Long-Term Trends of HIV Type 1 Drug Resistance Prevalence among Antiretroviral Treatment–Experienced Patients in Switzerland

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Background. Accurate quantification of the prevalence of human immunodeficiency virus type 1 (HIV-1) drug resistance in patients who are receiving antiretroviral therapy (ART) is difficult, and results from previous studies vary. We attempted to assess the prevalence and dynamics of resistance in a highly representative patient cohort from Switzerland.

Methods. On the basis of genotypic resistance test results and clinical data, we grouped patients according to their risk of harboring resistant viruses. Estimates of resistance prevalence were calculated on the basis of either the proportion of individuals with a virologic failure or confirmed drug resistance (lower estimate) or the frequency-weighted average of risk group–specific probabilities for the presence of drug resistance mutations (upper estimate).

Results. Lower and upper estimates of drug resistance prevalence in 8064 ART-exposed patients were 50% and 57% in 1999 and 37% and 45% in 2007, respectively. This decrease was driven by 2 mechanisms: loss to follow-up or death of high-risk patients exposed to mono– or dual–nucleoside reverse-transcriptase inhibitor therapy (lower estimates range from 72% to 75%) and continued enrollment of low-risk patients who were taking combination ART containing boosted protease inhibitors or nonnucleoside reverse-transcriptase inhibitors as first-line therapy (lower estimates range from 7% to 12%). A subset of 4184 participants (52%) had $\geq$1 study visit per year during 2002–2007. In this subset, lower and upper estimates increased from 45% to 49% and from 52% to 55%, respectively. Yearly increases in prevalence were becoming smaller in later years.

Conclusions. Contrary to earlier predictions, in situations of free access to drugs, close monitoring, and rapid introduction of new potent therapies, the emergence of drug-resistant viruses can be minimized at the population level. Moreover, this study demonstrates the necessity of interpreting time trends in the context of evolving cohort populations.

During the past decade, combination antiretroviral therapy (cART) has markedly decreased morbidity and mortality among HIV-1–infected patients in the Western world [1, 2]. However, therapy success is compromised if the virus becomes antiretroviral resistant [3–6]. Drug resistance mutations emerge rapidly under nonsuppressive antiretroviral treatments because of the fast replication of HIV-1 [7–9] and the error-prone reverse transcription process [10] with its high mutation rate. There is a general concern that the problem

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of drug resistance against cART will inevitably worsen with prolonged duration of antiretroviral therapy (ART) and eventually leave many HIV-1–infected patients without treatment options [11, 12]. Our overall aim was to reexamine those predictions in light of the recent advances in HIV medicine, such as the registration of new antiretroviral compounds. We assessed drug resistance prevalence over time in ART-experienced patients of the Swiss HIV Cohort Study with genotypic information available. Moreover, we sought to extend those estimates to the study population without available drug resistance tests by estimating their risk for the presence of drug resistance mutations on the basis of treatment history and measurements of HIV RNA concentration.

METHODS

Study population. The Swiss HIV Cohort Study is a nationwide cohort study with continuous enrollment and semiannual study visits [2]. The Swiss HIV Cohort Study has been approved by the ethics committees of all participating institutions, and written informed consent is obtained from participants. The Swiss HIV Cohort Study drug resistance database contains the results of all genotypic tests performed by the 4 laboratories engaged in resistance testing in Switzerland stored in a central database (SmartGene; Integrated Database Network System version 3.5.0) [13]. Drug resistance was defined as the presence of $\geqslant$1 major mutation of the fall 2007 International AIDS Society–USA drug mutation list [14]. Mutations that confer resistance to fusion inhibitors were not considered. In addition, the following mutations listed as specific for etravirine were excluded, because several of them may be polymorphic, and inclusion of them would yield exaggerated prevalence estimates (A. U. Scherrer, V.v.W., H.F.G.; unpublished data): V90I, A98G, K101E/H/P, V106I, E138A, V179D/F/T, Y181V, and M230L.

This study included ART-experienced patients who attended at least 1 visit after 1 January 1999. For patients who initiated ART before enrollment in the Swiss HIV Cohort Study, inclusion was restricted to individuals with a sufficiently documented treatment history to assess their probability for the presence of drug resistance mutations. In particular, for each therapy started before Swiss HIV Cohort Study enrollment, $\geqslant$1 on-treatment HIV RNA measurement at least 180 days after therapy start was required for inclusion. To assess the impact of continuous enrollments and dropouts of participants on prevalence estimates, we repeated all analyses on a subset of individuals who had been seen in each year between 2002 (1 year after the introduction of lopinavir in Switzerland) and 2007. This subgroup was termed the "closed cohort," in contrast to the "open cohort," which included all patients seen since 1999.

Statistical analysis. To estimate the prevalence of drug resistance, we classified all cohort patients into 2 prespecified categories. The first group consisted of patients considered at high risk for the emergence of drug-resistant HIV, either because they had experienced virologic failure while receiving therapy or because they had been exposed to single or dual nucleoside reverse-transcriptase inhibitor (NRTI) therapy (virologic failure group). We defined virologic failure as 2 consecutive plasma HIV RNA levels >500 copies/mL after >180 days of ART or a single HIV RNA level >500 copies/mL followed by discontinuation or modification of treatment. The second group included individuals who were at low risk for the emergence of resistance because they were either not undergoing treatment or had remained virologically suppressed while receiving therapy, defined as at least 2 consecutive viral loads of <50 copies/mL while receiving the same treatment in a given year (low-risk group), whereby undetectable HIV RNA levels were coded as the detection limit minus 1 copy. All remaining patients were classified as having an unknown status (the unknown group). For an estimate of prevalence of resistance within these groups, genotypic tests were classified according to the patients' group memberships at time of sampling, and the proportion of tests with at least 1 major International AIDS Society–USA resistance mutation was calculated for each group. Tests from the low-risk and unknown groups were performed while the patients were not undergoing treatment, during the initial viral load decay while undergoing treatment, or during intermittent viremia (viral load, $\leqslant$500 copies/mL) while receiving therapy. It was assumed that, once detected, transmitted or acquired mutations would persist.

We derived lower-bound and upper-bound estimates of drug resistance prevalence. The upper bound was defined as the mean of group-specific probabilities of the presence of drug resistance mutations for the virologic failure, low-risk, and unknown groups, weighted by the respective group size. This approach assumed that patients with a genotypic test from the low-risk and unknown groups (i.e., those without indication for testing according to guidelines [15]) were representative of the remaining individuals from their respective groups. The lower bound estimate was calculated as the proportion of patients either belonging to the virologic failure group or who were members of the low-risk and unknown groups with test results positive for drug-resistant HIV. Linear time trends in prevalence estimates were assessed using a generalized linear model [16]. Trend analyses were stratified according to the first ART received: patients who had started with standard cART containing at least 3 drugs from 2 classes [17] and those who had initially received treatments not qualifying as cART, which were subsumed under the historic ART group. Most (89%) of these latter patients were treated with 1 or 2 NRTIs as first therapy; 4% had received 3 NRTIs that contained abacavir. The remaining patients had received non-NRTIs (NNRTIs) or protease inhibitors (PIs) combined with 1 NRTI. The cART group was further divided to account for the differences in potency

Table 1. Description of characteristics for ART-experienced participants.

Characteristics	Open cohort (n = 8064)	Closed cohort (n = 4184)
Characteristics at ART initiation		
Female sex	2530 (31.4)	1296 (31.0)
Age at first visit, median years (IQR)	44 (38–50)	46 (42–52)
Ethnicity		
White	6400 (79.4)	3564 (85.2)
Asian	251 (3.1)	123 (2.9)
Black	958 (11.9)	415 (9.9)
Hispanic	164 (2.0)	67 (1.6)
Unknown	291 (3.6)	15 (0.4)
Mode of HIV acquisition		
Heterosexual sex	3064 (38.0)	1545 (36.9)
Male-male sex	2783 (34.5)	1568 (37.5)
Injection drug use	1902 (23.6)	905 (21.6)
Other	315 (3.9)	166 (4.0)
Median year of ART initiation (IQR)	1998 (1996–2002)	1997 (1996–1999)
Type of initial ART		
Historic ART	3071 (38.1)	2012 (48.1)
cART	2233 (27.7)	1485 (35.5)
Potent cART	2760 (34.2)	687 (16.4)
CDC stage C event	1549 (19.2)	791 (18.9)
CD4 cell count, cells/mm^3		
No. of available measurements	6978	3513
Median (IQR)	222 (113–341)	230 (108–360)
HIV RNA level, $\log_{10}$ copies/mL		
No. of available measurements	5068	2258
Median (IQR)	4.85 (4.25–5.33)	4.81 (4.20–5.26)
Characteristic at last follow-up visit		
Last available CD4 cell count, median cells/mm^3(IQR)	454 (296–643)	507 (360–706)
Risk status for presence of drug-resistance mutations		
Any history of virologic failure	2708 (33.6)	1776 (42.4)
Any exposure to mono- or dual-drug NRTI therapy or history of virologic failure	3769 (46.7)	2478 (59.2)
Consistent virologic suppression while receiving ART	3104 (38.5)	1168 (27.9)
Unknown risk status	1191 (14.8)	538 (12.9)
Any genotypic resistance testing after ART initiation	3278 (40.6)	2200 (52.6)
M184V/I mutation	1357 (16.8)	955 (22.8)
Any NNRTI mutation	715 (8.9)	483 (11.5)
Any NRTI mutation (other than the M184V/I mutation)	1629 (20.2)	1109 (26.5)
Any PI mutation	1001 (12.4)	684 (16.3)
⩾1 Resistance mutation	2280 (28.3)	1526 (36.5)
Resistance to ⩾2 drug classes	1186 (14.7)	826 (19.7)
Resistance to 3 drug classes	312 (3.9)	224 (5.4)
Loss to follow-up	1298 (16.1)	NA
Death		
All causes	752 (9.3)	NA
AIDS related	218 (2.7)	NA

NOTE. Data are no. (%) of patients, unless otherwise indicated. The open cohort included all study participants seen at least once in the Swiss HIV Cohort Study since 1999. The closed cohort was defined as the subset of individuals with at least 1 study visit per year from 2002 through 2007. ART, antiretroviral therapy; cART, combination antiretroviral therapy; CDC, Centers for Disease Control and Prevention; IQR, interquartile range; NA, not applicable; NRTI, nucleoside reverse-transcriptase inhibitor; NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

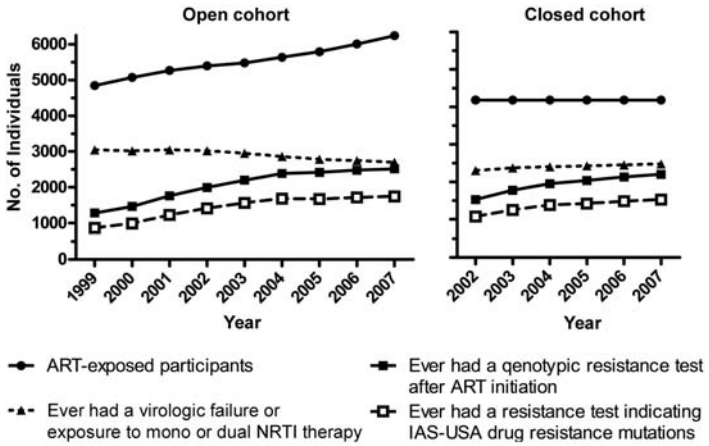

Figure 1. Evolution of antiretroviral treatment (ART)–experienced population from 1999 through 2007 *(A)* and of the subset of participants with at least 1 study visit per year from 2002 through 2007 *(B)*. IAS-USA, International AIDS Society-USA; NRTI, nucleoside reverse-transcriptase inhibitor.

between unboosted PIs (cART group) and newer treatments, including either an NNRTI or a ritonavir-boosted PI (potent cART group) [13, 18].

Sensitivity analyses were conducted by restricting estimation of prevalence to genotypic tests performed on treatment and by considering patients lost to follow-up as having experienced virologic failure. Conclusions were not altered by these analyses.

RESULTS

Patient demographic characteristics of the open and closed cohorts. From 1 January 1999 through 31 December 2007, a total of 8569 patients exposed to ART were observed in the Swiss HIV Cohort Study. Of these, 505 (5.9%) were excluded from the analysis because of insufficient information to assess their probability of harboring resistant viruses, leaving 8064 individuals, whom we defined as our open cohort. For the closed cohort, we only included the subset of 4184 patients active from 2002 through 2007 (table 1).

Figure 1*A* summarizes the evolution of the open cohort. The size of the ART-experienced population increased, whereas the population of patients with exposure to mono- or dual-NRTI treatment or with virologic failures diminished over time. The proportion of patients who had undergone genotypic resistance testing after initiation of ART also increased steadily, although the slowed growth from 2004 onward suggests that, in recent years, the numbers of patients with an indication for testing and tests performed have reached a steady state: fewer patients experienced virologic failure, and those who had experienced virologic failure were more likely to have undergone resistance testing. In fact, among patients who experienced virologic failure while receiving ART, 80% had undergone at least 1 genotypic resistance test by 2007, up from 41% in 1999 (data not shown).

Estimation of drug resistance prevalence. To determine the prevalence of resistance, we classified ART-exposed patients by their probability of harboring resistant viruses based on their treatment history. With use of genotypic information from all participants (open cohort), we estimated the probability of the presence of International AIDS Society–USA mutations at 77.1% (95% CI, 75.4–78.7; number of tests, 2516) for patients with exposure to mono- or dual-NRTI therapy or virologic failures (virologic failure group), 15.7% (95% CI, 12.4%–19.4%; number of tests, 440) for patients who were at low risk for the emergence of resistance because they were not undergoing treatment or had always remained virologically suppressed while receiving therapy (low-risk group), and 34.8%

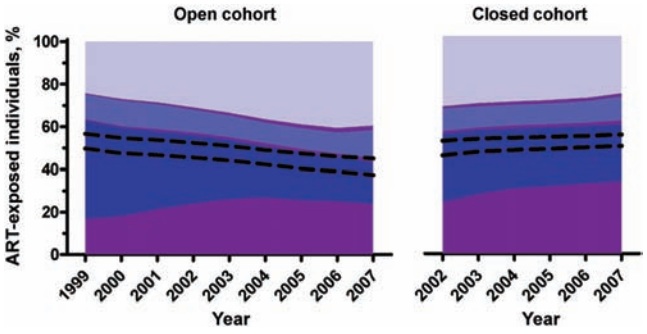

Figure 2. Estimate of the prevalence of drug resistance mutations. Antiretroviral treatment (ART)–experienced patients were classified according to their risk of harboring drug-resistant HIV: high probability due to exposure to mono– or dual–nucleoside reverse-transcriptase inhibitor therapy or because of virologic failures (*dark blue shaded area* plus adjacent *violet area* below), low risk for resistance emergence because always receiving or not receiving virologically suppressive therapies (*light blue area* plus adjacent *violet area* below), and patients with unknown status (*blue area with intermediate shading* intensity plus adjacent *violet area* below). Violet shaded areas indicate the subset of participants from a respective group with confirmed presence of drug resistance mutations. Broken lines, upper and lower prevalence estimates.

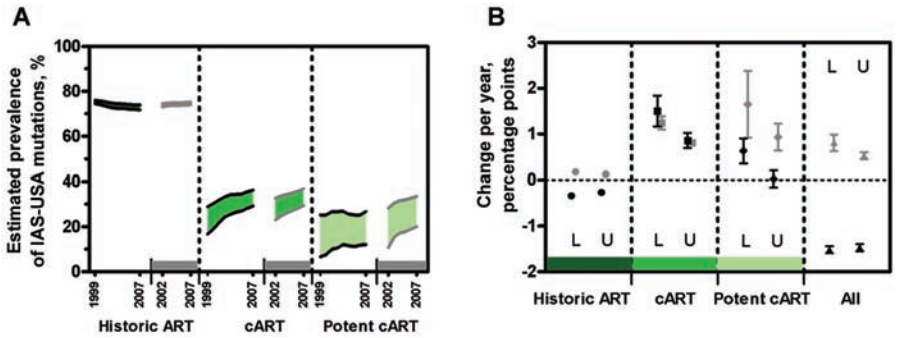

Figure 3. Prevalence and time trends of drug resistance by type of initial antiretroviral therapy (ART). *A,* Upper and lower prevalence estimates for all participants seen at least once since 1999 (open cohort) and the subset who were seen every year between 2002 and 2007 (closed cohort; indicated by gray bar on the x axis). *B,* Yearly change in prevalence derived from fitting a generalized linear regression model through the prevalence curves displayed in *A* and figure 2. *Black symbols,* estimates from the open cohort; *gray symbols,* estimates from the closed cohort. Estimates shown in the L columns show lower estimates, and those in the U columns show upper estimates. cART, combination antiretroviral therapy.

(95% CI, 29.6%–40.3%; number of tests, 322) for patients in the unknown group.

In the open cohort, the lower estimate of resistance prevalence for 2007, under the assumption that probabilities for resistance mutations in the low-risk and unknown groups were 0 unless confirmed by resistance testing (figure 2*A*), was 37.4%. For the upper estimate, resistance prevalence derived from tested patients in the low-risk and unknown groups was extrapolated to all untested individuals in these groups and yielded a prevalence of 45.1% for 2007. Those numbers were notably lower than estimates obtained for 1999 (49.7% [lower] and 56.6% [upper]). In the closed cohort, lower and upper

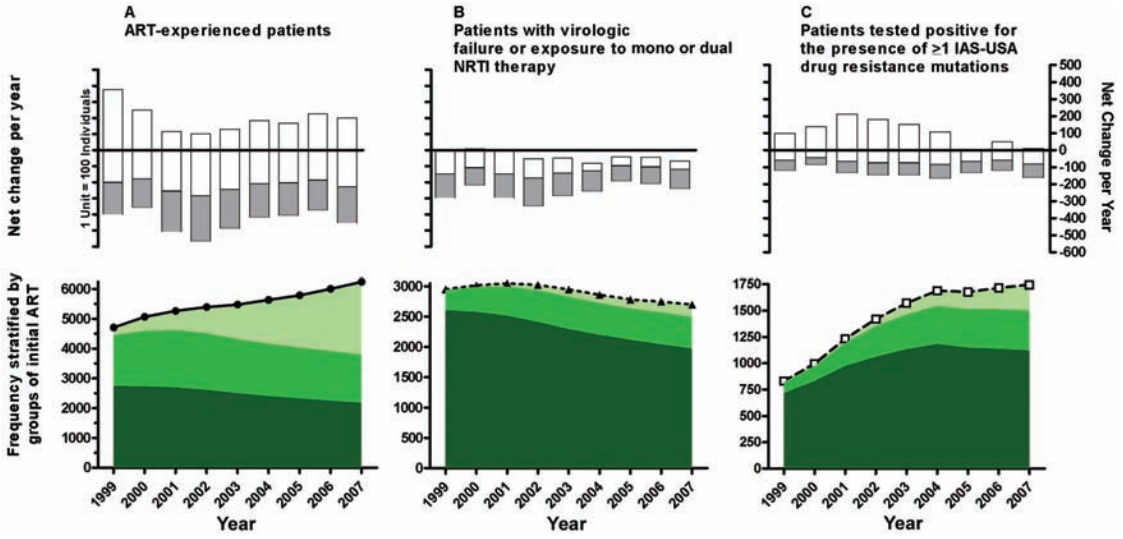

Figure 4. Evolution of the antiretroviral therapy (ART)–experienced Swiss HIV Cohort Study population. The graphs in *A, B,* and *C* display changes over time in the size of the ART-exposed population, the patient group with exposure to mono or dual nucleoside reverse transcriptase inhibitor (NRTI) therapy or at least 1 virologic failure event, and patients with drug resistance confirmed by genotypic testing, respectively. *Top row,* bar charts showing the yearly net change of the population; *gray shaded bars,* the magnitude of losses to follow-up and deaths; *white bars,* the number of patients newly joining a subpopulation, by starting ART *(A),* experiencing the first virologic failure *(B),* or testing positive for drug resistance mutations for the first time *(C).* The bars are arranged such that the numbers represented by the gray bar and the fraction of the white bar below the zero line cancel each other out. Thus, for all the panels, the net change per year is indicated by the upper edge of the white bars. A bar protruding above 0 indicates a net increase of a subpopulation in a given year, whereas bars ending below the zero line stand for a decrease. *Bottom row,* change in frequency of ART-experienced patients *(A),* patients with a virologic failure or exposure to mono– or dual–nucleoside reverse-transcriptase (NRTI) therapy *(B),* and patients harboring drug-resistant HIV, confirmed by genotypic resistance testing *(C); shaded areas,* the proportion of patients who initiated therapy with historic ART *(dark shade),* combination antiretroviral therapy (cART) containing unboosted protease inhibitors *(intermediate shade intensity),* or cART with boosted protease inhibitors or nonnucleoside reverse-transcriptase inhibitors *(light shade).* Note that black lines and symbols correspond to those in figure 1. IAS-USA, International AIDS Society-USA.

Table 2. Comparison of the actively observed study population, patients who were lost to follow-up, and patients who had died.

Characteristic	Patients who were still being observed in 2007[a] (n = 6014)	Patients lost to follow-up (n = 1298)	Patients who died (n = 752)	Adjusted OR (95% CI)[b]		P[c]
				Loss to follow-up	Death	
Female sex	1882 (31.3)	449 (34.6)	198 (26.3)	0.66 (0.56–0.77)	0.63 (0.51–0.77)	<.001
Age at ART initiation, median years (IQR)	45 (40–51)	40 (35–45)	43 (38–51)	NA[d]	NA[d]	
Mode of HIV acquisition						<.001
Heterosexual sex	2380 (39.6)	499 (38.4)	185 (24.6)	1.40 (1.15–1.71)	1.23 (0.96–1.57)	
Male-male sex	2275 (37.8)	306 (23.6)	202 (26.9)	Referent	Referent	
Injection drug use	1110 (18.5)	454 (35.0)	338 (44.9)	2.04 (1.55–2.69)	2.29 (1.65–3.16)	
Other	249 (4.1)	39 (3.0)	27 (3.6)	0.82 (0.54–1.22)	1.17 (0.74–1.86)	
Region of origin						<.001
Northwestern Europe	4321 (71.8)	851 (65.6)	643 (85.5)	Referent	Referent	
Sub-Saharan Africa	654 (10.9)	182 (14.0)	19 (2.5)	1.26 (0.99–1.60)	0.29 (0.17–0.48)	
Southern Europe	469 (7.8)	136 (10.5)	55 (7.3)	1.23 (0.98–1.55)	0.65 (0.47–0.88)	
Latin America	190 (3.2)	49 (3.8)	8 (1.1)	1.27 (0.88–1.83)	0.41 (0.20–0.85)	
South and East Asia	180 (3.0)	23 (1.8)	4 (0.5)	0.59 (0.36–0.96)	0.20 (0.07–0.55)	
Eastern Europe	106 (1.8)	25 (1.9)	12 (1.6)	1.33 (0.80–2.19)	1.12 (0.59–2.12)	
Other	94 (1.6)	32 (2.5)	11 (1.5)	1.64 (1.04–2.59)	0.85 (0.44–1.65)	
Type of initial therapy						.135
Historic ART	2091 (34.8)	552 (42.6)	428 (56.9)	Referent	Referent	
cART	1561 (26.0)	468 (36.1)	204 (27.1)	0.99 (0.81–1.22)	0.74 (0.57–0.97)	
Potent cART	2362 (39.3)	278 (21.4)	120 (16.0)	0.90 (0.68–1.19)	0.64 (0.44–0.94)	
Median year of ART initiation (IQR)	1999 (1996–2004)	1997 (1996–2000)	1996 (1995–1999)	NA[d]	NA[d]	
CD4 cell count at ART initiation, cells/mm^3						
No. of available measurements	5012	978	644	…	…	
Median (IQR)	220 (112–335)	227 (118–355)	180 (82.5–300)	NA[e]…	NA[e]	
Any history of hepatitis C virus coinfection	1404 (23.3)	514 (39.6)	380 (50.5)	1.30 (1.03–1.64)	1.59 (1.20–2.11)	.002
Any history of a CDC stage C event	1607 (26.7)	334 (25.8)	397 (52.8)	1.00 (0.85–1.17)	2.75 (2.30–3.28)	<.001
Any history of virologic failure	1838 (30.6)	490 (37.8)	380 (50.5)	1.24 (1.04–1.47)	1.31 (1.06–1.62)	.007
Any history of genotypic resistance testing	2406 (40.0)	486 (37.4)	386 (51.3)	0.56 (0.47–0.68)	0.71 (0.56–0.90)	<.001
Any history of detected drug resistance mutations	1665 (27.7)	325 (25.0)	290 (38.6)	0.88 (0.71–1.09)	1.02 (0.79–1.31)	.468

NOTE. Data are no. (%) of patients, unless otherwise indicated. Patients were considered lost to follow-up if they did not respond to written invitations for >14 months or if they wished to discontinue study participation. Only deaths occurring up to 180 days after study participation discontinuation were considered. ART, antiretroviral therapy; cART, combination antiretroviral therapy; CDC, Centers for Disease Control and Prevention; IQR, interquartile range; NA, not applicable.

[a] Reference outcome.

[b] The ORs are from multivariable polytomous logistic regression with the category "still alive in 2007" as base outcome. Adjustments were made for all covariables listed in the table.

[c] P values were obtained from likelihood ratio tests and indicate whether the inclusion of a variable significantly improved model fit.

[d] Age and year of ART initiation were included as confounders and modeled as cubic splines with knots at the 25th, 50th, and 75th centiles.

[e] The CD4 cell count at ART initiation was included as a confounder and modeled as a categorical variable with 4 groups on the basis of centiles and an additional category for missing data.

estimates were continuously increasing from 45.0% to 49.4% (lower) and from 51.7% to 54.6% (upper) from 2002 through 2007 (figure 2*B*); this was to be expected, however, because of our approach to carry forward detected resistance mutations. Different trends also emerged when analyses were repeated with stratifications for type of initial ART (figure 3). With the exception of the historic ART group, in whom resistance mutations are already frequent, prevalence of resistance generally appeared to be increasing over time. Change rates derived from lower estimates were 1.5 (open cohort) and 1.2 (closed cohort)

percentage points per year for the cART group and 0.6 (open) and 1.6 (closed) percentage points for the potent cART group, respectively (figure 3*B*). However, increases, especially those for lower estimates, tended to be much steeper during the first few years of our observational period (figure 3*A*), and thus, linear trends must be interpreted cautiously.

Shifts in study population as explanation for time trends. To explore reasons for the differences in time trends between the open and closed cohorts, we analyzed shifts in the distribution of patients exposed to different first-line treatments (historic ART group, cART group, and potent cART group), symbolic for different propensities for the presence of drug-resistant HIV. According to figure 4*A*, the number of patients who had initiated therapy with potent combinations increased steadily (2441 patients [39.1%]) and exceeded the number of patients from the historic ART category (2181 patients [35.0%]) by 2007. Figure 4*B* indicates a decrease in the number of patients with virologic failure or exposure to mono- or dual-NRTI therapy and who are, thus, at high risk for the emergence of drug resistance mutations. This decrease was caused by a continuous loss of patients exposed to historic ART as initial treatment from the study population, which was confirmed with a multinomial logistic regression model to study factors associated with losses to follow-up or deaths (table 2). Of further note, the availability of a genotypic drug resistance test was associated with a smaller probability for being lost to follow-up or death, most likely because this may also be an indicator for good patient compliance and regular attendance of physician appointments. After controlling for resistance testing, the presence of International AIDS Society–USA drug resistance mutations was not associated with a higher probability of death, although crude percentages would suggest so.

DISCUSSION

On the basis of data from a highly representative cohort for the HIV-1 epidemic in Switzerland, we estimate that drug resistance prevalence in ART-exposed patients decreased from 1999 through 2007 in the population of HIV-infected patients. Our upper estimate was 57% in 1999 and 45% in 2007, whereas our low estimate was 50% in 1999 and 37% in 2007. Such apparent time trends must be interpreted cautiously and in the context of the changing composition of the HIV-1–infected population over time. The proportion of patients exposed to historic ART, such as single-class NRTI therapy, generally regarded as a population with a high prevalence of drug-resistance mutations, decreased markedly. On the other hand, the patient group treated with combination therapy from the start and therefore at a much lower risk for the emergence of drug resistance grew over time, thus leading to a dilution effect. In contrast, when analyzing trends within a fixed subset of patients, drug resistance prevalence was increasing steadily as expected, yet at progressively smaller rates. Thus, our analysis demonstrates the potential biases and pitfalls of time trends derived from cohorts with continuous enrollment, if shifts in population composition are not considered.

Compared with other surveys, estimates of drug resistance prevalence from this study were considerably lower and most likely reflect the different methods. Most studies relied on analyses of drug resistance databases, which yielded probabilities for the presence of at least 1 drug resistance mutation of 76%–90% [19–24]. However, patients who had undergone drug resistance tests are not representative of the entire ART-exposed population, and studies of such patients tend to be biased toward patients who had experienced problems while undergoing therapy. For example, in the Swiss HIV Cohort Study in 2007, 44% of ART-exposed patients had never experienced a virologic failure and thus had no indication for drug resistance testing. Results from the present study are in line with a survey from the United States that relied on cross-sectional sampling, which estimated the prevalence of resistance mutations at 76% among viremic patients with an HIV RNA level >500 copies/mL [25]. Since viremic patients represented ~63% of the HIV-1–infected population, this yields an estimate of 48% for ART-exposed patients in the United States in 1998.

At the lower end of published estimates are the results from Pillay et al. [21], who obtained a prevalence in the United Kingdom of 17% in 2002 by dividing the number of patients who had ever had a positive drug resistance test result by the estimated number of treated patients in that year. Our approach extends their analysis by further including clinical and virologic information in the estimates, permitting an estimate of drug resistance prevalence in the population without resistance tests available.

Results from the analysis enclosing all participants seen since 1999 indicated an overall decrease of levels of drug resistance in the Swiss HIV Cohort Study, at first glance contradicting earlier predictions from mathematical models [12]. Yet those apparent trends were most likely caused by the turnover of high- and low-risk populations in the Swiss HIV Cohort Study. When reanalyzed within a fixed sample of patients (our closed cohort) or within groups of initial treatment, prevalence was increasing over time as predicted by the models. Those yearly increases were remarkably low, however. In their study from 2001, Blower et al. [11] considered a yearly rate of resistance emergence of 10%—an optimistic scenario. With use of virologic failure as a proxy for resistance emergence, we estimated rates of 4.7% (95% CI, 4.4%–5.1%) per 100 person-years of receiving ART for patients who had initiated treatment with cART and 2.1% (95% CI, 1.8%–2.4%) for those who had started with potent cART ($P < .001$, by log rank test) [13]. These lower rates most likely reflect the high standard of general health care in Switzerland and the introduction of boosted PIs.

Which of the estimation approaches presented herein may be the most realistic? We believe that lower estimates from the open cohort most closely resemble the situation of the HIV-infected population in Switzerland and are thus most relevant, because in patients without virologic failure or exposure to mono- or dual-NRTI treatment, the upper estimate approach makes a strong assumption of representativeness of individuals with confirmed genotypic resistance. Of the 4295 study participants who had never experienced virologic failure (i.e., the low-risk and unknown groups), 306 patients (7.1%) had test results that indicated the presence of resistance mutations. Of these 306 patients, 181 (59.2%) had also undergone a resistance test at baseline, and primary resistance mutations were detected in 142 (78.5%) of these 181 tests. Thus, upper estimates were disproportionately affected by primary drug resistance because prevalence of transmitted resistance is estimated to be 10% for Switzerland [26].

In turn, the lower method tended to underestimate prevalence, because pretreatment resistance testing has not been performed uniformly in individuals from the low-risk and unknown groups, although 64.5% of them had undergone at least 1 genotypic resistance test by 2007. Thus, assuming a primary resistance prevalence of 10% for these 35.5% untested patients yielded a new lower estimate of 40.7% for 2007, compared with 37.4% from the initial analysis, which suggests that the impact of testing bias on lower estimates was minimal in our sample.

The Swiss HIV Cohort Study is highly representative of the epidemic in Switzerland because it encompasses 49% of all diagnosed HIV-infected individuals (http://www.shcs.ch). Moreover, the Swiss HIV Cohort Study drug resistance database contains all genotypic resistance tests performed in Switzerland, making this one of the most comprehensive data sets on resistance worldwide. An assessment of completeness of this database revealed no systematic biases with regard to mode of HIV acquisition or ethnicity (V.v.W., B.L., H.F.G.; unpublished data). Thus, the open cohort approach should closely mirror the dynamics not only in Switzerland but also in other countries with a highly developed health care system. A potential limitation for interpretation is the loss to follow-up rate, which totalled 16% by the end of 2007. These patients were more likely to have acquired HIV infection by injection drug use or to originate from countries outside northwestern Europe (i.e., immigrants and asylum seekers)—populations that are known to be harder to reach and that tend to have a higher attrition from studies. In comparison to the closed cohort assessment, prevalence estimates from the open cohort were ~12% lower in 2007, thus suggesting an impact of losses to follow-up on our estimates. Most likely, the true bias is smaller than 12%, because the population included in the closed cohort tended to have a worse risk profile for virologic failures and, thus, emergence of resistance in terms of treatment history and the higher proportion of injection drug users (table 1).

To summarize, we conclude from our findings that HIV drug resistance, although still a significant problem in highly treated populations, appears to be moderating over time in highly developed health care systems with adequate resources. We speculate that resistance prevalence will further decrease at the population level because of the observed dilution effects, but also, and more importantly, because durable therapy success can more often be achieved with newer drugs and thus the emergence of new drug resistance is considerably slowed. The situation in developing countries, where state-of-the-art diagnostic tools often are not routinely available and therapeutic options are still limited, is likely to be different. In such settings, the possibility of increasing drug resistance requires close monitoring.

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