Geriatric Syndromes in People Living with HIV Associated with Ageing and Increasing Comorbidities: Implications for Neurocognitive Complications of HIV Infection

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Contents

Abstract Long-term survival of treated people living with HIV (PLWH) currently approaches that of the general population. The average age of PLWH is currently in the mid-50s in resource-rich countries and is predicted that over 40% of PLWH will be older than 60 within a decade. Similar trends have been confirmed in all communities of PLWH with access to antiretroviral therapies. However, the positive impact on survival has been challenged by several developments. Ageing PLWH

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have clinical features similar to the general population about 5–10 years older. In addition to the earlier occurrence of common age-related conditions common geriatric syndromes have also impacted this population prematurely. These are often difficult to evaluate and manage conditions usually of multifactorial aetiology. They include polypharmacy, frailty, impaired mobility and falls, sarcopenia, sensory impairment, and increasingly, non-dementing cognitive decline. Cognitive decline is of particular concern to PLWH and their care providers. In the general geriatric population cognitive impairment increases with age and occurs in all populations with a prevalence of over 25% in people over 80. Effective treatments are lacking and therefore minimizing risk factors plays an important role in maintaining healthspan. In the general population geriatric syndromes may increase the risk of cognitive decline. The corollary is that decreasing the risk of their development may limit cognitive impairment. Whether a similar status holds in PLWH is uncertain. This chapter will address the question of whether common geriatric syndromes in PLWH contribute to cognitive impairment. Common risk factors may provide clues to limit or delay cognitive decline.

Keywords Ageing · Antiretroviral therapy · Cognition · Geriatric syndromes · HIV

1 Introduction

1.1 Epidemiology of Ageing in HIV

According to the World Health Organization (WHO), current demographic trends in the ageing population represent an unprecedented societal phenomenon (WHO 2015). The global population of older persons is growing at a rate of 2% per year, much faster than that of the entire population (WHO 2015). Projections estimate that two billion people will be older than 60 years by 2050 (Bellantuono 2018).

Recent demographic changes occurring in people living with HIV (PLWH) are similar to those of the general population. PLWH now live longer due to effective and well-tolerated combinations of antiretroviral therapy (cART). As well, more people acquire HIV at an older age (Chambers et al. 2014; Lazarus and Nielsen 2010). These two distinct groups contribute to the current demographic profile of this population. A deeper understanding of the interaction between HIV, ageing and the changing clinical profile of PLWH is required to inform effective health care provision to PLWH.

1.2 Profile of Ageing People Living with HIV

Ageing PLWH experience heightened risk for multiple noninfectious chronic comorbidities (NICM). The increase in diabetes mellitus, cardiovascular disease, osteoporosis, chronic kidney and liver disease, non-AIDS related malignancies, chronic obstructive pulmonary disease and non-dementing cognitive decline is of multifactorial aetiology. These include a greater prevalence of traditional lifestyle-related risks as well as HIV-specific factors including immune activation and chronic inflammation (Althoff et al. 2019). As well, in ageing PLWH, NICMs often occur concurrently as complex "multi-morbidities" (MM) (Theou and Rockwood 2015).

However, simply diagnosing NICMs and MM does not fully reflect the complexity of ageing as a health condition. In geriatrics it is understood that two people with the exact same comorbid profile can have very different ageing trajectories. This variability has led geriatricians to introduce the concept of geriatric syndromes to better characterize clinical ageing in addition to the traditional evaluation of discrete clinical conditions. These are health conditions of multifactorial aetiology which occur when the accumulated effects of impairments in multiple systems render an older person vulnerable to biologic and environmental challenges (Inouye et al. 2007). For a given geriatric syndrome, multiple risk factors and multiple organ systems are often involved. Standard diagnostic strategies to identify underlying causes can sometimes be ineffective, burdensome, dangerous and costly. Therapeutic management of the clinical manifestations can be helpful even in the absence of a firm diagnosis or clarification of the underlying causes (Guaraldi et al. 2016). In the elderly, geriatric syndromes and measures of physical function are more predictive of self-reported health and mortality risk than diagnoses of specific diseases or MM alone (Erlandson et al. 2014; Koroukian et al. 2016). However, most existing management guidelines remain organ based and do not include formal assessment for geriatric conditions (Guaraldi and Palella 2017; Guaraldi et al. 2019).

In PLWH there is a greater prevalence of typical geriatric syndromes compared to age-matched uninfected persons, including frailty, polypharmacy, falls and dysmobility, impaired cognition and disability (Greene et al. 2015). Several HIV-specific factors contribute to this risk, including chronic inflammation, immune dysregulation, long-term ART toxicity and socio-behavioural risks (Guaraldi and Cossarizza 2017). Clinically it has been shown that treating comorbidities and the early initiation of ART may help to prevent the development of these syndromes (Greene et al. 2015).

1.3 Assessment of Older Patients Living with HIV

Comprehensive health care of the older adult extends beyond the traditional medical management of individual illnesses. It includes evaluation of multiple, often concurrently present issues including physical, cognitive, psychologic, social, financial,

environmental and spiritual components. The application of a comprehensive geriatric assessment (CGA) is based on the premise that an interdisciplinary evaluation of at-risk older persons by a team of health professionals may better identify a variety of treatable or manageable health problems. This approach leads to better health outcomes and quality of life (Stuck et al. 1993; Devons 2002). At present, the CGA approach has rarely been used in PLWH (Bitas et al. 2019), but issues regarding multimorbidity, cognitive impairment, frailty and disability are increasingly incorporated into the clinical assessment of older patients with HIV (Guaraldi et al. 2016). Although the amount of information to be evaluated during a CGA may seem overwhelming, various assessment tools used by the interdisciplinary team can reduce this burden (Elsawy and Higgins 2011). A patient-centred approach, in both geriatrics and HIV care, is essential for the success of any treatment plan to ensure it meets the particular needs of individual patients. Closer collaboration between HIV care providers and geriatricians should be considered in the appropriate setting.

2 Geriatric Syndromes

2.1 Polypharmacy

Polypharmacy, commonly defined in the general population as taking five or more different medications on a daily basis (Gnjidic et al. 2012), is an important clinical problem in PLWH (Gleason et al. 2013; Edelman et al. 2013). This is not a new phenomenon in HIV disease as patients have always taken multiple medications in order to maintain their health. In the mid-1990s the first generation of ART regimens generally included three different antiretrovirals (ARVs), each consisting of several tablets, all of which had to be taken three to four times daily, often according to strict dietary restrictions. These ARVs were taken in addition to drugs used for primary or secondary prophylaxis of various opportunistic infections and management of drug-related toxicities.

As in the general population polypharmacy increases the risk of poor adherence to ART (Stone et al. 2004), although adherence is generally better in older compared to younger PLWH. ART has been greatly simplified over the past 10–15 years, and many patients now take single daily regimens containing three distinct ARVs (Geretti and Tsakiroglou 2014). Nevertheless, PLWH still have a greater prevalence of polypharmacy than controls (Greene et al. 2014a; Gimeno-Gracia et al. 2015), given the increased prevalence of NICMs which often require drugs for prevention or therapy (Guaraldi et al. 2011).

Between 15 and 75% of PLWH in their 60s have polypharmacy and 14% of patients older than 65 take four or more non-ARV drugs, most of which are either vitamins and supplements or drugs for cardiovascular or neurologic disorders (Hasse et al. 2011). In a cohort of PLWH with a median age of 64, the average number of drugs taken was 13, of which only four were ARVs (Greene et al. 2014a). In the

general population older patients taking these many drugs have an increased risk of falls, frailty and mortality (Gnjidic et al. 2012).

Non-medically prescribed drug use is very common and often under-reported or misrepresented in the general population; this is a particular problem in PLWH. In addition to over-the-counter (OTC) drugs, patients often take recreational drugs and alternative care-related drugs. A large discrepancy exists between what the patient is actually taking and what their provider believes they are taking (Furler et al. 2004).

The consequences of polypharmacy in the elderly population are well known and include altered mental status, falls, increased hospitalization rate and mortality. As well, poor adherence to necessary drugs, increased incidence of adverse drug events (ADEs), drug–drug interactions (DDI) and use of inappropriate medications may also occur. Fifteen per cent of PLWH may take drugs with potential anticholinergic toxicity (Greene et al. 2014a) which may increase risk of falls and altered mental status. PLWH may be particularly susceptible to these complications because of increased rates of renal and hepatic dysfunction leading to altered drug metabolism. Medications have been shown to specifically contribute to increased risk of poor mobility and falls in PLWH (Erlandson et al. 2012; Richert et al. 2014). There are thus several routes by which polypharmacy can increase the risk of confusion and altered mental status in PLWH.

The EACS guidelines provide recommendations on managing ageing PLWH with polypharmacy. Figure 1 stresses the need to consider the impact of polypharmacy with regards to drug–drug interactions (DDI) and Potentially Inappropriate Medications (PIM). The former results from both the interactions between ART with NICM-related treatments as well as to the potential interaction among non-ART medication. DDI can be classified into five categories: class A (no know interaction), B (no action needed), C (monitor therapy), D (consider therapy modification) and X (avoid combination). PIM derives from age-related physiological changes that may impact pharmacokinetics and pharmacodynamics effects of drugs. This in turn can lead to inappropriate drug/dosage use. Assessment of PIM uses the Beers criteria which includes lists of medications and medication classes and drug–disease

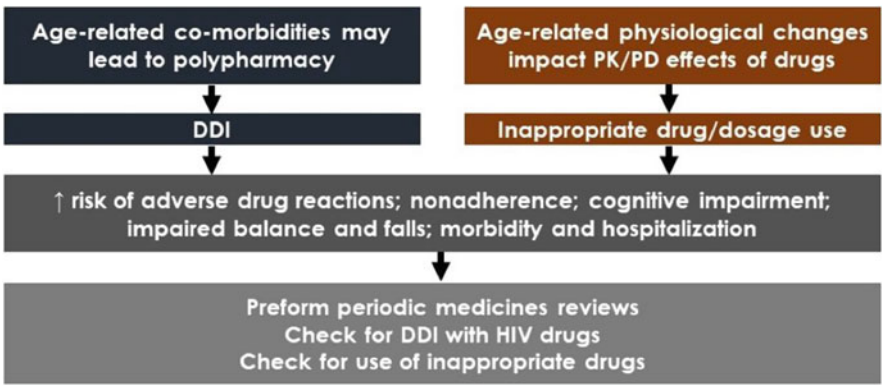

Fig. 1 Management of polypharmacy in OALWH. Freely adapted from EACS guidelines 2017 9.0

interactions that should be avoided in adults age 65 and older (American Geriatrics Society Beers Criteria Update Expert P 2012). DDIs and PIM may also increase risk of adverse drug reaction, non-adherence, cognitive impairment, impaired balance and falls, morbidity and hospitalization.

Although several studies have shown that overall adherence to ART is higher in older PLWH compared to younger controls, risk factors for poor adherence are also increased in older patients. This is a particular problem in PLWH with cognitive impairment, where it has been shown that adherence is decreased primarily in older PLWH who perform poorly on tests of executive function (Ettenhofer et al. 2009).

Sleep disturbances and pain syndromes occur commonly in the elderly, and have also been described in PLWH (Payne et al. 2013; Vosvick et al. 2004). They are frequently treated with drugs associated with increased risk of DDI. The co-administration of opioids and benzodiazepines has been shown to increase mortality in treated PLWH (Weisberg et al. 2015).

The frequency of medication-related problems in older PLWH was recently described in 89 community dwelling PLWH age 60 and older and age and sex-matched HIV-uninfected adults. The median number of medications was 13 (range 9–17) per participant. Compared to PLWH, the HIV-uninfected group was taking a median of 6 (IQR 3–10) medications ($P = 0.03$) with a median of 1 vitamin/herbal medication per participant. Sixty-two participants (70%) had at least one Category D (consider therapy modification) drug–drug interaction with a median of 1 (range 0–15; IQR 0–3) interaction per participant. Ten participants (11%) also had a Category X interaction (avoid combination). Most interactions were between an antiretroviral medication and a non-antiretroviral medication (152 [54%]), although approximately one-third of the interactions (99 [35%]) occurred between two non-antiretroviral agents. Fewer interactions (32 [11%]) occurred between two antiretroviral medications. Of the different drug–drug interaction pairs (101 [60%]), were deemed to be clinically significant by the clinical pharmacist (Greene et al. 2014a).

The following recommendations should be considered in the outpatient setting to help manage polypharmacy in older PLWH. Ideally an experienced pharmacist should be involved.

1. Patients should bring all prescription drugs at every visit, including over-the-counter and herbal medications; an annual medication reconciliation should be done
2. Determine patient adherence to medication and barriers if not adherent
3. Verify appropriate dosage and drug efficacy
4. Review drug–drug interactions
5. Use a “start low and go slow” approach where possible when starting new non-ART medications
6. Establish communication with other healthcare providers (physicians and caregivers)
7. Where possible suggest to use the same pharmacy for current medications
8. Assess for PIM (determine if medication is on Beers List) (Gleason et al. 2013)

In summary, polypharmacy is very common in PLWH and contributes to morbidity, cognitive impairment and mortality and requires increased vigilance on the part of providers involved in the complex care of ageing PLWH.

2.2 Falls and Impaired Mobility

One-third of the adults aged 65 and older sustain a fall each year and injuries due to falls are one of the most common causes of emergency room visits and loss of independence among ageing adults (Public Health Agency of Canada 2014; Lee et al. 2013). Falls in the elderly are usually a consequence of multiple interrelated factors including medical comorbidities, physical and sensory impairments, cognitive decline, polypharmacy and frailty (Public Health Agency of Canada 2014; Nobili et al. 2011). However, given that falls are most prevalent in the oldest old (i.e. over the age of 80) we may not fully appreciate the full magnitude of this issue in PLWH until a larger proportion has reached an older threshold. In a study of predominantly male PLWH with a median age of 57, 25.8% reported at least one fall within the previous year, and 12.5% reported a fall that resulted in an injury that required medical attention (Greene et al. 2015). Similarly, a report on falls among 359 PLWH (mean age 52, 85% male, 65% MSM and 21% with a history of IDU) found that 30% had experienced a fall in the previous year, and that among fallers, 61% were repeat fallers (Erlandson et al. 2012). Comparing non-fallers with recurrent fallers, the only demographic characteristics associated with being a recurrent faller were being female and being a smoker but the odds differed by less than 10% when adjusted for other factors. Falls were associated with comorbidities, including CVD, diabetes, neuropathy, arthritis and psychiatric disease; with each additional comorbid condition, the odds of recurrent falls increased by 1.7 (95% CI 1.5–2.1) (Erlandson et al. 2012). In a multivariate logistic model, difficulty with balance, exhaustion, diabetes, being female, unintentional weight loss, opiate use, sedative use, antidepressant use and having ever used didanosine were found to be significantly associated with recurrent falls. Since PLWH are known to have low bone density and increased fracture risk compared to their non-HIV peers, they are also likely to be at greater risk of morbidity when falls occur.

Mobility in the elderly is often assessed using the Short Physical Performance Battery (SPPB) which includes elements of lower extremity function such as balance, chair rise and gait speed (Guralnik et al. 2000). The SPPB predicts mortality in PLWH (Greene et al. 2014b). Physical performance assessments such as the SPPB can capture physical limitations prior to full disability among PLWH.

HIV-Associated Neurocognitive Disorder (HAND), discussed in detail elsewhere in this book series, refers to a spectrum of neurocognitive impairments in PLWH which includes executive dysfunction, memory impairment and motor dysfunction, plus psychomotor slowing, bradykinesia, coordination abnormalities and gait imbalance (Saylor and Sacktor 2016; Wendelken and Valcour 2012; Zamudio-Rodriguez

et al. 2018). Risk factors for dysmobility and falls may also predispose to HAND, and are in fact part of the definition of the outcome itself.

Despite a documented association, the temporal nature of the relationship between mobility, falls and cognitive function remains unclear, and few studies have directly assessed the impact of mobility and falls on cognition among PLWH. Indeed, most studies in the general population assess how cognitive function impacts falls, or they consider falls as the outcome. Falls are affected by the presence of cognitive function in the presence of dementia (Taylor et al. 2017), and mobility, falls and cognitive function are inter-related domains (Herman et al. 2010). The role of executive functioning in particular is thought to be critical in compensating for age-associated declines in motor function and the maintenance of falls-free gait in everyday situations that require complex integration of motor and cognitive processes. Among community dwelling older adults, those with poorer executive functioning were more likely to fall during a 5-year follow-up period compared to those with the highest executive functioning, and recurrent falls happened sooner for those with poorer executive functioning (Mirelman et al. 2012).

The relationship between vascular risk factors and neurocognitive performance in PLWH may also be relevant in this context, in that cardiovascular fitness influences mobility. In a cardiovascular disease (CVD) sub-study of the MACS Cohort, increased carotid intima medial thickness was associated with slower psychomotor speed and reduced memory (Becker et al. 2009). In the CHARTER cohort, waist circumference was associated with cognitive impairment (Becker et al. 2009), and in the START trial, higher Framingham-score determined cardiovascular risk was associated with worse neurocognitive test performance (Wright et al. 2015). More directly, studies have demonstrated a relationship between aerobic fitness and cognitive ability among older adults (Netz et al. 2011), and PLWH are known to have reduced aerobic fitness and physical function relative to their non-HIV peers (Oursler et al. 2006). CVD risk factors were associated with slower processing speed based on neuropsychological tests in a group of PLWH, and, compared to those with CVD who were treated with medication, those who were untreated had poorer test performance on processing speed, learning and memory, and executive function (Foley et al. 2010). In a small cross-sectional study of PLWH, those with a higher peak oxygen uptake on a treadmill test, signifying better fitness, were less likely to have mild neurocognitive disorder (OR 0.65, $p = 0.01$) and HIV-associated dementia (OR $= 0.65$, $p = 0.0006$) (Mapstone et al. 2013).

Polypharmacy impacts the risk of mobility impairment and falls in PLWH. One study found that falls risk increased 1.4 times (CI 1.3–1.6) with each prescribed medication, and that beta-blockers, opiates, antidepressants, antipsychotics and sedatives were significantly more commonly used among those who had previously had a fall compared to non-fallers after adjusting for the comorbidity being treated by those medications (Erlandson et al. 2012).

2.3 Frailty

Frailty is a condition of increased vulnerability to biologic and environmental insults, initially described in the elderly. It is generally understood to arise from the degradation of homeostatic mechanisms and is the result of an inability to respond to physiologic stressors. Its presence is associated with increased risk of several negative health outcomes. While the prevalence of frailty is highest in the very old, it can be observed throughout the life-course, and has been increasingly characterized among younger populations, including among individuals with acquired vulnerability states, such as childhood cancer survivors (Ness et al. 2015), diabetics (Cigolle et al. 2011), dialysis patients (Sy and Johansen 2017) and PLWH (Brothers et al. 2014; Desquilbet et al. 2007; Rees et al. 2013). As a geriatric syndrome it partially encompasses the complex overlapping effects of multimorbidity, functional decline and vulnerability to illness (O. A. R. Working Group on HIV and Aging 2012). Notably, mobility impairments and falls are also often incorporated within the concept of frailty.

Two dominant models of operationalizing frailty are commonly used in research settings, although others have been evaluated for their reliability and greater utility in the clinical setting. Both models have demonstrated that frail individuals experience a greater number of hospitalizations, falls, loss of functional independence, institutionalization and death compared to non-frail adults (Cawthon et al. 2007; Clegg et al. 2013).

The Fried frailty phenotype, the most common frailty metric used in the literature, views frailty as a syndrome distinct from ageing and other disease processes. It consists of five specific signs and symptoms: unintentional weight loss, exhaustion, low level of physical activity, slow motor performance and weakness (Fried et al. 2001). The presence of three or more is diagnostic of frailty; one or two of these components denote prefrail status, and their absence indicates a non-frail status (Zamudio-Rodriguez et al. 2018; Fried et al. 2001; Pathai et al. 2014; Thurn and Gustafson 2017).

The cumulative deficit model characterizes frailty as a state of vulnerability capturing an individual's overall general health status, and serves as an integrative marker of biological ageing as opposed to chronological age (Brothers et al. 2014; Rockwood and Mitnitski 2007). In this model, the continued accumulation of nonspecific health deficits across a range of systems – symptoms, disease, functional impairments, disabilities and lab abnormalities – all contribute to frailty (Brothers et al. 2014; Wallace et al. 2017). The benefit of a frailty index is that it can be constructed from any existing health dataset using a standardized procedure (Searle et al. 2008). When a sufficiently large number of readily accessible deficits, usually between 30 and 40, are included, the variables can be selected at random and yield comparable results for the risk of adverse outcomes by presenting the number of deficits accumulated as a proportion of the number of deficits measured in a summary score between 0 and 1. Although best used as a continuous measure, a cut-point of 0.25 has been used to distinguish frail from non-frail (Rockwood et al. 2007; Franconi et al. 2018).

The Veterans Aging Cohort Study Index (VACSI) is specific to PLWH and was initially developed as a mortality index. It is a clinical HIV and general biomarker-based index that includes CD4 count, HIV-1 RNA, haemoglobin, fibrosis-4, estimated glomerular filtration rate and hepatitis C co-infection. Conceptually it has similarities to the cumulative deficit model. However, unlike most frailty scales, age is included in the VACSI. It has been shown to predict hospitalizations, admissions to intensive care and death (Justice et al. 2013). It has also been used as a surrogate marker to identify frail PLWH (Womack et al. 2013; Akgun et al. 2014).

Among ageing PLWH the prevalence of frailty using the phenotype model ranges from 2.9 to 28.6% (Desquilbet et al. 2007; Levett et al. 2016; Zamudio-Rodriguez et al. 2017; Althoff et al. 2014). In the MACS, 12% of HIV+ men aged 50–64 were identified as frail versus 9% of HIV− men. Using similar criteria in the WIHS 17% of HIV+ women and 10% of HIV− women at midlife (mean age 39) were found to be frail (Gustafson et al. 2016). This can be compared with frailty rates of 4.1% for adults aged 50–64 and 17.1% for adults aged 65 and older in SHARE (Santos-Eggimann et al. 2009), and 9.9% in a systematic review of 15 studies (Collard et al. 2012). In studies that have assessed frailty using the frailty index, the mean FI has been found to be higher in PLWH than that seen in the general population, from 0.26 to 0.31 (Guaraldi et al. 2015).

In the pre-cART era, frailty was associated with advanced disease, wasting and low muscle mass, whereas today frailty in PLWH is associated with central adiposity, sarcopenia and the density of muscle fat (Hawkins et al. 2018). The introduction of cART has decreased the prevalence of frailty in PLWH. However, multiple factors associated with frailty persist in the current treatment era (Levett et al. 2016). Some factors include traditional HIV measures such as lower current and nadir CD4 cell count, CD4/CD8 ratio, detectable viral load, history of AIDS and longer time since diagnosis of HIV. Other factors are non-HIV specific and include age, low body mass index (BMI), depressive symptoms, lipodystrophy, hepatitis C coinfection, multiple falls in the previous year and lower cognitive performance (Brothers et al. 2014; Rees et al. 2013; Levett et al. 2016; Escota et al. 2015). Frailty in PLWH has been associated with cardiovascular disease, congestive heart failure, cancer and chronic infection such as cytomegalovirus and is also considered a risk factor for neurocognitive disorders (Zamudio-Rodriguez et al. 2018; Desquilbet et al. 2007). Interestingly, in an era when the majority of HIV+ individuals experience immune recovery, traditional clinical indices of HIV severity such as CD4 cell count, nadir CD4 count and detectable viral load are increasingly found to be poorly associated with frailty and other surrogate markers of vulnerability (Brothers et al. 2014; Guaraldi et al. 2015; Paul et al. 2018). Indeed, a frailty index based on deficit accumulation predicted survival and incident multimorbidity independently of HIV and behavioural risk factors (Guaraldi et al. 2015). This may signify the value of more general health indices in being able to discriminate risk among the immune-reconstituted HIV population of the cART era. Importantly, frailty is amenable to preventive strategies (Thurn and Gustafson 2017). Transitions in frailty have been documented in PLWH, characterizing both changes in frailty states (Gill et al. 2006) and frailty severity using the frailty index (Brothers et al. 2017). In the MHMC

cohort, 53% of participants improved (had a lower FI) after 4 years; 18.5% maintained their FI score, and 28.1% had a worse score; 3.0% died (Brothers et al. 2017). Given that frailty can account for interaction and redundancy across multiple systems, it may be increasingly valuable in describing the complex and interacting health problems among PLWH.

As with mobility and falls, it is unclear whether the relationship between frailty and cognitive function is temporal and causal, i.e. frailty impacts neurocognitive function, or the relationship is one of reverse causation, i.e. neurocognitive function affects frailty, or is correlational where both independently occur simultaneously. In the geriatric literature among non-HIV+ individuals, poor executive function and psychomotor speed increase the risk of frailty, whereas memory and language, which are hallmarks for Alzheimer's disease, do not (Yassuda et al. 2012; Macuco et al. 2012; Langlois et al. 2012).

Compared to non-HIV infected individuals, PLWH are nearly twice as likely to exhibit higher rates of cognitive impairment and when matched for age, to exhibit greater severity of frailty (Underwood et al. 2017). In a cross-sectional study of 122 PLWHIV with a mean age 57.5, Paul et al. examined select cognitive domains over and above clinical factors among frail and non-frail individuals using the Fried phenotype (Paul et al. 2018). They found that worse performance in executive function was associated with frailty but other domains were unrelated to frailty. Female sex and depression subscale scores were also significantly associated with frailty, whereas HIV markers of infection such as CD4 count and viral load were not. However, in a stepwise hierarchical model that included age and depressive symptoms there was no longer a significant association between executive function and frailty. Similarly, Zamudio-Rodriguez and colleagues found that after adjustment, pre-frailty was associated with MND, but frailty was not (Zamudio-Rodriguez et al. 2018).

Whereas HAND focuses on neurocognitive deficits, successful cognitive ageing (SCA) focuses on the successful end of the neurocognitive continuum, as measured by the absence of neurocognitive deficits and symptoms on neuropsychological and cognitive functioning tests. A number of studies have examined SCA among PLWH. Moore and colleagues found that 24.9% of PLWH compared to 40.0% of HIV-negative individuals experienced successful cognitive ageing (Moore et al. 2014). Further, a stairstep decline in SCA was noted based on HIV status and age from 47% among young HIV-negative participants, to 18.7% among older PLWH. Similarly, in a study among PLWH followed for at least 5 years, 32% were identified as experiencing successful cognitive ageing, but no association was found with cognitive reserve as has been seen in the general population (Malaspina et al. 2011; Yaffe et al. 2009). Frailty was significantly inversely associated with successful cognitive ageing among PLWH in the MHMC cohort, where successful cognitive ageing was defined as the absence of depressive symptoms, cognitive impairment and functional impairment, and frailty was assessed using a 37-item frailty index (Wallace et al. 2017). For each 0.1 point increase in the frailty index, the odds of successful cognitive ageing were reduced by 36%. This corresponded to a decrease in the odds of successful cognitive ageing by 12% for each additional

health deficit experienced. Moreover, the frailty index was the only variable found to be statistically significant in its ability to discriminate SCA (AUC 0.63; $p = 0.02$), including individual disease diagnoses and multimorbidity. Similarly, Oppenheim found that a higher frailty index was associated with worse global neurocognitive functioning after adjustment for age, employment and premorbid intellectual functioning. The individual components of verbal fluency, executive functioning, processing speed and motor skills were also significantly associated with worse frailty scores (Oppenheim et al. 2018).

Apart from HIV-related effects, several other mechanisms have been theorized to explain the connection between frailty and cognitive function. In addition to chronic inflammation, nutrition, cardiovascular risks, mental health, hormones and Alzheimer's disease pathology have all been related to both frailty and cognitive function and may hasten the onset of either for PLWH (Robertson et al. 2013). The presence of both frailty and HAND together may also exacerbate the negative effects of both. It was recently reported that poor health outcomes for PLWH over 2 years of observation were most common among those who were both frail and had neurocognitive impairment, with 74% of participants experiencing at least one of recurrent falls, worsening instrumental activities of daily living (IADL) limitation, or death (Kelly et al. 2018).

In summary, an understanding of the geriatric syndromes of falls, mobility and frailty in relation to neurocognitive functioning can better characterize and explain ageing trajectories of older PLWH. Frailty prevention efforts are essential for successful ageing without experiencing disability or loss of independence. Sarcopenia, depression and vascular risk factors may be targeted for prevention and mitigation. Conceptualizing PLWH in terms of successful cognitive ageing offers targets for intervention and possible preventive strategies. High socioeconomic status, good nutrition, physical activity, social interaction and cognitive remediation have been put forth as positive mediators in conceptual models. Proactive prevention strategies that preserve function should be the priority for the care of older populations living with HIV.

2.4 Sarcopenia

y composition changes are common complications in PLWH and cause important clinical consequences. Prior to the availability of effective ARVs, significant weight loss, comprising both fat mass and skeletal muscle, occurred often in patients with advanced disease. This condition was known as the AIDS Wasting Syndrome (Grinspoon et al. 2003). Significant loss of skeletal muscle independently predicted mortality (Kotler et al. 1989). Soon after the first generation of effective cART regimens became available in 1996 unexpected body composition changes in PLWH were identified. These were called by various evocative names, including the lipodystrophy syndrome. This term referred to two aetiologically distinct patterns of body fat changes which often developed concurrently in patients soon after

starting therapy: peripheral fat wasting, termed peripheral lipoatrophy (LA); and abdominal obesity, termed central lipohypertrophy (LH).

LA refers to the significant, diffuse loss of subcutaneous fat, most easily observed in the face, legs and buttocks. It is due to apoptosis of peripheral adipocytes and was aetiologically related to mitochondrial toxicity caused by first generation thymidine analogue reverse transcriptase inhibitors (azidothymidine and stavudine). The introduction of newer, safer ARVs has essentially resolved this complication as the original offending drugs are now used infrequently (Falutz 2011).

LH refers to the accumulation of ectopic fat, usually occurring as increased visceral adipose tissue, but also in the dorso-cervical fat pad (known commonly, and pejoratively, as "buffalo hump") and intra-mammary fat. LH is of multifactorial origin (Falutz 2011). Current "backbone" ARVs, including protease inhibitors and integrase strand transfer inhibitors, although rarely causing dyslipidemia and glucose homeostasis, complications which occurred with some early ARVs, are however still associated with abdominal obesity (McComsey et al. 2016). LA and LH, both singly and in combination, often led to mood disorders and discontinuation of life-saving ARVs (Shenoy et al. 2014; Crane et al. 2008; Corless et al. 2005).

Older PLWH may also develop physiologic, age-related changes in body composition, including peripheral lipoatrophy, increased central obesity and loss of lean body mass (Kuk et al. 2009; Shaw et al. 2007). These may mimic HIV/cART associated body composition changes.

Sarcopenia, a term introduced over 25 years ago, initially referred only to the loss of skeletal mass. As noted, it also occurred as part of the AWS. Skeletal mass can be determined using anthropometrics, bio-impedance analysis, computerized tomography, magnetic resonance imaging and as recently demonstrated, by ultrasound (Ticinesi et al. 2017) and methods employing tritiated Deuterium (Cawthon et al. 2019). Presently, it is most commonly and reliably quantified by dual-energy X-ray absorptiometry (DXA) (Edwards and Buehring 2015). The clinical assessment of sarcopenia is unreliable. The initial definition of sarcopenia referred only to the loss of skeletal muscle mass, defined as an index of DXA-determined appendicular lean mass (ALM/ht^2) (Baumgartner et al. 1998). Sarcopenia is now defined as the age and gender dependent loss of muscle mass and impaired function, most often determined as decreased hand-grip strength or low gait speed. Primary sarcopenia occurs in the absence of conditions known to cause weight loss and represents physiologic age-related changes. Secondary sarcopenia refers to loss of skeletal mass associated with disuse, disease, poor nutrition or malabsorption (Cruz-Jentoft et al. 2010a). Of concern to some PLWH, ongoing, low-level skeletal mass loss, of multifactorial aetiology, persists despite cART (Wasserman et al. 2014; Abdul Aziz et al. 2018).

In the general elderly population, physiologic sarcopenia occurs in about 30% of persons over 80; 20% over 65 will lose skeletal mass and have related functional impairment (Binkley and Cooper 2015). There is an overlap in risk factors for primary and secondary sarcopenia in the general population with several pathophysiologic conditions also occurring in treated PLWH. These can include genetic factors influencing muscle metabolism, hormonal dysregulation (e.g. hypogonadism and both growth hormone resistance and deficiency), mitochondrial dysfunction, life-

style (especially tobacco and alcohol use), deconditioning, multimorbidity and polypharmacy (Rolland et al. 2008). Polypharmacy, as noted above, is common in PLWH (Edelman et al. 2013). In the general population, polypharmacy is a risk factor for both sarcopenia (Konig et al. 2017) and cognitive decline (Jyrkka et al. 2011).

The consequences of sarcopenia in the elderly population are clinically nonspecific and thus this condition is often not included in the diagnostic evaluation. In the elderly, sarcopenia is now considered as a geriatric syndrome (Cruz-Jentoft et al. 2010b). It reduces functional status due to decreased endurance and poor mobility leading to increased falls, loss of independence and increased mortality (Visser and Schaap 2011). Sarcopenia is also an independent contributor to frailty (Landi et al. 2015), which, as noted, is itself associated with impaired cognition (Mitnitski et al. 2011). Importantly, sarcopenia may be directly associated with an increased risk of cognitive decline in the elderly (Chang et al. 2016). In ageing PLWH, a recent preliminary analysis, using a functional assessment of sarcopenia, demonstrated a decline of executive function (Montero-Odasso et al. 2019). Frailty, sarcopenia and impaired cognition may be linked via shared pathways including oxidative stress, immunosenescence, sleep disorders, chronic inflammation and insulin resistance. Sarcopenia has also been shown to be a risk factor for overall mortality in PLWH (Scherzer et al. 2011). In summary, the conditions by which sarcopenia may contribute to cognitive decline occur commonly in ageing PLWH.

2.5 Sensory Impairment

Other geriatric syndromes may also increase the risk of cognitive decline in treated PLWH. Sensory impairment, whether due to hearing impairment, decreased visual acuity, olfactory problems or peripheral neuropathy, is common in the elderly and clearly lead to important functional impairments, including cognition. Indeed, the presence of multisensory domain impairments may increase risk of dementia in a stepwise manner in both men and women older than 70 (Brenowitz et al. 2019). The mechanisms contributing to increased cognitive risk are complex and potentially bidirectional. Sensory impairments and cognitive decline may share common pathogenic mechanisms, including ageing-related and vascular risks. Other mechanisms include abnormalities in common anatomic regions (e.g. possible role of the hippocampus in cognition and auditory pathways) and common pathogenic mechanisms (e.g. amyloid-beta is present in Alzheimer's disease and cataracts). It is well known that sensory loss may lead to depression, social isolation and weakness through physical inactivity, all known risk factors for dementia (Whitson et al. 2018).

2.5.1 Visual Impairment

HIV-related Neuro-Retinal Disorder (HIV-NRD) is a novel condition consisting of abnormalities in retinal nerve fibre layers, possibly related to micro-infarcts and microangiopathy associated with chronic inflammation (Ashraf et al. 2015). This may lead to reduced contrast sensitivity, altered colour vision and peripheral visual field loss and has been shown to occur more often in PLWH than controls (Barteselli et al. 2014). Visual quality of life is impaired in PLWH with HIV-NRD (Ashraf et al. 2015) and is therefore a risk factor for cognitive decline.

In PLWH both the prevalence and incidence of macular degeneration is increased compared to controls. Ongoing immune activation and chronic inflammation in PLWH are contributing risks, similar to the general population (Jabs et al. 2015; Jabs et al. 2017, #181).

In the general population, ocular lens density increases with age leading to cataracts, an important cause of blindness and visual impairment worldwide. The human lens has been suggested as a model for ageing, as it may mirror distinct ageing-related processes in other parts of the body. In PLWH, especially untreated persons, the eye is a common site of involvement by opportunistic infections and AIDS-related malignancies. In treated individuals, AIDS manifestations occur much less often, although other complications have been documented. Immune recovery uveitis, chronic steroid use, diabetes and uveitis related to chronic inflammation may increase the risk of cataract formation. A large population-based study in Denmark determined that cataract surgery occurred almost twice as often in PLWH compared to seronegative persons, with the highest risk occurring in those with severe CD4 depletion (<200 cells/mL) (Rasmussen et al. 2011).

2.5.2 Hearing Impairment

In the general population, peripheral hearing impairment (HI or presbycusis) increases with age, is the most common sensory disability in the elderly, occurring in 25–40% of persons older than 65, and has been associated with cognitive impairment in some, but not all studies (Panza et al. 2015). The prospective Health ABC Study found a more than 55% increase in incident dementia in subjects with moderately severe peripheral HI at baseline in a large biracial cohort older than 70 (Deal et al. 2017). Possible mechanisms linking HI with cognitive decline include the resulting social isolation, loneliness, impaired verbal communication and possible effects on cognitive reserve. Vascular risks may predispose to both HI and cognitive impairment. Social isolation has been associated with biologic changes, such as inflammation, which may contribute to both cognitive decline and HI. At present, the link between HI and cognition has not been confirmed to be causal but an important association between the two conditions exists nevertheless.

In PLWH hearing may be impaired due to involvement of the cochlea and eighth cranial nerve. Some antiretroviral drugs cause mitochondrial damage which can

affect cochlear function. Recent analyses from the MACS cohort confirm that sensorineural HI is more common among older PLWH than controls, although no association with HIV or treatment-related parameters were found. Of concern, poorer hearing occurred at lower frequencies, which may predispose to increased communication difficulties (Torre et al. 2015). This finding of HI at predominantly lower frequencies was confirmed in another cohort (Luque et al. 2014). Although HI in the elderly impacts quality of life, there was no difference in the reported QoL, as assessed using the SF-36, between male and female PLWH and seronegative controls with HI in a combined analysis from the MACS and WIHS cohorts. The fact that the median age was only in the high 50s may be a possible explanation for the lack of observed association (Duong et al. 2016). No studies have yet evaluated cognition in PLWH with HI, but the risks are clearly present and such analyses are urgently needed. Treatment for HI in the elderly is available and may improve cognitive function (Miller et al. 2015).

2.5.3 Olfaction

The sensations of smell and taste are infrequently assessed clinically in the absence of specific complaints. The Health ABC Study assessed smell in over 1,800 subjects between age 70 and 79 and found abnormal results in 50%. Persons with abnormal results were more likely to have dementia as determined by use of typical medications, admission to hospital with a diagnosis of dementia, or abnormal scores on a modified mini-mental status exam (Brenowitz et al. 2019). Similar findings of impaired olfactory function in older subjects with either confirmed Alzheimer's disease or mild cognitive impairment compared to those with normal cognition were described using comprehensive olfactory evaluations (Peters et al. 2003). A large, prospective study of the relation between sensory impairments and mortality in community-dwelling persons with a mean age of 69 found that olfactory impairment, but not hearing or visual impairment, was independently associated with increased mortality over 13 years (Schubert et al. 2017).

Olfactory function has been infrequently assessed in treated PLWH. Small case series in the pre-cART era suggested that impaired smell did occur, but results may have been influenced by advanced disease and concurrent AIDS-related complications or CNS involvement. In a recent small study of middle-aged female Nigerians and seronegative controls using visual analogue scales, olfactory threshold discrimination and identification were within the normal range in the two groups, but the mean values were significantly lower in the PLWH (Fasunla et al. 2016). Several small studies have suggested that olfactory function is possibly more impaired in PLWH with cognitive impairment (Mueller et al. 2002; Razani et al. 1996).

2.5.4 Peripheral Neuropathy

Sensory neuropathy, of multifactorial aetiology, is common in treated PLWH with an estimated prevalence of 50–60% (Ellis et al. 2010). In a study of middle-aged, predominantly male African-American PLWH, most with advanced disease (50% CD4 < 200, 70% detectable HIV-RNA), and with a significant minority reporting psychologic or anxiety disorder and substance abuse, those with confirmed distal sensory polyneuropathy were more likely to perform worse on timed psychomotor tests, including information processing speed and executive function (Fellows et al. 2012). The authors suggested that neuropsychologic testing should be interpreted with caution in PLWH with sensory neuropathy as this may worsen their objective assessments. Peripheral neuropathy also contributes to chronic pain, impaired functional status, mood disorders and polypharmacy.

2.6 Clinical Implications, Translational Aspects and Future Directions

2.6.1 Clinical Implications

This chapter has presented the perspective that viewing health complications as geriatric syndromes rather than as traditionally determined, discrete conditions will be more helpful when considering the health and well-being of ageing PLWH, particularly in regard to cognitive decline. Assessing clinical problems in the general population in an interdisciplinary and comprehensive manner has proven outcome benefits in regard to patient outcomes, patient and care-giver satisfaction and enduring impact on quality of life.

We propose an adaptation of geriatric principles of assessment and care of the elderly for selected ageing PLWH utilizing a method commonly referred to as the Comprehensive Geriatric Assessment (CGA). The CGA is based on the premise that an interdisciplinary, multidimensional evaluation of at-risk older persons by a team of health professionals may better identify relevant treatable, or manageable health problems, compared to using the traditional "hub and spoke" system of centralized referral to multiple specialists. It also involves a cogent and rational plan for the care of the individual within their particular environment, being mindful of and respecting the diverse influences which may impact an individual. At present, the CGA approach has been infrequently used in PLWH, and its effectiveness is unknown. However, issues regarding the known increase in multimorbidity and its impact on polypharmacy, frailty and disability related to mobility limitations, sensory impairment and sarcopenia are already being incorporated into the clinical assessment of ageing PLWH, and therefore the ground is fertile for the introduction of the geriatric model of care.

2.6.2 Translational Aspects

The mechanisms contributing to increased cognitive risk are complex and potentially bidirectional. Frailty, sarcopenia and impaired cognition may be linked via shared pathways including chronic inflammation, oxidative stress, immune-senescence and insulin resistance. Sensory impairments, frailty and related disorders may share common pathogenic mechanisms with cognitive decline, including ageing-related and vascular risks. Other mechanisms include abnormalities in common anatomic regions (e.g. possible role of the hippocampus in cognition and auditory pathways) and common pathogenic mechanisms (e.g. amyloid-beta is present in Alzheimer's disease and cataracts). It is well known that sensory loss may lead to depression, social isolation and weakness through physical inactivity, all known risk factors for dementia. Sarcopenia and impaired mobility are often associated and may lead to cognitive decline by limiting social interaction and isolation. Complications associated with polypharmacy (drug–drug interactions, adverse drug effects, particularly those increasing the anticholinergic burden, and inappropriate drug prescribing) contribute to cognitive impairment.

Current "backbone" ARVs, including protease inhibitors and possibly integrase strand transfer inhibitors, although rarely causing dyslipidemia and glucose homeostasis, are still associated with abdominal obesity, which may contribute to metabolic complications. The investigation of this association is ongoing.

2.7 Future Directions in Terms of Basic Science/Health Services Delivery/Public Health

Research in ageing PLWH to elucidate the role of vascular risks related to metabolic complications and obesity, as well as the effects of social isolation and polypharmacy on ageing PLWH in predisposing to early cognitive decline, potentially augmented by the ongoing chronic inflammation, will harness emerging techniques ranging from the molecular to novel imaging modalities.

Studying whether minimizing risk factors play a role in maintaining healthspan in ageing PLWH is imperative as is the investigation of the predictors of successful ageing in this population. In this regard, understanding those factors which contribute to maximizing cognitive reserve is also necessary.

Interventions addressing risks of polypharmacy among HIV-infected persons are in their infancy and tools to identify overprescribing are lacking. Nevertheless, considerable experience exists from the early HAART era regarding management of and adherence to complex first-generation ARV drugs. Ideally, the historical lessons learned are adaptable to the management of PLWH receiving treatment for multiple comorbidities, which can lead to potentially complex drug–drug interactions and adverse drug effects, including but not exclusive to use of cART. The availability of easy to use mobile "Apps" has greatly facilitated the ability to assess

risk for drug interactions, for both clinicians and patients. The process of medication reconciliation is often enhanced by the involvement of clinical pharmacists working in conjunction with the HIV care team. Such collaborations are crucial and include the non-judgemental awareness on the part of care providers that recreational substance use, particularly alcohol and marijuana, is common among HIV-infected persons and can impact risks associated with polypharmacy.

In developing a public-health response to ageing, it is important not to just consider the approaches that alleviate losses associated with older age, but also those that may reinforce recovery, adaptation and psychosocial growth. In this perspective, WHO has recently built on a conceptual framework to consider the health status in an ageing individual. The term "healthy ageing" has been proposed to promote a positive approach to ageing that relies on reserves and preserved capacities in an individual, rather than accumulation of deficits. In 2015, the World Report on Ageing and Health attempted to combine clinical and public health outcomes for ageing by defining healthy ageing as the process of developing and maintaining the functional ability that enables well-being in older age. This construct derives from the relationship of two entities: "intrinsic capacity", defined as the composite of all cognitive and physical functioning of the individual, and "the environment".

Assessing intrinsic capacity is both a multidisciplinary and a multidimensional process, also intrinsic to the CGA as outlined above, and is designed to evaluate the individual's biology on the basis of five functional domains: locomotion, cognition, psychology, vitality and sensory. The intrinsic capacity construct might be considered an evolution of the frailty concept, taking into special consideration the need for the wide implementation of prevention, in relation to the continuum of the ageing process, and the opportunities offered by novel technologies. The investigation of this novel concept in ageing PLWH will be instructive.

3 Conclusions

In just over 35 years infection with HIV has been transformed from a nearly 100% fatal condition into a chronic disease. This has significantly altered the demographics of PLWH such that most persons with access to cART and who take the drugs reliably will have near-normal long-term survival. However, some of these ageing PLWH will be at increased risk of the premature onset of common bio-psycho-social consequences of ageing. This chapter has presented the perspective that viewing health complications as geriatric syndromes rather than as traditional discrete biomedical conditions will be more helpful when considering the health of ageing PLWH, particularly in regard to cognitive decline, one of the most common problems that all elderly persons face. In the general elderly population, assessing clinical problems in an interdisciplinary and comprehensive manner (using the CGA as detailed above) has proven outcome benefits. Its adaptation for selected ageing PLWH will be important in maintaining a successful healthspan.

In addition to the premature development of ageing-related disorders older PLWH are at increased risk of multimorbidity, as documented in the NA-ACCORD study, and its prevalence has increased over time (Wong et al. 2018). Hypercholesterolemia and chronic kidney disease were among the most common occurring comorbidities. In the general population, a longitudinal study of a healthy cohort with normal baseline cognition showed that the accumulation of new chronic diseases over time, particularly hypercholesterolemia and chronic kidney disease, was associated with deterioration in several cognitive domains, including verbal fluency, itself related to executive dysfunction and problem solving (Fabbri et al. 2016). Elsewhere in this issue, it is noted that executive dysfunction is a common finding in PLWH with HAND, with profound implications for maintaining independence and quality of life. From a management perspective, it is important to recall that many ageing-related comorbidities are lifestyle related and thus may be either preventable or modifiable with appropriate interventions. Some of these may also be appropriate in ageing PLWH.

At present, ageing PLWH remain at increased risk of diverse complications which may affect all aspects of their lives, particularly cognition, and which contribute to a shorter survival and poorer quality of life compared to the general population. It is the responsibility of everyone affected by HIV to continue to be proactive and to assure that evolving challenges will be met with the same determination and resourcefulness, which have been the characteristics of the response to HIV as it continues to impact society in profound ways.

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