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Frailty in people living with HIV: An Update

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Abstract

Purpose of Review: The HIV population is ageing with rising rates of frailty though strategies of how best to manage it remain ill-defined. It also remains unclear what the prevalence of frailty is within this cohort, how best to diagnose it and what factors are associated.

Recent Findings: The prevalence of frailty remains unclear due to heterogenous results. Routine screening in those 50+ is recommended and whilst the Fried Frailty Phenotype is currently preferred the Clinical Frailty Scale could be considered. No biomarkers are currently recommended. Looking at associated factors, HIV neurocognitive impairment and long-term alcohol usage has been shown to be associated with developing frailty whilst those who are frail have been shown to be less active and more likely to fall. NAFLD with fibrosis has been shown to be an indicator of metabolic age and the Pooled Cohort Equations has been shown to be more effective in diagnosing cardiovascular risk in frail people living with HIV.

Summary: Whilst the prevalence of frailty differs between countries, with the addition of prefrailty this represents a large proportion of older people living with HIV and services must have strategies in place of how to manage them. Further longitudinal studies are required.

Keywords: Frailty, Ageing, Geriatrics, HIV, AIDS

Practitioner Points

1. Frailty is common and can present earlier in people living with HIV and is associated with a higher burden of comorbidity and increased risk of mortality.
2. Multiple screening tools can be used to detect frailty in people living with HIV. Whilst the Fried Frailty Phenotype is the most common this relies on objective measures with recent evidence supporting the use of the Clinical Frailty Scale.
3. Whilst the prevalence of frailty in some cohorts remains small, the prevalence of prefrailty is much higher with studies demonstrating clear transitions towards frailty. HIV services should not only address those already frail but have strategies in place to manage those with prefrailty to slow, stop or reverse their transition.

Frailty in people living with HIV: An Update

Introduction

The average age of people living with HIV is increasing due to access to effective antiretroviral therapy (ART), improved management of coinfections and comorbidities and an increased rate of new cases in older people, meaning that by 2030 70% of people living with HIV are expected to be over 50[1-4**]. Those ageing with HIV demonstrate an accentuated ageing process with higher rates of multimorbidity and frailty and subsequent worse quality of life[2-5].

Frailty is a state of decreased homeostatic reserve resulting in increased vulnerability to endogenous and exogenous stressors and an increased risk of negative outcomes[6, 7]. A recent study identified that frailty is specifically associated with mortality and comorbidity in a sample including 598 HIV positive people[8**]. Gender differences exist with women living with HIV more likely to have worse physical function and quality of life[9].

Most commonly used is the Fried Frailty Phenotype (FFP), designed to identify frailty to aid mortality prediction[6]. It utilises five domains: unintentional weight loss, exhaustion, low physical activity, slow walking speed and low grip strength with scores of 3 or more determining frailty, 1-2 identifying pre-frailty and 0 as robust[6, 8**]. However, FFP scoring requires objective measurements for gait speed and grip strength and does not consider broader elements of frailty, such as cognition and psychosocial functioning[6]. Multiple alternative frailty tools exist, which have recently been outlined elsewhere[3**, 10-16].

The extension of the UNAIDS 90-90-90 target proposing that more than 90% of people living with HIV should have good health related quality of life highlights the importance of frailty, supported by its inclusion in updated European AIDS Clinical Society (EACS) Guidelines[17, 18]. Therefore, this review will explore the most recent advancements in the area (see Video, Supplemental Digital Content 1, which explores overview and Figure 1).

Prevalence

The prevalence of frailty amongst people living with HIV remains unclear though a recent systematic review of people over 50 living with HIV (26 studies, 6584 cases) using the FFP reported a pooled prevalence of 10.9% for frailty and 47.2% for prefrailty comparable to 11% and 42% of community-dwelling older adults, though heterogeneity between studies was high making comparison challenging[19*]. Further studies have been conducted since using various frailty diagnostic tools with the results summarised below (Table 1)[20-31**].

Frailty is dynamic process, with one study identifying that 7.5% of participants transitioned from frail to robust and 8.4% contrariwise throughout the study whilst another reported it was infrequent for people to go directly between robust and frail in either direction (<0.8%) with most transitioning via the prefrail category highlighting this group as an important target for intervention[27*, 31**].

The focus on frailty in people living with HIV research tends to be on high income countries despite the fact there are over 3 million people living with HIV in sub-Saharan Africa (SSA) aged over 50[32*]. Several studies have recently tried to establish the prevalence in SSA (Table 2) which is variable, impacted by the setting with participants in a Tanzanian study being recruited from an urban government hospital with access to free ART potentially explaining lower rates[32*-34]. Frailty was associated with female gender, older age, being single, not being on ART and coexisting depression[32*-34]. It's likely we will see a rise in the prevalence of frailty amongst people living with HIV in SSA particularly those in rural areas as seen in the recent studies from South Africa and Uganda, and larger studies are required in both urban and rural areas to guide strategies for managing these patients over the long-term[32*-34].

Diagnostic Tools

In a study of European HIV services (12 countries) frailty identification was viewed as important but the use of a validated frailty score less so which may stem from a lack of consensus regarding optimal diagnostic tool for those with HIV[35**]. EACS advocates for either the FFP or use of a Frailty Index (FI) though provides no further guidance on how to apply these[17]. The clinical challenges of the FFP have been described, and a universally applicable HIV-specific FI is not available, though adaptations of an Italian FI for people living with HIV could be used[36]. A Canadian study (n=143, 88% male, mean age 57) examined the concordance of the Clinical Frailty Scale (CFS), a 9-point judgement-based tool that evaluates specific domains including comorbidity, function, and cognition, and a FI to the FFP which showed a prevalence of 15% (CFS 14%; FI 26%), recommending the CFS due to its ease of use and lack of need for additional measurements, though it is only validated in those over 65[11, 37**]. A second Canadian study (n=101, 80% male, median age 56) utilised the Rotterdam Healthy Ageing Score (HAS) with only 39% of participants considered to be ageing healthily[38, 39]. The HAS correlates well with the FFP but is only validated in those aged over 55 and requires additional time-consuming assessments and is therefore not recommended to be used as an alternative[39]. A UK study (n=80, 80% male, median age 56) assessed frailty using gait speed (GS), timed-up-and-go test (TUGT), and a self-reported health questionnaire, with prevalence of 19%, 33% and 20% respectively though they noted that objective measures correlated more with clinical parameters but were more time consuming[12, 13, 40*, 41]. The TUGT is a valid and reliable test that is carried by asking a patient to get up from a chair, walk to a point three metres away, turn around and sit back down, with a time of ≥ 13.5 seconds being abnormal; individuals who take longer to perform it have been shown to have higher rates of frailty and falls and when used in studies in people living

with HIV it was found to be an acceptable test and more related to clinical parameters than other subjective tools[41-46]. Most important is having a robust screening process within a clinical service, using a tool that clinicians feel comfortable with and is acceptable to patients as all require further validation in people living with HIV.

Biomarkers

Several studies have explored potential biomarkers for frailty in the context of HIV (Table 3)[47*-54]. However, despite these further longitudinal studies with ethnically diverse samples are required to determine the clinical significance and applicability[47*-54].

Models of Care

Frailty identification is the first step, effective management must follow though the optimal care model is unknown. Currently there are six specialist services for older people living with HIV in the UK, though models and sub-focus (frailty, multimorbidity, menopause) differ[55]. The Silver Clinic in Brighton (n=52, 90% male, median age 67) has been running since 2016 combining assessment by a HIV clinician, Geriatrician and pharmacist with 67% of attendees being frail (FRAIL scale) and 50% having a geriatric syndrome[10, 56**]. The Sage Clinic in London (n=35, 77% male, median age 67) mirrors the Silver clinic with the addition of physiotherapists and occupational therapists, where 83% of attendees were frail (FFP) and affective disorders, cognitive disorders and falls were prevalent[57]. Chelsea and Westminster Hospital (UK) has had a dedicated HIV clinician led ageing clinic since 2009 with 744 people attending (93% male, mean age 56) with a high prevalence of polypharmacy (46.6%) and multimorbidity (69.3%) and have therefore created several joint clinics highlighting the importance of interdisciplinary working to provide holistic care[58**]. Comprehensive geriatric assessment (CGA) is a patient-centred, holistic assessment and management process used within Geriatric Medicine. It was applied to people living with HIV in a retrospective US study (n=105, 73% male, mean age 66.5) identifying 60% as frail or prefrail with the most common patient goals being staying alive, maintaining health, and financial stability[59**]. Finally, discussions regarding how to adapt during the COVID-19 pandemic highlight that self-reported frailty is complementary rather than a substitute for objective assessment therefore screening for frailty could be done via telemedicine with a positive screen triggering an in-person assessment[60-62].

Neurocognitive Impairment

Despite its prevalence, the link between neurocognitive impairment (NCI) link and frailty is not well researched in HIV[5, 63*, 64]. Analysis from the AIDS Clinical Trial Group A5322 cohort study (n=929, 81% male, median age 51) identified that on enrolment 16% had NCI whilst 6% were frail with baseline NCI associated with the development of frailty[65**]. A US study identified a higher likelihood of NCI in patients with either a FFP score of 1.25 or more (two in

clinical practice) or a CD4 count of 642 or less cells/mm [63*]. Another US study comparing people by serostatus (50 HIV+, 60 HIV-) and frailty status (FFP) found that in people living with HIV pre-frailty was associated with NCI, particularly processing speed, motor skills and delayed recall, highlighting the importance of incorporating interventions to maintain cognition early[64]. Another US study (n=105, 85% male, mean age 56, 19% frail by FFP) used machine learning analysis of brain MRI scans to determine factors associated with frailty finding that female sex, symptoms of depression or reduced cerebral blood flow in the right pallidum or the left occipital lobe on MRI had the highest association with frailty[66]. Lastly, a study showed that computerized cognitive rehabilitation therapy was deemed feasible amongst a group of older Ugandan adults and was found to improve immediate recall, working memory, verbal fluency and timed gait in those with HIV[67].

Physical Function and Rehabilitation

A retrospective study has shown that poor physical function, falls and frailty are all predictive of mortality in middle-aged people living with HIV[68]. A systematic review noted that the predominant factors contributing to poorer physical function include HIV severity, chronic inflammation and oxidative stress, peripheral and central nervous system dysfunction, and the presence of comorbidities[69**]. A US study (n=266, 81% male, median age 51) where 6% were frail (42% prefrail) showed 89% of participants were physically inactive and 37% had impaired physical function[70**]. Older age, black ethnicity, higher BMI, and physical inactivity were associated with physical function impairment whilst depression and hypertension were associated with frailty[70**]. Explanations for worse physical function have been explored within a UK study identifying that older people living with HIV had a higher proportion of myofibres with mitochondrial defects on muscle biopsy compared to negative controls which were independently associated with age, HIV status, 'low' physical performance capability and frailty, but not with prior exposure to "mitochondrially-toxic" NRTIs[71]. The Canada-International HIV and Rehabilitation Research Collaborative (CIHRRC) conducted a consultation with 69 international stakeholders creating seven research priorities including the impact of frailty[72*, 73]. The role of physiotherapist and occupational therapists in the assessment of frailty for people living with HIV is important with a UK based clinic incorporating these professionals reporting a high level of unmet needs; 54.5% being referred for therapy intervention, 24.2% to social services and 9.1% given a walking aid[74]. A recent review highlighted that exercise is effective in increasing aerobic capacity and muscle strength whilst also improving body composition and inflammatory outcomes[75*]. Exercise prescription should be based on the stage of HIV infection and for those who are asymptomatic should aim to engage in aerobic exercise 5 days a week and resistance exercise 3 days a week though lower targets are set for those who are symptomatic or have an AIDS diagnosis[69**]. Balance training is less researched but small studies suggest twice weekly balance training can improve balance and physical function and reduce the risk of frailty[69**]. Larger longitudinal studies are required to further explore rehabilitation and

exercise though a recent protocol has been published for a randomized trial examining the impact of high-intensity functional circuit exercise training delivered by live videoconferencing on older people living with HIV[76].

Falls

Falls comprise part of the frailty syndrome and are a predictor of poor outcomes for people living with HIV[77, 78]. A recent Brazilian systematic review demonstrated a frequency rate of 26% for any fall and 14% for frequent falls, with no increased risk of falls based on serostatus[79**]. A study using the FI showed an association between any fall and frailty whilst another utilising the FFP found it with recurrent falls[79**]. The authors noted that despite similar prevalence, falls occurred earlier in people living with HIV and were associated with frailty but also female gender, black ethnicity, advanced age, smoking, alcohol and use of illicit drugs, hepatitis C co-infection, NCI, polypharmacy, detectable viral load and not being on ART, whilst a higher CD4 count was protective[79**]. Efavirinez was shown to be associated with falls whereas the results for protease inhibitors were heterogenous meaning no clear association can be inferred[79**]. A sub-study of the EmERGE study evaluated frailty (FRAIL scale) and falls amongst stable people living with HIV using a smartphone application with 1373 people participating across five European sites (93% male, mean age 45) finding that 2% were frail (24% pre-frail), with a falls prevalence of 12% in the last year, 59% recurrent[80]. Fallers were older than non-fallers ($p=0.003$), and were more likely have prefrailty/ frailty ($p<0.001$)[80]. A UK based HIV frailty clinic reported 52.5% of attendees ($n=33$) had fallen at least once in the previous six months with 26.7% reporting a fracture[74]. In a study of women living with HIV those who repeatedly fell within a one year time frame were likely to be frail ($p=0.018$) or prefrail ($p=0.042$), whilst the FFP nor its components were associated with short-term odds of a single fall[81]. This means clinicians cannot use a first or single fall to determine frailty status in isolation, but for those who repeatedly fall there is a high chance that person is frail and should undergo falls assessment urgently to ascertain the cause and prevent serious injury[81]. Visual impairment is linked with falls with a US study retrospectively examining this in a mixed serostatus sample found that those with HIV were more likely to have perceived vision difficulty (21% vs. 13%; $p<0.01$) and those reporting difficulty in completing the study tasks had 11.2 times the increased odds of frailty (95% CI: 5.2-23.9)[82*]. Falls are common and HIV clinicians should therefore routinely enquire about them on review of patients over 50 with services having local protocols of how to further manage[17, 79**].

Polypharmacy

The association between polypharmacy and frailty is well established in the general population but not in people living with HIV despite them being more susceptible to harm from polypharmacy due to chronic inflammation, reduced organ system reserve, ongoing immune dysfunction, increased rates of renal and hepatic disease affecting drug metabolism and increased number of drug-drug interactions with ART[83*]. A US study compared people by serostatus (HIV+ $n=$

1762, 98% male, mean age 56; HIV- n= 2679, 91% male, mean age 57) and frailty status by FFP (Not frail: n=2794; FFP \geq 1: n=1647) and found that whilst frailty was uncommon (HIV+ 2%, HIV- 3%) there was a discrepancy by serostatuses with a mean of 6 non-ART medications in those with HIV versus 16 in those without[83*]. However, the impact of polypharmacy was greater in those with HIV where each additional non-ART medication increased the chance of scoring on a FFP domain 11% compared to 4% in those without HIV reinforcing the importance of polypharmacy management[83*]. A UK study in patients attending a specialist frailty clinic (n=42, 71% male, mean age 67) showed an average of seven non-ART medications, and a total of 73 drug-drug interactions of which 74% were interactions requiring dose adjustment of non-ART drugs and one significant interaction requiring cessation of a non-ART drug substantiating the role of HIV pharmacists in the management of polypharmacy[84].

Metabolic Health

The relationship between cardiovascular disease (CVD) and frailty amongst people living with HIV is not well established[85, 86*]. Sub-analysis of two large US HIV cohort studies; Women's Interagency HIV Study and the Multicenter AIDS Cohort Study (combined sample n=9184, 62% HIV+, 48% male) confirmed association between frailty (FFP) and CVD risk determined by Framingham risk score (FRS) and Pooled Cohort Equations (PCE) serostatus, though only high risk PCE was associated with frailty in women suggesting this may be the more clinically useful tool[86*]. A second US study found no additional benefit in PCE's ability to estimate CVD risk when frailty was added (p=0.05)[85]. Frailty was also found to be significantly associated with increased insulin resistance in people living with HIV[87]. Studies have also shown that liver steatosis and non-alcoholic fatty liver disease (NAFLD) with fibrosis are associated with frailty with NAFLD with fibrosis predicting frailty better than multimorbidity suggesting it could be used as an indicator of metabolic age[88, 89]. Finally, no studies have previously shown an association between alcohol usage and frailty which is thought to be related to the 'sick quitter' effect with those with recent cessation shown to be frailer often explained by poor health status preventing consumption[90, 91**]. High lifetime alcohol usage was positively associated with frailty among people living with HIV in an US study (n= 365, 69% male, mean age 48) reinforcing the importance of alcohol usage disorder screening and management[91**].

Conclusion

Prefrailty and frailty are likely key challenges on the horizon for those living with HIV and the services that support them. Screening for frailty is therefore paramount and whilst objective measures remain recommended (FFP) consideration should be given to the simpler, less time and resource intensive identification tools such as the CFS or single objective measures such as timed walk. Management of risk factors may reduce the chances of developing frailty therefore those identified as prefrail should also have access to holistic assessment, alongside those screening

positive for frailty. Further longitudinal studies with diverse populations are needed to ensure recommended strategies are applicable to all people ageing with HIV[9, 70**, 79**, 92].

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List of Supplemental Digital Content

1. Supplemental Digital Content 1. Video abstract that explores overview.mp4