance with ethical standards

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