Treatment Modification in Human Immunodeficiency Virus–Infected Individuals Starting Combination Antiretroviral Therapy Between 2005 and 2008

Luigia Elzi, MD, MSc; Catia Marzolini, PhD; Hansjakob Furrer, MD; Bruno Ledergerber, PhD; Matthias Cavassini, MD; Bernard Hirschel, MD; Pietro Vernazza, MD; Enos Bernasconi, MD; Rainer Weber, MD; Manuel Battegay, MD; for the Swiss HIV Cohort Study

Background: Adverse effects of combination antiretroviral therapy (CART) commonly result in treatment modification and poor adherence.

Methods: We investigated predictors of toxicity-related treatment modification during the first year of CART in 1318 antiretroviral-naive human immunodeficiency virus (HIV)–infected individuals from the Swiss HIV Cohort Study who began treatment between January 1, 2005, and June 30, 2008.

Results: The total rate of treatment modification was 41.5 (95% confidence interval [CI], 37.6–45.8) per 100 person-years. Of these, switches or discontinuations because of drug toxicity occurred at a rate of 22.4 (95% CI, 19.5–25.6) per 100 person-years. The most frequent toxic effects were gastrointestinal tract intolerance (28.9%), hypersensitivity (18.3%), central nervous system adverse effects (17.3%), and hepatic events (11.5%). In the multivariate analysis, combined zidovudine and lamivudine (hazard ratio [HR], 2.71 [95% CI, 1.95–3.83]; P < .001), nevirapine (1.95 [1.01–3.81]; P = .050), comedication for an opportunistic infection (2.24 [1.19–4.21]; P = .01), advanced age (1.21 [1.03–1.40] per 10-year increase; P = .02), female sex (1.68 [1.14–2.48]; P = .009), nonwhite ethnicity (1.71 [1.18–2.47]; P = .005), higher baseline CD4 cell count (1.19 [1.10–1.28] per 100/µL increase; P < .001), and HIV-RNA of more than 5.0 log₁₀ copies/mL (1.47 [1.10–1.97]; P = .009) were associated with higher rates of treatment modification. Almost 90% of individuals with treatment-limiting toxic effects were switched to a new regimen, and 85% achieved virologic suppression to less than 50 copies/mL at 12 months compared with 87% of those continuing CART (P = .56).

Conclusions: Drug toxicity remains a frequent reason for treatment modification; however, it does not affect treatment success. Close monitoring and management of adverse effects and drug–drug interactions are crucial for the durability of CART.

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eral antiretroviral drugs, but this association remains controversial.7,12-10 Moreover, the prevalence of adverse events affecting the central nervous system (CNS) during treatment with efavirenz, leading to treatment discontinuation in about 10% to 15% of patients19 was related to higher plasma levels20 and black ethnicity.21 Knowledge about the genes implicated in pharmacokinetics, mode of action, ef-
ficacy, and toxicity of drugs provides relevant results for clinical practice. For example, the presence of the HLA-B*5701 allele predicts an abacavir sulfate hypersensitivity reaction with potentially severe consequences.22,23

This study investigates factors associated with early CART modification owing to drug toxicity in antiretroviral-naive HIV-infected individuals who recently started CART within the SHCS. Specific objectives were to assess the probability of a treatment switch or discontinuation according to the most often recommended and prescribed antiretroviral regimens (ie, nonnucleoside reverse transcriptase inhibitor [NNRTI] vs protease-inhibitor [PI] based, efavirenz vs nevirapine, boosted atazanavir [atazanavir/r], and boosted lopinavir [lopinavir/r]), to explore risk factors of the most common toxic effects (ie, gastrointestinal tract intolerance, hypersensitivity, CNS adverse effects, and hepatic events) leading to a switch or discontinuation of therapy within the first year after starting CART, and to explore the impact of treatment modification on virologic and immunologic outcomes.

METHODS

STUDY DESIGN

We analyzed the SHCS database,24 a large prospective cohort study with continuous enrollment of HIV-infected individuals 16 years or older. Basic sociodemographic characteristics, data on the clinical course (occurrence of opportunistic infections or death), coinfection with hepatitis B and C viruses, antiretroviral therapy, co-
médication (prophylaxis and treatment of opportunistic infections, cardiovascular drugs, and treatment of hepatitis C virus and neoplasms), and immunologic and virologic variables are collected at enrollment into the study and every 6 months thereafter on standardized data collection forms. AIDS-defining diseases are re-
corded using the 1993 revised clinical definition of AIDS from the Centers for Disease Control and Prevention.25 The cause of death is reported using the International Statistical Classification of Diseases and Related Health Problems, 10th Revision.26

For the present analysis we used the SHCS database extract of January 2009.

STUDY POPULATION

Antiretroviral-naive HIV-infected individuals participating in the SHCS who started CART between January 1, 2005, and June 30, 2008, and had a follow-up of at least 6 months were eligible for this study. Pregnant women were excluded from this analysis because drug-related adverse events may affect this population differen-
tly, and women initiating CART for prevention of mother-to-child transmission often discontinue treatment after delivery.

DEFINITIONS

We defined CART as an antiretroviral regimen containing at least 3 drugs, that is, 2 nucleoside/nucleotide reverse-transcriptase inhibitors (NRTIs) in combination with an NNRTI or a PI, or 3 NRTIs. Antiretroviral regimens and the NRTI backbone were classified according to the preferred recommended regimens,4,5 that is, boosted atazanavir/r, lopinavir/r, efavirenz, nevirapine, zidovudine/lamivudine, abacavir/lamivudine, tenofovir/emtricitabine, or tenofovir/ lamivudine. We excluded individuals receiving investigational regimens containing CC-chemokine receptor 5 inhibitors or integrase inhibitors.

Treatment modification was defined as a switch or discontinu-
ation of CART within the first year. A switch to another regimen was defined as changing 1 or more drugs within 4 weeks after stopping CART. Discontinuation was defined as stopping any antiretroviral drug for at least 4 weeks. A switch from tenofovir-lamivudine to tenofovir-emtricitabine was not consid-
ered a treatment modification because it reflects the delayed availability of the new fixed formulation of tenofovir-emtricitabine in Switzerland in 2007. The main reason for treatment modification was classified as treatment failure, in-
tolerance and/or toxic effects, the patient’s choice, the physi-
cian’s decision, and other reasons. Information on drug con-
centration was used to investigate the occurrence of CNS adverse events in patients with available results.

Virologic suppression was defined as achieving HIV-RNA counts of less than 50 copies/mL at 12 months after starting CART.

STATISTICAL ANALYSIS

The primary end point was the time to the first treatment modi-
fication (ie, a switch to another antiretroviral regimen or dis-
continuation) during the first year after starting CART.

Basic sociodemographic characteristics, CD4 cell count, HIV viral load, and CART were compared using the χ2 test or Fisher exact test for categorical variables and the Mann-Whitney test for continuous variables. We used Kaplan-Meier curves to describe the cumulative incidence of treatment modification according to the most frequently recommended first-line antiretroviral regimens, and the curves were compared using log-rank tests. Risk factors of treatment switch or discontinu-
ation within the first year after starting CART were investigat-
eged using Cox proportional hazards models. All patients were censored at 1 year after starting CART if no treatment modifi-
cation or death had occurred.

All analyses were performed using commercially available software (Stata, version 9.2 for Windows; StataCorp, College Station, Texas).

STUDY POPULATION

Between January 1, 2005, and June 30, 2008, 1318 an-
tiretroviral-naive HIV-infected individuals participating in the SHCS started CART. Baseline characteristics according to the calendar year of starting CART are shown in Table 1. The median CD4 cell count at the start of CART increased from 198/µL (interquartile range [IQR], 107/µL-281/µL) in 2005 to 273/µL (186/µL-338/µL) in 2008 (P < .001), reflecting recent treatment guidance, whereas the proportion of patients with a prior AIDS-defining condition declined from 23.3% in 2005 to 10.7% in 2008 (P = .002). Although the proportion of patients starting a boosted PI-based regimen compared with an NNRTI-based regimen did not differ over time, once-daily regimens were increasingly used (37.9% in 2005 vs 62.0% in 2008; P < .001), reflecting the expand-
ing availability of new drugs and particularly formulations with a fixed combination of antiretrovirals.

**TREATMENT MODIFICATION DURING THE FIRST YEAR AFTER STARTING CART**

Of 1318 individuals starting CART, 391 (29.7%) modified their treatment (ie, switched or discontinued CART) during the first year, corresponding to 41.5 (95% confidence interval [CI], 37.6-45.8) treatment modifications per 100 person-years, half of them occurring within the first 3 months. The most frequent reasons for treatment modification were toxic effects (46.6%), followed by a physician's decision (22.8%), the patient's choice (16.9%), and treatment failure (5.9%). Overall, 297 individuals (76.0%) switched to a new antiretroviral regimen within 4 weeks after stopping CART, whereas 94 (24.0%) discontinued CART for at least 4 weeks. Among switchers, 48.8% modified the backbone and the third drug; 43.8%, the third drug only; and 6.4%, the backbone only. The most frequent reasons for treatment modification were toxic effects (46.6%), followed by a physician's decision (22.8%), the patient's choice (16.9%), and treatment failure (5.9%). Overall, 297 individuals (76.0%) switched to a new antiretroviral regimen within 4 weeks after stopping CART, whereas 94 (24.0%) discontinued CART for at least 4 weeks. Among switchers, 48.8% modified the backbone and the third drug; 43.8%, the third drug only; and 6.4%, the backbone only. The...
outcome in terms of virologic suppression to less than 50 copies/mL at 12 months was similar in individuals switched to another regimen compared with those who did not modify their treatment (87.9% vs 89.2%; \(P = .90\)). Similarly, no difference in the median CD4 cell count increase at 12 months was noted among switchers and individuals who did not change their treatment (169/µL vs 170/µL; \(P = .79\)). In contrast, patients discontinuing CART for longer than 4 weeks were less likely to achieve virologic suppression to less than 50 copies/mL (47.1%; \(P = .001\)) and immunologic recovery (median CD4 cell count increase of 107/µL; \(P = .002\)).

Individuals treated with zidovudine-lamivudine combined with lopinavir/r showed the highest rate of treatment modification (70.7 [95% CI, 57.7-86.8] treatment changes per 100 person-years), followed by tenofovir-emtricitabine with efavirenz (44.2 [26.2-74.7]) or lopinavir/r (44.1 [34.9-55.7]), abacavir-lamivudine with efavirenz (38.5 [24.6-60.3]), zidovudine-lamivudine with efavirenz (36.7 [24.2-55.7]), and tenofovir-emtricitabine with efavirenz (27.1 [21.7-33.7]) or atazanavir/r (24.1 [16.6-35.2]) (Figure, A). The probability of treatment modification tended to decrease for efavirenz and lopinavir/r and to increase for atazanavir/r and nevirapine during the study period. In a multivariate analysis (Table 2), the use of lopinavir/r and zidovudine-lamivudine was associated with higher treatment modification rates, as were female sex, nonwhite ethnicity, a prior AIDS-defining condition, and increasing baseline CD4 cell count.

TREATMENT MODIFICATION ATTRIBUTED TO DRUG INTOLERANCE AND/OR TOXICITY

During the first year of CART, 208 individuals (15.8%) modified their treatment because of drug

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**Figure.** Time to treatment modification during the first year after starting combination antiretroviral therapy (CART) according to the first-line antiretroviral regimen. A, Modifications for all reasons. B, Modifications because of toxic effects. ABC indicates abacavir sulfate; FTC, emtricitabine; 3TC, lamivudine; /r, boosted; TDF, tenofovir disoproxil fumarate; and ZDV, zidovudine.
intolerance and/or drug toxicity, corresponding to 22.4 (95% CI, 19.5-25.6) treatment modifications per 100 person-years, mostly (64.2%) during the first 3 months. No differences in the rate of treatment-limiting adverse events were observed during the study period ($P = .26$). Gastrointestinal tract intolerance was the most frequent toxic effect (28.9%), followed by hypersensitivity (18.3%), CNS adverse events (17.3%), and hepatic events (11.5%). The median time to treatment modification varied according to different toxic effects, ranging from 14 (IQR, 10-21) days for hypersensitivity to 66 (28-154) days for gastrointestinal tract intolerance, 72 (28-120) days for hepatic events, and 105 (50-228) days for CNS adverse events. Overall, 182 individuals (87.5%) switched to a new antiretroviral regimen, whereas 26 (12.5%) discontinued CART for at least 4 weeks. A large proportion of individuals achieved virologic suppression to less than 50 copies/mL at 12 months after starting CART regardless of treatment modification (85% vs 87%; $P = .56$) and the median increase in CD4 cell count was similar in both groups (166/µL vs 171/µL; $P = .94$). In contrast, only 58.2% of patients discontinuing CART for longer than 4 weeks achieved HIV-RNA suppression to less than 50 copies/mL at 12 months ($P < .001$) and showed a median CD4 cell count increase of 133/µL ($P = .02$).

In general, individuals starting an NNRTI-based regimen were less likely to modify their treatment compared with those treated with a PI ($P = .052$). The highest rate of treatment modification was noted among individuals starting zidovudine-lamivudine with lopinavir/r therapy (46.5 [95% CI, 36.0-60.0] treatment changes per 100 person-years), followed by tenofovir-emtricitabine with nevirapine therapy (32.1 [17.3-59.6]), zidovudine-lamivudine with efavirenz therapy (30.1 [18.7-48.5]), abacavir-lamivudine with efavirenz therapy (25.9 [15.1-44.7]), and tenofovir-emtricitabine with lopinavir/r therapy (15.1 [10.1-48.5]), efavirenz therapy (13.0 [9.5-17.9]), or atazanavir/r therapy (11.7 [6.8-20.2]) (Figure, B).

Efavirenz therapy was switched or discontinued mainly because of CNS adverse events (44.4%); lopinavir/r therapy, because of gastrointestinal tract intolerance (52.7%); and nevirapine therapy, after a hypersensitivity reaction (40.7%). The most frequent toxic effects related to the use of atazanavir/r were hepatic events (29.3%) and hypersensitivity (24.6%). In a multivariate analysis (Table 3), zidovudine-lamivudine (hazard ratio [HR], 2.71 [95% CI, 1.95-3.83]; $P < .001$), nevirapine (1.95 [1.01-3.81]; $P = .05$), concomitant treatment of opportunistic infections (2.24 [1.19-4.21]; $P = .01$), advanced age (1.21 [1.03-1.40] per 10-year increase; $P = .02$), female sex (1.68 [1.14-2.48]; $P = .009$), nonwhite ethnicity (1.71 [1.18-
Table 4. Treatment Modification During the First Year of CART According to Specific Toxic Effects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Gastrointestinal Tract Toxic Effect (n=80)</th>
<th>Hypersensitivity (n=38)</th>
<th>CNS Adverse Events (n=30)</th>
<th>Hepatic Events (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td>HR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Age, per 10-year increase</td>
<td>1.14 (0.86-1.52)</td>
<td>.36</td>
<td>1.22 (0.87-1.70)</td>
<td>.25</td>
</tr>
<tr>
<td>Female</td>
<td>1.29 (0.69-2.41)</td>
<td>.43</td>
<td>3.22 (1.61-6.45)</td>
<td>.001</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>2.20 (1.12-4.33)</td>
<td>.02</td>
<td>0.68 (0.30-1.52)</td>
<td>.35</td>
</tr>
<tr>
<td>CD4 cell count &gt;350/µL vs &lt;350/µL</td>
<td>4.12 (1.88-9.03)</td>
<td>&lt;.001</td>
<td>3.47 (1.29-9.33)</td>
<td>.01</td>
</tr>
<tr>
<td>HIV-RNA level, per log10 increase</td>
<td>1.23 (0.93-1.54)</td>
<td>.12</td>
<td>1.23 (0.89-1.68)</td>
<td>.21</td>
</tr>
<tr>
<td>Drug</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATV/r</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
<td>2.55 (1.01-6.42)</td>
</tr>
<tr>
<td>LPV/r</td>
<td>5.50 (2.67-11.3)</td>
<td>&lt;.001</td>
<td>0.48 (0.17-1.40)</td>
<td>.18</td>
</tr>
<tr>
<td>EFV</td>
<td>0.57 (0.12-2.35)</td>
<td>.53</td>
<td>1.05 (0.40-2.76)</td>
<td>.92</td>
</tr>
<tr>
<td>NVP</td>
<td>2.17 (0.58-8.16)</td>
<td>.36</td>
<td>3.33 (1.43-7.77)</td>
<td>.005</td>
</tr>
<tr>
<td>Backbone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF-FTC</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
<td>2.55 (1.01-6.42)</td>
</tr>
<tr>
<td>ZDV-3TC</td>
<td>2.19 (1.25-3.82)</td>
<td>.006</td>
<td>1.78 (0.83-3.80)</td>
<td>.14</td>
</tr>
<tr>
<td>ABC-3TC</td>
<td>0.71 (0.21-2.40)</td>
<td>.25</td>
<td>1.42 (0.56-3.64)</td>
<td>.46</td>
</tr>
<tr>
<td>Treatment for concomitant opportunistic infection</td>
<td>2.90 (0.78-6.76)</td>
<td>.13</td>
<td>3.16 (0.82-11.51)</td>
<td>.10</td>
</tr>
<tr>
<td>Calendar period</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007-2008 vs 2005-2006</td>
<td>0.82 (0.37-1.41)</td>
<td>.47</td>
<td>1.62 (0.83-3.17)</td>
<td>.16</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CNS, central nervous system; HR, hazard ratio. For other abbreviations, see Table 1.

*Adjusted for all variables listed in the table, based on multivariate analysis.

SPECIFIC DRUG INTOLERANCES AND TOXIC EFFECTS

Gastrointestinal Tract Intolerance

Gastrointestinal tract intolerance was the most frequent toxic effect, with 6.3 (95% CI, 4.9-8.1) treatment modifications per 100 person-years, mostly associated with the use of lopinavir/r and zidovudine-lamivudine. In a multivariate analysis, risk factors of gastrointestinal tract intolerance were lopinavir/r and zidovudine-lamivudine, nonwhite ethnicity, and baseline CD4 cell count of more than 350/µL (Table 4).

Hypersensitivity

Hypersensitivity was the main reason for 4.0 (95% CI, 2.9-5.5) treatment modifications per 100 person-years, mainly associated with the use of nevirapine. An increased risk of abacavir-related hypersensitivity was observed for the year 2005 (HR, 6.67 [95% CI, 1.34-33.01]; P=.02) but not thereafter, reflecting the introduction of the screening test for HLA-B*5701 in clinical practice. Hypersensitivity was more likely in women, in individuals with a baseline CD4 cell count of more than 350/µL, and in those receiving nevirapine (Table 4).

Hepatic Events

The rate of treatment-limiting hepatic event modification was 2.9 (95% CI 1.7-3.7) per 100 person-years, mainly associated with the use of atazanavir, which is known to cause elevation of indirect bilirubin levels. Treatment with atazanavir/r and comedication for opportunistic infection were independently associated with treatment modification coded as liver-related toxic effects (Table 4). Coinfection with hepatitis B or C virus did not increase the risk of treatment-related liver injury in this study.

CNS Adverse Events

The rate of treatment-limiting CNS adverse events was 3.8 (95% CI 2.7-5.2) per 100 person-years, clearly related to the use of efavirenz. In a multivariate analysis, treatment with efavirenz and female sex were independently associated with the occurrence of CNS adverse events (Table 4). In 196 patients with an available plasma drug concentration, higher efavirenz plasma levels were linked to higher treatment modification rates (P=.002). After adjustment for age, sex, ethnicity, and body mass index, efavirenz plasma level was the only factor associated with increased rates of treatment switch or discontinuation (P=.008).

COMMENT

This study, involving 1318 antiretroviral-naive HIV-infected individuals who started CART between January 1, 2005, and June 30, 2008, in a large cohort study, illustrates that drug toxicity remains a frequent prob-
lem in clinical practice, accounting for approximately half of all reasons for treatment switch or discontinuation during the first year of CART. Virologic and immunologic outcomes at 12 months were not impaired in individuals with treatment modification regardless of their reasons for change, suggesting that most people can achieve successful suppression using alternative antiretroviral regimens. Further findings of this study describe the toxicity-dependent time for treatment modification being the shortest for hypersensitivity and the longest for CNS adverse events. Also, a comparison of regimen-related toxic effects showed that the rate of therapy switch or discontinuation was lowest for patients treated with tenofovir-emtricitabine combined with atazanavir/r.

These findings are consistent with those from previous SHCS studies7,27 and other cohort studies,8,10-12,17,28-30 underlining the importance of close monitoring and adequate management of adverse effects and drug-drug interactions for the durability of CART in clinical practice. The discrepancy with lower treatment discontinuation rates (<10%) for new antiretroviral drugs reported in randomized clinical trials,14,15 probably reflects a selection bias because individuals with severe comorbidities are often excluded from clinical trials. On the other hand, the broad availability of new drugs with the possibility of once-daily dosing,31-33 and genetic factors influencing the pharmacokinetics of specific drugs and thus their plasma levels,18,21,32 also as suggested by the high proportion of patients switched to another antiretroviral regimen in our study. Among antiretroviral drugs, boosted lopinavir and zidovudine-lamivudine therapies were most frequently switched or discontinued during the first year of CART. No differences were observed between newer regimens, that is, tenofovir-emtricitabine combined with efavirenz or atazanavir/r, or abacavir-lamivudine combined with efavirenz, suggesting that these first-line regimens are suitable for long-term use.

In our study, women and individuals of nonwhite ethnicity were more likely to modify their antiretroviral treatment because of drug toxicity or intolerance. This may be explained by biological differences between the sexes and genetic factors influencing the pharmacokinetics of specific drugs and thus their plasma levels.19,21,32 Also, sociocultural barriers leading to a different perception of drug-related adverse events, as described among vulnerable populations, may play a role.21,28,29,33 Specific genetic tests can promptly influence treatment modification, as demonstrated in our study by the decreasing discontinuation rates of abacavir therapy after the introduction of screening for UGT1A1*5701.35

As previously reported,7 higher baseline CD4 cell counts were associated with increased rates of treatment discontinuation, frequently without switching to alternative drugs, suggesting a lower motivation to continue an antiretroviral regimen causing adverse effects in patients with less urgent indication for CART. On the other hand, patients who were treated for a concomitant opportunistic infection (cytomegalovirus, toxoplasmosis, Pneumocystis jiroveci pneumonia, tuberculosis, or atypical mycobacteria) were more likely to modify their treatment as a result of drug-drug interactions and cumulative drug toxicity. In older individuals, a higher incidence of toxic effects may reflect altered pharmacokinetics, impaired drug metabolism, and frequent comedication with a potential for drug-drug interactions. Detailed data on comedication, particularly the use of psychotropic and over-the-counter drugs, were not available for the present analysis; therefore, the confounding role of drug-drug interactions in treatment modification could not be fully assessed. Nevertheless, a recent study of the SHCS on the prevalence and clinical relevance of drug-drug interactions in HIV-infected individuals reported no significant influence on treatment change rates in patients with drug-drug interactions.35 Coinfection with hepatitis B or C virus was not associated with a higher risk of toxic effects from CART in our study. This is in contrast to data from earlier studies,12,17 possibly because of different antiretroviral drugs being used more recently; for example, in our study a very low proportion of patients were treated with didanosine or stavudine, which have been linked to liver injury.

Individuals starting lopinavir/r combined with zidovudine-lamivudine therapy and those with higher CD4 cell counts and therefore less symptomatic HIV disease were at highest risk of gastrointestinal tract intolerance that may compromise quality of life and lead to poor treatment adherence. This is in contrast to other cohort studies,8,36 in which gastrointestinal tract adverse events tended to be more common in people with lower CD4 cell counts. This difference may be explained by the higher proportion of patients with advanced HIV disease in earlier studies, where misclassification of gastrointestinal tract intolerance might have occurred because diarrhea, dysphagia, and weight loss are frequently associated with opportunistic infections.37 A hypersensitivity reaction was most likely in women with a higher baseline CD4 cell count who were treated with nevirapine. Severe hepatic events ranging from skin rash to Stevens-Johnson syndrome have been observed during the first weeks of treatment when nevirapine therapy was initiated in antiretroviral-naive women with a CD4 cell count of more than 250/µL.38,39 For these patients, alternative regimens should be chosen.4 Treatment-limiting hepatic events were mainly noted in individuals receiving atazanavir/r and a comedication. Atazanavir is known to cause reversible elevation of unconjugated bilirubin levels by competitive inhibition of the uridine diphosphate glucuronosyltransferase UGT1A1 in up to 50% of patients. Jaundice is more likely to develop in individuals homozygous for the UGT1A1*28 allele.40 In this context, treatment modification was probably related to the occurrence of jaundice and not to liver injury. However, the need of comedication, particularly concomitant treatment of opportunistic infections, may cause drug-drug interactions, leading to an increase in transaminase levels and thus treatment modification.41,42 Finally, CNS adverse events were linked to an efavirenz-containing regimen and were more frequently reported by women. However, in 196 individuals with available efavirenz plasma concentrations, after adjustment for age, sex, ethnicity, and body mass index, the efavirenz plasma level was the only factor associated with higher modification rates, suggesting that sex differences result from different drug concentrations and that women may benefit from closer monitoring and dose adjustment of efavirenz.20

The strengths of this study were the high number of patients treated with newer antiretroviral regimens according to recent guidelines and the availability of co-
medication data that included treatment of opportunistic infection and use of cardiovascular drugs. We acknowledge some limitations. Misclassification of the reason for treatment modification may have occurred because many factors may play a role in decision making. In particular, no code for treatment simplification exists in the SHCS as a reason for stopping a specific drug therapy, although these individuals have probably received codes indicating the reason as being the patient’s choice or the physician’s decision. Toxic effects of CART were investigated by the occurrence of treatment modification, but alterations in laboratory variables (renal and liver function and bilirubin level) were not checked. Moreover, some adverse events may be difficult for patients to understand and report. It is therefore possible that the overall occurrence of drug-related adverse effects has been underestimated. As stated, information on comedication was not complete because information on psychotropic and over-the-counter drugs was not collected in the SHCS database. In addition, data on treatment adherence were not considered for the present analysis. Also, therapeutic drug monitoring was not performed routinely, except for special indications, mainly if treatment toxicity or treatment nonadherence was clinically suspected.

In conclusion, high rates of CART switch remain a major issue in clinical practice. The availability of different treatment options may trigger CART modification within the first weeks and months. If treatment is modified, this is done early and, as shown in our study, does not compromise CART outcome. Further research should address whether, with wider testing of toxicity-related factors (e.g., genes associated with toxicity), first-line treatment regimens will be more robust in terms of durability.

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Correspondence: Manuel Battegay, MD, Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland (mbattegay@uhbs.ch).

Author Contributions: Dr Battegay had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Elzi, Furrer, Ledergerber, and Battegay. Acquisition of data: Elzi, Marzolini, Furrer, Cavassini, Hirschel, Vernazza, Bernasconi, Weber, and Battegay. Analysis and interpretation of data: Elzi, Marzolini, Furrer, Ledergerber, Weber, and Battegay. Drafting of the manuscript: Elzi and Battegay. Critical revision of the manuscript for important intellectual content: Elzi, Marzolini, Furrer, Ledergerber, Cavassini, Hirschel, Vernazza, Bernasconi, Weber, and Battegay. Administrative, technical, and material support: Elzi, Cavassini, Hirschel, Vernazza, Bernasconi, and Battegay. Supervision: Elzi and Battegay.

SHCS Group Members: Manuel Battegay, MD, University Hospital Basel, Basel; Enos Bernasconi, MD, Regional Hospital Lugano, Lugano; Jürg Boni, MD, Institute of Medical Virology, Zurich; Heiner C. Bucher, MD, MPH, Basel Institute for Clinical Epidemiology, Basel; Philippe Bürgisser, MD, University Hospital Lausanne, Lausanne; Alexandra Calmy, MD, University Hospital Geneva, Geneva; Sandro Cattacin, MD, University of Geneva, Geneva; Matthias Cavassini, MD, University Hospital Lausanne; Rolf Dubs, MD, University Hospital Zurich, Zurich; Matthias Egger, MD, PhD, University of Bern, Bern; Luigia Elzi, MD, MSc, University Hospital Basel; Marek Fischer, MD, University Hospital Zurich; Markus Flepp, MD, Klinik im Park, Zurich; Adriano Fontana, MD, University Hospital Zurich; Patrick Francioli, MD (President of the SHCS), University Hospital Lausanne; Hansjakob Furrer, MD (Chairman of the Clinical and Laboratory Committee), University Hospital Bern and University of Bern; Christoph A. Fux, MD, University Hospital Bern and University of Bern; Meri Gorgievski, MD, University of Bern; Huldrych Günthard, MD (Chairman of the Scientific Board), University Hospital Zurich; Hans H. Hirsch, MD, MSc, University Hospital Basel and University of Basel; Bernard Hirschel, MD, University Hospital Geneva; Irene Hosli, MD, University Hospital Basel; Christian Kahler, MD, Regional Hospital St Gallen, St Gallen; Laurent Kaiser, MD, University Hospital Geneva; Urs Karrer, MD, University Hospital Zurich; Christian Kind, MD, University Children’s Hospital, St Gallen; Thomas Klimkait, PhD, University of Basel; Bruno Ledergerber, PhD, University Hospital Zurich; Gladys Martinetti, MD, Institute of Microbiology, Bellinzona; Begona Martinez de Tejada, MD, University Hospital Geneva; Nicolas Müller, MD, University Hospital Zurich; David Nadal, MD, University Children’s Hospital, Zurich; Milos Opravil, MD, Hirsländer Clinich Schachen, Aarau; Fred Paccoud, MD, University Hospital Lausanne; Giuseppe Pantaleo, MD, University Hospital Lausanne; Sandro Cattacin, MD, University Hospital Zurich; Sandro Cattacin, MD, University Hospital Zurich; Marco Schmid, MD, University Hospital Zurich; Ursula Schmid, MD, Regional Hospital St Gallen; Rainer Weber, MD, University Hospital Zurich; Martin Rickenbach, MD (Head of Data Center), University Hospital Lausanne; Christoph Rudin, MD (Chairman of the Mother and Child Sub-study), University Children’s Hospital, Basel; Patrick Schmid, MD, Regional Hospital St Gallen; Detlev Schultze, MD; Institute of Microbiology, St Gallen; Jörg Schüpbach, MD, Swiss National Center for Retroviruses, Zurich; Roberto Speck, MD, University Hospital Zurich; Patrick Taffet, PhD, University Hospital Lausanne; Philipp Tarr, MD, University Hospital Bruderholz, Bruderholz; Amalio Telenti, MD, PhD, University Hospital Lausanne; Alexandra Trkola, PhD, University of Zurich, Zurich; Pietro Vernazza, MD, Regional Hospital St Gallen; Rainer Weber, MD, University Hospital Zurich; and Sabine Yerly, MD, University Hospital Geneva.

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