Risk of cerebrovascular events in persons with and without HIV: A Danish nationwide population-based cohort study

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Objective: To assess the risk of cerebrovascular events (CVE) in HIV-infected individuals and evaluate the impact of proven risk factors, injection drug abuse (IDU), immunodeficiency, highly active antiretroviral therapy (HAART) and family-related risk factors.

Design: Nationwide, population-based cohort study

Methods: The study population included all Danish HIV-infected individuals, a population-based comparison cohort and parents of both cohorts – all with no prior cerebral comorbidity. We computed incidence rate ratios (IRR) of overall CVE and CVE with and without proven risk factors, stratifying the analyses on IDU. Impact of immunodeficiency, HAART, protease-inhibitors, indinavir, didanosin, tenofovir and abacavir on risk of CVE was analyzed using time-dependent Cox regression analyses.

Results: HIV-infected individuals had an increased risk of CVE compared with the comparison cohorts (non-IDU HIV adjusted IRR 1.60; 95% CI: 1.32–1.94), (IDU HIV adjusted IRR 3.94; 95% CI: 2.16–7.16). The risk was increased with and without proven risk factors. A CD4 count $< 200$ cells/\( \mu \)l before start of HAART and exposure to abacavir increased the risk of CVE (adjusted IRR 2.26; 95% CI: 1.05–4.86) and (adjusted IRR 1.66; 95% CI: 1.03–2.68). Protease-inhibitors, indinavir, didanosin, tenofovir and HAART in general had no impact. Risk of CVE was only increased in the parents of IDU HIV-infected individuals.

Conclusion: HIV-infected individuals have an increased risk of CVE with and without proven risk factors. The risk is associated with IDU, low CD4 count and exposure to abacavir, but not with HAART. An association with family-related risk factors seems vague except for parents of IDUs.

Introduction

During the last decade, several studies have established an association between HIV infection and cardiovascular disease. Recent studies have shown an increased risk of myocardial infarction associated with HIV infection, highly active antiretroviral therapy (HAART) and abacavir [1–4].

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Received: 10 December 2010; revised: 23 May 2011; accepted: 27 May 2011.

DOI:10.1097/QAD.0b013e3283493fbo
Less attention has been paid to the possibly increased risk of cerebrovascular disease. Previous studies, which are primarily from the pre-HAART era, are inconclusive but favour an increased risk of stroke in HIV-infected individuals [4–23].

We conducted a Danish nationwide, population-based cohort study to examine the risk of cerebrovascular events (CVE) in HIV-infected individuals compared to the general population. As the underlying mechanism for a possibly increased risk of cerebrovascular disease is unclear, we further examined the impact of 1) proven risk factors, 2) risk factors often associated with HIV infection (e.g. injection drug abuse (IDU)), 3) immunodeficiency, 4) use of antiretroviral drugs, and 5) the HIV infection per se on risk of CVE. We further examined the risk of CVE in parents of HIV-infected individuals to evaluate the impact of family-related risk factors.

**Methods**

**Setting**

As of 1 January 2010 Denmark had a population of 5.5 million [24], with an estimated HIV prevalence of 0.1% among adults. Medical care, including antiretroviral treatment, is tax-supported and provided free-of-charge to all HIV-infected residents of Denmark. Treatment of HIV infection is restricted to eight specialized medical centres, where patients are seen on an outpatient basis at intended intervals of 12 weeks. During our study’s follow-up period, national criteria for initiating HAART were HIV-related disease, acute HIV infection, pregnancy, CD4 cell count < 300 cells/µl, and, until 2001, plasma HIV-RNA >100,000 copies/ml.

**Data sources**

We used the unique 10-digit civil registration number assigned to all individuals in Denmark to link data from the following registers:

*The danish hiv cohort study (DHCS)*

DHCS, which has been described in detail elsewhere, is a nationwide, prospective, population-based cohort study of all Danish HIV-infected individuals treated at Danish hospitals since 1 January 1995 [25,26].

*The danish civil registration system (DCRS)*

DCRS, established in 1968, stores information on vital status, residency, and immigration/emigration for all Danish residents [27].

*The danish national hospital registry (DNHR)*

DNHR, established in 1977, records data on all admissions to non-psychiatric hospitals in Denmark, classified according to the *International Classification of Diseases* [8th revision (ICD-8) until Dec 31 1993 and 10th revision (ICD-10) thereafter] [28].

*The danish cancer register (DCR)*

DCR, established in 1942, records all cancer diagnoses according to a modified edition of the *International Classification of Diseases* [7th revision (ICD-7) since 1943 and according to the 10th revision (ICD-10) and ICD-O (for oncology) since 1994 (The cancer diagnoses from 1978–1994 was later converted to ICD-10 and ICD-O)] [29].

**Study populations**

**HIV cohort**

We identified all Danish HIV-infected individuals older than 16 years at date of HIV diagnosis from DHCS. The index date was defined as the date of HIV diagnosis, date of arrival to Denmark or January 1 1995 whichever was more recent. Individuals diagnosed with cerebrovascular disease or cerebral comorbidity (defined as CNS tumour, cancer, lymphoma, metastasis, non-HIV-associated cerebral infections, HIV-associated cerebral opportunistic infections and AIDS dementia) prior to index date, were excluded (Appendix I, Figure 1).

**General population comparison cohort**

A comparison cohort consisting of 9 age- and gender matched population controls, who were alive and living in Denmark on index date and not diagnosed with cerebrovascular disease or cerebral comorbidity prior to index date of the HIV-infected individual, were identified from DCRS. Index date was defined as date of index date of the matched HIV-infected individual.

**Parent cohorts**

From DCRS we identified parents of all Danish HIV-infected individuals and their matched comparison cohort in whom the offspring was born after 1952 and for whom at least the mother was identifiable. Parents diagnosed with cerebrovascular disease and cerebral comorbidity prior to index date were excluded. Index date of the parents was defined as the start of the Danish National Hospital Registry (January 1 1977), date of arrival to Denmark or date of birth of the offspring which ever was more recent.

**Outcome measures**

The primary outcome was time to first ever CVE defined as the first date an individual was registered with a diagnosis of non-traumatic subarachnoid haemorrhage, intracerebral haemorrhage cerebral infarction, unspecified stroke or transient ischemic attack in DNHR. Diagnoses obtained from emergency rooms but not confirmed subsequently were not included. The diagnosis stroke sequel was included as CVE if no prior CVE diagnosis was registered and categorized as unspecified stroke.
Outcomes (CVE) were classified as “CVE with proven risk factor” if at least one risk factor, as defined in appendix I, was present. The remaining outcomes were classified as “CVE with no proven risk factors”.

Statistical analysis
Time was computed from index date until date of CVE, date of other cerebrovascular disease than CVE, 30 days prior to or within 30 days after an event (for cancer up to 90 days after an event) [30–41]. The remaining outcomes were classified as “CVE with no proven risk factors”.

Results
We identified 5,031 HIV-infected individuals of whom 536 (10.7%) were IDUs and 45,279 comparison cohort individuals. The median age at index date was almost identical in the non-IDU and IDU HIV-infected individuals (36.9 years vs. 35.6 years), but more non-IDU HIV-infected individuals than IDU HIV-infected individuals were older than 50 years at index date (15.3%/1.9%). Additional characteristics of HIV-infected individuals and the two matched comparison cohorts are provided in Table 1. The registered risk factors are provided in appendix II, Table 1.

Overall CVE was diagnosed in 123 (2.7%) non-IDU HIV-infected individuals (43.9% with no proven risk factors) and in 17 (3.2%) IDU HIV-infected individuals. In the comparison cohorts CVE was observed in 998 (2.5%) individuals from the non-IDU comparison group (40.7% with no proven risk factors) and 84 (1.7%) of the IDU comparison group (39.3% with no proven risk factors). Additional information on CVE subtypes is provided in Table 1.

The cumulated incidences of CVE for the four groups including 5 and 10 years risk of CVE after index date are shown in Fig. 1.

As illustrated in Table 2, we found a higher risk of total CVE in the HIV-infected population compared to the comparison cohorts. The risk was substantially higher in the IDU than the non-IDU HIV-infected population (adjusted IRR 3.94; 95% CI: 2.16–7.16 versus adjusted IRR 1.60; 95% CI: 1.30–1.95). The increased risk in the non-IDU HIV-infected individuals was due to a higher risk of CVE with (adjusted IRR 1.55; 95% CI: 1.19–2.03) and without proven risk factors (adjusted IRR 1.65; 95% CI: 1.21–2.26). Furthermore, the increased risk of CVE was mainly due to a statistically significant higher
We found a significantly increased risk of total CVE in non-IDU HIV-infected individuals with a CD4 count ≤ 200 cells/µL who had not initiated HAART (adjusted IRR 2.26; 95% CI: 1.05–4.86) (Table 3). After initiation of HAART the risk was identical to that of the pre-HAART period with a CD4 count > 200 cells/µL. In the period with low CD4 count before start of HAART, we also observed a higher risk of CVE with and without proven risk factors although this was statistically insignificant (Table 3). In individuals who had initiated HAART, risk of CVE was increased after first exposure to abacavir (adjusted IRR 1.66; 95% CI: 1.03–2.68). The risk, however, stayed high after first cessation of abacavir (as a fraction of patients re-initiated abacavir, only 70.2% of the remaining observation time was time without abacavir treatment). This was also seen for CVE with and without proven risk factors although the latter two results were statistically insignificant. Initiating PI, indinavir, didanosin or tenofovir did not change the estimated risk of CVE (Table 3).

The performed robustness analysis, in which 1) individuals registered with stroke sequelae as first diagnosis and 2) individuals registered with hepatitis C infection were excluded, showed no major changes in CVE risk estimates. We identified 2,509 mothers and 2,289 fathers of HIV-infected individuals as well as 21,982 mothers and 21,009 fathers of comparison cohort individuals (Appendix II, Table 3).
The parents were comparable with respect to age and place of birth and the median time of follow-up was almost 30 years for all groups (Appendix II, Table 2). The parents of the HIV-infected individuals had a slightly increased risk of CVE, which was almost exclusively driven by a substantially increased risk seen in the parents of offspring reporting IDU as route of HIV transmission (Table 4).

Table 2. Relative risk of cerebrovascular events (CVE) in HIV-infected individuals.

<table>
<thead>
<tr>
<th>Outcome:</th>
<th>Non-IDU HIV-infected individuals versus Comparison cohort individuals</th>
<th>IDU HIV-infected individuals versus Comparison cohort individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Adjusted*</td>
</tr>
<tr>
<td>Total cerebrovascular events (CVE)</td>
<td>1.60 (1.32–1.94)</td>
<td>1.60 (1.30–1.95)</td>
</tr>
<tr>
<td>Subarachnoid haemorrhage</td>
<td>1.85 (0.90–3.81)</td>
<td>1.72 (0.80–3.69)</td>
</tr>
<tr>
<td>Intracerebral haemorrhage</td>
<td>1.43 (0.68–3.03)</td>
<td>1.47 (0.67–3.20)</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>1.76 (1.22–2.53)</td>
<td>1.63 (1.10–2.41)</td>
</tr>
<tr>
<td>Unspecified stroke</td>
<td>1.48 (1.06–2.07)</td>
<td>1.54 (1.08–2.16)</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>1.58 (1.08–2.33)</td>
<td>1.64 (1.10–2.44)</td>
</tr>
<tr>
<td>CVE with proven risk factors</td>
<td>1.54 (1.19–1.99)</td>
<td>1.55 (1.19–2.03)</td>
</tr>
<tr>
<td>CVE without proven risk factors</td>
<td>1.68 (1.25–2.25)</td>
<td>1.65 (1.21–2.26)</td>
</tr>
<tr>
<td>Stratified on gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.61 (1.31–2.00)</td>
<td>1.59 (1.29–1.97)</td>
</tr>
<tr>
<td>Female</td>
<td>1.37 (0.76–2.46)</td>
<td>1.69 (0.89–3.23)</td>
</tr>
<tr>
<td>Stratified on route of HIV transmission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>1.31 (1.00–1.73)</td>
<td>1.31 (0.99–1.74)</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>1.90 (1.41–2.56)</td>
<td>1.95 (1.40–2.70)</td>
</tr>
</tbody>
</table>

IRR, Incidence rate ratio. 95% CI: Confidence Interval  
*Adjusted for country of birth (Denmark versus outside Denmark) and stratified according to the initial match criteria (age and gender).  
MSM: men who have sex with men.
Discussion

We found a higher risk of CVE in HIV-infected individuals than in the general population comparison cohorts. The risk was higher for both CVE with and without proven risk factors. In the non-IDU HIV-infected population immunodeficiency (CD4 count < 200 cells/μl) before start of HAART and treatment with abacavir almost doubled the risk of CVE, while PI, indinavir, didanosine, tenofovir or HAART in general had no impact on the risk of CVE. Finally, the risk of CVE was only increased in the parents of HIV-infected individuals who reported IDU as route of transmission.

Table 3. Impact of CD4 cell count, HAART and abacavir on risk of cerebrovascular events (CVE) in HIV-infected individuals with no intravenous drug abuse (Non-IDU HIV).

<table>
<thead>
<tr>
<th>Time-updated variables:</th>
<th>Total CVE (IRR)</th>
<th>CVE with proven risk factors (IRR)</th>
<th>CVE without proven risk factors (IRR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 &gt; 200 cells/μl and non-HAART</td>
<td>1 (ref)**</td>
<td>1 (ref)**</td>
<td>1 (ref)**</td>
</tr>
<tr>
<td>CD4 &lt; 200 cells/μl and non-HAART</td>
<td>2.28 (1.09–4.76)</td>
<td>2.26 (1.05–4.86)</td>
<td>2.26 (1.05–4.86)</td>
</tr>
<tr>
<td>On HAART before first exposure to protease inhibitors</td>
<td>1.53 (0.65–3.55)</td>
<td>1.17 (0.50–2.75)</td>
<td>1.17 (0.50–2.75)</td>
</tr>
<tr>
<td>On HAART before first exposure to protease inhibitors</td>
<td>1.00 (0.59–1.69)</td>
<td>0.80 (0.47–1.36)</td>
<td>0.80 (0.47–1.36)</td>
</tr>
<tr>
<td>On HAART after first exposure to protease inhibitors</td>
<td>1 (ref)**</td>
<td>1 (ref)**</td>
<td>1 (ref)**</td>
</tr>
<tr>
<td>On HAART after first exposure to indinavir</td>
<td>1.08 (0.70–1.68)</td>
<td>0.98 (0.61–1.58)</td>
<td>0.98 (0.61–1.58)</td>
</tr>
<tr>
<td>On HAART after first exposure to tenofovir</td>
<td>0.94 (0.55–1.60)</td>
<td>1.01 (0.58–1.76)</td>
<td>1.01 (0.58–1.76)</td>
</tr>
<tr>
<td>On HAART after first exposure to didanosin</td>
<td>1 (ref)**</td>
<td>1 (ref)**</td>
<td>1 (ref)**</td>
</tr>
<tr>
<td>On HAART after first exposure to didanosin</td>
<td>0.89 (0.55–1.44)</td>
<td>0.75 (0.45–1.24)</td>
<td>0.75 (0.45–1.24)</td>
</tr>
<tr>
<td>On HAART before first exposure to abacavir</td>
<td>1.69 (1.07–2.68)</td>
<td>1.66 (1.03–2.68)</td>
<td>1.66 (1.03–2.68)</td>
</tr>
<tr>
<td>On HAART after first exposure to abacavir</td>
<td>1.67 (1.04–2.67)</td>
<td>1.58 (0.94–2.65)</td>
<td>1.58 (0.94–2.65)</td>
</tr>
</tbody>
</table>

Table 4. Relative risk of cerebrovascular events (CVE) in parents of HIV-infected individuals.

<table>
<thead>
<tr>
<th>Outcome:</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cerebrovascular events (CVE)</td>
<td>1.16 (1.02–1.33)</td>
<td>1.15 (1.01–1.32)</td>
</tr>
<tr>
<td>CVE with proven risk factors</td>
<td>1.19 (1.00–1.42)</td>
<td>1.10 (0.92–1.31)</td>
</tr>
<tr>
<td>CVE without proven risk factors</td>
<td>1.12 (0.91–1.38)</td>
<td>1.10 (0.90–1.36)</td>
</tr>
</tbody>
</table>

Stratified by transmission group of the offspring:

| MSM: | 1.10 (0.91–1.31) | 1.06 (0.88–1.27) |
| Heterosexually: | 0.98 (0.73–1.32) | 0.99 (0.74–1.33) |
| IDU: | 1.85 (1.38–2.49) | 2.06 (1.53–2.76) |

IRR, Incidence rate ratio; 95% CI: Confidence Interval *Adjusted for age, gender, calendar year and country of birth. Analyses on protease inhibitors, tenofovir and abacavir were also adjusted for CD4 cell count.

Table 4. Relative risk of cerebrovascular events (CVE) in parents of HIV-infected individuals.
access to several Danish registries allowed us to identify population-based comparison cohorts and extract data on family members. Furthermore, data on study endpoints and co-morbidity were obtained from the same data sources, thereby minimising the impact of misclassification on our relative risk estimates. Importantly, we excluded patients with opportunistic cerebral infections, HIV dementia, non-HIV-associated cranial neoplasia, and CNS neoplasia in order to avoid misclassification. We adjusted the analyses for potential confounding factors and further stratified all analyses on the basis of IDU. To make sure that the increased risk of CVE was not due to potential misclassification of individuals with IDU, we performed a robustness analysis excluding all non-IDU HIV-infected individuals with hepatitis C infection and saw no changes in our estimates. We are not aware of other studies with a similar design.

Due to the study design, we had no access to patient files or results of imaging techniques and had to rely on hospital registry-based discharge diagnoses in order to identify diagnoses of CVE. We are aware that there might be some misclassification in CVE diagnoses as well as in the diagnoses used to exclude individuals with CNS comorbidity. Previous studies have shown that DNHR tends to overestimate the prevalence of cerebrovascular disease [42,43], but the access to modern diagnostic tools has probably increased the validity of stroke diagnoses today [42]. As the Danish National Hospital registry was not initiated until January 1977, some parents might have had a CVE prior to study inclusion, why some parents might have stroke sequelae categorised as endpoint in our study. Nevertheless, as age of the parents at study inclusion was low and did not differ markedly between the compared groups, we presume that this phenomenon has not biased our relative risk estimates substantially. Furthermore, sensitivity analysis, in which we excluded individuals registered in DNHR with stroke sequelae as first ever CVE, did not change our risk estimates. Since we used the same source of data to ascertain CVE for all study subjects, we presume that any potential misclassification was non-differential and therefore did not influence our estimates of relative risk. Low socioeconomic status is associated with a higher risk of stroke which is partly explained by a greater burden of classical risk factors [44]. We could not directly adjust for socioeconomic status. However, as we stratified the analyses on IDU, evaluated the impact of risk factors and analyzed the risk of CVE in the parents of the two groups, this was indirectly accounted for. We did not have information on non-antiretroviral medication or smoking status of which the latter is a highly important risk factor. This could invalidate the potential causal association of CVE and HIV. However, COPD, excessive alcohol consumption and other conventional risk factors were included in the analyses, many of which are highly associated with smoking [45]. Abuse of cocaine, amphetamine, ecstasy and related drugs are important risk factors for stroke in young adults [41]. But, as we had no access to information on the drug itself, we included all IDU, registered as route of HIV infection in DHCS, as a surrogate marker of drug abuse in general. We are aware of the potential bias this might introduce as some non-IDU drug abusers might have been lost and as the frequency of the drug abuse and the effect of being clean or in a treatment program with e.g. methadone could not be accounted for.

In a case-control study from South Africa, Hoffmann et al. found that cryptogenic stroke, but not stroke in general, was more common in the HIV-positive population, than in an age- and gender-matched HIV-negative control population [11]. In contrast, Engström et al. conducted a retrospective study of 1600 AIDS patients with an age below 45 years (patients with competing opportunistic infections were not excluded) and found that 0.75% had been diagnosed with cerebral infarction, which was compared with an annual incidence of 0.025% for cerebral infarction in the background population between 35 and 45 years [6]. Cole et al. studied AIDS patients with no opportunistic CNS infections, HIV dementia or IDU, and found a relative risk of stroke, which was increased by a factor 10 (adjusted relative risk 10.4; 95% CI: 4.9–22.0) compared to a non-AIDS population from the same region [17]. HIV-infected individuals however, who did not fulfill the criteria for AIDS were included in the control group. In accordance with Cole et al., we revealed that HIV-infected individuals with no concomitant cerebral comorbidity have an increased risk of CVE. We presume that the differences in the risk estimates in these reports rely on differences in characteristics of the study populations, definitions and access to data on cerebrovascular endpoints. We found a relative risk of CVE in IDU HIV-infected individuals, which was more than twice that of the non-IDU HIV population which emphasizes the impact of drug abuse. A number of possible mechanisms to explain this phenomenon have been thoroughly discussed elsewhere [41,46]. Despite the awareness of drug abuse as a risk factor of CVE and the link between HIV and IDU, most risk estimates in other studies are biased by this confounder [5–10,15,16,18–20,22].

The increased risk of cerebrovascular disease in HIV-infected individuals has been ascribed to several different pathological mechanisms such as cerebral opportunistic infections, associated vasculitis or vasculopathies, intracranial neoplasm, endocarditis and coagulation disorders [46,47]. As studies have found a higher prevalence of smoking in HIV-infected individuals than in the general population of the same age [48,49], it has been speculated whether a HIV-positive status simply serves as a marker for differences in the prevalence of conventionally risk factors [48]. However, in our study an uneven distribution of risk factors could not solely explain the...
increased risk of CVE, as both the relative risk of CVE with and without proven risk factors were increased. Smoking is a strong predictor of CVE [32,45]. In a meta-analysis by Shinton et al. smoking increased the risk of stroke almost 3 fold in a population less than 55 years [45]. Due to the lack of information on smoking in our comparison cohorts we were not able to address the impact of this risk factor and cannot exclude that an increased frequency of smoking in the HIV-infected population partly explains the increased risk of CVE we observed.

In accordance with our results some studies have observed an increased risk of stroke in HIV-infected individuals with low CD4 counts [14,20]. Whether this association is due to the immunodeficiency per se, an association with the increased risk of cerebral opportunistic diseases or a general deteriorated condition in these patients has to be established.

Few studies have examined the impact of HAART on risk of cerebrovascular disease [4,13,16,19,22,23]. The two largest studies, in which conflicting results of HAART-exposure were found, used composite endpoints [13,16]. A study from Thailand reported a twofold increased risk of stroke after start of HAART which contrasts the observations from an American study which found no correlation [23], and a Spanish study which observed a protective effect of HAART [22]. In our analyses HAART did not influence the risk of CVE.

Abacavir has been associated with an increased risk of myocardial infarction, but the causal pathway for this effect is still controversial [3,4,50]. An association between abacavir and risk of stroke however could not be demonstrated in the D:A:D study [4]. We observed a higher risk of CVE in HIV-infected individuals on abacavir irrespective of low CD4 cell count. PI, indinavir, didanosin and tenofovir on the contrary showed no such association. We presume that the mechanisms for this phenomenon are equivalent to that seen for myocardial infarction, but we cannot exclude that patients with an a priori increased risk of CVE had a higher chance of being treated with abacavir (channeling bias) [3,50].

We registered an increased risk of CVE in parents of IDU HIV-infected individuals. This association suggests that family-related risk factors are a complex combination of shared socio-economic factors, a possible tendency to “risk taking behaviour” and a genetic component [51,52].

We conclude that HIV infection is associated with an increased risk of CVE with and without proven risk factors. The risk is associated with IDU, low CD4 cell count, and treatment with abacavir, but not with HAART in general. Family-associated risk factors seem vaguely associated with increased risk of CVE in HIV-infected individuals.

Acknowledgments

We are grateful to the staff of our clinical departments for their continuous support and enthusiasm. We thank Preben and Anna Simonsen’s Foundation, the NOVO Nordic Foundation, University of Southern Denmark and the Clinical Institute of Copenhagen University for financial support.

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Drafting of the article: Rasmussen LD.

Critical revision of the article for important intellectual content: Rasmussen LD, Engsig FN, Pedersen C, Gerstoft J, Kronborg G, Christensen H, Obel N.

Final approval of the article: Rasmussen LD, Engsig FN, Pedersen C, Gerstoft J, Kronborg G, Christensen H, Obel N.

 Provision of study materials or patients: Pedersen C, Kronborg G, Gerstoft J, Obel N.

 Statistical expertise: Rasmussen LD, Engsig FN, Obel N.

 Obtaining of funding: Obel N.

 Administrative, technical, or logistic support: Rasmussen LD, Obel N.

 Collection and assembly of data: Pedersen C, Kronborg G, Gerstoft J, Obel N.

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 Conflicts of interest: N Obel has received research funding from Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, GlaxoSmithKline, Abbott, Boehringer Ingelheim, Janssen-Cilag and Swedish Orphan Drugs.

 FN Engsig has received research funding from Merck Sharp & Dohme.
C. Pedersen has received research funding from Abbott, Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, GlaxoSmithKline, Swedish Orphan Drugs and Boehringer Ingelheim.

J Gerstoft has received research funding from Abbott, Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Pharmacia, GlaxoSmithKline, Swedish Orphan Drugs and Boehringer Ingelheim.

H Christensen has received honorariums and sponsorships from Boehringer-Ingelheim, Abbott/Solvay, Medtronic, Sanofi-Avenis and Attietch.

LD Rasmussen and G Kronborg report no conflicts of interest.

References


Appendix I

World Health Organization International Disease Classification (ICD) Codes, ICD-8 and ICD-10 used for the present classification.

CEREBROVASCULAR DISEASE:

SUBARACHNOID HAEMORRHAGE:

ICD8: 43000–43099
ICD 10: I60.0–I60.9

INTRACEREBRAL HAEMORRHAGE:

ICD8: 43100, 43108–43190, 43198–43199
ICD 10: I61.0–I61.9

CEREBRAL INFARCTION:

ICD8: 43200–43299, 43309–43399, 43409–43499
ICD 10: I63.0–I63.9

UNSPECIFIED STROKE:

ICD 8: 43600–43699
ICD 10: I64.9

TRANSIENT ISCHEMIC ATTACK:

ICD8: 43509–43599
ICD 10: G45.0–G45.9

OTHER CEREBROVASCULAR DISEASES:

ICD8: 43101, 43191, 43709–43799, 43809–43899
ICD 10: I62.0–I62.9, I65.0–I65.9, I66.0–I66.9, I67.0–I67.9, I68.0–I68.8, G46.0–G46.8

STROKE SEQUELS:

ICD 10: I69.0–I69.8

*Cases registered with two or more subgroups of cerebrovascular disease on the same date were categorized with the specific diagnosis (subarachnoid haemorrhage, intracerebral haemorrhage, cerebral infarction, unspecified stroke and transient ischaemic attack) in preference for the unspecific diagnoses (other cerebral vascular disease or stroke sequel) and diagnoses belonging to the longest admission were preferred. Next the primary diagnosis (A-diagnosis) was chosen over the secondary diagnosis (B-diagnosis). Cases in which this method did not identify a specific diagnosis were categorized as unspecified stroke.

CEREBRAL COMORBIDITY:

CEREBRAL INFECTIONS INCLUDING OPPORTUNISTIC DISEASES:

ICD8: 013.00–013.99, 019.19, 036.09, 040.00–040.09, 045.09–045.99, 046.99, 052.01, 053.02, 054.03, 055.01, 056.01, 062.09–062.99, 063.09–063.99, 064.99, 065.99, 066.00–066.09, 071.99, 072.02, 075.01, 090.49, 094.00–094.99, 130.09–130.99, 320.09–320.99, 322.00–322.09, 323.00–323.01, 323.03–323.09, 324.00–324.09
ICD10: A06.6, A17.0–17.1, A32.1, A39.0, A52.1–52.3, A81.0–89.9
B00.3–00.4, B01.0–01.1, B02.0–02.1, B05.0–05.1, B06.0, B22.0, B25.3, B26.1–26.2, B45.1, B58.2, B90.0, B94.1
G00.0–06.1, G07.9, G09.9

Co-morbidity diagnoses from The Danish HIV Cohorte Study: Toxoplasmosis, Cryptococcus, Lymphoma – further sub classified to cerebral lymphoma), PML, aids demenia, CMV chorioretinitis

CEREBRAL CANCER/TUMOR/LYMPHOMA/METASTASIS:

8920–8923, 8930–8932, 8935, 8954

ICD10: C69.0–72.9 C75.1–75.3, C79.3, D32.0–33.9, D35.2–35.4, D42.0–43.9, D44.3–44.5

RISK FACTORS:

Outcomes (CVE) were classified as “CVE with proven risk factor” if at least one of the following risk factors was registered in DNHR, DCR or DHCS prior to or within 30 days after an event (for cancer up to 90 days after an event): diabetes, hypertension, atrial fibrillation/flutter, hyperlipidemia, myocardial infarction, heart failure, patent foramen ovale, sick sinus syndrome, cardiomyopathy, mitral and/or aortic valve disease, peripheral arteriosclerosis, carotid artery stenosis, obesity, excessive alcohol intake, increased- or impaired coagulation, chronic kidney disease, chronic obstructive pulmonary disease, infectious endocarditis, cancer and IDU if registered as route of HIV transmission in the HIV patient.

ATIAL FLUTTER/FIBRILATION:

ICD 8: 427.93, 427.94

ICD 10: I48.9

HYPERTENSION:

ICD 8: 400.09–404.99, 410.09, 412.09, 413.09, 414.09, 435.09, 437.00–437.09, 438.09

ICD 10: I10.9–15.9

MYOCARDIAL INFARCTION:

ICD 8: 410.9, 410.99

ICD 10: I21.0–22.9

HEART FAILURE:


ICD 10: I50.0–50.9

CARDIOMYOPATHY:

ICD8: 746.40–746.49

ICD10: I42.0–43.8

SICK SINUS SYNDROME:

ICD 10: I49.5

PATENT FORAMEN OVALE:

ICD 8: 746.40–746.49

ICD 10: Q21.1

MITRAL AND AORTIC VALVE DISEASE:

ICD 8: 394.00–396.99

ICD 10: I05.0–06.9, I08.0–08.9, I34.0–35.9

DIABETES:

ICD 8: 249.00–250.09

ICD 10: E10.0–14.9

EXCESSIVE ALCOHOL CONSUMPTION:

ICD 8: 291.09–291.99, 303.09–303.90

ICD 10: F10.1–10.9

PERIFERAL ATHEROSCLEROSIS:

ICD 8: 440.20–440.30

ICD 10: I70.2

CAROTID ARTERY STENOSIS:

ICD 8: 432.90

ICD 10: I65.2

HYPERLIPIDEMIA:

ICD 8: 279.00
Appendix II

Fig. 1 Summary of the study design.
HIV and risk of cerebrovascular events Rasmussen et al.

Table 1 Proven risk factors diagnosed in HIV-infected individuals and comparison cohort individuals.

<table>
<thead>
<tr>
<th>Proven risk factors registered prior to and up to 30 days (90 days for malignancy) after the end of the observation period:</th>
<th>Non-IDU HIV-infected individuals (n = 4,495)</th>
<th>Comparison cohort individuals (n = 40,455)</th>
<th>IDU HIV-infected Individuals (n = 536)</th>
<th>Comparison cohort individuals (n = 4,824)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction, N (%)</td>
<td>123 (2.7)</td>
<td>749 (1.9)</td>
<td>8 (1.5)</td>
<td>64 (1.3)</td>
</tr>
<tr>
<td>Heart failure, N (%)</td>
<td>83 (1.8)</td>
<td>513 (1.3)</td>
<td>17 (3.2)</td>
<td>33 (0.7)</td>
</tr>
<tr>
<td>Patent foramen ovale, N (%)</td>
<td>3 (0.1)</td>
<td>32 (0.1)</td>
<td>3 (0.2)</td>
<td>1 (0.0)</td>
</tr>
<tr>
<td>Sick sinus syndrome, N (%)</td>
<td>3 (0.1)</td>
<td>35 (0.1)</td>
<td>0 (0)</td>
<td>1 (0.0)</td>
</tr>
<tr>
<td>Cardiomyopathy, N (%)</td>
<td>28 (0.6)</td>
<td>160 (0.4)</td>
<td>3 (0.6)</td>
<td>16 (0.3)</td>
</tr>
<tr>
<td>Mitral and/or aortic valve disease, N (%)</td>
<td>27 (0.6)</td>
<td>228 (0.6)</td>
<td>9 (1.7)</td>
<td>21 (0.4)</td>
</tr>
<tr>
<td>Atrial flutter/Atrial fibrillation, N (%)</td>
<td>62 (1.4)</td>
<td>711 (1.8)</td>
<td>2 (0.4)</td>
<td>55 (1.1)</td>
</tr>
<tr>
<td>Carotid artery stenosis, N (%)</td>
<td>9 (0.2)</td>
<td>38 (0.1)</td>
<td>0 (0)</td>
<td>3 (0.1)</td>
</tr>
<tr>
<td>Arterial hypertension, N (%)</td>
<td>219 (4.9)</td>
<td>2,418 (6.0)</td>
<td>19 (3.5)</td>
<td>250 (5.2)</td>
</tr>
<tr>
<td>Hyperlipidemia, N (%)</td>
<td>122 (2.7)</td>
<td>1,148 (2.8)</td>
<td>2 (0.4)</td>
<td>133 (2.8)</td>
</tr>
<tr>
<td>Obesity, N (%)</td>
<td>54 (1.2)</td>
<td>1,211 (3.0)</td>
<td>4 (0.7)</td>
<td>168 (3.5)</td>
</tr>
<tr>
<td>Excessive alcohol consumption, N (%)</td>
<td>275 (6.1)</td>
<td>1,483 (3.7)</td>
<td>128 (23.9)</td>
<td>176 (3.6)</td>
</tr>
<tr>
<td>Diabetes, N (%)</td>
<td>147 (3.3)</td>
<td>1,445 (3.6)</td>
<td>16 (3.0)</td>
<td>137 (2.7)</td>
</tr>
<tr>
<td>Peripheral arteriosclerosis, N (%)</td>
<td>39 (0.9)</td>
<td>273 (0.7)</td>
<td>9 (1.7)</td>
<td>14 (0.3)</td>
</tr>
<tr>
<td>Chronic kidney disease, N (%)</td>
<td>68 (1.5)</td>
<td>244 (0.6)</td>
<td>12 (2.2)</td>
<td>21 (0.4)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease, N (%)</td>
<td>109 (2.4)</td>
<td>682 (1.7)</td>
<td>48 (9.0)</td>
<td>56 (1.2)</td>
</tr>
<tr>
<td>Thrombophilia and other coagulation disorders including thrombocytopenia, N (%)</td>
<td>151 (3.4)</td>
<td>282 (0.7)</td>
<td>27 (5.0)</td>
<td>43 (0.9)</td>
</tr>
<tr>
<td>Endocarditis, N (%)</td>
<td>8 (0.2)</td>
<td>38 (0.1)</td>
<td>45 (8.4)</td>
<td>4 (0.1)</td>
</tr>
<tr>
<td>Malignancy, N (%)</td>
<td>558 (12.4)</td>
<td>1,831 (4.5)</td>
<td>24 (4.5)</td>
<td>183 (3.8)</td>
</tr>
</tbody>
</table>

Table 2 Characteristics of parents of HIV-infected individuals and comparison cohort individuals.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mothers of HIV positive individuals (N = 2,509)</th>
<th>Fathers of Comparison cohort individuals (N = 21,982)</th>
<th>HIV positive individuals (N = 2,289)</th>
<th>Comparison cohort individuals (N = 21,009)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at index date, median years (IQR)</td>
<td>38.0 (31.8–44.7)</td>
<td>37.5 (31.6–43.9)</td>
<td>41.0 (34.1–48.5)</td>
<td>40.3 (33.8–47.5)</td>
</tr>
<tr>
<td>Number in whom observation time started after 1. January 1977 (%)</td>
<td>296 (11.8)</td>
<td>2,343 (10.7)</td>
<td>282 (12.3)</td>
<td>2,417 (11.5)</td>
</tr>
<tr>
<td>Born in Denmark, N (%)</td>
<td>2,354 (93.8)</td>
<td>21,318 (97.0)</td>
<td>2,189 (95.6)</td>
<td>20,553 (97.8)</td>
</tr>
<tr>
<td>Duration of follow up: Duration of follow-up, person years</td>
<td>70,430</td>
<td>647,168</td>
<td>58,412</td>
<td>561,407</td>
</tr>
<tr>
<td>Duration of follow-up, median years (IQR)</td>
<td>296 (11.8)</td>
<td>2,343 (10.7)</td>
<td>2,189 (95.6)</td>
<td>2,417 (11.5)</td>
</tr>
<tr>
<td>Death, N (%)</td>
<td>641 (25.5)</td>
<td>4,380 (19.9)</td>
<td>809 (35.3)</td>
<td>6,634 (31.6)</td>
</tr>
<tr>
<td>Emigration, N (%)</td>
<td>2 (0.1)</td>
<td>0 (0)</td>
<td>3 (0.1)</td>
<td>4 (0)</td>
</tr>
<tr>
<td>First hospitalisation for cerebrovascular event (CVE) after index date: Total no. of CVE, N (%)</td>
<td>245 (9.8)</td>
<td>2,003 (9.1)</td>
<td>316 (13.8)</td>
<td>2,851 (13.6)</td>
</tr>
<tr>
<td>Subarachnoid haemorrhage, N (%)</td>
<td>19 (0.8)</td>
<td>153 (0.7)</td>
<td>13 (0.6)</td>
<td>77 (0.4)</td>
</tr>
<tr>
<td>Intracerebral haemorrhage, N (%)</td>
<td>24 (1.0)</td>
<td>151 (0.7)</td>
<td>31 (1.4)</td>
<td>186 (0.9)</td>
</tr>
<tr>
<td>Cerebral infarction, N (%)</td>
<td>63 (2.5)</td>
<td>501 (2.3)</td>
<td>85 (3.7)</td>
<td>746 (3.6)</td>
</tr>
<tr>
<td>Unspecified stroke, N (%)</td>
<td>92 (3.7)</td>
<td>734 (3.3)</td>
<td>120 (5.2)</td>
<td>1,178 (5.6)</td>
</tr>
<tr>
<td>CVE with proven risk factors, N (%)</td>
<td>147 (6.0)</td>
<td>1,179 (5.5)</td>
<td>208 (9.1)</td>
<td>1,741 (8.3)</td>
</tr>
<tr>
<td>CVE without proven risk factors, N (%)</td>
<td>98 (4.0)</td>
<td>824 (3.9)</td>
<td>108 (4.7)</td>
<td>1,110 (5.3)</td>
</tr>
<tr>
<td>Median age of CVE, median years (IQR)</td>
<td>65.5 (59.3–73.6)</td>
<td>66.9 (59.1–73.8)</td>
<td>65.9 (60.1–72.8)</td>
<td>66.8 (60.3–73.5)</td>
</tr>
<tr>
<td>Risk of CVE after 5 years, % (95%CI):</td>
<td>0.32 (0.15–0.61)</td>
<td>0.28 (0.22–0.36)</td>
<td>0.75 (0.45–1.17)</td>
<td>0.47 (0.38–0.57)</td>
</tr>
<tr>
<td>Risk of CVE after 10 years, % (95%CI):</td>
<td>0.68 (0.42–1.07)</td>
<td>0.68 (0.57–0.79)</td>
<td>1.68 (1.21–2.27)</td>
<td>1.38 (1.23–1.54)</td>
</tr>
</tbody>
</table>