All cause mortality in the Swiss HIV cohort study from 1990 to 2001 in comparison with the Swiss population

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**Design:** Mortality within the Swiss HIV Cohort Study for the years 1990–2001 was compared with the mortality of the general Swiss population.

**Methods:** Standardized mortality ratios (SMR) and life tables were calculated for strata defined by combinations of gender and HIV transmission group. The effect of dropouts was investigated with a sensitivity analysis and by analysing CD4 cell counts before dropout.

**Results:** During the study period 10,977 individuals had at least one cohort visit with a median observation time of 46 months. A total of 3630 patients died and 2290 dropped out. SMR decreased from 79.3 [95% confidence interval (CI), 77.2–81.5] before the introduction of highly active antiretroviral treatment (HAART) in 1996 to 15.3 (95% CI, 14.2–16.4) thereafter. For persons who acquired HIV infection by injecting drug use (IDUs), the SMR decreased from 98.2 (95% CI, 94.9–103.5) to 40.9 (95% CI, 37.0–44.8) after 1996; for all other HIV transmission groups the SMR decreased from 69.2 (95% CI, 66.9–71.6) to 9.4 (95% CI, 8.5–10.4). Thus, IDUs had significantly lower survival in comparison with other patient groups after 1996. Patients who had started HAART during the time period in which this treatment was available, had even lower SMRs.

**Conclusions:** Although overall survival has improved considerably since the introduction of HAART, cohort life expectancy remains below that of the Swiss population. We noted, however, substantial differences in mortality among subgroups, and the results indicate that the additional risk related to injection drug use before 1996 had been masked by HIV-associated mortality.

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mortality ratios for HIV-infected patients who had started a protease inhibitor-containing therapy in France [5]. Jäggy et al. calculated excess mortality rates in selected subpopulations of the Swiss HIV Cohort Study (SHCS) to estimate mortality in the period of HAART [6].

However, the evolution of total mortality in the SHCS has not been assessed in detail and life tables have not, to our knowledge, been calculated for a HIV positive population. Life tables are based on age-specific death rates of the year in which they are constructed and therefore give a cross-sectional view of the mortality during a given year. The life span of each individual is projected on the basis of the actual death rates in a given population [7]. This is the key difference to classical survival analysis (such as Kaplan–Meier curves and Cox regression), where every individual is followed for a certain time period. This study analyses the mortality of HIV-infected persons in general. HIV-related mortality itself is not evaluated. A particular aim was to compare mortality among different HIV transmission groups before and after introduction of HAART.

Methods

Study population
The SHCS is a prospective multi-centre cohort study with continuous enrolment of HIV-infected patients aged 16 years and older. Enrolment is independent of the stage of disease or the degree of immuno-suppression. Information about demographics, HIV-associated diseases, medications and laboratory parameters is collected in a standardized way at registration and follow-up visits at intervals of 6 months. Informed consent is obtained from all participants. The SHCS includes an estimated 70% of all patients with AIDS in Switzerland [8,9]. The demographical characteristics (sex, risk group and age at diagnosis of AIDS) of the SHCS participants are similar to those of the overall HIV positive population in Switzerland. More than 12 600 patients have been enrolled and around 5400 are currently being followed. More details are given elsewhere [9,10].

For this study we included all participants of the SHCS who had a follow-up visit or died between 1 January 1990 and the 31 December 2001. Mortality data for the Swiss population were obtained from the Swiss Federal Office of Statistics and the Human Mortality Database [11].

Analysis
Three different approaches to the analysis of mortality were used.

1. For each year the risk of death was calculated by dividing the number of patients who died during that year by the number of patients under observation at the beginning of the year. To illustrate the relation to treatment changes, the proportion of patients receiving different types of antiretroviral treatment (one drug only and combinations of two, three and more than three substances) at 1 January of each year was calculated for each year.

2. Standardized mortality ratios (SMRs) were calculated as the ratio of the number of observed deaths to the number of expected deaths in strata defined by gender and transmission group [injecting drug-users (IDUs), non-IDUs: overall and stratified by heterosexual and homosexual men]. In addition, SMRs for patients who had started HAART were calculated. HAART was defined as a combination therapy of at least three antiretroviral treatments containing protease inhibitors or non-nucleoside reverse transcriptase inhibitors. Expected number of deaths were calculated for each calendar year by multiplying the age-, sex- and calendar year-specific death rate of the general Swiss population with the mid-year cohort population (mean number of patients followed at 1 January of two consecutive years). Ninety-five percent confidence intervals for the SMRs were calculated according to Chiang [7].

3. Standard abridged life tables (grouping age in 5-year intervals) were calculated for the same strata as for the SMRs (combination of gender and transmission groups). The number of deaths and the person-years of follow-up for each age interval and subgroup were summed over the 6 years before the introduction of HAART (1990–1995) and over the 5 years after HAART was introduced (1997–2001). The year 1996 was omitted, since the effect of HAART was not fully developed by then. The respective survival functions and 95% confidence intervals (CI) were calculated.

Dropouts
Participants were defined as dropouts in the following situations: withdrawal of consent, moving out of Switzerland or missing all appointments for at least 14 months. If a patient returned after 14 months, he or she was again included into the cohort and was no longer considered a dropout.

The possible impact of dropouts was explored with a sensitivity analysis of the SMR calculations and with an examination of the last CD4 cell count before leaving the study both pre-HAART and during HAART for IDUs and non-IDUs.

For the sensitivity analysis, lower-bound SMRs were obtained by excluding deaths that occurred after dropout, but have nevertheless been reported. This method
has the advantage that the study population is clearly defined but the disadvantage that it does not take into account all available information. Upper-bound SMRs were calculated by the assumption that all dropouts died 14 months after their last follow-up visit.

In order to explore patients’ immune status before leaving the study, we defined three groups of escape-events: Patients who have not participated in the study for at least 14 months, but later returned (the break group), patients who did not return (the dropouts group) and patients who have died (the deaths group).

Escape-events were classified by year, where the date of leaving was defined as last follow-up date plus 14 months for the break- and the dropout group, and the year of death for those who died. If a drop out or break patient was known to have later died, he was then categorized under ‘death’ for that year in which the death occurred.

Thus defined, a patient could have escape events in different years. For the first escape, the last CD4 cell count within 2 months before the date of leaving the study was determined. The median of these CD4 cell counts was compared both before and after the introduction of HAART for all three escape-groups and stratified by IDUs and non-IDUs.

**Results**

**Patient characteristics and overall risk of death**

Between 1 January 1990 and 31 December 2001, 10,977 patients had at least one cohort visit. Seventy-one percent of the participants were men. 7037 patients were seen or have died during the period of HAART, of whom 5393 had started HAART.

During the study period 3630 patients died and 2290 patients dropped-out. The median age at death varied from 33 to 41 years (Table 1). Women were more likely to drop out than men, with dropout rates of 25 and 19%, respectively \((P < 0.001)\). A similar difference was observed between IDUs and non-IDUs, with dropout rates of 26 and 18%, respectively \((P < 0.001)\).

The yearly risk-of-death declined significantly from 13% in the years before 1995 to 3% after 1998, while the prevalence of therapies combining three or more drugs increased to more than 70% after 1998 (Fig. 1).

**Standardized mortality ratios**

The overall SMR has decreased from 79.3 (95% CI, 77.2–81.5) before the era of HAART to 15.3 (95% CI, 14.2–16.4) thereafter, and varied substantially by sex and anamnesis of injecting drug consumption.
Table 1. The SMRs of the transmission categories ‘heterosexual’ and ‘homosexual men’ were very similar to the overall non-IDU group (results not shown). If, in the second period, only patients who had started HAART are considered, the SMRs are 1.4- to 1.7-fold lower for all strata. The mean SMR has not declined as strongly for IDUs (from 98.2 pre-HAART to 40.9 during HAART) as for non-IDUs (from 69.2 pre HAART to 9.4 during HAART) and in every stratum the mean SMR was lower for men than for women.

Abridged life tables and survival functions

An example of a life table for the SHCS population is given in Appendix 2. Although the derived survival curves (Fig. 2) are similar for different transmission groups before HAART became available, survival for IDU patients is much lower in comparison with non-IDUs in the HAART era. The transmission groups ‘heterosexual’ and ‘homosexual men’ were not different from the overall non-IDU group (results not shown).

Dropouts

A total of 6705 of the SHCS participants have had at least one break, have dropped-out or have died. The first ‘escape event’ was a break for 2473 patients, a dropout for 1650 patients and death for 2582 participants.

Measured CD4 cell counts within 2 months prior to the first escape event were available for 4131 individuals. The median CD4 cell counts before the escape events for the dropout group were more similar to the values of the break group than those of the deceased (Table 2). This similarity to the break group was observed in the pre-HAART as well as the HAART era irrespective of the transmission group.

The sensitivity analysis shows that with the upper-bound scenario SMRs are considerably higher than the values in the main approach where dropouts were not taken into account and that, also under this scenario, the SMRs decrease strongly in the HAART era (Fig. 3). The values of the SMR of the total population within the upper-bound scenario are 114.2 and 39.6 for the pre-HAART and HAART eras, respectively. For IDUs the SMRs reduce from 147.4 to 93.9 and for non-IDUs from 96.9 to 24.9.

Discussion

The SHCS reflects quite well the situation of persons living with advanced HIV disease in Switzerland [8,12]. This study, involving more than 52 100 person-years of follow-up, showed that even though mortality has substantially decreased since the introduction of HAART, overall survival and life expectancy in the SHCS remain considerably below that of the general population.
Swiss population. The main results obtained were the following.

1. The probability of death was reduced significantly from nearly 0.13 in 1990 to 0.03 in 2001.
2. Mortality varied dramatically among strata defined by transmission group and over time. In the period of HAART SMRs are consistently lower for patients who have started HAART.
3. Before HAART became available, mortality in persons who acquired HIV infection by injecting drug use was similar to mortality in other HIV positive patients. In the HAART era, mortality was much higher for IDUs compared to non-IDUs.

Table 2. Median and inter-quartile range (IQR) of CD4 cell counts before leaving the study.

<table>
<thead>
<tr>
<th>Group of breaks</th>
<th>Number of participants</th>
<th>Median CD4 (IQR) Pre-HAART era (years 1990–1995)</th>
<th>Median CD4 (IQR) HAART era (years 1997–2001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-IDU</td>
<td>701</td>
<td>490 (320–680)</td>
<td>400 (207–628)</td>
</tr>
<tr>
<td>IDU</td>
<td>834</td>
<td>460 (300–680)</td>
<td>249 (229–587)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group of dropout</th>
<th>Number of participants</th>
<th>Median CD4 (IQR) Pre-HAART era (years 1990–1995)</th>
<th>Median CD4 (IQR) HAART era (years 1997–2001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-IDU</td>
<td>456</td>
<td>374 (212–620)</td>
<td>360 (205–568)</td>
</tr>
<tr>
<td>IDU</td>
<td>348</td>
<td>394 (212–618)</td>
<td>349 (229–587)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group of deaths</th>
<th>Number of participants</th>
<th>Median CD4 (IQR) Pre-HAART era (years 1990–1995)</th>
<th>Median CD4 (IQR) HAART era (years 1997–2001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-IDU</td>
<td>303</td>
<td>130 (49–282)</td>
<td>135 (32–338)</td>
</tr>
<tr>
<td>IDU</td>
<td>166</td>
<td>374 (212–620)</td>
<td>350 (212–562)</td>
</tr>
</tbody>
</table>

*Patients who came back after more than 14 months. HAART, highly active antiretroviral therapy.
Overall mortality
Studies in many countries have reported a marked decrease of mortality since the introduction of HAART [1–4]. Although the reported magnitude of decrease is similar, direct comparisons are often difficult because of differences in methods or in the composition of study populations.

Standardized mortality ratios
SMRs showed marked differences in mortality between strata and between the pre-HAART and HAART era. The SMRs for the first period were 2.4- (IDU) to more than 7-fold (non-IDU) higher than in the HAART era. The upper-bound scenario of the sensitivity analysis confirms the strong decrease of the SMRs in the HAART era and that the mortality reduction in IDUs is lower than in non-IDUs.

Even in the HAART era not all patients were treated. Among those who should be treated, some refuse to take HAART because they fear its side effects or they feel that the treatment is too complicated. A physician’s perception that the patient would not comply with treatment is yet another reason for not prescribing HAART [13]. If the analysis was restricted to patients who have ever started treatment with HAART in the HAART era, the SMRs are lower in all strata. This decrease reflects the high mortality rate in patients who should have been treated but were not.

For the years 1997 to 2001 the SMRs for the patients who had started HAART therapy are comparable with those reported in a similar study in the French population [5]. However, calculation of SMRs does not completely remove the influence of differences in population composition and therefore these SMRs are not directly comparable with those presented herein.

Jäggy et al. [6] limited their analysis to a specific subgroup of the Swiss HIV Cohort. In our study we analysed mortality irrespective of concomitant disease and treatment outcome and thus our estimates of mortality were higher.

Higher SMRs for women in comparison with men of all transmission groups are an artefact of the fact that, in the Swiss population, men in the age range 20 to 45 years experience a higher mortality rate than women [14], whereas in the SHCS death rates for men and women are comparable (results not shown). The survival functions indicate, however, that the absolute risk of death is similar for both genders (results not shown) as has already been reported [15,16].

Fig. 3. Sensitivity analysis of standardized mortality ratios (SMR): the main approach where deaths after abandonment of the study are included (cubes), the lower-bound scenario without deaths after abandonment (circles) and the upper-bound scenario if all abandoning patients are counted as death 14 months after their last follow-up (triangles).
Abridged life tables and survival functions
Comparing the survival curve of the Swiss population with the survival curves of various groups of patients in the SHCS, it is again clearly apparent that the overall mortality of HIV-positive patients is still substantially higher than the mortality of the general Swiss population.

Before HAART was introduced, the survival functions of IDU and non-IDU patients were similar: HIV infection seems to have masked the effect of injecting drug use with respect to mortality during this period. After the introduction of HAART, overall mortality in the IDU patients decreased less than in non-IDU patients. Since IDUs are more likely to drop-out from the study than non-IDUs (P < 0.001) and some of the dropouts are likely to have died, we underestimated mortality of the IDUs in our main approach. Therefore, the difference between IDUs and non-IDUs since HAART has been introduced, is even greater than shown.

The limited effect of HAART in IDUs has been observed by other authors [17–19]. Possible explanations for this are decreased access to treatment and delay in starting therapy [13,20–22], poorer adherence [23–25] and more frequent non-AIDS-related deaths [26–30].

Access to treatment and delay in starting therapy no longer seems to be a major problem in the SHCS as the treatment situation and the CD4 values at the initiation of HAART are similar for IDUs and non-IDUs [31]. This is in contrast to the year 1999 in which it has been shown that those patients in the SHCS who acquired HIV through injecting drug use had a significantly higher risk of receiving inadequate treatment [13]. It has to be noted that in Switzerland the obligatory health insurance covers the cost for antiretroviral treatment.

Co-infection with hepatitis C in the SHCS is especially high for IDUs (92%) compared with non-IDUs (7%) and also the proportion of patients dying of liver disease was higher for IDU-patients [32].

Analysis of dropouts
The overall dropout-rate of 21% (2290 of 10 977) is high. Assuming different scenarios about the fate of these will affect the results of the analysis.

The upper-bound scenario of the SMRs (in which it is assumed that all dropouts have died shortly after their last follow-up visit) seems not to be realistic since the CD4 cell counts before dropping-out were closer to the values observed in the break group than to the last available measurement for patients who died. The values in the dropout group were generally lower than the values in the break group. This result is consistent with the fact that some of these dropout-patients had died. CD4 values were comparable for IDUs and non-IDUs for all escape groups except the group of deaths during HAART. For this group the CD4 values before death seem to be higher for IDUs: this result confirms the fact that IDUs die more often from non-AIDS related deaths.

Limitations
Although life tables facilitate comparison of mortality over extended periods of time, they are based on current mortality rates which are likely to change in the future. The calculation of SMRs cannot completely remove the influence of differences in overall population composition. Further, it is very probable that some patients who are lost from follow-up have died, and thus the number of deaths included in the analysis may be under-estimated.

Conclusions
The calculations of SMRs and of survival curves both clearly demonstrate that, during the period in which HAART has been available, mortality remains higher in HIV-positive patients than in the general Swiss population. The differences are substantial among subgroups. However, this observed mortality pattern probably does not apply to a newly HIV-infected individual. The situation might improve in the future with the development of new drugs or the situation might decline with increased resistance to therapeutic drugs and an increased impact of side effects. As new treatments for HIV appear, it will continue to be important to identify differential response to those treatments across demographic groups.

Acknowledgements
We thank Barbara Perrenoud from the Swiss Federal Office of Statistics, Neuchâtel for providing the Swiss death and population records for the years 1989 to 1996 and Mariabeth Silkey for carefully reading the manuscript.

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References


11. Human mortality database. University of California, Berka (USA), and Max Planck Institute for Demographic Research (Germany). Available at www.mortality.org.


Appendix 1

The members of the Swiss HIV Cohort Study are:


Appendix 2

See overleaf
### Life table for the total cohort population for the years 1997 to 2001

<table>
<thead>
<tr>
<th>Age (x&lt;sub&gt;i&lt;/sub&gt; to x&lt;sub&gt;i+1&lt;/sub&gt;)</th>
<th>nDx</th>
<th>Px</th>
<th>Mx</th>
<th>ax</th>
<th>qx</th>
<th>Lx</th>
<th>Tx</th>
<th>Ex</th>
<th>p0j</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 *</td>
<td>374</td>
<td>77642</td>
<td>0.00481</td>
<td>0.1</td>
<td>0.005</td>
<td>99569</td>
<td>5514856</td>
<td>55.1</td>
<td>1.000</td>
</tr>
<tr>
<td>1–4 *</td>
<td>78.5</td>
<td>320268</td>
<td>0.00025</td>
<td>0.4</td>
<td>0.001</td>
<td>397850</td>
<td>5415287</td>
<td>54.4</td>
<td>0.995</td>
</tr>
<tr>
<td>5–9 *</td>
<td>49</td>
<td>422106</td>
<td>0.00012</td>
<td>0.5</td>
<td>0.001</td>
<td>496973</td>
<td>5017437</td>
<td>50.5</td>
<td>0.994</td>
</tr>
<tr>
<td>10–14 *</td>
<td>70</td>
<td>427267</td>
<td>0.00016</td>
<td>0.5</td>
<td>0.001</td>
<td>496626</td>
<td>4520464</td>
<td>45.5</td>
<td>0.994</td>
</tr>
<tr>
<td>15–19 *</td>
<td>171</td>
<td>417068</td>
<td>0.00041</td>
<td>0.5</td>
<td>0.002</td>
<td>495914</td>
<td>4023838</td>
<td>40.5</td>
<td>0.993</td>
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<tr>
<td>20–24</td>
<td>6</td>
<td>491</td>
<td>0.01222</td>
<td>0.5</td>
<td>0.059</td>
<td>480720</td>
<td>3527924</td>
<td>35.6</td>
<td>0.991</td>
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<tr>
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<td>45</td>
<td>2116</td>
<td>0.02127</td>
<td>0.5</td>
<td>0.101</td>
<td>442507</td>
<td>3047204</td>
<td>32.7</td>
<td>0.932</td>
</tr>
<tr>
<td>30–34</td>
<td>133</td>
<td>5310</td>
<td>0.02505</td>
<td>0.5</td>
<td>0.118</td>
<td>394291</td>
<td>2604697</td>
<td>31.1</td>
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<tr>
<td>35–39</td>
<td>175</td>
<td>6759.5</td>
<td>0.02589</td>
<td>0.5</td>
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<td>347134</td>
<td>2210406</td>
<td>29.9</td>
<td>0.739</td>
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<tr>
<td>40–44</td>
<td>121</td>
<td>3910.5</td>
<td>0.03094</td>
<td>0.5</td>
<td>0.144</td>
<td>301354</td>
<td>1863272</td>
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<tr>
<td>45–49</td>
<td>76</td>
<td>2116</td>
<td>0.03592</td>
<td>0.5</td>
<td>0.165</td>
<td>255134</td>
<td>1561918</td>
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<tr>
<td>50–54</td>
<td>38</td>
<td>1377</td>
<td>0.02760</td>
<td>0.5</td>
<td>0.129</td>
<td>217238</td>
<td>1306784</td>
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<td>0.464</td>
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<tr>
<td>55–59</td>
<td>29</td>
<td>765.5</td>
<td>0.03788</td>
<td>0.5</td>
<td>0.173</td>
<td>184752</td>
<td>1089546</td>
<td>26.9</td>
<td>0.405</td>
</tr>
<tr>
<td>60 +</td>
<td>31</td>
<td>838.5</td>
<td>0.03697</td>
<td>1.000</td>
<td>904794</td>
<td>904794</td>
<td>27.0</td>
<td>0.335</td>
<td></td>
</tr>
</tbody>
</table>

*Data from the total Swiss population, since no data are available in SHCS for these age groups. Age, age interval (in years); nDx, observed number dying in interval (x<sub>i</sub>, x<sub>i+1</sub>); Px, midyear population; Mx, death rate in interval (x<sub>i</sub>, x<sub>i+1</sub>); ax, fraction of last age interval of life; qx, probability of dying in interval (x<sub>i</sub>, x<sub>i+1</sub>); Lx, number of years lived in interval (x<sub>i</sub>, x<sub>i+1</sub>); Tx, total number of years lived beyond age x; Ex, expectation of life at age x; p0j, survival function.