

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

Aysel Gueler^{a,*}, André Moser^{a,b,*}, Alexandra Calmy^c,
Huldrych F. Günthard^{d,e}, Enos Bernasconi^f, Hansjakob Furrer^g,
Christoph A. Fux^h, Manuel Battegayⁱ, Matthias Cavassini^j,
Pietro Vernazza^k, Marcel Zwahlen^a, Matthias Egger^{a,l},
for the Swiss HIV Cohort Study, Swiss National Cohort

Objectives: To estimate life expectancy over 25 years in HIV-positive people and to compare their life expectancy 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. Life expectancy 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: In all, 16 532 HIV-positive patients and 927 583 residents were included. Life expectancy at age 20 of HIV-positive individuals increased from 11.8 years [95% confidence interval (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 life expectancy across educational levels emerged with cART. In the most recent cART period, life expectancy at age 20 years was 52.7 years (95% CI 46.4–60.1) with compulsory education, compared to 60.0 years (95% CI 53.4–67.8) with higher education. Estimates for the general population were 61.5 and 65.6 years, respectively. Male sex, smoking, injection drug use, and low CD4⁺ cell counts at enrolment were also independently associated with mortality.

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

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^aInstitute of Social and Preventive Medicine (ISPM), ^bDepartment of Geriatrics, Inselspital, Bern University Hospital, University of Bern, ^cDivision of Infectious Diseases, University of Geneva, Geneva, ^dDivision of Infectious Diseases and Hospital Epidemiology, University Hospital of Zurich, ^eInstitute of Medical Virology, University of Zurich, Zurich, ^fDivision of Infectious Diseases, Regional Hospital Lugano, Lugano, ^gDepartment of Infectious Diseases, Bern University Hospital, and University of Bern, ^hDivision of Infectious Diseases, Cantonal Hospital Aarau, Aarau, ⁱDivision of Infectious Diseases & Hospital Epidemiology, University of Basel, Basel, ^jDivision of Infectious Diseases, Department of Medicine, University Hospital of Lausanne, University of Lausanne, Lausanne, ^kDivision of Infectious Diseases, Cantonal Hospital of St. Gallen, St. Gallen, Switzerland, and ^lCentre for Infectious Disease Epidemiology and Research (CIDER), University of Cape Town, Cape Town, South Africa.

Correspondence to Professor Matthias Egger, Institute of Social and Preventive Medicine (ISPM), University of Bern, Finkenhubelweg 11, CH-3012 Bern, Switzerland.

Tel: +41 31 631 35 11; fax: +41 31 631 35 20; e-mail: matthias.egger@ispm.unibe.ch

* Aysel Gueler and André Moser contributed equally to the writing of this article.

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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 in 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 in 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 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 3-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 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 injection drug use (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/ μ l 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/ μ l 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, 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, \geq 350 cells/ μ l), 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 modeled 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

In all, 17 169 patients were enrolled in the SHCS, of whom 637 (3.7%) patients were excluded: 155 were aged less than 20 years, one patient had an erroneous enrolment date, and 481 patients had no follow-up data recorded. In all, 16 532 patients were thus included: 11 916 (72.1%) were men, 11 304 (68.4%) were treatment-naïve at enrolment, and 4707 (28.5%) had a history of current or past IDU. Median follow-up was 6.30 years [interquartile range (IQR) 2.5–13.0 years], median age was 35 years (IQR 29–42 years), and the median CD4⁺ cell count at enrolment was 332 cells/ μ l (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 median CD4⁺ cell count at enrolment was higher in the monotherapy than in the dual therapy era, and increased thereafter, to 369 cells/ μ l in the most

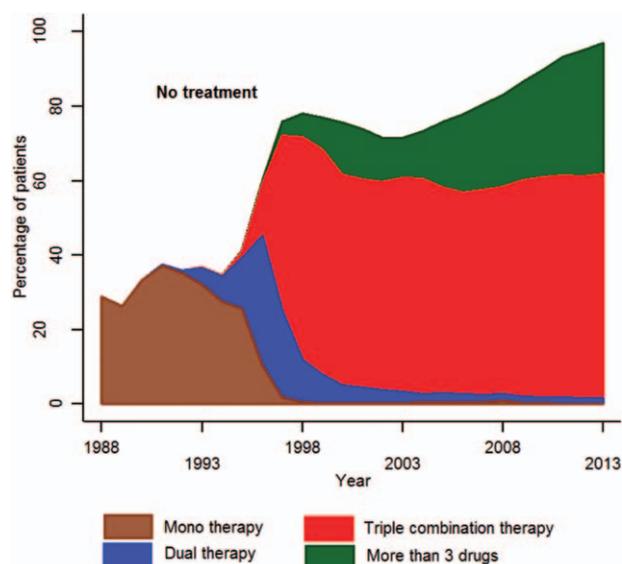


Fig. 1. Introduction of monotherapy, dual therapy, and triple combination antiretroviral therapy (cART) in the Swiss HIV cohort (1988–2013).

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					
MSM	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].

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

In all, 4579 deaths were recorded during the study period. The proportion of patients who died during follow-up declined from 65.1% (2489/3821) among patients

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

Characteristics	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/ μ l	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. cART, combination antiretroviral therapy; IQR, interquartile range.

enrolled in the monotherapy era to 2.4% (101/4257) 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 years 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 (Fig. 2).

Differences in life expectancy across educational level emerged with the introduction of cART (Fig. 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 49.4 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/ μ l, 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 2 and Figure 3 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 to 63.0 years overall, and from 61.1 to 61.5 years in people with compulsory education, from 61.2 to 62.2 years in those with vocational training and from 65.4 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%

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					
MSM	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/ μ l	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/ μ l	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)
\geq 350 cells/ μ l	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 survival 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.

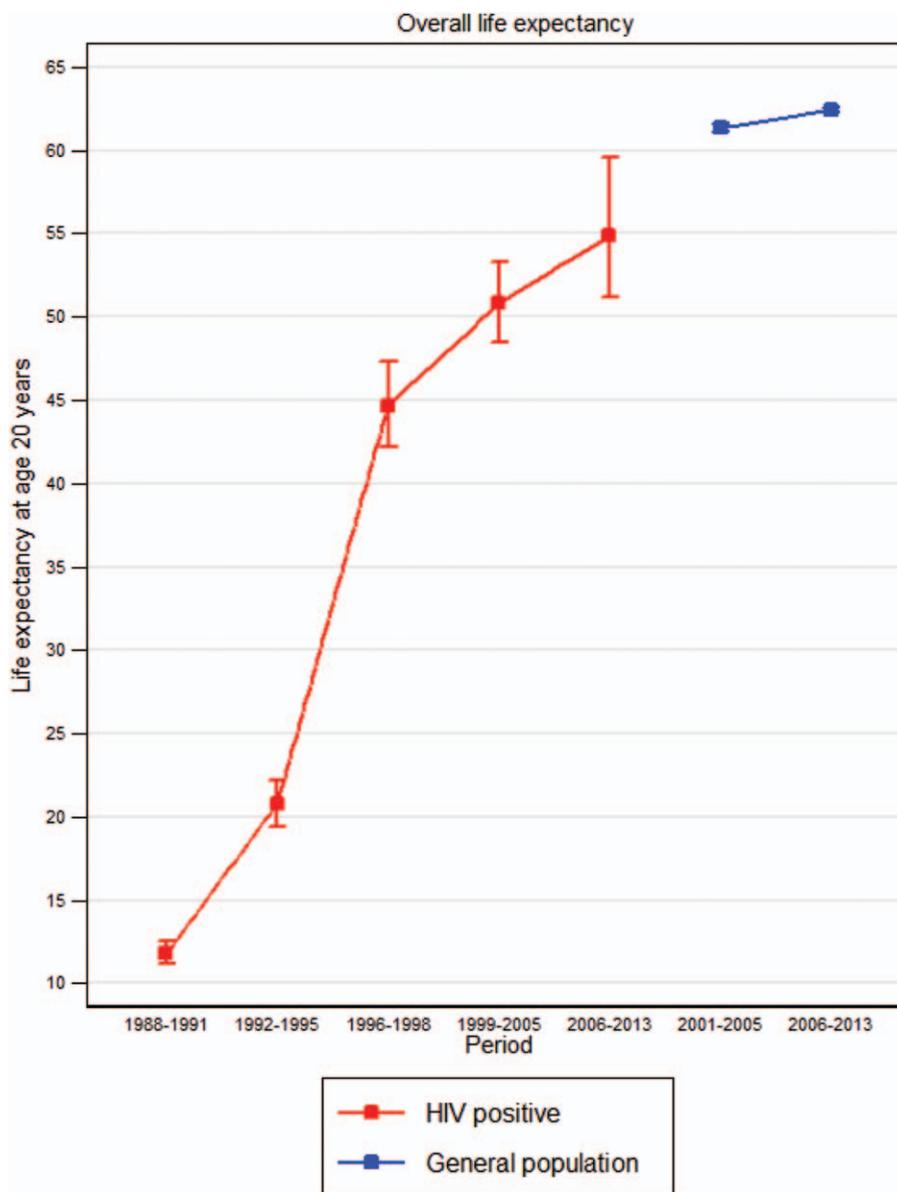


Fig. 2. Life expectancy at age 20 years in patients enrolled in the Swiss HIV Cohort Study, from monotherapy (1988–1991) to recent combination ART era (2006–2013), and in a matched sample from the general Swiss population (2001–2013). ART, antiretroviral therapy.

(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.

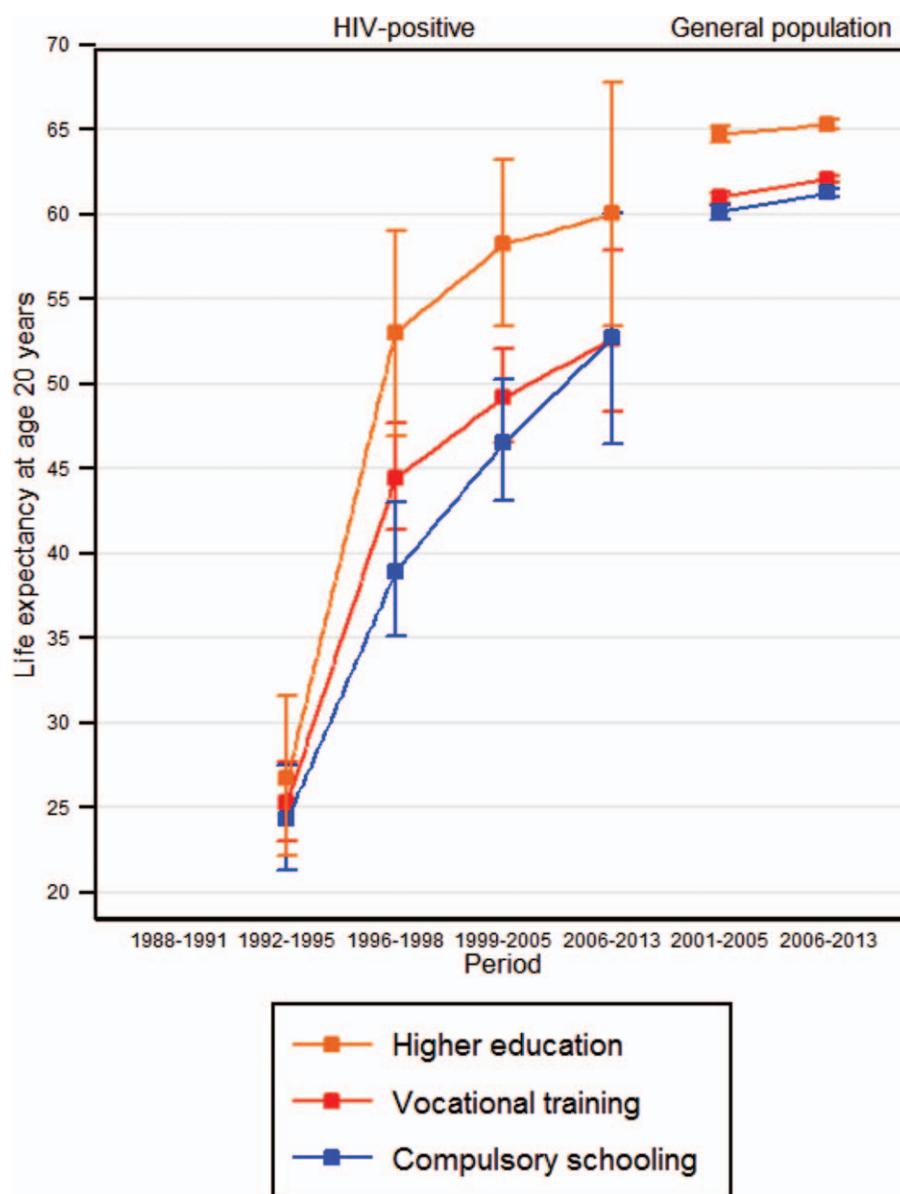


Fig. 3. Life expectancy at age 20 years by education in patients enrolled in the Swiss HIV Cohort Study, from dual therapy (1992–1995) to recent combination ART era (2006–2013), and in a matched sample from the general Swiss population (2001–2013). ART, antiretroviral therapy.

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 behaviors, including health-seeking behaviors, 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

Table 4. Determinants of mortality in the Swiss HIV Cohort Study (1992–2013).

	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	<i>P</i> value	Hazard ratio (95% CI)	<i>P</i> value
Sex		<0.001		0.003
Male vs. 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/ μ l)		<0.001		<0.001
<200 cells/ μ l (reference)	1		1	
200–349 cells/ μ l	0.52 (0.47–0.59)		0.76 (0.64–0.90)	
\geq 350 cells/ μ l	0.35 (0.31–0.39)		0.71 (0.60–0.82)	
CDC clinical stage C		<0.001		0.06
Stage C vs. stage A, B	2.33 (2.09–2.59)		1.18 (0.99–1.41)	

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 1351 patients with missing values in other variables. CDC, Centers for Disease Control and Prevention; CI, confidence interval.

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 behaviors, 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 comorbidities associated with sexual orientations and behaviors, illicit drug use, or ART. 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, 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 comorbidities were not collected before 2000, and data on others were collected only from 2008 onwards. In a Danish study, the higher prevalence of comorbidities 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 neighborhood 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 neighborhoods than in neighborhoods 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 neighborhoods of lower

socio-economic position, but there was no clear association between neighborhood 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 counseling 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].

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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), Scherrer A (Head of Data Centre), Schmid P, Speck R, Stöckle M, Tarr P, Trkola A, Vernazza P, Weber R, Yerly S.

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Conflicts of interest

H.F.G. 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. H.F.'s institution has received unrestricted grants from several pharmaceutical industry involved in antiretroviral medications. M.B.'s institution has received unrestricted grants from the pharmaceutical industry involved in antiretroviral medications.

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References

1. Guaraldi G, Cossarizza A, Franceschi C, Roverato A, Vaccher E, Tambussi G, *et al.* **Life expectancy in the immune recovery era: the evolving scenario of the HIV epidemic in northern Italy.** *J Acquir Immune Defic Syndr* 2014; **65**:175–181.
2. Samji H, Cescon A, Hogg RS, Modur SP, Althoff KN, Buchacz K, *et al.* **Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada.** *PLoS One* 2013; **8**:e81355.
3. van Sighem AI, Gras LAJ, Reiss P, Brinkman K, de Wolf F. **ATHENA national observational cohort study. Life expectancy of recently diagnosed asymptomatic HIV-infected patients approaches that of uninfected individuals.** *AIDS* 2010; **24**:1527–1535.
4. The Antiretroviral Therapy Cohort Collaboration. **Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies.** *Lancet* 2008; **372**:293–299.
5. Lohse N, Hansen A-BE, Pedersen G, Kronborg G, Gerstoft J, Sørensen HT, *et al.* **Survival of persons with and without HIV infection in Denmark, 1995–2005.** *Ann Intern Med* 2007; **146**:87–95.
6. May MT, Gompels M, Delpech V, Porter K, Orkin C, Kegg S, *et al.* **Impact on life expectancy of HIV-1 positive individuals of CD4+ cell count and viral load response to antiretroviral therapy.** *AIDS* 2014; **28**:1193–1202.

7. Sabin CA. **Do people with HIV infection have a normal life expectancy in the era of combination antiretroviral therapy?** *BMC Med* 2013; **11**:251.
8. Hill A, Pozniak A. **A normal life expectancy, despite HIV infection?** *AIDS* 2010; **24**:1583–1584.
9. Wandeler G, Johnson LF, Egger M. **Trends in life expectancy of HIV-positive adults on ART across the globe: comparisons with the general population.** *Curr Opin HIV AIDS* 2016; **11**:492–500.
10. Hasse B, Tarr PE, Marques-Vidal P, Waeber G, Preisig M, Mooser V, *et al.* **Strong impact of smoking on multimorbidity and cardiovascular risk among human immunodeficiency virus-infected individuals in comparison with the general population.** *Open forum Infect Dis* 2015; **2**:ofv108.
11. Friis-Moller N, Weber R, Reiss P, Thiebaut R, Kirk O, D'Arminio MA, *et al.* **Cardiovascular disease risk factors in HIV patients: association with antiretroviral therapy. Results from the DAD study.** *AIDS* 2003; **17**:1179–1193.
12. Mdodo R, Frazier EL, Dube SR, Mattson CL, Sutton MY, Brooks JT, *et al.* **Cigarette smoking prevalence among adults with HIV compared with the general adult population in the United States: cross-sectional surveys.** *Ann Intern Med* 2015; **162**: 335–344.
13. Galvan FH, Bing EG, Fleishman JA, London AS, Caetano R, Burnam MA, *et al.* **The prevalence of alcohol consumption and heavy drinking among people with HIV in the United States: results from the HIV Cost and Services Utilization Study.** *J Stud Alcohol* 2002; **63**:179–186.
14. Dartell M, Rasch V, Kahesa C, Mwaiselage J, Ngoma T, Junge J, *et al.* **Human papillomavirus prevalence and type distribution in 3603 HIV-positive and HIV-negative women in the general population of Tanzania: the PROTECT study.** *Sex Transm Dis* 2012; **39**:201–208.
15. Akhtar-Khaleel WZ, Cook RL, Shoptaw S, Surkan PJ, Teplin LA, Stall R, *et al.* **Long-term cigarette smoking trajectories among HIV-seropositive and seronegative MSM in the Multicenter AIDS Cohort Study.** *AIDS Behav* 2016; **20**:1713–1721.
16. Kilander L. **Education lifestyle factors and mortality from cardiovascular disease and cancer. A 25-year follow-up of Swedish 50-year-old men.** *Int J Epidemiol* 2001; **30**:1119–1126.
17. Meara ER, Richards S, Cutler DM, Cutler DM. **The gap gets bigger: changes in mortality and life expectancy, by education, 1981–2000.** *Health Aff* 2008; **27**:350–360.
18. Spoerri A, Schmidlin K, Richter M, Egger M, Clough-Gorr KM. **Individual and spousal education, mortality and life expectancy in Switzerland: a national cohort study.** *J Epidemiol Commun Health* 2014; **68**:804–810.
19. Steingrimsdóttir OA, Næss Ø, Moe JO, Grøholt E-K, Thelle DS, Strand BH, *et al.* **Trends in life expectancy by education in Norway 1961–2009.** *Eur J Epidemiol* 2012; **27**:163–171.
20. Schoeni-Affolter F, Ledergerber B, Rickenbach M, Rudin C, Günthard HF, Telenti A, *et al.* **Cohort profile: the Swiss HIV Cohort study.** *Int J Epidemiol* 2010; **39**:1179–1189.
21. Bopp M, Spoerri A, Zwahlen M, Gutzwiller F, Paccaud F, Braun-Fahrlander C, *et al.* **Cohort profile: the Swiss National Cohort: a longitudinal study of 6.8 million people.** *Int J Epidemiol* 2009; **38**:379–384.
22. Ledergerber B, von Overbeck J, Egger M, Luethy R. **The Swiss HIV cohort study: rationale, organization and selected baseline characteristics.** *Soz und Praeventivmedizin* 1994; **39**:387–394.
23. **Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults.** *Morb Mortal Wkly Rep* 1992; **41** (RR-17):1–20.
24. Fellegi IPP, Sunter ABB. **A theory of record linkage.** *J Am Stat Assoc* 1969; **64**:1183–1210.
25. Fair M. **Generalized record linkage system: Statistic Canada's record linkage software.** *Austrian J Stat* 2004; **33**:37–53.
26. Renaud A. **Methodology Report: Coverage Estimation for the Swiss Population Census 2000.** Neuchâtel: Swiss Federal Statistical Office; 2004. Available from <https://www.bfs.admin.ch/bfsstatic/dam/assets/341896/master> [Accessed 8 November 2016].
27. Antinori A, Coenen T, Costagliola D, Dedes N, Ellefson M, Gatell J, *et al.* **Late presentation of HIV infection: a consensus definition.** *HIV Med* 2011; **12**:61–64.
28. Lenart A. **The Gompertz distribution and maximum likelihood estimation of its parameters: a revision.** *MPDIR Work Pap* 2012; **49**:0–19.
29. Hsieh JJ. **A general theory of life table construction and a precise abridged life table method.** *Biom J* 1991; **33**:143–162.
30. Galobardes B, Shaw M, Lawlor D a, Lynch JW, Davey SG, Davey Smith G. **Indicators of socioeconomic position (part 1).** *J Epidemiol Community Health* 2006; **60**:95–101.
31. Legarth R, Omland LH, Kronborg G, Larsen CS, Pedersen C, Gerstoft J, *et al.* **Educational attainment and risk of HIV infection, response to antiretroviral treatment, and mortality in HIV-infected patients.** *AIDS* 2014; **28**:387–396.
32. Socio-economic Inequalities and HIV Writing Group for Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) in EuroCoord. Socio-economic Inequalities and HIV Writing Group for Collaboration of Observational HIV Epidemiological. Rese, Lodi S, Dray-Spira R, Touloumi G, Braun D, Teira R, *et al.* **Delayed HIV diagnosis and initiation of antiretroviral therapy: inequalities by educational level, COHERE in EuroCoord.** *AIDS* 2014; **28**:2297–2306.
33. Gebhardt M, Rickenbach M, Egger M. **Impact of antiretroviral combination therapies on AIDS surveillance reports in Switzerland. Swiss HIV Cohort Study.** *AIDS* 1998; **12**:1195–1201.
34. Thurnheer MC, Weber R, Toutous-Trellu L, Cavassini M, Elzi L, Schmid P, *et al.* **Occurrence, risk factors, diagnosis and treatment of syphilis in the prospective observational Swiss HIV Cohort Study.** *AIDS* 2010; **24**:1907–1916.
35. Obel N, Omland LH, Kronborg G, Larsen CS, Pedersen C, Pedersen G, *et al.* **Impact of non-HIV and HIV risk factors on survival in HIV-infected patients on HAART: a population-based nationwide cohort study.** *PLoS One* 2011; **6**:e22698.
36. May M, Gompels M, Delpech V, Porter K, Orkin C, Kegg S, *et al.* **Impact on life expectancy of HIV-1 positive individuals of CD4+ cell count and viral load response to antiretroviral therapy.** *AIDS* 2014; **28**:1193–1202.
37. Moser A, Panczak R, Zwahlen M, Clough-Gorr KM, Spoerri A, Stuck AE, *et al.* **What does your neighbourhood say about you? A study of life expectancy in 1.3 million Swiss neighbourhoods.** *J Epidemiol Commun Health* 2014; **68**:1125–1132.
38. Gueler A, Schoeni-Affolter F, Moser A, Bertisch B, Bucher HC, Calmy A, *et al.* **Neighbourhood socio-economic position, late presentation and outcomes in people living with HIV in Switzerland.** *AIDS* 2015; **29**:231–238.
39. Helleberg M, May MT, Ingle SM, Dabis F, Reiss P, Fätkenheuer G, *et al.* **Smoking and life expectancy among HIV-infected individuals on antiretroviral therapy in Europe and North America.** *AIDS* 2015; **29**:221–229.
40. Antiretroviral Therapy Cohort C. Zwahlen M, Harris R, May M, Hogg R, Costagliola D, *et al.* **Mortality of HIV-infected patients starting potent antiretroviral therapy: comparison with the general population in nine industrialized countries.** *Int J Epidemiol* 2009; **38**:1624–1633.
41. Kaulich-Bartz J, Dam W, May MT, Lederberger B, Widmer U, Phillips AN, *et al.* **Insurability of HIV-positive people treated with antiretroviral therapy in Europe: collaborative analysis of HIV cohort studies.** *AIDS* 2013; **27**:1641–1655.
42. Zahnd C, Salazar-Vizcaya L, Dufour J-F, Müllhaupt B, Wandeler G, Kouyos R, *et al.* **Modelling the impact of deferring HCV treatment on liver-related complications in HIV coinfecting men who have sex with men.** *J Hepatol* 2016; **65**:26–32.