Risk Factors for Cognitive Impairment in HIV-1–Infected Persons With Different Risk Behaviors

Diana De Ronchi, MD; Irma Faranca, MD; Domenico Berardi, MD; Paolo Scudellari, MD; Marco Borderi, MD; Roberto Manfredi, MD; Laura Fratiglioni, MD, PhD

Context: Although it is well established that acquired immunodeficiency syndrome dementia complex mainly develops in patients with advanced human immunodeficiency virus 1 (HIV-1) infection and severe immunosuppression, other factors that might increase the risk of early neuropsychological abnormalities are controversial.

Objective: To identify risk factors for HIV-1–related cognitive impairment.

Design: Case-control study.

Setting: Division of Infectious Diseases, University of Bologna.

Participants: We studied 272 consecutive individuals: 90 HIV-1–seronegative, 88 asymptomatic HIV-1–seropositive, and 94 symptomatic HIV-1–seropositive persons.

Main Outcome Measures: Cognitive impairment was defined as poor performance on at least 2 of the 7 neuropsychological tests included in the battery. Cutoff scores for poor performance on a test were established as 2 or more SDs lower than the mean of the seronegative group in the corresponding risk behavior strata: injecting drug users, homosexual/bisexual, and heterosexual participants. The following risk factors were studied: age, sex, education, risk behaviors, HIV-1 stage, lymphocyte count, and antiretroviral therapy.

Results: Compared with individuals with higher levels of education, those with less than 6 years of schooling had an odds ratio (OR) of 17.2 (95% confidence interval [CI], 3.6-83.3) for cognitive impairment, independent of age, sex, disease stage, antiretroviral therapy, and risk behavior. Compared with injecting drug users, homosexual/bisexual and heterosexual participants had ORs of 9.6 (95% CI, 2.2-42.7) and 6.3 (95% CI, 2.2-18.3), respectively, for cognitive impairment. Use of antiretroviral treatment (any vs none) was associated with lower prevalence of cognitive impairment (OR, 0.1; 95% CI, 0.0-0.3). Compared with persons with high CD4+ cell counts (>500/µL), those with low (<200/µL) and moderate (200-499/µL) CD4+ cell counts had adjusted ORs of 8.6 (95% CI, 1.0-71.0) and 6.9 (95% CI, 1.0-48.4), respectively. The presence of prominent depressive symptoms did not change the results.

Conclusions: Low educational level, low CD4+ cell count, and homosexual/bisexual and heterosexual risk behaviors are risk factors for cognitive impairment in HIV-1–seropositive persons. Antiretroviral therapy exerts a beneficial effect against cognitive impairment in symptomatic individuals. Homosexual/bisexual and heterosexual persons who survive longer are expected to be the group at highest risk for cognitive impairment. However, the protective effect of antiretroviral therapy may balance this increased risk.

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PARTICIPANTS AND METHODS

STUDY POPULATION

The study sample included consecutive outpatients examined at the Division of Infectious Diseases, University of Bologna. Participants were recruited between December 1, 1994, and December 1, 1997. Every person attending the outpatient service was asked to participate. All patients underwent a neurological examination before enrollment. We excluded from the sample individuals affected by previous or current cerebral opportunistic infections or other neurological diseases and psychiatric disorders (eg, schizophrenia and delusional, mood, and anxiety disorders).

Informed consent was requested from all individuals before enrollment, and the protocol of the research was approved by the ethical committee of the University of Bologna. Confidentiality was strictly maintained: forms that linked personal identifiers and data were available only to one of us (D.D.), and these forms were kept in a locked file.

HIV-1 INFECTION

All participants were evaluated with HIV-1 serological tests using standardized methods: enzyme-linked immunosorbent assay (Behring Enzygnost Anti-HIV 1/2 Plus; Behring, Marburg, Germany), confirmed by Western blot (Chiron Riba HIV-1/HIV-2 SIA; Chiron Corp, Emeryville, Calif). On the basis of this analysis, participants were divided into HIV-1–seronegative and HIV-1–seropositive groups. Staging in asymptomatic and symptomatic participants was performed according to the Centers for Disease Control and Prevention (CDC) criteria,15 without taking into account the CD4+ cell count. Information concerning CD4+ cell counts was available for 133 (73.1%) of 182 seropositive persons, who were grouped by CD4+ cell count36: less than 200/µL, 200 to 499/µL, and 500/µL or greater. Finally, according to self-reported at-risk behavior, people were classified into 4 groups: (1) homosexuals/bisexuals, (2) heterosexuals, (3) IDUs, and (4) hemophiliacs. Concerning IDUs, a “significant” history of drug abuse was required, that is, abuse of psychoactive drugs for more than 5 years, with a use frequency of at least 3 times per week.29 No individuals in our sample, according to self-reported at-risk behavior, reported both homosexual/bisexual and IDU behaviors.

DATA COLLECTION

Individuals underwent a comprehensive clinical examination and then evaluation by a neuropsychologist. The clinical examination included a semistructured interview concerning sociodemographic variables, education, expressed in years; medical history; personal psychiatric history, including previous and current psychoactive substance use disorders; and previous and current antiretroviral treatment. Data were obtained from an informant (usually a close relative) when the participant was cognitively impaired. A medical and neurological examination was performed, and neurological data were collected. Blood samples were obtained for HIV-1 serological examination and CD4+ cell count.

During the second contact, a neuropsychological evaluation and a psychiatric assessment were conducted by

Continued on next page

pairement in less-educated individuals. Two of these studies included well-educated, middle class, asymptomatic homosexual men, and 1 included asymptomatic IDUs. Only 1 study included different risk behaviors (including IDU), different disease severity, and various educational levels. However, the study population was derived from developing and developed countries, in which education may be an indicator of different factors.

Apart from education, other factors have been sporadically associated with a higher occurrence of dementia and cognitive impairment in HIV-1–infected patients: increased age, female sex, decreased hemoglobin levels, lower body mass index, vitamin B12 deficiency, previous traumatic brain injury, and concurrent depressive symptoms. Conversely, antiretroviral treatment has been found to protect against dementia and cognitive impairment.

This study was designed to explore the role of all the previously suggested risk factors for HIV-1–related cognitive impairment by using a risk behavior–adjusted definition of cognitive impairment. The data are gathered from a longitudinal study on HIV-1 infection that is ongoing in Bologna.

RESULTS

Between December 1, 1994, and December 1, 1997, 272 consecutive outpatients were examined and did not have any of the exclusion criteria (such as schizophrenia, delusional disorders, mood disorders, or anxiety disorders). Of these, 90 (33%) were HIV-1 seronegative and 182 (67%) were HIV-1 seropositive (88 asymptomatic and 94 symptomatic persons).

Concerning the sociodemographic characteristics of HIV-1–seronegative individuals, there were no significant differences in the various risk behaviors on age (almost half of the persons were aged <28 years). All the HIV-1–seronegative hemophiliacs were obviously men, but between homosexuals/bisexuals and heterosexuals and IDUs, no significant differences were found on sex. Conversely, 86% of the homosexuals/bisexuals and heterosexuals had more than 8 years of education, whereas only 30% of IDUs and 63% of hemophiliacs were highly educated.

Among HIV-1–seropositive persons, on the basis of performance on the neuropsychological battery, 37 seropositive individuals were classified as cognitively impaired and 145 as non–cognitively impaired. The prevalence of cognitive impairment according to sociodemographic, clinical, and immunological characteristics of HIV-1–seropositive persons is reported in Table 2. Prevalence was higher in participants with less than 6 years of education than in more highly educated people, in persons with no antiretroviral treatment than in treated people, and in heterosexuals than in IDUs and hemophiliacs.
specialists (D.D. and I.F.). The HIV-1 serostatus and any ongoing antiretroviral treatment were unknown to the examiners. Depression was assessed using the Hamilton Depression Rating Scale, with a score of at least 16 indicating the presence of prominent depressive symptoms. The neuropsychological battery included tests that were used in previous studies concerning HIV-1 and cognition: Verbal Fluency, the Rey 15 Words Short Term and Long Term, and subtests of the Wechsler Adult Intelligence Scale (digit span, digit symbol, vocabulary, and block design). The neuropsychological battery was administered in a fixed order.

**DEFINITION OF COGNITIVE IMPAIRMENT**

Cognitive impairment related to HIV-1 has been defined on the basis of a cognitive battery for which cutoff scores for each test were derived from normative values or from HIV-1-seronegative controls. However, a wide range of neuropsychological deficits are associated with substance abuse, and hemophiliacs are more likely to have cognitive deficits due to brain damage compared with homosexuals/bisexuals and heterosexuals. In our sample, seronegative hemophiliacs had had cerebral vascular accidents, although with no permanent neurological deficits on neurological examination.

Thus, risk behaviors were considered in the definition of cognitive impairment. Cognitive impairment was defined as poor performance on at least 2 of the 7 neuropsychological tests included in the battery. Poor performance on a test was considered as a score of 2 or more SD lower than the mean of the seronegative group in the corresponding risk behavior strata (IDUs, hemophiliacs, and other risk behaviors). Table 1 reports the mean ± 2 SD scores for each test, according to different risk behaviors, in the seronegative group.

**DATA ANALYSIS**

The association between putative risk factors and cognitive impairment was analyzed by using odds ratios (ORs) from logistic regression models. Different logistic regression models were performed for the entire population of HIV-1-seropositive persons and separately for asymptomatic and symptomatic HIV-1-seropositive individuals by using cognitive impairment as the dependent variable, dichotomized into impaired vs not impaired.

Independent variables were entered into the models as follows: (1) age as a continuous variable; (2) education as an indicator variable (<6 years, 6-8 years, and >8 years) and as a dichotomous variable (<6 years vs >5 years); (3) sex (female vs male); (4) risk behavior as an indicator variable (homosexual/bisexual, heterosexual, IDU, and hemophiliac) and as a dichotomous variable (IDU/hemophiliac vs homosexual/bisexual and heterosexual); (5) CD4+ cell count was used by contrasting lower (<200/µL) and moderate (200-499/µL) levels with high levels (≥500/µL); (6) stage of HIV-1 infection (symptomatic vs asymptomatic); (7) presence of prominent depressive symptoms; and (8) antiretroviral treatment (any vs none).

Finally, sensitivity analysis of missing CD4+ cell counts was conducted by producing 2 extreme imputations. This analysis assumed that all participants with missing CD4+ cell counts had counts of 499/µL or less (imputation 1) or counts of 500/µL or greater (imputation 2). All the analyses were repeated in these 2 imputations.

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**Table 1. Performance of 90 HIV-1−Seronegative Individuals on Each Test of the Cognitive Battery**

<table>
<thead>
<tr>
<th>Test</th>
<th>Heterosexuals and Bisexuals/Homeosexuals (n = 50)</th>
<th>Injecting Drug Users (n = 24)</th>
<th>Hemophiliacs (n = 16)</th>
<th>Total (N = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Fluency†</td>
<td>41.3 ± 20.8</td>
<td>34.4 ± 20.2</td>
<td>15.4 ± 10.8</td>
<td>34.9 ± 27.0</td>
</tr>
<tr>
<td>WAIS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit span</td>
<td>9.8 ± 5.2</td>
<td>9.4 ± 6.2</td>
<td>11.4 ± 5.4</td>
<td>10.6 ± 5.6</td>
</tr>
<tr>
<td>Vocabulary†</td>
<td>12.7 ± 4.6</td>
<td>10.1 ± 6.0</td>
<td>12.2 ± 4.0</td>
<td>11.9 ± 5.4</td>
</tr>
<tr>
<td>Digit symbol‡</td>
<td>10.7 ± 6.2</td>
<td>8.6 ± 4.4</td>
<td>9.8 ± 5.4</td>
<td>10.0 ± 6.0</td>
</tr>
<tr>
<td>Block design†</td>
<td>12.6 ± 5.6</td>
<td>9.8 ± 5.6</td>
<td>15.6 ± 4.2</td>
<td>12.4 ± 6.6</td>
</tr>
<tr>
<td>Rey 15W-ST†</td>
<td>49.4 ± 15.4</td>
<td>41.8 ± 19.4</td>
<td>28.4 ± 15.0</td>
<td>43.7 ± 22.6</td>
</tr>
<tr>
<td>Rey 15W-LT†</td>
<td>10.7 ± 6.0</td>
<td>8.7 ± 6.0</td>
<td>4.7 ± 4.2</td>
<td>9.1 ± 7.2</td>
</tr>
</tbody>
</table>

Values, given as mean ± 2 SDs, were used as risk behavior–adjusted cutoff scores to identify individuals with cognitive impairment. HIV-1 indicates human immunodeficiency virus 1; WAIS, Wechsler Adult Intelligence Scale; and 15W-ST and 15W-LT, 15 Words Short Term and Long Term.

†P < .001 among individuals with different risk behaviors.
‡P < .05 among individuals with different risk behaviors.

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Results of 4 logistic regression models, in which different putative risk factors were entered one by one into the first block of variables (age, sex, and education), are reported in Table 3. Participants with low educational levels had high ORs in all 4 models. In Italy, the first degree of education is achieved after 5 years of schooling, and the second level after 3 more years. Therefore, 3 categories of education were chosen: (1) less than 6 years, (2) 6 to 8 years, and (3) more than 8 years. Adjusted ORs for HIV-1–related cognitive impairment were 18.9 (95% confidence interval [CI], 3.7-97.6) in participants with less than 6 years of education and 1.3 (99% CI, 0.5-3.2) in subjects with 5 to 8 years of education compared with individuals with 9 or more years of education. Based on these results, we further analyzed education, contrasting individuals with less than 6 years of education with those with more than 5 years of education.

When antiretroviral treatment and risk behavior were introduced into the fourth logistic regression model (Table 3), the OR for low educational level more than doubled.
Antiretroviral therapy (Table 3, models 3 and 4) was consistently inversely associated with cognitive impairment. A high OR for HIV-1–related cognitive impairment in homosexual/bisexual and heterosexual risk behaviors compared with IDU risk behavior (Table 3, model 4) was detected. All previous results were confirmed when the data were adjusted for prominent depressive symptoms.

Analyses were repeated separately for symptomatic and asymptomatic persons (Table 4). The results for symptomatic individuals were similar to those for the entire population. For asymptomatic individuals, although a similar trend was observed for all the risk factors, only homosexual/bisexual and heterosexual risk behaviors emerged as significantly associated with cognitive impairment (OR, 15.7; 95% CI, 3.1-78.9; P = .001).

The CD4+ cell counts were available for 133 HIV-1–seropositive persons (73%). Results of logistic regression analysis, in which the lack of CD4+ cell count was the dependent variable, showed that persons without CD4+ cell counts were more frequently women (OR, 2.2; 95% CI, 1.0-71.0), and in individuals with moderate CD4+ cell counts did not differ regarding other sociodemographic and clinical aspects. Among individuals with CD4+ cell counts, 46% of IDUs and hemophiliacs had low CD4+ cell counts vs only 23% of homosexuals/bisexuals and heterosexuals (χ² = 7.0; P = .03).

When CD4+ cell count was used instead of CDC stage in regression models equal to those reported in Table 3, the adjusted OR for HIV-1–related cognitive impairment among individuals with low CD4+ cell counts was 8.6 (95% CI, 1.0-71.0), and in individuals with moderate CD4+ cell counts the OR was 6.9 (95% CI, 1.0-48.4) compared with persons with high CD4+ cell counts. The ORs for the other risk factors were similar to those reported in Table 3.

Finally, sensitivity analysis of missing CD4+ cell counts was performed. When the relation between HIV-1–related cognitive impairment and age, sex, educational level, CDC stage, antiretroviral treatment, risk behavior, and CD4+ cell count was analyzed using the method reported in the “Data Analysis” subsection, the following results were obtained:

- Imputation 1 (all participants with missing CD4+ cell counts were assumed to have counts ≤499/µL): ORs in relation to increasing age, female sex, low educational level, antiretroviral treatment, IDU and hemophilic risk behavior, and low CD4+ cell count were 1.0, 1.7, 16.4, 0.1, 0.1, and 4.5, respectively.

- Imputation 2 (all participants with missing CD4+ cell counts were assumed to have counts ≥500/µL): ORs in relation to increasing age, female sex, low educational level, antiretroviral treatment, IDU and hemophilic risk behavior, and low CD4+ cell count were 1.0, 2.0, 19.5, 0.1, 0.1, and 3.6, respectively.

The main findings from this study are summarized as follows:

1. Low educational level emerged as an independent risk factor for HIV-1–related cognitive impairment.

2. Homosexuals/bisexuals and heterosexuals had higher risk for HIV-1–related cognitive impairment than did IDUs, even after adjustment for CD4+ cell count.

3. Antiretroviral therapy was consistently inversely associated with cognitive impairment.

4. Persons who were seropositive for HIV-1 and had severe immunosuppression showed a higher risk of cognitive impairment.

**EDUCATION AND HIV-1–RELATED COGNITIVE IMPAIRMENT**

In agreement with Stern,19 Maj,20 and Satz21 and their colleagues, our findings suggest that low educational level (<6 years) increases the risk of HIV-1–related cognitive impairment in HIV-1–seropositive persons (asymptomatic and symptomatic). The association between low educational level and HIV-1–related cognitive impairment was independent of all other putative risk factors.
RISK BEHAVIOR AND HIV–1–RELATED COGNITIVE IMPAIRMENT

In our study, homosexuals/bisexuals and heterosexuals had a higher risk for HIV–1–related cognitive impairment than did IDUs. This finding is in disagreement with the suggested hypothesis that IDUs, for multiple reasons, could have more rapid progression to HIV–1–related cognitive impairment than persons with other risk behaviors.6,13,29-34 A first explanation for the discrepancy lies in the cognitive impairment definition adopted in this study. In fact, including risk behavior in the definition of cognitive impairment discounts the effect of other factors related to the IDU risk behavior, which could lead to cognitive deficits per se. Moreover, individuals with IDU risk behavior have higher mortality rates than patients with other risk behaviors.52 This might reduce the number of IDUs with cognitive impairment in the pool of prevalent cases. Alternatively, because of the high mortality rates, persons with IDU risk behavior have reduced survival time after HIV–1 infection, which might be proportionally related to the risk of cognitive impairment. Finally, IDUs are less likely to receive or follow new antiretroviral measures.52

IMMUNOLOGICAL STATUS AND ANTIRETROVIRAL THERAPY IN RELATION TO HIV–1–RELATED COGNITIVE IMPAIRMENT

Individuals seropositive for HIV–1 who had severe immunosuppression showed a higher risk of cognitive impairment, in agreement with results of other studies.3-11 This association is supported by a neuroimaging study33 in which, within the gray matter, cerebral volume loss was related to a low CD4+ cell count. Conversely, we did not observe any significant difference in cognitive impairment prevalence related to CDC stage criteria. This result could be explained by the fact that the CD4+ cell count represents a more sensitive indicator of immunological progression of HIV–1 infection than CDC stage.25 It has been suggested6 that a low CD4+ cell count may be a reliable marker of rapid AIDS dementia complex progression, indicating high viral and central nervous system seeding. Limited information was available in our study concerning disease duration because for most participants the date of the onset of infection was unknown. Adjustment for CD4+ cell count partially adjusts for the duration of infection.

Our finding of a protective effect of antiretroviral therapy for cognitive impairment is in agreement with most studies3,13,20,34 and in line with clinical trials suggesting that antiretroviral therapy is effective in increasing the CD4+ cell count. We found that this is true for symptomatic individuals.

AGE AND SEX AS POSSIBLE RISK FACTORS FOR HIV–1–RELATED COGNITIVE IMPAIRMENT

We did not observe increasing age as a risk factor for cognitive impairment. This result is inconsistent with other studies of HIV–1–associated dementia complex.1,9,19,22 One

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**Table 3. Adjusted Odds Ratios for HIV–1–Related Cognitive Impairment From 4 Logistic Regression Models**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Model 1 (95% Confidence Interval)</th>
<th>Model 2 (95% Confidence Interval)</th>
<th>Model 3 (95% Confidence Interval)</th>
<th>Model 4 (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (for increment of 1 y)</td>
<td>1.0 (1.0-1.1)</td>
<td>1.0 (1.0-1.1)</td>
<td>1.0 (1.0-1.1)</td>
<td>1.0 (0.9-1.1)</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.9 (0.8-4.2)</td>
<td>1.9 (0.8-4.2)</td>
<td>2.3 (1.0-5.6)</td>
<td>1.6 (0.6-4.8)</td>
</tr>
<tr>
<td>&lt;6 y of education</td>
<td>6.3 (1.8-21.6)</td>
<td>6.4 (1.8-22.5)</td>
<td>8.4 (2.2-32.2)</td>
<td>17.2 (3.6-82.3)</td>
</tr>
<tr>
<td>Symptomatic HIV–1</td>
<td>0.9 (0.4-1.9)</td>
<td>0.8 (0.4-1.6)</td>
<td>0.1 (0.1-0.4)</td>
<td>0.1 (0.0-0.3)</td>
</tr>
<tr>
<td>Antiretroviral therapy</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Risk behaviors</td>
<td>Homosexuals/bisexuals</td>
<td>...</td>
<td>...</td>
<td>9.6 (2.2-42.7)</td>
</tr>
<tr>
<td></td>
<td>Heterosexuals</td>
<td>...</td>
<td>...</td>
<td>6.3 (2.2-18.3)</td>
</tr>
<tr>
<td></td>
<td>Hemophiliacs</td>
<td>...</td>
<td>...</td>
<td>0.3 (0.0-2.5)</td>
</tr>
<tr>
<td></td>
<td>Injecting drug users</td>
<td>...</td>
<td>...</td>
<td>1.0 (Referent)</td>
</tr>
</tbody>
</table>

**Table 4. Adjusted Odds Ratios for HIV–1–Related Cognitive Impairment According to CDC Stage From 4 Logistic Regression Models**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Asymptomatic Persons (n = 88) (95% CI)</th>
<th>Symptomatic Persons (n = 94) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (for increment of 1 y)</td>
<td>1.0 (0.9-1.1)</td>
<td>1.0 (0.9-1.1)</td>
</tr>
<tr>
<td>Female sex</td>
<td>2.2 (0.6-8.3)</td>
<td>1.3 (0.3-6.3)</td>
</tr>
<tr>
<td>&lt;6 y of education</td>
<td>5.7 (0.2-130.7)</td>
<td>27.2 (3.8-195.1)</td>
</tr>
<tr>
<td>Antiretroviral therapy</td>
<td>0.5 (0.1-2.5)</td>
<td>0.0 (0.0-0.2)</td>
</tr>
<tr>
<td>Homosexuals/bisexuals and heterosexuals</td>
<td>15.7 (3.1-78.9)</td>
<td>5.2 (1.1-24.0)</td>
</tr>
</tbody>
</table>

*HIV–1 indicates human immunodeficiency virus 1.*
reason for a lack of association in the present study may be because of the high degree of homogeneity in age of the sample and the high proportion of IDUs, who have lower mean age than individuals with other risk behaviors in our population.

Rates of cognitive impairment were higher for women, in agreement with the findings of Chiesi et al,9 who reported higher rates of AIDS dementia complex among women. However, when risk behaviors were introduced into the model, the association between sex and cognitive impairment was not present. Previous reporting of female sex as a risk factor for AIDS dementia complex may be because the latter study9 did not adjust for risk behaviors in the definition of cognitive impairment.

In conclusion, low educational level, low CD4+ cell count, and homosexual/bisexual and heterosexual risk behaviors are risk factors for cognitive impairment in HIV-1-seropositive persons. Antiretroviral therapy exerts a beneficial effect against cognitive impairment in symptomatic individuals.

The generalizability of these findings may be questioned, as the extent to which our participants are representative of persons with different risk behaviors or HIV-1 infection is unknown. For instance, the exclusion of persons affected by previous or current psychiatric disorders may limit the generalizability of our results. Nevertheless, our sample may be considered representative of at least Italian HIV-1-seropositive persons because a similar distribution in age, sex, and risk behaviors has been reported by Chiesi et al9 for the inception cohort of the Italian National AIDS Registry.

We are aware that even missing a few cognitively impaired individuals, because of small numbers in some education strata, may modify the finding concerning education and cognitive impairment. Nevertheless, we feel confident in our findings, as selection bias due to dropouts, if present, was minimal. Indeed, there were only 2 dropouts in the whole sample. Diagnostic bias was minimized by the use of a reliable neuropsychological battery and by the fact that risk behaviors were considered in the definition of cognitive impairment, which also adjusted indirectly for education. Last, contrary to many previous investigations conducted in the research field, persons were consecutively recruited from outpatient units to which they had been referred for medical advice.

Major changes in the AIDS epidemic have taken place in recent years, and our findings have important implications for HIV-1 surveillance programs. Our findings suggest that homosexual/bisexual and heterosexual persons who survive longer are expected to be the group at highest risk for cognitive impairment. However, the protective effect of antiretroviral therapy may balance this increased risk. Further studies based on larger populations and incident cognitive impairment cases are needed to confirm these data and to understand if some years of education can decrease the risk of HIV-1-related cognitive impairment or whether other factors, acting in the first decade of life, are the real determinants.

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Author contributions: Study concept and design (Drs De Ronchi and Fratiglioni); acquisition of data (Drs De Ronchi, Faranca, Borderi, and Manfredi); analysis and interpretation of data (Drs De Ronchi, Berardi, Scudellari, and Fratiglioni); drafting of the manuscript (Drs De Ronchi and Fratiglioni); critical revision of the manuscript for important intellectual content (Drs De Ronchi, Faranca, Berardi, Scudellari, Borderi, Manfredi, and Fratiglioni); statistical expertise (Drs De Ronchi and Fratiglioni); obtained funding (Dr De Ronchi); administrative, technical, and material support (Drs De Ronchi, Faranca, Scudellari, Borderi, and Fratiglioni); study supervision (Drs De Ronchi, Berardi, Scudellari, Manfredi, and Fratiglioni).

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