Measures of Physical and Mental Independence Among HIV-Positive Individuals: Impact of Substance Use Disorder

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Abstract

With the transition of HIV infection from an acute to a chronic disease after the introduction of antiretroviral medications, there has been an increased focus on long-term neurocognitive and other functional outcomes of HIV patients. Thus, we assessed factors, particularly history of a substance use disorder, associated with time to loss of measures of physical or mental independence among HIV-positive individuals. Data were obtained from the National NeuroAIDS Tissue Consortium. Kaplan–Meier and Cox proportional hazards regression analyses were used to estimate the time since HIV diagnosis to loss of independence, and to identify associated risk factors. HIV-positive participants who self-identified as physically ($n = 698$) or mentally ($n = 616$) independent on selected activities of daily living at baseline were eligible for analyses. A history of substance use disorder was associated with a higher hazard of loss of both physical and mental independence [adjusted hazard ratio (HR) = 1.71, 95% confidence interval (95% CI): 1.07–2.78; adjusted HR = 1.67, 95% CI: 1.11–2.52, respectively]. After adjusting for substance use disorder and other covariates, older age at diagnosis and female gender were associated with higher hazards of loss of both physical and mental independence, non-white participants had higher hazards of loss of physical independence, whereas participants with an abnormal neurocognitive diagnosis and fewer years of education had higher hazards of loss of mental independence. In summary, history of substance use disorder was associated with loss of measures of both physical and mental independence. The nature of this link and the means to prevent such loss of independence need further investigation.

Keywords: HIV, activities of daily living, physical independence, mental independence, neuroAIDS, substance abuse

Introduction

HIV HAS LARGELY BECOME a chronic disease in the United States since the introduction of combination anti-retroviral treatment (cART) in the mid-1990s that extended the life expectancy of people living with HIV/AIDS (PLWHA).^{1–4} Therefore, there is a need to focus on the long-term outcomes of living with HIV, including neurocognitive and behavioral sequelae.⁵ Studies have suggested an association between neurocognitive decline in PLWHA and aging.

This puts many at risk, as more than a quarter of HIV-infected individuals in the United States are older than the age of 50.^{2,3,5–11} Thus, a number of recent studies have focused on the neurocognitive function of older HIV-infected individuals and the possibility of additive or interactive effects of HIV and aging.^{7–12}

Although HIV-associated dementia (HAD) is rare in the cART era, recent studies have revealed the continued persistence of more mild-to-moderate forms of central nervous system disorders, which together are known as HIV-associated

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neurocognitive disorders (HAND), affecting a maximum of 50% of people with HIV.^{13–15} However, in many cases, HAND does not affect activities of daily living (ADLs), which are important metrics in assessing long-term disease outcomes. Deficits in ADLs, in particular loss of independence, can negatively affect the quality of life and lifespan.

Assessment of the factors associated with time to loss of independence in certain ADLs in the era of cART may help public health professionals and healthcare practitioners working with HIV-infected patients to better understand how to modify disease progression. Studies on HAND often utilize ADLs to differentiate symptomatic neurocognitive disorders from asymptomatic ones, but they require at least two to be impaired, in addition to abnormality in an additional measure of functional decline.^{13,16,17} However, some ADLs may not apply to subjects in a uniform manner (e.g., depending on circumstances, some do not cook, drive, do home repairs, or child care; and the use of the telephones, in aspects such as remembering numbers and dialing, has changed due to cell phones and internet use). Therefore, in this study, we focused on two ADLs that are important for one's autonomy (bathing and dressing, largely physically limited), and one that is critical for healthcare, that is, managing one's medications (largely dependent on mental ability).

In this study, we focused on substance use disorder (abuse or dependence), a frequent comorbidity in PLWHA, and secondarily on other participants' sociodemographic and clinical characteristics. Substance use disorder may influence the risk of contracting HIV as well as the life expectancy of someone infected with HIV.^{4,10} However, some reports suggest that HAND frequency may not be related to substance abuse history.¹⁸ By examining how substance use changes the progression of loss of physical or mental independence in these ADLs, community-based public health organizations and healthcare institutions can tailor interventions for HIV-infected substance users to encourage better outcomes in this high-risk population.

Currently, there are little or no conclusive data available regarding the temporal relationship between HIV diagnosis and the loss of independence in ADLs. To address that issue, we measured the time to loss of independence in a mental ADL (measured by participants' ability to manage medications) and two physical ADLs (measured by participant's ability to bathe and dress) in a well-characterized population of HIV infected people, and we then examined factors that were potentially associated with the onset of functional declines. We hypothesized that HIV-positive subjects with a history of substance use disorder would have a shorter time to loss of physical or mental independence in these relevant measures.

Materials and Methods

Data from the National NeuroAIDS Tissue Consortium's (NNTC) longitudinal multicenter cohort were used in the analysis. The NNTC was founded in 1998 as a research consortium that was composed of four U.S. sites: California NeuroAIDS Tissue Network (San Diego, CA), Manhattan HIV Brain Bank (New York, NY), National Neurological AIDS Bank (Los Angeles, CA), and Texas NeuroAIDS Research Center (Galveston, TX).¹⁹ NNTC participants were volunteers who were prospectively recruited from clinics,

hospitals, and local communities of the participating clinical sites. NNTC enrollment criteria included agreement to be an organ donor for research on demise.

At baseline, participants provided informed consent and received a neurological exam, structured neuropsychological testing, and a psychiatric assessment that included the World Health Organization World Mental Health Composite International Diagnostic Interview (CIDI) or the Psychiatric Research Interview for Substance and Mental Disorder (PRISM).^{20–22} Participants completed standardized questionnaires on medication adherence and ADL. The ADL form utilized by the NNTC was a slightly modified version of the Lawton and Brody's Instrumental Activities of Daily Living scale. This instrument collects self-reported data on a subject's ability to perform a variety of activities, including bathing, dressing, and medication management.²²

Participants completed standardized questionnaires or interviews on sociodemographic information and medical, medication, psychiatric, and substance abuse history. When available, medical records were used to validate self-reported information. Participants also underwent a series of laboratory tests using blood plasma, cerebrospinal fluid and urine specimens, as well as neuromedical and neurocognitive exams. Medical history updates, examinations, and laboratory tests were repeated every 6–24 months depending on participants' health (those in declining health were seen more frequently to increase the chance of assessment before tissue donation) and likelihood of loss to follow-up (those who were more likely to be lost to follow-up were seen more frequently to minimize attrition). Some participants were followed only by telephone.¹⁹

For analyses, we selected NNTC participants who were at least 19 years old, HIV positive, had at least two NNTC study visits, and were independent on the selected ADLs at the time of enrollment in the NNTC cohort between January 1, 1998 and May 1, 2015. In addition, only participants with complete data were included in the analyses. The analyses were approved by the University of Nebraska Medical Center Institutional Review Board.

The primary outcomes were time to loss of the selected physical or mental ADLs. The date that loss of independence was first reported after the baseline visit was selected as the time of the event.

Mental independence was scaled according to a participant's current ability to manage medications. Participants who always selected "I plan and take medications without problems" or "I am able to take care of my own medications, but choose to have someone else do it for me" were classified as mentally independent, whereas participants who at any time during follow-up selected "I have some trouble following my medication schedule, and sometimes make mistakes" or "I am unable to track my own medications" were classified as not independent.

Physical independence was scaled according to a participant's current ability to bathe and dress. Participants who always selected "I handle all my bathing needs by myself," and "I am able to dress myself and pick out my own clothes," or "I dress myself, but someone else must pick out the clothes for me" were classified as physically independent. Participants who at any time during the follow-up responded that sometimes, often, or always they needed help when bathing or getting dressed were classified as not independent.

Time to event was the time, in years, from the first recorded HIV diagnosis (midpoint of the year of diagnosis, i.e., July 2) to loss of independence, end of study period (May 1, 2015), death, loss to follow-up, withdrawal, or administrative censoring.

The primary exposure was history of substance use disorder that was measured by using the CIDI or the PRISM at baseline, which was consistent with the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria. Using these instruments, participants were classified as positive or negative for lifetime history of substance use disorder based on current or past abuse or dependence on alcohol, cannabis, cocaine, opiates, hallucinogens, sedatives, stimulants, or other drugs.

Covariates considered in the analysis included sociodemographic factors (age at diagnosis, gender, and years of education), clinical site, HIV- and non-HIV-related neurocognitive diagnosis, HIV risk group, presence of HIV-related conditions (progressive multifocal leukoencephalopathy, lymphoma, disseminated mycobacterium avian complex, wasting, cytomegalovirus end-organ disease, and visceral Kaposi's sarcoma), disease duration at baseline, number of non-HIV-related comorbidities (hypertension, diabetes, hyperlipidemia, viral hepatitis, end-stage liver disease, chronic renal disease, cardiac disease, chronic obstructive pulmonary disease, cerebrovascular disease, non-AIDS defining cancer, and lipodystrophy), and previous recorded study status.

Statistical analysis

We tallied the percentage of participants who were physically independent at baseline and lost independence during the study period overall and by characteristics of interest. We repeated the process for participants who were mentally independent and lost independence during the study period. Kaplan-Meier survival analysis was done to estimate the mean time to loss of the measures of physical or mental independence within categories of each covariate and the main exposure.

Cox proportional hazards regression was used to determine crude hazard ratios (HR) for the association between exposure of interest (i.e., substance use disorder history) and loss of physical or mental independence, adjusting for confounders. All the covariates were entered into a multivariable Cox proportional hazards regression (full model). Using stepwise backward elimination, we obtained a final adjusted model (partial model) that included covariates that were associated with a >10% change in the HR estimate between the outcome and substance use disorder. We used two-sided $\alpha=0.05$ and SAS 9.4 (SAS Institute, Inc., Cary, NC) for all statistical analyses.

Results

Over a 17-year period, 2,900 participants were enrolled in the NNTC cohort. Of these, 1,048 participants met the initial overall eligibility criteria (i.e., HIV-positive participants aged 19 and older with at least 2 visits). Furthermore, at baseline, 875 participants were physically independent and 760 participants were mentally independent. After excluding those participants with missing data, 698 (79.8%) participants remained for the assessment of time to loss of the measure of physical independence and 616 (81.1%) remained for the assessment of time to loss of the measure of mental independence.

Eligible participants were mostly men (4/5), and more than half of them were white. Fifty-eight percent of participants had a history of substance use disorder (i.e., abuse or dependence). Substance use disorder was more common among men than women (3:2 ratio; $p<.0001$), among those with an HIV diagnosis at an earlier age ($p<.03$), among non-blacks ($p<.01$), and among those with 12–13 years of education versus those who were less or more educated ($p<.033$). Almost half of the participants had an HIV-related positive neurocognitive diagnosis. Nearly three-quarters of participants were positive for any HIV-related condition, or had at least one non-HIV-related comorbidity (Table 1).

Overall, 698 participants were physically independent at baseline and had an average HIV disease duration of 16.6 (95% CI: 16.1–17.1) years at the time of NNTC study entry. At the end of the study period (May 1, 2015), 297 (42.6%) participants were still actively enrolled in the NNTC cohort, though 36 out of 297 (12.1%) had lost physical independence (bathing and/or dressing). An additional 214 (30.6%) were deceased (18.2% of whom had lost physical independence before death), and 187 were lost to follow-up, withdrawn, or administratively censored (15.0% of them had lost physical independence). Thus, 103 out of 698 (14.8%) physically independent participants at baseline lost physical independence during the study period after an average of 24.8 years since their HIV diagnosis.

A higher percentage (16.8%) of participants with substance use disorder reported loss of physical independence, compared with 11.9% of participants without a history of substance use disorder (crude HR: 1.40; 95% CI: 0.93–2.11; adjusted HR: 1.71; 95% CI: 1.05–2.78). In addition, women had double the hazard of losing physical independence compared with men, even after adjusting for substance use disorder and other confounders (adjusted HR: 2.37; 95% CI: 1.50–3.77). Participants who were older also had higher hazards of losing physical independence versus younger participants (Table 2).

Overall, 616 participants were mentally independent at baseline and had an average HIV disease duration of 16.2 (95% CI: 15.7–16.8) years at the time of NNTC study entry. At the end of the study period, 281 (45.5%) participants were still actively enrolled in the NNTC cohort, though 61 out of 281 (21.7%) had lost mental independence (medication management). An additional 184 (29.9%) were deceased (23.4% of whom had lost physical independence before death), and 151 were lost to follow-up, withdrawn, or administratively censored (17.9% of them had lost physical independence). Thus, 131 out of 616 (21.3%) mentally independent participants at baseline lost mental independence during the study period after an average of 23.2 years since their HIV diagnosis.

Seventy-nine out of 355 (22.2%) participants who had a history of substance use disorder lost mental independence, compared with 52 out of 261 (20.9%) participants without a history of substance use disorder. After adjustment, participants with substance use disorder had a higher hazard of loss of mental independence versus those without it (adjusted HR: 1.67; 95% CI: 1.11–2.52).

Other participant characteristics, such as older age at diagnosis, fewer years of education, and an abnormal neurocognitive diagnosis (HIV and non-HIV related), were also associated with a higher hazard of losing mental

TABLE 1. PARTICIPANTS' DISTRIBUTION AND TIME TO LOSS OF INDEPENDENCE BY SELECTED VARIABLES (NATIONAL NEUROAIDS TISSUE CONSORTIUM; 1998–2015)

Variable	<i>Physically independent patients at baseline (n=698)^a</i>			<i>Mentally independent patients at baseline (n=616)^a</i>		
	Total n	Lost physical independence n (%)	Time (years) to loss of physical independence; mean (SE) ^b	Total n	Lost mental independence n (%)	Time (years) to loss of mental independence; mean (SE) ^b
Age at diagnosis						
<29 years	264	36 (13.7)	25.4 (0.4)	228	47 (20.6)	23.2 (0.4)
29–36 years	210	34 (16.2)	21.9 (0.4)	189	47 (24.9)	22.2 (0.5)
>36 years	224	33 (14.7)	22.4 (0.4)	199	37 (18.6)	22.9 (0.6)
Gender						
Male	552	67 (12.1)	23.1 (0.2)	500	89 (17.8)	23.8 (0.3)
Female	146	36 (25.7)	23.0 (0.7)	116	42 (36.2)	19.7 (0.7)
Race						
White	382	45 (11.8)	22.5 (0.2)	347	68 (19.6)	23.6 (0.4)
Black	257	49 (19.1)	23.9 (0.5)	214	54 (25.2)	21.4 (0.4)
Native American	26	5 (19.2)	19.3 (0.8)	24	3 (12.5)	20.0 (0.7)
Other/multiracial ^c	33	4 (12.1)	22.9 (1.0)	31	6 (19.4)	21.1 (1.3)
Ethnicity						
Non-Hispanic	535	81 (15.1)	24.8 (0.3)	467	97 (10.8)	22.8 (0.3)
Hispanic	163	22 (13.5)	22.9 (0.4)	149	34 (12.8)	22.7 (0.6)
Years of education						
<12 years	207	34 (16.4)	24.1 (0.6)	169	54 (31.9)	21.0 (0.6)
12–13 years	236	37 (15.7)	22.1 (0.3)	215	44 (20.5)	22.0 (0.4)
>13 years	255	32 (12.5)	23.2 (0.3)	232	33 (14.2)	23.9 (0.4)
Substance use disorder history						
No	294	35 (11.9)	23.2 (0.3)	261	52 (20.9)	22.7 (0.4)
Yes	404	68 (16.8)	24.4 (0.4)	355	79 (22.2)	23.0 (0.4)
Clinical site						
CNTN	276	51 (18.5)	21.3 (0.4)	230	55 (23.9)	21.6 (0.5)
MHBB	219	31 (14.2)	22.3 (0.3)	182	58 (31.9)	21.8 (0.6)
NNAB	140	20 (14.3)	25.3 (0.5)	143	15 (10.5)	24.0 (0.4)
TNRC	63	1 (1.6)	11.7 (0.0)	61	3 (4.9)	17.3 (0.2)
NC diagnoses						
Normal	200	21 (10.5)	22.8 (0.3)	189	25 (13.2)	24.1 (0.4)
NC impairment	110	13 (11.8)	25.4 (0.7)	105	20 (19.0)	23.0 (0.7)
Mild NC disorder	148	29 (19.6)	21.3 (0.5)	127	29 (22.8)	19.5 (0.4)
HIV-associated dementia	50	7 (14.0)	19.6 (0.7)	36	11 (30.6)	16.5 (0.7)
Other/uncertain NP impairment ^d	190	33 (17.4)	22.0 (0.4)	159	46 (28.9)	22.1 (0.6)
HIV risk group						
Blood product recipient	12	3 (25.0)	21.0 (2.5)	10	2 (20.0)	11.0 (0.6)
Heterosexual exposure	139	25 (18.0)	23.6 (0.7)	114	26 (22.8)	18.2 (0.5)
IV drug user	67	9 (13.4)	21.5 (0.6)	50	16 (32.0)	19.8 (0.7)
Male to male sex	301	35 (11.6)	23.3 (0.3)	280	42 (15.0)	23.9 (0.3)
More than 1 risk group	179	31 (17.3)	21.9 (0.4)	162	45 (27.8)	22.3 (0.6)
Presence of any HIV-related conditions ^e						
No	184	25 (13.6)	22.4 (0.3)	161	51 (32.1)	22.3 (0.5)
Yes	514	78 (15.2)	24.5 (0.3)	455	80 (17.6)	23.1 (0.3)
No. of non-HIV-related comorbidities ^f						
None	196	20 (10.2)	22.6 (0.4)	177	25 (14.1)	23.3 (0.6)
1	240	42 (17.5)	21.5 (0.4)	199	57 (28.6)	21.1 (0.5)
2 or more	262	41 (15.6)	25.1 (0.4)	240	49 (20.4)	23.8 (0.4)
Total	698	103 (14.8)	24.8 (0.3)	616	131 (21.3)	23.2 (0.3)

^aAll values reported percentages of participants in each group (physically independent at baseline or mentally independent at baseline) who lost physical or mental independence, respectively.

^bTime since HIV diagnosis to loss of independence among participants who lost independence.

^cOther/multiracial included Asian, Native Hawaiian/Pacific islanders, and multiracial.

^dOther/uncertain NP impairment included other non-HIV-related causes, uncertain causes, test not done, or unable to reliably assign a neurocognitive diagnosis.

^eHIV-related conditions included lymphoma, progressive multifocal leukoencephalopathy, disseminated MAC, wasting, CMV end-organ disease, and visceral Kaposi's sarcoma.

^fComorbidities included hypertension, diabetes, hyperlipidemia, viral hepatitis, chronic renal disease, cardiac disease, chronic obstructive pulmonary disease, cerebrovascular disease, non-AIDS defining cancer, and lipodystrophy.

CMV, cytomegalovirus; CNTN, California NeuroAIDS Tissue Network; MAC, mycobacterium avian complex; MHBB, Manhattan HIV Brain Bank; NNAB, National Neurological AIDS Bank; NP, neuropsychological; SE, standard error; TNRC, Texas NeuroAIDS Research Center.

TABLE 2. CRUDE AND ADJUSTED HAZARD RATIOS FOR LOSS OF PHYSICAL INDEPENDENCE BY SELECTED VARIABLES (NATIONAL NEUROAIDS TISSUE CONSORTIUM; 1998–2015)

Variable	Physically independent at baseline (n=698)		
	Crude HR (95% CI)	Adjusted HR (95% CI) full model ^a	Adjusted HR (95% CI) partial model ^a
Age at diagnosis	1.03 (1.00–1.05)	1.06 (1.03–1.09)	1.06 (1.03–1.08)
Gender			
Male	Ref.	Ref.	Ref.
Female	2.18 (1.45–3.27)	2.21 (1.29–3.76)	2.37 (1.50–3.77)
Race			
White	Ref.	Ref.	Ref.
Black	1.77 (1.18–2.65)	2.30 (1.39–3.80)	2.44 (1.49–3.99)
Native American	2.16 (0.85–5.46)	1.99 (0.72–5.51)	1.97 (0.73–5.30)
Other/multiracial ^b	1.26 (0.45–3.51)	1.30 (0.43–3.92)	1.15 (0.40–3.30)
Ethnicity			
Non-Hispanic	Ref.	Ref.	Ref.
Hispanic	0.81 (0.55–1.19)	1.35 (0.43–3.92)	1.38 (0.81–2.34)
Years of education	0.94 (0.88–1.00)	0.99 (0.92–1.07)	0.99 (0.92–1.06)
Substance use disorder history			
No	Ref.	Ref.	Ref.
Yes	1.40 (0.93–2.11)	1.76 (1.07–2.88)	1.71 (1.05–2.78)
Clinical site			
CNTN	Ref.	Ref.	Ref.
MHBB	0.56 (0.36–0.88)	0.37 (0.18–0.65)	0.28 (0.15–0.51)
NNAB	0.55 (0.33–0.92)	0.34 (0.18–0.65)	0.39 (0.22–0.69)
TNRC	0.06 (0.01–0.41)	0.04 (0.01–0.26)	0.04 (0.01–0.29)
NC diagnoses			
Normal	Ref.	Ref.	Ref.
NC impairment	1.22 (0.61–2.45)	1.01 (0.50–2.06)	1.03 (0.51–2.08)
Mild NC disorder	2.04 (1.16–3.58)	2.13 (1.18–3.79)	2.17 (1.23–3.86)
HIV-associated dementia	1.59 (0.68–3.75)	1.70 (0.70–4.12)	1.83 (0.76–4.40)
Other/uncertain NP impairment ^c	1.77 (1.02–3.05)	1.54 (0.86–2.75)	1.54 (0.88–2.72)
HIV risk group			
Blood product recipient	Ref.	Ref.	N/A
Heterosexual exposure	0.81 (0.25–2.70)	1.87 (0.51–6.91)	N/A
IV drug user	0.54 (0.15–1.98)	1.05 (0.26–4.41)	N/A
Male to male sex	0.38 (0.12–1.25)	1.29 (0.33–4.30)	N/A
More than 1 risk group	0.65 (0.20–2.14)	1.29 (0.33–5.04)	N/A
Presence of any HIV-related conditions ^d			
No	Ref.	Ref.	N/A
Yes	1.45 (0.92–2.27)	1.80 (0.97–3.36)	N/A
No. of non-HIV-related comorbidities ^e	0.96 (0.84–1.09)	1.03 (0.89–1.20)	N/A

^aEach variable is adjusted for all other variables listed in the column.

^bOther/multiracial included Asian, Native Hawaiian/Pacific islanders, and multiracial.

^cOther/uncertain NP impairment included: other non-HIV-related causes, uncertain causes, test not done, or unable to reliably assign a neurocognitive diagnosis.

^dHIV-related conditions included lymphoma, progressive multifocal leukoencephalopathy, disseminated MAC, wasting, CMV end-organ disease, and visceral Kaposi's sarcoma.

^eComorbidities included hypertension, diabetes, hyperlipidemia, viral hepatitis, chronic renal disease, cardiac disease, chronic obstructive pulmonary disease, cerebrovascular disease, non-AIDS defining cancer, and lipodystrophy.

95% CI, 95% confidence interval; HR, hazard ratio; N/A, not applicable.

independence, after controlling for substance use disorder and other covariates (Table 3). A higher percentage of women (36.2% vs. 17.8% of men) lost mental independence during the study period. The average time to loss of mental independence was shorter for women (19.7 years) than men (23.8 years). In addition, women had a higher hazard of losing mental independence compared with men, even after adjusting for substance use disorder and other confounders (adjusted HR: 1.52; 95% CI: 1.00–2.29).

Discussion

In this study, subjects with a history of substance use disorder had 1.71 times higher and 1.67 times higher hazard of losing measures of physical and mental independence, respectively, compared with participants without a history of substance use disorder, after controlling for other characteristics. These findings suggest that an association exists between substance abuse and dependence and a decline in functional ability among HIV-positive individuals. This

TABLE 3. CRUDE AND ADJUSTED HAZARD RATIOS FOR LOSS OF MENTAL INDEPENDENCE BY SELECTED VARIABLES (NATIONAL NEUROAIDS TISSUE CONSORTIUM; 1998–2015)

Variable	<i>Mentally independent at baseline (n=616)</i>		
	<i>Crude HR (95% CI)</i>	<i>Adjusted HR (95% CI) full model^a</i>	<i>Adjusted HR (95% CI) partial model^a</i>
Age at diagnosis	1.02 (1.00–1.04)	1.04 (1.02–1.07)	1.03 (1.01–1.06)
Gender			
Male	Ref.	Ref.	Ref.
Female	2.30 (1.59–3.32)	1.46 (0.92–2.32)	1.52 (1.00–2.29)
Race			
White	Ref.	Ref.	Ref.
Black	1.33 (0.93–1.90)	1.23 (0.78–1.93)	1.13 (0.77–1.68)
Native American	0.79 (0.25–2.50)	0.65 (0.19–2.15)	0.84 (0.26–2.74)
Other/multiracial ^b	1.29 (0.56–2.97)	1.56 (0.64–3.85)	1.22 (0.52–2.88)
Ethnicity			
Non-Hispanic	Ref.	Ref.	Ref.
Hispanic	1.24 (0.84–1.83)	1.15 (0.73–1.82)	1.18 (0.76–1.84)
Years of education	0.88 (0.83–0.93)	0.91 (0.85–0.97)	0.91 (0.85–0.97)
Substance use disorder history			
No	Ref.	Ref.	Ref.
Yes	1.06 (0.75–1.51)	1.68 (1.09–2.58)	1.67 (1.11–2.52)
Clinical site			
CNTN	Ref.	Ref.	Ref.
MHBB	1.03 (0.71–1.49)	0.88 (0.47–1.62)	0.81 (0.49–1.33)
NNAB	0.30 (0.17–0.53)	0.28 (0.15–0.56)	0.25 (0.14–0.45)
TNRC	0.13 (0.04–0.40)	0.10 (0.03–0.34)	0.10 (0.03–0.31)
NC diagnoses			
Normal	Ref.	Ref.	Ref.
NC impairment	1.61 (0.89–2.89)	1.65 (0.90–3.02)	1.72 (0.95–3.14)
Mild NC disorder	2.06 (1.21–3.53)	2.04 (1.18–3.54)	2.11 (1.22–3.63)
HIV-associated dementia	3.21 (1.58–6.53)	4.70 (2.21–9.96)	4.63 (2.20–9.72)
Other/uncertain NP impairment ^c	2.42 (1.49–3.94)	1.72 (1.03–2.86)	1.68 (1.02–2.79)
HIV risk group			
Blood product recipient	Ref.	Ref.	N/A
Heterosexual exposure	1.78 (0.42–7.50)	2.38 (0.50–11.37)	N/A
IV drug user	2.12 (0.49–9.21)	2.39 (0.49–11.69)	N/A
Male to male sex	0.78 (0.19–3.23)	1.95 (0.41–9.38)	N/A
More than 1 risk group	1.63 (0.40–6.71)	2.12 (0.47–10.37)	N/A
Presence of any HIV-related conditions ^d			
No	Ref.	Ref.	N/A
Yes	0.65 (0.45–0.91)	1.20 (0.72–1.98)	N/A
No. of non-HIV related comorbidities ^e	0.87 (0.77–0.97)	0.91 (0.79–1.06)	N/A

^aEach variable is adjusted for all other variables listed in the column.

^bOther/multiracial included Asian, Native Hawaiian/Pacific islanders, and multiracial.

^cOther/uncertain NP impairment included: other non-HIV-related causes, uncertain causes, test not done, or unable to reliably assign a neurocognitive diagnosis.

^dHIV-related conditions included lymphoma, progressive multifocal leukoencephalopathy, disseminated MAC, wasting, CMV end-organ disease, and visceral Kaposi's sarcoma.

^eComorbidities included hypertension, diabetes, hyperlipidemia, viral hepatitis, chronic renal disease, cardiac disease, chronic obstructive pulmonary disease, cerebrovascular disease, non-AIDS defining cancer, and lipodystrophy.

result is consistent with prior reports, which suggested that HIV-positive individuals with substance use disorders have more problems with everyday functioning and higher morbidity than individuals who are singly affected (either HIV positive or HIV negative with a substance use disorder).^{23–25}

Older age at diagnosis was associated with higher hazards of losing signs of either physical or mental independence (HR: 1.06 and 1.03 of losing physical and mental independence, respectively; for every 1-year difference in age). This result is in agreement with the report by Ávila-Funes *et al.*,²⁶ which noted that being older than 50 years was associated with ADL disability among HIV-positive patients.²⁷

Women had a higher hazard of losing these indicators of physical or mental independence compared with men, after accounting for substance use disorder and other characteristics. This finding may be related to biological differences between genders, such as greater musculature of men compared with women, differential reporting bias, or systematic gender differences related to diagnosis, treatment, and disease progression.

A higher number of years of education was inversely associated with the hazard of losing mental independence (adjusted HR=0.91 for every additional year of education). Our results differ from those of Ávila-Funes *et al.*,²⁶ who

found an association between years of education and physical ADL (which included dressing and bathing), but not mental ADL (which included medication management). However, their ADL definitions were broader than ours, and their study included only HIV patients who were 50 years and older.²⁷

The hazard of loss of measures of physical or mental independence was higher for participants with an abnormal neurocognitive diagnosis. Specifically, participants with HAD reported the shortest time to loss of mental independence, that is, 16.5 years (adjusted HR: 4.63, 95% CI: 2.20–9.72 vs. participants with a normal neurologic diagnosis). Even less severe neurocognitive disorders (meeting criteria for mild neurocognitive disorder, or those with neurocognitive impairment not severe enough to be classified as an HIV syndromic disorder) increased the hazard of losing mental independence (adjusted HR: 2.11, 95% CI: 1.22–3.63; adjusted HR: 1.68, 95% CI: 1.02–2.79, respectively). These findings add to the current belief that neurocognitive dysfunction is related to dependence in a variety of ADLs.²⁸

This study had some limitations. Participants might have not been representative of all HIV-positive cases, since they likely represented cases at a higher risk for death who agreed to donate their organs. The presence of missing data (8%–20%) might have introduced bias if data were not missing completely at random. For example, certain deaths might have been related to severe substance misuse disorder, potentially leading to selective survival of the less severe substance misuse cases and underestimation of the HR. All substances were grouped together; however, we cannot exclude that misuse of different types of substances might have produced differential outcomes in regards to loss of physical or mental independence.

With any self-reported data, misclassification bias is a possible concern. Nonetheless, self-reports of ADL functioning are practical ways to assess participants' ability to complete physical and mental ADLs during normal daily activities. A limitation of the original ADL questionnaires was that, although they contained multiple questions related to ADLs, answers to some of those questions (e.g., making home repairs, social activities, and cooking) might have been related more to personal preferences, demographic, or socioeconomic status than independence. For this reason, we only selected variables that all independent participants would be likely to perform (managing medications, dressing, and bathing).

Lastly, we measured time to loss of independence since diagnosis. However, we only had ADL measurements since the time of enrollment. Thus, although we selected individuals who were independent at the time of enrollment, we might have overestimated the length of time between diagnosis and loss of independence (i.e., if transient loss of independence occurred between diagnosis and enrollment time). Survivor bias is also possible, because only individuals who were still independent at enrollment were included in the analyses. Strengths of this study include the multiyear cohort design and large sample size.

Conclusions

In the age of cART, with HIV-positive individuals living longer than ever before, there is an increased need to focus on their everyday functioning. Among HIV-positive partici-

pants, a history of substance use disorder increased the hazard of losing measures of physical or mental independence. Given this association, health professionals should consider additional interventions when planning health treatments and outpatient social services for HIV-positive patients.

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