Gender Differences in HIV Progression to AIDS and Death in Industrialized Countries: Slower Disease Progression Following HIV Seroconversion in Women

Inmaculada Jarrín, Ronald Geskus, Krishnan Bhaskaran, Maria Prins, Santiago Perez-Hoyos, Roberto Muga, Ildefonso Hernández-Aguado, Laurence Meyer, Kholoud Porter, Julia del Amo, and the CASCADE Collaboration

To evaluate sex differences in human immunodeficiency virus (HIV) disease progression before (pre-1997) and after (1997–2006) introduction of highly active antiretroviral therapy, the authors used data from a collaboration of 23 HIV seroconverter cohort studies from Europe, Australia, and Canada restricted to the 6,923 seroconverters infected through injecting drug use and sex between men and women. Within a competing risk framework, they used Cox proportional hazards models allowing for late entry to evaluate sex differences in time from HIV seroconversion to death, to acquired immunodeficiency syndrome (AIDS), and to each first AIDS-defining disease and death without AIDS. While no significant sex differences were found before 1997, from 1997 onward, women had a lower risk of AIDS (adjusted cumulative relative risk (aCRR) = 0.76, 95% confidence interval (CI): 0.63, 0.90) and death (adjusted hazard ratio = 0.68, 95% CI: 0.56, 0.82) than men did. Compared with men, women also had lower risks of AIDS dementia complex (aCRR = 0.23, 95% CI: 0.07, 0.74), tuberculosis (aCRR = 0.60, 95% CI: 0.39, 0.92), Kaposi's sarcoma (aCRR = 0.27, 95% CI: 0.07, 0.99), lymphomas (aCRR = 0.47, 95% CI: 0.23, 0.96), and death without AIDS (aCRR = 0.74, 95% CI: 0.56, 0.98). Sex differences in HIV disease progression have become larger and statistically significant in the era of highly active antiretroviral therapy, supporting a stronger impact of health interventions among women.

acquired immunodeficiency syndrome; antiretroviral therapy, highly active; cohort studies; death; disease progression; HIV

Abbreviations: aCRR, adjusted cumulative relative risk; AIDS, acquired immunodeficiency syndrome; CASCADE, Concerted Action on SeroConversion to AIDS and Death in Europe; CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus.
Before highly active antiretroviral therapy (HAART) was available, most seroconverter and seroprevalent cohorts from European countries described either no sex differences or a somewhat slower rate of disease progression to acquired immunodeficiency syndrome (AIDS) and death among women (1–7). Data on this issue have been, and still are, contradictory. Early reports from individuals infected with human immunodeficiency virus (HIV) in the United States, mainly those with AIDS, suggested a shorter survival time for women compared with men (8, 9). Regarding clinical manifestations, only two seroprevalent cohort studies in the pre-HAART era are known to have evaluated the effect of sex on progression to specific AIDS-defining diseases (10, 11), and they reported that women were at increased risk of toxoplasmosis and herpes simplex virus ulcerations compared with men in the same transmission category (11). Another multicenter study found that women were at increased risk of bacterial pneumonia and at reduced risk of Kaposi’s sarcoma (10).

In the HAART era, studies from the United States, largely using data from seroprevalent cohorts, continue to report worse outcomes in HIV-infected women compared with men (12, 13), although the authors highlight that the socioeconomic indicators for the women in those studies are much worse than those for the men. Conversely, evidence has been increasing, largely from European seroconverter cohorts, that women, compared with men, have slower disease progression to AIDS and death (14–18). The Spanish Multicenter Study Group of Seroconverters (GEMES), with high numbers of injecting drug users (7, 15, 18), has consistently reported slower HIV progression rates among women, and better outcomes were also found for the women, mainly infected heterosexually, in a French cohort study of HIV seroconverters (SEROCO) (14). We previously reported that female injecting drug users tended to live longer than their male counterparts (17). In most studies, sex differences were smaller for progression to AIDS compared with death, suggesting the impact of competing non-HIV mortality (1). However, these findings are not consistent, and analyses may have been underpowered to test for sex differences in time to individual AIDS conditions.

To our knowledge, no study to date has looked at sex differences in time to individual AIDS-defining conditions and changes over time in AIDS and non-AIDS mortality in male and female seroconverters in the same transmission category. Such analyses would deal with possible confounding by duration of HIV infection, which cannot be accounted for when seroconversion date is unknown, and enable exploration of clinical outcomes in the course of disease progression in men and women with similar lifestyles. In this paper, we analyze data from the Concerted Action on SeroConversion to AIDS and Death in Europe (CASCADE) collaboration evaluating changes over time in the effect of sex on survival, on progression to AIDS, and on the risk of developing each specific AIDS-defining disease as the first AIDS event and death without AIDS.

**MATERIALS AND METHODS**

**Study population**

We analyzed data from a collaboration of 23 HIV seroconverter cohort studies in Europe, Australia, and Canada. Details of the CASCADE collaboration appear elsewhere (19); briefly, all cohorts include people infected with HIV-1 for whom date of seroconversion can be reliably estimated. Analyses were restricted to seroconverters infected through injecting drug use and sex between men and women because we wanted to compare men and women of similar lifestyles. We also excluded children less than 15 years of age at seroconversion. Ethnic group (classified as White, Black, and other) was obtained for 26 percent of seroconverters.

**Statistical analyses**

Descriptive analysis of patients’ characteristics at enrollment was carried out. Sex differences in demographic and clinical characteristics were assessed through the nonparametric Mann-Whitney test for continuous variables and the $\chi^2$ test for categorical data.

We divided follow-up time into two calendar periods: pre-1997 and 1997 onward. These categories best described the risk change in AIDS and mortality trends over time based on the Akaike Information Criterion and also reflected the availability of HAART in industrialized countries. For each calendar period, we calculated the proportion of person-time spent in the three treatment categories—antiretroviral therapy naïve, antiretroviral therapy experienced but currently not using this therapy or using a non-HAART regimen, and those using HAART—stratifying by exposure category and sex.

We defined AIDS in accordance with clinical criteria from the 1993 Centers for Disease Control and Prevention case definition (20). The AIDS-defining diseases were grouped as follows (all ≥20 events): candidiasis, cryptococcosis, cryptosporidiosis, cytomegalovirus, AIDS dementia complex, herpes simplex disease, Kaposi’s sarcoma, AIDS-defining lymphomas, Pneumocystis carinii pneumonia, progressive multifocal leucoencephalopathy, recurrent pneumo-nia, tuberculosis (pulmonary and extrapulmonary), cerebral toxoplasmosis, HIV wasting syndrome, and other mycobacterial diseases not including tuberculosis. All other AIDS-defining events (cervical cancer ($n=16$), focal brain lesion ($n=2$), isosporiasis ($n=1$), leishmaniasis ($n=9$), salmonella bacteraemia ($n=6$), and diagnosis unknown ($n=72$)) were grouped together because of the few events observed for each.

We calculated incident rates for each AIDS diagnosis. We allowed for this event to occur as an initial or subsequent event, counting all person-time before death or the last clinic visit, and stratifying by calendar period and sex.

We investigated sex differences in time from seroconversion to death, to AIDS, and to each initial AIDS-defining disease and death without AIDS by using Cox proportional hazard models, allowing for late entry of individuals at the time of enrollment into the original cohort so, to control for survivorship bias, they could begin to contribute from a time later than estimated seroconversion (21).

For analyses of time to death, individuals were censored on the date they were last seen alive. To assess the effect of sex on progression to AIDS (death without AIDS considered as a competing event) and to each specific AIDS-defining disease or death without AIDS as the first event, two different
approaches for analyzing competing risk data were used: modeling the cause-specific instantaneous hazard (22, 23) and modeling the cause-specific cumulative incidence hazard (24, 25).

Estimating cause-specific instantaneous hazards involves a standard Cox model with respect to censoring (i.e., individuals experiencing a competing event as a first event are censored at this time when considering the event of interest), but the interpretation is different. Estimates from this model are interpreted as the effect of factors on the instantaneous risk of developing the event of interest conditional on not having experienced any event so far.

In contrast, estimates from the cause-specific cumulative incidence hazard can be interpreted as the effect of factors on the cumulative incidence of the event of interest and can be approximated by censoring individuals failing from a competing event different from that of interest at their administrative censoring time. Because right-censoring strategies for estimating the effect of factors on the cumulative incidence of each competing event in the presence of time-dependent covariates such as calendar period are not sufficiently covered in the literature, we used two different administrative censoring dates: end of individuals’ total follow-up (26) and end of the calendar period (27). For the former, individuals experiencing a competing event different from that of interest are censored at the end of their total follow-up, ultimately August 2006. For the latter, individuals developing a competing event, which is not the event of interest, are right censored at the end of the calendar period in which the competing event was experienced.

Results derived from modeling either the cause-specific instantaneous hazard or the cause-specific cumulative incidence hazard comparing two different types of administrative censoring dates (i.e., end of total follow-up and end of the calendar period) are given in Web tables 1 and 2 (posted on the Journal’s website (http://aje.oupjournals.org/)). However, for the sake of brevity, only those results derived from modeling the cumulative incidence hazard by using the end of the calendar period as the administrative censoring date are presented in this paper.

All models were stratified by cohort and were adjusted for the following potential confounders: exposure category (injecting drug use and sex between men and women) and age at estimated seroconversion (continuous). Models were not adjusted for changes in CD4+ cell counts and HIV RNA viral load levels because date of seroconversion is more informative for these analyses. To investigate whether the effect of sex had changed over calendar period, we included interaction terms between sex and calendar period in multivariate models. Wald tests were used to derive p values. All statistical analyses were performed by using Stata software (version 9.0; Stata Corporation, College Station, Texas) (28).

RESULTS

Of 6,923 seroconverters included in the analysis of survival (table 1), 3,414 (49 percent) were women and 3,509 (51 percent) were men. Median seroconversion dates were 1994 (1990–1999) for the women and 1993 (1989–1997) for the men. Of the 1,784 subjects for whom information on ethnic group was available, women were more likely than men to be Black (9.3 percent vs. 3.9 percent). In the analysis of progression to AIDS, 575 women and 842 men progressed to the disease. A total of 430 women and 808 men died, 130 and 272 of whom, respectively, died without having AIDS.

### TABLE 1. Characteristics of patients included in the analyses, CASCADE collaboration, pre-1997 and 1997–2006

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 3,509; 50.7%)</th>
<th>Women (n = 3,414; 49.3%)</th>
<th>Total (n = 6,923; 100.0%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td><strong>Exposure category</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injecting drug user</td>
<td>2,070</td>
<td>59.0</td>
<td>1,027</td>
</tr>
<tr>
<td>Sex between men and women</td>
<td>1,439</td>
<td>41.0</td>
<td>2,387</td>
</tr>
<tr>
<td><em><em>Median age in years at seroconversion (IQR</em>)</em>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29 (25–35)</td>
<td>1,461</td>
<td>41.8</td>
<td>2,387</td>
</tr>
<tr>
<td>Ethnic group†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>992</td>
<td>94.4</td>
<td>639</td>
</tr>
<tr>
<td>Black</td>
<td>41</td>
<td>3.9</td>
<td>68</td>
</tr>
<tr>
<td>Other</td>
<td>18</td>
<td>1.7</td>
<td>26</td>
</tr>
<tr>
<td><strong>Subjects in each calendar period‡</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-1997 only</td>
<td>604</td>
<td>17.2</td>
<td>408</td>
</tr>
<tr>
<td>1997 onward only</td>
<td>1,178</td>
<td>33.6</td>
<td>1,403</td>
</tr>
<tr>
<td>Both periods</td>
<td>1,727</td>
<td>49.2</td>
<td>1,603</td>
</tr>
</tbody>
</table>

* IQR, interquartile range.
† Ethnic group data were recorded for 1,784 subjects.
‡ Calendar period for which each patient contributed to the analysis.
When we considered the closest CD4 measurement per person at different stages of HIV disease, median values within 3 months of HIV seroconversion were higher in women than in men in both periods: pre-1997 (688 cells/µl vs. 558 cells/µl, p < 0.001) and 1997 onward (558 cells/µl vs. 460 cells/µl, p < 0.001). Women also had higher median values than men did in the 3 months prior to starting HAART. For women, lower cumulative risks were suggested for AIDS dementia complex, tuberculosis, *P. carinii* pneumonia, and lymphomas, although differences were not significant. From 1997 onward, these lower risks for women were not shown). Table 3 shows the frequency and rate per 1,000 person-years of initial and subsequent AIDS-defining diseases and death without AIDS. The data are stratified by calendar period and sex.

In an adjusted model of the cumulative incidence of each specific AIDS-defining disease as the first AIDS event or death without an AIDS diagnosis, we observed a pattern similar to that observed for AIDS overall (figure 2). Before 1997, there were no significant differences between men and women regarding the cumulative risk of most specific AIDS-defining diseases, except for Kaposi’s sarcoma, with women showing a lower cumulative risk compared with men (aCRR = 0.06, 95 percent CI: 0.01, 0.41), as expected. For women, lower cumulative risks were suggested for AIDS dementia complex, tuberculosis, *P. carinii* pneumonia, and lymphomas, although differences were not significant. From 1997 onward, these lower risks for women became statistically significant, except for *P. carinii* pneumonia. Compared with men, women were at a significantly lower risk of AIDS dementia complex (aCRR = 0.23, 95 percent CI: 0.07, 0.74), tuberculosis (aCRR = 0.60, 95 percent CI: 0.39, 0.92), Kaposi’s sarcoma (aCRR = 0.27, 95 percent CI: 0.07, 0.99), and lymphomas (aCRR = 0.47, 95 percent CI: 0.23, 0.96). The risk of death without AIDS was lower for women compared with men in both periods, although differences were significant for only the period 1997 onward (aCRR = 0.74, 95 percent CI: 0.56, 0.98). We found a similar sex effect in time from HIV seroconversion to AIDS, to death, and to each initial AIDS-defining disease when adjusting for ethnic group in the subset of patients for whom this information was available (data not shown).
In separate analyses, we evaluated sex differences in the cumulative incidence of AIDS (overall) and of each first specific AIDS-defining disease by censoring individuals experiencing a competing event different from that of interest at the end of their total follow-up. These analyses did not alter our results (data not shown). Finally, excluding the 72

### TABLE 3. Frequency and rate (per 1,000 person-years) of occurrence of initial and subsequent AIDS*-defining diseases and death without AIDS by sex, in the eras pre-1997 and 1997 onward, CASCADE collaboration

<table>
<thead>
<tr>
<th></th>
<th>Pre-1997</th>
<th></th>
<th>1997 onward</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men No.</td>
<td>Rate</td>
<td>Women No.</td>
<td>Rate</td>
</tr>
<tr>
<td>Person-years at risk</td>
<td>9,295</td>
<td>7,576</td>
<td>12,874</td>
<td>14,065</td>
</tr>
<tr>
<td>AIDS dementia complex</td>
<td>60</td>
<td>6.5</td>
<td>30</td>
<td>4.0</td>
</tr>
<tr>
<td>Bacterial pneumonia</td>
<td>27</td>
<td>2.9</td>
<td>14</td>
<td>1.8</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>136</td>
<td>14.6</td>
<td>97</td>
<td>12.8</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td>16</td>
<td>1.7</td>
<td>5</td>
<td>0.7</td>
</tr>
<tr>
<td>Cryptosporidiosis</td>
<td>21</td>
<td>2.3</td>
<td>14</td>
<td>1.8</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>61</td>
<td>6.6</td>
<td>58</td>
<td>7.7</td>
</tr>
<tr>
<td>Herpes simplex disease</td>
<td>13</td>
<td>1.4</td>
<td>10</td>
<td>1.3</td>
</tr>
<tr>
<td>HIV* wasting syndrome</td>
<td>79</td>
<td>8.5</td>
<td>50</td>
<td>6.6</td>
</tr>
<tr>
<td>MAI*</td>
<td>42</td>
<td>4.5</td>
<td>37</td>
<td>4.9</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>75</td>
<td>8.1</td>
<td>37</td>
<td>4.9</td>
</tr>
<tr>
<td>PCP*</td>
<td>134</td>
<td>14.4</td>
<td>64</td>
<td>8.4</td>
</tr>
<tr>
<td>PML*</td>
<td>10</td>
<td>1.1</td>
<td>6</td>
<td>0.8</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>46</td>
<td>4.9</td>
<td>40</td>
<td>5.3</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>27</td>
<td>2.9</td>
<td>6</td>
<td>0.8</td>
</tr>
<tr>
<td>Lymphomas</td>
<td>31</td>
<td>3.3</td>
<td>18</td>
<td>2.4</td>
</tr>
<tr>
<td>Other AIDS-defining disease†</td>
<td>23</td>
<td>2.5</td>
<td>24</td>
<td>3.2</td>
</tr>
<tr>
<td>Death without AIDS</td>
<td>129</td>
<td>13.9</td>
<td>58</td>
<td>7.7</td>
</tr>
</tbody>
</table>

* AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; MAI, mycobacterial diseases not including tuberculosis; PCP, Pneumocystis carinii pneumonia; PML, progressive multifocal leucoencephalopathy.

† Includes cervical cancer, focal brain lesion, isosporiasis, leishmaniasis, salmonella bacteriemia, and diagnosis unknown.
seroconverters with unknown AIDS diagnosis did not change the results.

DISCUSSION

Compared with men, HIV-infected women in industrialized countries survive longer following HIV seroconversion. Furthermore, the effect of sex on HIV progression and survival has changed over calendar period; before the widespread introduction of HAART in 1997, differences in mortality between men and women were of small magnitude and borderline statistical significance, whereas, from 1997 onward, women had a 32 percent lower risk of death compared with men. Women also experienced lower risks of both progression to AIDS and non-AIDS mortality only after 1997. These benefits occurred despite a slightly lower proportion of women on HAART in each HIV exposure group compared with their male counterparts.

When individual AIDS-defining disease was considered, women experienced significantly lower cumulative risks than men for most AIDS-defining disease after 1997, but these differences were statistically significant for only AIDS dementia complex, tuberculosis, Kaposi’s sarcoma, and lymphomas. Of note, these four AIDS-defining diseases were also less frequent in women compared with men before 1997, although differences in only Kaposi’s sarcoma were statistically significant at that time. Some of these differences have been described in the HIV-negative population (e.g., tuberculosis and Kaposi’s sarcoma) and are attributable to lower exposure to other coinfections such as *Mycobacterium tuberculosis* (29) and human herpesvirus 8. Human herpesvirus 8 infection is more common in men having sex with men and people originating from sub-Saharan Africa. However, adjusting for ethnic group did not explain this effect, and, unfortunately, the role of undisclosed homosexuality could not be explored any further.

Compared with men, HIV-negative women have also been reported to have a lower incidence of non-Hodgkin lymphoma (30). As for AIDS dementia complex, estrogens have been suggested to have a neuroprotective effect, in both experimental animal research and epidemiologic studies (31), but further research is necessary to explore this association.

Women had a lower mortality rate than men in the period 1997 onward for both all-cause mortality and death without AIDS. It is noteworthy that, although not statistically significant, mortality for women was lower for both all-cause mortality and death without AIDS before 1997. Our results provide additional support for and more convincing evidence regarding previous findings reported by some groups in a European setting (14–18, 32). However, in the United States, HIV-infected women from the Women’s Interagency HIV Study have been reported to have higher accident or injury-related mortality rates than men from the Multicenter AIDS Cohort Study (13), and the HIV-infected women from the HIV Epidemiologic Research Study did not experience reductions in their overall mortality rates after HAART was introduced (33). Although there are important differences in study design and type of outcome analyzed in many of the articles reviewed, the large differences encountered between these studies in Europe and the United States probably reflect severe socioeconomic differences between the study populations, inclusion or exclusion of gay men, and differences in health care systems between the two regions.


![FIGURE 2. Effect of sex (reference category: men) on the cumulative incidence of each acquired immunodeficiency syndrome (AIDS)-defining disease as the first AIDS event or death without AIDS in the eras pre-1997 and 1997 onward, CASCADE collaboration. HIV, human immunodeficiency virus; MAI, mycobacterial diseases not including tuberculosis; PCP, *Pneumocystis carinii* pneumonia; PML, progressive multifocal leucoencephalopathy, CI, confidence interval.](https://academic.oup.com/aje/article-abstract/168/5/532/92937)
It is well known that, for most causes, mortality rates for age-matched, HIV-negative women from industrialized countries are lower than those for men (34–35). The reason for these sex differences in mortality is not well understood and may be attributable to both genetic and environmental factors (34–36). Healthier lifestyles and lower rates of violent death among women are often proposed, but the potential role of biologic causes cannot be excluded (although they are difficult to test) (34–37). Women have been described as having lower viral loads than men, but studies reporting those findings did not find an association with differences in HIV progression rates by sex (38, 39). In both studies, a biologic mechanism was cautiously proposed as an explanation but remains unclear. Assuming there may be a mixture of genetic and environmental causes, changes over time are most likely attributable to external causes.

In our study, we found that women fared better than men, although the difference in prognosis was not evident until HAART became available despite similar proportions of person-time spent on HAART, suggesting that women respond better to health interventions. Women were started on HAART when their CD4 cell counts were slightly higher, although it is unlikely to be a major contributor given that the absolute difference was low. This is no surprise because, in settings where levels of gender equity in access to care are acceptable, women, compared with men, have been reported to have healthier behaviors, more conscious health-seeking patterns, and higher adherence rates to medication (1, 34, 35, 40, 41). Most studies examining response to HAART suggest that women respond equally well or even better than men do (1), although a higher rate of treatment interruptions among women—suggesting a higher rate of intolerance to medication—has also been reported (42). It is likely that HAART, in lowering the risk of death, renders visible again gender differences in mortality that exist in the general population.

A number of limitations and potential sources of bias that may influence results merit discussion. One important possibility is that women followed up in CASCADE from 1997 onward may originate from a population with a better socioeconomic profile than that of the other women; women in the earlier periods were more likely to be partners of male injecting drug users. Although this could potentially be true from what we know of the HIV epidemic in Europe, such detailed information is not pooled within CASCADE. At any rate, given the higher proportion of women from non-European backgrounds in later time periods (data not shown), it is unlikely that these women had better socioeconomic profiles than their (White) European counterparts. It could also be argued that our results could be confounded by socioeconomic status, but, for socioeconomic status to confound the better outcomes in HIV-infected women, we should have to assume that women are wealthier than men, which is not usually the case. When we adjusted for ethnicity in a subset of patients for whom this information was available, results remained unchanged. Likewise, behavioral differences in health-seeking patterns, one of the possible explanations for our results, are not measured in CASCADE. Our results are also likely to be sensitive to the ascertainment of events and loss to follow-up. However, differential loss to follow-up by sex is unlikely to have had a major role since CASCADE cohorts are either under active follow-up or perform cross-checks with national AIDS and death registries.

We obtained similar findings when modeling the effect of sex on either the cause-specific instantaneous hazard or the cause-specific cumulative incidence hazard of AIDS (overall) and of each first AIDS-defining disease and death without AIDS. Where some endpoints may have experienced a large change in risk over calendar period, such that the number at risk for the other events changed dramatically, and those changes are different between men and women, results from the cause-specific instantaneous hazard and those derived from the cause-specific cumulative incidence hazard may differ more substantially.

The question about whether the survival advantage observed for women has a fundamental biologic basis cannot be answered. However, our study indicates that, in settings with small gaps in gender inequality and universal access to care, HIV-infected women fare better than their male counterparts in the era of HAART.

**ACKNOWLEDGMENTS**

CASCADE has been funded through grants from the European Union (BMH4-CT97-2550, QLK2-2000-01431, QLRT-2001-01708, and LSHP-CT-2006-018949). Inmaculada Jarrin is funded by Red de Investigación en SIDA (RIS) (grant RD06/0006) and is supported by Centro de Investigación Biomédica en Red (CIBER) Public Health.

The authors are grateful to Alicia Llacer for her useful comments on the Discussion section of the manuscript. The CASCADE collaboration is integrated by the following:

**Steering Committee—**Julia del Amo (Chair), Laurence Meyer (Vice Chair), Heiner Bucher, Geneviève Chêne, Deenan Pillay, Maria Prins, Magda Rosinska, Caroline Sabin, and Giota Touloumi; Co-ordinating Centre—Kholoud Porter (Project Leader), Krishnan Bhaskaran (Scientific Coordinator), Sarah Walker, Abdel Babiker, and Janet Darbyshire; Clinical Advisory Board—Heiner Bucher, Andrea de Luca, Martin Fisher, Cécile Gouyard, and Roberto Muga; Collaborators—**Australia: Sydney AIDS Prospective Study and Sydney Primary HIV Infection cohort (John Kaldor, Tony Kelleher, Linda Gelgor, Tim Ramacciotti, David Cooper, and Don Smith); Canada: South Alberta clinic (John Gill); Denmark: Copenhagen HIV Seroconverter Cohort (Louise Brunn Jørgensen, Claus Nielsen, and Court Pedersen); Estonia: Tartu Lükool (Iria Lutsar); France: Aquitaine cohort (Geneviève Chêne, Francois Dabis, Rodolphe Thiebaut, and Bernard Masquelier), French Hospital Database (Dominique Costagliola), Lyon Primary Infection cohort (Philippe Vanhems), SEROCO cohort (Laurence Meyer and Faroudy Boufassa); Germany: German cohort (Osamah Hamouda and Claudia Kucherer); Greece: Greek Haemophilia cohort (Giota Touloumi, Nikos Pantazis, Angelos Hatzakis, Dimitrios Paraskis, and Anastasia Karafotidou); Italy: Italian Seroconversion Study (Giovanni Rezza, Maria Dorrucci, Benedetta Longo,
and Claudia Balotta); The Netherlands: Amsterdam Cohort Studies among homosexual men and drug users (Maria Prins, Liselotte van Asten, Akke van der Bij, Ronald Geskus, and Roel Coutinho); Norway: Oslo and Ulleval Hospital cohorts (Mette Sannes, Oddbjorn Brubakk, Anne Eskild, and Johan N. Bruun); Poland: National Institute of Hygiene (Magdalena Rosinska); Portugal: Universidade Nova de Lisboa (Ricardo Camacho); Russia: Pasteur Institute (Tatyana Smolskaya); Spain: Badalona IDU hospital cohort (Roberto Muga and Jordi Tor), Barcelona IDU Cohort (Patricia Garcia de Olalla and Joan Cayla), Madrid cohort (Julia del Amo and Jorge del Romero), Valencia IDU cohort (Santiago Pérez-Hoyos, Ildefonso Hernandez Aguado, and Josefina Belda); Switzerland: Swiss HIV cohort (Heiner Bucher, Martin Rickenbach, and Patrick Franciolli); Ukraine: Perinatal Prevention of AIDS Initiative (Ruslan Maloyuta); and United Kingdom: Edinburgh Hospital cohort (Ray Brettley), Health Protection Agency (Valerie Delpech, Sam Lattimore, Gary Murphy, John Parry, and Noel Gill), Royal Free hemophilia cohort (Kholoud Porter, Anne Johnson, Andrew Phillips, Abdel Babiker, Janet Darbyshire, and Valerie Delpech), University College London (Deenan Pillay), and University of Oxford (Harold Jaffe).

All authors were involved in setting up the cohort and conceptualizing the design. Inmaculada Jarrin and Julia del Amo asked the research question presented in this manuscript. All authors were involved in data collection. Inmaculada Jarrin was responsible for statistical analyses and was supervised by Ronald Geskus and Kholoud Porter. Inmaculada Jarrin and Julia del Amo wrote the first draft of the paper. All authors were involved in interpreting the data and commented on interim drafts. All authors reviewed the final manuscript. Inmaculada Jarrin and Krishnan Bhaskaran had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the analysis. Conflict of interest: none declared.

REFERENCES

26. Babiker A, Darbyshire J, Pezzotti P, et al. Changes over calendar time in the risk of specific first AIDS-defining events...