

Switching from protease inhibitors to efavirenz: differences in efficacy and tolerance among risk groups: a case–control study from the Swiss HIV Cohort

Bernard Hirschel^a, Markus Flepp^b, Heiner C. Bucher^c,
Claudine Zellweger^d, Amalio Telenti^e, Thomas Wagners^f,
Enos Bernasconi^g, Bruno Ledergerber^b, and the Swiss HIV Cohort*

Objectives: Many patients have simplified their therapy by replacing protease inhibitors (PI) with efavirenz. In a large cohort study representative of clinical practice, we compared outcomes in patients who replaced PI with efavirenz (switchers), with patients who continued on PI (non-switchers). We investigated the likelihood of virological failure in switchers and non-switchers, and the tolerance of efavirenz-containing regimens in different transmission risk groups.

Design, setting, and methods: Using the database of the Swiss HIV Cohort Study, we identified patients who switched from PI-containing to efavirenz-containing highly active antiretroviral therapy for reasons of tolerance, toxicity, or convenience. Switchers were matched to non-switchers on the basis of calendar time, CD4 cell count, and viral load.

Results: The probability of virological failure was less in patients who switched to efavirenz values after one year: 9.4% [95% confidence interval (CI) 5.5–15.9] versus 27.2% (95% CI 21.5–34.1), odds ratio (OR) for failure 0.34. The effect was more pronounced when injection drug users (IDU) were omitted from the analysis (OR 0.19, 95% CI 0.09–0.43); it was absent in IDU (OR 0.95, 95% CI 0.44–2.04). IDU stopped efavirenz more frequently during the first 2 months of treatment than non-IDU [22.6% (95% CI 11.5–41.6) versus 6.6% (95% CI 3.6–11.8) at 2 months]. No difference between IDU and non-IDU was evident when the frequency of stopping indinavir or nelfinavir was measured.

Conclusion: Switchers had less virological failure and less chance of further treatment changes than non-switchers. However, efavirenz was less successful in IDU than in other transmission categories.

© 2002 Lippincott Williams & Wilkins

AIDS 2002, **16**:381–385

Keywords: HAART, efavirenz, cohort study, matched case-control study, HIV, HIV protease inhibitors

From the ^aDivision of Infectious Diseases, Geneva University Hospital, CH-1211 Geneva 14, Switzerland; ^bDivision of Infectious Diseases, University Hospital, Zurich, Switzerland; ^cBasel HIV Research Center, Medizinische Universitäts-Poliklinik, Kantonsspital, Basel, Switzerland; ^dDivision of Infectious Diseases, Inselspital, CH-3000 Bern, Switzerland; ^eDivision des Maladies Infectieuses, Centre Hospitalier Universitaire Vaudois, 1011 Lausanne, Switzerland; ^fDivision of Infectious Diseases, Kantonsspital, St Gallen, Switzerland; and ^gOspedale Civico, Lugano, Switzerland.

*For members of the Swiss HIV Cohort see Appendix.

Correspondence to: Bernard Hirschel, Division of Infectious Diseases, Geneva University Hospital, CH-1211 Geneva 14, Switzerland.

E-mail: hirschel@dminov1.hcuge.ch

Received: 10 July 2001; revised: 27 July 2001; accepted: 13 September 2001.

Introduction

Combination therapy including protease inhibitors (PI) reduces HIV-related morbidity and mortality [1,2]. Non-nucleoside reverse transcriptase inhibitors represent an alternative to PI. When used in patients who had not been treated with antiretroviral medication before, the combination of efavirenz, zidovudine and lamivudine was of comparable or greater efficacy in lowering viral load, than the comparative regimen with the PI indinavir, zidovudine and lamivudine [3].

Many patients, for reasons of convenience and to avoid side-effects, have switched from PI-based therapy to non-nucleoside reverse transcriptase inhibitors. Such was certainly the case among patients of the Swiss HIV Cohort Study (SHCS). Data from cohort studies can provide information on the relative merits of competing therapies. They have the advantage of being closer to a 'real life' situation by avoiding the selection inherent in recruiting patients for clinical trials.

In the present paper, we have compared outcomes in patients who switched to efavirenz for reasons unrelated to virological failure, with patients who continued their PI-based regimen.

Patient selection and methods

The SHCS currently includes more than 11 000 patients who are followed every 6 months at seven centres in Switzerland [4]. Viral loads (HIV-Monitor Test, Roche, Basel, Switzerland) and CD4 cell counts are determined, on average every 3 months. The reasons for treatment changes are recorded, according to predetermined categories: 'virological failure', 'toxicity/tolerance', 'unknown', and 'other'. The instructions specify that treatment changes for reasons of convenience, or patient's or physician's preference, must be scored as 'other'.

In order to find patients who had switched from PI to efavirenz for reasons unrelated to virological failure, we searched the March 2001 database of the SHCS for individuals fulfilling four conditions: (i) they had to have taken indinavir, ritonavir or nelfinavir in a previous regimen; (ii) they had to discontinue PI at the start of efavirenz treatment; (iii) their HIV-1-RNA level at the time of the switch to efavirenz had to be below 400 copies/ml; and (iv) the stated reason for switching therapy had to be 'tolerance/toxicity' or 'other', as opposed to 'virological failure' or 'unknown'. We found 191 patients who fulfilled these conditions.

The 191 patients (the 'switchers') were matched with 'non-switchers', using the following criteria: (i) HIV-

RNA level detectable but less than 400 copies/ml, undetectable, meaning usually less than 50 copies/ml; (ii) treatment-naïve before starting highly active antiretroviral therapy (HAART) (yes/no); (iii) calendar time of switch (± 4 months); (iv) CD4 cell count at matching date ($\pm 20\%$); and (v) age ($\pm 20\%$). Each switcher was matched to two non-switchers. Successful matching was accomplished for 184 switchers (96% of all switchers identified) with 368 non-switchers.

We analysed the following endpoints by means of Kaplan-Meier life-table methods and Cox proportional hazards regression: (i) the risk of a single HIV-1-RNA determination above 1000 copies/ml after the date of switching or the matching date in non-switchers; (ii) the probability of any treatment changes after the date of switching or the matching date in non-switchers; (iii) the probability of stopping efavirenz after the date of switching; and (iv) the probability of stopping indinavir or nelfinavir after starting these drugs in all patients.

All reported *P* values are two-sided. We used Stata software (version 7.0; Stata Corp., College Station, TX, USA) for statistical analyses.

Results

Matching ensured that the 184 switchers and 368 non-switchers were similar with regard to sex (29.4% female), age (median 40 versus 38 years), CD4 cell count (median 503 versus 486 cells/mm³), matching date (both medians 08/99), duration of follow-up (0.93 versus 0.85 years), and HIV-RNA levels at the time of switch, (33.2% detectable between 50 and 400 copies/ml, 9.2% undetectable below 400 copies/ml, and 57.6% undetectable below 50 copies/ml), and the proportion who were treatment naïve before HAART (25.0%). Switchers and non-switchers were also similar with regard to the duration of antiretroviral therapy before the date of switching (or the matching date in non-switchers, median 2.58 versus 2.47 years, *P* = 0.41 by the Wilcoxon rank-sum test), and viral load before antiretroviral therapy (4.73 and 4.66 logs, *P* = 0.75).

Intravenous drug users (IDU) were under-represented among switchers (16.9 versus 30.4%, *P* < 0.001), whereas men having sex with men were over-represented.

Fig. 1 shows the probability of developing virological failure (defined as a value of HIV-RNA above 1000 copies/ml). In this figure, switchers who abandoned efavirenz ('backswitchers') and non-switchers who later changed to efavirenz ('late switchers') were censored at the time of treatment change. The prob-

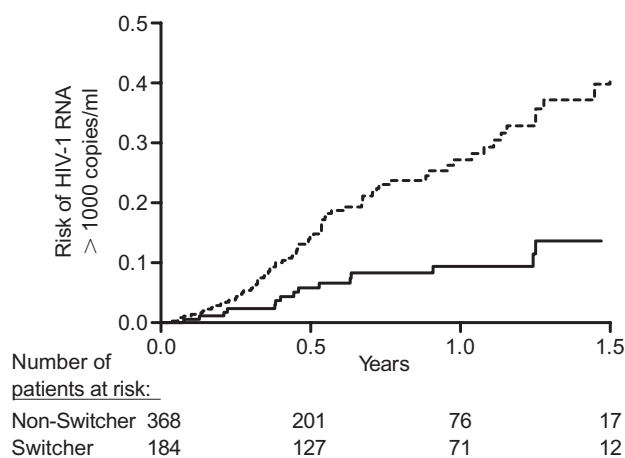


Fig. 1. Probability of virological failure. (See text for details). - - - Non-switcher; — switcher. Log rank test $P < 0.0001$.

ability of experiencing virological failure was less in patients who switched to efavirenz (values after one year: 9.4% [95% confidence interval (CI) 5.5–15.9] versus 27.2% (95% CI 21.5–34.1).

Using univariate Cox regression analysis, we determined that compared with non-switchers, switchers had an odds ratio (OR) for viral failure of 0.33 (95% CI 0.19–0.57). The effect was even more pronounced when IDU were omitted from the analysis (OR 0.19, 95% CI 0.09–0.43); it was absent in IDU (OR 0.95, 95% CI 0.44–2.04). In patients who had received antiretroviral drugs before HAART the OR was 0.29 (95% CI 0.15–0.57), and in those who were antiretroviral naive before HAART the OR was 0.44 (95% CI 0.18–1.1). The analysis was repeated, but without censoring post-switch treatment changes. The risk of treatment failure remained significantly smaller in the switchers (OR 0.47, 95% CI 0.29–0.77).

As expected for a population with well-controlled viraemia and relatively elevated CD4 cell counts,

clinical events were rare (a total of five CDC class B or C [5] events, or deaths in switchers, compared with 11 in non-switchers, $P > 0.1$). Neither were there any statistically significant differences in CD4 cell counts between switchers and non-switchers at any time until 1.5 years after the matching date.

We determined the probability of further changes in treatment, in switchers and non-switchers. After a period of approximately 2 months, when both curves overlap, switchers were less likely to experience further treatment changes than non-switchers: 40% (95% CI 32–49) in switchers, and 60% (95% CI 54–67) in non-switchers after one year. In the univariate Cox model the respective odds ratio was 0.54 (95% CI 0.41–0.71, $P < 0.001$). This may be a reflection of the toxicities of efavirenz, which usually occur during the first few weeks of treatment, but weaken thereafter [6].

Fig. 2a compares, among switchers, those in the IDU transmission category and all others. The probability of discontinuing efavirenz is greater in the IDU group, particularly during the first month ($P < 0.01$). Fig. 2b compares the discontinuation rate of the PI, nelfinavir and indinavir, in all patients (switchers and non-switchers), again comparing IDU with non-IDU. A non-significant trend towards less discontinuation in IDU is apparent ($P = 0.08$). Taken together, Fig. 2a and b suggest that intravenous drug users discontinue efavirenz more frequently as do other transmission categories, whereas no such difference is apparent for PI.

Discussion

The SHCS collects data on a large proportion of HIV-positive patients in Switzerland. These data reflect prevailing medical practice; in particular, no attempt is made to standardize treatment. Patients in the study represent the HIV-infected population in Switzerland. In December 2000, 25.6% were in the intravenous

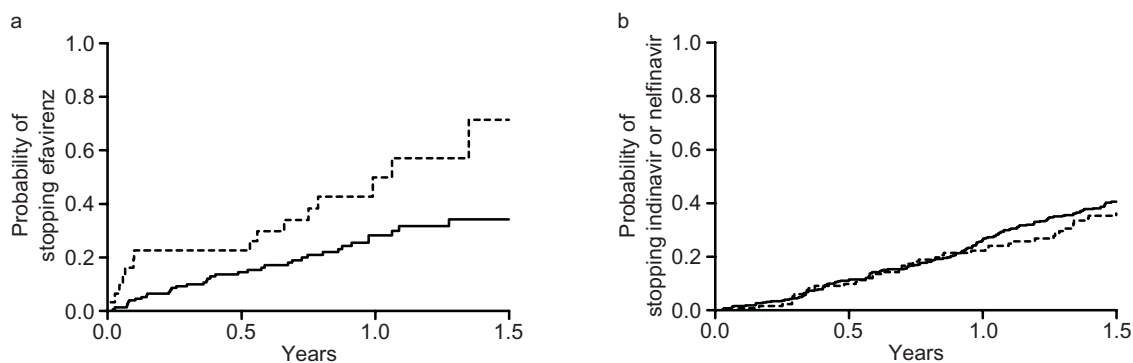


Fig. 2. Probability of stopping efavirenz (a) and protease inhibitors (b). (See text for details). - - - Injection drug users; — non-injection drug users. Log rank test (a) $P = 0.010$; (b) $P = 0.081$.

drug use transmission category. This is in marked contrast to prospective randomized studies in which few intravenous drug users participate (for instance 10% in the largest published randomized trial of efavirenz [3]).

Many patients have switched from PI to efavirenz, since this drug was introduced to Switzerland in 1999. Using very stringent criteria, we selected those patients who switched for reasons of convenience or tolerance, as opposed to those who switched because PI-containing regimens failed to suppress the viral load. We then matched the switchers with non-switchers, taking care to control for the variables expected to influence outcome, such as viral load, CD4 cell counts, and antiretroviral treatment before HAART. Remarkably, 75% of patients had not been antiretroviral treatment naive before HAART.

A comparison of switchers with non-switchers suggests that both the virological efficacy and the tolerability of efavirenz-containing regimens was satisfactory. Indeed, switchers had a lesser probability of experiencing virological failure (defined as a viral load greater than 1000 copies/ml) than non-switchers, and this effect was particularly strong when the analysis was restricted to transmission categories other than IDU (odds ratio for failure 0.19). A comparison of the probability of further treatment changes suggested that the efavirenz-containing combination was more likely to be continued, in particular after an initial period of 2 months.

In comparison with other transmission categories, IDU were under-represented among switchers. We do not know why this would be so, but speculate that physicians hesitated to introduce efavirenz in IDU because of a perception that its central nervous system effects would be less well tolerated in IDU than in other patients, or that efavirenz interferes with methadone substitution [7]. We found that the probability of stopping efavirenz during the first 2 months was much greater in IDU, whereas no such difference was apparent with PI (see Fig. 2a and b). The reasons cited by the IDU for stopping efavirenz were 'intolerance or side-effects': 73%, and 'other': 27%. This provides strong circumstantial evidence that the perception about the decreased tolerance of efavirenz by IDU is indeed true.

Many patients on PI desire to simplify their therapy. Decreasing the number of drugs to two or one leads to an unacceptable failure rate [8]. However, combining three drugs in a lesser number of pills might be possible, for instance by using the combination of abacavir, lamivudine, and zidovudine [9]. This combination is as active as continuing PI in patients who had been antiretroviral naive before HAART, but has a high failure rate in patients who had received zidovu-

dine or lamivudine before HAART. Our data suggest that replacing PI by efavirenz is another excellent alternative, especially in transmission categories other than IDU, and in patients who had already been antiretroviral experienced before HAART.

Acknowledgements

The authors would like to thank the numerous practitioners for their continuous support of the SHCS, the study nurses for their dedicated work, Professor Luc Perrin for stimulating discussion, and last but not at least the patients for participating in a study without direct benefit for themselves.

Sponsorship: This study was financed in the framework of the Swiss HIV Cohort Study, supported by the Swiss National Science Foundation (grant no 3345-062041).

References

1. Ledergerber B, Egger M, Opravil M, *et al.* **Clinical progression and virological failure on highly active antiretroviral therapy in HIV-1 patients: a prospective cohort study.** *Swiss HIV Cohort Study. Lancet* 1999, **353**:863–868.
2. Carr A, Samaras K, Thorisdottir A, Kaufmann GR, Chisholm DJ, Cooper DA. **Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study.** *Lancet* 1999, **353**:2093–2099.
3. Staszewski S, Morales-Ramirez J, Tashima KT, *et al.* **Study. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults.** *N Engl J Med* 1999, **341**:1865–1873.
4. Sudre P, Rickenbach M, Taffé P, Janin P, Volkart AC, Francioli P, and the Swiss HIV Cohort Study. **Clinical epidemiology and research on HIV infection in Switzerland: the Swiss HIV Cohort Study 1988–2000.** *Schweiz Med Wochenschr* 2000, **130**: 1493–1500.
5. Centers for Disease Control. **1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults.** *MMWR* 1992, **41**:1–19.
6. Adkins JC, Noble S. **Efavirenz.** *Drugs* 1998, **56**:1055–1064.
7. Marzolini C, Troillet N, Telenti A, Baumann P, Decosterd LA, Eap CB. **Efavirenz decreases methadone blood concentrations.** *AIDS* 2000, **14**:1291–1292.
8. Pialoux G, Raffi F, Brun-Vezinet F, *et al.* **A randomized trial of three maintenance regimens given after three months of induction therapy with zidovudine, lamivudine, and indinavir in previously untreated HIV-1-infected patients.** *N Engl J Med* 1998, **339**:1269–1276.
9. Opravil M, Hirschel B, Lazzarin A, *et al.* **Simplified maintenance therapy with abacavir + lamivudine + zidovudine in patients with HAART-induced long-term suppression of HIV-1 RNA.** *J Infect Dis* 2002 (in press).

Appendix

The members of the Swiss HIV Cohort Study are: M. Bategay (Chairman of the Scientific Board), E. Bernasconi, H. Bucher, Ph. Bürgisser, M. Egger, P. Erb, W. Fierz, M. Flepp (Chairman of the Clinical

and Laboratory Committee), P. Francioli (President of the SHCS, Centre Hospitalier Universitaire Vaudois, CH-1011-Lausanne), H.J. Furrer, M. Gorgievski, H. Günthard, P. Grob, B. Hirschel, Th. Klimkait, B. Ledergerber, M. Opravil, F. Paccaud, G. Pantaleo,

L. Perrin, J.-C. Piffaretti, M. Rickenbach (Head of Data Center), C. Rudin, P. Sudre, V. Schiffer, J. Schupbach, A. Telenti, P. Vernazza, Th. Wagners, R. Weber. See <http://www.shcs.ch> for up-to-date information on the Swiss HIV Cohort Study.