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Emergence of Acquired HIV-1 Drug Resistance Almost Stopped in Switzerland: A 15-Year Prospective Cohort Analysis

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(See the Editorial Commentary by Richman on pages 1318–9.)

Background. Drug resistance is a major barrier to successful antiretroviral treatment (ART). Therefore, it is important to monitor time trends at a population level.

Methods. We included 11 084 ART-experienced patients from the Swiss HIV Cohort Study (SHCS) between 1999 and 2013. The SHCS is highly representative and includes 72% of patients receiving ART in Switzerland. Drug resistance was defined as the presence of ≥1 major mutation in a genotypic resistance test. To estimate the prevalence of drug resistance, data for patients with no resistance test was imputed based on the patient's risk of harboring drug-resistant viruses.

Results. The emergence of new drug resistance mutations declined dramatically from 401 to 23 patients between 1999 and 2013. The upper estimated prevalence limit of drug resistance among ART-experienced patients decreased from 57.0% in 1999 to 37.1% in 2013. The prevalence of 3-class resistance decreased from 9.0% to 4.4% and was always <0.4% for patients who initiated ART after 2006. Most patients actively participating in the SHCS in 2013 with drug-resistant viruses initiated ART before 1999 (59.8%). Nevertheless, in 2013, 94.5% of patients who initiated ART before 1999 had good remaining treatment options based on Stanford algorithm.

Conclusions. Human immunodeficiency virus type 1 drug resistance among ART-experienced patients in Switzerland is a well-controlled relic from the era before combination ART. Emergence of drug resistance can be virtually stopped with new potent therapies and close monitoring.

Keywords. HIV-1 drug resistance; prevalence; emergence; treatment-experienced patients; antiretroviral activity.

Drug resistance is a major barrier to successful treatment and eradication of human immunodeficiency virus type 1 (HIV-1) infections [1]. It limits treatment options markedly [2, 3]. The emergence of drug resistance became less frequent with the introduction of combination antiretroviral treatment (cART) [4–10], which is highly effective at suppressing HIV replication in infected individuals [11–13]. In the last decade, even more potent drugs and new drug classes came on the market and extended the treatment options for HIV-1–infected individuals [14–19]. However, drug-resistant viral strains still emerge when viral suppression is insufficient, because of either the use of suboptimal regimens or poor adherence. In addition to drug resistance acquired during treatment, the transmission of drug-resistant strains is a threat [20–22]. It reduces the chances of long-lasting successful treatment [23]. For public health and prevention strategies, and to assess requirements for new drugs, it is important to monitor the spread of drug resistance in the HIV-infected population and to evaluate the remaining treatment options for patients infected with drug-resistant viral strains.

In the current study, we aimed to study the trends of HIV-1 drug resistance prevalence in the Swiss HIV Cohort Study (SHCS) during 15 years in antiretroviral treatment (ART)–experienced individuals. We intended to illustrate how the burden of drug resistance has changed since the introduction of newer, more potent drugs and changing treatment recommendations. We also aimed to characterize the remaining treatment options of patients who were actively participating in the SHCS in 2013.

METHODS

Study Population and Design

We included ART-experienced patients from the SHCS who attended ≥1 study visit between 1 January 1999 and 31 December

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[a]Members of the Swiss HIV Cohort Study are listing in the Acknowledgments.

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2013. The SHCS is an ongoing, nationwide, multicenter, clinic-based observational study with continuous enrollment and semiannual study visits. The SHCS has been approved by the ethical committees of all participating institutions, and written informed consent has been obtained from all participants [24]. Patients were excluded from the analysis if they started ART before registration in the SHCS with insufficient information of the treatment or viral load history.

Drug resistance information was obtained from the SHCS drug resistance database, which contains genotypic resistance tests (GRTs) performed by all authorized laboratories in Switzerland. Sequences are stored in a central database (SmartGene; Integrated Database Network System version 3.6.13). All laboratories perform population-based sequencing [5, 20]. The SHCS is highly representative and includes 72% of the patients receiving ART in Switzerland. The drug resistance database includes, in addition to the routinely collected samples, >11 000 samples from the biobank analyzed by systematic retrospective sequencing [20, 24].

In addition to GRTs stored in the SHCS drug resistance database, we had access to the Bundesamt für Sozialversicherungen (BSV) database. The BSV database is run by the Swiss public health authorities and includes 100% of GRTs performed in Switzerland between 2003 and 2013. The 4 laboratories with permission to perform resistance testing mandatorily need to enter all sequences into BSV database. However, we had no related clinical information for the subset of non-SHCS GRTs in the BSV database. To analyze the representativeness of the SHCS drug resistance database, we compared the proportion of GRTs with drug resistance mutations between SHCS and non-SHCS samples. We found no evidence for a different pattern between the 2 subsets (see Supplementary Figure 1).

We studied cumulative drug resistance, defined as the presence of ≥1 major mutation from the International Antiviral Society–USA mutations list 2014 in ≥1 GRT (mutations printed in bold on the International AIDS Society-USA mutation list) [2]. Three-class resistance was defined as the occurrence of ≥1 major mutation against 3 of the following 4 drug classes: nucleoside/nucleotide reverse-transcriptase inhibitors (NRTIs), nonnucleoside reverse-transcriptase inhibitor (NNRTIs), protease inhibitors (PIs), or integrase inhibitors (INIs). Mutations against enfuvirtide or maraviroc were not considered because these 2 drugs were only rarely used.

Because the potency of ART has changed over time, we stratified the population in 3 groups based on the date of ART initiation. The first group included patients who started ART before 1 January 1999. In this time period most patients received single-class therapies (mainly single- or dual-NRTI therapies) and regimens containing unboosted PIs. The second group included patients who started ART between 1 January 1999 and 31 December 2006, when potent cART became well established and most patients received cART containing 2 NRTIs and a ritonavir-boosted PI or an NNRTI. The third group contained patients who started ART between 2007 and 2013. Since 2007 and 2008, darunavir and raltegravir have been available in Switzerland, which improved the treatment of ART-experienced patients substantially [14, 15, 19, 25].

Prevalence Estimate

The yearly prevalence of drug resistance was estimated for all actively participating patients between 1999 and 2013. For the prevalence estimation, we imputed data for ART-experienced patients without resistance tests. For this purpose, we stratified patients into 3 groups based on the risk of harboring drug resistance mutations. The high-risk group included patients who had ever experienced a virological failure or who were treated with single- or dual-NRTI therapy for >28 days. A virological failure was defined as either 2 consecutive viral loads >500 HIV-1 RNA copies/mL or 1 viral load >500 HIV-1 RNA copies/mL followed by a treatment change if the patient had experienced ≥180 days of continuous ART or ≥90 days of ART if viral suppression was reached (<50 HIV-1 RNA copies/mL) [5]. The low-risk group included patients who remained virologically suppressed while receiving treatment (≥2 viral loads <50 HIV-1 RNA copies/mL while receiving the same treatment in a given year or 1 viral load <50 HIV-1 RNA copies/mL before treatment change). The third group included the remaining patients, who had an unknown risk status.

We estimated a lower and upper limit for the prevalence of drug resistance based on the following criteria. For the upper limit, we calculated the proportion of drug resistance for each risk group among patients who had a GRT after ART initiation. We assumed that patients in the respective risk groups without GRT had the same risk (proportion) of drug resistance. In contrast, for the lower limit, patients without GRT were considered to have no mutation when they belonged to the group with low or unknown risk (those with detected viral resistance were still counted). Patients in the high-risk group with no GRT were assumed to have the same risk (proportion) of drug resistance as those in the high-risk group with a GRT. The prevalence of 3-class resistance was calculated in the same way.

Remaining Treatment Options

We analyzed the remaining treatment options for patients who were actively participating in the SHCS in 2013 and who had a GRT performed after ART initiation. To estimate the activity of antiretroviral drugs, we calculated the genotypic sensitivity score (GSS) based on the Stanford algorithm (version 7.0). Full activity of drugs was assumed when the Stanford score was <15 (GSS, 1), intermediate activity between 15 and 59 (GSS, 0.5), and no activity when the Stanford score was >59 (GSS, 0). We calculated the GSS of an optimized treatment. For the optimized treatment the 2 most active NRTIs from a given list were considered (the list included zidovudine or stavudine [only one could be chosen], emtricitabine or lamivudine, abacavir or didanosine, and tenofovir), along with the most active PI (amprenavir, atazanavir,

darunavir, indinavir, lopinavir, nelfinavir, saquinavir, or tipranavir) and/or the most active NNRTI (nevirapine, efavirenz, etravirine, or rilpivirine); the INIs considered included raltegravir, elvitegravir. and dolutegravir. Statistical analyses were performed with Stata SE software (version 14.0; StataCorp).

Table 1. Characteristics of Antiretroviral Treatment (ART)-Experienced Patients Stratified by the Year of First ART Initiation

Characteristics	All (n = 11 084)	Year of First ART Initiation		
		Before 1999 (n = 3730)	1999–2006 (n = 3910)	2007–2013 (n = 3444)
General characteristics				
Female sex, No. (%)	3218 (29.0)	1093 (29.3)	1297 (33.2)	828 (24.0)
Ethnicity, No. (%)				
Nonwhite	2159 (19.5)	352 (9.4)	931 (23.8)	876 (25.5)
White	8678 (78.3)	3168 (84.9)	2945 (75.3%)	2565 (74.5)
Unknown	244 (2.2)	210 (5.6)	34 (0.9)	0 (0)
Age, median (IQR), y	47 (39.0–53)	50.0 (44–56)	47.0 (40–53)	42 (35–49)
Mode of HIV acquisition, No. (%)				
Heterosexual	4166 (37.6)	1094 (29.3)	1792 (45.8)	1280 (37.2)
Injection drug use	2081 (18.8)	1151 (30.9)	694 (17.8)	236 (6.8)
Male-male sex	4395 (39.6)	1349 (36.2)	1263 (32.3)	1783 (51.8)
Other or unknown	442 (4.0)	136 (3.6)	161 (4.1)	145 (4.2)
Characteristics at ART initiation				
Year of ART initiation, median (IQR)	2001 (1997–2008)	1996 (1994–1997)	2002 (1999–2004)	2010 (2008–2011)
Type of initial ART, No. (%)				
Single- or dual-NRTI treatment[a]	3125 (28.2)	2751 (73.8)	318 (8.1)	56 (1.6)
Historic cART[b]	2210 (19.9)	966 (25.9)	1216 (31.1)	28 (0.8)
Potent cART[c]	5749 (51.9)	13 (0.3)	2376 (60.8)	3360 (97.6)
CDC stage C event, No. (%)	2325 (21.0)	1000 (26.8)	854 (21.8)	471 (13.7)
CD4 cell count, median (IQR), cells/mm^3	243 (125–361)	235.0 (117–350)	203 (96–321)	290 (188–400)
CD4 cell count, No. of available measurements	10 238	3304	3653	3281
HIV RNA level, median (IQR), $\log_{10}$ copies/mL	4.8 (4.2–5.3)	4.7 (4.1–5.2)	4.9 (4.3–5.4)	4.7 (4.2–5.2)
HIV RNA level, No. of available measurements	8323	1548	3536	3239
Any GRT before ART initiation, No. (%)	6465 (58.3)	980 (26.3)	2583 (66.1)	2902 (84.3)
Known baseline drug resistance mutation, No. (%)	562 (5.1)	79 (2.1)	205 (5.2)	278 (8.1)
Characteristic at last follow-up visit				
Risk status for presence of drug-resistance mutations, No. (%)				
Any exposure to single- or dual- NRTI therapy or history of virological failure	2897 (26.1)	2662 (71.4)	194 (5.0)	41 (1.2)
Consistent virological suppression during ART	6616 (59.7)	567 (15.2)	2996 (76.6)	3053 (88.7)
Unknown risk status	1571 (14.2)	501 (13.4)	720 (18.4)	350 (10.2)
Any GRT after ART initiation	4567 (41.2)	2811 (75.4)	1422 (36.4)	334 (9.7)
Resistance mutation ever detected	3202 (28.9)	2096 (56.2)	771 (19.7)	335 (9.7)
New resistance mutation acquired during ART[d]	684 (10.6)	333 (34.0)	306 (11.9)	45 (1.6)
NNRTI resistance	1120 (10.1)	667 (17.9)	326 (8.3)	127 (3.7)
NRTI resistance	2794 (25.2)	1994 (53.5)	621 (15.9)	179 (5.2)
PI resistance	1409 (12.7)	1058 (28.4)	271 (6.9)	80 (2.3)
1-Class resistance	1520 (13.7)	876 (23.5)	377 (9.6)	267 (7.8)
2-Class resistance	1198 (10.8)	809 (21.7)	329 (8.4)	60 (1.7)
3-Class resistance	470 (4.2)	399 (10.7)	63 (1.6)	8 (0.2)
4-Class resistance	14 (0.1)	12 (0.3)	2 (0.1)	0 (0.0)
Loss to follow-up	2010 (18.1)	854 (22.9)	842 (21.5)	314 (9.1)
Death				
AIDS related	262 (2.4)	150 (4.0)	94 (2.4)	18 (0.5)
All causes	1167 (10.5)	695 (18.6)	401 (10.3)	71 (2.1)

Abbreviations: ART, antiretroviral treatment; cART, combination ART; CDC, Centers for Disease Control and Prevention; GRT, genotypic resistance test; HIV, human immunodeficiency virus; IQR, interquartile range; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse-transcriptase inhibitor; PI, protease inhibitor.

[a] Single- or dual-NRTI treatment and 1-class treatment.

[b] Historic cART was a regimen containing unboosted PIs or <3 drugs.

[c] Potent cART was a regimen containing 3 drugs from ≥2 classes (not unboosted PI).

[d] Only patients with GRT before ART initiation were considered (see "Characteristics at ART initiation").

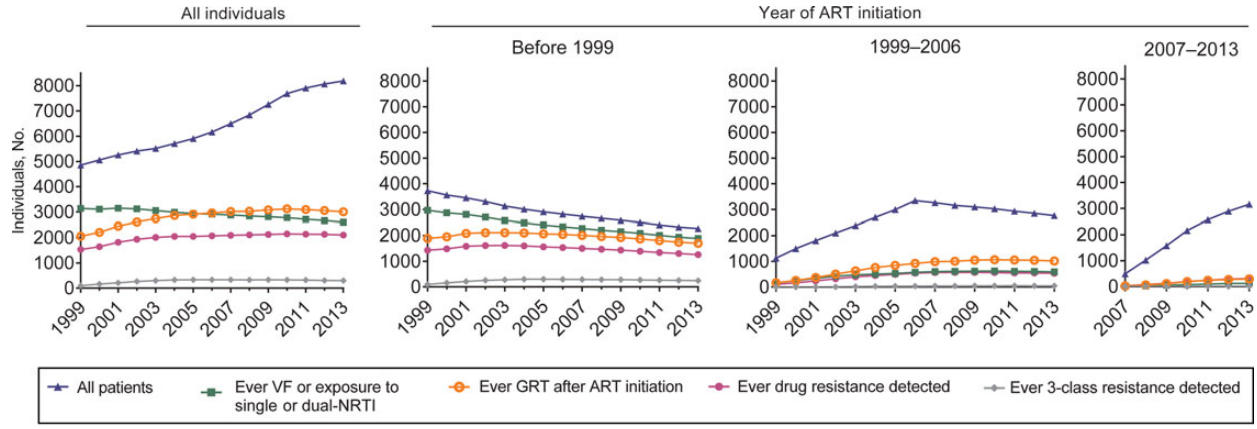

Figure 1. Antiretroviral treatment (ART)–experienced patients between 1999 and 2013 stratified by the year of ART initiation. Abbreviations: GRT, genotypic resistance test; NRTI, nucleoside/nucleotide reverse-transcriptase inhibitor; VF, virological failure.

RESULTS

Study Population

We included 11 084 ART-experienced patients who had ≥1 study visit in the SHCS between 1999 and 2013 (Table 1). We had to exclude 1234 of 12 318 potentially eligible patients because of insufficiently documented treatment histories before registration in the SHCS. We subdivided the population based on the date of ART initiation. The year of ART initiation was (1) before 1999 for 3730 (33.7%) patients, (2) between 1999 and 2006 for 3910 (35.3%), and (3) after 2006 for 3444 (31.1%). In the first group, 73.8% of patients initiated treatment not with cART (73.8%), mainly single- or dual-NRTI therapies, and 25.9% started a historic cART regimen including unboosted PIs or <3 drugs (historic cART). In the second group, most patients received potent cART (60.8%) and in the third group almost all patients initiated ART with a potent regimen (97.6%). The latter patients were healthier at ART initiation. They had fewer AIDS-defining illnesses diagnosed and higher CD4 cell counts at the time of ART initiation.

Patients With Drug Resistance Mutations Detected

The absolute number of treatment-experienced patients with a drug resistance mutation detected remained very stable in the last 10 observation years (about 2000 patients), although the number of patients receiving ART increased substantially, from 5516 in 2003 to 8189 in 2013 (Figure 1). This analysis included all SHCS enrollees who were actively followed up in a given year (ie, excluding death and losses to follow-up). Overall, 28.9% of ART-experienced patients were ever detected with a drug resistance mutation. This proportion was highest in patients who started ART before 1999 (56.2%) and declined to 19.7% and 9.7% among patients who started ART in 1999–2006 or 2007–2013, respectively. In the third group only 45 of 2092 (1.6%) patients with a GRT before the start of treatment acquired drug resistance mutations during ART. The majority of patients in the latest group with drug resistance detected during ART had already been infected with HIV strains harboring drug resistance mutations before starting treatment (278 of 323; 86.1%).

Major Source for Drug Resistance in 2013

Most patients who carried drug-resistant viral strains in 2013 started ART before 1999 (59.8%) or between 1999 and 2006 (25.4%) (see Supplementary Table 1). The large proportion of patients with a study visit in 2013 who started ART after 2006 contributed only slightly to the total number of patients with drug resistance (14.8%). Most 3-class–resistant viruses emerged in patients who started ART before 2007. In 2013, only 8 patients who started ART after 2006 carried 3-class–resistant viruses. This corresponds to 2.7% of all patients with 3-class resistance.

Emergence of Newly Acquired Drug Resistance Mutations

The decline of newly diagnosed drug resistance mutations and 3-class–resistant strains is illustrated in Figure 2. In 1999, a total of 401 patients had newly detected drug-resistant viruses. This number steadily decreased and reached a minimum of 23 patients in 2013. Accordingly, the number of patients with newly diagnosed 3-class–resistant viral strains decreased from a maximum of 69 patients in 2000 to a minimum of 3 in 2013.

Estimated Prevalence of Drug Resistance and 3-Class Resistance

As a result of the decline in detection of new drug resistance mutations and the increasing number of patients receiving ART, the estimated prevalence of drug resistance among ART-experienced individuals decreased steadily since 1999 (Figure 3). The upper limit declined from 57.0% in 1999 to 37.1% in 2013, and the lower limit from 51.7% to 30.8%, respectively. The estimated prevalence of 3-class resistance was halved from 9.0% to 4.4% between 1999 and 2013. This observation was driven by the increasing number of ART-experienced patients who started ART in recent years and who had sustained viral suppression without acquiring drug resistance.

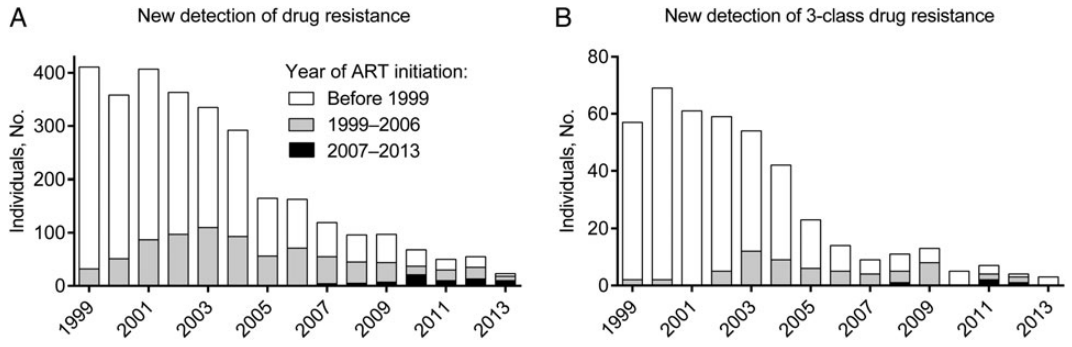

Figure 2. Patients with newly detected drug-resistant (*A*) or 3-class–resistant (*B*) viral strains, stratified by the year of antiretroviral treatment (ART) initiation: before 1999, 1999–2006, or 2007–2013.

The estimated prevalence of drug resistance varied largely between the different treatment initiation groups. A large proportion of patients who started treatment before 1999 were estimated to have drug-resistant viruses (63.7%–68.3%) or 3-class–resistant viruses (12.3% and 12.9%). The ranges for the prevalence of drug resistance and 3-class resistance among

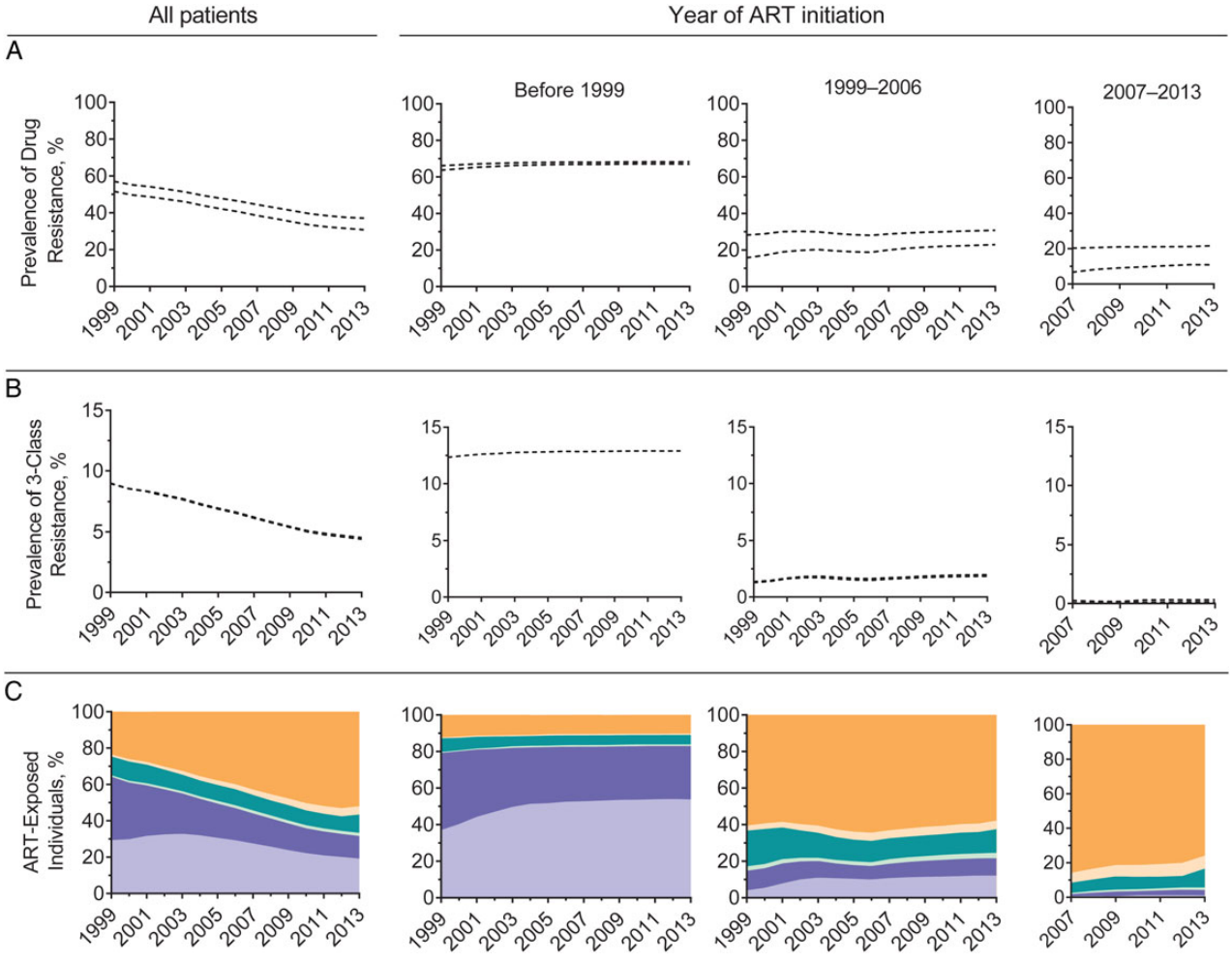

Figure 3. Estimated prevalence of drug resistance. *A*, Estimated prevalence range (upper and lower limits) of drug resistance. *B*, Estimated prevalence range of 3-class resistance. Patients were stratified by the year of antiretroviral treatment (ART) initiation: before 1999, 1999–2006, or 2007–2013. *C*, Prevalence was estimated according to the patient's risk of harboring drug resistance mutations. Patients with low risk for drug resistance (always suppressed viral load) are depicted in gold, those with a high risk (previous virological failure or exposure to single– or dual–nucleoside/nucleotide reverse-transcriptase inhibitor therapy) in purple, and those with an unknown risk in teal. The lighter-colored portions below the respective risk groups represent individuals with confirmed drug resistance.

patients who started ART between 1999 and 2006 were 15.8%–30.8%, and 1.3%–2.0%, respectively. Additional improvement was observed in patients who started ART after 2006. The ranges for the estimated prevalence of drug resistance and 3-class resistance were 10.9%–21.7% and 0.1%–0.3%, respectively.

To assess the effect of continuous enrollments and dropouts of participants on prevalence estimates, we restricted the above analysis to 5450 individuals who attended ≥1 study visit every year between 2007 and 2013. The upper limit of the prevalence increased from 43.8% to 45.9%, and the lower limit from 37.7% to 40.3%. Three-class resistance increased from 6.1% to 6.7% (see Supplementary Figure 2).

Remaining Treatment Options

Most patients in whom a GRT was performed during treatment (3005 GRTs from the protease/reverse-transcriptase, 335 GRTs from the integrase gene) and who were actively participating in the SHCS in 2013 had excellent treatment options (see Supplementary Figure 3). The situation was most critical for NRTIs and NNRTIs. No fully active NRTI was available for 33.8%, 6.0%, and 0.7% of patients who started ART before 1999, between 1999 and 2006, and after 2006, respectively, and 14.4%, 9.9%, and 8.2% of those patients had no fully active NNRTI left. However, in all groups, 97.6% of the patients had ≥1 NNRTI with intermediate activity left. Of patients who started ART before 1999, between 1999 and 2006, and after 2006, 11.6%, 1.4%, and 0.3%, respectively, had no fully active PI, and 4.4%, 0%, and 1.1% had no fully susceptible INI left.

When the 2 NRTIs with the best activity were combined with the NNRTI or the PI with the best activity (3-drug combination), 2628 of 3005 patients had a GSS ≥2 (87.5%). When treatment was optimized by combining the 2 NRTIs with the best activity with the NNRTI and the PI with the best activity (4-drug combination), even more patients (2906 of 3005; 96.7%) had a GSS ≥2. The GSS was lowest in the group starting ART before 1999, in which 1604 of 1697 patients (94.5%) had a GSS ≥2 (see Supplementary Table 2). Of 335 patients with a GRT performed from the integrase, 324 had ≥1 fully active INI left (97.8%). Thirty-four patients with a GSS <2 in the optimized 4-drug combination had the integrase sequenced. Three of 34 (8.8%) had no fully susceptible INI left; hence, these patients are running out of treatment options.

DISCUSSION

Our results showed that the burden of drug resistance and multiclass resistance in the SHCS is mainly a relic from the era before highly active ART was introduced. We demonstrated that the vast majority of treated patients who initiated treatment in more recent years did not acquire drug resistance. These patients usually had a pretreatment resistance test done and were treated with a highly effective first-line ART. As a result of the effective suppression of viral replication, the prevalence of drug resistance in the SHCS was steadily decreasing. Patients with multiclass-resistant viral strains benefited most from the introduction of new drugs and new drug classes. Most of them had treatment options with drugs estimated to be fully active. In addition, the achievement of sustained viral suppression among patients with multidrug-resistant viruses will most likely reduce the chance of transmission of drug-resistant viruses, although a considerable source of transmission has been identified in drug-naive patients [20, 26, 27].

Monitoring HIV-1 drug resistance is important for assessing requirements for new drug and for modeling the spread of resistance. Our study confirmed the trend of decreasing prevalence of HIV drug resistance in resource-rich settings [7–10, 28]. The estimated prevalence of drug resistance in treatment-experienced patients in the SHCS was between 30.8% and 37.1% in 2013. Most previous studies reported a higher prevalence [8–10, 28]. The differences can most likely be explained by the fact that for those prevalence estimates only patients with a GRT were included. As an exception, Bontell and colleagues [7] reported a lower prevalence of drug resistance in Sweden, 1.1% among ART-experienced patients in 2009. This is most likely an underestimation because cumulative resistance was ignored and the fact that patients with suppressed viral load might have drug-resistant viral strains was not taken into account.

Our study is based on the highly representative SHCS [24]. Since 1996, approximately 80% of all patients with newly diagnosed HIV infection were enrolled in the SHCS [20]. The documented treatment history and viral load measurements allowed us to estimate the prevalence of drug resistance in patients in whom no GRT was performed. In addition, we had access to all non-SHCS GRTs performed in Switzerland between 2003 and 2013. The proportions of GRTs with drug resistance mutations were similar in SHCS and non-SHCS GRTs (see Supplementary Figure 1), which suggests that there was no strong selection bias. We had to exclude patients because of incomplete information before registration in the SHCS, but based on the available information we found no evidence of a different resistance pattern in these patients (see Supplementary Figure 4).

The situation in resource-limited settings is not comparable to that in Switzerland. In these settings, low genetic barrier drugs are mainly used as first-line treatments, and patients stay longer on failing regimens owing to limited viral load testing. This leads to the selection of primary mutations as well as the corresponding secondary mutations that compensate for the loss of fitness. Such strains might be transmitted and fixed in the population [22, 27, 29]. Accordingly, drug resistance will continue to be a major problem in resource-limited settings, and the problem of HIV drug resistance should not be minimized.

Switzerland comes very close to the Word Health Organizations target 90-90-90 (meaning that 90% of all HIV-infected individuals in a population should be diagnosed, that 90% of those should be treated and that 90% should achieve viral suppression below 50 copies/mL) [30], but many resource-rich countries have not yet achieved these goals. Thus, the situation

in Switzerland has to be interpreted with care and cannot be automatically translated to other resource-rich settings [30–32].

We demonstrated that the emergence of HIV-1 drug resistance has been dramatically reduced with the introduction of new drugs and modern treatment strategies, particularly in the period after 2007. New emergence of 3-class resistance on ART is almost nonexistent [30, 31]. Globally, the danger of transmission of resistant and multiclass-resistant viruses, however, may remain or increase, especially because of ART scale-up in settings with limited options for potent drugs, monitoring, and diagnostic tests [29]. Therefore, monitoring drug resistance will remain important for securing treatment success in patients with HIV infection. Nevertheless, our study demonstrates the potential of modern treatment strategies, including consequent drug resistance testing, to virtually stop the acquisition of drug resistance in HIV-1 infection.

Supplementary Data

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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