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Authors

Lam, Jennifer O
Hou, Craig E
Hojilla, J Carlo
et al.

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Comparison of dementia risk after age 50 between individuals with and without HIV infection

Jennifer O. LAM, PhD, MPH[1], **Craig E. HOU, MD**[2], **J. Carlo HOJILLA, RN, PhD**[1,3], **Alexandra N. ANDERSON, MPH**[1], **Paola GILSANZ, ScD**[1], **Stacey E. ALEXEEFF, PhD**[1], **Tory LEVINE-HALL, MPH**[1], **Nicole HOOD, MPH**[1], **Catherine LEE, PhD**[1], **Derek D. SATRE, PhD**[1,3], **Michael J. SILVERBERG, PhD, MPH**[1]

[1]Division of Research, Kaiser Permanente Northern California, 2000 Broadway, Oakland, CA, 94612, USA

[2]South San Francisco Medical Center, Kaiser Permanente Northern California, 1200 El Camino Real, 4th Floor MOB, South San Francisco, CA 94080, USA

[3]Department of Psychiatry and Behavioral Sciences, Weill Institute for Neurosciences, University of California, San Francisco, 401 Parnassus Avenue, San Francisco, CA, 94143, USA

Abstract

Objective: To compare risk of dementia after age 50 by HIV status among individuals in a primary care setting.

Design: Observational cohort study; participants were identified from 2013–2017 and followed through 2019.

Methods: Participants were people with HIV (PWH) on antiretroviral therapy (ART) and demographically-similar people without HIV (PWOH), all ≥50-years-old and with no prior diagnosis of dementia. The study setting was Kaiser Permanente Northern California, an integrated healthcare delivery system in the U.S. Incident dementia diagnoses and baseline data on sociodemographics, smoking, alcohol use, other substance use, and clinical factors were gathered from the electronic health record. Cumulative proportion of incident dementia by HIV status was assessed using Kaplan-Meier curves. Unadjusted and adjusted hazard ratios (HR) for incident dementia by HIV status were generated using Cox proportional hazards models with age as the time scale.

Results: The study included 5,381 PWH and 119,022 PWOH (average age at baseline: 57 and 58 years, respectively). Incident dementia was diagnosed in 117 PWH and 2,427 PWOH. By age 80, 25.8% of PWH and 13.8% of PWOH had been diagnosed with dementia, corresponding with an unadjusted HR of 1.98 (95% CI=1.64–2.39). After adjustment for sociodemographic, substance use, and clinical factors, including frequency of outpatient visits, the risk of dementia among PWH remained elevated (vs. PWOH, adjusted HR=1.58, 95% CI=1.31–1.92).

Corresponding author: Jennifer Lam, PhD, MPH; Division of Research, Kaiser Permanente Northern California; 2000 Broadway, Oakland, CA 94612, USA; Phone: (510) 891-3438; Jennifer.O.Lam@kp.org.

Conclusions: Compared with PWOH, PWH were at 58% higher risk for dementia despite HIV treatment with ART. Research is needed to investigate the potential benefits of targeted risk factor management or earlier cognitive screening in this population.

Keywords

aging; cognitive impairment; comorbidity; dementia; HIV-associated neurocognitive disorder; substance use

BACKGROUND

The neurocognitive consequences of untreated HIV infection have been well-documented.[1] Prior to the availability of antiretroviral therapy (ART), HIV-associated dementia resulting from the effects of uncontrolled HIV infection on the brain was one of the most frequent diagnoses among people with HIV (PWH).[2–4] Typically occurring in patients with advanced HIV disease, prognosis was often poor, with a median survival of 6 months following dementia diagnosis.[2] In the context of suppressive ART, HIV-associated dementia is rare. In the U.S., the prevalence of HIV-associated dementia has declined from 15–20% pre-ART to 1–2% in the ART era,[5–8] and the incidence has dropped by 40–50%.[9, 10]

Despite the effectiveness of ART in suppressing HIV replication and reducing cognitive impairment among PWH, its protection against neurocognitive dysfunction is incomplete.[5, 8, 11] An estimated 30–50% of PWH have some degree of cognitive impairment, collectively called HIV-associated neurocognitive disorder (HAND)and ranging from asymptomatic neurocognitive impairments detectable only upon neuropsychological testing to severe cognitive deficits that impact daily functioning.[6, 7, 12–15] The reasons for persistent cognitive impairments among PWH are not entirely clear but may reflect the combined influences of chronic HIV-mediated inflammation, lasting effects of prior HIV-related disease, as well as non-HIV factors such as substance use, cardiovascular disease and psychiatric comorbidity, all of which are prevalent in HIV populations.[16] As PWH advance in age, another hypothesis is that HIV infection may lower the threshold for clinical presentation of age-associated neurodegenerative disease, resulting in neurocognitive dysfunction at younger ages.[4, 17]

Given that many PWH are now over age 50 and have near-normal life expectancy on effective ART,[18–20] a growing concern is that they will experience a disproportionate burden of dementia in later life.[16, 21, 22] Indeed, neuroimaging studies have shown persistent microstructural brain abnormalities and progressive brain atrophy in PWH despite virologic suppression,[5, 23–28] contributing to an expanding body of literature which suggests that older PWH may experience premature or accelerated cognitive decline and greater neurocognitive morbidity than their HIV-uninfected counterparts.[29, 30]

Studies on the effects of HIV and aging on neurocognitive outcomes have yielded mixed results and therefore, the risk of dementia among older PWH remains unclear.[15, 22, 30–33] Prior studies have been limited by cross-sectional design, lack of data on confounding factors for dementia, and insufficient sample size to evaluate the relatively rare outcome of

dementia. In some settings, ART uptake has been low, limiting attempts to disentangle the effects of HIV from other contributing causes of dementia. Further, the clinical relevance of asymptomatic and mild forms of HAND identified only upon specific testing has been debated, and few studies have described clinically-apparent dementia diagnosed in routine primary care.[34]

To date, dementia in older PWH has not been well-characterized outside of research settings, with one study examining dementia in U.S. veterans[35] and no prior studies comparing dementia risk among ART-treated PWH and HIV-uninfected controls in the general population. In an initial attempt to contribute in this area, we used primary care data from a healthcare system in the U.S. to describe incident dementia in a large, contemporary cohort of ART-treated PWH compared with demographically-similar PWOH.

METHODS

Study design, setting and participants

We conducted an observational cohort study of patients at Kaiser Permanente Northern California (KPNC) from July 2013 to December 2019. KPNC is an integrated healthcare delivery system serving 4.2 million individuals, including over 9,600 PWH. KPNC patients are demographically similar to the insured adult population in the underlying catchment area.[36] Most PWH within KPNC are over 50 years of age, similar to the age distribution of PWH in the State of California and in the U.S., with some regional differences.[37]

KPNC maintains an internal HIV Registry which captures all known cases of HIV infection, verified by chart review. Most PWH in KPNC are followed by HIV specialists in clinics within Departments of Adult and Family Medicine, and therefore receive both HIV and general medical care from the same providers and clinics as PWOH. In a less common model of care, PWH receive HIV care from HIV specialists within Infectious Disease clinics and their general medical care from non-HIV primary care providers.

Study participants were selected from an established cohort of KPNC patients with and without HIV who had active KPNC membership between July 2013 and December 2017 and who were frequency-matched by age, sex and race/ethnicity. Patients were eligible for this study if they were ≥50-years-old, had ≥6 prior months of continuous KPNC membership, and had no prior diagnosis of dementia. HIV-infected patients were required to be on ART, defined as having ≥1 prescription fill for ART in the past year. Participants were followed from the date of meeting all inclusion criteria until dementia diagnosis, last day of continuous KPNC membership (allowing gaps of up to 90 days), death, or end of the study on December 31, 2019. The study protocol was approved by the KPNC Institutional Review Board, with a waiver of informed consent.

Dementia diagnosis

Incident dementia diagnoses were ascertained from the electronic health record (EHR). Dementia was defined by International Classification of Diseases codes (Supplemental Table 1) from inpatient and outpatient visits. This set of codes was based on chart review of an independently sampled cohort of KPNC patients. ICD codes which resulted in <70%

positive predictive value (PPV) for dementia were excluded from the case definition, resulting in a final set of codes with comparable PPV in PWH (PPV=93%; 64/69) and PWOH (PPV=97%, 114/117; p=0.21). Data were also gathered on the type of dementia diagnosis (e.g. Alzheimer's disease, vascular dementia).

Covariates

Covariates known or hypothesized to be associated with dementia were gathered from the EHR at baseline.[16, 38, 39] These included: 1) sociodemographics, including age, sex, race/ethnicity, and Neighborhood Deprivation Index (composite variable representing neighborhood-level education, income, housing, and employment) [40]; 2) substance use-related factors, including smoking, unhealthy levels of alcohol use, and substance use disorder; and 3) clinical factors, including cardiovascular disease, diabetes, obesity, depression, hepatitis C virus (HCV) infection and healthcare utilization (number of outpatient visits in the past year). For PWH, data were collected on CD4 cell count and HIV RNA level at baseline and at time of dementia diagnosis. These covariates are defined in more detail in Supplemental Table 2.

Statistical Analyses

Dementia types were compared descriptively by HIV status. Cumulative proportion of incident dementia by HIV status was assessed using Kaplan-Meier curves, with age as the time scale, and compared using log rank tests. Hazard ratios (HR) for incident dementia by HIV status were generated using Cox proportional hazards models also with age as the time scale. To assess the contributions of covariates to risk of dementia, a series of nested adjusted models were constructed, first including sociodemographic factors only, then adding substance use-related factors, and finally adding clinical factors.

Sensitivity analyses were conducted: 1) excluding individuals with detectable HIV RNA (>200 copies/ml) at baseline, which was used as a proxy for ART non-adherence; and 2) excluding individuals with prior advanced immunodeficiency (CD4 count <200 cells/μl), which has been associated with long-term neurologic effects.[17] To assess whether accounting for the competing risk of death would qualitatively change hazard ratios, a sensitivity analysis was also conducted using Fine-Gray subdistribution proportional hazards models.[41] All sensitivity analyses adjusted for the same sociodemographic, substance use, and clinical factors included in the fully adjusted Cox proportional hazards model. As the overall goal of this study was to estimate the relative rate of dementia by HIV status among event-free individuals, Cox proportional hazards regression was chosen as the primary modeling method over Fine-Gray regression, which would have been appropriate if the goal was instead to evaluate cumulative incidence or predict prognosis. However, Fine-Gray regression was performed as a sensitivity analysis to confirm that the direction of the risk estimate did not change after accounting for deaths during follow-up. Analyses were conducted using Stata 16 (College Station, TX). A 2-tailed p-value of <0.05 was considered statistically significant.

RESULTS

The study included 5,381 PWH and 119,022 PWOH (Table 1). Participants were similar on the matching factors of age, sex, and race/ethnicity, with approximately 91% male, 65% White, 15% Black and 13% Hispanic. The average age at baseline was 57 years (standard deviation [SD]=7) in PWH and 58 years (SD=9) in PWOH. PWH were less likely to be obese, have diabetes, or report unhealthy alcohol use, and were more likely to be current smokers or have any history of depression, HCV infection or substance use disorder. All PWH included in the study were treated with ART. At baseline, an estimated 97% were virally-suppressed, 67% had CD4 ≥500 cells/μl, and 40% had a history of advanced immunodeficiency (CD4 <200 cells/μl).

During follow-up (mean 4.7 years), 117 (2.2%) PWH and 2,427 (2.0%) PWOH were diagnosed with dementia, 1,300 (24.2%) PWH and 31,499 (26.5%) PWOH ended their KPNC membership or had a ≥90-day gap in membership, and 262 (4.9%) PWH and 4,586 (3.9%) of PWOH died. At the end of follow-up, 3,702 (68.8%) PWH and 80,510 (67.6%) PWOH were still alive and without a diagnosis of dementia.

The average age at dementia diagnosis was 67 years in PWH (SD=9) and 78 years (SD=11) in PWOH. Of the 96 (out of 117) PWH with an HIV RNA measurement at dementia diagnosis, 87 (91%) had HIV RNA <200 copies/ml. Diagnoses of unspecified dementia were the most common in both people with and without HIV (50% of 139 total dementia diagnoses among 117 PWH; 47% of 3,085 total dementia diagnoses among 2,427 PWOH), followed by diagnoses of other specified dementias (24% in PWH and 22% in PWOH) and vascular dementia (22% in PWH and 18% in PWOH; Table 2). Overall, 14/117 (12%) PWH and 476/2,427 (20%) PWOH were diagnosed with multiple dementia types on the date of incident dementia diagnosis.

The cumulative proportion of individuals diagnosed with dementia by age 80 was 25.8% (95% CI=19.9–33.0) in PWH and 13.8% (95% CI=13.0–14.7) in PWOH (log rank p<0.001, Figure 1). In Cox models, risk of dementia was greater in PWH (vs. PWOH, unadjusted HR= 1.98, 95% CI=1.64–2.39; Table 3). In a series of nested Cox models, risk was attenuated slightly when adjusting for substance use, cardiovascular disease, diabetes and obesity (<10% decrease per covariate). Adjusting for depression resulted in a 19% decrease in risk (Table 3). Models did not adjust for HCV infection because there were few cases of dementia (n=3) among HCV/HIV-coinfected individuals. In fully adjusted models accounting for sociodemographic, substance use, and clinical factors, risk of dementia remained significantly higher among PWH (vs. PWOH, adjusted HR=1.58, 95% CI=1.31–1.92).

In a sensitivity analysis excluding PWH with detectable viral load at baseline, the adjusted HR was 1.50 (95% CI=1.23–1.83), similar to the fully adjusted final model (1.58, 95% CI=1.31–1.92). After excluding PWH with prior advanced immunodeficiency, the adjusted HR was greater (1.77; 95% CI=1.37–2.29) but was not significantly different than the fully adjusted final model (1.58, 95% CI=1.31–1.92). After accounting for deaths during follow-

up, risk of dementia remained higher among PWH (adjusted subdistribution HR=1.40, 95% CI=1.15–1.71).

DISCUSSION

Worldwide, there are 4.2 million individuals aged 50 years and older who are living with HIV, and this is the most rapidly growing segment of the HIV population in the U.S.[19, 20] Age-associated dementia is becoming an increasingly prominent concern for PWH and their healthcare providers. This study contributes evidence that older PWH are at significantly elevated risk for dementia despite receiving ART.

The finding that dementia was diagnosed on average 10 years earlier among PWH (67 years vs. 78 years at diagnosis) is consistent with other studies which report premature aging in PWH, characterized by both younger age at diagnosis and rapid accrual of aging-related conditions.[16, 42, 43] In this study, overall dementia risk in PWH was partially explained by cardiovascular disease, obesity, diabetes and depression, all of which are more common in HIV populations[42, 44] and which can adversely affect cognitive health.[38] As HIV primary care evolves to include management of multiple chronic conditions,[42, 44, 45] improved clarity is needed on how the severity and treatment of these comorbidities may influence dementia risk. Screening for treatable causes of cognitive impairment among PWH may also offer the potential for early intervention to reduce risk of developing dementia.

Notably, PWH remained at 58% increased risk for dementia even after accounting for medical and psychiatric comorbidities and other dementia risk factors and at 40% increased risk for dementia after additionally accounting for the competing risk of death. This residual elevated risk may be due to non-modifiable factors such as HIV-mediated inflammation, HIV acquisition in the pre-ART era, brain injury from previously untreated HIV infection, or paradoxically, the neurotoxic effects of ART.[8, 16, 46] While we hypothesized that prior advanced immunodeficiency would explain some of the elevated dementia risk among PWH, our sensitivity analysis which excluded previously immunodeficient PWH resulted in a moderately enhanced estimate of dementia risk (adjusted HR=1.77) compared with the original analysis (adjusted HR=1.58). This may be explained by the fact that PWH with more severe HIV disease were more likely to seek care and initiate ART. It may also reflect our capture of a ‘survival cohort’, where individuals with more advanced HIV who successfully regain immunocompetence have a distinct neurocognitive risk profile compared with those who did not survive. Our results suggest that in addition to risk factor management, HIV patients in the current ART era could benefit from close monitoring of cognitive function regardless of HIV disease history.

While ART use remains the cornerstone of maintaining cognitive health in PWH,[47] we observed elevated dementia risk even among ART-treated individuals, including those who successfully achieved virologic suppression. The relationship between HIV control and dementia is likely bidirectional; uncontrolled HIV can result in dementia, but memory loss may also compromise adherence to ART.[48] This is illustrated in our population where an estimated 10% of PWH had detectable HIV RNA at dementia diagnosis. Early recognition of cognitive impairment in HIV patients is therefore critical, especially since poor ART

adherence has been linked to poor overall health outcomes and increased all-cause mortality.[49] Implementing novel strategies to help patients maintain long-term adherence to ART in the context of competing health concerns would be an important component of geriatric HIV care, especially as HIV care models increasingly involve ‘task-sharing’ or ‘task-shifting’ of HIV management across medical disciplines.[44]

Overall, the findings from this study contribute to the understanding of dementia in a primary care-based population of PWH, extending the rich literature in this area generated from observational research cohorts. Several key differences in this study compared with previous studies should be noted. First, examinations of cognition among PWH in research settings have largely focused on HAND, which includes not only HIV-associated dementia but also asymptomatic neurocognitive impairment and mild neurocognitive disorder, defined according to the Frascati consensus research criteria for diagnosing and categorizing HAND.[50] In contrast, our estimates are based on symptomatic dementia identifiable in a primary care setting and excludes mild cognitive impairment. Additionally, we provide some of the first descriptive data on the frequencies of age-associated dementias among PWH at incident dementia diagnosis. Second, HAND criteria do not completely align with guidelines for diagnosis of age-associated dementias in the general population. At present, there are no widely used dementia diagnostic guidelines specifically for PWH in clinical settings.[51] However, it is recognized that the clinical presentation of dementia in PWH can be varied and that there is increasing overlap of HIV-related and aging-related cognitive deficits, resulting in the emergence of dementias of increasingly complex and mixed etiology.[17, 52, 53] While our study makes use of robust EHR data to describe dementia in a recent cohort of PWH, methods to more precisely distinguish dementia subtypes among PWH in clinical practice is still an emerging field of research.[51, 54] Third, the detection of dementia in clinical practice can be less sensitive than the structured interviews, neuropsychological testing, and functional assessments conducted in research settings. Therefore, estimated proportions of individuals with dementia are likely conservative due to potential under-recognition of dementia by patients and providers. Also, the detection of dementia in clinical practice is subject to inherent variability across providers in clinical judgment and patient evaluation. We cannot rule out the possibility that providers may be more attuned to cognitive complaints in patients with HIV, resulting in higher rates of dementia diagnosis in this group. However, we did not find substantial differences in ICD coding patterns by HIV status and chart review confirmed comparable PPV of ICD codes across groups.

This is the first study sufficiently powered to compare risk of dementia in ART-treated PWH and PWOH in the general population. A major advantage was the availability of data on ART prescriptions and HIV RNA levels, which enabled evaluation of dementia in PWH receiving ART and with otherwise stable HIV disease. Our findings build on those of a recently published study by Bobrow and colleagues investigating risk of dementia among 2,228 primarily male U.S. veterans with and without HIV.[35] The study reported 57 cases of incident dementia in veterans with HIV and 33 cases in those without HIV. Despite their smaller sample size and use of a narrower case definition for dementia, findings were consistent with our study in that PWH were more likely to be diagnosed with dementia (adjusted HR=1.50, 95% CI=0.96–2.35) even after accounting for demographics, substance use, education, income, and the competing risk of death. An important difference is that all

PWH in our study were ART-treated whereas only 61% of PWH in the Veteran's cohort were ART-treated. This difference may explain their finding that 19% of PWH had a diagnosis of HIV-associated dementia during follow-up. It is notable that despite these differences in study population and design, we found a remarkably similar overall elevated risk of dementia among older PWH after accounting for confounding causes of dementia. These results contrast with a cohort study conducted in Taiwan by Yang and colleagues which evaluated whether HIV infection was associated with risk of developing dementia in 1,261 PWH and 3,783 age- and sex-matched controls.[55] The authors concluded that PWH were not at increased risk for dementia (adjusted HR=0.85, 95% CI=0.19–2.89). However, due to small sample size and only 1 ART-treated PWH developing dementia during follow-up, interpretation of results from the Taiwan study, and comparison to our study and the Veteran's study, are limited.

This study had several limitations. First, due to the short study period, we were unable to assess how patterns of ART use and HIV RNA control over time may have affected dementia risk. However, the majority (97%) of PWH with a recent HIV RNA measurement at baseline had undetectable HIV viral load and all PWH had at least 1 ART prescription fill in the past year indicating that this was a cohort with well-treated HIV disease. Therefore, our findings would be highly relevant to PWH in the current ART era who have access to care. Second, study participants were mostly male (91%), which could limit generalizability. However, our HIV population was representative of the HIV population in California that would most likely be seen in clinical practice.[37] Third, analyses were based on data collected for clinical rather than research purposes. Therefore, individual-level data on educational attainment and lifestyle factors (e.g., diet, exercise) were not available. Fourth, it is possible that some mild or moderate cases of HAND were misclassified as dementia and ICD-coded as 'Dementia in conditions classified elsewhere' (as defined by Bobrow and colleagues in the Veteran's study).[35] However, this diagnosis was relatively rare (6 out of 117, or 5%, of dementia diagnoses in PWH) and thus is unlikely to have significantly altered our results. Fifth, due to the relatively small number of total dementia cases among PWH (n=117), we did not evaluate risk of dementia stratified by subtype. Lastly, without neuroimaging, cerebrospinal fluid and other biomarker data, we could not evaluate potential differences in the underlying causes of dementia by HIV status. However, we capture clinically relevant dementia which would be important regardless of pathophysiology, and thus, our conclusions regarding risk factor management and cognitive screening among PWH would still apply.

This study had several unique strengths. First, the study was conducted in an integrated healthcare delivery system providing comprehensive medical care to a large and well-characterized HIV population with consistent longitudinal follow-up. Second, we had a well-matched comparator HIV-uninfected population from the same healthcare setting and with a similar model of care. Third, the breadth of data available in the EHR enabled adjustment for multiple individual-level dementia-related comorbidities. And lastly, the dementia case definition was verified via chart review and the study was restricted to a recent time period minimizing cohort effects due to variation in ART management or dementia diagnostic and coding practices over time.

CONCLUSION

Despite effective ART, PWH are at elevated risk for developing dementia in older age and are diagnosed with dementia on average 10 years earlier than demographically-similar PWOH. Younger age at dementia onset among PWH could result in substantial health burden, diminishing the benefits of improved longevity achieved with HIV treatment. Additional research on risk factors for dementia among people with treated HIV may help identify strategies and priority targets for dementia prevention beyond ART use alone.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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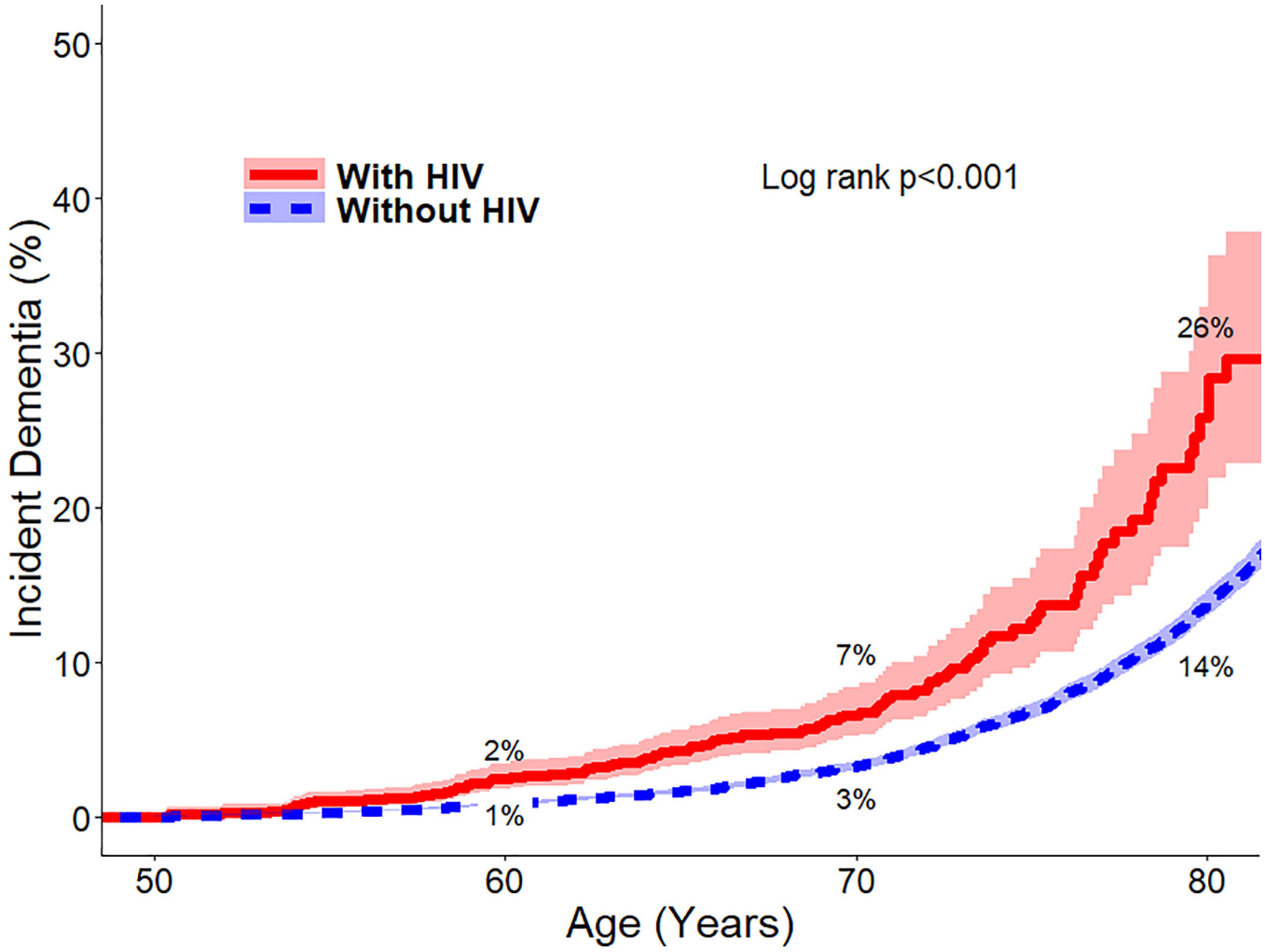

Figure 1. Cumulative proportion of incident dementia diagnoses by HIV status.

The percentages of individuals diagnosed with incident dementia were obtained from Kaplan-Meier curves, with age as the time scale, and are displayed with a solid red line for people with HIV and a dashed blue line for people without HIV, both with 95% confidence bands. The difference between the curves was assessed using the log rank test. Numbers adjacent to the curves are the percentages of individuals diagnosed with dementia at ages 60, 70 and 80 years.

Table 1.

Baseline characteristics of study participants, by HIV status

Characteristic[a]	With HIV N=5,381 n (%)	Without HIV N=119,022 n (%)
Age (years)		
50–59	3,916 (72.8)	86,120 (72.4)
60–69	1,225 (22.8)	19,925 (16.7)
70–79	211 (3.9)	8,962 (7.5)
≥80	29 (0.5)	4,015 (3.4)
Male	4,936 (91.7)	108,250 (90.9)
Race/Ethnicity		
White, non-Hispanic	3,387 (65.6)	74,312 (64.8)
Black, non-Hispanic	778 (15.1)	18,307 (16.0)
Hispanic	690 (13.4)	15,030 (13.1)
Other	310 (6.0)	7,099 (6.2)
Neighborhood Deprivation Index[b]		
Quartile 1 (highest SES)	1,623 (30.2)	29,360 (24.7)
Quartile 2	1,105 (20.5)	29,962 (25.2)
Quartile 3	1,274 (23.7)	30,126 (25.3)
Quartile 4 (lowest SES)	1,379 (25.6)	29,574 (24.8)
Smoking status		
Never	1,697 (40.2)	36,838 (50.1)
Former	1,808 (42.8)	27,256 (37.0)
Current	722 (17.1)	9,491 (12.9)
Unhealthy alcohol use[c]	244 (7.8)	8,046 (12.2)
Substance use disorder	2,069 (38.5)	29,598 (24.9)
Cardiovascular disease	730 (13.6)	15,617 (13.1)
Diabetes	765 (14.2)	18,540 (15.6)
Obesity[d]	986 (18.8)	40,478 (39.8)
Depression	2,176 (40.4)	16,917 (14.2)
Hepatitis C virus infection[e]	202 (3.8)	1,345 (1.1)
Mean number of outpatient visits in prior year (SD)	16.7 (21.6)	8.5 (14.0)
CD4 count (cells/μl)[f]		
≥500	2,964 (67.3)	-
200–499	1,274 (28.9)	
<200	164 (3.7)	
Prior advanced immunodeficiency[g]	2,121 (39.7)	-
HIV suppression[h]	4,300 (96.9)	-
Mean duration of HIV infection in years (SD)	17.1 (7.9)	-

Abbreviations: SD=standard deviation; SES=socioeconomic status; PWH=people with HIV; PWOH=people without HIV

[a] Data were missing for some characteristics: race/ethnicity (4.0% of PWH, 3.6% of PWOH), smoking status (21.4% of PWH, 38.2% of PWOH), unhealthy alcohol use (41.9% of PWH, 44.3% of PWOH), obesity (2.2% of PWH, 14.4% of PWOH), CD4 count (18.2%) and HIV RNA (17.6%). For each characteristic, percentages of the total with non-missing data are shown.

[b] Neighborhood Deprivation Index: Composite variable representing neighborhood-level education, income, housing, employment, and occupation; proxy for socioeconomic status.

[c] Unhealthy alcohol use was defined as follows: For women of any age and men ≥65-years-old, having ≥4 drinks in a day at least once in the past 90 days or ≥8 drinks per week on average; for men <65-years-old, ≥5 drinks in a day at least once in the past 90 days or ≥15 drinks per week on average.

[d] Body mass index ≥30 kg/m^2.

[e] Any prior positive HCV antibody or HCV RNA test.

[f] Most recent CD4 measurement.

[g] Ever CD4 count <200 cells/μl.

[h] <200 copies/ml of HIV RNA; based on most recent HIV RNA measurement.

Table 2.

Dementia types identified at incident dementia diagnosis in people with HIV (N=117) and without HIV (N=2,427)[a]

Dementia type	With HIV n (%)	Without HIV n (%)
Alzheimer's disease	4 (2.9)	328 (10.6)
Vascular dementia	30 (21.6)	553 (17.9)
Parkinson's dementia	0 (0.0)	62 (2.0)
Dementia with Lewy bodies	3 (2.2)	27 (0.9)
Frontotemporal dementia	0 (0.0)	10 (0.3)
Other specified dementia[b]	33 (23.7)	664 (21.5)
Unspecified dementia	69 (49.6)	1,441 (46.7)

[a]14 (12.0%) people with HIV and 476 (19.6%) people without HIV were diagnosed with multiple dementia types on the date of incident dementia diagnosis.

[b]Includes diagnoses of amnestic disorder, cerebral degeneration, idiopathic normal pressure hydrocephalus, neurologic neglect syndrome, and dementia and other persistent mental disorders due to other known conditions. There were no cases of Creutzfeldt–Jakob disease identified. See Supplemental Table 1 for detailed list of definitions and ICD codes.

Table 3.

Risk of incident dementia in people with HIV (N=5,381) estimated using a series of nested Cox proportional hazards models

Adjusted for:[a]	**Adjusted Hazard Ratio (95% CI) Reference: People without HIV (N=119,022)**
Age (as time scale)	1.98 (1.64–2.39)
Plus other sociodemographics[b]	2.00 (1.66–2.42)
Plus substance use[c]	1.91 (1.58–2.30)
Plus cardiovascular disease	1.89 (1.56–2.28)
Plus diabetes and obesity	1.84 (1.52–2.22)
Plus depression	1.65 (1.37–2.01)
Plus outpatient visit frequency	1.58 (1.31–1.92)

Abbreviations: CI=confidence interval

[a] Covariates included in models were collected at baseline. See Supplemental Table 2 for covariate definitions.

[b] Sex, race/ethnicity, and Neighborhood Deprivation Index (ie. composite variable representing neighborhood-level education, income, housing, employment, and occupation; proxy for socioeconomic status).

[c] Smoking, unhealthy alcohol use, and substance use disorder.