Functional Impairment, Disability, and Frailty in Adults Aging with HIV-Infection

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Abstract

The integration of antiretroviral therapy (i.e., ART) into HIV care has dramatically extended the life expectancy of those living with HIV. However, in comparison to similar HIV-uninfected populations, HIV-infected persons experience an excess of morbidity and mortality with an early onset of aging complications including neurocognitive decline, osteoporosis, impaired physical function, frailty, and falls. Recent consensus guidelines encourage clinicians and researchers to consider functional impairment of HIV-infected adults as a measure to understand the impact of aging across a range of abilities. Despite the importance of assessing function in persons aging with HIV infection, a lack of consistent terminology and standardization of assessment tools has limited the application of functional assessments in clinical or research settings. Herein, we

distinguish between different approaches used to assess function, describe what is known about function in the aging HIV population, and consider directions for future research.

Introduction

The demographics of the HIV epidemic are changing and currently, approximately one-half of the people living with HIV in the United States are age 50 or older [1]. The high priority on understanding the interaction between age and HIV infection is illustrated by a recent summary report from the HIV and Aging Consensus Project [2••]. In comparison to similar HIV-uninfected populations, HIV-infected persons, even when on effective antiretroviral therapy (ART), experience an excess of morbidity and mortality [3, 4]. Persons on ART have early onset of aging complications including neurocognitive decline [5], osteoporosis and fractures [6–8], impaired physical function [9–11], frailty [12–16], and falls [17]. Thus, over the past decade, the focus of HIV management has gradually shifted from management of acquired immune deficiency syndrome (AIDS) complications to the management of chronic non-infectious co-morbidities in an increasingly older and more complex patient population.

In geriatric medicine, the overarching goals of care for older adults include the prevention of functional decline, maintenance of independence, and preserved health-related quality of life (HR-QoL). Prevention of functional decline is an important component of independence and HR-QoL [18], and functional limitations are strong predictors of disability, nursing home admission, and death [19]. Indeed, some geriatricians have proposed that assessment of functional status should be routinely included in the clinical assessment as a "sixth vital sign" [20]. The functional complications of aging were first identified as a priority area in HIV and aging research following the observation of an increased prevalence of a frailty-related phenotype in HIV-infected men from the Multicenter AIDS Cohort Study (MACS) [12]. In a recent report published by the Office of AIDS Research, the importance of understanding the pathophysiology of physical function and frailty was again identified as a high priority topic [21••]. Experts in the field have encouraged clinicians and researchers to consider functional capacity as a measure to understand the impact of aging across a range of abilities [2••, 21••, 22, 23].

Despite the importance of function in aging persons with or without HIV infection, the concept of "function" and the terminology used to describe its multiple dimensions may be confusing. The terms "functional limitations", "functional impairment", "comorbidity", "quality of life", "disability", and "frailty" are often used interchangeably to describe dynamically different processes among aging adults. The goals of this review are to: (i) distinguish between different terms used to describe function and the corresponding measures, (ii) describe what is known about function in the aging HIV population, and (iii) consider directions for future research in aging with HIV infection.

Functional Impairment and Disability

The Disablement Model originally conceptualized by Nagi and extended by Verbrugge and Jette links pathology, physical impairment, functional limitation, and disability [24, 25]. According to this model, an underlying pathology may lead to an "impairment" at the tissue, organ, or body system level, which results in a "functional limitation", and can lead ultimately to "disability" (Fig. 1). For example: a prior injury (pathology) results in arthritis of the knee (impairment), slow gait speed and difficulty rising from a chair (limitations), and eventual confinement to a wheelchair (disability).

In research settings, functional limitations are typically assessed via self-report or objective, standardized tests of physical performance that are predictive of subsequent disability and mortality. These tests include, among others, short gait speed (over 4-6 meters), longer corridor walk (typically 400 meters or distance covered in 6 minutes), a short physical performance battery (SPPB), and the timed-up and go test [26–29, 30•, 31, 32]. Because these tests are measured in controlled settings, functional measurements may not include environmental influences that determine the impact of the functional limitation on the day-to-day activities of older adults.

"Disability" describes the difficulty or dependency in carrying out activities in the environment. Thus disability is a social phenomenon in which the ability to complete a task is dependent upon what is expected of an individual within the social, cultural, and physical environment, and dependent upon the individual's ability to cope with the underlying impairment [33]. Rather than the controlled tests of specific functional limitations, disability is subjective and is typically assessed by self-report of difficulty in completing specific tasks. Commonly used assessment methods include questionnaires targeting difficulty or dependency in completing one or more independent activities of daily living (IADLs) or activities of daily living (ADLs). IADLs assess higher level physical and cognitive functioning including medication and finance management, meal preparation, shopping, transportation arrangement, and telephone use [34], while ADLs include more basic functions of dressing, bathing, toileting or continence, transferring, and feeding [35]. Importantly, the model of disability is a dynamic process that reflects changes in both the individual and the environment. For example, disability following a hip fracture may improve with physical therapy, although the prior level of function is often not attainable [24].

In an attempt to standardize definitions of disability and functional limitation, the International Classification of Functioning, Disability, and Health (ICF) framework was developed in 2001 [36–38]. Despite an emphasis on routine use of the ICF framework by international agencies, uptake in the US, particularly in research studies, has been limited. The ICF describes function in separate domains of cognition, mobility, self-care, getting along, life activities, and participation through a standardized WHO Disability Assessment Schedule (WHODAS; version 2.0). The assessment is applicable across cultures, provides a direct conceptual link to the ICF, and takes between 5-20 minutes to administer or complete [38, 39].

Many studies use a self-report of HR-QoL as a measure of self-reported functional limitations or disability. Although HR-QoL also encompasses the impact of disease or injury on limitations, functional state, and participation in activity, the focus is on the individual's values and expectations rather than the impairment [40]. Thus, discrepancies between performance-based and self-reported measures are frequently reported [41–43]. For example, in the Groningen Longitudinal Aging Study, subjects with more depressive symptoms and those with lower levels of perceived physical competence were more likely to underestimate self-reported functioning [44]. Furthermore, older adults with HIV-infection diagnosed early in the AIDS era represent a survival cohort who may have a higher threshold for reporting functional limitations [45]. The ability to complete a task is influenced by what an individual can do (capability), what an individual wants to do (motivation), and what an individual believes they can do (perception) [41]. Although both performance based- and self-reported measures encompass capability, motivation, and perception to an extent, performance-based measures emphasize capability (often in a controlled testing environment) while self-reported measures assess the perception of one's ability to accomplish tasks in his or her living environment and self-efficacy questionnaires assess an individual's motivation.

Functional Impairment and Disability among Adults Aging with HIV Infection

Functional impairments in HIV/AIDS were initially reported in association with AIDS or AIDS wasting syndrome, most often found among persons with high HIV-1 RNA or CD4 count <200 cells/μL. Over the last two decades, multiple objective tools to assess functional impairments have been used in the clinical and research settings to identify subtle to overt differences in exercise tolerance, grip strength, balance, gait speed, and chair rise time among people with HIV. Results of these studies are summarized in Table 1. Although these studies have made important contributions to our understanding of the functional impairment and disability process in people with HIV infection, methodological differences limit comparisons between studies or to other studies of HIV-uninfected cohorts. For example, gait speed has been measured over courses of 2.4 meters, 3.33 meters, 8 meters, 30 feet, 400 meters, or by distance walked in 6 minutes.

Self-report of physical function has also been used to assess functional impairments in HIV infection. The MACS and Veterans Aging Cohort Study (VACS) used self-report to compare function in HIV-infected and HIV-uninfected subjects with similar behavioral risk and similar demographics, and thus limited many of the recognized and unrecognized confounding variables encountered when matching HIV-infected to national cohorts or smaller cohorts of HIV-uninfected subjects. Among 1800 men from the MACS, self-reported physical function from the short form (SF)-36 physical function domains was significantly worse among HIV-infected persons and associated with lower CD4 count or AIDS, white race, and a trend toward higher glucose. In multivariate models, lower physical function was a risk factor for diabetes [46, 47]. In the VACS, self-reported physical function was not significantly different between 889 HIV-infected and 647 HIV-uninfected veterans. Although increased age was associated with impaired physical function in both HIV-infected and uninfected subjects, comorbidity was a stronger predictor of self-reported function and disability than age [48]. Among 262 HIV-infected and uninfected older and

younger adults from the HIV Neurobehavioral Research Program, greater comorbid burden was a stronger predictor of both self-reported physical and mental function than HIV status or age [49].

Increased risk of disability in HIV was recognized early in the AIDS epidemic. One of the largest early studies to address disability in the pre-ART era (1988-1991) included 728 patients: 14 % reported difficulties in IADLs only and 4 % in both ADLs and IADLs. Dependency in IADLs or ADLs was strongly associated with AIDS diagnosis and lower CD4 counts. In regression models including CD4 and AIDS diagnosis, ADL or IADL dependency was associated with a significantly shorter survival time [50].

Several studies have investigated associations between disability and HIV in the era of effective ART. In a survey of HIV-infected adults in British Columbia in the ART era, 92 % of 614 participants reported at least one impairment and one-third had more than ten impairments. Activity limitations were reported by 81 % and participation restrictions by 93 %, with significantly greater restrictions among persons with CD4 < 200 compared to >500 cells/ μL. High rates of self-reported depression were closely associated with social role restriction [51]. Among nearly 800 HIV-infected subjects in the United Kingdom (mean age of 40.4 years), 28 % reported difficulty with mobility, 19 % difficulty with self-care, and 38 % difficulty with usual activities. Health status decreased with increasing age, lower education, and unemployment, and was much lower among those with CD4 < 200 cells/μL or VL >50 copies/mL [52]. In a smaller study of 179 subjects including four groups of younger and older, HIV-infected and HIV-uninfected persons, age and HIV status had synergistic effects on IADLs and ADLs; HIV but not age had an independent main effect on both measures [53]. In a cohort of over 1900 patients at the University of Alabama (median age 43.6 years), self-reported impairments in mobility, usual activities, and self-care were significantly associated with pain, mood, and older age [54]. In summary, even in the ART era, dependence in IADLs or ADLs appears to exceed that observed in HIV-uninfected persons and is strongly associated with AIDS or low CD4 T-cell count and depression.

Frailty

In contrast to disability, frailty is a geriatric syndrome caused by dysregulation in multiple physiologic systems including immunologic, endocrine, hematologic, musculoskeletal, and cardiovascular [55, 56]. Using the Cardiovascular Health Study cohort, Linda Fried operationalized five components commonly recognized in frailty (slowness, weakness, shrinking, low levels of activity, and exhaustion) to validate one of the most commonly used indices [55, 57]. The frailty pheno-type is associated with high vulnerability for adverse health outcomes including hospitalization, morbidity, and mortality [33, 58, 59]. The presence of multiple deficits acts synergistically to increase an individual's vulnerability to illness or hospitalization [55, 60]. Variations of Fried's frailty phenotype are used throughout the geriatric literature, but often substitute the tools used to assess one of the components, use different population cut-points to determine the frail threshold, or may use less than the five components. Thus, the definition of frailty can vary across studies. Additionally, the overlap between the frailty components and depression symptoms and lack of a neurocognitive assessment may limit the sensitivity and specificity of Fried's frailty

phenotype in some populations [61, 62]. Other definitions of frailty have been tested with variable uptake in the clinical and research setting and include: the Tilburg Frailty Indicator [63], the Groningen Frailty Indicator [64], the Edmonton Frail Scale [65], the FRAIL scale [66], and the more commonly used Frailty Index introduced by Rockwood, et al. [67–70]. Despite over a decade of experience in using the frailty phenotype first described by Fried et al., the best way to assess and measure frailty is still debated among geriatricians [58, 61, 70–73].

Frailty among Adults Aging with HIV Infection

The immunologic and phenotypic similarities observed in both frailty and AIDS were first brought to attention by investigators from the MACS in 1992 [74]. To further explore these similarities, data from the MACS were used to create a *frailty related* phenotype, approximating four of the five domains of Fried's frailty phenotype. A strong association was observed between HIV infection and the MACS frailty-related phenotype with findings most pronounced among men with low CD4 lymphocyte count (<350 cells/μL), high viral load (100,000 copies/mL), clinically defined AIDS, longer duration of HIV infection and older age [12]. A subsequent study in this population found a markedly higher prevalence of a frailty-related phenotype in the pre-ART era (1994-1995) among individuals with AIDS (24 %) compared to the post-ART era, 2000-2005 (10 %), or compared to persons without AIDS in the pre- or post-ART era (3.3 % and 2.9 %, respectively). The authors estimated that a decrease of CD4 lymphocyte count of 250 cells/μL and a 10 year increase in age had similar effects on the prevalence of the frailty-related phenotype [14]. Furthermore, an increased risk of subsequent AIDS or mortality was observed among men without AIDS when the frailty-related phenotype was sustained over at least two visits [13]. In 2007, the MACS introduced the 4-m walk into study visits, allowing for the use of Fried's five component frailty phenotype rather than the frailty-related pheno-type. In a subsequent study using Fried's frailty phenotype, those with frailty at one or more visits were more likely to have HIV infection, a history of AIDS, lower CD4 lymphocyte count, and less likely to have an undetectable viral load. Furthermore, HIV-infected men were more likely to manifest frailty at multiple study visits in comparison to HIV-uninfected men, and those with both HIV and AIDS were more likely to convert from a non-frail to frail phenotype [75•].

The association between frailty and low CD4 lymphocyte count or an AIDS diagnosis has been replicated in other cohorts. In the Women's Interagency HIV Study (WIHS), frailty was higher among HIV-infected women with AIDS (12 %) or a CD4 lymphocyte count <100 cells/μL (20 %), compared to HIV-uninfected women (8 %), HIV-infected women without AIDS (7 %), or HIV-infected women with CD4 count 500cells/μL (6 %) [16]. Among intravenous drug users in the AIDS Linked to the IntraVenous Experience (ALIVE) Cohort, 14.5 % of the HIV-infected participants were frail compared with 11.4 % of the HIV-uninfected participants. Of note, this is the only study that has shown that presence of the frailty phenotype in HIV-infected persons is associated with an increased mortality risk independent of HIV infection. Importantly, the impact of both HIV infection and frailty had a synergistic effect on mortality (mortality OR = 2.6 with HIV infection; OR = 3.3 with frailty; and OR = 7.1 with both HIV and frailty) [76•].

Other studies have reported a prevalence of frailty between 5-33 % among HIV-infected persons in routine HIV care [15, 77–80]. In the Washington University Infectious Diseases Clinic, frailty was associated with older age, low current and nadir CD4 count and longer time since HIV diagnosis, lower albumin, greater comorbidity and depression, more hospitalizations, and unemployment [15]. Similar findings were observed in the Study to Understand the National History of HIV/AIDS (SUN Study), where 5 % of participants were frail, and frailty was associated with hepatitis C, depression, older age, unemployment, and a history of opportunistic infection [77]. In another cohort, of 359 patients receiving care for HIV infection, 27 (8 %) met frailty criteria by Fried's frailty phenotype, and the odds for frailty increased with the number of comorbidities (most notably psychiatric disease, chronic pain, and viral hepatitis), lower physical activity, smoking, and lack of employment. Although frailty was associated with CD4 count <200 cells/μL, no association was noted between frailty and age [9].

One of the first reports of frailty in an African setting evaluated 504 subjects (216 HIV-infected on ART, 32 HIV-infected not on ART, and 256 HIV-uninfected) from Cape Town. Frailty by Fried's criteria was highest in the HIV-infected cohort not on ART (28 %) in comparison to those on ART (18 %) and HIV-uninfected (13 %). Among ART-treated individuals, lower CD4 count (<500 cells/μL) and lower body mass index (BMI) were associated with frailty [80].

In summary, overlap between HIV and frailty have been recognized since early in the AIDS epidemic, and frailty continues to be most frequently recognized among HIV-infected persons not on ART, with low CD4 t-cell count, or high HIV-1 RNA. Variations in the frailty definition limit the comparisons of frailty prevalence between study populations, however the factors consistently associated with frailty can lead to a greater understanding of the pathophysiology and potential interventions in HIV-infected populations.

Are Functional Impairment, Disability, and Frailty Measures Interchangeable?

Although often overlapping, disability and frailty can differ greatly with respect to pathophysiology, prognosis, and treatment of impairment [33]. Although functional status and frailty are both predictors of poor outcomes, and frail persons often show functional limitations, frailty is a state of heightened vulnerability marked by more than simply a decline in function (Fig. 1) [81]. Some authors consider frailty a "pre-disability" state, in which a stressor can trigger the progression to disability [81, 82]. Although one can return to the pre-disability state, function rarely achieves previous levels experienced. Functional limitations and subsequent disability are often the result of expected aging complications (i.e., arthritis), and management may include rehabilitation therapy to regain function or minimize limitations and assistive devices to enable completion of activities, thereby preventing further decline and social isolation [33]. In contrast, frailty requires an investigation into potential underlying causes of weakness, weight loss, and poor exercise tolerance, with interventions focused on minimizing further loss of weight and muscle through resistance training, nutritional supplementation, and cardiovascular rehabilitation. Similar to disability, frailty may have social or environmental influences including access to food, physical inactivity, and depression. Interventions to improve functional limitations,

disability, or frailty may all improve quality of life, with further enhancement provided through mental health care, improved social support networks, and spiritual support [33].

To illustrate the distinction between functional limitations and frailty, we compared the SPPB to the classification of frailty by Fried's phenotype in 359 HIV-infected persons on ART. Among the 27 persons that were identified as frail, less than one-half had significant impairment on the short physical performance battery (SPPB, score <9), and four had a perfect score [9]. Conversely, of the 26 persons with significant impairment on the SPPB (score <9), three were non-frail, ten were pre-frail, and 13 were frail. The modest agreement across instruments can be explained, in part, by the characteristics of the assessments: the frailty phenotype is a global assessment with subjective components that overlap with depressive symptoms, whereas the SPPB focuses on lower extremity function [9, 30•, 55, 61, 83–85]. These results support the consensus that frailty and functional impairments or disability are complementary, but not interchangeable, constructs.

Future Directions

Measurement of functional impairment, disability, or frailty in the clinical assessment of HIV-infected persons is invaluable in understanding the current needs and future prognosis of persons aging with HIV. These assessments, however, require a time commitment from both the provider and the patient. Thus, identifying the most effective tools for use in clinical and research settings is important to understand and meet the needs of those aging with HIV.

As tools to assess function, disability and frailty are already routinely used in the clinical and research settings in geriatrics and gerontology, we propose that they should have similar application in HIV care and research. Accordingly, research is needed to identify the measures of impairment, disability, and/or frailty that may be most appropriately and effectively applied in the evaluation of persons aging with HIV. Useful measures could include a stand-alone assessment such as gait speed, or may complement other risk assessment tools in HIV, such as the VACS Index [86]. Similar to the development of the VACS Index, we should consider a tool that is simple, cost-effective, requires minimal time and effort from clinicians, and provides a valid assessment of the outcome of interest [86]. In this context, we propose several considerations for the development, use, and interpretation of functional and frailty assessments.

First, we should recognize that the tools used in the clinical setting and research settings may be different, with the outcome of interest determining the appropriate tool. If the need is to evaluate a patient for home health needs or nursing home placement, an assessment of dependency in IADLs or ADLs should be used. For a research study designed to understand the pathophysiology of weakness during aging with HIV infection, a standardized, objective measurement of strength without the influence of the environment (i.e., chair-rise-time or grip strength) would be an appropriate tool. Second, consideration should be given to whether tools should predict outcomes specifically in HIV-infected persons, or if more general tools should be implemented. For instance, as described above, in prior studies utilizing Fried's frailty pheno-type or a frailty-like phenotype (e.g., MACS), frailty in the HIV-infected persons was consistently associated with low CD4 count, high viral load, and

depressive symptoms. A tool to identify frailty that considers HIV-specific factors or depressive symptoms could be a more specific and sensitive predictor of vulnerability among HIV-infected persons. Third, to the extent possible, standardized tools should be implemented and interpreted using standardized criterion so that outcomes can easily be compared across clinical and research settings. Varying definitions between studies limit the generalizability and reduce the ability to compare or combine findings from different study populations. Use of standardized tools that are used in large aging cohorts (i.e., the SPPB in the Baltimore Longitudinal Study of Aging) may allow for comparison to a standard norm of healthy aging adults.

Importantly, tools for assessing and measuring function, disability, and frailty must be tested and validated as predictors of relevant outcomes (i.e., hospitalization, morbidity, mortality) in HIV-infected populations. The frailty assessment validated in the Cardiovascular Health Study was developed to predict hospitalizations, institutionalization, and mortality in a general population older than 65 and is thought to serve as a more important prognostic tool in persons 80 years or older [87], thus use of this tool in a younger HIV-infected population with different comorbidities to predict similar outcomes should first be established. Similarly, the SPPB is a standardized, objective assessment of lower extremity performance established in an elderly population that may be limited by a ceiling effect in younger individuals with higher level of performance. For studies of younger HIV-infected persons, consideration should be given to use of an expanded version of the SPPB which has been previously proposed for use in younger persons [88]. The modifications improve discrimination of physical function at the higher end of the functional spectrum. We are currently validating these tests in a larger population for prediction of clinical outcomes such as falls, fall-related injuries, hospitalizations, and deaths.

Lastly, consideration should be given to the routine use of a measure of functional impairment, disability, or frailty as outcomes in clinical trials in HIV infection. For example, in an interventional trial of a new ART agent or a therapy to decrease immune activation or inflammation, a change in chair rise ability or gait speed would provide an inexpensive, clinically relevant, easily obtainable measure of benefit or harm from an investigational therapy.

Conclusions

As the focus of HIV management has shifted to the management of chronic non-infectious co-morbidities in an increasingly older and more complex population, ascertainment of an individual's ability to maintain independence is of increasing importance. Both functional limitations and frailty are strong predictors of subsequent disability, loss of independence and death. Variations in the tools, and their application, limit the comparisons that can be made across and between studies. Identification of the most appropriate tools for the outcomes of interest, and validation and standardization of the tools in a population of middle-aged and older HIV-infected adults, will improve the usefulness of functional and frailty assessments at the bedside and in the research setting.

Acknowledgments

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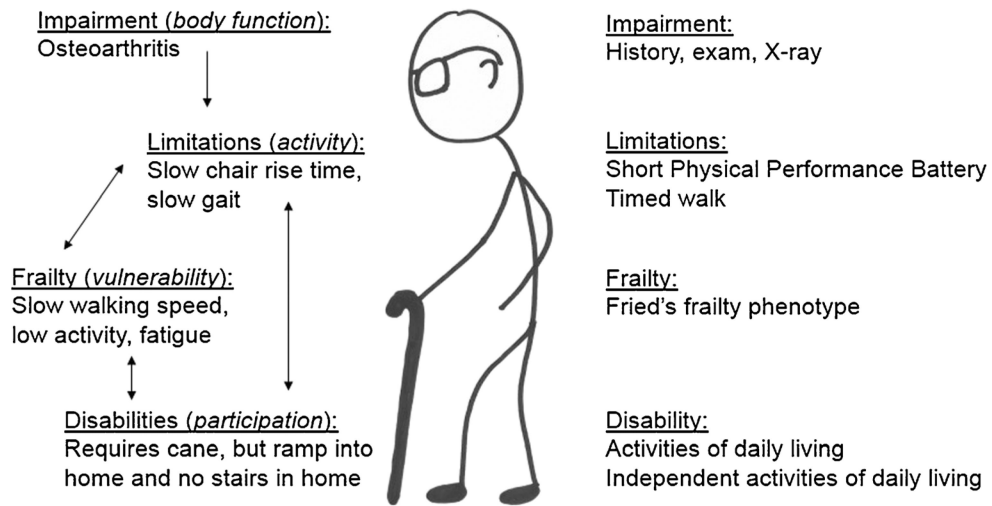
Fig. 1.
The relationships between the manifestations of impairment, limitations, frailty, and disability in an older man with osteoarthritis (left) and examples of the tools used to define each concept (right)

Table 1

Functional impairments in studies of HIV-infected persons

Ref	Study population	Age	Physical function outcome	Other findings
Oxygen consumption (VO2) and or gait speed (6-minute walk distance, 6-MWD or 30-foot timed gait test)				
[89]	49 HIV+	46	90 % reached at least 8 METS with VO2 peak 31.4±4.8 ml/kg/min	Negative correlation between age or BMI and VO2 peak
[90]	37 HIV+ 37 HIV- (Nigeria)	36	Lower VO2 max 30.1 ±5.6 ml/kg/min and less distance covered on 6- MWD 443±93.3- m in HIV+	No significant correlation between physical health or mental health component of SF-12 and performance-based function
[91]	37 HIV+	59	Mean VO2 peak 20.30±6.37 ml/kg/min and Functional Status Questionnaire score of 30.5±3.2.	Higher VO2 peak was associated with lower frequency of severe neurocognitive impairment
[92]	180 HIV+ 160 HIV-	40+	6-MWD not significantly different in HIV + (426-m) vs HIV- (421-m). Both groups performed below the expected distance (576-m)	Chronic cough and decreased FEV1 % were associated with poor performance in HIV + group
[93]	24 HIV + (wasting)	37	Mean/median 6-MWD values not reported	6-MWD inversely correlated with lower extremity muscle area and lean body mass.
[94]	83 HIV+ 57 HIV- (Zambia)	34	ART-treated HIV + had significantly faster 30-ft timed gait test (10.8± 0.6 sec) compared to HIV- (12.3±0.2 sec) or HIV+ not on ART (12.3±0.3 sec)	Gender, but not age, was significant covariate in the relationship between HIV serostatus and gait speed
[95]	1439 HIV+ 87 HIV-	37	30-ft gait test 9.5±1.1 sec in HIV- (n=85), 9.8±1.5 sec in asymptomatic HIV (n=165), 11.8±4 sec in symptomatic HIV (n=113), and 11.1 ± 2.4 sec in AIDS (n= 1122).	Gait significantly slower in symptomatic HIV/AIDS vs asymptomatic HIV or HIV; correlated with age, stage of neurocognitive disorder, and education
[96]	860 HIV + subjects	34	Baseline gait speed not reported.	Significant improvement in gait speed from baseline to subsequent visits, associated with younger age, lower HIV-1 RNA, and greater CD4 at baseline.
Grip Strength				
[97]	50 HIV+ 30 HIV- men	50	Grip strength of the HIV + (38.5 kg) similar to HIV- controls (37.7 kg), HIV + with lipodystrophy (35.0 kg) had significantly lower grip strength than HIV- (41.0 kg).	Lipodystrophy, lower lean body mass, and higher sTNFR-II were independently associated with lower grip strength
[98]	200 HIV+ 3000 HIV- (S.Africa)	NR	Mean/median grip strength values not reported. Grip strength was significantly lower (4.73 kg weaker) in HIV + compared to HIV- older adults.	Reported WHO Disability Assessment Scores. HIV + adults >50 yrs had higher scores (23.0 points) compared to HIV- adults <50 (6.2 points)
Combination measures				
[99]	11 HIV+ 21 HIV- (Brazil)	65	Baseline 5x chair rise time 9.25 sec in HIV + vs 10.22 sec in HIV; 2.4-m walk time was 2.0 sec in HIV + and 2.4 sec in HIV-	Chair rise improved to 6.6 sec HIV+/8.5 sec HIV; gait speed improved to 1.6 sec in HIV+/1.8 sec HIV- with resistance exercise
[100]	40 HIV+ (Brazil)	NR	3.33 m walk was faster in those with CD4 ± 200 cells/jL (2.9±0.1 sec) versus ±200 cells/jL (3.3±0.1 sec).	Gait speed and time to put on shoes was increased in older adults. Gait speed was 14 % slower in those with CD4 count <200 cells/jjL
[101]	65 HIV + women	49	Median SPPB score 11, and 20 % had an SPPB score of 9 or lower.	Low SPPB associated with comorbidities, smoking, but no differences in current or nadir CD4 count.
[11]	324 HIV+	48	53 % had impairment on 5-x chair rise, 23.6 % in 6-MWD, 10.5 % on timed up-and-go, 9.9 % on one-leg standing balance, 10.6 % on functional reach, and 1.5 % on Berg Balance; 61 % had poor performance in >1 test.	A longer time since HIV, lower BMI among younger and higher BMI among older was associated with poorer performance. No association with CD4, ART, or d-drugs

Ref	Study population	Age	Physical function outcome	Other findings
[102•]	354 HIV+	48	Baseline 5x chair rise time was 9.8 sec and 6-MWD 549-m. 5x chair rise declined by 0.24 s/year and 6-MWD by 11 m/year from baseline to year 2.	Decline in 5x chair rise associated with injection drug use, cerebral AIDS conditions, and diabetes but not CD4, VL, or ART.
[10]	32 HIV+ 47 HIV− men	46 and 56	V02 peak 21.4±5.9 mL/kg/min; 6-MWD 539±82-m; grip 41.6±7.3 kg, 83.6± 11 % predicted max heart rate in HIV + men.	HIV + 41 % lower V02 peak, 8 % lower 6-MWD, 10 % lower grip strength compared to HIV−. Age and OI history associated with lower V02 peak, but not CD4, VL, or ART regimen
[45]	43 HIV + men	58	V02 peak 18.4±5.6 mL/kg/min; 6-MWD 514±91-m; grip 39.6±7.4 kg. 46 % of the subjects reached predicted maximum heart rate or respiratory quotient during treadmill testing.	V02 peak correlated with 6-MWD, grip strength and quadriceps strength. HTN was only comorbidity associated with V02 peak
[103]	40 HIV+ 83 HIV−	43	HIV + had significantly worse performance on nearly all balance tests and with fine finger movements.	
[104]	80 HIV+	54	Gait speed on 4.572-m walk: 1.1 m/sec for men, 1.03 m/sec for females. Grip strength 41.0 kg in men and 29 kg in women	Gait slower (0.88 m/sec vs 1.1 m/sec) in sarcopenic men compared to overall men. Grip lower in sarcopenic men (29 kg)
[105]	121 HIV+ 86 HIV−	38	HIV was associated with impaired balance, impaired gait speed (8-m), and impaired gait initiation time.	Synergistic interaction between HIV infection and BMI was observed in several measures of both gait and balance
[106]	78 HIV− 89 HIV+	39	HIV + significantly worse balance than HIV−, no differences between HIV + by ART/no ART/ or NRTI-only. No significant between group differences on gait speed and cadence, 5x chair rise time, or turn time (values not provided)	Higher CD4 count was associated with better balance and higher HIV-1 RNA with greater impairment on vibrotactile sensation
[107]	22 HIV− 31 HIV+ 43 HIV+/EtOH use 27 HIV−/EtOH use	42	HIV + Et group trended towards worse performance than any other groups on all upper motor tests. On the lower limb tests, HIV + subjects had significantly poorer performance than controls in 2 of 3 balance measures conducted with eyes closed	No association between performance and CD4 count or AIDS.
[79]	21 HIV + young 20 HIV + older	32 and 57	Grip ranged from 19.9 kg in older women, 27.7 kg in younger women, 33.6 kg in older men, and 37.2 kg in younger men. 50 % of older and 67 % of younger reached level 4 or 5 on Wii Balance.	Trend towards lower neuropsychological scores and verbal learning scores in older vs younger, & significantly lower memory
[108]	27 HIV+	49	Mean 6-MWD = 593±73-m, V02 peak = 22.6±5.0 ml/kg/min, respiratory exchange ratio = 1.08±0.10, treadmill max work capacity = 125±46 W	40 % had impaired knee extensor activation that was associated with weakness, decreased force, and lower work rates, but was unrelated to muscle size or V02 peak.
[109]	40 HIV+	58	Defined a ±frail± population by impairment in the PPT, V02 peak, or ADL/IADL difficulty. V02 peak was 18±6 mL/kg/min in frail vs 23±5 in non-frail; PPT 29 ±2 in frail vs 33 ±1 in non-frail; gait speed over 50 ft was 89±10 m/min in frail vs 102±14 m/min in non-frail	Impairment was significantly greater among those with greater BMI, waist circumference, fat mass, and trunk fat
[9]	359 HIV+	51	SPPB score = 11.1 ±1.6 points, chair rise pace–0.5±0.2 rises/sec, grip strength = 39.0±0.3 kg , 400-m walk time = 1.4±0.37 m/sec, 13 % SPPB score of 9	SPPB was associated with # of comorbidities, diabetes, low physical activity, and pain. Lower performance on 400-m walk was associated with # of comorbidities, obesity, diabetes, arthritis, lung disease, and pain

Age presented as mean or median when available; *METS* metabolic equivalents, *V02* oxygen consumption, *6-MWD* 6-minute walk distance, *FEV1* forced expiratory volume in 1 sec, *sTNFR-II* soluble tumor necrosis factor receptor-II, *NR* not reported, *SPPB* Short Physical Performance Battery, *Et* alcohol, *ADL* activities of daily living, *IADL* independent activities of daily living, *OI* opportunistic infection, *W* watts, *PPT* Physical Performance Test