Durability and Outcome of Initial Antiretroviral Treatments Received during 2000–2005 by Patients in the Swiss HIV Cohort Study

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Background. Little is known about time trends, predictors, and consequences of changes made to antiretroviral therapy (ART) regimens early after patients initially start treatment.

Methods. We compared the incidence of, reasons for, and predictors of treatment change within 1 year after starting combination ART (cART), as well as virological and immunological outcomes at 1 year, among 1866 patients from the Swiss HIV Cohort Study who initiated cART during 2000–2001, 2002–2003, or 2004–2005.

Results. The durability of initial regimens did not improve over time ($P = .15$): 48.8% of 625 patients during 2000–2001, 43.8% of 607 during 2002–2003, and 44.3% of 634 during 2004-2005 changed cART within 1 year; reasons for change included intolerance (51.1% of all patients), patient wish (15.4%), physician decision (14.8%), and virological failure (7.1%). An increased probability of treatment change was associated with larger $CD4^+$ cell counts, larger human immunodeficiency virus type 1 (HIV-1) RNA loads, and receipt of regimens that contained stavudine or indinavir/ritonavir, but a decreased probability was associated with receipt of regimens that contained tenofovir. Treatment discontinuation was associated with larger $CD4^+$ cell counts, current use of injection drugs, and receipt of regimens that contained nevirapine. One-year outcomes improved between 2000–2001 and 2004–2005: 84.5% and 92.7% of patients, respectively, reached HIV-1 RNA loads of <50 copies/mL and achieved median increases in $CD4^+$ cell counts of 157.5 and 197.5 cells/μL, respectively ($P < .001$ for all comparisons).

Conclusions. Virological and immunological outcomes of initial treatments improved between 2000–2001 and 2004–2005, irrespective of uniformly high rates of early changes in treatment across the 3 study intervals.

Combination antiretroviral therapy (cART) for the treatment of human immunodeficiency virus (HIV) infection has substantially reduced HIV-related morbidity and mortality [1–3], and current guidelines suggest that cART has to be continued throughout life [4]. In 1999, we reported on initial experiences with cART in the Swiss HIV Cohort Study during 1995–1998 and described a substantial 1-year probability of treatment change of 45.5% (95% confidence interval [CI], 43.5%–47.5%) among the 2674 patients analyzed [5]. In the subgroup of 1157 individuals who were treatment naive before starting cART, the 1-year probability of treatment change was 37.0% (95% CI, 34.1%–40.1%). Over the past few years, several new drugs with improved efficacy, tolerability, and more-convenient administration in terms of the number of pills, frequency of intake, and restrictions in diet have become available. In light of these improvements, we hypothesized that the durabil-

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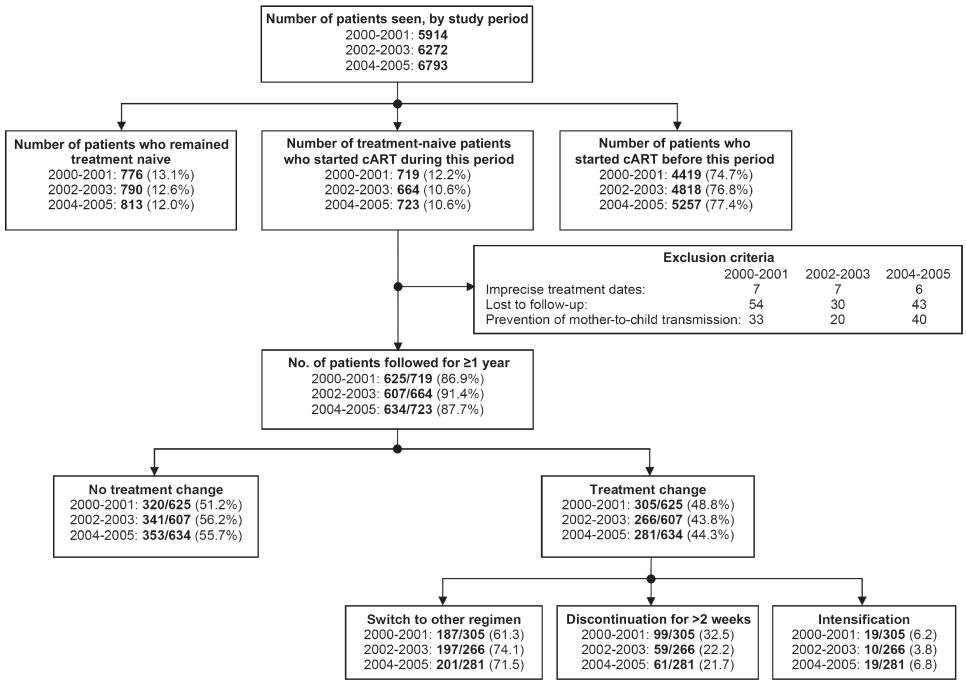

Figure 1. Characteristics of combination antiretroviral therapy (cART) use and change among patients starting their first cART regimen.

ity of initial cART regimens has improved in recent years. To test this hypothesis, we analyzed time trends of durability of initial cART regimens, reasons for and predictors of early treatment changes, and virological and immunological outcomes 12 months after the start of treatment.

PATIENTS AND METHODS

Patients. We selected patients who were participating in the Swiss HIV Cohort Study, a prospective cohort with continual enrollment of HIV-1–infected patients aged ⩾16 years [6]. Each patient is followed up at 1 of 7 outpatient HIV clinics in cities across Switzerland, including Zurich, Lausanne, Bern, Basel, Geneva, St. Gallen, and Lugano, as well as at several affiliated hospitals and private physicians' offices. Clinical information is collected prospectively on standardized questionnaires and complemented with a semiannual structured interview and a set of prespecified hematological, immunological, virological, and serological analyses at least every 6 months. Since 2000, all dates on which treatment with antiretroviral drugs was stopped and started, including reasons for stopping, have been recorded by the treating physicians as part of the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) protocol [7]. For each of 3 study periods—2000–2001, 2002–2003, and 2004–2005—we focused the analyses on patients who were starting cART for the first time. For a patient to be eligible for analysis, the dates on which treatment was started and stopped had to be known, and they could not have been lost to follow-up during the 1-year period after initiating treatment. We excluded pregnant women who had initiated ART for the prevention of mother-to-child transmission, because such treatment is often discontinued after birth if HIV infection does not require continued cART. The study was approved by the local ethical review boards, and written informed consent was obtained from all participants.

cART. We classified changes to cART as treatment switch (i.e., replacement of at least 1 drug in the regimen), treatment cessation or discontinuation for ⩾2 weeks (hereafter jointly referred to as "discontinuation"), and treatment intensification (i.e., addition of new drugs to an otherwise unchanged regimen). Discontinuation of treatment for <2 weeks was not classified as treatment change if the patient resumed the initial treatment; however, if 1 or more drugs were replaced, such discontinuation was classified as treatment switch. Reasons for switching or stopping treatment were classified as (1) treatment failure, (2) intolerance or adverse events, (3) patient wish, (4) physician decision, and (5) other.

We categorized cART regimens on the basis of the most frequently used nucleoside reverse-transcriptase inhibitor (NRTI) backbones (i.e., zidovudine/lamivudine, stavudine/lamivudine, tenofovir/emtricitabine or lamivudine, and didanosine/another NRTI) and third drugs (i.e., the nonnucleoside reverse-transcriptase inhibitors (NNRTIs) efavirenz and nevirapine; the protease inhibitors (PIs) lopinavir/ritonavir; nelfinavir, indinavir/ritonavir, and atazanavir/ritonavir, and the NRTI abacavir). We also defined regimens with respect to class, as follows: triple-NRTI treatment, PI-based treatment, NNRTI-based treatment, or 3-class treatment.

Table 1. Baseline characteristics of persons starting their first antiretroviral treatment regimen, by study period.

Characteristic	2000–2001	2002–2003	2004–2005	P[a]
Male sex	430/625 (68.8)	420/607 (69.2)	445/634 (70.2)	.86
Age				
Included in analysis	625	607	634	
Median (IQR), years	37 (32–44)	38 (32–45)	39 (33–47)	.002
Race				
White	492/625 (78.7)	467/607 (76.9)	489/634 (77.1)	.95
Black	90/625 (14.4)	95/607 (15.7)	100/634 (15.8)	
Other	43/625 (6.9)	45/607 (7.4)	45/634 (7.1)	
Injection drug use				
Never	485/625 (77.6)	512/607 (84.3)	535/634 (84.4)	.009
Past history[b]	51/625 (8.2)	36/607 (5.9)	41/634 (6.5)	
Active	89/625 (14.2)	59/607 (9.7)	58/634 (9.1)	
Body mass index[c]				
Included in analysis	623	607	634	
Median (IQR)	22.1 (20.2–24.5)	22.6 (20.5–25.3)	22.8 (20.7–25.3)	.006
Past history of clinically defined AIDS	184/625 (29.4)	151/607 (24.9)	155/634 (24.4)	.085
HBV infection				.007
Seronegative or vaccinated	280/609 (46.0)	304/598 (50.8)	342/618 (55.3)	
Seropositive inactive	286/609 (47.0)	268/598 (44.8)	241/618 (39.0)	
Current infection	43/609 (7.1)	26/598 (4.3)	35/618 (5.7)	
Active HCV infection	138/621 (22.2)	88/601 (14.6)	99/626 (15.8)	.001
HIV-1 RNA load				
Included in analysis	510	521	573	
Median (IQR), $\log_{10}$ copies/mL	4.9 (4.4–5.3)	5.0 (4.6–5.5)	5.1 (4.5–5.5)	.003
$CD4^+$ cell count				
Included in analysis	511	523	573	
Absolute, median (IQR), cells/μL	175 (72–289)	195 (102–291)	195 (101–270)	.065
$<$200 cells/μL	298 (58.3)	269 (51.4)	297 (51.8)	.044

NOTE. Data are no. of patients analyzed or no. of patients with the characteristic/no. analyzed (%), unless otherwise indicated. HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range.

[a] By the test for trend.

[b] Includes patients who were participating in an opiate-maintenance program during the study period.

[c] Defined as the weight in kilograms divided by the height in meters squared.

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infection. Patients were classified as having active HBV infection, if they tested positive for HBV surface antigen (HBsAg), HBV e antigen (HBeAg), or HBV DNA; as vaccinated, if they tested positive for anti-HBsAg and negative for antibody to HBV core antigen (anti-HBc); as seropositive with inactive infection, if they tested negative for HBsAg, HBeAg, and HBV DNA and positive for anti-HBc; and as seronegative, if they tested negative for anti-HBc. Patients were classified as having HCV coinfection, if they tested positive for antibody to HCV (anti-HCV) and HCV RNA; they were classified as not having HCV coinfection, if they tested negative for anti-HCV or if they tested positive for anti-HCV and negative for HCV RNA.

End points. The primary end point was the first treatment change during the 12-month period after starting cART. Secondary end points were virological and immunological treatment responses 12 months after starting cART. Virological response was defined as the suppression of the viral load to a level less than the limit of detection (i.e., $<$50 copies/mL). Immunological response was defined as the median absolute $CD4^+$ cell count at 12 months and the median increase in the $CD4^+$ cell count between baseline and month 12 of cART. Individuals who died within 1 year after starting treatment were considered for analysis of the primary end point but excluded from analyses of the secondary end points.

Statistical analyses. Time was measured from the start of cART to the first treatment change $\leqslant$1 year later. Individuals without treatment change within the 12-month interval were censored after 12 months of therapy or on the date of death, whichever occurred first. Kaplan-Meier curves were used to describe the cumulative incidence of treatment change on the basis of study period, regimen type, backbone, and third drug. We used log-rank tests and tests for trend to detect differences in the Kaplan-Meier curves across the 3 study periods.

Table 2. Characteristics of initial combination antiretroviral therapy received by persons starting their first regimen, by study period.

Variable	2000–2001 (n = 625)	2002–2003 (n = 607)	2004–2005 (n = 634)	P
Regimen				
Triple NRTI	44 (7.0)	48 (7.9)	22 (3.5)	<.001
PI based	366 (58.6)	259 (42.7)	307 (48.4)	
NNRTI based	200 (32.0)	298 (49.1)	303 (47.8)	
3 classes	15 (2.4)	2 (0.33)	2 (0.32)	
NRTI backbone				
Zidovudine/3TC	444 (71.0)	508 (83.7)	377 (59.5)	<.001
Stavudine/3TC	74 (11.8)	24 (4.0)	6 (0.95)	
Tenofovir/FTC or 3TC	0	17 (2.8)	184[a] (29.0)	
Didanosine/other NRTI	49 (7.8)	44 (7.2)	33 (5.2)	
Other NRTI combinations	58 (9.3)	14 (2.3)	34 (5.4)	
Third drug				
Efavirenz	180 (28.8)	269 (44.3)	278 (43.8)	<.001
Lopinavir/ritonavir	31 (5.0)	186 (30.6)	230 (36.3)	
Nelfinavir	228 (36.5)	65 (10.7)	12 (1.9)	
Indinavir/ritonavir	80 (12.8)	4 (0.66)	1 (0.16)	
Nevirapine	19 (3.0)	29 (4.8)	24 (3.8)	
Abacavir	23 (3.7)	37 (6.1)	5 (0.79)	
Atazanavir/ritonavir	0	1 (0.16)	48 (7.6)	
Other unboosted PIs	27 (4.3)	1 (0.16)	9 (1.4)	
Other boosted PIs	14 (2.2)	4 (0.66)	9 (1.4)	
Other (including 3-class regimens)	23 (3.7)	11 (1.8)	18 (2.8)	

NOTE. FTC, emtricitabine; NNRTI, nonnucleoside reverse-transcriptase inhibitors; NRTI, nucleoside or nucleotide reverse-transcriptase inhibitors; PI, proteinase inhibitors; 3TC, lamivudine.

[a] Includes 134 patients who received 3TC and 50 patients who received FTC.

We used χ^2 and Fisher exact tests to compare proportions and Wilcoxon and Kruskal-Wallis tests to compare continuous variables across different study groups. Time trends in virological and immunological outcomes after 12 months of therapy were assessed with χ^2 tests for linear trend, for the percentages of patients with an HIV-1 RNA load of <50 copies/mL, and nonparametric tests for trend, for the absolute $CD4^+$ cell counts at 12 months and changes in the $CD4^+$ cell count from baseline.

For the analysis of predictors of treatment change, we discarded the group of patients for whom treatment change was classified as treatment intensification, because of small sample sizes (<20 such patients for each study period). We assumed that predictors for treatment switch differed from predictors for treatment discontinuation and modeled these 2 competing outcomes by means of multinomial logistic regression, using the group of patients without a treatment change as the reference group.

$CD4^+$ cell count strata (<200, 200–350, and >350 cells/μL) and HIV-1 RNA load strata (>5 $\log_{10}$ copies/mL and ≤5 $\log_{10}$ copies/mL) were taken from the most recent treatment guidelines [4]. Additional covariables were age (per 10-year increase), sex, clinically defined AIDS (i.e., Center for Disease Control and Prevention stage C disease [8]), hepatitis B and/or C virus coinfection, injection drug use (never, former or currently in an opiate-maintenance program, and current), and antiretroviral treatment.

We used Stata, version 9.2 (StataCorp), for all analyses. All P values were calculated by 2-sided tests without correction for multiple tests.

RESULTS

Characteristics of cART use and treatment change during the study periods are outlined in figure 1. Of treatment-naive patients newly starting cART during the study intervals, 625 (86.9%) of 719 during 2000–2001, 607 (91.4%) of 664 during 2002–2003, and 634 (87.7%) of 723 during 2004–2005 were eligible for analysis. Baseline characteristics of the study population are detailed in table 1. There was a significant increase in the median age over the study periods. This finding is compatible with a concomitant reduction in the proportion of younger individuals infected through injection drug use, owing to prevention efforts such as needle exchange programs. This also explains the reduction in the proportion of patients with active HCV infection. Characteristics of the initial antiretroviral treatments are given in table 2. The composition of antiretroviral regimens

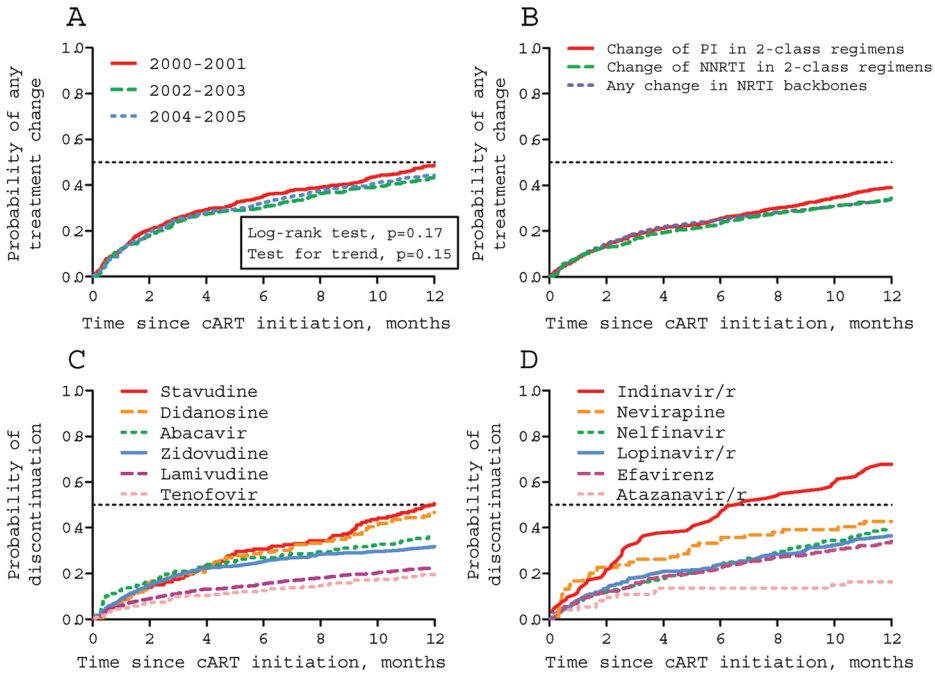

Figure 2. Time to first combination antiretroviral treatment (cART) change, by study period *(A)*, drug class *(B)*, nucleoside or nucleotide reverse-transcriptase inhibitor type *(C)*, and nonnucleoside reverse-transcriptase inhibitor and protease inhibitor type *(D)*.

changed significantly over time, mostly because of the introduction of new drugs (i.e., tenofovir, emtricitabine, and atazanavir), an increased use of NNRTI-based regimens, and use of boosted PIs.

Durability of initial cART. As shown in figures 1 and 2*A*, the percentage of patients who changed treatment within the first 12 months did not change significantly over the 3 periods: 48.8% (95% CI, 45.0%–52.8%) changed during 2000–2001, 43.8% (95% CI, 39.8%–47.7%) changed during 2002–2003, and 44.3% (95% CI, 40.6%–48.3%) changed during 2004–2005 ($P = .15$, by the test for trend). The 12-month probability of treatment change for all 3 periods combined was 45.6% (95% CI, 43.4%–47.9%). The hazard of treatment change was higher in the first 2 months (as shown by the steeper slope of the curve during this period) and then remained constant through month 12 of treatment. Of interest, although no significant time trends were present for the overall rates of treatment change, treatment switch, or treatment intensification, the trend for treatment discontinuation over the 3 periods was highly significant, with 99 patients (15.8%) discontinuing cART during 2000–2001, 59 (9.7%) discontinuing during 2002–2003, and 61 (9.6%) discontinuing during 2004–2005 ($P = .0006$).

The probabilities of treatment switch, by drug class, were also very similar (figure 2*B*). At 12 months, 39.2% (95% CI, 36.1%–42.4%) of PIs in PI-containing regimens, 34.3% (95% CI, 31.2%–37.7%) of NNRTIs in NNRTI-containing regimens, and 33.7% (95% CI, 31.6%–35.9%) of NRTIs had been modified. Substantial differences, however, could be found in the analyses of the probability of discontinuation of individual drugs. The Kaplan-Meier curves for individual NRTIs are displayed in figure 2*C*; Kaplan-Meier curves for PIs and NNRTIs are displayed in figure 2*D*. The 12-month probabilities of discontinuation of NRTIs ranged from 19.7% (95% CI, 15.2%–25.3%) for tenofovir to 50.6% (95% CI, 43.4%–58.3%) for stavudine, and the 12-month probabilities of discontinuation of PIs or NNRTIs ranged from 16.4% (95% CI, 9.7%–27.1%) for atazanavir to 42.9% (95% CI, 33.1%–54.1%) for nevirapine. Formal significance testing of the differences was not performed because the curves are not independent (i.e., each patient has data reflected in >1 curve).

The analysis of 1-year discontinuation rates across the 3 periods showed significant increases for stavudine (45% [95% CI, 37%–54%], 64% [95% CI, 48%–79%], and 89% [95% CI, 61%–99%], respectively, during 2000–2001, 2002–2003, and 2004–2005; $P = .0072$, by the test for trend) and abacavir (27% [95% CI, 17%–39%], 36% [95% CI, 27%–49%], and 55% [95% CI, 38%–73%], respectively; $P = .0031$), a slight increase for lopinavir (23% [95% CI, 11%–42%], 35% [95% CI, 29%–42%], and 40% [95% CI, 34%–46%], respectively; $P = .055$), and a significant decrease for lamivudine (28% [95% CI, 24%–31%], 22% [95% CI, 18%–25%], and 19% [95% CI, 16%–23%], respectively; $P = .0014$).

Reasons for treatment change. Intolerance (51.1% of patients), patient wish (15.4%), and physician decision (14.8%) were the most frequent reasons for treatment change within the first year, and there was little variation across the 3 study periods (figure 3*A*). Intolerance was the most frequent reason for treatment switch (61.0%, 59.9%, and 57.2% of patients, respectively, during 2000–2001, 2002–2003, and 2004–2005; $P = .45$, by the

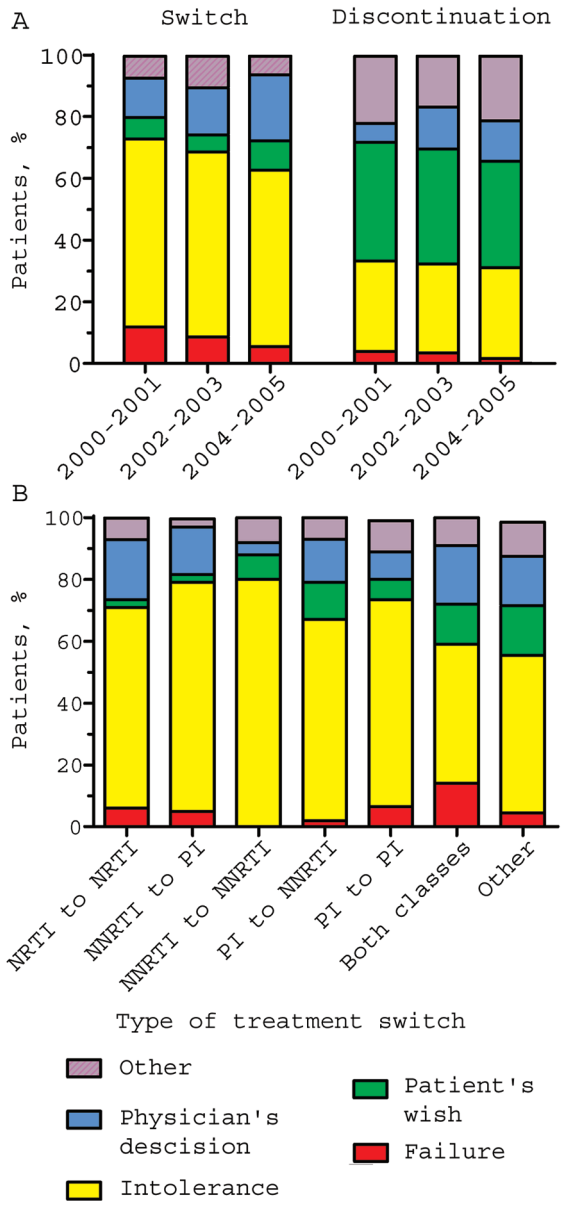

Figure 3. Reasons for changing the initial antiretroviral treatment regimen during the first year of therapy, by study period *(A)* and type of treatment switch among 2-class regimens *(B)*.

test for trend), followed by physician decision (12.8%, 15.2%, and 21.4% of patients, respectively; $P = .023$). Virological or immunological treatment failure became less than half as frequent (11.8%, 8.6%, and 5.5% of patients, respectively, during the 3 study periods; $P = .027$). The most frequent reasons for treatment interruption were patient wish (38.4%, 37.3%, and 34.4% of patients, respectively, during the 3 study periods) and intolerance (29.3%, 28.8%, and 29.5% of patients, respectively), and there was no indication of a time trend ($P > .1$ for all comparisons).

Predictors of treatment change. Results from univariable and multivariable multinomial logistic regression analyses of predictors of switch and discontinuation in the first 12 months of therapy are displayed in table 3. Higher baseline $CD4^+$ cell counts, higher HIV-1 RNA loads, and regimens that contained stavudine or indinavir/ritonavir were associated with an increased risk of treatment switch, whereas NRTI backbones with tenofovir/emtricitabine or tenofovir/lamivudine were associated with a lower risk. No demographic characteristics were associated with treatment switch, and we did not find increased risks for injecting drug users or individuals coinfected with hepatitis viruses. However, current use of injection drugs was highly associated with treatment discontinuation. Additional predictors for discontinuation were higher $CD4^+$ cell counts and regimens containing nevirapine. These predictors were present for both female and male patients (data not shown).

Virological, immunological, and clinical outcomes after 12 months. Table 4 summarizes virological and immunological outcomes across the 3 study periods 12 months after initiating cART. Trend analyses showed significant improvements in virological efficacy (defined as achievement of an HIV-1 RNA load of $<$50 copies/mL) over time, ranging from 87.1% of patients with any change in treatment to 96.9% with no change in treatment. Immunological responses (defined as the increase in the $CD4^+$ cell count increase from baseline and the absolute $CD4^+$ cell count at 12 months) generally exhibited similar patterns. Interestingly, the increase in $CD4^+$ cell count over time were attenuated in patients who did not change treatment. This could have been the result of a saturation effect, given that the virological response was $>$90% in all 3 periods, or could have been influenced by the fact that treatment for patients with a higher $CD4^+$ cell count was more likely to be switched. Of note, a new clinical AIDS-defining event was experienced by 37 patients (5.9%) during 2000–2001, 29 (4.8%) during 2002–2003, and 28 (4.4%) during 2004–2005, and 11 (1.8%), 8 (1.3%), and 8 (1.26%), respectively, died before the end of the 12-month study interval. The patients who died were not included in the outcome analyses described above.

DISCUSSION

In this analysis of 1866 participants from the Swiss HIV Cohort Study who first started cART between 2000 and 2005, we found that a substantial percentage (45.6%) had their treatment changed $\leq$1 year after it was initiated. No significant difference in the percentages of patients who changed treatment was observed between the study periods, and treatment change was more likely to occur among these patients than among those who started their first cART regimen during 1995–1998, for whom the probability of switching was 37.0% (B.L., unpublished data) [5]. Similar time trends towards shorter times to treatment change during recent years were described for the Veterans Affairs virtual cohort and were attributed to an increase in the number of alternative regimens [9]. During our study, the

Table 3. Multinomial logistic regression analysis of predictors of combination antiretroviral treatment (cART) switch and discontinuation during the first 12 months of cART among 1518 persons receiving their first regimen.

	Switch, analysis type				Discontinuation, analysis type			
	Univariable		Multivariable		Univariable		Multivariable	
Predictor	RRR (95% CI)	*P*	RRR (95% CI)	*P*	RRR (95% CI)	*P*	RRR (95% CI)	*P*
Study period								
2000–2001	1		ND[a]		1		ND[a]	
2002–2003	1.15 (0.87–1.53)	.33	ND[a]		0.67 (0.45–0.99)	.044	ND[a]	
2004–2005	1.10 (0.84–1.46)	.48	ND[a]		0.57 (0.38–0.85)	.005	ND[a]	
Female sex	1.11 (0.87–1.42)	.38	1.22 (0.94–1.57)	.13	1.07 (0.75–1.53)	.70	1.00 (0.68–1.48)	.97
Age, per 10-year increase	1.05 (0.94–1.16)	.42	1.04 (0.93–1.17)	.45	0.85 (0.72–1.00)	.055	0.91 (0.75–1.09)	.30
Injection drug use								
Never	1		1		1		1	
Past or in DTP	1.14 (0.73–1.80)	.56	1.40 (0.79–2.49)	.25	2.64 (1.50–4.65)	.001	1.84 (0.88–3.87)	.11
Current	0.72 (0.48–1.08)	.11	0.92 (0.54–1.58)	.76	4.18 (2.80–6.23)	<.001	3.06 (1.65–5.67)	<.001
Active HBV infection	0.90 (0.55–1.45)	.66	1.00 (0.60–1.64)	.99	0.95 (0.48–1.91)	.89	1.01 (0.49–2.10)	.98
HCV infection	0.82 (0.60–1.12)	.21	0.77 (0.48–1.24)	.29	3.15 (2.21–4.49)	<.001	1.47 (0.82–2.66)	.20
Previous diagnosis of clinically defined AIDS	1.06 (0.80–1.41)	.66	1.01 (0.75–1.37)	.94	1.27 (0.86–1.88)	.23	1.46 (0.95–2.25)	.084
$CD4^+$ cell count, cells/ μL								
<200	1.23 (0.95–1.59)	.11	1.09 (0.83–1.43)	.54	1.05 (0.72–1.54)	.80	0.91 (0.60–1.39)	.68
200–350	1		1		1		1	
>350	1.62 (1.14–2.31)	.007	1.50 (1.04–2.17)	.029	2.19 (1.36–3.51)	.001	2.33 (1.41–3.86)	.001
HIV-1 RNA load >5 $\log_{10}$ copies/mL	1.33 (1.07–1.67)	.012	1.35 (1.07–1.71)	.013	0.90 (0.65–1.26)	.55	1.16 (0.81–1.65)	.43
Regimen								
PI based	1		ND[a]		1		ND[a]	
NNRTI based	0.97 (0.77–1.22)	.79	ND[a]		0.78 (0.55–1.11)	.17	ND[a]	
Triple NRTI	1.04 (0.60–1.79)	.90	ND[a]		1.70 (0.89–3.27)	.11	ND[a]	
3 classes	11.0 (1.32–92.2)	.027	ND[a]		4.75 (0.29–76.6)	.27	ND[a]	
NRTI backbone								
Zidovudine/3TC	1		1		1		1	
Stavudine/3TC	1.26 (0.78–2.03)	.34	1.57 (0.93–2.66)	.091	1.11 (0.55–2.26)	.77	1.28 (0.59–2.79)	.54
Tenofovir/FTC or 3TC	0.56 (0.39–0.82)	.003	0.65 (0.43–0.97)	.035	0.50 (0.27–0.91)	.024	0.56 (0.29–1.10)	.094
Didanosine/other NRTI	1.83 (1.16–2.90)	.009	2.06 (1.29–3.31)	.003	1.88 (1.00–3.50)	.048	1.71 (0.87–3.34)	.12
Other NRTI combinations	1.26 (0.72–2.20)	.42	1.21 (0.67–2.21)	.53	1.41 (0.66–3.02)	.38	1.37 (0.59–3.18)	.46
Third drug								
Efavirenz	1		1		1		1	
Lopinavir/ritonavir	1.16 (0.88–1.54)	.29	1.09 (0.81–1.45)	.57	1.25 (0.80–1.95)	.34	1.10 (0.69–1.75)	.70
Nelfinavir	0.93 (0.66–1.31)	.68	0.81 (0.57–1.15)	.24	1.99 (1.26–3.12)	.003	1.52 (0.93–2.47)	.096
Indinavir/ritonavir	2.65 (1.47–4.77)	.001	2.28 (1.24–4.17)	.008	1.96 (0.76–5.07)	.17	1.17 (0.43–3.16)	.76
Nevirapine	1.02 (0.54–1.92)	.95	0.94 (0.49–1.79)	.85	2.74 (1.32–5.67)	.007	2.41 (1.10–5.25)	.027
Abacavir	0.73 (0.36–1.49)	.38	0.78 (0.37–1.61)	.50	2.36 (1.09–5.12)	.029	1.85 (0.81–4.21)	.14
Atazanavir/ritonavir	0.41 (0.18–0.94)	.034	0.52 (0.22–1.26)	.15	0.83 (0.28–2.44)	.74	1.02 (0.31–3.29)	.98
Other unboosted PIs	0.48 (0.18–1.30)	.15	0.36 (0.13–1.03)	.058	0.34 (0.05–2.60)	.30	0.24 (0.03–1.97)	.19
Other boosted PIs	1.05 (0.38–2.87)	.93	0.99 (0.34–2.84)	.98	1.87 (0.50–6.91)	.35	1.31 (0.32–5.40)	.71
Other, including 3-class regimen	2.27 (1.00–5.15)	.051	1.97 (0.84–4.58)	.12	2.49 (0.77–8.10)	.13	1.70 (0.47–6.16)	.42

NOTE. Patients for whom cART did not change served as the reference group. Patients with treatment intensification and patients with incomplete sets of covariables were excluded from the analysis. See Patients and Methods for definitions of cART switch and discontinuation. CI, confidence interval; DTP, opiate-maintenance program; HBV, hepatitis B virus; HCV, hepatitis C virus; NRTI, nucleoside or nucleotide reverse-transcriptase inhibitor; NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, proteinase inhibitor; RRR, relative risk ratio.

[a] Collinear with several other variables, especially individual drugs (i.e., those in NRTI backbones or third drugs).

Table 4. Virological and immunological outcomes 12 months after initiation of combination antiretroviral therapy (cART) among persons receiving their first regimen, by study period.

cART change status, outcome	2000–2001	2002–2003	2004–2005	*P*[a]
Overall, intent-to-treat				
HIV-1 RNA load <50 copies/mL	503/595 (84.5)	532/587 (90.6)	567/612 (92.6)	<.001
$CD4^+$ cell count, cells/μL				
Increase from baseline	157.5 (70–272)	176.5 (72–288)	197.5 (110–302)	<.001
Absolute, month 12	336.5 (219–523)	371 (233–533)	393 (277–525)	<.001
No change				
HIV-1 RNA <50 copies/mL	288/319 (90.3)	321/338 (95.0)	338/349 (96.9)	<.001
$CD4^+$ cell count, cells/μL				
Increase from baseline	183 (87.5–302.5)	184 (99–296)	203.5 (117–300)	.20
Absolute, month 12	369 (243–534)	374 (246–536)	394 (270–511)	.59
Any change, intent-to-treat[b]				
HIV-1 RNA load <50 copies/mL	215/276 (77.9)	211/249 (84.7)	229/263 (87.1)	.004
$CD4^+$ cell count, cells/μL				
Increase from baseline	132 (44–220)	145 (49–266)	193.5 (94–315)	<.001
Absolute, month 12	305 (193–478)	360 (222–533)	390 (279–571)	<.001
Switch or intensification[c]				
HIV-1 RNA load <50 copies/mL	175/200 (87.5)	186/201 (92.5)	202/215 (94.0)	.020
$CD4^+$ cell count, cells/μL				
Increase from baseline	148.5 (92–236)	171 (58–286)	200 (121–318)	.003
Absolute, month 12	305 (193–457)	362 (213–540)	387 (277–566)	<.001

NOTE. Data no. of patients with the characteristic/no. analyzed (%) or median (interquartile range). See Patients and Methods for definitions of cART change.

[a] By tests for trend across the 3 study periods.
[b] Including persons who discontinued cART.
[c] Excluding persons who discontinued cART.

number of alternative regimens prescribed for >1% of patients increased from 11 during 2000–2001 and 2002–2003 to 16 during 2004–2005. At a recent conference, Egger [10] highlighted an association between the probability of treatment change and the number of alternative regimens by showing that the rate of treatment change in South Africa (~22% within 12 months after initiating therapy), where there are few cART alternatives, is about half the rate observed in Switzerland, where there are many alternatives.

We have shown that newer drugs, such as atazanavir (which was not approved for first-line treatment in Switzerland during the periods analyzed) and tenofovir, that are part of first-line regimens are changed less often, but this had not yet translate into a reversal of time trends, because the number of patients starting with such combinations was still relatively small and limited to the most recent period analyzed. We did, however, observe a clear reduction in discontinuation rates for lamivudine, which parallels the increased use of lamivudine/tenofovir and the decreased use of lamivudine/stavudine.

Unlike other studies of treatment switching, this analysis focused on predictors of 2 distinct outcomes, treatment change and treatment discontinuation, in multinomial logistic regression models. Demographic characteristics such as age, sex, injection drug use, and disease stage did not appear to affect the probability of treatment change. However, compared with patients with a $CD4^+$ cell count of 200–350 cells/μL at baseline, individuals with counts of >350 cells/μL were more likely to change treatment (multivariable relative risk ratio, 1.62; $P = .029$). This difference is reflected in the reason for treatment change, with higher percentages of changes occurring because of intolerance (66.2% vs. 62.1%) and patient wish (12.5% vs. 6.8%) among patients with a $CD4^+$ cell count of >350 cells/μL than among those with a count of 200–350 cells/μL. The higher rates of treatment changes among patients with a baseline HIV-1 RNA load of >5 $\log_{10}$ copies/mL, however, are predominantly attributable to intolerance (62.0% for an HIV-1 RNA load of >5 $\log_{10}$ copies/mL vs. 54.6% for a load of $\leq$5 $\log_{10}$ copies/mL).

We found higher rates of treatment changes for regimens containing didanosine or ritonavir-boosted indinavir, both of which, according to current guidelines, are no longer recommended as constituents of initial therapy, because of their greater potential for toxicity [4].

We did not find evidence of increased rates of treatment change among patients with HBV or HCV coinfection. This finding differs from data reported by the EuroSIDA study group [11, 12] but concurs with data from the University of North Carolina Center for AIDS Research [13]. On the other hand, univariable analysis revealed that HCV coinfection and injection

drug use appeared to affect the probability of treatment discontinuation. In the multivariable model, only current injection drug use was significantly associated with treatment interruption. Conclusions need to be drawn with caution, because injection drug use and HCV coinfection are highly collinear. Reasons for treatment discontinuation tend to support the hypothesis that lifestyle or dependency-related personal motivations, rather than HCV-associated problems, lead to an increased probability of treatment discontinuation: among patients without and patients with HCV infection, intolerance was stated as the reason for treatment discontinuation for 28.4% and 30.7%, respectively ($P = .72$), and patient wish was cited for 30.5% and 49.3%, respectively ($P = .006$).

Favorable time trends could be shown for virological and immunological efficacy, in terms of both the frequency of treatment change owing to treatment failure and the HIV-1 RNA load and $CD4^+$ cell count after 12 months of treatment. In the intent-to-treat population who began treatment during 2004–2005, the percentage of patients with an HIV-1 RNA load of <50 copies/mL at 1 year of treatment (92.6% [567 patients]) was higher than that reported in randomized clinical trials [14–17]. In the AIDS Clinical Trials Group A5095 study [15], for example, the combination of zidovudine/lamivudine/efavirenz, which was also frequently used in our study, resulted in viral loads of <50 copies/mL at 48 weeks in 80%–90% of patients, even when missing data were ignored. The per-protocol analysis from the KLEAN (Kaletra versus Lexiva with Epivir and abacavir in ART-naive patients) study, which compared ritonavir-boosted fosamprenavir with lopinavir, showed that 88% and 89% of patients, respectively, achieved HIV-1 RNA loads of <50 copies/mL [14]. The difference may partly be explained by the selection criteria we used in our study. Indeed, if we assume that all 22 individuals from the 2004–2005 group with no HIV-1 RNA data at 1 year had a viral load of >50 copies/mL, the success rate decreases to 89.4% (567 of 634 patients), and if, in addition, all 43 patients during this period who were lost to follow-up did not have a virological response, the success rate decreases to 83.4% (567 of 677 patients).

The strength of this clinic-based study is its representativity: almost 70% of all persons with AIDS (i.e., CDC stage C disease) in Switzerland are included. Although we have tried to limit the number of excluded patients, a small bias introduced by individuals lost to follow-up cannot be excluded. Another limitation is related to the coding of reasons for discontinuation of individual drugs, which is often multifaceted, especially if no obvious events such as virological failure or acute adverse events are present. Because there is no code for treatment simplification (such as a convenience switch to a once-daily regimen), the reason given for such a change may be specified as either patient wish or physician decision. Unfortunately, we could not include information on adherence to cART, because collection of this information only started in May 2003.

The decision about when and how to start antiretroviral treatment is often the result of a long dialogue between physicians and their patients, during which the pros and cons of early versus deferred initiation and of different regimens are weighed with regard to expected adverse effects, pill burden, and mode of intake. Fortunately, differences in the antiviral activity of currently recommended initial regimens, if present at all, are negligible. Ideally, the first regimen should last for many years, because intolerance may, for some patients, lead to discouragement and negatively impact their commitment to treatment, including adherence. Indeed, we found the best 1-year virological outcome among individuals for whom treatment did not change. However, virological outcome was almost similarly excellent among persons who changed their initial treatment early during the course of cART.

In conclusion, we found that the frequency of early treatment change after initiation of antiretroviral therapy did not decrease between 2000 and 2005 but that, nevertheless, virological and immunological outcomes improved over time.

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