DOI: 10.1097/QAD.0000000000001335

# Life expectancy in HIV-positive persons in Switzerland: matched comparison with general population

Running head: Life expectancy among HIV-infected people

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## Abstract

***Objectives:*** To estimate life expectancy (LE) over 25 years in HIV-positive people and compare their LE with recent estimates for the general population, by education.

***Methods:*** Patients aged 20 years or older enrolled in the Swiss HIV Cohort Study 1988-2013 were eligible. Patients alive in 2001 were matched to up to 100 Swiss residents, by sex, year of birth, and education. LE at age 20 was estimated for monotherapy (1988-1991), dual therapy (1992-1995), early combination antiretroviral therapy (cART, 1996-1998), later cART (1999-2005) and recent cART (2006-2013) eras. Parametric survival regression was used to model life expectancy.

***Results:*** 16,532 HIV-positive patients and 927,583 residents were included. LE at age 20 of HIV-positive individuals increased from 11.8 years (95% CI 11.2-12.5) in the monotherapy era to 54.9 years (95% CI 51.2-59.6) in the most recent cART era. Differences in LE across educational levels emerged with cART. In the most recent cART period, LE at age 20 years was 52.7 years (95% CI 46.4-60.1) with compulsory education, compared to 60.0 years (53.4-67.8) with higher education. Estimates for the general population were 61.5 years and 65.6 years, respectively. Male sex, smoking, injection drug use and low CD4 counts at enrolment were also independently associated with mortality.

***Conclusion:*** In Switzerland educational inequalities in LE were larger among HIV-infected persons than in the general population. Highly educated HIV-positive people have an estimated LE similar to Swiss residents with compulsory education. Earlier start of cART and effective smoking cessation programs could improve HIV-positive LE further and reduce inequalities.

***Keywords:*** Life expectancy; HIV; combination antiretroviral therapy; cART; mortality; SHCS, Switzerland

## Introduction

Estimates of life expectancy are of obvious importance to individuals who are HIV-positive, and important to monitor and predict the progress of the HIV/AIDS epidemic and to plan health services. Several studies have examined life expectancy in HIV-positive people in the era of combination antiretroviral therapy (cART) [1–6]. In recent years, the question has arisen whether in some settings life expectancy of HIV-positive people may have reached that observed in the general population [7,8]. A recent review expressed life expectancy at age 20 years of HIV-positive individuals on cART as a percentage of life expectancy in the general or HIV-negative population and found that percentages ranged from 60% in Rwanda to 90% in Canada [9].

Comparisons of life expectancy in HIV-positive people and the general population are fraught with difficulties, particularly in high-income countries. People living with HIV have lifestyles and behaviors that may reduce their life expectancy, regardless of their HIV infection. For example, HIV-positive people have higher rates of smoking, alcohol and recreational drug use, and higher rates of other sexually transmitted co-infections and hepatitis C [10–14]. Ideally, lifestyle and behaviors would be measured comprehensively both in the HIV-positive and the general population, using standardized methods. However, such data are not available from the vital registration systems used to estimate life expectancy in the general population. Matching HIV-positive people to members of the general population for variables that are associated with lifestyles and behaviors is one way to address this issue. The level of education is associated with lifestyles both in HIV-positive people and the general population [15,16], and the association of education with life expectancy is well documented in many general populations [17–19].

The Swiss HIV Cohort Study (SHCS) is a nationwide, prospective cohort study of HIV-infected patients [20]. Established in 1988, the SHCS is one of the longest-running HIV cohort study worldwide. Level of education is assessed in categories that match those used by the Swiss National Cohort (SNC) [21], a census-based longitudinal study of mortality in Switzerland. We analyzed life expectancy in the SHCS 1988-2013 and compared life expectancy across levels of education with life expectancy in the general Swiss population, using the data from the SNC.

## Materials and methods

### Data sources

The Swiss HIV Cohort Study (SHCS) has been described in detail elsewhere [20,22]. Adults aged 16 years or older are followed up at University outpatient clinics, Cantonal hospitals and private practices. Clinical stage is classified according to the clinical criteria of the Centers for Disease Control and Prevention (CDC) [23]. Socio-demographic, behavioral, and clinical parameters are collected at enrolment and then in 6-monthly intervals. CD4 cell counts, HIV-1 viral load (determined with Roche Amplicor HIV-1 Monitor Assay) and other laboratory results are collected at three-monthly follow-up visits. Antiretroviral treatment is documented at enrolment and follow-up visits. All participants aged 20 years and older enrolled in the SHCS between 1 January 1988 and 31 December 2013 were eligible for the present analysis.

The Swiss National Cohort (SNC) is a longitudinal study of mortality in the resident population of Switzerland, based on the 1990 and 2000 national censuses [21]. In brief, deterministic and probabilistic record linkage [24] was performed using the Generalized Record Linkage System [25] to link census records to a death record or an emigration record, based on a set of key variables that are available in all data sets (sex, date of birth, place of residence, marital status, religion, nationality, profession and, if applicable, date of birth of partner and date of birth of children). Enumeration in the Swiss census was near-complete: for the 2000 census, coverage is estimated at 98.6% [26]. For the present study, analyses were restricted to residents aged 20 years or older. We drew a random sample of up to 100 individuals from census 2000 for each patient enrolled in the SHCS and alive on 1 January 2001, matched for sex, year of birth and level of education.

### Comparisons and definitions

The two datasets allowed consistent definitions of educational level as higher education, vocational training or compulsory school. We further examined life expectancy by period of enrolment into the study, defined by the type of ART available during the period: the monotherapy era (1988-1991), dual therapy era (1992-1995), early cART era (1996-1998), later cART era (1999-2005) and recent cART era (2006-2013). Estimates of life expectancy were calculated for each treatment era by educational level, main source of income, HIV transmission

group, history of IDU, smoking status and presentation at enrolment. Late presentation was defined as a person with HIV first presenting for care with a CD4 cell count less than 350 cells/µl or with an AIDS-defining event [27]. Presentation with advanced HIV disease was defined as presentation with a CD4 cell count less than 200 cells/µl or with AIDS: patients presenting with advanced disease are a subgroup of late presenters. Smoking status was classified as never, former or current. Individuals who had used injection drugs within 6 months of registration were classified as current IDU. Former IDU was defined as other documented IDU prior to registration. We defined transmission groups as heterosexual, men have sex with men (MSM), IDU, and other/unknown (including mother to child transmission and blood transfusions). We defined exposure to hepatitis C virus (HCV) as positive anti-HCV or HCV-RNA tests, and chronic hepatitis B as positive HBs-antigen or HBV-DNA tests.

### Statistical analysis

We used parametric survival regression to model life expectancy. Estimates of life expectancy were calculated assuming a Gompertz distribution [28,29], overall and by education and other subgroups with at least 100 patients and at least 20 deaths. We used univariable and multivariable Cox models to examine the association between education and mortality, adjusting for sex, injection drug use (never, former, current), smoking (never, former, current), CD4 cell count at enrolment (<200, 200-349, ≥350 cells/µL) and clinical stage (CDC clinical stage C versus A/B). In all models, age was the underlying time scale. Observation time was measured from enrolment to the time the outcome occurred or the last date information was recorded. In the matched general population sample we modelled age at death or age at 31 December 2013, with age at 1 January 2001 as delayed entry information. In sensitivity analyses, we excluded patients with a history of current or past IDU. Data were analyzed in Stata (Stata Corp., College Station, Texas, USA, version 13.1) and R (R Foundation for Statistical Computing, Vienna, Austria, version 3.0.2). Results are presented as estimates of life expectancy and hazard ratios, with 95% confidence intervals (CIs).

## Results

A total of 17,169 patients were enrolled in the SHCS of whom 637 (3.7%) patients were excluded: 155 were aged less than age 20 years, one patient had an erroneous enrolment date and 481 patients had no follow-up data recorded. A total of 16,532 patients were thus included; 11,916 (72.1%) were men, 11,304 (68.4%) were treatment-naïve at enrolment, and 4,707 (28.5%) had a history of current or past IDU. Median follow-up was 6.30 years (IQR 2.5-13.0 years), median age was 35 years (interquartile range (IQR) 29-42 years), and the median CD4 cell count at enrolment was 332 cells/μL (IQR 167-536). The matched general population sample from the SNC included 927,583 individuals aged 20 years or older on 1 January 2001.

### Characteristics of HIV-positive patients by therapy era and education

Figure 1 shows the introduction of monotherapy and combination therapies over time. Median age increased from 31 years in the monotherapy era to 38 years in the recent cART era (Table 1). Data on education and source of income was missing in most patients in the monotherapy era but was near-complete in more recent years, showing an increase in the proportion of study participants with higher education, and an increase in patients in work. MSM were the most common transmission group in all eras except for the monotherapy era when patients with a history of IDU dominated. The proportion of patients with a history of current or past IDU declined, from 50.2% in the monotherapy era to 9.8% in the most recent cART era. Smoking was not assessed consistently in the earlier periods but appears to have declined in the most recent cART era. The proportion of participants from sub-Saharan Africa increased from 2.1% in the monotherapy era to 16.0% in the most recent cART era. Compared to patients with compulsory school only, patients with higher education were more likely to be MSM, to be working in higher or middle management and less likely to be smokers or IDU (Supplemental Table S1, http://links.lww.com/QAD/B13).

Table 2 shows the clinical and laboratory characteristics of the 11,304 participants who were treatment-naïve at enrolment. The percentage of patients in CDC clinical stage C declined from 16.0% during the monotherapy era to 6.4% in the most recent cART era. The median CD4 cell count at enrolment was higher in the monotherapy than in the dual therapy era and increased thereafter, to 369 cells/μL in the most recent cART era. The prevalence of exposure to hepatitis

C and of chronic hepatitis B declined as testing expanded during the study period. Patients with higher education had slightly higher CD4 cell counts at enrolment, and were less likely to present with advanced disease than patients with compulsory education. They were also less likely to have been exposed to hepatitis C or to have chronic hepatitis B (Supplementary Table S2, http://links.lww.com/QAD/B13).

### Life expectancy in HIV-positive people

A total of 4,579 deaths were recorded during the study period. The proportion of patients who died during follow-up declined from 65.1% (2489/3821) among patients enrolled in the monotherapy era to 2.4% (101/4254) among those enrolled in the most recent cART era. Table 3 presents estimates of life expectancy at age 20 years across the five treatment periods, by socio-demographic and clinical characteristics at enrolment. Overall, life expectancy at age 20 of HIV-positive individuals enrolled in the SHCS increased from 11.8 years (95% CI 11.2-12.5) in the monotherapy era to 54.9 years (95% CI 51.2-59.6) in the most recent cART era (Figure 2).

Differences in life expectancy across educational level emerged with the introduction of cART (Figure 3). For example, in the most recent cART era, life expectancy at age 20 years was 52.7 years among participants with compulsory education, compared to 60.0 years among those with higher education. In the same period, estimated life expectancy was 35.8 years among patients who contracted HIV through IDU but above 50 years for the other transmission groups; it was 49.3 years in current smokers compared to 59.0 years in never smokers. Life expectancy was also influenced by presentation at enrolment. For example, in the most recent cART period life expectancy at age 20 was 47.6 years among patients presenting with a CD4 cell count below 200 cells/μL, and 46.3 years among those presenting with AIDS (Table 3).

The educational gradient in life expectancy at age 20 years was attenuated when excluding patients with a history of current or past IDU but patients with higher education continued to have a higher life expectancy than those with less education (Supplementary Table S3, http://links.lww.com/QAD/B13). Similarly, in Cox regression models including patients enrolled 1992 to 2013, lower educational level continued to be associated with mortality after adjustment for history of IDU, smoking, CD4 cell count at enrolment and sex (Table 4).

### Comparisons with the general population

Figure 1 and Figure 2 present estimates of life expectancy at age 20 years during periods 2001-2005 and 2006-2013 for the matched sample from the general Swiss population. Whereas life expectancy increased substantially in the HIV-positive population, only slight increases were observed in the general population, from 62.3 years to 63.0 years overall, and from 61.1 years to 61.5 years in people with compulsory education, from 61.2 years to 62.2 years in those with vocational training and from 65.4 years to 65.6 years in people with higher education. In the most recent cART period, HIV-positive people continued to have an estimated life expectancy that was lower than their peers from the general population. It was 91.5% (95% CI 84.6%-98.4%) of the matched general population for patients with higher education, 84.5% (95% CI 78.8%-90.3%) for patients with vocational training and 85.6% (95% CI 76.7%-94.6%) for patients with compulsory education. Life expectancy in highly educated patients was similar to the life expectancy of individuals from the general population with compulsory education only.

## Discussion

We estimated life expectancy at age 20 years in HIV-positive patients enrolled in the SHCS over 25 years and during five treatment periods, from the monotherapy era end of the 1980s to the recent years of potent cART. Life expectancy increased, with the most substantial increase observed when cART was first introduced (1996-1998). Life expectancy continued to increase thereafter and was highest in the most recent cART period, with greater life expectancy among those with higher education compared to those with compulsory education only. The comparison with the Swiss population showed that in the most recent cART period, life expectancy continued to be lower in HIV-positive people overall, and lower within each educational category. Of note, HIV-positive people with higher education had an estimated life expectancy similar to individuals from the general population with compulsory education.

Education is frequently used as an indicator of socio-economic position [30]. It is usually completed in early adulthood and therefore suitable for analyses of life expectancy in young adults. Educational level will act as a distal cause, by influencing lifestyles and behaviours, including health seeking behaviours, which in turn will translate into proximal, direct causes, for example IDU or late presentation to care. The level of education attained reflects both early life

and family circumstances and adult resources, including material resources, knowledge and cognitive functioning. The well-educated will be more receptive to health education messages, and better able to communicate with and access health services [30]. In our study lower education was associated with IDU and smoking, but not with late presentation to care. An analysis of the Danish HIV Cohort Study also showed no association between educational attainment and late presentation [31]. In contrast, a pooled analysis of European HIV cohorts found that presentation with advanced HIV disease was more common in the less educated [32].

### Strengths and weaknesses

To our knowledge this is the first study of life expectancy in HIV-positive people spanning 25 years, and the first comparison of HIV-positive life expectancy with the general population that was matched for educational level. Initiated in 1988, the SHCS is one of the longest running HIV cohort studies worldwide. The study collects detailed socio-demographic, behavioral, clinical and laboratory data and has national coverage: comparisons with official AIDS notifications and drug sales data show that approximately 69% of all persons living with HIV/AIDS in Switzerland participate in the SHCS, and that 75% of antiretroviral drug prescriptions relate to study participants [20,33]. The rich data allowed us to estimate life expectancy in different antiretroviral treatment periods, by education and other subgroups defined by socio-economic, behavioral and clinical status. The comparison with a random sample of over 1 million Swiss residents, which was matched for education and therefore to some extent for lifestyle and behaviours, is another strength of the present analysis.

We acknowledge that matching for education may achieve groups that are reasonably comparable with respect to some risk factors, for example smoking, but not for risk factors or co-morbidities associated with sexual orientations and behaviours, illicit drug use or antiretroviral therapy. Our analysis has other limitations. Some variables of interest, for example smoking, were not collected consistently in the earlier years, the collection of others, for example occupational status, was abandoned in later years, and other variables, for example alcohol intake, or were introduced only recently and therefore not used in the present analyses. Data collection on illicit drug use was introduced in 2007, and annual syphilis testing was abandoned in 1998 and re-introduced in 2004. Of note, syphilis was frequent among MSM and persons reporting casual sexual partners [34]. Similarly, data on some cardiovascular co-morbidities were

not collected before 2000, and data on others were collected only from 2008 onwards. In a Danish study the higher prevalence of co-morbidities explained a substantial proportion of the excess mortality observed in the HIV-positive population compared to the general population [35]. The number of HIV-positive people included in the analysis was large overall, but small in some subgroups, for example for migrant groups, or for patients with chronic hepatitis, which precluded the calculation of meaningful estimates of life expectancy. Finally, although the coverage of the SHCS is national [20,33], it is unlikely to be fully representative of all patients living with HIV/AIDS in Switzerland

### Results in context with other studies

Several studies have estimated life expectancy in HIV-positive people living in Europe or the United States of America [1–5,36]. However, only one analysis, from the Danish HIV Cohort Study, included a matched comparison group from the general population, which was matched for place of residence [5]. Like education, the neighbourhood of residence is a powerful measure of socio-economic position but matching in the Danish study was possible only at the level of large municipalities [5]. In Switzerland, life expectancy is considerably higher in people living in affluent neighbourhoods than in neighbourhoods of low socio-economic position [37], and the place of residence also matters in HIV infection [38]. Late presentation was more common and virologic response to cART less common in HIV-positive individuals living in neighbourhoods of lower socio-economic position, but there was no clear association between neighbourhood and mortality [38].

As expected, life expectancy was higher among those who never injected drugs compared to ever users, among never smokers compared to former and current smokers, and among those who presented late compared to those who did not, confirming the results from previous studies [1–5,36]. In line with a recent analysis from the ART Cohort Collaboration [39], current smoking was associated with a substantially lower life expectancy: in the most recent cART era, the difference in life expectancy between current and never smokers was almost 10 years. Our results support the notion that HIV-positive smokers on successful cART may lose more life-years to smoking than to their HIV infection [39].

### Implications for clinicians or policymakers

Our study has important implications for counselling Swiss HIV-positive patients on their long-term prognosis, and our estimates may be relevant to other high-income countries that provide universal access to ART. Our results are also relevant to social policy, for example in the context of life insurance. Differences in life expectancy were of the same order of magnitude as the differences observed between groups of individuals with different levels of education from the general population, which lends further support to the notion that HIV-positive people should be granted access to life cover, at reasonable rates [40,41]. Unfortunately, access to life insurance continues to be limited for some HIV-positive individuals, either because they are rejected by providers based on the HIV infection, or because premiums are prohibitively high. Finally our study suggests that life expectancy among HIV-positive persons could be further improved and educational inequalities reduced by earlier start of cART, effective smoking cessation programs tailored to the HIV-positive population, and early treatment of chronic hepatitis C and B infections, before liver fibrosis develops [42].

## Acknowledgements

This study was supported by grants from Swiss National Science Foundation to the Swiss HIV Cohort Study (SHCS Project 762, grant number 148522) and to the Swiss National Cohort (grant number 148415). We are grateful to the patients, study nurses and care providers who participated in the SHCS over the 25 years covered in this study. The members of the Swiss HIV Cohort Study are: Aubert V, Barth J, Battegay M, Bernasconi E, Böni J, Braun DL, Bucher HC, Burton-Jeangros C, Calmy A, Cavassini M, Dollenmaier G, Egger M, Elzi L, Fehr J, Fellay J, Furrer H (Chairman of the Clinical and Laboratory Committee), Fux CA, Gorgievski M, Günthard H (President of the SHCS), Haerry D (deputy of "Positive Council"), Hasse B, Hirsch HH, Hoffmann M, Hösli I, Kahlert C, Kaiser L, Keiser O, Klimkait T, Kouyos R, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Marzolini C, Metzner K, Müller N, Nadal D, Nicca D, Pantaleo G, Rauch A (Chairman of the Scientific Board), Regenass S, Rudin C (Chairman of the Mother & Child Substudy), Schöni-Affolter F (Head of Data Centre), Schmid P, Speck R, Stöckle M, Tarr P, Trkola A, Vernazza P, Weber R, Yerly S.

## Conflicts of interest

HFG has been an adviser and/or consultant for Gilead, Boehringer Ingelheim, Merck, and Bristol-Myers Squibb and has received unrestricted research and educational grants from Roche, Gilead, GlaxoSmithKline, and Merck Sharp and Dohme. HF's institution has received unrestricted grants from several pharmaceutical industry involved in antiretroviral medications. MB's institution has received unrestricted grants from pharmaceutical industry involved in antiretroviral medications.

All other authors declare that they have no conflict of interest.

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**Table 1.** Socio-demographic characteristics of patients aged 20 years or older at enrolment in the Swiss HIV Cohort Study, by treatment eras.

| | **Monotherapy** (1988–1991) | **Dual therapy** (1992–1995) | **Early cART** (1996–1998) | **Later cART** (1999–2005) | **Recent cART** (2006–2013) |
|---|---|---|---|---|---|
| **No. of participants** | 3821 (23.1) | 2392 (14.5) | 2335 (14.1) | 3727 (22.5) | 4257 (25.8) |
| **No. of women** | 1027 (22.3) | 607 (13.2) | 722 (15.6) | 1192 (25.8) | 1068 (23.1) |
| **Median (IQR) age (years)** | 31 (27–37) | 33 (28–39) | 35 (30–41) | 37 (31-43) | 38 (31–46) |
| **Education** | | | | | |
| Higher education | 236 (6.2) | 312 (13.0) | 436 (18.7) | 827 (22.2) | 1374 (32.3) |
| Vocational training | 792 (20.7) | 1067 (44.6) | 1229 (52.6) | 1773 (47.6) | 1932 (45.4) |
| Compulsory school | 441 (11.5) | 576 (24.1) | 650 (27.8) | 1112 (29.8) | 926 (21.8) |
| Other/unknown | 2352 (61.6) | 437 (18.3) | 20 (0.9) | 15 (0.4) | 25 (0.6) |
| **Main source of income** | | | | | |
| Work | 2 (0.1) | 703 (29.4) | 1270 (54.4) | 2042 (54.8) | 2686 (63.1) |
| Welfare benefits | 0 | 391 (16.4) | 807 (34.6) | 1252 (33.6) | 1027 (24.1) |
| Family support | 0 | 94 (3.9) | 224 (9.6) | 393 (10.5) | 494 (11.6) |
| Other/unknown | 3819 (99.9) | 1204 (50.3) | 34 (1.5) | 40 (1.1) | 50 (1.2) |
| **HIV transmission group** | | | | | |
| Men who have sex with men | 1191 (31.2) | 857 (35.8) | 750 (32.1) | 1256 (33.7) | 2163 (50.8) |
| Heterosexual contact | 783 (20.5) | 615 (25.7) | 873 (37.4) | 1719 (46.1) | 1607 (37.8) |
| Injection drug user | 1744 (45.6) | 835 (34.9) | 618 (26.5) | 604 (16.2) | 276 (6.5) |
| Other/unknown | 103 (2.7) | 85 (3.6) | 94 (4.0) | 148 (4.0) | 211 (5.0) |
| **Injection drug use** | | | | | |
| Never | 1903 (49.8) | 1453 (60.7) | 1616 (69.2) | 3015 (80.9) | 3838 (90.2) |
| Former | 1532 (40.1) | 628 (26.3) | 485 (20.8) | 441 (11.8) | 396 (9.3) |
| Current | 386 (10.1) | 311 (13.0) | 234 (10.0) | 271 (7.3) | 23 (0.5) |
| **Smoking** | | | | | |
| Never | 188 (4.9) | 318 (13.3) | 550 (23.6) | 1362 (36.5) | 1815 (42.6) |
| Former | 110 (2.9) | 145 (6.1) | 198 (8.5) | 504 (13.5) | 664 (15.6) |
| Current | 708 (18.5) | 769 (32.2) | 1145 (49.0) | 1790 (48.0) | 1765 (41.5) |
| Unknown | 2815 (73.7) | 1160 (48.5) | 442 (18.9) | 71 (1.9) | 13 (0.3) |
| **Region of origin** | | | | | |
| Switzerland and North-West Europe | 3266 (85.5) | 1905 (79.6) | 1746 (74.8) | 2403 (64.5) | 2579 (60.6) |
| Southern Europe | 319 (8.4) | 253 (10.6) | 189 (8.1) | 308 (8.3) | 320 (7.5) |
| Sub-Saharan Africa | 79 (2.1) | 96 (4.0) | 197 (8.4) | 565 (15.2) | 680 (16.0) |
| Latin America | 39 (1.0) | 45 (1.9) | 51 (2.2) | 112 (3.0) | 222 (5.2) |
| Asia, Eastern Europe | 60 (1.6) | 57 (2.4) | 82 (3.5) | 220 (5.9) | 326 (7.7) |
| Other/unknown | 58 (1.5) | 36 (1.5) | 70 (3.0) | 119 (3.2) | 130 (3.1) |

Analysis based on 16,532 individuals. IQR, interquartile range. Numbers (percentages) are shown unless otherwise stated.

**Table 2.** Clinical and laboratory characteristics patients who were treatment-naïve at enrolment into the Swiss HIV Cohort Study, by treatment eras.

| **Characteristic** | **Monotherapy** (1988–1991) | **Dual therapy** (1992–1995) | **Early cART** (1996–1998) | **Later cART** (1999–2005) | **Recent cART** (2006–2013) |
|---|---|---|---|---|---|
| Number of patients | 3308 | 1926 | 1267 | 2319 | 2484 |
| Median CD4 cell count (IQR), cells/µl | 360 (170-590) | 290 (120-517) | 334 (169-534) | 351 (194-536) | 369 (223-541) |
| Median HIV-RNA $log_{10}$ (IQR), copies/ml | - | - | 4.5 (3.8-5.0) | 4.6 (3.9-5.1) | 4.6 (3.9-5.1) |
| Exposure to hepatitis C | 55.6% (79/142) | 42.8% (264/617) | 37.2% (371/998) | 19.4% (413/2132) | 6.3% (142/2270) |
| Chronic hepatitis B | 8.7% (105/1208) | 7.8 % (89/1134) | 5.5% (62/1134) | 6.9% (154/2243) | 5.0% (117/2341) |
| Late Presentation | 53.0% (1745/3295) | 59.9% (1154/1926) | 55.6% (705/1267) | 54.3% (1258/2319) | 49.5% (1230/2484) |
| Presentation with advanced HIV disease | 33.4% (1089/3264) | 40.3% (775/1922) | 32.9% (417/1267) | 29.5% (684/2319) | 23.7% (588/2484) |
| Presentation with AIDS | 21.6% (714/3308) | 20.9% (403/1926) | 14.7% (186/1267) | 12.4% (287/2319) | 8.2% (203/2484) |

Analysis based on of 11,304 individuals. IQR, interquartile range.

**Table 3.** Life expectancy at age 20 years in the Swiss HIV Cohort Study, by treatment era.

| | Life expectancy (95% CI) | | | | |
|---|---|---|---|---|---|
| | **Monotherapy** (1988–1991) | **Dual therapy** (1992–1995) | **Early cART** (1996–1998) | **Later cART** (1999–2005) | **Recent cART** (2006–2013) |
| **Overall life expectancy** | 11.8 (11.2-12.5) | 20.8 (19.4-22.2) | 44.7 (42.2-47.3) | 50.8 (48.5-53.3) | 54.9 (51.2-59.6) |
| **Education** | | | | | |
| *Higher education* | - | 26.7 (22.2-31.6) | 53.0 (46.9-59.0) | 58.2 (53.4-63.2) | 60.0 (53.4-67.8) |
| *Vocational training* | - | 25.3 (23.0-27.7) | 44.4 (41.4-47.7) | 49.2 (46.5-52.1) | 52.6 (48.3-57.9) |
| *Compulsory school* | - | 24.3 (21.3-27.5) | 38.9 (35.1-43.0) | 46.5 (43.1-50.3) | 52.7 (46.4-60.1) |
| **Main source of income** | | | | | |
| *Work* | - | 32.8 (29.2-36.5) | 55.0 (50.9-58.9) | 63.9 (59.3-68.4) | 62.9 (56.2-70.9) |
| *Welfare benefits* | - | 15.8 (13.6-18.4) | 31.5 (29.0-34.1) | 39.4 (36.9-42.0) | 48.0 (43.4-53.0) |
| **HIV transmission group** | | | | | |
| *Men who have sex with men* | 8.9 (8.1-9.8) | 22.9 (20.5-25.4) | 52.7 (48.6-57.1) | 57.3 (53.5-61.5) | 56.8 (51.8-63.6) |
| *Heterosexual contact* | 15.3 (13.7-17.21) | 29.6 (26.1-33.3) | 49.5 (45.8-53.6) | 53.1 (50.2-56.2) | 56.7 (51.7-62.8) |
| *Injection drug use* | 12.4 (11.5-13.3) | 15.7 (14.2-17.4) | 27.3 (25.3-29.5) | 31.3 (28.8-33.4) | 35.8 (30.6-41.5) |
| **Injection drug use** | | | | | |
| *Never* | 11.3 (10.4-12.2) | 25.1 (23.1-27.2) | 51.9 (49.0-55.1) | 54.6 (52.2-57.1) | 57.2 (53.1-62.5) |
| *Former* | 12.2 (11.4-13.1) | 16.9 (15.0-18.9) | 29.9 (27.4-32.5) | 33.5 (30.9-36.3) | 39.6 (34.4-45.1) |
| *Current* | 12.2 (10.6-14.0) | 15.2 (12.9-17.7) | 24.7 (21.7-27.9) | 29.0 (25.8-32.4) | - |
| **Smoking** | | | | | |
| *Never* | - | - | - | 65.2 (60.1-70.6) | 59.0 (53.5-65.7) |
| *Former* | - | - | - | 56.4 (51.2-62.1) | 54.6 (48.2-61.8) |
| *Current* | - | - | - | 42.8 (40.7-45.2) | 49.4 (45.2-54.6) |
| **Presentation at enrolment*** | | | | | |
| *CD4 cell count <200 cells/µl* | 3.2 (2.9-3.6) | 6.5 (5.5-7.6) | 35.1 (30.2-40.3) | 46.7 (42.6-51.2) | 47.6 (41.9-54.3) |
| *200-349 cells/µl* | 11.2 (9.9-12.5) | 26.0 (21.7-30.6) | 48.0 (40.3-55.6) | 50.2 (45.0-55.9) | 54.0 (47.0-63.0) |
| *≥350 cells/µl* | 25.2 (23.5-27.1) | 44.5 (40.2-48.6) | 59.9 (52.8-66.0) | 53.0 (48.7-57.9) | 63.9 (54.8-76.0) |
| *Late presentation* | 6.1 (5.6-6.7) | 12.1 (10.6-13.6) | 41.1 (36.8-45.5) | 48.7 (45.5-52.3) | 53.2 (48.2-59.5) |
| *Presentation with advanced HIV disease* | 3.5 (3.2-3.9) | 7.3 (6.2-8.4) | 36.0 (31.2-41.0) | 46.5 (42.7-50.8) | 49.1 (43.5-55.5) |
| *Presentation with AIDS* | 2.4 (2.2-2.7) | 4.4 (3.7-5.2) | 29.1 (23.4-35.3) | 42.1 (37.1-47.7) | 46.3 (38.4-54.9) |

Results from Gompertz parametric regression models. Univariate analyses based on 16,532 patients.
CI, confidence interval.
- , not estimated due to large amount of missing data or small number of patients and deaths.

**Table 4.** Determinants of mortality in the Swiss HIV Cohort Study, 1992-2013.

| | Univariable analysis | | Multivariable analysis | |
|---|---|---|---|---|
| | **Hazard Ratio (95% CI)** | ***P* value** | **Hazard Ratio (95% CI)** | ***P* value** |
| **Sex** | | <0.001 | | 0.003 |
| *Male versus female* | 1.35 (1.21 – 1.51) | | 1.26 (1.08 – 1.46) | |
| **Education** | | <0.001 | | 0.04 |
| *Compulsory school (Reference)* | 1 | | 1 | |
| *Vocational training* | 0.89 (0.80 – 0.99) | | 0.90 (0.78 – 1.05) | |
| *Higher education* | 0.68 (0.59 – 0.79) | | 0.76 (0.62 – 0.94) | |
| **Injection drug use** | | <0.001 | | <0.001 |
| *Never (Reference)* | 1 | | 1 | |
| *Former* | 2.43 (2.17 – 2.73) | | 2.95 (2.51 – 3.48) | |
| *Current* | 2.88 (2.50 – 3.33) | | 4.06 (3.31 – 4.99) | |
| **Smoking** | | <0.001 | | <0.001 |
| *Former (Reference)* | 1 | | 1 | |
| *Never* | 0.72 (0.56 – 0.92) | | 0.87 (0.67 – 1.11) | |
| *Current* | 2.37 (1.91 – 2.94) | | 1.91 (1.53 – 2.38) | |
| **CD4 cell count (cells/µl)** | | <0.001 | | <0.001 |
| *<200 cells/µl (Reference)* | 1 | | 1 | |
| *200-349 cells/µl* | 0.52 (0.47 – 0.59) | | 0.76 (0.64 – 0.90) | |
| *≥350 cells/µl* | 0.35 (0.31 – 0.39) | | 0.71 (0.60 – 0.82) | |
| **CDC clinical stage C** | | <0.001 | | 0.06 |
| *Stage C versus Stage A, B* | 2.33 (2.09 – 2.59) | | 1.18 (0.99 – 1.41) | |

CI, confidence interval. P value from Wald test for overall association.

Results from Cox proportional hazard models stratified by treatment era (dual therapy, early cART, later cART, recent cART). The monotherapy era was excluded due to missing data on educational attainment.

Univariable analysis based on 12,214 patients, after exclusion of 497 patients with unknown educational attainment. Multivariable analysis based on 10,863 patients, after exclusion of a further 1,351 patients with missing values in other variables.

**Figure 1.** Introduction of monotherapy, dual therapy and triple combination therapy (cART) in the Swiss HIV Cohort, 1988-2013.

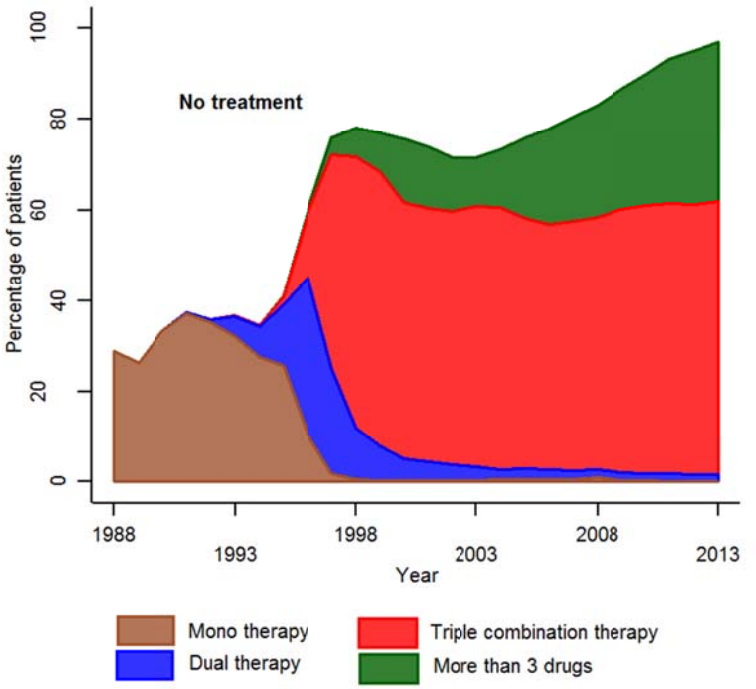

**Figure 2.** Life expectancy at age 20 years in patients enrolled in the Swiss HIV Cohort Study, from monotherapy (1988-1991) to recent combination ART era (2006-2013) and in a matched sample from the general Swiss population (2001-2013).

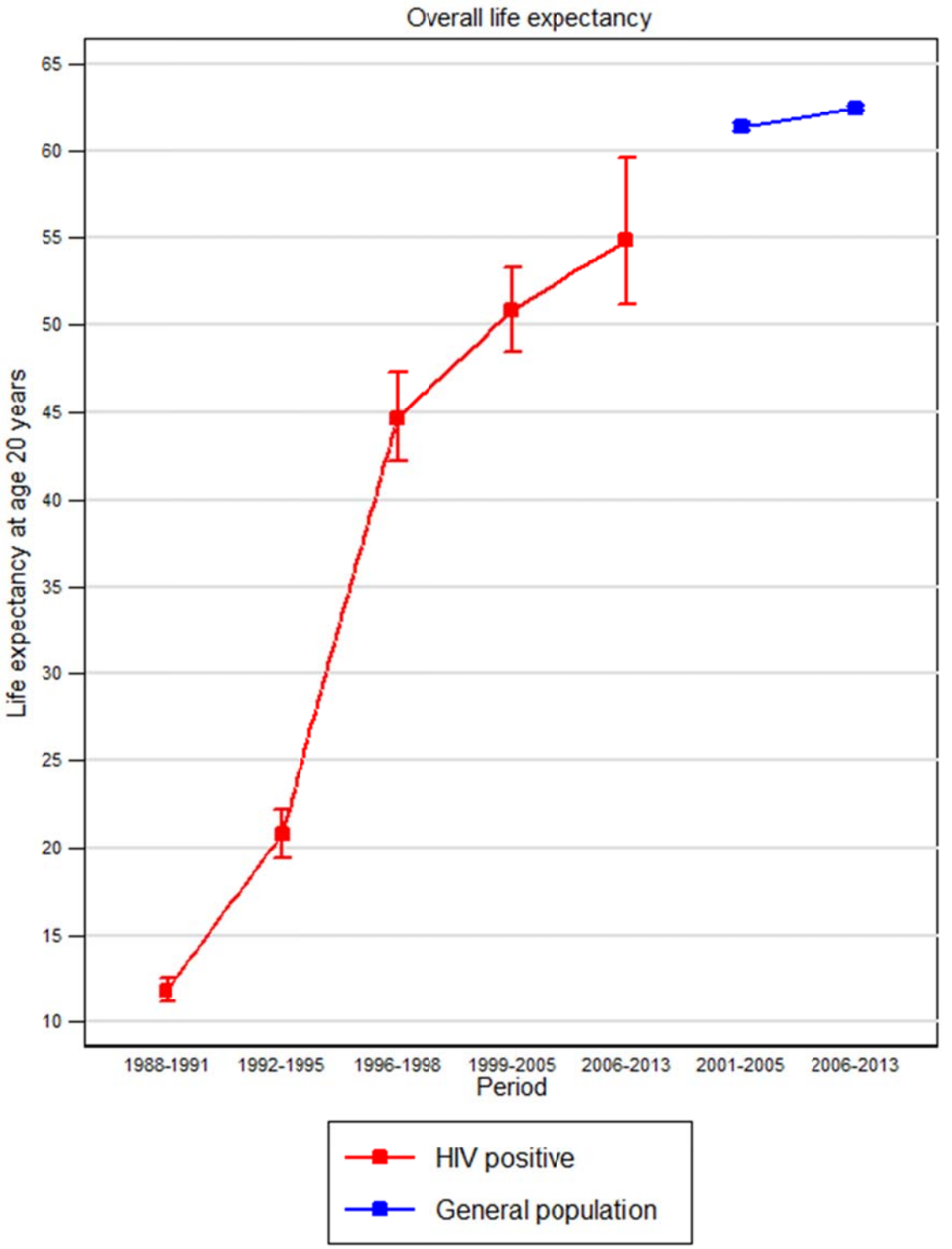

**Figure 3.** Life expectancy at age 20 years by education in patients enrolled in the Swiss HIV Cohort Study, from dual therapy (1992-1995) to recent combination ART era (2006-2013) and in a matched sample from the general Swiss population (2001-2013).