Incidence and Impact on Mortality of Severe Neurocognitive Disorders in Persons With and Without HIV Infection: A Danish Nationwide Cohort Study

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Objective. The risk of neurocognitive disorders in human immunodefiency virus (HIV)–infected patients in the era of highly active antiretroviral therapy (HAART) is controversial. We aimed to compare the incidence and impact on mortality of severe neurocognitive disorders (SNCDs) in HIV-infected patients with that of the background population.

Methods. The method used was a nationwide, population-based cohort study using Danish registries. We calculated incidence rates, incidence rate ratios, mortality rate ratios, and Kaplan–Meier tables to estimate the incidence of and survival after SNCD in HIV-infected patients, compared with a general population control cohort matched by age and sex.

Results. We observed 32 cases of SNCDs among 4452 HIV-infected patients and 120 cases of SNCDs among 62 328 population control subjects. The overall risk of SNCD among HIV-infected patients was 1.0 case per 1000 person-years (PYR), compared with 0.23 cases per 1000 PYR for population control subjects but became 0.35 cases/1000 PYR after 2004, compared with 0.27 cases/1000 PYR in population control subjects. The absence of HAART and a low CD4 lymphocyte count increased the risk of SNCD. The mortality among HIV-infected patients with SNCD was higher than that among population controls with SNCD (median survival, 4.3 years vs 9.7 years [$P = .02$]).

Conclusion. HIV-infected patients have an increased risk of SNCD, but the risk is low and has, in recent years, become comparable to that seen in the background population. In contrast, the mortality remains high among HIV-infected patients diagnosed with SNCD.

During the past decade, highly active antiretroviral therapy (HAART) for human immunodeficiency virus (HIV) has decreased morbidity and mortality substantially in the HIV-infected population [1, 2]. It is still debated to what extent the HIV-infected population experiences increased risk of morbidity associated with non-HIV-defining cancers, cardiovascular diseases, and accelerated aging [3]. Before HAART, neurocognitive disorders (NCDs) were major threats to the HIV-infected population, especially in late stages of the disease [4]. It is controversial whether HIV-infected patients are still at increased risk of NCDs despite HAART [5, 6]. Several studies have observed persistent and even slightly increased risk of NCDs in HIV-infected patients on HAART [7–11]. An increased risk of NCDs in HIV-infected patients on HAART could be induced by chronic HIV infection and persistent inflammation in the central nervous system (CNS) despite HAART

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[12–14], which may subsequently lead to increased deposition of β-amyloid in the CNS of HIV-infected patients [15] and eventually to Alzheimer dementia [16].

We aimed to estimate the risk of severe neurocognitive disorders (SNCDs) in HIV-infected patients in the HAART era, and compare the risk with that of a matched HIV-uninfected general population control cohort. Furthermore, we determined the impact of SNCDs on mortality in the HIV-infected and HIV-uninfected populations.

METHODS

Study Design

In the first part of the study, the study populations were a nationwide cohort of HIV-infected patients and a cohort of HIV-uninfected individuals matched by age and sex. The outcome was time to a first diagnosis of an SNCD. In the second part of the study, the outcome was time to death, and we determined the impact of SNCDs on mortality in the 2 cohorts.

Setting

In 2007, Denmark had a population of 5.5 million, with an estimated HIV infection prevalence of ~0.07% among adults [17]. Patients with HIV infection are treated in 1 of the country's 8 specialized medical centers, where they are seen on an outpatient basis at intended intervals of 12 weeks. Antiretroviral treatment is provided free of charge to all HIV-infected residents in Denmark and prescribed according to international guidelines.

Data Source

We used the unique 10-digit civil registration number assigned to all individuals in Denmark to link the data sources described below.

The danish HIV cohort study. The Danish HIV Cohort Study (DHCS) is a population-based prospective nationwide cohort study of all HIV-infected individuals ⩾16 years at time of HIV infection diagnosis and who have been treated at Danish HIV centers since 1 January 1995 [18]. Patients are consecutively enrolled, and multiple registrations are avoided using the unique 10-digit civil registration number assigned to all individuals in Denmark at birth or immigration. Data are updated annually and include demographic characteristics, date of HIV infection, AIDS-defining events, date and cause of death, and antiretroviral treatment. CD4 lymphocyte counts and HIV RNA measurements are extracted electronically from laboratory data files.

The Danish civil registration system. From the Danish Civil Registration System(DCRS), which has stored information on all Danish residents since 1968, we extracted information of date of birth, sex, location of residence, dates of emigration or immigration, and date of death [19].

The Danish national hospital registry. Since its establishment in 1977, the Danish National Hospital Registry (DNHR) has kept records of all in-patient admissions to non-psychiatric hospitals in Denmark. Data from outpatient and emergency department visits were added in 1995. Each record includes the dates of admission and discharge, 1 primary diagnosis and up to 19 discharge diagnoses coded according to the *International Classification of Diseases, Eighth Revision (ICD-8)* until 1993, and the *Tenth Revision (ICD-10)* from 1994 onward. One of the discharge diagnoses is designated as the primary diagnosis. The diagnosis codes are recorded at the time of discharge by the medical doctor responsible for discharging the patient [20].

Study Population

HIV-infected population. The study included all patients in DHCS who received a diagnosis of HIV infection after the age of 16 and before 1 June 2008, lived in Denmark at time of the HIV infection diagnosis, and did not receive a diagnosis of SNCD before the HIV infection diagnosis. In our study, the index date was defined as the date of HIV infection diagnosis for all cohort members except those who received a diagnosis of HIV infection before 1997. For these latter patients, the index date was set as 1 January 1997.

General population control cohort. From the DCRS, we identified 14 population controls for each HIV-infected patient, matched by age (month and year of birth) and sex. For the population controls, the index date was defined as the index date of the HIV-infected patients to whom they were matched. The population controls had to be alive and living in Denmark on the index date. Because of the nature of the study, the population controls were not systematically screened for HIV infection.

Outcomes and Other Studied Variables

Definition of SNCDs. SNCDs were defined as the following diagnoses in the DNHR: senile and pre-senile dementia, Alzheimer dementia, degenerative dementia, alcoholic dementia, vascular dementia, AIDS dementia, post-infectious dementia, epileptic dementia (*ICD-8* diagnosis 29009–29309, or *ICD-10* diagnosis G300–G319, F0–F039, or F051), or a diagnosis of AIDS dementia in DHCS.

Comorbidity. Comorbidity data were categorized with Charlson Index scores based on discharge diagnoses registered in the DNHR before the index date for both populations [20]. The Charlson comorbidity index scoring system assigns between 1 and 6 points to a range of diseases, with the points' sum serving as the comorbidity measure for each patient during previous hospital contacts [21]. We captured the comorbid diseases with use of the *ICD-8* and *ICD-10* codes [22]. AIDS-defining diagnoses were not included. We defined 3 modified comorbidity levels according to the Charlson index: low = 0 (Charlson score = 0), medium = 1 (Charlson score of 1–2), or high = 2 (Charlson score >2).

We defined alcohol abuse as being registered in DNHR with ≥1 of the following diagnoses prior to the index date: *ICD-8* codes 291.00–291.99, 571.09, 571.10, 303.00–89, 303.91–99 and *ICD-10* codes K 70.0–70.9, F10.2–10.9, G31.2. Injection drug use (IDU) was defined as having IDU reported as the route of HIV transmission. Chronic hepatitis C virus (HCV) infection was defined as positive tests for HCV antibodies and/or HCV RNA.

Statistics

Part one, incidence study. We computed time from the index date (1 January 1997 or date of HIV infection diagnosis) to date of a first SNCD diagnosis, death, loss to follow-up, emigration, or 1 June 2008, whichever came first. Incidence rates (IRs) for SNCDs were calculated for 1000 person-years at risk (PYR), with 95% confidence intervals (CIs), and were stratified by age and sex. Cox regression analysis was performed to estimate unadjusted incidence risk ratios (IRRs) and IRRs adjusted for the modified Charlson comorbidity index (0, 1, or 2). In these analyses, the first date with a CD4 lymphocyte count ≤350 cells/μL before HAART initiation, the date of HAART initiation, and the date of first CD4 lymphocyte count ≥350 cells/μL after HAART initiation were introduced as time-dependent variables. Late presenters were defined as individuals presenting with a CD4 lymphocyte count <200 cells/μL or AIDS within 3 months after their first test positive for HIV.

Part two, mortality study. We computed time from the index date to date of death, emigration, or 1 June 2008, whichever came first. For the populations with SNCD, the Kaplan–Meier estimator was used to construct survival curves in which time was calculated from date of SNCD diagnosis to the first of date of death, emigration, or 1 June 2008. We calculated mortality rate ratios (MRRs) for HIV-infected patients and population controls who received a diagnosis of SNCD. MRRs were estimated using Cox regression analyses stratified according to the initial match criteria (age and sex). For HIV-infected patients and population controls, the date of a first SNCD was introduced in the Cox regression analyses as time-dependent variables.

The study was approved by the Danish Data Protection Agency. SPSS statistical analysis software, version 15.0 (Norusis; SPSS) and R software version 2.8.1 (the GNU Project), were used for data analysis.

RESULTS

Characteristics of the Study Population

The study population included 4 452 HIV-infected patients and 62,328 individuals in the general population control cohort (Table 1). Because of the matched-study design, patients and population controls were well matched in terms of age at index date and sex, and furthermore, they were equally distributed in terms of emigration and loss to follow-up. Median age was 37 years (interquartile range [IQR] 31–45) and the sex ratio male-to-female was 3:1. During the study period, the HIV-infected cohort accumulated 32 394 person-years of observation (PYR), and the population controls presented a total of 515 467 PYR. Almost half of the HIV-infected patients (46%) had received a diagnosis of HIV infection before 1 January 1997, and 1 133 (25%) had had received an AIDS-defining diagnosis prior to study inclusion. Eighty percent of the HIV-infected patients started HAART before or during the study period. One hundred thirty-one of the HIV-infected patients (3%) received a diagnosis of a neuro-AIDS-defining event other than AIDS dementia (cerebral toxoplasmosis, cryptococcosis, tuberculosis, lymphoma, cytomegalovirus [CMV], or progressive multifocal leukoencephalopathy [PML]) prior to study inclusion.

Part One, Incidence Study

Characteristics of the SNCD patients. During the study period, we observed 32 SNCD events in the HIV-infected patient cohort and 120 SNCD events in the general population control cohort. Of the 32 diagnoses of SNCD in the HIV-infected patients, 12 (37.5%) were AIDS dementia. Demographic characteristics of HIV-infected patients and population controls who received a diagnosis of SNCD are presented in Table 2. The HIV-infected patients who received a diagnosis of SNCD were younger than the population controls, had less comorbidities, and were less likely to receive a diagnosis of alcohol abuse. No HIV-infected patients had developed other neuro-AIDS conditions before a diagnosis of SNCD. Among HIV-infected patients, 65% received a diagnosis of HIV infection at least 10 years before an SNCD diagnosis, 66% were treated with HAART (of whom 71% had an undetectable viral load), and only 25% had CD4 lymphocyte count <100 cells/μL (Table 2). Nine HIV-infected patients were well controlled from a virological, immunological, and clinical standpoint, and had no other non-HIV causes of SNCD. Three patients were considered as late presenters (diagnosed in 1997, 2003, and 2006).

Absolute risk of developing SNCDs. In the HIV-infected population, the absolute risk of developing SNCDs was 1.0 case/1000 PYR, compared with 0.23 cases/1000 PYR for the population controls (Table 3). Figure 1 shows IRs of SNCDs for HIV-infected patients and population controls stratified by calendar periods (1997–2000, 2001–2004, and 2005–2008); the risk of SNCD decreased dramatically in the HAART era, whereas the risk in the general population control cohort increased slightly. Table 3 shows IRs for HIV-infected patients according to sex, CD4 lymphocyte count, HCV status, IDU, and alcohol abuse. Injection drug users and patients with alcohol abuse had an increased risk of SNCD. The IR of SNCD in HIV-infected patients who received a diagnosis after 1 January 1997 was slightly lower than that in the HIV-infected patients diagnosed before 1997.

Table 1. Characteristics of HIV-Infected Patients and Population Controls

Variables	HIV-infected patients (n = 4452)	Population controls (n = 62,328)
Age, years, median (IQR)	37.1 (31.2–44.9)	37.1 (31.2–44.9)
Male, no (%)	3327 (74.7)	46 578 (74.7)
Modified Charlson comorbidity index[a], no (%)		
0	4023 (90.4)	57 783 (92.7)
1	380 (8.5)	4013 (6.4)
2	49 (1.1)	532 (0.9)
Alcohol abuse, no (%)	156 (3.5)	747 (1.2)
Duration of follow-up, years, median (IQR)		
Total	7.8 (3.8–11.4)	
⩾350 CD4 before HAART	0.6 (0.05–2.6)	
<350 CD4 before HAART	0.3 (0.06–1.2)	
<350 CD4 under HAART	1.1 (0.26–2.8)	
⩾350 CD4 under HAART	6.3 (3.3–9.1)	
Loss to follow-up, no (%)	16 (0.4)	27 (0.1)
Migration, no (%)	174 (3.9)	884 (1.4)
Infection risk factors, no (%)		
MSM	1943 (43.7)	
Heterosexual	1693 (38.0)	
IDU	479 (10.8)	
Others or unknown	334 (7.5)	
White race, no (%)	3347 (78.7)	
Diagnosis of HIV infection before 1 January 1997, no (%)	2040 (45.8)	
HAART during study period, no (%)	3583 (80.5)	
CD4 lymphocyte count at index date, median (IQR), cells/μL	300 (140–490)	
Neuro-AIDS[b], no (%)	131 (2.9)	
AIDS before inclusion, no (%)	1133 (25.4)	
HCV infection, no (%)	366 (8.2)	

NOTE. HAART: highly active antiretroviral therapy; HCV: hepatitis C virus; IDU: injection drug use; IQR: interquartile range; MSM: men who have sex with men.

[a] Modified Charlson index: Charlson scale 0 = 0; 1–2 = 1; and >2 = 2.

[b] Neuro-AIDS corresponds to a history of cerebral toxoplasmosis, cryptococcosis, tuberculosis, lymphoma, PML, or CMV prior to study inclusion.

Incidence rate ratios of SNCD. Overall, HIV-infected patients had a 4.2-fold increased risk of developing SNCDs compared with population controls. The risk increased substantially for the HIV-infected patients when the CD4 lymphocyte count decreased to <350 cells/μL (adjusted IRR, 10.1). After immune reconstitution developed after initiating HAART (CD4 cell count >350 cells/μL), IRRs decreased to a level comparable to that observed for HIV-infected patients with CD4 cell counts >350 cells/μL in the pre-HAART period. For both periods, however, the risk of developing SNCDs was clearly increased compared with the population controls. After immune reconstitution developed during HAART, HIV-infected patients without IDU had a risk of SNCDs that was only twice that of the population controls (Table 4).

Part Two, Mortality in SNCD Patients

A total of 19 HIV-infected patients and 42 population controls died after a diagnosis of SNCD. Kaplan–Meier curves for the 2 populations with SNCDs are shown in Figure 2. The impact of SNCDs on mortality in HIV-infected patients was 2-fold higher than in the population controls (P = .02). The HIV-infected patients with SNCDs had a 26.3-fold increased risk of death (95% CI, 12.2–56.9), compared with the population controls without SNCDs. In addition, the mortality in the population controls who received a diagnosis of SNCDs was almost 8 times higher than that among those who did not receive a diagnosis of SNCDs (MRR, 7.5 [95% CI, 5.1–11.0]).

DISCUSSION

In this nationwide population-based cohort study, we found that the risk of SNCD decreased substantially in the HAART era, and after 2004, it was comparable to that observed in the background population. The absence of HAART and a low CD4 lymphocyte count increased the risk of SNCD. Furthermore, the mortality of HIV-infected patients who received a diagnosis of

Table 2. Characteristics of Patients with Severe Neurocognitive Disorders (SNCDs): HIV-Infected and Population Controls

Variables	HIV-infected patients with SNCDs (n = 32)	Population controls with SNCDs (n=120)
Age, median (IQR), years	44.5 (36.5–52.2)	53.2 (46.9–63.5)
Males, no (%)	27 (84.4)	110 (91.7)
Period of diagnosis		
1997–2000, no (%)	14 (44)	23 (19)
2001–2004, no (%)	14 (44)	45 (38)
2005–2008, no (%)	4 (12)	52 (43)
Modified Charlson comorbidity index, no (%)		
0	29 (90.6)	84 (70)
1	2 (6.3)	29 (24.2)
2	1 (3.1)	7 (5.8)
Alcohol abuse, no (%)	3 (9.4)	19 (15.8)
Infection risk factors, no (%)		
MSM	14 (43.8)	
Heterosexual	10 (31.3)	
IDU	6 (18.8)	
Others or unknown	2 (6.3)	
White race, no (%)	28 (87.5)	
Diagnosis of HIV infection before 1 January 1997, no (%)	21 (65.6)	
HAART at the date of SNCD diagnosis, no (%)	21 (66)	
CD4 lymphocyte count at index date, median (IQR),cells/μL	263 (88–414)	
CD4 lymphocyte count at date of SNCD diagnosis, cells/μL	255 (109–365)	
Viral load below detection level at date of SNCD diagnosis, no (%)	15/21 (71)	
Late presenters, no (%)	3 (9.4)	
Neuro-AIDS other than SNCD, no (%)	0 (0)	
AIDS, no (%)	11 (34.4)	
Chronic HCV infection, no (%)	2 (6.3)	

NOTE. HAART: highly active antiretroviral therapy; IDU: injection drug use; IQR: interquartile range.

SNCD was high and substantially higher than that observed in HIV-uninfected patients who received a diagnosis of SNCD.

The major strengths of the study are its nationwide population-based design, combined with complete follow-up and the capacity to compare incidence of SNCD with that observed in an age- and sex-matched general population control cohort. Access to complete data on hospitalization, antiretroviral treatment, and CD4 lymphocyte counts allowed us to adjust for comorbidity and to estimate the impact of immunodeficiency and antiretroviral therapy on the risk of developing SNCD.

Two potential biases may have lead to an overestimation of incidence of SNCD in HIV-infected patients: (1) the frequent hospital contacts of Danish HIV-infected patients may make them more prone to have symptoms of SNCDs recorded in national registries, and (2) of note, our study compared SNCDs in 2 populations of which one, by definition, could not develop HIV dementia. However, we found IRs of SNCD in HIV-infected patients equivalent to that in other comparable studies [7, 8], and after 2004, IRs were close to that of population controls. In addition, population controls may have been infected with HIV without receiving a diagnosis of the disease. We presume, however, that this misclassification is of minor importance, as the incidence of undiagnosed HIV infection in the Danish population is suggested to be <0.02%.

The study outcome was based on discharge diagnoses, which could underestimate the true incidence of neurocognitive disorders, especially in patients with discrete symptoms. However, we presume that these factors are not very prominent in the pathogenesis of SNCDs conversely to mild cognitive impairments [23], and we focused the analysis exclusively on SNCDs, in accordance with other studies with similar designs [7, 8]. The risk of SNCD has been linked to HIV replication in the CNS and, thereby, to the penetration and effectiveness of antiretroviral therapy in the brain, sometimes expressed as CNS penetration-effectiveness [24]. We did not perform an analysis on CNS penetration-effectiveness, because its clinical relevance remains a matter of debate [5].

We observed that the risk of SNCD was 1.0 case/1000 PYR, which is in accordance with that observed by other cohort studies [7, 8]. It has been presumed that HIV-infected patients

Table 3. Incidence Rates of Severe Neurocognitive Disorders (SNCD) in HIV-Infected Patients and Population Controls

Variables	Diagnosis of SNCD	PYR	Incidence rate, cases per 1000 PYR
HIV-infected patients	32	32 394	1.0 (0.7–1.4)
Population controls	120	515 466	0.23 (0.19–0.28)
HIV-infected patients			
Sex			
Female	5	8382	0.60 (0.25–1.43)
Male	27	24 012	1.12 (0.77–1.64)
CD4 count, cell/μL			
<200	13	10 911	1.19 (0.69–2.05)
200–500	15	14 113	1.06 (0.64–1.76)
>500	4	7370	0.54 (0.20–1.45)
AIDS history before SNCD			
No	21	24 483	0.86 (0.56–1.32)
Yes	11	7911	1.39 (0.77–2.51)
HCV			
Chronic infection	2	3047	0.66 (0.16–2.62)
Negative or cleared	30	29 347	1.02 (0.71–1.46)
IDU			
Yes	6	3390	1.81 (0.81–4.02)
No	26	28 984	0.90 (0.61–1.32)
Alcohol abuse			
Yes	3	956	3.14 (1.01–9.72)
No	29	31 438	0.92 (0.64–1.33)
Alcohol abuse or IDU			
Yes	9	3921	2.29 (1.19–4.41)
No	23	28 473	0.81 (0.54–1.22)
HIV-infected patients who received a diagnosis of HIV infection from 1 January 1997			
Overall			
HIV-infected patients	11	12 968	0.85 (0.47–1.53)
Population controls	42	19 9336	0.21 (0.16–29)

NOTE. HCV: hepatitis C virus ; PYR: person-years at risk.

receiving effective HAART may still suffer from chronic neuron inflammation [14,25–27], leading to increased risk of SNCD [5, 9, 10, 28]. In contrast to these hypotheses, we did not observe an increased risk of SNCD, but we found a decreased risk over time, which may be related to better efficacy and safety of antiretrovirals and better access of care for HIV-infected patients.

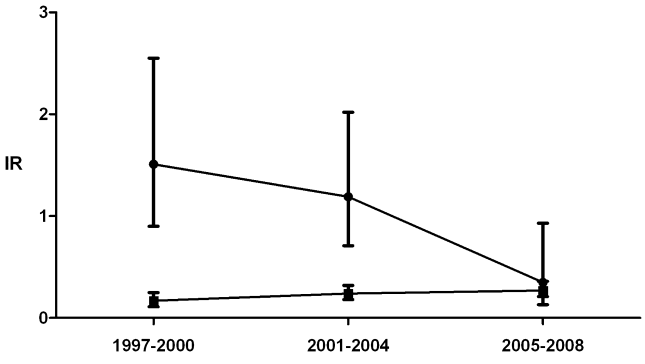

Figure 1. Incidence rates (IR) (per 1,000 PYR, 95% confidence intervals [CI]) for severe neurocognitive disorders in HIV-infected patients *(filled circles)* and population controls *(squares),* by period: 1997–2000, 2001–2004, and 2005–2008.

In accordance with previous findings, we observed an increased risk of SNCD among patients with low CD4 lymphocyte counts [4, 7, 29]. Of importance, the risk seemed to be increased in patients with a CD4 lymphocyte count <350 cells/μL, irrespective of HAART. In addition, the optimal protective level of the CD4 lymphocyte count seemed to be 500 cells/μL (Table 3), which contrasts with classical AIDS dementia, for which a CD4 cell count cutoff of ~100 cells/μL has been established to be protective [4].

According to the concept of a neuron sanctuary for HIV infection [30] and the assumption of increased risk of chronic neuron inflammation in long-term survivors [14,25–27], some authors have claimed the emergence of a new subgroup of AIDS dementia complex characterized by the development of SNCDs in virologically well-controlled patients with a noncompromised immune system [28, 29]. The emergence of this new presentation of AIDS dementia could be attributable to an

Table 4. Incidence Rate Ratios (IRRs) for Severe Neurocognitive Disorders (SNCDs) in HIV-Infected Patients, Compared to Population Controls

Period	Diagnosis of SNCD	PYR	Unadjusted IRR	Adjusted IRR[a]
All HIV-infected patients				
⩾350 CD4, before HAART	4	5379	3.6 (1.3–9.8)	3.6 (1.3–9.6)
<350 CD4, before HAART	7	3132	10.5 (4.9–22.7)	10.1 (4.7–21.7)
<350 CD4, receiving HAART	8	5912	6.3 (3.1–13.0)	5.8 (2.8–11.9)
⩾350 CD4, receiving HAART	13	17 970	2.9 (1.7–5.2)	2.8 (1.6–4.9)
HIV-infected patients without IDU				
⩾350 CD4, non-HAART	3	4546	3.1 (1–9.7)	3.2 (1.0–10.0)
<350 CD4, non-HAART	6	2410	11.3 (4.9–25.8)	11.2 (4.9–25.5)
<350 CD4, receiving HAART	6	5166	5.2 (2.3–11.8)	4.8 (2.1–11.1)
⩾350 CD4, receiving HAART	10	16 598	2.3 (1.2–4.4)	2.2 (1.2–4.2)

NOTE. HAART: highly active antiretroviral therapy; IDU: injection drug use ; IRR: incident rate ratio; PYR: person-years at risk.
[a]Adjusted for modified Charlson comorbidity index.

increased risk of Alzheimer dementia in HIV-infected patients [16], the occurrence of a new kind of discordant HIV encephalitis in virologically well-controlled patients [31], or an immunological burn-out for which the trigger factor remains poorly documented [28, 32]. In our study, the 9 well-controlled HIV-infected patients without any other explanation for the SNCD may have had this form of dementia. Of interest, only 3 patients who received a diagnosis of SNCD were late presenters.

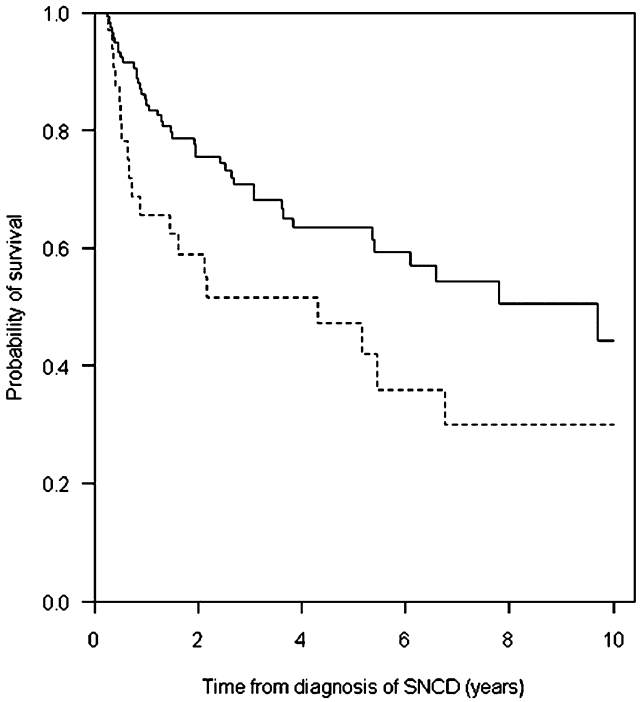

Figure 2. Kaplan–Meier survival curves for HIV-infected patients *(dotted line)* and population controls *(solid line)* who received a diagnosis of severe neurocognitive disorders (SNCDs). Median survival time in HIV-infected patients who received a diagnosis of SNCD was 4.3 years (95% confidence interval [CI], 0.13–8.5), compared with 9.7 years (95% CI, 5.1–14.6) for population controls. Log rank test: $P = .2$.

IDU and alcohol abuse are clearly linked to SNCDs [33]. In accordance, we observed an increased risk of SNCD in patients reporting IDU as route of HIV infection and a high fraction of HIV-infected and HIV-uninfected demented patients received a diagnosis of alcohol abuse. The link between IDU and AIDS dementia, which was prominent before the introduction of HAART, has become less clear in recent years [7, 34, 35] because of aggressive HIV therapies, changes in behavior of injection drug users, better-tolerated medicine, and optimized access to care for this population. HCV infection is strongly linked to IDU, but we did not observe any difference in risk of SNCD according to HCV infection status.

None of the HIV-infected patients with SNCD had a history of other neuro-AIDS diseases (cerebral toxoplasmosis, cryptococcosis, tuberculosis, lymphoma, PML, or CMV encephalitis) prior to the SNCD diagnosis. We presume that case patients who have received these neuro-AIDS diagnoses, become cognitively impaired and are not registered with AIDS dementia or non-AIDS SNCDs, but are categorized as having complications of the primary neuro-AIDS disease.

SNCDs and Mortality

Several studies have reported a high mortality rate among HIV-infected patients with SNCD [36–38]. In a study by Dore et al [39], the median survival time in patients with SNCD increased from 1 to 4 years after the introduction of HAART; we observed a median survival time of 4.3 years in the HIV-infected patients after SNCD diagnosis. In addition, our findings indicate that the mortality rate of SNCD among HIV-infected patients is clearly higher than in population controls (median survival time, 4.3 years vs 9.7 years). We presume that decreased compliance in

patients with SNCD may have increased the risk of HIV-related disease and thereby increased mortality in this group of patients.

We conclude that, even in the HAART era, HIV-infected patients have an increased risk of SNCD, compared with the background population. However, the risk has decreased over time and is now comparable to that in the background population. The mortality, however, remains high among HIV-infected patients who receive a diagnosis of SNCD.

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