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Prevalence and risk factors for human immunodeficiency virus–associated neurocognitive impairment, 1996 to 2002: Results from an urban observational cohort

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To assess prevalence and risk factors for human immunodeficiency virus (HIV)-related neurocognitive impairment (NCI), the authors performed a 7-year survey in the period 1996 to 2002. A total of 432 patients were examined. HIV-related NCI was diagnosed in 238 patients (55.1%), meeting the HIV dementia (HIV-D) criteria in 45 (10.4%). The prevalence of both NCI and HIV-D did not change significantly during the study period. Compared with patients without NCI, patients with NCI were older (40.4 versus 38.2 years; $P = .003$), had a higher prevalence of positive HCV serology (61.1% versus 38.9%; $P = .003$), and a lower nadir CD4 cell count (156 versus 222 cells/μl; $P < .001$). Compared with patients seen during 1996 to 1999, patients with NCI seen during 2000 to 2002 were older (40.7 versus 38.8 years; $P = .004$), had a less advanced disease stage (previous acquired immunodeficiency syndrome [AIDS] 28.8% versus 65.7%; $P < .001$) and a higher nadir CD4 count (174 versus 132 cells/μl; $P = .026$). This study showed an unchanged prevalence of both HIV-related NCI and HIV-D in the period 1996 to 2002. The authors found evidences for new additional potential risk factors for HIV-related NCI (older age, lower nadir CD4 count, positive hepatitis C virus [HCV] serology), and for a change of risk factors for NCI in the late highly active antiretroviral therapy (HAART) era (older age, less advanced disease, higher nadir CD4 count). *Journal of NeuroVirology* (2005) **11,** 265–273.

Keywords: highly active antiretroviral therapy; HIV dementia; HIV infection; neurocognitive impairment; prevalence

Introduction

Human immunodeficiency virus (HIV)-1 infection can be complicated by neurocognitive impairment (NCI) that is characterized by psychomotor slowing, impairment of memory and attention, disturbances in processing speed, and behavioral manifestations (Navia and Price, 1987). The most severe form of HIV-related NCI is the HIV-1–associated dementia (HIV-D), a subcortical dementia, characterized by severe impairment of cognitive capacities with marked functional impairment. Typically, HIV-D evolves insidiously over a period of weeks or months and, before the introduction of highly active antiretroviral therapy (HAART) as a standard of care, HIV-D developed in more than 20% of HIV-infected patients. Aside HIV-D, some patients develop less severe forms of NCI, either a subclinical impairment or a mild

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impairment interfering, at least mildly, with day-to-day functioning.

Epidemiological and clinical studies have provided evidences for a change in HIV-associated NCI in the era of HAART. Since the introduction of HAART as a standard of care there has been a decline in the incidence of HIV-D as presenting manifestation of acquired immunodeficiency syndrome (AIDS) (Dore *et al*, 1999; Sacktor *et al*, 2001; D'Arminio Monforte *et al*, 2004). However, the reduced incidence of HIV-D as an AIDS-defining disease may underestimates the prevalence of HIV-related NCI. Ferrando and colleagues (1998) reported an estimated prevalence of nearly 20% of the less severe form of NCI in symptomatic HIV-positive patients in the early HAART era. With regard to HIV-D, literature data on the prevalence of this disease are contrasting. Whereas some authors showed an unchanged prevalence (Sacktor *et al*, 2002), others reported an increase in the prevalence of HIV-D (Dore *et al*, 2003). Thus, updated data on the prevalence of HIV-related NCI and of HIV-D are still needed. Such data are needed because neuropathologic studies consistently show an high prevalence of HIV-D, that continues to be detected in at least 25% of the cases (Masliah *et al*, 2000), with a trend toward an even increase in prevalence in the era of HAART (Neuenburg *et al*, 2002).

Moreover, risk factors for HIV-D are changing. Whereas in the pre-HAART era the mean CD4 cell count at the time of HIV-D diagnosis was between 50 and 100 cells/μl, nowadays it seems increased significantly (Dore *et al*, 1999).

Thus, now that HIV-infected patients are living longer due to the availability of HAART, the overall prevalence and risk factors for the different forms of NCI in the HAART era are of particular interest. New antiretrovirals have recently been approved, and 20 antiretroviral drugs, with different ability to reach the neurological compartment, are currently licensed for clinical use in HIV disease. Studies are needed to increase our understanding of the prevalence and risk factors for HIV-associated NCI over extended period of time, but to our knowledge, there are no data on the prevalence and risk factors for HIV-related NCI for the last 7 years of HAART.

For these reasons we report on the prevalence and risk factors for HIV-related NCI in a population sample of HIV-positive patients followed in large referral HIV-clinic in Rome, Italy, from 1996 to 2002.

Results

Patient's characteristics

HIV-related NCI was diagnosed in 238 patients (55.1%), meeting the criteria for HIV-D in 45 cases (10.4%). The remaining 194 patients were classified as neurocognitively unimpaired. The characteristics of the 432 study patients are shown in Table 1, which also shows the demographic and clinical characteristics of the patients by neurocognitive diagnosis. Neurocognitively impaired and unimpaired patients did not differ in terms of gender, hemoglobin, current CD4 cell count, current plasma viral load, peak plasma viral load by clinical history, and antiretroviral (ARV) and HAART exposure. Impaired patients were older (40.4 versus 38.2 years; $P = .003$), less educated (10.1 versus 12.2 years; $P < .001$), and had a higher prevalence of positive HCV serology (61.1% versus 38.9%; $P = .003$). Patients with NCI were more frequently previously intravenous drug users as HIV transmission modality (44.5% versus 31.4%; $P = .011$), had a more advanced HIV disease stage (Centers for Disease Control and Prevention [CDC] group C 45.0% versus 21.1%; $P < .001$), and had a lower nadir CD4 cell counts by clinical history (156 versus 222 cells/μl; $P < .001$).

Prevalence of neurocognitive impairment and mean NPZ scores by calendar year

Overall 55.1% of patients met the criteria for impairment. The prevalence of NCI among the study patients did not change significantly across the study period, ranging from 46.5% in 2000 to 72.7% in 1999 ($P = .86$; chi-square for trend) (Figure 1).

Figure 2 depicts mean NPZ8 score at neuropsychological evaluation in patients with NCI. Mean NPZ8 scores also did not change significantly across the study period ($P = .60$; analysis of variance [ANOVA]).

To determine the impact of HAART availability on neuropsychological performance, we have looked at NPZ8 scores among 192 patients taking HAART at the time of the neuropsychological evaluation. Mean NPZ8 scores did not change significantly across the study period in those patients ($P = .67$; ANOVA) (Figure 3).

Factors related to neurocognitive impairment by early and late HAART era

To determine whether demographic and HIV illness characteristics of impaired patients differed by

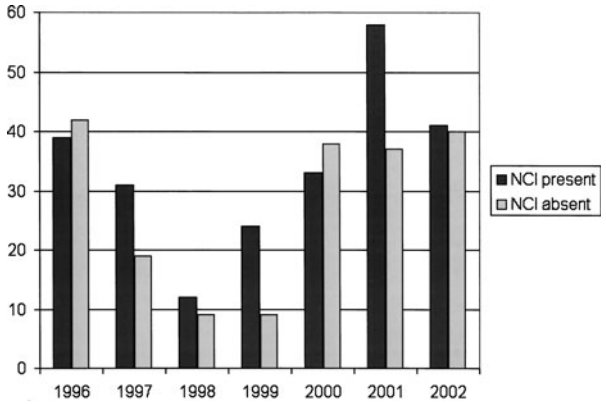

Figure 1 Number of HIV-positive patients with and without neurocognitive impairment (NCI) by calendar year ($P = .86$; chi-square for trend).

Table 1 Demographic and HIV illness characteristics in the 432 study patients by neurocognitive diagnosis

		Neurocognitive impairment		
	All patients (n = 432)	*Present (n = 238)*	*Absent (n = 194)*	*P*
Age in years, mean (±SD)	39.4 (±7.6)	40.4 (±7.6)	38.2 (±7.3)	.003
Education in years, mean (±SD)	11.1 (±3.7)	10.1 (±3.6)	12.2 (±3.4)	<.001
Gender, *n* (%) male	306 (70.8)	177 (74.4)	129 (66.5)	.088
HIV transmission modality, *n* (%)				
Intravenous druguse	167 (38.7)	106 (44.5)	61 (31.4)	.011
MSM	87 (20.1)	38 (16.0)	49 (25.3)	
Heterosexuality	157 (36.3)	78 (32.8)	79 (40.7)	
Unknown	21 (4.9)	16 (6.7)	5 (2.6)	
HIV clinical stage, *n* (%)				
CDC group A or B	284 (65.7)	131 (55.0)	153 (78.9)	<.001
CDC group C	148 (34.3)	107 (45.0)	41 (21.1)	
Positive HCV serology, *n* (%)	175 (40.5)	107 (61.1)	68 (38.9)	.003
Positive HBsAg, *n* (%)	40 (9.3)	24 (60.0)	16 (40.0)	.306
Hemoglobin, g/dl, mean (±SD)	13.7 (±5.4)	13.9 (±7.8)	13.5 (±1.7)	.507
CD4 cell count/μl, mean (±SD)	285 (±233)	301 (±231)	265 (±234)	.117
CD4 cell count/μl, *n* (%)				
<50	72 (16.7)	37 (15.5)	35 (18.0)	.118
50–199	111 (25.8)	55 (23.1)	56 (28.9)	
200–499	179 (41.3)	99 (41.7)	80 (41.2)	
>500	70 (16.2)	47 (19.7)	23 (11.9)	
Nadir CD4 cell count/μl, mean (±SD)	186 (±160)	156 (±143)	222 (±172)	<.001
Plasma HIV RNA, log copies/ml, mean (±SD)	3.90 (±1.34)	3.93 (±1.39)	3.86 (±0.75)	.665
Plasma HIV RNA copies/ml, *n* (%)				
<500	104 (24.1)	54 (22.7)	50 (25.8)	.239
500–50,000	152 (35.2)	73 (30.7)	79 (40.7)	
>50.000	149 (30.5)	86 (36.1)	63 (32.5)	
Peak plasma HIV RNA, log copies/ml, mean (±SD)	4.89 (± 0.85)	4.90 (±0.92)	4.87 (±0.75)	.631
ARV exposure, *n* (%)				
Naive	108 (25.0)	58 (24.4)	50 (25.8)	.739
On ARV therapy	324 (75.0)	180 (75.6)	144 (74.2)	
HAART exposure in 259 patients taking HAART, *n* (%)				
<12 months	132 (51.0)	56 (51.9)	75 (50.0)	.801
≥12 months	127 (49.0)	52 (48.1)	75 (50.0)	
Mean HAART duration in 259 patients taking HAART, months (±SD)	19.5 (±20.3)	19.3 (±20.5)	19.6 (±20.2)	.908

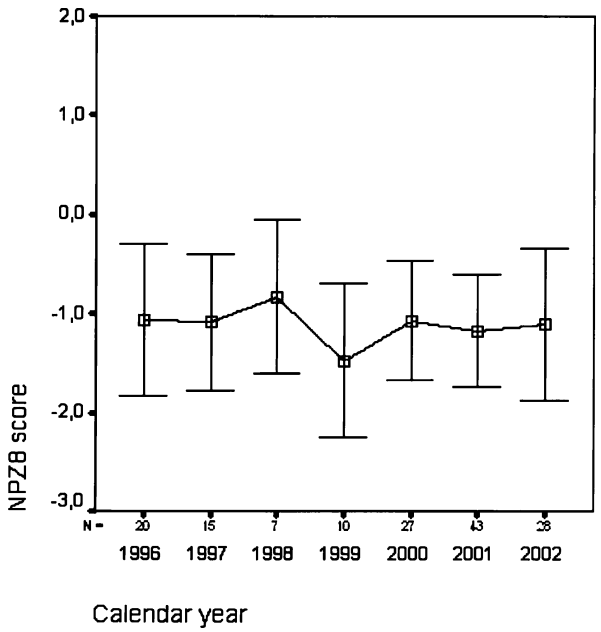

Figure 2 Mean NPZ8 scores in 150 HIV-positive patients with neurocognitive impairment, by calendar year ($P = .60$; ANOVA).

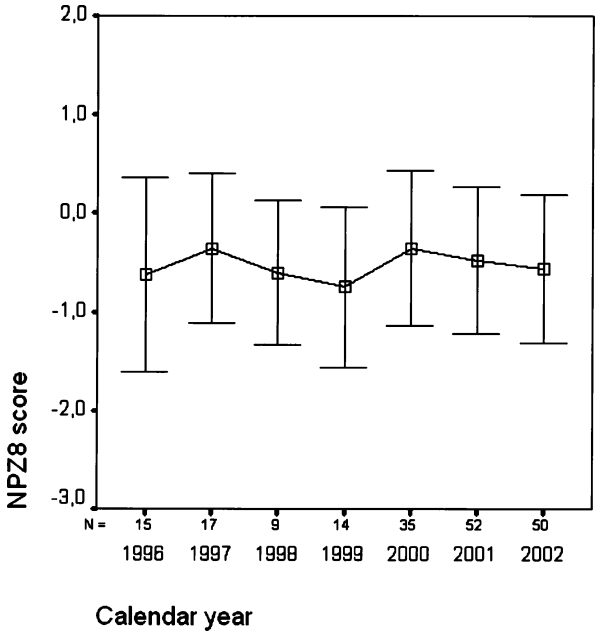

Figure 3 Mean NPZ8 scores in 192 HIV-positive patients on HAART at the time of the neuropsychological examination, by calendar year ($P = .67$; ANOVA).

calendar year of HAART, the study period was divided between 1996 to 1999 and 2000 to 2002, when HAART regimens including either NNRTIs or lopinavir/ritonavir were largely used. All impaired patients ($n = 238$) were evaluated. We assessed a number of known demographic and HIV illness–associated risk factors for HIV-related NCI, including age, years of education, gender, HIV transmission modality, CDC clinical stage, positive hepatitis C virus (HCV) serology, positive hepatitis B surface (HBs) antigen, hemoglobin level, current CD4 cell count, nadir CD4 cell counts by clinical history, current plasma viral load, peak plasma viral load by clinical history, ARV exposure, and HAART exposure.

In our Institute, during the first half of 1996 antiretroviral-treated patients were receiving mono- or dual nucleoside reverse transcriptase inhibitors (NRTI) therapy, because protease inhibitor became available only after June 1996. Among the 238 impaired patients seen during the entire study period, 58 patients were antiretroviral naïve at the time of the neuropsychological examination, whereas 180 patients were receiving at least one antiretroviral drug: one or two NRTIs in 30 patients seen during 1996, and HAART in the remaining 150 patients.

Impaired patients seen during 1996 to 1999 and during 2000 to 2002 did not differ in terms of gender, years of education, HIV transmission modality, positive HCV serology, positive HBs antigen, hemoglobin level, current CD4 cell count, current plasma viral load, peak plasma viral load by clinical history, or severity of cognitive impairment meeting the HIV-D criteria (Table 2). Patients seen during 2000 to 2002 were older (40.7 years versus 38.8 years; $P = .004$), had a less advanced HIV clinical stage (CDC group C 28.8% versus 65.7%; $P < .001$), and had a higher nadir CD4 cell count by clinical history (174 versus 132 cells/μl; $P = .026$). HAART exposure was higher in patients seen during 2000 to 2002 when compared with patients seen during 1996 to 1999. Among the 150 impaired patients receiving HAART at the time of neuropsychological examination, the proportion of

Table 2 Variables associated with neurocognitive impairment, by calendar year

	All impaired patients (n = 238)	*Impaired patients, 1996–1999 (n = 106)*	*Impaired patients, 2000–2002 (n = 132)*	*P*
Age in years, mean (±SD)	40.4 (±7.6)	38.8 (±7.5)	40.7 (±7.5)	.004
Education in years, mean (±SD)	10.1 (±3.6)	9.9 (±3.7)	10.4 (±3.7)	.290
Gender, *n* (%) male	177 (74.4)	74 (69.8)	103 (78.0)	.179
HIV transmission modality, *n* (%)				
Intravenous drug use	106 (44.5)	52 (49.0)	54 (40.9)	.230
MSM	38 (16.0)	18 (17.0)	20 (15.2)	
Heterosexuality	78 (32.8)	29 (27.4)	49 (37.1)	
Other/unknown	16 (6.7)	7 (6.6)	9 (6.8)	
HIV clinical stage, *n* (%)				
CDC group A or B	131 (54.5)	37 (34.3)	94 (71.2)	<.001
CDC group C	107 (45.5)	69 (65.7)	38 (28.8)	
Positive HCV serology, *n* (%)	107 (45.0)	48 (57.1)	59 (49.2)	.319
Positive HBsAg, *n* (%)	24 (10.1)	13 (21.7)	11 (13.6)	.258
Hemoglobin, g/dl, mean (±SD)	13.5 (±1.7)	13.5 (±1.8)	13.6 (±1.6)	.653
CD4 cell count/μl, *n* (%)				
<50	37 (15.5)	15 (14.3)	22 (16.7)	.553
50–119	55 (23.1)	29 (27.6)	26 (19.7)	
200–499	98 (41.2)	41 (39.0)	57 (43.2)	
>500	47 (19.7)	20 (19.0)	27 (20.5)	
CD4 cell count/μl, mean (±SD)	301 (±231)	287 (±221)	313 (±240)	.388
Viral load copies/ml, *n* (%)				
<500	54 (22.7)	17 (16.0)	37 (28.0)	.256
500–50,000	73 (30.7)	28 (26.4)	45 (34.1)	
>50,000	86 (36.1)	39 (36.8)	47 (35.6)	
Plasma HIV RNA log copies/ml, mean (±SD)	3.93 (±1.39)	4.16 (±1.30)	3.78 (±1.44)	.052
Nadir CD4 cell count/μl, mean (±SD)	156 (±143)	132 (±129)	174 (±152)	.026
Peak plasma HIV RNA log copies/ml, mean (±SD)	4.90 (±0.92)	4.91 (±0.94)	491 (±0.91)	.887
Impairment meeting HIV-D criteria, *n* (%)	45 (18.9)	24 (22.6)	21 (15.9)	.244
ARV exposure, *n* (%)				
Naïve	58 (24.4)	18 (17.0)	40 (30.3)	.022
On ARV therapy	180 (75.6)	88 (83.0)	92 (69.7)	
HAART exposure in 150 patients taking HAART, *n* (%)				
<12 months	75 (50.0)	38 (65.5)	37 (40.2)	.004
≥12 months	75 (50.0)	20 (34.5)	55 (59.8)	
Mean HAART duration in 150 patients taking HAART, months (±SD)	19.6 (±20.2)	10.8 (±12.4)	25.1 (±22.2)	<.001
Plasma viral load in 150 patients taking HAART, *n* (%)				
>500 cp/ml, *n* (%)	94 (62.7)	38 (65.5)	56 (61.0)	.203
≤500 cp/ml, *n* (%)	48 (32.0)	14 (24.1)	34 (37.0)	

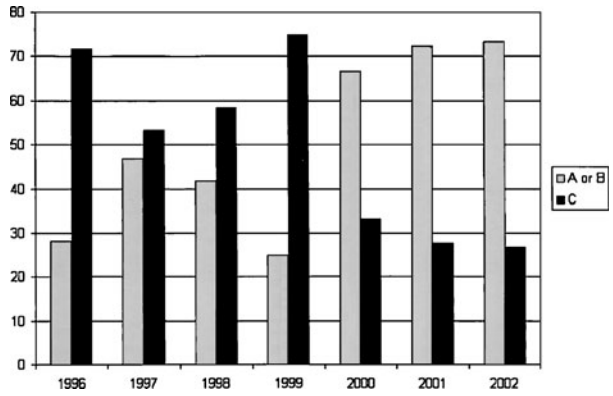

Figure 4 Proportion of subjects with stage C HIV disease among 238 patients with HIV-related neurocognitive impairment, by calendar year ($P < .0001$; chi-square for trend).

patients with plasma viral load below 500 copies/ml did not differ between early and late HAART era (Table 2). The prevalence of previous AIDS clinical events for patients with NCI was 72% in 1996 and decreased to 27% in 2002, showing a statistically significant decreasing trend ($P < .0001$; chi-square for trend) (Figure 4).

Discussion

We performed a 7-year survey on prevalence and risk factors for HIV-related NCI in patients referred for neuropsychological examination in the period January 1996 to December 2002 in a large urban HIV clinic. Our study showed an unchanged prevalence of HIV-related NCI through the entire study period, in a population sample of patients that included 60% of subjects receiving HAART for a mean of 19 months. Moreover, NPZ8 scores did not change significantly during the entire study period, both among patients with NCI and among patients who were receiving HAART at the time of neuropsychological examination. We found evidences for new additional potential risk factors for HIV-related NCI: older age, lower nadir CD4 cell count by clinical history, and positive HCV serology. Our data provided also evidence for a change of risk factors for NCI over time during the HAART era. Impaired patients seen during the late HAART era tended to be older, with less advanced disease, and with higher nadir CD4 cell count by clinical history, when compared with impaired patients seen in the early HAART era.

The reduced incidence of HIV-D since the introduction of HAART was first reported by Dore and colleagues (1999) and subsequently confirmed and extended by other studies. A decline in the incidence of HIV-D, from 21/1000 person-year to 10/1000 person-year, in the HAART era was reported by Sacktor and colleagues (2001). More recently, a 45% rate of annual decrease for HIV-D incidence as AIDS-defining illness in the period 1994 to 2002 was reported in a prospective study in 70 European centers (D'Arminio Monforte *et al*, 2004). However, the reduced incidence of HIV-D as presenting clinical manifestation might underestimates the current prevalence and clinical impact of HIV-related NCI and HIV-D. A cross-sectional analysis published in 1998 showed an overall prevalence of neurocognitive impairment of 37% among patients taking HAART (Ferrando *et al*, 1998). Sacktor and colleagues (2002) showed that there were no differences in the occurrence of HIV dementia or abnormalities in neuropsychological tests in patients seen between 1994 and 1999. Dore and colleagues (2003) reported that proportion of AIDS cases with ADC increased from 5.2% in 1993 to 1995 to 6.8% in 1996 to 2000 among the Australian AIDS notification data. However, to our knowledge, data on the prevalence of HIV-related NCI and HIV-D in observational clinical cohorts have not been updated. These data are needed because large autopsy series consistently show an high prevalence of HIV-D, that continues to be detected in at least 25% of the cases (Masliah *et al*, 2000), with a trend toward an even increase in prevalence in the era of HAART (Neuenburg *et al*, 2002). The data of our observational clinical cohort are consistent with autopsy studies. We found that the prevalence of HIV-related NCI, as detected by comprehensive neuropsychological and clinical examinations, ranged from 46.5% in 2000 to 62.0% in 1997, with an overall prevalence of 55.1%, in an unselected population sample of 432 patients that included 60% of subjects receiving HAART for a mean of 19 months. The prevalence of HIV-D did also not change between 1996 and 1999 and 2000 and 2002. Although the selection criteria might have overestimated the prevalence of NCI, our data indicate that the prevalence of HIV-related NCI have been remaining almost unchanged over a period of 7 years of HAART. This finding reinforces the concept that the HIV-related NCI is still a prevalent condition despite the availability of HAART as a standard of care.

The unchanged prevalence of HIV-related NCI and HIV-D could be due to several factors: the prolonged survival of HIV-infected patients, the exposure to other disorders that could affect cognition, the limited access to the brain of some antiretrovirals, and the persistence of preexisting HIV-related cognitive deficits not reversible with HAART. The overall prevalence of HIV-related NCI might still be high due to the impact of HAART on the natural history of HIV disease. Whereas in the pre-HAART era the mean survival in patients with HIV-D was 6 months, now it has significantly increased. Although the cognitive impairment is at least partly reversible with antiretroviral therapy, a consistent proportion of cognitively impaired patients continues to show an abnormal neuropsychological performance despite more than 3 years of HAART (Tozzi *et al*, 2001). Thus, many patients with HIV-D are living longer while facing the persistence of cognitive

deficits of various degrees, perhaps as a results of neuronal loss.

As already known from the literature, HIV-related NCI was associated with lower education, lower education, intravenous drug use as HIV transmission modality, and advanced HIV disease. However we found evidences for new additional potential risk factors for HIV-related NCI: older age, lower nadir CD4 cell count by clinical history, and positive HCV serology.

Data suggesting an association of neurocognitive impairment with increasing age have recently been reported. In a 1-year longitudinal follow-up study, Becker and colleagues (2004) reported that the prevalence of cognitive disorders among HIV-positive patients over 50 years was significantly greater than in patients younger than 50 years. They conclude that age is a significant risk modifier for prevalent neuropsychological disorder (Becker *et al*, 2004). Justice and colleagues (2004) recently found a higher prevalence of memory neurocognitive problems with increasing age in HIV-positive patients. In our cohort, impaired patients were older than unimpaired subjects, supporting the hypotheses that aging could be an important risk factor for NCI.

In our study a low nadir CD4 cell count was significantly associated with NCI. Impaired patients had a nadir CD4 cell count of 156 cells/μl, whereas in unimpaired patients the nadir CD4 cell count was 222 cells/μl. To our knowledge our is among the first report to show an association between nadir CD4 cell count and NCI. It has been recently postulated that both nadir CD4 count and disease duration could be two potentially new risk factors in the HAART era, with low nadir CD4 cell count allowing HIV to access the brain and HAART unable to eradicate the virus from the CNS, ultimately leading to cognitive decline (Brew, 2004), despite the HAART-induced immune recovery. The absence of association between CD4 cell count at the time of the neuropsychological evaluation with cognitive impairment support this hypotheses.

The association of positive HCV serology with cognitive impairment in HIV-infected patients was recently reported in the literature. HCV, as well as HIV, has been associated with significant deficits in sustained attention and psychomotor speed (Hilsabeck *et al*, 2002; Forton *et al*, 2002). Hepatitis C, in association with HIV, may lead to more profound neurocognitive impairment. In a small study Letendre and colleagues (2002) reported that HCV/HIV-coinfected patients were more likely to be neurocognitively impaired than patients with HCV or HIV alone. In a cross-sectional study on advanced HIV patients, Ryan and colleagues (2004) showed both a trend for HIV/HCV-coinfected patients to perform worse neurocognitively and a higher prevalence of HIV-D among HCV-positive patients. We found that impaired patients had a higher prevalence of positive HCV serology then unimpaired subjects, supporting the hypotheses that HCV infection can be a risk factor for NCI.

We also found evidences for a change for risk factors for HIV-related NCI over time during the HAART era. When compared with impaired patients seen during 1996 to 1999, impaired patients seen during the 2000 to 2002 era tended to be older, with less advanced disease, and with higher CD4 cell count by clinical history. Data providing evidences for a change in HIV-associated NCI in the era of HAART has recently appeared in the literature. The association of HIV-related NCI with higher CD4 cell count was first reported by Dore and colleagues (1999). Whereas in the pre-HAART era the mean CD4 cell count at the time of HIV-D diagnosis was between 50 and 100 cells/μl, nowadays it has increased significantly. In our cohort, patients seen in the late HAART era had a higher nadir CD4 cell count then patients seen during early HART era. Moreover, consistent with the increase in nadir CD4 cell count, a significant difference was seen in the CDC clinical stage at the time of neuropsychological evaluation by calendar year. Whereas in 1996 more than 70% of patients with HIV-related NCI have already had at least one AIDS-defining clinical event, the proportion of patients with a previous AIDS diagnoses fell to less than 30% in 2002, showing a highly significant decreasing trend. To our knowledge our data are among the first to show an association between a less advanced diseases stage and NCI in the late HAART era. The reason for the association of HIV-related NCI with higher CD4 cell count by clinical history and with less advanced disease stage is not clear. However, our data are consistent with other repot from the literature, and support the hypotheses of new potentially new risk factors for HIV-related NCI: nadir CD4 cell count and disease duration (Brew, 2004).

HAART exposure was greater in patients with NCI seen during 2000 to 2002 than in patients seen in 1996 to 1999. The significantly greater HAART exposure could be explained by the longer availability of HAART as a standard of care, rather than by a reduced efficacy of antiretroviral regimens. The unchanged proportion of patients with plasma HIV RNA below 500 copies/ml support this explanation.

Our study differs from previous ones on the topic in several regards. First, our data were obtained in an unselected population sample of different risk group categories representative of patients seen in routine practice. Second, our study covered 7 years of HAART. To our knowledge such a long extended survey was never reported in the literature.

Our study had some limitations. The inclusion criteria may have selected for more patients with neurocognitive impairment. Thus, our patients might be not fully representative of people with HIV infection and might have overestimated the prevalence of NCI and of HIV-D. However, this does not diminish the importance of the unchanged prevalence of HIV-related NCI. Second, we examined the prevalence of

neurocognitive impairment in patients referred for the first time for neuropsychological examination and no prospective data on cognitive performance in patients receiving HAART were available. Thus our study do not allow any conclusion on the impact of HAART on neurocognitive function. Finally there was on age-matched control group. Because the cumulative number of AIDS cases reported in subjects aged over 50 years has increased significantly (Mack and Ory, 2003), an increase in age could be expected not only for HIV-D but also for other AIDS-defining conditions.

In conclusion, our data, obtained in an unselected population of HIV-infected patients referred for neuropsychological examination and representative of subjects seen in routine practice, indicate an unchanged prevalence of HIV-related NCI during 1996 to 2002 despite the wide availability of HAART, and a change in risk factors for NCI. Coinfection with HCV, increasing age, nadir CD4 cell count, and less advanced HIV disease now appear as important risk factors for cognitive dysfunctions. Clinicians should be aware of the prevalence, risk factors, and potential clinical implications of neurocognitive impairment in HIV-positive patients.

Methods

Patients and setting
Patients were recruited at the National Institute for Infectious Diseases Lazzaro Spallanzani, Rome, Italy, which provides care for HIV infection to more then 3500 patients. Between January 1996 and December 2002 all patients with HIV infection referred for the first time for neuropsychological examination were considered eligible for the study. A total of 494 patients were screened. Sixty-two patients were excluded because of potentially confounding factors for HIV-related NCI, such as concurrent opportunistic infections ($n = 6$), opportunistic infections or tumors of the central nervous system (CNS) ($n = 9$), non–HIV-related major neurological or psychiatric disorders ($n = 10$), current use of illicit drugs or opioid analgesics, or alcohol dependence ($n = 25$). Two patients were excluded because Italian was not their native language. Ten patients refused to be examined. The remaining 432 patients were recruited into the study and represent the study population.

Reasons for neuropsychological examination in these patients included signs or symptoms of suspected cognitive impairment (240 patients), assessment of cognitive functions before initiation of HAART (38 patients, including 11 patients with primary HIV infection), severe immunodeficiency (CD4 cell count below 200/mm^3), and/or antiretroviral treatment failure (154 patients). Some patients ($n = 111$) were enrolled in previous studies to evaluate the effect of HAART on HIV-associated NCI (Tozzi *et al*, 2001) and the association of HIV-related NCI with quality of life (Tozzi *et al*, 2003). This study was conducted according to an internal protocol approved by the local Ethics Committee.

Study measures
After comprehensive clinical evaluation and laboratory testing, patients were administered a standardized neuropsychological testing. Neurological examination and brain imaging studies were performed in patients with impaired results on neuropsychological testing.

Epidemiological and demographic data were obtained, and a general physical examination was performed. Current and past medications were recorded. The following data were abstracted from the patient's clinical records within 1 month of the neuropsychological testing: duration of HIV infection, HIV disease stage, treatment history, CD4 cell count, plasma HIV RNA, and routine laboratory testing. Routine laboratory measures were targeted to detect HIV-related complications, drug-related adverse events, and clinical events that could affect cognitive function.

Neuropsychological testing
A battery of 17 standardized neuropsychological tests was administered by a trained neuropsychologist (P.B.) and required approximately 90 min to complete. Tests were selected to be sensitive to a comprehensive range of different cognitive domains: mental flexibility (Trail Making B, Stroop Colour Word, Controlled Oral-Word), concentration and speed of mental processing (Trail Making A, WAIS-R Digit Span, WAIS-R Digit Symbol, Corsi Cube Test, Stroop Word and Colour), memory (Rey Auditory Verbal Learning Test [RAVLT], Rey Complex Figure [delayed], Babcook Story Recall Test), visuospatial and constructional (Rey Complex Figure, Copy Trial), and fine motor functioning (Lafayette Grooved Pegboard). The score of each test was adjusted for age and years of education as described by Lezak (1983) and by Spinnler and Tognoni (1987).

Neurologic examination and diagnostic criteria for cognitive impairment
Neuropsychological testing was used to identify subjects with cognitive impairment. Neuropsychological tests were examined by the consultant neurologist and the neuropsychologist. Subjects were classified as having or not having a cognitive impairment according to their performance relative to age- and gender-adjusted normative data (Lezak, 1983; Spinnler and Tognoni, 1987). Cognitive impairment was defined as performance greater than one standard deviation below the normative mean on at least two neuropsychological tests or two standard deviations below the mean on at least one test. A general neurological examination was performed by the consultant neurologist in patients with impaired

neuropsychological examinations. A brain magnetic resonance imaging (MRI) was also performed in impaired patients to exclude confounding concomitant illnesses. The diagnosis of HIV-related cognitive impairment required the exclusion, by laboratory measures, detailed neurological examinations and brain imaging studies, of other conditions that could explain the finding. The American Academy of Neurology (1991) criteria were used to determine whether the degree of impairment met the criteria for HIV-D or for cognitive impairment without dementia.

NPZ scores

The neuropsychological score resulting from each test was transformed into a *z*-score using a reference population consisted of 346 HIV patients deemed not impaired based on neuropsychological examination. The *z*-scores were obtained by the formula: (subject quantitative score − reference population mean)/reference population standard deviation (Sidtis *et al*, 1993). An NPZ8 score was obtained. This formula was calculated separately for patients belonging to four different classes of age and from three different classes of education year, using separate population reference (age: <30, 30–34, 35–39, ≥40; education: 5–10 years, 11–15 years, ≥16 years). Each *z*-score was adjusted so that negative values indicated below-average performance. The NPZ8 score was derived as an average of eight individual *z*-score from selected neuropsychological test (Trail Making A, Trail Making B, Lafayette Grooved Pegboard dominant hand, Lafayette Grooved Pegboard nondominant hand, WAIS-R Digit Span [Backword], WAIS-R Digit Symbol, and Rey Auditory Verbal Learning Test, and Rey Auditory Verbal Learning Test after 15 min). NPZ8 scores could be calculated for 317 out of 432 patients.

Statistical methods

Comparisons between impaired and not impaired patients or between impaired patients who underwent neuropsycological test in 1996 to 1999 and in 2000 to 2002, were made by Student's *t* test for continuous variables and Fisher's exact test for categorical variables.

ANOVA was used to analyze average NPZ8 scores in different calendar year. Chi-square for trend was used for testing trend in prevalence of neurocognitive impairment by calendar year.

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