Disability among Middle-Aged and Older Persons with HIV Infection

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Running Head: Disability in HIV

Summary: Self-reported disability among HIV-infected older adults is strongly associated with neurocognitive impairment and socioeconomic or other lifestyle factors, but not with other comorbidities or HIV-related factors. Potentially modifiable factors (smoking, low physical activity) were identified as targets for interventions designed to reduce IADL impairment.

Abstract:

Objective: Older HIV-infected adults may experience higher rates of frailty and disability than the general population. Improved understanding of the prevalence, risk factors, and types of impairment can better inform providers and the healthcare system.

Methods: This was an observational study of HIV-infected participants within the ACTG A5322 HAILO study with self-reported disability by the Lawton-Brody Instrumental Activities of Daily Living (IADL) Questionnaire and frailty, measured by 4-m walk time, grip strength, self-reported weight loss, exhaustion, and low activity. Logistic regression models identified characteristics associated with any IADL impairment. Agreement between IADL impairment and frailty was assessed using the weighted kappa statistic.

Results: Of 1015 participants, the median age was 51 years,15% were ≥ 60 years, 19% were female, 29% Black, and 20% Hispanic. At least one IADL impairment was reported in 18% of participants, most commonly with housekeeping (48%) and transportation (36%) and least commonly with medication management (5%). In multivariable models, greater disability was significantly associated with neurocognitive impairment, lower education, Medicare/Medicaid insurance (vs. private/other coverage), smoking, and low physical activity. Although a greater proportion of frail participants had IADL impairment (52%) compared to non-frail (11%) persons, agreement was poor (weighted kappa < 0.18, 95% CI 0.13, 0.23).

Conclusion: IADL disability occurs frequently among middle-aged and older HIV-infected adults on effective ART. Potentially modifiable risk factors (smoking, physical activity) provide targets for interventions to maintain independent living. Systematic recognition of persons at greater risk for disability can facilitate connection to resources that may help preserve independence.

Key words: HIV; disability; neurocognitive impairment; physical activity; frailty

Introduction:

The success of antiretroviral therapy (ART) has changed the characteristics of the HIV/AIDS epidemic, such that an estimated 70% of persons living with HIV may be older than age 50 by 2030 [1]. Within this aging HIV-infected population, an increased risk for and burden of age-associated co-morbidities is seen, including cardiovascular disease, chronic kidney disease, osteoporosis, and neurocognitive disorders [2-7]. This growing burden of age-related comorbidities may predispose ART-treated HIV-infected persons to a particularly vulnerable or frail state with a heightened risk of disability [8].

The phenotype of frailty is characterized by vulnerability to adverse health outcomes, and incorporates domains of weight loss, weakness, low physical activity, poor endurance, and slow gait [9]. In contrast, disability refers to difficulty in completing daily tasks and activities[10], and may include difficulties in higher-level tasks such as medication management and food preparation(Instrumental Activities of Daily Living, IADLs), or basic needs such as bathing and feeding (Activities of Daily Living, ADLs). While frailty and other measures of physical, cognitive, and mental health impairment are strong predictors of disability, ultimately an individual's own expectations of ability and the physical and social environment are key components of disability [10-12]. Thus, the experience of disability may vary widely among individuals with similar symptoms, depending on important socioeconomic factors that allow that individual to live independently. Although frailty and disability are commonly and interchangeably used to describe older adults in poor health, they are distinct concepts that describe aspects of physical and cognitive health related to aging. These distinctions are important when anticipating the needs of aging persons: changes in physical health, disability, and frailty may disproportionally impact health-related quality of life (QoL) or independence. Furthermore, coordination of local resources may mitigate disability, while interventions to reduce frailty may involve exercise, nutrition, and management of underlying comorbidities.

Multiple studies in the current ART treatment era indicate that older, HIV-infected adults are at increased risk of both frailty [13] and disability [14, 15]. Prevalence rates of disability vary widely in the population, and by cultural contexts: among HIV-infected adults aged 50 or older in San Francisco, 39% reported difficulty in at least 1 IADL [16] while 18% of HIV-infected adults aged 50 or older in Mexico City reported an IADL difficulty [17]. Among HIV-infected adults, disability, as measured by IADLs, ADLs, or other measures, has been associated with older age, HIV-related characteristics such as low CD4 count [15], depression [18], lower physical activity [19] and neurocognitive impairment [2, 20]. The identification of factors that contribute to disability, particularly if modifiable, can inform development of interventions to prevent or limit disability in the vulnerable population of older, HIV-infected adults and ultimately improve QoL. We recently published the characteristics associated with frailty in the AIDS Clinical Trials Group (ACTG) Study A5322, or the HIV Infection, Aging, and Immune Function Long-Term Observational Study (HAILO) [21]. The goals of this analysis were to examine the prevalence of and characteristics associated with disability among HIV-infected adults in HAILO, and explore the overlap between disability and frailty.

Methods:

Study Population

The ACTG Study A5322, or HAILO, is a prospective observational study of HIV-infected persons aged ≥ 40 years who received randomized assignment of their initial ART regimen through an ACTG interventional trial and were followed long-term in the ACTG A5001 observational study after their randomized trial participation ended. HAILO enrollment occurred in 2013-2014; ongoing visits occur every 6 months. The current analysis reports on cross-sectional findings at HAILO entry (baseline).

IADL

Disability was assessed at baseline with the Lawton-Brody Instrumental Activities of Daily Living (IADL) Questionnaire [22] using self-reported limitations in performing eight tasks: housekeeping, money management, cooking, transportation, telephone use, shopping, laundry, and medication management.

Frailty

Frailty was evaluated at baseline using the Fried's frailty assessment, which includes 5 components: 4-meter walk speed, grip strength, and self-reported unintentional weight loss in the past 12 months, exhaustion, and low activity [9, 21]. Individuals meeting 3-5 components were categorized as frail, those with 1 or 2 as pre-frail, and those with no components as non-frail.

Demographics

Health insurance was categorized as no coverage, Medicare or Medicaid, private insurance, or other coverage. Education was categorized as high school education or less. Smoking was defined as current, prior, or never smoker. Self-reported alcohol use in the past 30 days was defined as abstainer (0 drinks) light drinker (men <7 drinks/week, women <3; no binge drinking), moderate drinker (men 7-14 drinks/week, women 3-7; no binging) or heavy drinker (men >14 drinks/week, women >7 OR any binge drinking). Binge drinking (men ≥5 drinks, women ≥4 within a 2-hour period) was also included using the categories "no drinking", "no binge drinking", "binge drinking once a month", or "binge drinking more than once a month". Substance use was self-reported as current use of marijuana, cocaine, heroin, amphetamines, , or non-prescribed, controlled medications.

HIV Characteristics

HIV-related characteristics included pre-ART CD4 T-lymphocyte count (cells/μL, CD4) and HIV-1 viral load (VL), and CD4, CD4/CD8 ratio, and VL at baseline. ART exposure included both initial (randomized) and baseline regimen. ART exposure was categorized as a protease inhibitor (PI), non-nucleoside reverse transcriptase inhibitor (NNRTI), or integrase strand transfer inhibitor (INSTI), each with a nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) backbone; or other combination therapy. Prior exposure to stavudine (D4T), didanosine (DDI), or zidovudine (ZDV), years of cumulative NNRTI or INSTI use, and years of any ART therapy were also considered.

Co-morbidities

BMI >30 kg/m^2 was considered obese. Change in weight was calculated from entry in ACTG A5001 to baseline. Physical activity was self-reported using the International Physical Activity Questionnaire [23]; outcomes were dichotomized as low (≤ 2) or moderate/high (≥ 3) days per week of moderate or vigorous intensity physical activity. HCV infection was defined by a positive HCV serology. Hyperlipidemia was described using a continuous variable and categorizing fasting low density lipoprotein (LDL) cholesterol. Malignancy was defined as any malignancy (except non-melanoma skin cancer) within five years of enrollment. Renal disease was defined as estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2 at least 3 months apart with no intervening eGFR ≥60; eGFR was calculated using the CKD-EPI equation. Diabetes was defined as 2 consecutive non-fasting glucose >200 mg/dL, or 2 fasting glucose ≥126 mg/dL within 1 year, diagnosed diabetes, or hemoglobin A1C level ≥6.5%. Hypertension was defined as use of hypertensive medications, diagnosed hypertension, or systolic blood pressure ≥140 or diastolic ≥90 mmHg at 2 consecutive visits. Depression was defined as current use of an antidepressant medication, ongoing diagnosis of major depression, or ≥ grade 3 major depression symptoms using Division of AIDS criteria [24]. Neurocognitive impairment

was assessed using the ALLRT Neuroscreen [2], with sex, age, race/ethnicity and education-adjusted scores for Trails-Making A, Trails-Making B, and Digit Symbol. Neurocognitive impairment was defined as having ≥1 test score ≥2 standard deviations below the mean, or ≥2 separate test scores that were ≥1 standard deviation below the mean.

Statistical Analyses

The proportion of individuals with an IADL impairment, defined as difficulties in 1 and ≥2 IADL categories, overall and by age, and the frequency of difficulties in each IADL category were summarized. Demographic, behavioral and clinical characteristics of individuals with and without IADL impairment were compared using Chi Square, Fisher's Exact or Kruskal-Wallis tests. The agreement between IADL (0, 1 and ≥2 categories) and frailty (non-frail, pre-frail and frail) was assessed using weighted kappa statistics. To identify independent predictors of IADL impairment, we defined the outcome as self-report of difficulties in ≥1 IADL category and used logistic regression modeling. Covariates with a p-value <0.10 in univariable models were retained in the multivariable model; when more than one definition of a covariate was evaluated, the definition with the largest effect estimate was retained.

Results:

Of 1015 participants at HAILO baseline, the median age was 51 (IQR: 46-56) years: 15% were ≥ age 60, 19% female, 29% Black, and 20% Hispanic. Eighty percent of participants had health insurance coverage, including 32% with Medicare or Medicaid and 41% with private health insurance. Most participants had well-controlled HIV infection: 67% of participants had CD4 > 500 cells/μL s and 94% had a VL<200 copies/mL. Additional baseline characteristics are shown in Table 1.

Sixty-three (6%) participants had 2 or more impairments in IADLs and 115 (11%) had 1 impairment. By age, 15% of participants <45 years of age had one or more impairment, 18% of those 45-64 years old, 21% of those 65-74 years old, and 25% of those 75 years or older. The most common difficulties were with housekeeping (48%), transportation (36%) or shopping (28%); the least common difficulties were with medication management (5%) or use of the telephone (12%), Table 2.

Findings from univariable and multivariable models are summarized in Table 3. In the multivariable model, lower education, Medicare or Medicaid insurance (vs private insurance), current smoking, and lower physical activity were associated with IADL impairment. Neurocognitive impairment at baseline was the only comorbidity significantly associated with IADL impairment (Table 3). Notably, no HIV characteristics (CD4 count, CD4/CD8 ratio) were associated with IADL impairment in the multivariable model.

Lastly, we assessed the agreement between categorizations of disability and frailty. As previously reported [21], 62 (6%) participants were identified as frail and 377 (37%) pre-frail. Of the participants who underwent both IADL and frailty assessments (98%), 52% (N=32) of frail participants reported having at least one IADL impairment, 21% (n=80) of pre-frail participants had at least one impairment, and only 11% (n=62) of non-frail persons had an IADL impairment (Figure 1). A weighted kappa score indicated limited agreement between frailty and disability (weighted kappa <0.18, 95% CI 0.13, 0.23). Among non-frail participants (n=508 in multivariable model), IADL impairment was associated with lower education (OR 3.86 [95% CI 1.95, 7.64], p<0.001), current smoking (OR 2.38 [95%CI 1.09, 5.22], p=0.03) and Medicare or Medicaid insurance (vs private insurance) (OR 2.22 [95% CI 0.99, 5.0], p=0.53). Among pre-frai/frail participants (n=381), IADL impairment was associated with neurocognitive impairment (OR 2.10 [95% CI 1.16, 3.78]; p=0.014), Medicare or Medicaid insurance (vs private insurance) (OR 2.38

[95% CI 1.22, 4.64], p=0.01), and lower physical activity (OR 2.28 [95% CI 1.28, 4.03], p=0.005).

Discussion:

In this well-characterized cohort of middle-aged and older adults with well-controlled HIV infection, we found a higher than expected prevalence of disability with IADLs. A recent publication using NHANES data found a markedly lower (6-8%) prevalence of IADL disability among participants aged 65-74, compared to nearly 20% in our HIV-infected population over the age of 50 [25]. The prevalence of disability in HAILO is similar or slightly lower than two recent publications that reported upon HIV-infected persons aged 50 or older [16, 17]. One of these two studies, which was from Mexico City, showed overall rates of disability similar to those seen in this cohort, with IADL impairment in 18% of participants over age 50. In contrast, the second study reported on a San Francisco cohort with IADL impairment of 39% including a higher proportion of participants over age 60. The San Francisco study population was drawn largely from a safety-net clinic where nearly all patients were publicly insured, while 41% of our population had private insurance. We postulate that the different disability rates among cohorts reflect differing perceptions of disability, differences in the family unit, and variable access to senior resources. Our findings complement these other studies of older HIV-infected persons, and highlight the 2 to 3 times higher rate of IADL impairment observed across cohorts compared to the general population, especially among middle-aged adults.

As in prior studies [18-20, 26], neurocognitive impairment was a strong predictor of IADL, and in our study was the comorbidity most strongly associated with risk of IADL disability. Although earlier initiation of ART decreases the development of neurocognitive impairment among HIV-infected persons [27], several factors including ART toxicity, prior opportunistic infections, cerebrovascular disease, and age-associated cognitive decline may further adversely impact neurocognitive function among older, HIV-infected adults in the current ART era [28].

Regardless of the causes, even mild cognitive impairment may result in a loss of function that impairs daily living [20] and quality of life [29]. Given these factors, neurocognitive function should be considered routinely when evaluating disability in older HIV-infected persons.

Consistent with the concept of disability as a social phenomenon, we found a strong association between disability and socioeconomic (education, health insurance) and lifestyle factors (smoking, physical activity). While these socioeconomic variables may merely serve as a proxy for other key factors not readily ascertainable in our cohort, including financial resources, employment, and housing access, the prominence of social and economic factors as important factors in an individual's experience of disability is notable. The effects of socioeconomic factors on prevalent disability may be explained by the inability to mobilize resources. Aging HIV-infected adults may face unique challenges with service utilization, including ageism at HIV-specific resource centers, or HIV or gender identity/sexual identity stigma from other resource centers that may cater to older adults in the general population, such as senior centers or churches [30]. Many older, HIV-infected adults have tenuous relationships with family, and therefore rely on other, often inconsistent, forms of social support when it comes to day-to-day needs [31]. Economic challenges may be exacerbated by periods of temporary disability or participation restrictions, which in turn have an effect on the ability to return to work [32-34]. Unhealthy lifestyle behaviors, including smoking and limited physical activity as identified in this analysis, are more frequently observed among populations with lower socioeconomic status regardless of HIV serostatus [35]. Lastly, in the general older adult population there is evidence that socioeconomic disadvantages may exert cumulative adverse effects over the lifetime of an individual [36]. Thus, when considering the social and environmental aspects of disability, it is perhaps not surprising that these socioeconomic and lifestyle factors were more significant than other health or physical function-related measures.

We did not observe statistically significant associations between disability and age, HIV-related characteristics, and comorbidities other than neurocognitive impairment, although associations between disability and age may have been limited by the number of older participants in our population. Surprisingly, depression was not associated with disability; associations of HIV-related characteristics with depression have previously been well-described. Early in the AIDS era, CD4 count, viral load, AIDS wasting syndrome, and HIV associated neurocognitive disorder (HAND) were commonly associated with disability [37]; studies in the current era suggest that CD4 count and depression are still contributing factors [17, 18, 26]. The impact of specific ART regimens on disability has not been well-described previously, and no association was detected in our study. Nevertheless, the introduction of effective ART has decreased the incidence of severe neurocognitive impairment and reduced IADL disability, even after accounting for HIV disease severity and status and demographic variables [38] . The lack of apparent associations between disability and many evaluated comorbidities stands in contrast to limited prior study findings where comorbidity was associated with greater IADL disability [39], impaired physical function [40], and frailty [13]. Overall, these findings highlight the importance of evaluating disability outside of the context of other correlates of health status.

As geriatric syndromes, both frailty and disability are key considerations in the care of older adults, with or without HIV infection. Although the terms are often used interchangeably, the concepts of frailty and disability are distinct, each with unique contributing factors and interventions for treatment and prevention [9]. As such, we have demonstrated that although IADL impairment was more common in persons with increasing frailty, nearly 50% of frail individuals did not have IADL impairments while IADL impairments were seen in 11% of non-frail participants. Although similar characteristics predicted both frailty and disability (e.g. insurance, education, physical activity, neurocognitive impairment) other characteristics that had predicted frailty (i.e. obesity, smoking)[13] were unrelated to disability. Furthermore, different

characteristics were associated with disability among those identified as frail (physical activity, neurocognitive impairment) than those that were not frail (education). A recent emphasis on use of the International Classification of Function to define disability across international clinical and research settings provides a similar distinction between concepts of “activity limitation” (as might be seen with grip and gait components of the frailty definition) and “participation restriction” (including limitations in IADLs), where restrictions are moderated by an individual’s ability to respond to those deficits within their environment [10-12].

The strengths of our study include use of a well-characterized cohort with detailed ART use data, use of a validated instrument for measuring neurocognitive function, and identification of a number of factors that may be related to disability. The study population includes participants in over 30 U.S. sites, thus incorporating a diverse range of participants that vary by age, gender, race, ethnicity, risk factors for HIV acquisition, rural versus urban, and Southern versus Northern characteristics that may influence one’s self-perception and experience of disability.

The study is not without limitations: due to the cross-sectional nature of the study, a causal relationship between IADL impairment and participant characteristics cannot be assumed. Our population was predominantly male, and perceived difficulty in certain IADL tasks could differ between men and women, particularly with roles traditionally assigned to a specific gender. The participants in this study have been enrolled in ART treatment trials and observational studies for a median of 7.8 years, and are likely not fully representative of the broader HIV-infected population. Lastly, as an individual’s own support and environment determine their perceived and real ability to function independently, conclusions from this study may not be broadly applicable to all HIV-infected persons.

In summary, we found that self-reported disability among HIV-infected older adults is strongly associated with neurocognitive impairment and socioeconomic or other lifestyle factors,

but not with other comorbidities or HIV-related factors. Our findings identified modifiable factors (smoking, low physical activity) as potential targets for interventions designed to reduce IADL impairment and to maintain independent living. Interventions aimed at improving socioeconomic status and support networks of those aging with HIV would likely have a significant beneficial impact on health, but would be increasingly challenging to implement at a systemic level. Lastly, by identifying persons at highest risk for disability, health providers can ensure that daily needs are met and these individuals are linked to appropriate resources.

NOTES

Author contributions:

KME, KW, and KT developed the analysis and interpretation. KW performed the data analysis under the supervision of KT. NJ and KME prepared the first draft of the manuscript. All authors contributed to the study design, implementation, interpretation of data, reviewed and revised the manuscript, and approved of the final draft.

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Conflicts of Interest:

RCK receives grant support from Gilead Sciences and has consulted for Gilead Sciences and Theratechnologies, FJP is a consultant and/or on the speakers bureau for Gilead Sciences, Janssen Pharmaceuticals, Merck and Co. and Bristol Myers Squibb. BT has received honoraria

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Figure Legend:

Frequency of any disability in Instrumental Activities of Daily Living (IADL) among categories of non frail, pre-frail, and frail participants in the HAILO Study.

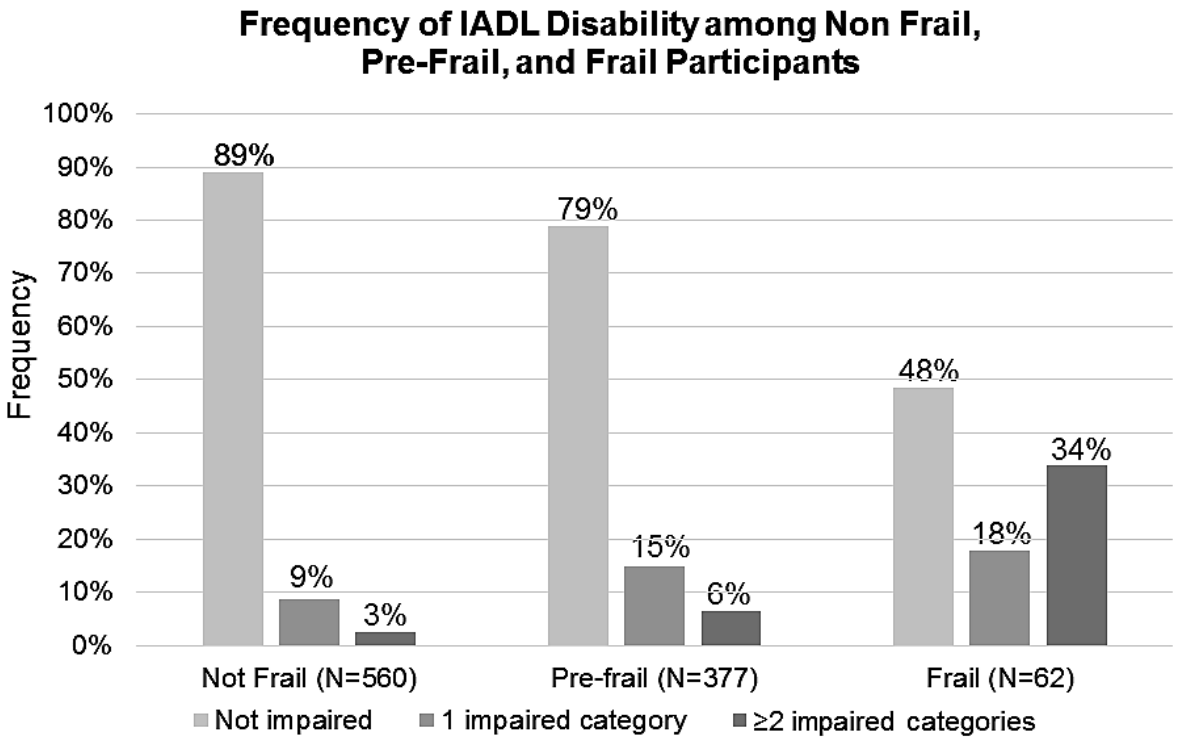

Table 1. Participant Characteristics at Baseline (Entry into HAILO, A5322), Overall and by IADL Impairment Group

Characteristic		Total (N=1015)	IADL impairment at baseline: Not impaired (N=837)	1 impaired category (N=115)	≥ 2 impaired categories (N=63)	P-Value
Age at baseline (years)**	≤44	203 (20%)	172 (21%)	23 (20%)	8 (13%)	0.42
	45-64	752 (74%)	618 (74%)	84 (73%)	50 (79%)	
	65-74	56 (6%)	44 (5%)	8 (7%)	4 (6%)	
	≥75	4 (0%)	3 (0%)	0 (0%)	1 (2%)	
Age at baseline (years)	<50	449 (44%)	382 (46%)	48 (42%)	19 (30%)	0.19
	50-59	415 (41%)	332 (40%)	50 (43%)	33 (52%)	
	≥60	151 (15%)	123 (15%)	17 (15%)	11 (17%)	
Sex	Male	818 (81%)	688 (82%)	90 (78%)	40 (63%)	0.001
	Female	197 (19%)	149 (18%)	25 (22%)	23 (37%)	
Race/Ethnicity	White Non-Hispanic	488 (48%)	430 (51%)	42 (37%)	16 (25%)	<.001
	Black Non-Hispanic	297 (29%)	238 (28%)	30 (26%)	29 (46%)	
	Hispanic (Regardless of Race)	203 (20%)	148 (18%)	39 (34%)	16 (25%)	
	Other*	25 (2%)	19 (2%)	4 (3%)	2 (4%)	
Years of education	Less than high school	151 (15%)	96 (11%)	32 (28%)	23 (37%)	<.001
	High school	225 (22%)	172 (21%)	38 (33%)	15 (24%)	
	More than high school	639 (63%)	569 (68%)	45 (39%)	25 (40%)	
Health insurance at baseline	No medical coverage	199 (20%)	149 (18%)	35 (30%)	15 (24%)	<.001
	Medicare/Medicaid	323 (32%)	234 (28%)	48 (42%)	41 (65%)	
	Private	421 (41%)	393 (47%)	24 (21%)	4 (6%)	
	Other	63 (6%)	53 (6%)	8 (7%)	2 (3%)	
	Unknown/missing	9 (1%)	8 (1%)	0 (0%)	1 (2%)	
Frailty status at baseline	Non-frail	560 (55%)	498 (59%)	48 (42%)	14 (22%)	<.001
	Pre-frail	377 (37%)	297 (35%)	56 (49%)	24 (38%)	
	Frail	62 (6%)	30 (4%)	11 (10%)	21 (33%)	
	Missing	16 (2%)	12 (1%)	0 (0%)	4 (6%)	
CD4 at baseline (cells/mm^3)	<350	125 (12%)	95 (11%)	18 (16%)	12 (19%)	0.19
	350-500	205 (20%)	175 (21%)	22 (19%)	8 (13%)	
	>500	679 (67%)	562 (67%)	75 (65%)	42 (67%)	
	Missing	6 (1%)	5 (1%)	0 (0%)	1 (2%)	
CD4/CD8 Ratio at baseline	>0.4	886 (87%)	740 (88%)	98 (85%)	48 (76%)	0.028
	≤0.4	114 (11%)	86 (10%)	15 (13%)	13 (21%)	
	Missing	15 (1%)	11 (1%)	2 (2%)	2 (3%)	
HIV RNA at baseline (copies/ml)	<200	959 (94%)	793 (95%)	109 (95%)	57 (90%)	0.59
	Missing	3 (0%)	2 (0%)	0 (0%)	1 (2%)	
Initial randomized ARV regimen	NRTI-backbone + PI	464 (46%)	385 (46%)	48 (42%)	31 (49%)	0.80
	NRTI-backbone + NNRTI	241 (24%)	199 (24%)	28 (24%)	14 (22%)	
	NRTI-backbone + INSTI	107 (11%)	83 (10%)	16 (14%)	8 (13%)	
	Other	203 (20%)	170 (20%)	23 (20%)	10 (16%)	
ART regimens at baseline	NRTI-backbone + PI	401 (40%)	324 (39%)	47 (41%)	30 (48%)	0.05
	NRTI-backbone + NNRTI	389 (38%)	332 (40%)	45 (39%)	12 (19%)	
	NRTI-backbone + INSTI	192 (19%)	154 (18%)	19 (17%)	19 (30%)	
	Other	33 (3%)	27 (3%)	4 (3%)	2 (3%)	
Hepatitis C serology positivity	Positive	121 (12%)	86 (10%)	22 (19%)	13 (21%)	0.002
Smoking at baseline	Never smoker	421 (41%)	367 (44%)	37 (32%)	17 (27%)	<0.001
	Prior smoker	337 (33%)	282 (34%)	34 (30%)	21 (33%)	
	Current smoker	257 (25%)	188 (22%)	44 (38%)	25 (40%)	
Alcohol use	Abstainer	376 (37%)	295 (35%)	54 (47%)	27 (43%)	0.11

Characteristic		Total (N=1015)	IADL impairment at baseline			P-Value
			Not impaired (N=837)	1 impaired category (N=115)	≥ 2 impaired categories (N=63)	
	Light	368 (36%)	318 (38%)	33 (29%)	17 (27%)	
	Moderate	62 (6%)	52 (6%)	7 (6%)	3 (5%)	
	Heavy	169 (17%)	143 (17%)	14 (12%)	12 (19%)	
	Missing	40 (4%)	29 (3%)	7 (6%)	4 (6%)	
Binge drinking	Abstainer	376 (37%)	295 (35%)	54 (47%)	27 (43%)	0.13
	No binging	445 (44%)	381 (46%)	42 (37%)	22 (35%)	
	Binge once/month	77 (8%)	65 (8%)	6 (5%)	6 (10%)	
	Binge >1/month	81 (8%)	70 (8%)	6 (5%)	5 (8%)	
	Missing	36 (4%)	26 (3%)	7 (6%)	3 (5%)	
Active substance use	Yes	209 (21%)	167 (20%)	29 (25%)	13 (21%)	0.30
	Missing	48 (5%)	34 (4%)	9 (8%)	5 (8%)	
Days of vigorous/moderate activities/week	≥3 days of physical activity	507 (50%)	447 (53%)	45 (39%)	15 (24%)	<0.001
	Missing	57 (6%)	40 (5%)	11 (10%)	6 (10%)	
Body mass index	Underweight	6 (1%)	3 (0%)	2 (2%)	1 (2%)	0.32
	Normal weight	321 (32%)	258 (31%)	43 (37%)	20 (32%)	
	Overweight	388 (38%)	324 (39%)	43 (37%)	21 (33%)	
	Obese	284 (28%)	240 (29%)	27 (23%)	17 27%)	
	Missing	16 (2%)	12 (1%)	0 (0%)	4 (6%)	
Cardiovascular disease		60 (6%)	43 (5%)	13 (1%)	4 (6%)	0.031
Renal disease		102 (10%)	82 (10%)	10 (9%)	10 (16%)	0.27
Liver disease		8 (1%)	4 (0%)	3 (3%)	1 (2%)	0.040
Diabetes		142 (14%)	101 (12%)	24 (21%)	17 (27%)	<0.001
Hypertension		757 (75%	619 (74%	88 (77%)	50 (79%)	0.56
High LDL cholesterol	>130 mg/dL	219 (22%)	183 (22%)	22 (19%)	14 (22%)	0.84
Depression		89 (9%)	68 (8%)	11 (10%)	10 (16%)	0.11
Cancer (within 5 years)		32 (3%)	25 (3%)	4 (3%)	1 (2%)	0.72

*Other race is defined as Asian/Pacific Islander, American Indian/ Alaskan Native, or more than one race
IADL, impairment in activities of daily living; ART, antiretroviral therapy; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; NNRTI, Non-nucleoside reverse-transcriptase inhibitors; INSTI, integrase strand transfer inhibitor
** Age categories used for comparison with NHANES data

Table 2. Type of Impairment Present Among Participants with at Least One IADL Impairment

Type of Impairment	Total (N=178)	IADL impairment at baseline: 1 impaired category (N=115)	IADL impairment at baseline: ≥2 impaired categories (N=63)
Housekeeping difficulty	48%	39%	63%
Transportation difficulty	36%	25%	56%
Shopping difficulty	28%	10%	59%
Laundry difficulty	20%	4%	48%
Finance management difficulty	14%	10%	21%
Cooking difficulty	15%	7%	29%
Difficulty in using the phone	12%	2%	30%
Difficulty with medications	5%	2%	11%

Table 3 Associations of Demographics, HIV and Comorbidities with Impairment in IADL

Variables	Category	Univariable Model (N=1015)		Multivariable Model (N=873)	
		Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Female (vs Male)		1.70 (1.17,2.48)	0.005	1.25 (0.75,2.09)	0.39
Race (vs White, non-Hispanic)	Black, non-Hispanic	1.84 (1.24,2.73)	0.003	0.94 (0.56,1.58)	0.82
	Hispanic + Other*	2.68 (1.79,4.00)	<0.001	1.46 (0.8,2.67)	0.21
Baseline age (vs 40-49 years)	50-59 years	1.43 (1.00,2.03)	0.05	1.41 (0.9,2.2)	0.13
	≥ 60 years	1.30 (0.80,2.11)	0.29	0.92 (0.47,1.77)	0.8
High school education or less (vs > high school)		3.28 (2.35,4.57)	<0.001	**2.16 (1.38,3.4)**	**<0.001**
Health insurance (vs Medicare/Caid)	No coverage	0.88 (0.59,1.32)	0.54	0.97 (0.57,1.66)	>0.90
	Private+Other	0.22 (0.15,0.34)	<0.001	**0.45 (0.27,0.75)**	**0.002**
Baseline CD4 cell counts (vs >500) cells/mm^3	< 350 cells/mm^3	1.52 (0.96,2.39)	0.07	0.78 (0.34,1.8)	0.56
	350-500 cells/mm^3	0.82 (0.53,1.27)	0.38	0.81 (0.46,1.41)	0.45
CD4/CD8 ratio ≤0.4 at baseline (vs >0.4)		1.65 (1.04,2.62)	0.03	1.38 (0.63,3.04)	0.43
Baseline ARV regimen (vs NRTI-backbone+PI)**	NRTI-backbone + NNRTI	0.72 (0.50,1.05)	0.09		
	NRTI-backbone + INSTI	1.04 (0.67,1.60)	0.87		
	Other	0.94 (0.37,2.34)	0.89		
NNRTI in ARV regimens at baseline		0.72 (0.51,1.01)	0.06	1.24 (0.78,1.99)	0.37
Integrase inhibitor in ARV regimens at baseline		1.42 (0.98,2.05)	0.06	1.27 (0.77,2.12)	0.35
Positive hepatitis C serology (vs Never)		2.14 (1.39,3.29)	<0.001	1.41 (0.8,2.49)	0.24
History of smoking (vs never)	Prior smoker	1.33 (0.88,1.99)	0.17	1.16 (0.68,1.96)	0.59
	Current smoker	2.49 (1.68,3.71)	<0.001	**2.55 (1.54,4.24)**	**<0.001**
Current alcohol use at baseline (vs no drinking)	Light Drinker	0.57 (0.39,0.84)	0.005	0.82 (0.51,1.33)	0.43
	Moderate/Heavy Drinker	0.67 (0.44,1.04)	0.07	0.97 (0.56,1.68)	>0.90
<3 days of vigorous/mod activities/week (vs ≥ 3)		2.15 (1.52,3.05)	<0.001	**1.95 (1.28,2.97)**	**0.002**
Neurocognitive impairment at baseline		3.48 (2.37,5.12)	<0.001	**2.29 (1.4,3.76)**	**0.001**
Cardiovascular disease		1.95 (1.08,3.51)	0.03	1.8 (0.87,3.71)	0.11
Liver disease		4.79 (1.19,19.33)	0.03	3.36 (0.39,28.9)	0.27
Diabetes		2.18 (1.45,3.27)	<0.001	1.46 (0.84,2.56)	0.18

Outcome modeled is difficulties in ≥1 category of IADL

Other covariates considered but not associated ($p \geq 0.10$) with IADL impairment in univariable models included: nadir CD4 count, pre-ART CD4 count and HIV-1 viral load, initial ARV regimen, prior exposure to DDI, D4T, or ZDV on or before baseline, years since ARV initiation, cumulative years of NNRTI or integrase inhibitor use, substance use, any alcohol use, weekly amount of alcohol use, obesity at ART initiation or baseline, weight change in first year of ART initiation and between A5001 entry and A5322 baseline, baseline LDL, depression, history of renal disease, hypertension, history of cancer within 5 years

*Other race is defined as Asian/Pacific Islander, American Indian/ Alaskan Native, or more than one race

** Baseline ARV regimen was not included in multivariable model as it was correlated with NNRTI in baseline regimen and integrase inhibitor in baseline regimen variables

ARV, antiretroviral therapy; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; NNRTI, Non-nucleoside reverse-transcriptase inhibitors; integrase, integrase inhibitor; ZDV, zidovudine; DDI, didanosine, D4T, stavudine, LDL, low-density lipoprotein