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ORIGINAL RESEARCH

Trends over time of virological and immunological characteristics in the Swiss HIV Cohort Study*

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Background

The long-term outcome of antiretroviral therapy (ART) is not assessed in controlled trials. We aimed to analyse trends in the population effectiveness of ART in the Swiss HIV Cohort Study over the last decade.

Methods

We analysed the odds of stably suppressed viral load (ssVL: three consecutive values <50 HIV-1 RNA copies/mL) and of CD4 cell count exceeding 500 cells/μL for each year between 2000 and 2008 in three scenarios: an open cohort; a closed cohort ignoring the influx of new participants after 2000; and a worst-case closed cohort retaining lost or dead patients as virological failures in subsequent years. We used generalized estimating equations with sex, age, risk, non-White ethnicity and era of starting combination ART (cART) as fixed co-factors. Time-updated co-factors included type of ART regimen, number of new drugs and adherence to therapy.

Results

The open cohort included 9802 individuals (median age 38 years; 31% female). From 2000 to 2008, the proportion of participants with ssVL increased from 37 to 64% [adjusted odds ratio (OR) per year 1.16 (95% CI 1.15–1.17)] and the proportion with CD4 count >500 cells/μL increased from 40 to >50% [OR 1.07 (95% CI 1.06–1.07)]. Similar trends were seen in the two closed cohorts. Adjustment did not substantially affect time trends.

Conclusions

There was no relevant dilution effect through new participants entering the open clinical cohort, and the increase in virological/immunological success over time was not an artefact of the study design of open cohorts. This can partly be explained by new treatment options and other improvements in medical care.

Keywords: antiretroviral therapy, cohort study, effectiveness, time trends

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Introduction

Combination antiretroviral therapy (cART) has dramatically reduced morbidity and mortality in HIV-infected persons with access to care [1–3]. Since 1996, the number of anti-HIV drugs in different classes has increased, providing numerous potent and well-tolerated regimens to choose from, especially in resource-rich countries.

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The efficacy of new drugs is assessed in short-term randomized clinical trials lasting 48 to 96 weeks in selected target populations which often exclude participants with potentially poor prognoses such as patients with ongoing opportunistic diseases, substance dependencies, coinfections, and other somatic or psychiatric comorbidities [4]. Findings can therefore not easily be generalized to all treated individuals, and to long-term outcome. Large clinical cohort studies have the potential to assess the population effectiveness of ART if they are reasonably representative [5,6]. However, findings from open cohort studies can also be biased in the case of poor retention of people with potentially bad prognosis or inclusion of new participants with potentially good prognosis. These handicaps can be partly overcome by modifying the analysis, excluding, for instance, new participants, or constructing worst-case scenarios where those lost to follow-up are counted as failures. In an analysis of resistance data we have shown the feasibility of this 'closed cohort' approach [7].

We aimed to analyse time trends and the relative contribution of different predictors to virological and immunological outcomes in HIV-infected persons on ART, and particularly to study whether the outcome differed when the effects of flux of participants into or out of a large representative cohort study from 2000 to 2008 were taken into account.

Methods

Patients

The Swiss HIV Cohort Study (SHCS), established in 1988, continuously enrols HIV-1-infected individuals aged 16 years or older at 5 university out-patient clinics, 2 large state hospitals, 14 regional hospitals, and 39 private practices [8,9]. Follow-up visits with structured questionnaires and predefined laboratory tests are scheduled semiannually. In addition, all HIV-1 and hepatitis C virus (HCV) viral loads as well as CD4/3/8 cell counts from routine visits are recorded. The study was approved by local ethical review boards, and written informed consent was obtained from all individuals.

Virological outcomes

All HIV-1 viral load determinations for each person seen between January 2000 and December 2008 were evaluated in consecutive groups of three values. Viral load categories were assigned for every measurement over time between the second value and second to last value with the following criteria.

- *Stably suppressed:* three consecutive HIV-1 RNA values below the detection limit (<50 copies/mL).
- *Improving:* a detectable value followed by two undetectable values.
- *Failing:* an undetectable value followed by two detectable values.
- *Stable failure:* three consecutive detectable viral load values.
- *Unstable:* all combinations not falling into one of the above categories.
- Periods of *ART interruption* were treated as a separate category.

Immunological outcomes

These were based on longitudinal CD4 cell counts stratified as <200, 200–349, 350–499 and ≥ 500 cells/μL.

Cohort analyses

The *open cohort* included SHCS participants with at least three HIV-1 viral load determinations between 2000 and 2008.

The *closed cohort* constituted a subgroup of the open cohort with participants seen from 2000 onwards but with new participants not allowed to enter the data set.

To determine the extent to which time trends are affected by attrition bias, we also applied a *worst-case scenario* to the closed cohort by retaining participants who died or were lost to follow-up. Similar to the missing equals failure approach applied in randomized clinical trials of antiviral drugs, we classified these individuals as virologically failing in each subsequent year after their last viral load determination.

Definitions

Self-reported adherence, data for which have been collected since July 2003, is classified according to the number of missed doses within 4 weeks prior to a cohort visit (0, 1 or >1 missed doses) as described previously [10]. Hepatitis B virus (HBV) infection was considered active if HBV surface (HBs) antigen, HBV envelope (HBe) antigen or HBV DNA was positive. HCV infection was considered active if HCV RNA was positive.

Statistical methods

For logistic regression analyses of time trends and cofactors, we restricted the cohorts to participants who had started ART. The stably suppressed category for virological endpoints and the CD4 count >500 copies/μL stratum for immunological endpoints were separately analysed using generalized estimating equation (GEE) models allowing repeated measures per patient. Time trends were quantified by using individual calendar years with indicator variables,

and tests for trend included calendar year as a single continuous variable.

As the frequency of viral load determinations varied depending on the clinical status of the patient (i.e. less monitoring during stable first-line treatments with good adherence *vs.* more frequent monitoring in salvage treatment situations), we only used the last viral load category or CD4 stratum per year for each individual, as most participants were seen at least once per year. The effect of the length of the interval between viral load determinations was further analysed in sensitivity analyses (see below).

The following fixed covariables were included in multivariable models to assess the extent of potential confounding: sex, transmission category, ethnicity (non-White *vs.* White), and era of starting ART (before 1997 *vs.* 1997 onwards). Time-updated covariables were age (strata: <40, 40–49, 50–59 and ≥ 60 years), number of new drugs in the regimen (strata: 0, 1, 2 and ≥ 3), use of novel drug classes [fusion inhibitors, chemokine (C-C motif) receptor 5 (CCR5) antagonists and integrase inhibitors] in the regimen, hepatitis B/C infection (active *vs.* inactive), and Centers for Disease Control and Prevention (CDC) stage (C *vs.* A or B). To account for potential reverse causality, we lagged the time-updated treatment by 1 year and considered the effect to last for 1 year. These associations are thus not depicting an immediate effect of a new drug – which is more likely to be prescribed shortly after virological failure – but rather the effect of a drug that was introduced 12–24 months prior to the current virological or immunological assessment. Time-updated information on adherence and whether the participant lives in a stable partnership were analysed in separate models limited to the years 2004–2008, because that information was not available for the first years of the study period. In the models for the closed cohort where individuals lost to follow-up or death were accounted for, we could not include time-updated variables other than age because these were not known after a person left the cohort.

Several sensitivity analyses were performed to test the robustness of the findings. First, we changed the lagging windows for the introduction of new drugs from 12–24 months to 6–12 and 24–36 months, respectively. Secondly, we analysed the influence of intervals of >6 months between individual viral load determinations in the data triplets.

We used Stata SE 11.0 (StataCorp, College Station, TX) for all analyses.

Results

Selection of participants

A total of 10 213 participants were seen in the SHCS from 1 January 2000 to 31 December 2008. Of these, 9802 (96.0%) contributed at least three viral load determinations and constituted the open cohort for the descriptive analyses. The closed cohort is a subgroup restricted to the 5235 participants who had a visit in 2000. The majority of these individuals (91.7%) had entered the cohort prior to 2000. Sixty-four per cent of participants were seen in university out-patient clinics or large district hospitals, 6% in affiliated regional hospitals, and 30% in private practices. Reflecting the changing epidemic in Switzerland, with an increase in the number of HIV-infected immigrants, the open cohort includes more non-Caucasian individuals and fewer persons who have been infected with HIV via injecting drug use (Table 1).

Table 1 Characteristics of individuals at their first visit in the Swiss HIV Cohort Study from 2000 to 2008

	Open cohort	Closed cohort (no new patients after 2000)
Number of participants [*n* (%)]	9802 (100)	5235 (100)
Year of first visit [*n* (%)]		
2000	5235 (53)	5235 (100)
2001	716 (7.3)	
2002	615 (6.3)	
2003	605 (6.2)	
2004	570 (5.8)	
2005	527 (5.4)	
2006	526 (5.4)	
2007	510 (5.2)	
2008	498 (5.1)	
Female sex [*n* (%)]	3002 (31)	1596 (30)
Age (years)		
Median (IQR)	38 (33–44)	38 (34–44)
<40 years [*n* (%)]	5681 (58)	2939 (56)
40–49 years [*n* (%)]	2752 (28)	1516 (29)
50–59 years [*n* (%)]	953 (9.7)	546 (10)
≥ 60 years [*n* (%)]	416 (4.2)	234 (4.5)
Non-White ethnicity [*n* (%)]	1968 (20)	772 (15)
Mode of HIV infection [*n* (%)]		
Homosexual	3600 (37)	1816 (35)
Injecting drug use	2095 (21)	1454 (28)
Heterosexual/other	4107 (42)	1965 (37)
Active hepatitis B infection [*n* (%)]	427 (4.4)	241 (4.6)
Active hepatitis C infection [*n* (%)]	1675 (17)	1122 (21)
CD4 count (cells/μL) [median (IQR)]	410 (260–596)	430 (270–625)
CDC stage C [*n* (%)]	2023 (21)	1291 (25)

The open cohort includes all persons contributing at least three viral load determinations during this time period. The closed cohort is a subset without new entries after 2000.

Follow-up information

The 9802 persons in the open cohort contributed 57 808 years of follow-up. By the end of 2008, 1522 (16%) were lost to follow-up and 903 (9.2%) individuals had died. During follow-up, 197 091 viral load triplets were collected. Participants contributed a median of 38 [interquartile range (IQR) 26–50] viral load determinations and the median

interval between consecutive measurements was 91 (IQR 68–119) days. In 91% of the triplets, the interval was <6 months and in 99% it was <12 months. Thirteen per cent of total follow-up time was prior to starting ART, and 13% was during periods of treatment interruption. Forty-seven per cent of follow-up time was accumulated in the stably suppressed viral load category, 10% in the improving category, 8.5% in the unstable category, 1.9% in the failing category, and 6.8% in the stable failure category. When limited to follow-up times on ART, the corresponding numbers for the viral load categories were 63% stably suppressed, 14% improving, 11% unstable, 2.6% failing, and 9.1% stable failure.

Time trends in the open cohort

Figure 1a illustrates trends over time for the viral load categories in the open cohort taking into account the last viral load category per patient and year. The percentage of treatment-naïve individuals remained stable at 13% throughout. This was a result of a balance between the influx of new participants, of whom an increasing proportion were treatment-naïve (2001, 31%; 2008, 44%), and participants starting treatment while followed in the cohort. Treatment interruptions peaked at 15% in 2002 and then declined steadily to 5.4% in 2008. The proportion of participants in the stably suppressed viral load category increased substantially from 37% in 2001 to 64% in 2008 [crude odds ratio (OR) 1.18 per year; 95% confidence interval (CI) 1.17–1.19; $P<0.0001$], while those with stable virological failure decreased from 15% in 2000 to 2.4% in 2008. The proportion of individuals in the intermediate categories (improving, unstable and failing) diminished only slightly over time, from 25% in 2000 to 18% in 2008.

As shown in Figure 2a, the average CD4 lymphocyte count similarly increased with time despite the influx of new participants, some of whom were untreated, presenting late with lower CD4 cell counts. However, the percentage of participants with CD4 count ≥ 500 cells/μL fluctuated between 40 and 41%, before rising to 51% in 2008. The test for trend resulted in an OR of 1.06 (95% CI 1.05–1.07) per year ($P<0.0001$).

Time trends in the closed cohort

Of the 5235 participants in 2000, 3680 (70%) were still followed in 2008, and constitute the closed cohort. Figure 1b shows the time trends for the closed cohort. The majority of the 609 individuals (12%) who were treatment-naïve in 2000 started ART during follow-up; in 2008, only 73 of 3680 individuals (2.0%) were still treatment-naïve. Compared with the open cohort (Fig. 1a), the percentage of participants in the stably suppressed virological category in 2008 in the closed cohort was higher (72% *vs.* 64% for the open cohort). However, the time trends for the stably suppressed category did not change in the closed cohort [OR 1.18 (95% CI 1.17–1.19) per year] when compared with the open cohort. Thus, the improvement in the virological success of ART between 2000 and 2008 was not an artefact of new treatment-naïve participants entering the cohort over time and starting potent first-line ART.

The CD4 cell count distribution over time for the closed cohort is shown in Figure 2b. Differences compared with the open cohort were minimal. The percentage with CD4 count ≥ 500 cells/μL rose from 40% in 2000 to 55% in 2008, resulting in an OR of 1.05 (95% CI 1.04–1.06) per year ($P<0.0001$).

Time trends in the 'worst-case' closed cohort accounting for individuals lost to follow-up and deaths

The time trends are displayed in Figure 1c. As expected, the increase over time in the proportion of participants in the stably suppressed viral load category was attenuated because individuals who died or were lost to follow-up continued to contribute in each year. Nevertheless, the increase from 38% in 2000 to 51% in 2008 remained highly significant, with an OR of 1.08 (95% CI 1.07–1.08) per year ($P<0.0001$), indicating that survivor or attrition bias may have explained some but not all observed improvements over time.

Predictors of stable virological suppression among persons who started ART

Table 2 displays the results of uni- and multivariable logistic GEE models for stably suppressed viral load in the open and closed cohorts, respectively. Multivariable models were repeated for a subset of data from 2004 to allow the inclusion of information on stable partnership and adherence; factors that were not collected from the beginning of the study. All models were consistent. They confirmed a more than threefold higher odds of experiencing three consecutive viral load values below 50 copies/mL in 2008 compared with 2000. Adjustment for the numerous co-factors did not affect the estimates for calendar year, indicating that other factors must have changed over time. Clearly, treatment interruptions and poor adherence showed the strongest negative associations with stably suppressed viral load. The negative effects of a history of injecting drug use, active HCV infection, which is highly collinear with injecting drug use, and non-White ethnicity were attenuated after adjustment for adherence. Further negative predictors were CDC stage C disease and active HBV infection; whereas being in a stable partnership, having initiated ART after

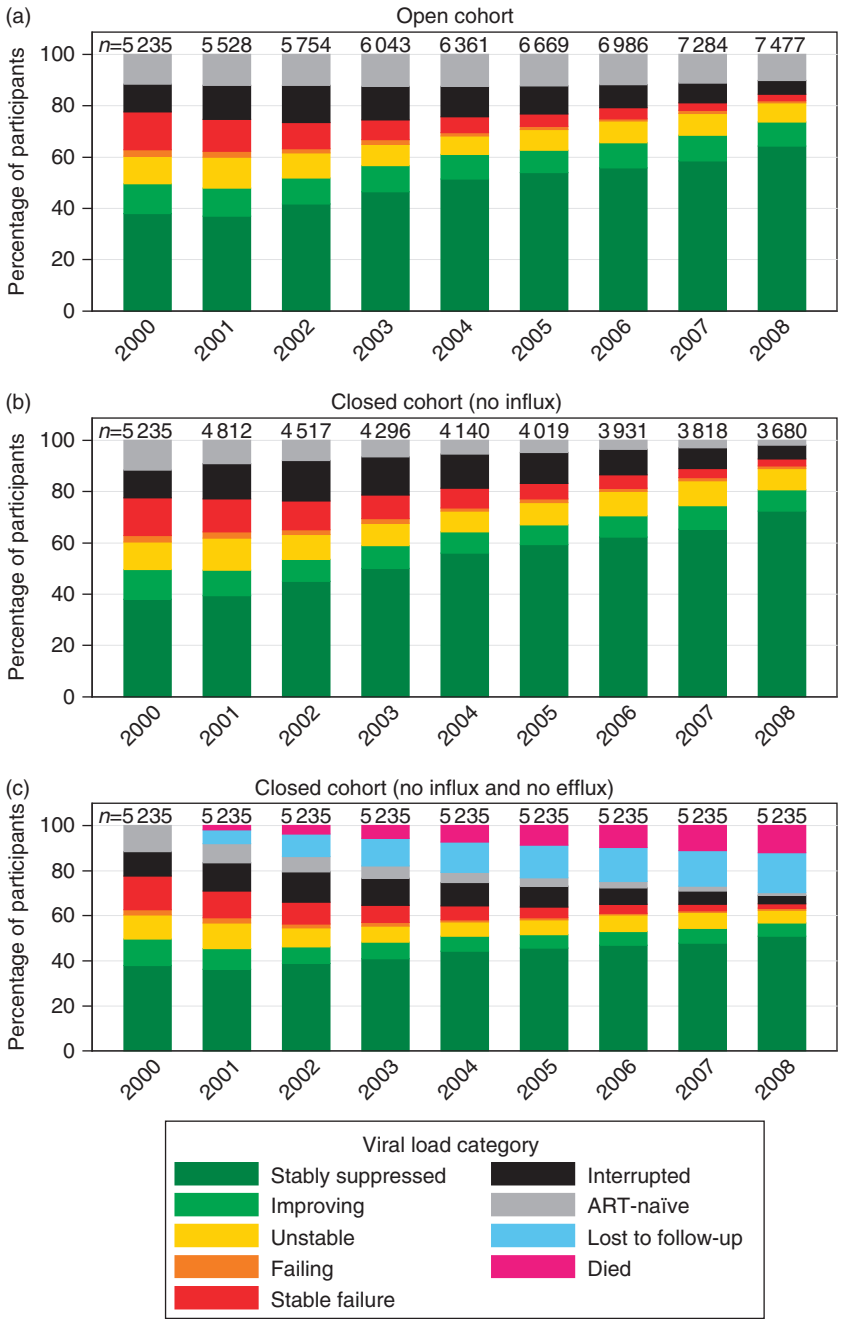

Fig. 1 Trends over time of viral load categories. (a) Trends for all 9802 individuals with at least three viral load determinations available in total between 2000 and 2008 (open cohort). (b) Trends for a closed cohort of 5235 persons who had been seen in 2000. (c) Trends for the closed cohort where patients who died or were lost to follow-up were retained in the risk set. Numbers above the bars indicate the size of the cohorts over time. ART, antiretroviral therapy.

1996 and having started new drugs in the past 1–2 years were positively associated with achieving a stably suppressed viral load.

The adjusted ORs for reaching a stably suppressed viral load for the open and closed cohorts from 2000 to 2008 were 1.16 (95% CI 1.15–1.17) per year and 1.17 (95% CI 1.15–1.18) per year, respectively. These values overlapped with the crude estimates for the entire open and closed (i.e. including treatment-naïve persons) cohorts shown in Figures 1a and b. From 2004 to 2008, when adjustment

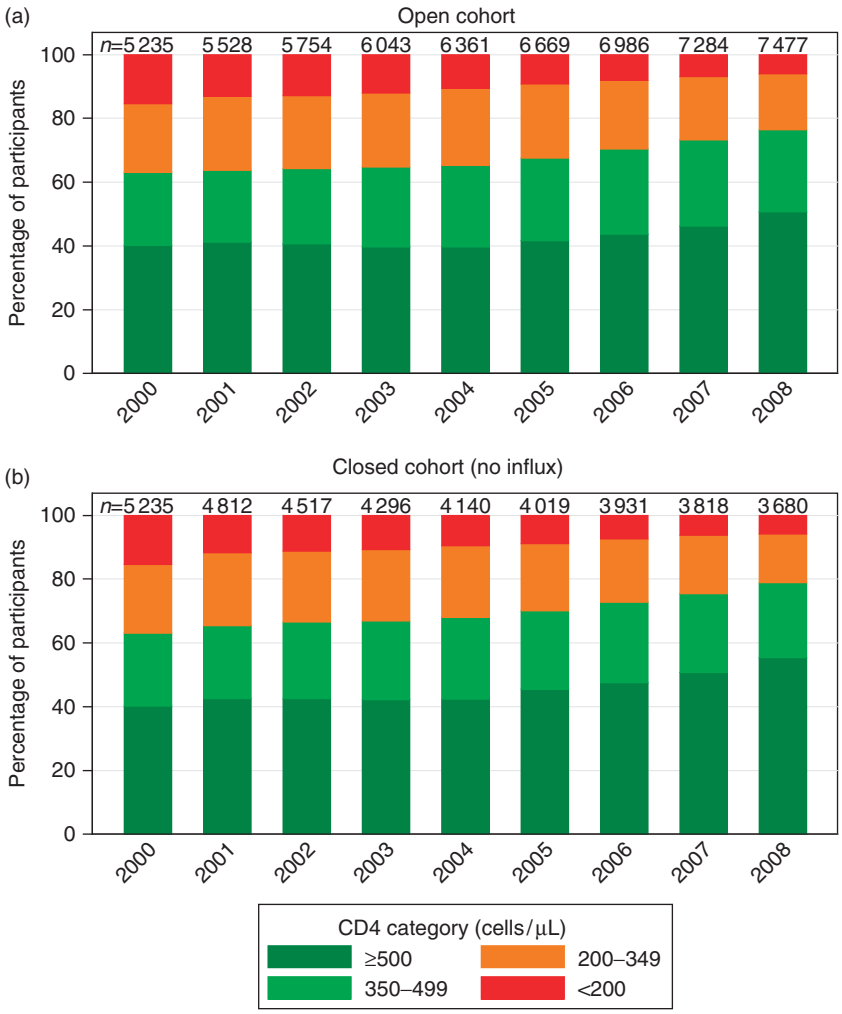

Fig. 2 CD4 count categories after starting antiretroviral therapy (ART) in the open (a) and closed (b) cohorts. Cohorts correspond to the respective panels of Figure 1. Numbers above the bars indicate the size of the cohorts over time.

included adherence and information on stable partnership, the adjusted estimates for the open and closed cohorts were slightly attenuated, with ORs of 1.10 (95% CI 1.08–1.11) and 1.09 (95% CI 1.07–1.11) per year, respectively. In the 'worst-case' model with persons lost to follow-up and deaths retained in the denominator, the adjusted estimates for continuous calendar year support a highly significant time trend [OR 1.06 (95% CI 1.05–1.07) per year; $P < 0.001$], comparable to the crude estimate [OR 1.08 (95% CI 1.07–1.08)] corresponding to Figure 1c.

Predictors of CD4 counts > 500 cells/μL among persons who started ART

Table 3 displays the various models for the immunological endpoint, adjusted for the same variables as the virological endpoint. The odds of having a CD4 cell count > 500 cells/μL in 2008 were 1.6–1.8 compared with 2000. As in the descriptive analysis of the entire cohort (Fig. 2), the positive calendar year effect started to emerge after 2004. Female sex, younger age, living in a stable partnership, and having started one new drug in the last 1–2 years were positively associated with having a high CD4 cell count. As for the virological endpoint, treatment interruptions, non-White ethnicity, infection via injecting drug use, active HBV infection, and CDC stage C showed significant negative associations. Again, the negative association with active HCV infection in the univariable model disappeared after adjustment, probably because of collinearity with injecting drug use.

Adjusted ORs of having a CD4 count > 500 cells/μL for continuous calendar year from 2000 to 2008 were 1.07 (95% CI 1.06–1.07) and 1.10 (95% CI 1.05–1.16) for the open and closed cohorts, respectively. In the models for 2004–2008 incorporating adherence and information on

Table 2 Predictors of stably suppressed viral load, defined as three consecutive HIV-1 RNA determinations <50 copies/mL after starting antiretroviral therapy (ART)

	Open cohort			Closed cohort		
	Univariable OR (95% CI) ($n = 8677$)	Multivariable OR (95% CI) ($n = 8677$)	Multivariable* OR (95% CI) ($n = 7210$)	Univariable OR (95% CI) ($n = 4626$)	Multivariable OR (95% CI) ($n = 4626$)	Multivariable* OR (95% CI) ($n = 3666$)
Year						
2000	1.00 (reference)	1.00 (reference)	–	1.00 (reference)	1.00 (reference)	–
2001	0.94 (0.89–1.00)	0.98 (0.92–1.05)	–	0.99 (0.93–1.05)	1.01 (0.95–1.08)	–
2002	1.15 (1.08–1.23)	1.32 (1.23–1.42)	–	1.20 (1.13–1.29)	1.39 (1.29–1.50)	–
2003	1.40 (1.30–1.49)	1.66 (1.54–1.78)	–	1.43 (1.34–1.54)	1.72 (1.59–1.86)	–
2004	1.74 (1.62–1.86)	2.07 (1.93–2.23)	1.00 (reference)	1.74 (1.62–1.88)	2.11 (1.94–2.28)	1.00 (reference)
2005	1.94 (1.80–2.08)	2.30 (2.13–2.48)	1.08 (1.01–1.16)	1.96 (1.81–2.12)	2.36 (2.16–2.57)	1.10 (1.02–1.19)
2006	2.11 (1.97–2.27)	2.36 (2.19–2.55)	1.10 (1.03–1.18)	2.16 (2.00–2.34)	2.47 (2.26–2.70)	1.13 (1.04–1.23)
2007	2.43 (2.26–2.61)	2.61 (2.42–2.83)	1.20 (1.12–1.29)	2.38 (2.20–2.59)	2.60 (2.37–2.84)	1.18 (1.07–1.29)
2008	3.23 (3.00–3.47)	3.27 (3.02–3.55)	1.48 (1.38–1.60)	3.18 (2.91–3.47)	3.30 (2.99–3.63)	1.50 (1.36–1.65)
Sex						
Female	0.87 (0.81–0.92)	1.05 (0.95–1.14)	1.06 (0.95–1.17)	0.86 (0.79–0.94)	1.02 (0.90–1.15)	1.08 (0.93–1.24)
Age†						
<40 years	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
40–49 years	1.14 (1.06–1.22)	1.03 (0.95–1.11)	1.02 (0.93–1.13)	1.12 (1.02–1.23)	1.01 (0.91–1.13)	1.01 (0.89–1.15)
50–59 years	1.34 (1.21–1.49)	1.17 (1.04–1.33)	1.13 (0.99–1.30)	1.36 (1.19–1.56)	1.14 (0.97–1.33)	1.08 (0.90–1.30)
≥ 60 years	1.35 (1.16–1.57)	1.13 (0.94–1.35)	1.06 (0.86–1.31)	1.41 (1.16–1.73)	1.20 (0.95–1.51)	1.19 (0.89–1.59)
Ethnicity						
Non-White	0.87 (0.81–0.94)	0.80 (0.72–0.88)	0.83 (0.73–0.93)	0.79 (0.70–0.89)	0.78 (0.67–0.91)	0.87 (0.72–1.04)
Transmission category						
MSM	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Injecting drug use	0.70 (0.64–0.76)	0.84 (0.75–0.95)	0.98 (0.86–1.12)	0.72 (0.65–0.80)	0.79 (0.69–0.92)	0.91 (0.76–1.08)
Heterosexual intercourse/other	0.92 (0.86–0.98)	0.95 (0.87–1.05)	0.97 (0.87–1.08)	0.91 (0.83–1.00)	0.93 (0.82–1.06)	0.94 (0.80–1.09)
Stable partner in the last 6 months†	1.15 (1.08–1.23)	–	1.17 (1.09–1.25)	1.15 (1.06–1.25)	–	1.18 (1.08–1.29)
Adherence† (number of missed doses over the last 4 weeks)						
0	1.00 (reference)	–	1.00 (reference)	1.00 (reference)	–	1.00 (reference)
1	0.86 (0.80–0.93)	–	0.85 (0.79–0.92)	0.83 (0.76–0.91)	–	0.81 (0.74–0.90)
≥ 2	0.49 (0.45–0.54)	–	0.53 (0.48–0.59)	0.48 (0.43–0.54)	–	0.51 (0.45–0.57)
CDC stage C†	1.16 (1.08–1.25)	0.81 (0.75–0.87)	0.85 (0.78–0.93)	1.20 (1.09–1.31)	0.79 (0.69–0.92)	0.90 (0.80–1.02)
Active hepatitis B infection	0.71 (0.63–0.82)	0.82 (0.71–0.94)	0.87 (0.73–1.03)	0.68 (0.58–0.81)	0.75 (0.63–0.90)	0.80 (0.65–1.00)
Active hepatitis C infection	0.77 (0.72–0.83)	0.92 (0.83–1.02)	0.88 (0.78–1.00)	0.81 (0.74–0.89)	0.94 (0.82–1.06)	0.93 (0.80–1.09)
Started ART after 1996	1.31 (1.22–1.40)	1.33 (1.23–1.43)	1.21 (1.11–1.33)	1.22 (1.12–1.32)	1.54 (1.41–1.70)	1.36 (1.22–1.52)
Number of new drugs in the past 1–2 years†						
0	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1	1.33 (1.26–1.38)	1.21 (1.15–1.27)	1.14 (1.06–1.23)	1.18 (1.11–1.24)	1.10 (1.03–1.16)	1.02 (0.94–1.12)
2	1.33 (1.24–1.43)	1.14 (1.05–1.23)	1.01 (0.91–1.13)	1.21 (1.12–1.32)	1.08 (0.99–1.19)	0.99 (0.86–1.14)
≥ 3	1.47 (1.39–1.56)	1.44 (1.34–1.54)	1.35 (1.22–1.49)	1.29 (1.18–1.41)	1.32 (1.19–1.45)	1.32 (1.08–1.60)
New drug class in past 1–2 years†	2.05 (1.45–2.91)	1.17 (0.81–1.69)	1.00 (0.67–1.49)	2.31 (1.57–3.42)	1.36 (0.90–2.05)	1.21 (0.75–1.96)
ART interrupted†	0.015 (0.013–0.017)	0.014 (0.012–0.016)	0.025 (0.022–.029)	0.015 (0.013–0.018)	0.016 (0.015–0.021)	0.038 (0.032–0.045)

Results from uni- and multivariable generalized estimating equations are adjusted for all variables listed.
*The assessment of adherence started during 2003 and sociodemographic questions regarding partnerships were introduced during 2000. Therefore we included these two variables in a second multivariable model which is limited to the years 2004 onwards.
†Time-updated variables.
CDC, Centers for Disease Control and Prevention; CI, confidence interval; MSM, men who have sex with men; OR, odds ratio.

stable partnership, the estimates were 1.15 (95% CI 1.13–1.17) and 1.12 (95% CI 1.10–1.14) per year, respectively (all $P<0.001$).

Sensitivity analyses

The estimates for calendar year were unaffected by the choice of lagging window (6–12, 12–24 or 24–36 months) for the introduction of new drugs and classes. Similarly, the introduction of an additional variable coding for long delays of >6 months between viral load determinations did not alter the findings.

Discussion

This study of a large national observational cohort demonstrated a continuous improvement of virological and immunological effectiveness of ART over recent years.

Table 3 Predictors of CD4 count ≥ 500 cells/μL after starting antiretroviral therapy (ART)

	Open cohort			Closed cohort		
	Univariable OR (95% CI)	Multivariable OR (95% CI)	Multivariable* OR (95% CI)	Univariable OR (95% CI)	Multivariable OR (95% CI)	Multivariable* OR (95% CI)
Year						
2000	1.00 (reference)	1.00 (reference)	–	1.00 (reference)	1.00 (reference)	–
2001	1.06 (1.00–1.11)	1.07 (1.01–1.13)	–	1.10 (1.05–1.16)	1.12 (1.06–1.18)	–
2002	1.04 (0.98–1.10)	1.07 (1.01–1.14)	–	1.10 (1.04–1.17)	1.13 (1.07–1.20)	–
2003	1.00 (0.94–1.07)	1.02 (0.96–1.09)	–	1.08 (1.01–1.15)	1.10 (1.02–1.17)	–
2004	1.04 (0.97–1.11)	1.05 (0.98–1.12)	1.00 (reference)	1.08 (1.01–1.16)	1.09 (1.01–1.17)	1.00 (reference)
2005	1.15 (1.07–1.23)	1.16 (1.08–1.24)	1.13 (1.07–1.19)	1.23 (1.15–1.32)	1.24 (1.15–1.33)	1.16 (1.09–1.24)
2006	1.30 (1.22–1.39)	1.29 (1.21–1.39)	1.29 (1.22–1.36)	1.32 (1.22–1.42)	1.31 (1.21–1.41)	1.25 (1.17–1.33)
2007	1.48 (1.38–1.59)	1.44 (1.35–1.55)	1.45 (1.37–1.54)	1.46 (1.36–1.58)	1.43 (1.32–1.55)	1.38 (1.29–1.48)
2008	1.83 (1.71–1.96)	1.73 (1.62–1.86)	1.77 (1.66–1.88)	1.75 (1.62–1.89)	1.68 (1.55–1.82)	1.60 (1.48–1.72)
Sex						
Female	1.02 (0.95–1.10)	1.25 (1.14–1.37)	1.19 (1.07–1.32)	1.13 (1.03–1.25)	1.28 (1.13–1.45)	1.18 (1.01–1.36)
Age†						
<40 years	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
40–49 years	0.81 (0.75–0.88)	0.77 (0.70–0.83)	0.78 (0.70–0.85)	0.82 (0.74–0.91)	0.84 (0.75–0.94)	0.88 (0.77–1.00)
50–59 years	0.85 (0.76–0.96)	0.69 (0.61–0.78)	0.68 (0.59–0.78)	0.89 (0.76–1.03)	0.74 (0.63–0.87)	0.70 (0.58–0.84)
≥ 60 years	0.66 (0.56–0.79)	0.51 (0.42–0.62)	0.50 (0.40–0.62)	0.63 (0.50–0.79)	0.48 (0.38–0.61)	0.48 (0.36–0.64)
Ethnicity						
Non–White	0.74 (0.68–0.81)	0.60 (0.54–0.66)	0.58 (0.49–0.66)	0.84 (0.74–0.95)	0.69 (0.60–0.80)	0.67 (0.56–0.81)
Transmission category						
MSM	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Injecting drug use	0.57 (0.52–0.63)	0.52 (0.46–0.59)	0.57 (0.49–0.66)	0.57 (0.51–0.64)	0.49 (0.42–0.56)	0.55 (0.46–0.67)
Heterosexual intercourse/other	0.83 (0.77–0.90)	0.86 (0.78–0.95)	0.91 (0.81–1.01)	0.97 (0.87–1.07)	0.86 (0.75–0.98)	0.95 (0.81–1.11)
Stable partner in the last 6 months†	1.16 (1.10–1.23)	–	1.14 (1.08–1.21)	1.19 (1.10–1.28)	–	1.17 (1.08–1.26)
Adherence† (number of missed doses over the last 4 weeks)						
0	1.00 (reference)	–	1.00 (reference)	1.00 (reference)	–	1.00 (reference)
1	0.97 (0.91–1.03)	–	1.00 (0.94–1.06)	0.95 (0.88–1.03)	–	0.97 (0.90–1.05)
≥ 2	0.86 (0.80–0.93)	–	0.97 (0.90–1.06)	0.85 (0.77–0.93)	–	0.94 (0.86–1.04)
CDC stage C†	0.60 (0.56–0.65)	0.55 (0.51–0.60)	0.66 (0.60–0.72)	0.57 (0.52–0.63)	0.51 (0.46–0.57)	0.65 (0.57–0.73)
Active hepatitis B infection	0.66 (0.57–0.77)	0.71 (0.62–0.82)	0.72 (0.60–0.86)	0.67 (0.56–0.79)	0.70 (0.60–0.83)	0.70 (0.56–0.87)
Active hepatitis C infection	0.79 (0.72–0.87)	1.00 (0.90–0.12)	0.98 (0.86–1.12)	0.79 (0.71–0.88)	1.02 (0.90–1.16)	1.01 (0.86–1.19)
Started ART after 1996	1.09 (1.01–1.17)	0.96 (0.88–1.04)	0.95 (0.87–1.05)	1.42 (1.30–1.55)	1.40 (1.27–1.54)	1.38 (1.23–1.55)
Number of new drugs in the past 1–2 years†						
0	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1	1.15 (1.11–1.20)	1.11 (1.06–1.15)	1.11 (1.06–1.17)	1.10 (1.05–1.15)	1.06 (1.01–1.11)	1.07 (1.01–1.15)
2	1.02 (0.96–1.08)	0.95 (0.89–1.01)	1.02 (0.94–1.10)	0.93 (0.87–1.00)	0.88 (0.82–0.95)	0.96 (0.86–1.06)
≥ 3	0.85 (0.80–0.89)	0.83 (0.79–0.87)	0.84 (0.78–0.90)	0.84 (0.78–0.90)	0.80 (0.74–0.87)	0.85 (0.75–0.95)
New drug class in past 1–2 years†	1.04 (0.86–1.27)	1.04 (0.84–1.29)	0.94 (0.74–1.19)	0.96 (0.79–1.17)	1.00 (0.81–1.25)	0.88 (0.69–1.11)
ART interrupted†	0.40 (0.37–0.42)	0.39 (0.37–0.42)	0.34 (0.30–0.38)	0.39 (0.36–0.42)	0.37 (0.34–0.40)	0.30 (0.26–0.35)

Results from uni- and multivariable generalized estimating equations are shown.
*The assessment of adherence started during 2003 and sociodemographic questions regarding partnerships were introduced during 2000. Therefore we included these two variables in a second multivariable model which is limited to the years 2004 onwards.
†Time-updated variables.
CDC, Centers for Disease Control and Prevention; CI, confidence interval; MSM, men who have sex with men; OR, odds ratio.

Between 2000 and 2008, the proportion of participants with three consecutive viral load values <50 copies/mL increased from 37 to 64% and the proportion with CD4 counts >500 cells/μL rose from 40 to >50%. In our study we were able to adjust for adherence, treatment interruptions, stable partnership and active hepatitis virus coinfections without appreciable effects on the time trends, but the improvements could only partially be attributed to the numerous predictors tested, including the use of new drugs. Of note, we did not find a relevant dilution effect through new participants entering our open clinical cohort over time. Assigning the most unfavourable outcome to individuals who were lost to follow-up or died did attenuate but not offset the time trends. Because, by definition, the number of individuals lost to follow-up increases, a favourable time trend for virological effectiveness is artificially reduced. Further, in a resource-rich country with universal health care, most individuals will continue to receive adequate care and ART outside the cohort.

Our findings are consistent with the results from a collaboration of five HIV clinics analysing time trends of virological success during the early years of combination

ART from 1996 to 2002 [11]. The authors attributed some of the observed improvements to better starting regimens, and concluded that additional factors, such as increasing clinical experience, may have played an important role. Clearly, the experience of care providers continues to improve, and greater physician experience is related to better survival [12], earlier adoption of new treatments [13] and increased adherence to treatment [14]. In addition, societal factors such as further reductions of HIV-related stigma and improvement in knowledge of patients may also have played a role [15].

In addition to the superior virological outcome, we found that there was an improvement in immunological status over time, especially after 2004. Contrary to our expectations, time trends for the proportion of individuals with CD4 lymphocyte counts >500 cells/μL did not differ between the open and closed cohorts despite the constant influx of new patients with median CD4 counts of 360 cells/μL in 2001 and 420 cells/μL in 2007 (data not shown). This supports observations from the analyses of the virological endpoint suggesting a negligible bias of time trend analyses by cohort design.

A strength of our study is its national representativeness, allowing the assessment of population effectiveness, which complements efficacy results from clinical trials. Of note, a recent comparison with sales data from pharmaceutical companies revealed that 75% of the antiretroviral drugs sold in Switzerland from 2006 to 2008 [9] were prescribed to participants in the SHCS. A further strength of the SHCS is the structured semiannual collection of data on a large number of clinical, sociodemographic and behavioural characteristics by physicians and study-nurses who provide primary care to a substantial proportion of these participants both in large teaching hospitals and in private practices.

Our descriptive analyses are limited to active cohort participants, and predictors for success were analysed in individuals who started ART. For a complete assessment of population effectiveness, additional information regarding the number of undiagnosed HIV-infected individuals and the number of HIV-infected persons not yet in medical care would be needed.

In conclusion, we found an improvement of virological and immunological effectiveness from 2000 to 2008 in a large observational cohort study. This trend appeared robust in different models of cohort analyses, was not explained by design limitations of open cohort studies, and was only partially explained by changing co-factors such as new drugs or improved adherence over time. The finding that the proportion of HIV-infected persons with stably suppressed viral load at the population level has been increasing to such levels may have further implications for HIV prevention [16] and should encourage efforts to implement widespread test-and-treat programmes [17], also in developing countries.

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