

Increased Prevalence of Neurocognitive Impairment in Aging People Living With Human Immunodeficiency Virus: The ANRS EP58 HAND 55–70 Study

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Background. There are limited data on the comparative prevalence of neurocognitive impairment (NCI) in aging people living with human immunodeficiency virus (PLHIV) and people not living with HIV.

Methods. This was a cross-sectional study of PLHIV randomly matched by age (± 4 years), gender, and education with 5 HIV-uninfected individuals from the CONSTANCES cohort. PLHIV were fluent in French and sequentially included during routine outpatient visits if aged 55–70 years, with HIV viral load < 50 copies/mL, and lymphocyte T-CD4 level ≥ 200 cells/ μ L in the past 24 and 12 months, respectively. The primary outcome was NCI as defined by the Frascati criteria. Multivariate normative comparison (MNC) and -1.5 standard deviations in ≥ 2 neurocognitive domains were secondary outcomes of NCI.

Results. Two hundred PLHIV were matched with 1000 controls. Median age was 62 years, and 85% were men. In PLHIV, the median T-CD4 lymphocyte level was 650 cells/ μ L, and median nadir T-CD4 lymphocyte level was 176 cells/ μ L. NCI was found in 71 (35.5%) PLHIV and in 242 (24.2%) controls (odds ratio [OR], 1.74; 95% confidence interval [CI], 1.25, 2.41). After adjusting for confounders, HIV remained significantly associated with NCI (OR, 1.50; 95% CI, 1.04, 2.16). Adjusted results were similar with NCI defined by MNC (OR_{MNC}, 2.95; 95% CI, 1.13, 3.50) or -1.5 SD (OR_{-1.5}, 2.24; 95% CI, 1.39, 3.62).

Conclusions. In this matched study of aging individuals, HIV was significantly associated with an increased risk of NCI after adjusting for major confounders. Results were confirmed with more stringent NCI classifications.

Clinical Trials Registration. NCT02592174.

Keywords. HIV; neurocognitive impairment; aging; Frascati criteria; HAND.

Since the advent of combined antiretroviral therapy (cART), the life expectancy for people living with human immunodeficiency virus (PLHIV) has substantially increased in resource-rich settings [1, 2]. Causes of morbidity and mortality have shifted from AIDS to non-AIDS-defining diseases [3, 4], and studies have found high proportions of neurocognitive impairment (NCI) in PLHIV, ranging from 19% to 67% [5–10]. NCI prevalence has varied widely in studies due to differing demographic characteristics and comorbidity burdens of study individuals, as well

as the neurocognitive tests and classifications that were used. In PLHIV taking cART with controlled HIV viremia, the prevalence of NCI has been lower, albeit still substantial, ranging from 19% to 30% [5–7]. The incidence of NCI is expected to rise in PLHIV as the population ages [11]. There are, however, limited data on NCI prevalence or incidence in older PLHIV [5–10].

NCI prevalence may be higher in PLHIV compared to the general population. This could solely reflect the increased prevalence of NCI-associated risk factors in this population [12–17], such as cardiovascular disease or depression. Additionally, HIV infection may also be an additional risk factor and potentially the primary contributor of NCI in PLHIV [18], as studies have shown an association between NCI and HIV-related factors such as detectable viral load [6], current CD4 levels [19], nadir CD4 levels [6, 20], and history of AIDS [21]. However, clinical studies have found contradictory results. In the CIPHER study, there was no significant difference in severity or prevalence of NCI in 248 PLHIV and 45 men who have sex with men (MSM) not

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living with HIV [22]. In the MACS cohort, there was no association between HIV and NCI in 428 PLHIV and 207 MSM not living with HIV after adjusting for education, depression, and race [23]. The COBRA cohort showed, however, baseline poorer global cognitive performances in 134 virologically controlled PLHIV and 79 demographically similar controls not living with HIV, but the association with HIV was not addressed [24].

Further studies to evaluate the prevalence of NCI in aging PLHIV are thus needed, as well as studies to assess the association between HIV and NCI. In our study, we compared the prevalence of NCI in PLHIV aged 55 to 70 years with controlled viral load with an age, gender, and education matched control population of people not living with HIV, adjusting for a wide variety of confounding factors including behavioral and social factors.

METHODS

Study Design and Populations

The France REcherche Nord&Sud Sida-hiv Hépatites (ANRS) étude physiopathologique (EP) 58 HIV-associated neurocognitive disorder (HAND) 55–70 study was a cross-sectional study that compared the prevalence of NCI in a population of PLHIV matched by age (± 4 years), gender, and education level with controls from the general population.

To limit selection bias, PLHIV were systematically and sequentially recruited by their HIV care provider during a routine clinical outpatient visit at 6 French hospitals if all of the following conditions were met: age between 55 and 70 years, living with HIV-1, HIV viral load < 50 copies/mL in the past 24 months, a T-CD4 lymphocyte level ≥ 200 cells/ μ L in the past 12 months, a signed informed consent, and having health insurance. A maximum of 2 viremic blips, defined by a transient elevation of viral load ≥ 200 copies/mL, was allowed. Individuals were excluded if they were confused, illiterate, or nonfluent in French; had an ongoing or past history of brain disease with clinical sequelae; had major psychiatric syndromes, sensorial loss, or an extensive neurocognitive evaluation in the prior 6 months; or were vulnerable (under tutorship, guardianship, or imprisoned). The study prespecified that a third of all individuals should be included in each of the following age ranges: 55–59 years, 60–64 years, and 65–70 years.

The matched individuals not living with HIV from the CONSTANCES cohort were recruited from 17 social security health screening centers. These individuals had identical inclusion and exclusion criteria as the PLHIV participants, except for the immunovirological criteria. The CONSTANCES cohort, which included 200 000 individuals in February 2019, is a large, randomly selected cohort of the French population of salaried workers (professionally active or retired) and their families, aged 18–69 years at inception [25]. In this cohort, all individuals aged ≥ 45 years undergo extensive neurocognitive assessment.

Cognitive, Functional Evaluations and Endpoints

After a centralized CONSTANCES training program, neuropsychologists performed standardized evaluations of functional and neurocognitive capacities and used identical electronic case report forms in both populations [26, 27]. Cognitive functions and functional evaluations were assessed using the trail making test (TMT) A–B for executive function, the digit symbol substitution task of the Wechsler Adult Intelligence Scale-IV (WAIS-IV) for speed of information processing, the digital finger tapping test for motor skills, word fluency and formal lexical and semantic evocation for language, and the free and cued selective reminding test for episodic memory. Functional capacities were evaluated with 4 items of the instrumental activities of daily living (IADL) scale. For our study, we used the baseline neurocognitive assessments.

Norms (mean and standard deviation [SD]) for each test were determined per age strata (55–59, 60–64, and 65 to 70 years) and gender using neurocognitive scores from the CONSTANCES cohort ($n = 18\,740$) and were used to calculate age and gender z scores. Impaired functional capacities were defined as mild if 1 item or severe if 2 or more items from the 4-item IADL scale showed reduced capacity. The primary endpoint was the presence of NCI according to the Frascati criteria, used to define HAND in PLHIV [18] (see [Supplementary Materials](#) for further details). The Frascati criteria were used solely to compare NCI in both populations and not to attribute NCI to HIV infection, as the controls were not living with HIV.

Frascati criteria with a threshold of less than -1.5 SD from the norm and multivariate normative comparison (MNC) [28] in 2 or more neurocognitive domains were secondary outcomes used to potentially lower the false-positive rates of the Frascati criteria [29]. MNC is able to control the family-wise error (the probability of falsely diagnosing individuals as cognitively abnormal) by making a single multivariate comparison of the complete cognitive profile of an individual with the distribution of all the cognitive profiles of the control sample.

Covariates

Investigators recorded characteristics of both populations using similar self-administered or investigator-led questionnaires, including hypercholesterolemia, diabetes, hypertension, the Center for Epidemiologic Studies–Depression (CES-D) scale for depressive symptomatology (cutoff ≥ 17) [30], smoking status, alcohol consumption, physical activity, immunovirological characteristics (HIV viral load, T-CD4, and T-CD8 lymphocyte measures), and history of AIDS-defining diseases. Definitions of each covariate are listed in the [Supplementary Materials](#).

Statistical Analyses

We used multiple imputation by chained equations [31] to impute 2.8% of the data (ie, missing values) that otherwise would

have led to exclusion of 24% of the individuals. Missing values in outcome variables were not imputed.

First, we described and compared the main characteristics of PLHIV and people not living with HIV using univariable conditional logistic regression and the associated Wald test to take into account the matched design. We then assessed the association between NCI and covariates using mixed univariable logistic regression (with the Wald test), including matching classes as a random effect to account for the intraclass correlation. In this analysis, we tested the effects of sociodemographic (age, gender, education, and living alone), health and behavioral (hypercholesterolemia, diabetes, cardiovascular disease, hypertension, smoking, alcohol consumption, cannabis consumption, and physical activity), and depression variables. We assessed the adjusted association between HAND and covariates using mixed multivariable logistic regression in 2 models. The first included HIV and the variables used for matching nonexposed individuals from the CONSTANCES cohort (age, gender, and education level). The second model added potential confounding factors with a univariable P value <0.20 . The first 2 univariable analyses were performed on the crude dataset. Multivariable models were then fitted on 20 imputed datasets, and results were pooled by simulations. For each fit, 500 parameter values were drawn randomly from the posterior distribution ($500 \times 20 = 10\,000$ values), and mean parameters with 95% confidence intervals (CIs) were computed. We tested association between HIV and NCI with a variant of the likelihood ratio test for multiple imputed datasets.

The same multivariable approach was used for the -1.5 SD cutoff and the MNC secondary outcomes. A sensitivity analysis used the primary outcome with the same factors in multivariable analysis but excluded individuals with 1 or more missing variables. We also tested for an interaction between age and HIV on NCI, as defined by the 3 possible outcomes.

Our sample size calculation was based on a prior NCI evaluation of 2000 volunteers not living with HIV with the same neurocognitive tests in the GAZEL cohort [32]. Using the Frascati criteria [18], the prevalence of NCI in individuals aged 55–70 years in GAZEL was 17%. We assumed a 27% prevalence of NCI in matched PLHIV under cART with controlled viral load. We initially estimated that 194 PLHIV and 387 controls should be included for an estimated odds ratio (OR) of NCI of 1.8 in PLHIV with a type 1 error of 5% and 80% power. However, to further increase statistical power, we randomly matched 1 PLHIV to 5 controls from the CONSTANCES cohort according to gender, age, and 3 education levels, as numbers of controls accrued were sufficient.

Ethics

Written informed consent was obtained from each patient before enrollment. The protocol was performed in accordance with the Declaration of Helsinki and French law for biomedical

research and was approved by the CPP Sud méditerranée I Ethics Committee (Marseille, France). Authorizations for the CONSTANCES cohort were obtained from the ethical review board (IRB INSERM 01-011) and the French Data Protection Authority (CNIL 910486).

RESULTS

In total, 209 PLHIV were included in the study between 26 January 2016 and 27 October 2017. Nine individuals were excluded from analysis—5 did not meet inclusion criteria: 1 had a T-CD4 lymphocyte count of 105 cells/mL; 1 had a viral load of 1600 copies/mL; 1 had important visual sequel of cytomegalovirus retinitis; 1 declared himself autistic, impeding neurocognitive testing; and 1 was administered the wrong tests. Four other individuals did not complete neurocognitive tests or the self-administered questionnaire.

Two hundred PLHIV were randomly matched by age (± 4 years), gender, and education level with 1000 individuals from the CONSTANCES cohort. Their characteristics are listed in [Table 1](#). PLHIV significantly differed from the general population as they were less often from mainland France, were more frequently active smokers and cannabis consumers, had increased rates of cardiovascular and chronic kidney disease, had depressive symptomatology (CES-D ≥ 17), were less physically active, more often lived alone, and were more often MSM. Hypercholesterolemia and diabetes were similarly distributed in both populations.

We classified NCI in 71 PLHIV (35.5%) and in 242 controls (24.2%) (OR, 1.74; 95% CI, 1.25–2.41). Distributions of NCI according to the Frascati criteria in both populations are shown in [Table 2](#). Most impaired individuals were asymptomatic neurocognitively impaired (ANI). Only 3 individuals (0.30%) from the CONSTANCES cohort and 1 PLHIV (0.05%) were classified as having HIV-associated dementia. Neurocognitive tests significantly differed between groups in the TMT-A, TMT-B, and WAIS-IV ([Supplementary Figure 1](#)).

A total of 292 individuals (24%) had 1 or more missing values; 254 (25%) in the CONSTANCES cohort and 38 (19%) in PLHIV. Odds of having missing data were reduced in PLHIV (OR, 0.68; 95% CI, .46–1.00). Other missing variables associated with HIV status are described in the [Supplementary Materials](#).

Adjusting for the matching variables only in model 1, HIV was associated with NCI (OR, 1.74; 95% CI, 1.26–2.41). Further adjusting for confounders, that is, physical activity, diabetes, hypertension, cardiovascular disease, smoking status, CES-D ≥ 17 , alcohol consumption, and living alone, HIV remained significantly associated with NCI (OR, 1.5; 95% CI, 1.04–2.16). A sensitivity analysis that excluded individuals with 1 or more missing variables from the models did not substantially change our findings as HIV remained associated with NCI in the final model (OR, 1.84; 95% CI, 1.24–2.70; [Table 3](#)).

Table 1. Main Characteristics of People Living With Human Immunodeficiency Virus (HIV) and People Not Living With HIV

| Characteristic | People Not Living With HIV (CONSTANCES cohort) (n = 1000) | People Living With HIV (n = 200) | P Value ^a |
|---|--|----------------------------------|----------------------|
| Age median (min, max), y | 62 (55–70) | 62.7 (55.1–71) | ... |
| 55–59 | 340 (34.0) | 68 (34.0) | ... |
| 60–64 | 325 (32.5) | 65 (32.5) | ... |
| 65–70 | 335 (33.5) | 67 (33.5) | ... |
| Male gender (%) | 850 (85.0) | 170 (85.0) | ... |
| Education level (%) | | | |
| Primary (<6 years) | 175 (17.5) | 35 (17.5) | ... |
| Secondary (6–12 years) | 435 (43.5) | 87 (43.5) | ... |
| Superior (>12 years) | 390 (39.0) | 78 (39.0) | ... |
| Geographic origin (%) ^b | | | |
| Mainland France (%) | 885 (88.5) | 128 (64.0) | ... |
| Other European country (%) | 45 (4.5) | 42 (21.0) | ... |
| North Africa (%) | 42 (4.2) | 20 (10.0) | ... |
| Sub-Saharan Africa (%) | 4 (0.4) | 4 (2.0) | ... |
| Other (%) | 20 (2.0) | 6 (3.0) | ... |
| Men who have sex with men (%) | 28 (3.8) | 96 (61.5) | <.0001 |
| Center for Epidemiologic Studies–Depression ≥17 (%) | 146 (16.3) | 62 (32.3) | <.0001 |
| Hypercholesterolemia (%) | 480 (49.0) | 95 (48.2) | .84 |
| Diabetes (%) | 103 (10.6) | 29 (14.8) | .09 |
| Cardiovascular disease ^c (%) | 71 (7.2) | 40 (20.2) | <.0001 |
| Hypertension (%) | 563 (57.0) | 127 (65.5) | .03 |
| Chronic kidney disease (%) | 26 (2.6) | 21 (10.5) | <.0001 |
| Lives alone (%) | 87 (8.9) | 73 (36.5) | <.0001 |
| Smoking | | | <.0001 |
| Never (%) | 363 (38.9) | 61 (31.9) | ... |
| Past (%) | 467 (50.0) | 78 (40.8) | ... |
| Active (%) | 104 (11.1) | 52 (27.2) | ... |
| Cannabis consumption | | | <.0001 |
| Never (%) | 793 (87.3) | 122 (62.9) | ... |
| Yes but not during the last year (%) | 102 (11.2) | 43 (22.2) | ... |
| Yes during the last year (%) | 13 (1.4) | 29 (14.9) | ... |
| Alcohol consumption | | | <.0001 |
| Abstinent (%) | 55 (5.9) | 37 (19.2) | ... |
| Moderate (%) | 726 (77.8) | 100 (51.8) | ... |
| Harmful (%) | 152 (16.3) | 56 (29.0) | ... |
| Physical activity | | | .09 |
| None (%) | 234 (25.2) | 52 (27.1) | ... |
| Moderate (%) | 361 (38.9) | 87 (45.3) | ... |
| Intensive (%) | 332 (35.8) | 53 (27.6) | ... |
| HIV-related characteristics | | | |
| Years since HIV diagnosis, median (IQR) | NA | 21 (15–27) | ... |
| T-CD4 lymphocyte levels, median (IQR), cells/μL | NA | 653 (488–790) | ... |
| T-CD4/CD8 lymphocyte ratio, median (IQR) | NA | 0.82 (0.59–1.22) | ... |
| T-CD4 lymphocyte nadir, median (IQR), cells/μL | NA | 176 (82–260) | ... |
| History of AIDS-defining events ^d (%) | NA | 48 (24) | ... |
| History of hepatitis C virus infection (%) | NA | 33 (17) | ... |

Abbreviations: CONSTANCES, Cohorte des consultants des Centres d'examen de santé; HIV, human immunodeficiency virus; IQR, interquartile range; NA, not available.

^aConditional logistic regression Wald test.

^bFour individuals did not answer in the People Not Living With HIV group.

^cCardiovascular disease was defined as any of chronic stable angina, myocardial infarction, peripheral vascular disease, stroke, or lower limb arteritis.

^dOf the AIDS diseases, 5 were brain toxoplasmosis, and 1 was HIV encephalopathy.

Using the -1.5 SD from the norm cutoff classification, these numbers were 40 (20.0%) and 93 (9.3%) (unadjusted OR [OR_{1.5}], 2.47; 95% CI, 1.64–3.73). Using the MNC criteria, 27 (14.6%) PLHIV and 60 (6.6%) controls were impaired (unadjusted OR for

MNC [OR_{MNC}], 2.45; 95% CI, 1.51–3.99). In both multivariable analyses, HIV remained associated with cognitive impairment whether defined by -1.5 SD (OR_{1.5}, 2.24; 95% CI, 1.39–3.62) or MNC (OR_{MNC}, 2.00; 95% CI, 1.13–3.50; [Table 3](#)).

Table 2. Neurocognitive Impairment According to the Primary and Secondary Outcomes, With Details on Categories of Impairment According to People Living With Human Immunodeficiency Virus (HIV) and People Not With HIV

| Variable | People Living Without HIV (CONSTANCES cohort) (n, %) n = 1000 | People Living With HIV (n, %) n = 200 |
|--|---|---------------------------------------|
| Frascati criteria | | |
| NCI | 242 (24.2) | 71 (35.5) |
| Asymptomatic neurocognitively impaired | 192 (19.2) | 49 (24.5) |
| Mild neurocognitive disorder | 47 (4.7) | 21 (10.5) |
| HIV-associated dementia | 3 (0.3) | 1 (0.5) |
| | –1.5 standard deviation of the norm cutoff classification | |
| NCI | 93 (9.3%) | 40 (20%) |
| Multivariate Normative Comparison^a | | |
| NCI | 60 (6.4%) | 27 (14.6%) |

Term “HIV-associated dementia” used despite the fact that individuals from CONSTANCES were not living with HIV, as defined in the Frascati criteria.

Abbreviations: CONSTANCES, Cohorte des consultants des Centres d'examens de santé; HIV, human immunodeficiency virus; NCI, neurocognitive impairment.

^aFor the multivariate normative comparison (MNC) classification, 935 individuals from CONSTANCES and 200 people living with HIV were analyzed, as the MNC classification needs the fulfillment of all tests for single multivariate comparison of the complete cognitive profile of an individual.

Based on the *z* score, prevalence of NCI using the Frascati criteria, –1.5 SD classification, and MCI classifications according to age strata and HIV exposure groups are shown in [Figure 1](#). No interaction between age and HIV status was objectified with any neurocognitive outcome ([Table 4](#)).

DISCUSSION

Using identical neurocognitive assessment, we found that the prevalence of NCI [18] was significantly increased in PLHIV aged >55 years compared to age, gender, and education matched controls and that HIV was independently associated with NCI after adjusting for important confounders. Using a more conservative threshold for definition of an abnormal domain of less than –1.5 SD from the norm and MNC, HIV was still associated with NCI.

In our study, prevalence of NCI according to the Frascati criteria (35.5%) was in line with the prevalence in studies of individuals with controlled HIV viremia of between 19% and 30% [5–7]. The slightly higher prevalence in our study could be due to the skewed higher median age, as most previous studies were performed in younger populations. The fact that the majority of NCI cases classified as ANI followed by MND is in line with previous studies of HAND in PLHIV [6, 9]. Despite being valid, use of the 4-question IADL instead of the 8-question IADL or a large panel of functional tests might have underestimated functional impairment. Also, survival bias, which is inherent to our cross-sectional design, may have selected increasingly fit individuals and limited the number of individuals with MND. Moreover, our results of increased prevalence of NCI in PLHIV seem robust, as the adjusted ORs of HIV were still significantly associated with NCI in HAND sensitivity analyses (excluding individuals with missing characteristics) and using the more stringent definitions of less than –1.5 SD from the norm in 2 neurocognitive domains and MNC.

The increased prevalence of cardiovascular risk factors, cannabis consumption, hypertension, and chronic kidney disease is in line with previous studies [16, 33], as well as the increased rate in depressive symptomatology [34]. Multimorbidity, to which aging PLHIV are more prone than their counterparts not living with HIV, has been linked in the general population to mental health issues, including depression [35]. The differences in social behavior are important, particularly in physical activity and living conditions, as well as the rates of depression in our study. These factors may explain, at least in part, the increased prevalence of NCI in PLHIV, but HIV remained significantly associated with NCI after adjusting for them.

Interestingly, it is in the COBRA cohort in which PLHIV and the control group (median age 56 years) had similar demographic and lifestyle characteristics that a difference in NCI prevalence was revealed [24]. In the MACS cohort (median age 48 years) [23], HIV status was not significantly associated with poorer cognitive test performances. In this cohort, the lower median ages, rates of AIDS history (11%), high median T-CD4

Table 3. Association Between Living With Human Immunodeficiency Virus and Cognitive Impairment Using Different Outcomes

| Outcome | Unadjusted | | Model 1 ^a | | Model 2 ^b | |
|-------------------------------------|------------------|--------------------|----------------------|--------------------|----------------------|--------------------|
| | OR [CI 95%] | LRT <i>P</i> Value | OR [CI 95%] | LRT <i>P</i> Value | OR [CI 95%] | LRT <i>P</i> Value |
| NCI Frascati (inferred) | 1.74 [1.25–2.41] | .0011 | 1.74 [1.26–2.41] | .0002 | 1.50 [1.04–2.16] | .02 |
| NCI Frascati (sensitivity analysis) | 1.87 [1.30–2.70] | .0011 | 1.88 [1.30–2.71] | .001 | 1.84 [1.21–2.79] | .005 |
| –1.5 standard deviation | 2.47 [1.64–3.73] | <.0001 | 2.46 [1.65–3.70] | <.0001 | 2.24 [1.39–3.62] | .001 |
| Multivariate normative comparison | 2.45 [1.51–3.99] | .0006 | 2.44 [1.51–3.95] | <.0001 | 2.00 [1.13–3.50] | .008 |

Analysis of the Frascati criteria (with multiple imputations of missing characteristics inferred), neurocognitive impairment with Frascati in the sensitivity analysis (excluding individuals with missing characteristics), –1.5 standard deviation as the lower limit for normality of domains tested, or multivariate normative comparison are shown. For more details, see the Methods section.

Abbreviations: CI, confidence interval; LRT, likelihood ratio test; NCI, neurocognitive impairment; OR, odds ratio.

^aModel 1 adjusted for age, gender, and education level (matching characteristics).

^bModel 2 with additional adjustment for physical activity, diabetes, hypertension, cardiovascular disease, smoking, depressive symptomatology (Center for Epidemiologic Studies–Depression ≥17), alcohol consumption, and living alone.

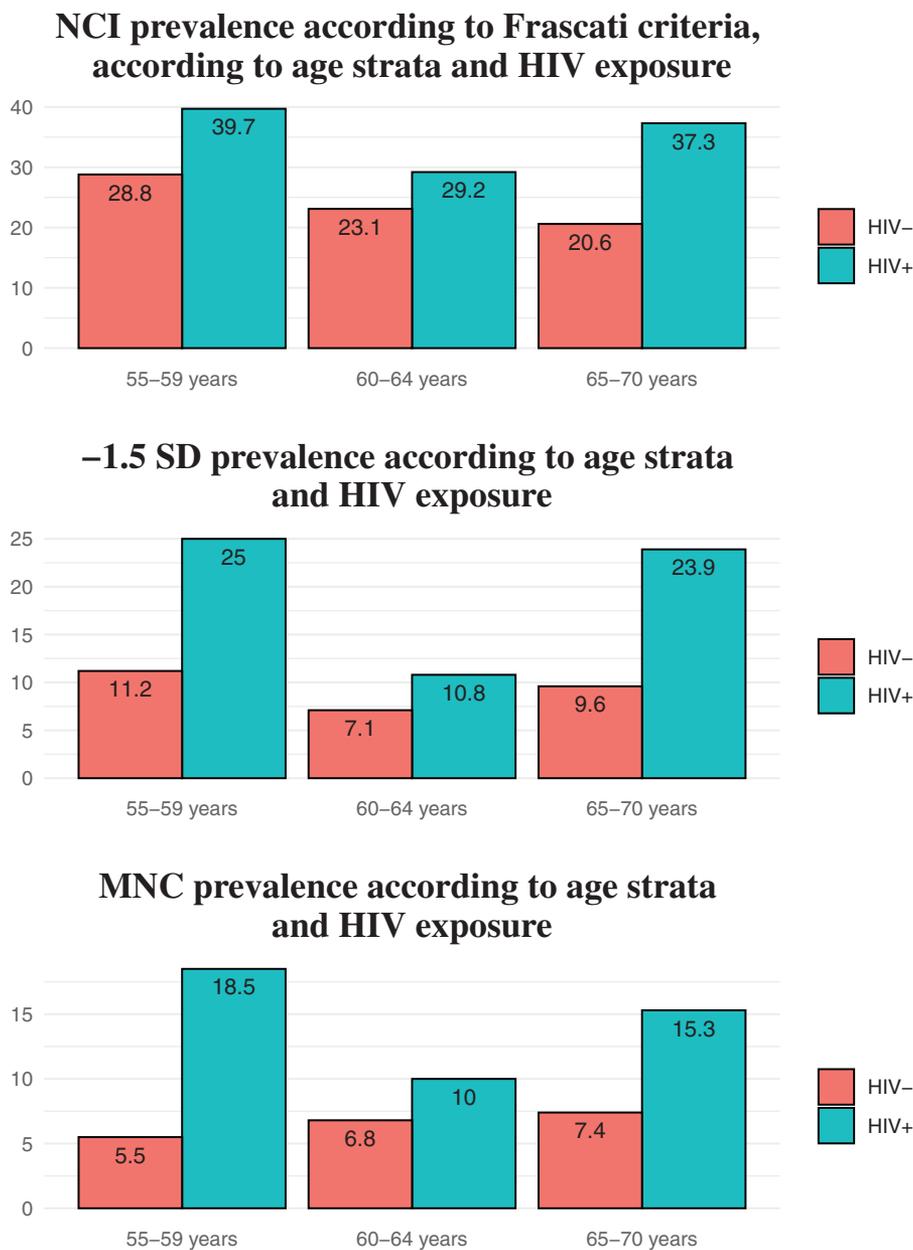


Figure 1. Prevalence of neurocognitive impairment using the Frascati criteria, -1.5 standard deviation cutoff, or multivariate normative comparison classifications according to age strata and human immunodeficiency virus exposure groups. Abbreviations: HIV, human immunodeficiency virus; MNC, multivariate normative comparison; NCI, neurocognitive impairment; SD, standard deviation.

lymphocyte nadir (295 cells/ μ L), and prevalence of cardiovascular factors, depressive symptomatology, and recreational drug use may have contributed to the lack of association.

Aging is an important factor in the cognitive decline in PLHIV as well as in the general population [36, 37]. There was no interaction between age and HIV on associations with NCI, despite an age span of 15 years. However, the cross-sectional nature of the analysis and a lack of power to address this issue hinder any firm conclusion on a potential interaction, which would benefit from further studies. Also, survival bias limits interaction analysis of age with HIV. In the COBRA study

[24], there was no evidence of accelerated brain pathology in PLHIV who underwent magnetic resonance imaging (MRI) or of neurocognitive performance after a median follow-up of 2 years, but the MACS cohort showed a greater-than-expected effect of aging on episodic memory and motor function in individuals with AIDS [38].

The association between HIV and NCI is probably related to multifactorial etiologies. HIV-specific patterns of brain abnormality on MRI have recently been identified and could be the result of chronic brain immune activation despite controlled HIV viremia [39–41]. ANI was associated with specific

Table 4. Tests of Interaction of Age and Human Immunodeficiency Virus Status in Multivariate Analyses

| Outcome | Model 1 | | Model 2 | |
|---|-----------------|--------|-----------------|--------|
| | OR [CI 95%] | PValue | OR [CI 95%] | PValue |
| HIV:age on neurocognitive impairment (Frascati) | 1.17 [.85–1.63] | .34 | 1.12 [.99–1.26] | .50 |
| HIV:age on multivariate normative comparison | 0.69 [.42–1.12] | .14 | 0.66 [.55–.79] | .11 |
| HIV:age on –1.5 standard deviation | 1.00 [.67–1.5] | .99 | 0.92 [.8–1.06] | .68 |

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio.

frontal white matter atrophy, while MND was characterized by more widespread subcortical atrophy [40]. In another study, long-standing virologically controlled PLHIV were found to have widespread abnormalities in white matter microstructure, with abnormalities correlating with cognitive function and systemic immune activation [41]. In our study, the high rates of past immunosuppression may therefore have significantly impacted neurocognitive outcomes, as previously published [21].

Our study has several limits. Individuals recruited in the CONSTANCES cohort may have a health effect bias, as using volunteers may introduce selection bias, even in studies that use random recruitment from an appropriate sampling base [42]. However, matching on the education level in our study reduced the risk of this bias. Also, there were more missing variables in individuals with NCI in the CONSTANCES controls than in PLHIV, which could have overestimated NCI prevalence in PLHIV. However, the primary analysis, with missing variables imputed to include all individuals, limited the impact of this bias. Finally, despite all the matching and extensive adjustments, there might be remaining residual unaccounted confounders.

In conclusion, in this carefully age, gender, and education matched study, with a control group selected from a national cohort and using identical methods of neurocognitive assessment, we found a 74% increased risk of NCI in an aging population of PLHIV. This association persisted after adjusting for comorbid and social confounding factors and considering more stringent outcome measures.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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