Rates of suicide are elevated in patients with chronic conditions, including, for example, cancer (1, 2), diseases of the CNS such as multiple sclerosis (3), and HIV infection. A recent study of HIV-infected patients in several U.S. cities found that about one-fifth of patients reported suicide ideation in the previous week (4). Before the introduction of highly active antiretroviral therapy (HAART), it had been shown repeatedly that patients with HIV infection are more likely to die by suicide than are HIV-negative individuals (5, 6). This is not surprising, considering the bleak prognosis of HIV infection and AIDS in the pre-HAART era. Stigma, discrimination, and social isolation may also contribute to elevated suicide rates, and anxiety and depression are common in HIV-infected patients (7, 8). Substance abuse is also frequent in this population and has been shown to be related to suicide (9).

The introduction of HAART in 1996 has led to a substantial reduction in HIV-associated morbidity and mortality (10, 11). Given the improved prognosis for patients with HIV infection, one might expect lower suicide rates in the HAART era. HAART is not a cure, however, and it is associated with adverse effects, including mood disorders (12) and other effects that could lead to suicidal ideation (4).

A recent study comparing treatment changes in the Swiss HIV Cohort Study and two cohorts in Cape Town, South Africa, has shown that in both settings, suicide rates tended to be higher in older patients, in men, in injection drug users, and in patients with advanced clinical stage of HIV illness. An increase in CD4 cell counts was associated with a reduced risk of suicide.

It is unclear whether and to what extent HAART has affected suicide rates. It is also unclear to what extent suicides in HIV-infected patients are associated with diagnosed and treated conditions such as depression. Finally, rates of suicide in HIV-infected patients may be affected by factors not related to HIV infection, that is, by trends in the general population. We analyzed time trends and risk factors for suicide in the Swiss HIV Cohort Study and compared them with trends and risk factors in the general population of Switzerland.

Results: From 1988 to 2008, 15,275 patients were followed in the Swiss HIV Cohort Study for a median duration of 4.7 years. Of these, 150 died by suicide (rate 158.4 per 100,000 person-years). In men, standardized mortality ratios declined from 13.7 (95% CI=11.0–17.0) in the pre-HAART era to 3.5 (95% CI=2.5–4.8) in the late HAART era. In women, ratios declined from 11.6 (95% CI=6.4–20.9) to 5.7 (95% CI=3.2–10.3). In both periods, suicide rates tended to be higher in older patients, in men, in injection drug users, and in patients with advanced clinical stage of HIV illness. An increase in CD4 cell counts was associated with a reduced risk of suicide.

Conclusions: Suicide rates decreased significantly with the introduction of HAART, but they remain above the rate observed in the general population, and risk factors for suicide remain similar. HIV-infected patients remain an important target group for suicide prevention.

(Am J Psychiatry 2010; 167:143–150)
Method

All patients enrolled in the Swiss HIV Cohort Study were included in the analysis. A dedicated survey was conducted to collect more detailed information on psychiatric conditions and treatments in patients who died by suicide. Data from the Swiss National Cohort were used to compare suicide rates and risk factors for suicide in HIV-infected patients with those in the general population.

Swiss HIV Cohort Study

The Swiss HIV Cohort Study (www.shcs.ch) is a multicenter cohort study with continuous enrollment of HIV-infected patients age 16 years and older (16). Enrollment started in 1988 and is independent of the stage of disease or the degree of immunosuppression. Information about demographic characteristics, HIV-associated diseases, medications, and laboratory parameters is collected in a standardized way using questionnaires at registration and follow-up visits at 6-month intervals. At each follow-up visit, the physician records whether the patient received any psychiatric treatment since the last visit. Causes of death are classified into suicide, drug overdose, accident, murder, HIV-related, other, and unknown. Informed consent is obtained from all participants. The Swiss HIV Cohort Study includes an estimated 40% of all HIV-positive patients in Switzerland and 70% of all patients with an AIDS diagnosis. A patient was considered lost to follow-up if he or she did not return to the clinic for at least 14 months. Only patients who had potentially 14 months of follow-up were included in the analysis of loss to follow-up.

For this study, a questionnaire on mental disorders in patients who died by suicide was developed and pilot-tested at two sites. The questionnaire collected more detailed information on psychiatric treatment, alcohol abuse, and suicide attempts and was completed by clinical staff at participating centers based on information extracted from the patients’ charts. The final version

<table>
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<th>Variable</th>
<th>Patients Who Died by Suicide</th>
<th>All Other Patients</th>
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</tr>
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<tr>
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<tr>
<td>Median age at enrollment and interquartile range (years)</td>
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</table>

* Based on chi-square and Wilcoxon rank-sum tests comparing the pre-HAART and HAART eras.

b CDC=Centers for Disease Control and Prevention.

IQR=interquartile range.
Swiss National Cohort

The Swiss National Cohort (www.swissnationalcohort.ch) is a longitudinal study of mortality based on the linkage of individual anonymous data from the 1990 and 2000 censuses with the routine mortality files held at the Federal Office of Statistics (17). For the present study, the mortality files from December 4, 1990 (the date of the 1990 census), to December 31, 2005, were linked to the census records using probabilistic record linkage. The resulting database included 6,873,687 people. Of 937,637 deaths recorded during the study period, 875,269 (93.3%) could be linked to a census record. Causes of death were coded according to ICD-8 up to 1994 and ICD-10 from 1995 onward. Registration of deaths is near complete for people dying in Switzerland.

Data Analysis

Patient characteristics were compared using chi-square tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. Outcomes were all deaths from suicide (code “suicide” in the Swiss HIV Cohort Study, ICD-8 codes E950–959 and ICD-10 codes X60–X84 in the Swiss National Cohort). Crude suicide rates were calculated by calendar year and also analyzed for different periods, including the pre-HAART (1988–1995) and HAART (1996–2008) periods. For some analyses, the HAART period was further divided into the early HAART period (1996–1998) and the later HAART period (1999–2008). To examine the separate effects of time period (pre-HAART versus HAART) and changes in immune status, we performed a time-updated analysis including baseline CD4 counts and the difference between each subsequent count and the baseline count as described by Diggle et al. (18). Analyses were also adjusted for several baseline variables: age (per 10-year increase), sex, nationality (Swiss versus other), risk group (injection drug use versus other route of infection), CDC clinical stage (A, B, or C), and psychiatric treatment in the 6 months before enrollment (yes or no).

Poisson regression was used to obtain standardized mortality ratios comparing suicide rates in the Swiss HIV Cohort Study with rates in the Swiss National Cohort. For each year, the expected number of suicides was calculated using age-specific (in 5-year age groups) and sex-specific rates from the Swiss National Cohort. This was necessary because the age distribution and the proportion of women in the Swiss HIV Cohort Study changed over time. In the general population, suicide rates increase with age and are lower in women than in men. In sensitivity analyses, we also included deaths of undetermined intent (codes E980–E989 in ICD-8; Y10–Y34 in ICD-10) to examine whether differences in suicide rates between HIV-infected patients and the general Swiss population could be due to differential coding of causes of death. In this analysis, we excluded individuals infected through intravenous drug use: accidental overdoses may have been misclassified as suicides in this population. Also, the proportion of patients infected through injection drug use declined over time in the Swiss HIV Cohort Study (19, 20). In the Swiss HIV Cohort Study, predictors of suicide were analyzed separately for the pre-HAART and the HAART eras using multivariate Poisson regression, adjusting for age, sex, nationality, transmission group, clinical stage, and psychiatric treatment at enrollment, as detailed above. Similar analyses were conducted with data from the Swiss National Cohort for the whole study period. Finally, we identified factors associated with psychiatric treatment in the 6 months before enrollment using logistic regression. Results are presented as rates per 100,000 person-years, standardized mortality ratios, rate ratios, and odds ratios with 95% confidence intervals.

Results

Characteristics of HIV-Infected Patients in the Pre-HAART and HAART Eras

A total of 15,275 HIV-infected patients were included in the analysis; 7,783 (51.0%) were enrolled in the pre-HAART era and 7,492 (49.0%) in the HAART era (Table 1). Patients enrolled in the HAART era were older, more likely to be female, less likely to have a history of injection drug use, less likely to be in an advanced clinical stage, and less likely to...
have Swiss nationality than those in the pre-HAART era. Among patients who died by suicide, the proportion of females doubled from the pre-HAART to the HAART era. Also, the proportion receiving psychiatric treatment at enrollment and the proportion ever having been in psychiatric treatment increased.

**Trends in Suicide Rates in HIV-Infected Patients and the General Population**

Overall, 150 HIV-infected patients died by suicide during 94,692 person-years of follow-up, for a rate of 158.4 per 100,000 person-years. In the general population, 5,808,602 individuals ages 16 to 85 years were followed up for 28.9 million person-years. Of 6,335 suicides in this age group, 5,562 (88%) could be linked to a census record (for a rate of 19.2 per 100,000 person-years) and thus were included in the present analysis. Trends in rates of suicide in comparison with the general Swiss population are shown in Figure 1. In HIV-infected men, suicide rates declined from 447.3 per 100,000 person-years (95% CI=359.7–556.1) during the pre-HAART era to 90.1 (95% CI=64.7 to 125.5) during the later HAART era. In women, the corresponding rates were 149.7 (95% CI=82.9–270.4) and 63.1 (95% CI=35.0–114.0), respectively. Rates also declined in the general population, from 32.6 to 25.9 per 100,000 person-years in men and from 12.9 to 11.1 per 100,000 person-years in women (Figure 1, middle panel).

The standardized mortality ratios comparing HIV-infected patients with the general population were, during the pre-HAART era, 13.7 (95% CI=11.0–17.0) in men and 11.6 (95% CI=6.4–20.9) in women; during the 1996–1998 period, 3.5 (95% CI=1.8–6.7) in men and 7.0 (95% CI=2.2–21.6) in women; and during the 1999–2008 period, 3.5 (95% CI=2.5–4.8) in men and 5.7 (95% CI=3.2–10.3) in women (Figure 1, lower panel). Overall, 319 deaths of undetermined intent were recorded in the Swiss National Cohort. When we excluded patients infected through intravenous drug use from the Swiss HIV Cohort Study and added the causes of undetermined intent to the deaths coded as suicides in the Swiss National Cohort, the standardized mortality ratios for the three periods shown in Figure 1 were, in men, 11.0 (95% CI=8.3–14.5), 3.0 (95% CI=1.3–6.7), and 2.5 (95% CI=1.6–3.8), respectively, and in women, 5.1 (95% CI=1.3–20.3), 8.9 (95% CI=2.2–35.6), and 4.3 (95% CI=1.8–10.2), respectively.

The decline in suicide rates in the Swiss HIV Cohort Study remained in multivariate analyses with time-updated CD4 counts: the adjusted relative risk comparing the pre-HAART and HAART eras was 0.24 (95% CI=0.16–0.38; p<0.001). An increase in CD4 cell counts was associated with a reduced risk of suicide: the rate ratio was 0.89 (95% CI=0.81–0.98) per 100 cells/µL.

**Risk Factors for Suicide in HIV-Infected Patients and the General Population**

Table 2 summarizes risk factors for suicide. In both HIV-infected patients and the general population, the risk of suicide was higher in older individuals, in men,
Discussion

Suicide is an important public health problem in Switzerland: about 1,400 suicides are recorded annually, and Swiss suicide rates are in the top third in Europe and in the top quintile worldwide (21). We found that in HIV-infected patients, suicide rates declined substantially after the introduction of HAART, in both men and women, with a somewhat steeper decline in men. The association of increasing suicide rates with declining CD4 cell counts supports the hypothesis that HAART-related improvements in disease status may be responsible for the reduction in suicide rates over time. Comparisons with the general population showed that despite this decline, suicide rates remained well above those observed in the general population; the standardized mortality ratio in recent years was 3.5 in HIV-infected men and 5.7 in HIV-infected women.

Clinical Characteristics of Patients Who Died by Suicide

Of 150 questionnaires on mental disorders in patients who died by suicide, 136 were completed (response rate 91%). All questionnaires were completed by medical staff at the participating infectious disease clinics. The results are summarized in Table 3. The majority of patients (N=84, 62%) had a diagnosis of mental illness, which was typically made after the diagnosis of HIV infection. Depression was the most common diagnosis, followed by anxiety/stress disorders and psychotic disorders. Other diagnoses included borderline syndromes (N=5), bipolar disorders (N=2), paranoia (N=2), and others (N=4). A history of injection drug use, alcohol abuse, and attempted suicide was common. The most common possible reason for suicide indicated on the questionnaires, in both the pre-HAART and HAART eras, was progression of HIV infection, followed by psychosocial problems.

A significant minority of patients (36.6% in the pre-HAART era and 23.2% in the HAART era) had not been treated for their mental condition. Predictors of psychiatric treatment included period (adjusted odds ratio=1.95 [95% CI=1.68–2.27] comparing pre-HAART and HAART eras), age (adjusted odds ratio per 10-year increase=0.91 [95% CI=0.83–0.99]), nationality (adjusted odds ratio=1.35 [95% CI=1.14–1.59] comparing Swiss with other nationals), and current use of injection drugs (adjusted odds ratio=3.12 [95% CI=2.68–3.62]).
Study was one of the first HIV cohort studies worldwide (16) and includes about 40% of all patients with HIV and about 70% of patients with AIDS in the country (22). Our results are therefore likely to be representative for Switzerland and may also apply to other high-income settings. A strength of our study was the inclusion of data from the Swiss National Cohort (17), which allowed us to compare time trends in suicide rates and risk factors between HIV-infected patients and the general population.

Our study also had several limitations. The suicide rate used to calculate the expected number of suicides was based on all suicides recorded in the general population, which will include suicides in HIV-infected patients. However, the number of suicides in HIV-infected patients is small compared to the total number of suicides, and the bias introduced by their inclusion is negligible. Some variables that were associated with suicide in the general population (e.g., marital status) were not collected consistently in the Swiss HIV Cohort Study and therefore could not be considered. Sexual orientation is another potential risk factor for suicide. However, because of the limited number of suicides in the HAART era, we were unable to examine its influence in this study. Also, our analysis did not consider differences between the HIV-infected population and the general population other than gender and age. Lifestyle risk factors differ between HIV-infected and noninfected populations. For example, a collaborative analysis of HIV cohort studies found that over 50% of HIV-infected patients were smokers (23). Smoking is associated with higher rates of suicide; however, this is unlikely to reflect a causal association (24).

Injection of intravenous drugs is relevant in this context since it is often difficult to distinguish between accidental fatal overdoses and suicides (25). It would therefore have been preferable to calculate standardized mortality ratios by comparing rates of suicide and overdose between injection drug users who were and were not infected by HIV, but the latter rates are not available in Switzerland. Differences in the coding of deaths could also have introduced bias: a death in an HIV-infected patient may have been more likely to be coded as a suicide, particularly in a patient infected through injection drug use, than a death in the general population. We examined the effect of these potential biases in a sensitivity analysis that excluded injection drug users from the group of HIV-infected patients and included deaths of undetermined intent in the general population. We found that suicide rates remained substantially higher in HIV-infected patients than in the general population.

Despite the substantially improved prognosis with HAART, the life expectancy of HIV-positive patients remains lower than in the general population (11). Furthermore, quality of life is impaired even in patients treated with HAART (26), and many patients suffer from the stigma and social exclusion associated with HIV infection (27, 28). The prevalence of depression is high in HIV-infected patients (29, 30). A diagnosis of mental illness in those who died by suicide was more common in the HAART era than in the pre-HAART era, and patients were more likely to be treated for mental illness in the HAART era. Our study thus indicates that in the pre-HAART era, high suicide rates were driven by disease progression, which at that time could not be prevented, whereas in the HAART era, mental illness has become relatively more important. However, although the number of patients receiving psychiatric care increased, even in the HAART era a substantial proportion of patients remained untreated. These results provide a compelling rationale to improve psychiatric care, including mental health screening and greater access to pharmacological and psychological treatment. Finally, we stress that the survey of mental illness in patients who died by suicide also had limitations: questionnaires were completed by infectious disease specialists, rather than by the treating psychiatrists, and depended on a review of charts. Also, there was no comparison group of patients who did not die by suicide.

With the exception of rural China, suicide rates are higher in men than in women worldwide (31). In the 1995–2000 period, the suicide rate globally was 26.7 per 100,000 for men and 9.3 per 100,000 for women, for a gender ratio of 2.9 (32). Among the HIV-infected patients included in this study, the adjusted gender ratio was 2.8 in the pre-HAART era but declined to 1.3 in the HAART era, reflecting the fact that the introduction of HAART was associated with a more substantial reduction in suicide rates in men than in women. Risk factors for suicide are known to differ between genders. For example, a population-based study in Denmark found that unemployment, retirement, being single, and sickness absence were risk factors in men, and having a young child was protective in women (33). A history of hospitalization for mental illness was a strong risk factor for suicide in both men and women.

Suicide rates also declined in the general population, but this decline was much smaller than the one observed in HIV-infected patients, and it was less pronounced than in other countries during the same period. In Germany, for example, suicide rates in the general population decreased from 24 per 100,000 in 1982 to 14 per 100,000 in 2000 (34). Of note, active euthanasia is a criminal offense in Switzerland, but assisting someone in dying by suicide is legal if the motive is not selfish (35). The article of the Swiss penal code (article 115) is from 1918 and was never intended to regulate assisted suicide, but it is used by right-to-die societies to legally offer such assistance to their members (36). The final step must be taken by the member, by ingesting the lethal dose of barbiturates or starting the injection infusion (36). A review of 748 suicides assisted by one right-to-die society (including 55 suicides of patients with HIV/AIDS) showed that the number of cases increased from 1990 to 2000 (36). Furthermore, in contrast to Germany and other countries, Switzerland has no national suicide prevention program (32).
How do standardized mortality ratios for suicide in HIV-infected patients compare to those in patients with other chronic conditions? In a large Swedish study of cancer patients, the ratio was 1.9 for men and 1.6 for women (1). Similarly, in an international study including over 725,000 women, the standardized mortality ratio for breast cancer was 1.4 (37). A ratio of a similar magnitude, 2.3, was found in Swedish patients with multiple sclerosis (38). Other diseases and conditions that have been shown to be associated with a higher risk of suicide include end-stage renal disease (ratio of 1.84, 95% CI=1.5–2.3) (39), amyotrophic lateral sclerosis (ratio of 5.8, 95% CI=3.6–8.8) (40), and spinal cord injury (ratio in men, 4.7, 95% CI=1.9–9.7, and in women, 19.2, 95% CI=1.8–70.5) (41). The standardized mortality ratios for suicide observed in our study indicate a higher risk of suicide in HIV-infected patients than in patients with other life-threatening conditions, even in the HAART era.

References


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