

Switch to etravirine for HIV-positive patients receiving statin treatment: a prospective study

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ABSTRACT

Background Lifestyle changes and statins are the cornerstones in management of dyslipidaemia in patients with HIV infection. Replacement of an antiretroviral therapy (ART) component is a proposed therapeutic strategy to reduce cardiovascular risk. In dyslipidaemic patients with HIV infection, we assessed the efficacy of replacing boosted protease inhibitor (bPI) or efavirenz (EFV) by etravirine (ETR) as an alternative to statin therapy.

Materials and methods A prospective, open-label, multicentre, 12-week study of patients with HIV infection on ART including bPI or EFV, and statin treatment. Four weeks after statin interruption, bPI or EFV was switched to ETR (400 mg, 8 weeks) if serum low-density lipoprotein cholesterol (LDL-C) was ≥ 3 mM. The primary endpoint was the proportion of patients on ETR with no indication for statin treatment at study completion. Serum levels of HIV RNA, lipids and biomarkers of cardiovascular disease were also measured. (ClinicalTrials.gov: NCT01543035).

Results The 31 included patients had a HIV-1 RNA < 50 copies/mL (median age, 52 years; median CD4, 709 cell/mL; median LDL-C, 2.89 mM), 68% were on EFV, and 32% were on bPI. At week 4, 27 patients switched to ETR. At study completion, 15 patients (56%) on ETR did not qualify for statin treatment. After the ETR switch, serum levels of the cardiovascular biomarkers sICAM and MCP1/CCL2 decreased by 11.2% and 18.9%, respectively, and those of CCL5/RANTES and tissue inhibitor of metalloproteinase-1 increased by 14.3% and 13.4%, respectively, indicating reduced cardiovascular risk. There were no notable treatment-related adverse events.

Conclusions Replacing bPI or EFV by ETR is a viable strategy to obviate primary prevention statin treatment.

Keywords Cardiovascular disease biomarkers, dyslipidaemia, etravirine, HIV, statins.

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Introduction

Dyslipidaemia is common among HIV-infected individuals and has been associated with the HIV infection itself and antiretroviral treatment-induced metabolic disorders [1–6].

Dyslipidaemia is associated with the development of cardiovascular disease in patients with HIV infection on antiretroviral therapy (ART) [7–9]. Moreover, plasma levels of several markers of cardiovascular disease are positively associated

with HIV RNA replication [10]. Therefore, patients with HIV infection are often prescribed lipid-lowering drugs, such as statins, for primary prevention of cardiovascular disease. However, the relationship between specific antiretroviral drugs, known risk factors and biological markers is unclear.

The replacement of antiretroviral drugs rather than adjunction of an antilipidaemic drug is a recommended strategy in the 2013 European AIDS Clinical Society (EACS) guidelines [11], considering the potential risk of drug–drug interactions

1 between ART and statins [12] and the importance of reducing
2 pill burden. This treatment strategy might also decrease the
3 levels of atherosclerotic inflammatory biomarkers.

4 We have, together with other groups, previously highlighted
5 the beneficial effect of etravirine (ETR) on lipid profile [13,14],
6 and we aimed to investigate the efficacy and safety of replacing
7 ritonavir-boosted lopinavir (LPV/r), atazanavir (ATZ/r), dar-
8 unavir (DRV/r) or efavirenz (EFV) with etravirine (ETR) as a
9 strategy to obviate statin treatment in patients with suppressed
10 viraemia (HIV RNA below 50 copies/mL) and no history of
11 cardiovascular events.

12 In addition, we assessed the effects of this treatment on
13 serum levels of biomarkers of endothelial activation, pro-ath-
14 erosclerotic inflammatory cytokines and chemokines, adipocy-
15 tokines, and metalloproteases and their inhibitors.

17 Subjects and methods

19 Study design and population

20 This was a 12-week prospective, open-label, multicentre, phase
21 III study carried out in six sites participating in the Swiss HIV
22 Cohort Study (SHCS) in Switzerland between February 2012
23 and December 2013. The study was approved by the ethics
24 committee of each site and conducted according to good clinical
25 practices [15] and applicable laws and regulations. All
26 patients provided informed consent (ClinicalTrials.gov identifier,
27 NCT01543035).

28 Eligible for study inclusion were HIV-infected adults (18–
29 70 years old) with stable, undetectable HIV-1 RNA (< 50 cop-
30 ies/mL for at least the 3 previous months) on combined ART
31 with boosted ATZ, DRV, LPV or EFV, and on statin therapy for
32 primary prevention since at least 3 months, with no history of
33 hyperlipidaemia before ART initiation. Noninclusion criteria
34 were as follows: > 20% 10-year cardiovascular risk using the
35 Swiss Atherosclerosis Association GSLA score [16], use of sta-
36 tins before ART initiation, diabetes and history of drug resis-
37 tance mutation (except for K103N).

38 At baseline, all participants interrupted their statin treatment
39 **4** for 4 weeks. At week 4, patients with serum levels of low-
40 density lipoprotein cholesterol (LDL-C) \geq 3 mM, that is those
41 qualifying for continued statin treatment, were switched from
42 the ongoing bPI or EFV to ETR, 400 mg (2 tablets of 200 mg)
43 once daily for 8 weeks, while patients who had lower levels of
44 LDL-C continued the ongoing ART without statin treatment.
45 All patients were followed up for the subsequent 8 weeks, with
46 an optional visit 2 weeks after the ETR switch to assess possible
47 side effects. We performed laboratory biochemical tests for
48 lipid profile, liver function, glycaemia, HIV-1 RNA and
49 cardiovascular risk profile, as well as clinical assessment at
50 baseline (week 0), switch to ETR (week 4) and end of study
51 (week 12).

Outcomes

The primary endpoint of the study was the proportion of
patients not qualifying for statin treatment 8 weeks after the
ETR switch, that is at study completion (week 12). The need for
statin treatment was determined according to the 2013 treat-
ment guidelines of the EACS for patients with low-to-moderate
risk of cardiovascular disease on the basis of the Framingham
Hard CHD Score [17] and the Swiss cardiovascular risk score
GSLA. In a post hoc analysis, we applied the recently issued
2013 ACC/AHA guidelines (10-year atherosclerosis and car-
diovascular risk) [18].

Secondary endpoints included changes in serum level of
lipids and biomarkers relative to baseline at week 4 for all
included patients; changes relative to week 4 at the end of
study were determined for patients who switched to ETR. We
also recorded serum levels of HIV RNA at baseline and study
completion.

Biochemical determinations

Lipid profile determination was performed centrally (LAP
Number 4658701, AU-ID 1190700; Covance Laboratory, Meyrin,
Switzerland). LDL-C was calculated with the Friedwald for-
mula or measured directly if triglycerides (TG) were above
4.52 mM. All other tests were performed locally in quality
controlled, SHCS (Swiss HIV Cohort Study, www.shcs.ch)-
affiliated laboratories. All the above tests were performed at
week 0, 4 and 12. HIV-1 RNA was measured using Roche
COBAS TaqMan HIV-1 test version 2.0 (COBAS AmpliPrep;
Roche Diagnostic, Basel, Switzerland) and was considered
undetectable if below 50 copies/mL.

Inflammatory markers were measured retrospectively, at
study completion, at the Department of Laboratory Medi-
cine, Cardiology Laboratory of the University Hospital of
Geneva.

We performed batch measurements using colorimetric **5**
enzyme-linked immunosorbent assay (ELISA) following man-
ufacturer's instructions for serum soluble intercellular adhesion
molecule-1 (sICAM-1), soluble vascular cell adhesion molecu-
le-1 (sVCAM-1), interleukin-6 (IL-6), monocyte chemoattractant
protein-1 (MCP1)/CCL2 and tumour necrosis factor-alpha
(TNF-alpha; all from BioLegend, San Diego, CA, USA); for tis-
sue inhibitor of metalloproteinase-1 (TIMP-1), TIMP-2, matrix
metalloproteinase-8 (MMP-8), macrophage inflammatory
protein-1 (MIP-1) beta/CCL4, regulated upon activation, nor-
mal T-cell expressed and secreted (RANTES)/CCL5, E-selectin,
L-selectin, C-reactive protein (CRP) and leptin (all from Ray-
Biotech Inc., Norcross, GA, USA); for serum tissue inhibitors of
metalloproteases, TIMP-1, TIMP-2 and TIMP-3 (all from Ab-
cam, Cambridge, MA, USA); for serum adiponectin, MMP-8,
MMP-9 and soluble (s)P-selectin (all from R&D Systems,

Minneapolis, MN, USA); and for plasma D-dimer (Technoclone GmbH, Vienna, Austria). Mean intra- and interassay coefficients of variation (CV) were below 15% for all markers.

6 The limits of detection of the markers were as follows: 0.78 ng/mL for sICAM-1, 1.56 ng/mL for sVCAM-1, 24.69 pg/mL for TIMP-1, 1.6 pg/mL for TIMP-2, 156 pg/mL for TIMP-3, 0.312 ng/mL for MMP-9, 8.23 pg/mL for MMP-8, 2.74 pg/mL for RANTES/CCL5, 24.69 pg/mL for E-selectin, 0.99 ng/mL for sP-selectin, 0.102 ng/mL for L-selectin, 2.469 pg/mL for CRP, 15.6 pg/mL for TNF-alpha, 7.8 pg/mL for IL-6, 1.64 pg/mL for leptin, 3.9 ng/mL for adiponectin, 7.8 pg/mL for MCP1/CCL2, 4.10 pg/mL for MIP-1beta/CCL4 and 212 ng/mL for D-dimer.

Among promising cardiovascular mediators involved in atherosclerotic acceleration in patients with HIV [10,19], we focused on markers of endothelial activation (soluble adhesion molecules, such as sICAM, sVCAM, E-Selectin, sP-selectin, L-Selectin), pro-atherosclerotic molecules cytokines and chemokines (CRP, IL-6, TNF-alpha, MCP1/CCL2, MIP-1beta/CCL4 and CCL5/RANTES), adipocytokines (leptin and adiponectin) and coagulation factors (D-dimer). Considering the potential vulnerable properties of metalloproteases on atherosclerotic plaques [20,21], we investigated serum levels of the collagenase MMP-8, the gelatinase MMP-9 and their tissue inhibitors (TIMP-1, TIMP-2 and TIMP-3).

Data collected during the study visits, including laboratory values, were monitored and entered into a CRF compliant electronic database (SecuTrial®).

Safety assessment

Adverse events were graded according to the Division of AIDS (DAIDS) Table for Grading of Severity of Adult Adverse Events (version 1.0 December 2004, Clarification August 2009, www.niaid.nih.gov). Reporting of severe adverse events was to be compliant with applicable Swiss laws and regulations.

All included patients were followed up for safety assessment until the week 12 visit.

Statistical analysis

Sample size estimation. The following hypotheses were made: during the 4 weeks without statin treatment, up to 10% of the patients would show LDL-C value below the threshold level of 3 mM and therefore would not be eligible for the drug switch to ETR. The proportion of patients in need of statin treatment would decrease to 25% at study completion. With a power of 80% and a significance level of 5%, we estimated a total of 40 eligible patients would be required to show a decrease of at least 25% of patients in need of statin.

Data analysis. Baseline characteristics included the following: age, weight, sex, menopausal status, pregnancy, smoking status, systolic blood pressure, myocardial infarct/stroke in first-degree relative, diabetes, treated hypertension, cardiovascular risk level (GSLA score [16], Framingham Hard CHD Score [17]), HIV stage according to the Centre for Disease Control (CDC) classification, ongoing ART treatment [use of (non)nucleoside reverse transcriptase inhibitors ((N)NRTI), ritonavir-boosted protease inhibitor (bPI), integrase inhibitors], statin treatment, total cholesterol (TC), high-density lipoprotein (HDL-C), LDL-C, TG, CD4 cell count and HIV-1 RNA. The quantitative variables were summarized as median and interquartile ranges (IQR), while qualitative variables were presented as frequencies or percentages.

The primary endpoint, defined as the proportion of patients not qualifying anymore for statin treatment 12 weeks after inclusion into the study (i.e. after 8 weeks of ETR treatment) according to EACS 2013 recommendations [11], was analysed using McNemar chi-squared test with a threshold of 5%. We repeated a similar analysis using the Swiss cardiovascular risk score GSLA [16] and 2013 ACC/AHA guideline (10 year ASCVD risk) [18].

We analysed changes in lipid profile and biomarkers as change from baseline to week 4 for all the 31 enrolled patients and as change from week 4 to week 12 (8 weeks) for the 27 patients who switched to ETR. Both absolute and percentage changes were assessed and compared using a Wilcoxon matched-pair signed-rank test with an alpha threshold of 5%. Correlations between continuous variables were evaluated using Spearman's rank correlation test.

Univariable and multivariable logistic regressions were performed to identify factors associated with the impact of ETR switch on statin indication. The univariable logistic regression model included age, sex (women vs. men), time since HIV diagnosis (> 10 years vs. ≤ 10 years), CD4 cell count (> 500 cell/mL vs. ≤ 500 cell/mL), baseline ART class (EFV vs. bPI-based regimen), known hypertension (Yes vs. No), smoking status (active smoker vs. nonsmoker), LDL-C at week 4 after statin interruption, statin half-lives ['long acting' (atorvastatin and rosuvastatin) vs. 'short acting' (pravastatin) [22]] and the 8-week percentage change relative to week 4 (weeks 4–12) of the four biomarkers MCP1/CCL2, sICAM, CCL5/RANTES and TIMP-1, which changes were statistically significant between the 2 time points. The multivariable linear regression model included all variables with a $P < 0.200$ in the univariable model.

The frequency of adverse event of all patients until study completion was recorded regardless of the ETR switch. We also analysed modification of liver and kidney function [ASAT (UI), ALAT (UI), serum creatinine (μM)] and glycaemia (mM) from

week 4 to week 12 for all patients who completed the trial. Eight-week absolute changes were assessed and compared using a Wilcoxon matched-pair signed-rank test with an alpha threshold of 5%.

All statistical analyses were performed using STATA Statistical Software, Release 12.0 (Stata Corporation, College Station, TX, USA). The study results were reported according to STROBE statement [23].

Results

Baseline characteristics

From February 2012 to April 2013, 34 patients were screened at the six study sites within the SHCS (Fig. 1). Three patients were not included, each for one of the following reasons: history of known hypercholesterolaemia before ART initiation, > 20% cardiovascular disease risk score according to Swiss guidelines and statin interruption during the screening period. Of the 31 enrolled patients, a majority were men ($n = 25$, 81%). Median age was 52 years (IQR, 46–60 years; Table 1). All participants had a long history of HIV infection with a median of 11.5 years (IQR, 7.7–18.9) since diagnosis. At enrolment, the median CD4 cell count was 709 cells/mL (IQR, 543–851 cells/mL), and all patients had HIV-1 RNA ≤ 50 copies/mL. The ART combination at inclusion included EFV for 21 patients (68%), while 10 patients (32%) were on a ritonavir-boosted regimen (5 on LPV/r, 4 on ATV/r, 1 on DRV/r). Twelve patients (39%) were active smokers, 10 patients (32%) were treated for high blood pressure, and 2 patients had a family history of cardiovascular disease. Statin treatment was pravastatin for 15 patients (48%), rosuvastatin for 13 patients (42%) and atorvastatin for 3

patients (10%), with 9 patients (69%) on a daily dose of rosuvastatin at 10 mg or higher, 12 patients (80%) on pravastatin at 40 mg or higher and 2 patients (67%) on atorvastatin at 20 mg or higher.

Changes in lipid profile 4 weeks after statin withdrawal

Between week 0 and week 4, median LDL-C increased by 31.0%, median TC increased by 21.9%, and median TG increased by 28.4% (Table 2). These changes were statistically significant ($P < 0.001$), and no significant change was observed in HDL-C (Fig. 2). Two participants had an LDL value < 3 mM and were therefore not switched to ETR. Of the remaining patients, 2 were excluded because of HIV-1 RNA > 50 copies/mL or the drug resistance mutation M184V. Therefore, of the 31 included patients, 27 patients switched to the ETR treatment.

Statin indication at study completion (8 weeks after switch to ETR)

At study completion, of the 27 patients who switched to ETR, 25 patients (93%) had a viral load below the detection threshold of 50 copies/mL (two patients had a VL between 50 and 100 copies/mL). We observed statistically significant decreases in total cholesterol (-0.88 mM), LDL-C (-0.49 mM) and TG (-0.51 mM) between weeks 4 and 12 (Fig. 2).

Primary efficacy endpoint

At study completion, 15 (56%) of the 27 patients who switched to ETR did not qualify for statin treatment according to EACS recommendations ($P = 0.0001$) and 14 (52%) patients accord-

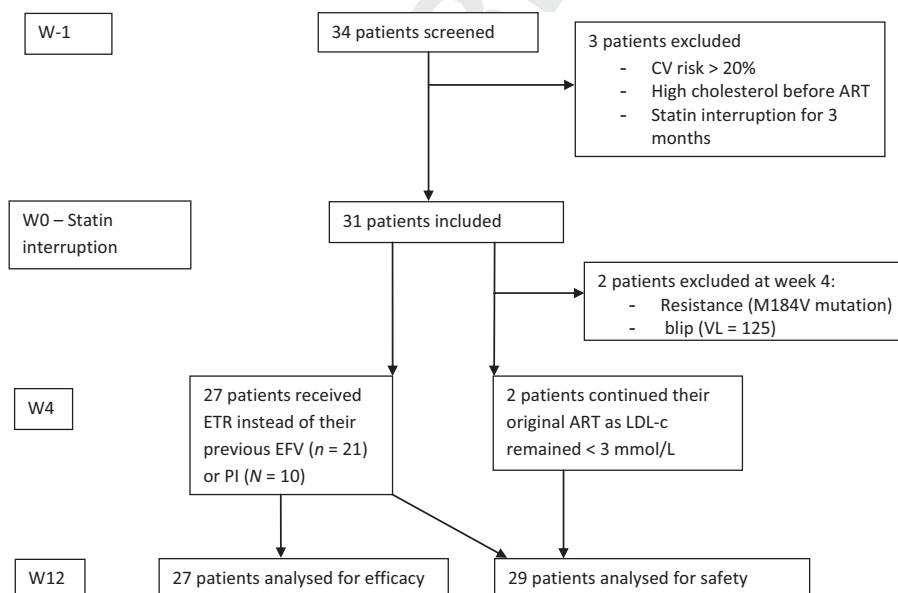


Figure 1 Study flow chart. The flow chart illustrates recruitment and intervention flow of all the patients who were screened at the six participating sites.

Table 1 Baseline characteristics of the 31 included patients

| Characteristic | Value |
|--|------------------|
| Age, years, median (IQR) | 51.7 (46.2–59.6) |
| Weight, kg, median (IQR) | 70 (64–82) |
| Gender | |
| Men | 25 (81%) |
| Women | 6 (19%) |
| Menopausal women | 4 (67%) |
| Active Smoker | 12 (39%) |
| Myocardial infarction or stroke in 1st degree related person | 2 (7%) |
| Known hypertension | 10 (32%) |
| GSLA score | |
| Low risk < 10% | 29 (94%) |
| Moderate risk 10–20% | 2 (6%) |
| CD4 ⁺ cells/mL (IQR) | 709 (543–851) |
| Time since HIV diagnosis, years (IQR) | 11.5 (7.7–18.9) |
| HIV staging (CDC categories) | |
| A | 15 (48%) |
| B | 8 (26%) |
| C | 8 (26%) |
| On ART treatment | 31 (100%) |
| First-line regimen | 3 (10%) |
| Current NNRTI | 21 (68%) |
| Current NRTI | 31 (100%) |
| Current PI | 10 (32%) |
| Current INI | 1 (3%) |
| HIV RNA ≤ 50 copies/mL | 31 (100%) |
| Statins in use at study entry | |
| Atorvastatin | 3 (10%) |
| Pravastatin | 15 (48%) |
| Rosuvastatin | 13 (42%) |

IQR, interquartile range; CDC, Centre for Disease Control, USA; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INI, integrase inhibitor.

ing to the Swiss GSLA scores ($P = 0.0001$). A *post hoc* analysis was performed to evaluate the study results using the new American 2013 ACC/AHA guidelines: only 10 patients (37%) would not qualify anymore for statin treatment ($P = 0.002$; Fig. 3).

9 Cardiovascular biomarkers

Absolute and percentage changes in inflammatory biomarkers were not significantly different between baseline and week 4 after the statin interruption (Table 2). In patients who switched to ETR, we observed a decrease in sICAM levels of 11.2% ($P = 0.039$) and a decrease in MCP1/CCL2 levels of 18.9% ($P = 0.017$) between weeks 4 and 12, that is during the 8 weeks of ETR administration. In addition, the levels of the pro-atherosclerotic chemokine CCL5/RANTES increased by 14.3% ($P = 0.012$), and those of TIMP-1 increased by 13.4% ($P = 0.039$). Other biomarkers showed no significant changes between the different time points, while D-dimers, IL-6 and TNF-alpha remained below the detection thresholds throughout the study period.

Adjusted multivariable analysis

The only variable found to be related to the absence of indication for statin treatment at study completion after 8 weeks on ETR was age [OR: 1.18 (95% CI, 1.02–1.37)], after adjustment for both LDL-C at week 4 [OR: 0.17 (95% CI, 0.02–1.36)] and percentage change of TIMP-1 biomarker [OR: 1.02 (95% CI, 1.00–1.01); Table 3].

Safety

No serious adverse event was reported during the study. One patient discontinued ETR treatment on his own initiative after 24 days due to dizziness, fatigue and depression, which were graded as mild by the investigator. Fifteen clinical events were reported in 11 patients. All events were graded as mild or moderate in severity and none were judged by the investigator to be related to the study drug, or the statin interruption. Nine events were considered possibly related to ETR: one case of grade 1 rash occurred 2 weeks after ETR initiation, and a case of acute renal failure was reported at the end of the study period. Events of dizziness, vomiting, left intercostal pain and a grade 1 elevation of alanine aminotransferase were considered as related to the ETR treatment. No significant increase in liver function test was recorded, but a small significant increase in serum creatinine (+4 μM , IQR –2 to 9, $P = 0.018$) and a decrease in glycaemia (–0.25 mM, IQR –0.60 to 0.15, $P = 0.028$) were observed in the 29 patients who completed the trial, although without clinical impact.

Discussion

Our study shows that HIV-infected individuals on statin treatment in whom the boosted PI or EFV was replaced with ETR can avoid the use of statins in 56% of the cases (primary efficacy endpoint). Over the study period, these patients showed a significant decrease in the levels of serum lipids

Table 2 Lipid profile and cardiovascular biomarker values

| | Patients who stopped statin (n = 31) Median (IQR) | | Patients who switched to etravirine (n = 27) Median (IQR) | | 8-week percentage change (Week 4-Week 12) |
|--|---|--|---|---|---|
| | Week 0 | 4-week absolute change (Week 0-Week 4) | Week 4 | 8-week absolute change (Week 4-Week 12) | |
| <i>Lipids profile</i> | | | | | |
| LDL-C (mM) | 2.89 (2.59 to 3.54) | 0.99 (0.54 to 1.52)*** | 4.30 (3.75 to 4.75) | -0.49 (-1.16 to 0.17)* | -11.86 (-24.17 to 3.94)* |
| HDL-C (mM) | 1.53 (1.27 to 1.68) | -0.07 (-0.19 to 0.05) | 1.46 (1.25 to 1.46) | 0.01 (-0.17 to 0.09) | 0.68 (-7.33 to 6.67) |
| Total cholesterol (mM) | 5.68 (5.04 to 6.24) | 1.25 (0.78 to 1.60)*** | 6.97 (6.44 to 7.36) | -0.88 (-1.38 to -0.31)*** | -13.21 (-19.12 to 3.85)*** |
| Triglycerides (mM) | 1.63 (1.22 to 2.62) | 0.39 (0 to 0.62)* | 2.08 (1.37 to 3.01) | -0.51 (-1.16 to -0.06)** | -27.36 (-39.23 to 4.65)** |
| <i>Biomarkers</i> | | | | | |
| Endothelial activation | | | | | |
| sICAM (ng/mL) | 278.66 (223.69 to 336.79) | 2.00 (-72.12 to 71.14) | 272.46 (225.6 to 355.42) | -34.45 (-67.04 to 18.74)* | -11.21 (-22.72 to 4.58)* |
| sVCAM (ng/mL) | 426 (366.66 to 560.2) | -54.87 (-123.71 to 47.31) | 382.95 (289.33 to 510.44) | 8.33 (-52.19 to 78.57) | 2.67 (-9.07 to 28.96) |
| E-Selectin (ng/mL) | 33.66 (25.45 to 44.88) | -1.56 (-10.14 to 5.42) | 33.65 (18.82 to 49.15) | -2.85 (-7.66 to 6.43) | -7.75 (-24.12 to 22.58) |
| sP-selectin (ng/mL) | 93.53 (66.86 to 116.05) | -2.26 (-27.95 to 13.31) | 89.07 (50.76 to 105.32) | -3.93 (-17.53 to 9.99) | -3.8 (-19.62 to 11.99) |
| L-Selectin (ng/mL) | 1783.36 (1174.5 to 2721.42) | 168.45 (-345.32 to 602.46) | 1953.64 (1399.46 to 2500.62) | -121.57 (-829.88 to 657.93) | -7.93 (-34.91 to 43.88) |
| Pro-atherosclerotic molecules cytokines and chemokines | | | | | |
| CRP (µg/mL) | 2.98 (0.51 to 9.25) | 0.15 (-2.37 to 1.42) | 2.60 (1.28 to 7.53) | -0.55 (-2.75 to 2.2) | -20.05 (-46.88 to 82.22) |
| IL-6 pg/mL | 7.80 (7.80 to 7.80) | 0 (0 to 0) | 7.80 (7.80 to 7.80) | 0 (0 to 0) | 0 (0 to 0) |
| TNF-alpha (pg/mL) | 15.60 (15.60 to 15.60) | 0 (0 to 0) | 15.60 (15.60 to 15.60) | 0 (0 to 0) | 0 (0 to 0) |
| MCP1/CCL2 (pg/mL) | 102.17 (74 to 188.66) | 2.03 (-19.72 to 33.4) | 114.73 (73.8 to 179.89) | -14.24 (-34.38 to 0.98)* | -18.92 (-32.57 to -0.94)* |
| MIP-1beta/CCL4 (pg/mL) | 104.27 (81.4 to 135.17) | 1.87 (-13.2 to 20.31) | 102.79 (74.84 to 125.35) | -2.74 (-11.48 to 9.79) | -3.97 (-11.15 to 15.09) |
| CCL5/RANTES (ng/mL) | 69.53 (33.46 to 103.89) | -3.42 (-28.4 to 8.09) | 46.88 (38.25 to 72.55) | 6.89 (-9.92 to 26.33) | 14.27 (-14.84 to 80.72)* |
| <i>Adipocytokines</i> | | | | | |
| Leptin (ng/mL) | 3.87 (1.83 to 14.03) | -0.19 (-1.95 to 0.61) | 2.68 (1.41 to 8.27) | 0.1 (-1.04 to 1.44) | 9.28 (-32.38 to 79.67) |
| Adiponectin (µg/mL) | 6.55 (4.5 to 9.65) | 0.03 (-0.78 to 1.76) | 7.46 (4.77 to 10.23) | -0.55 (-2.57 to 0.52) | -12.85 (-26.77 to 8.67) |
| <i>Metalloproteases and inhibitors</i> | | | | | |
| MMP-9 (ng/mL) | 502.28 (358.78 to 719.29) | 6.41 (-192.38 to 74.81) | 411.18 (305.09 to 723.02) | -51.8 (-218.3 to 43.95) | -12.88 (-38.63 to 32.57) |
| MMP-8 (ng/mL) | 3.18 (1.75 to 4.7) | -0.44 (-1.6 to 0.73) | 2.72 (1.17 to 4.26) | -0.24 (-1.04 to 0.93) | -14.55 (-44.22 to 41.19) |
| TIMP-1 (ng/mL) | 433.74 (354.16 to 549.09) | -11.77 (-96.5 to 89.51) | 429.51 (338.51 to 523.25) | 66.31 (-39.23 to 297)* | 13.43 (-9.02 to 100.03)* |
| TIMP-2 (ng/mL) | 68.53 (60.98 to 85.73) | -0.61 (-9.47 to 17.42) | 73.68 (62.27 to 82.67) | -1.41 (-12.21 to 22.17) | -1.94 (-11.76 to 27.34) |
| TIMP-3 (ng/mL) | 2.7 (1.99 to 4.7) | -0.13 (-1.04 to 0.81) | 2.49 (1.58 to 4.22) | -0.18 (-1.43 to 0.52) | -11.19 (-46.92 to 38.76) |

CRP, C-reactive protein; IL, interleukin; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; MMP, matrix metalloproteinase; RANTES, regulated upon activation, normal T-cell expressed and secreted; sICAM, serum soluble intercellular adhesion molecule; sVCAM, soluble vascular cell adhesion molecule; TIMP, tissue inhibitor of metalloproteinase; TNF, tumour necrosis factor.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.0001$.

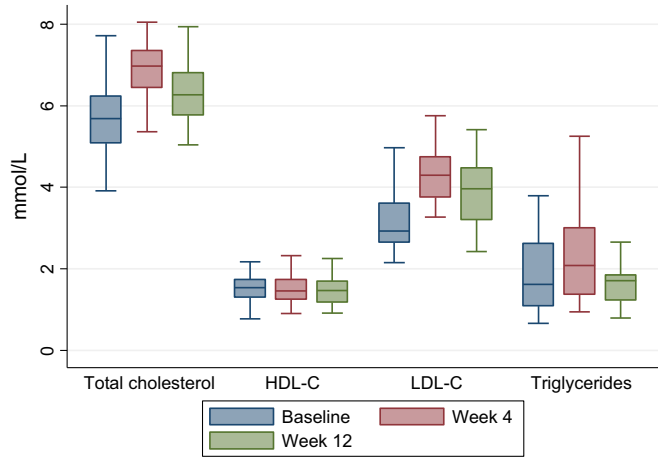


Figure 2 Lipid profiles at week 0, week 4 and week 12 in the 27 patients who switched to etravirine (ETR). The serum levels of total cholesterol, low-density cholesterol, high-density cholesterol and triglycerides were measured at baseline (week 0), 4 weeks after stopping statin treatment (week 4) and 8 weeks after switch to ETR (week 8) in the 27 patients who qualified for the ETR switch out of the 31 included patients. Values presented are the median and interquartile ranges.

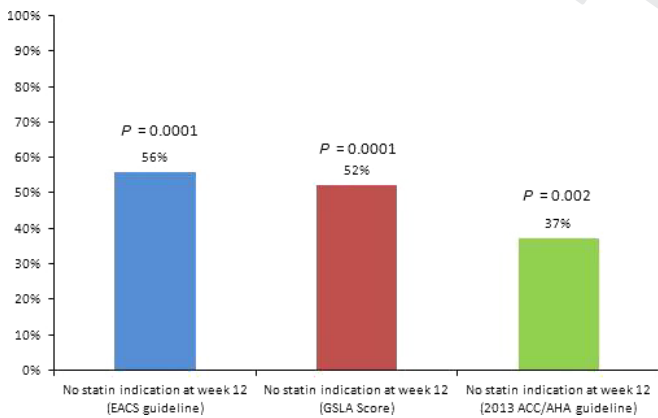


Figure 3 Proportion of patients not qualifying for a statin treatment after 8 weeks of etravirine treatment. The criteria for qualifying for statin treatment were according to the European AIDS Clinical Society (EACS) latest recommendations (blue bar), GSLA (red bar) or 2013 ACC/AHA recommendations (green bar).

(although not as large as when they were on statin treatment) and in pro-inflammatory markers, suggesting reduced risk of cardiovascular disease.

In addition, we confirmed that statin interruption did not cause any serious adverse event as expected from an earlier

report [24], and no cardiovascular disease was observed during the 12-week study period.

Traditional CV risk factors, HIV-induced immune activation as well as the metabolic consequences of some antiretroviral drugs contribute to a twofold increase in the risk of cardiovascular disease in HIV-infected patients. Recommended preventive interventions target modifiable risk factors such as smoking and dyslipidaemia. Replacing a combined ART component by a lipid-friendly drug has many advantages, including economic and practical considerations. However, despite the positive effect on lipids of ETR, a drug such as EFV is available in combination as a single fixed-dose pill and is often preferred by patients. Other drugs may have a safety and lipid-neutral profile similar to ETR, but have not been evaluated so far with the objective of a statin-sparing strategy.

Our results confirm the observations from clinical trials comparing newer drugs with standard treatments including boosted PI. In the Switch-EE study [13], patients switched to ETR had lower lipid plasma levels than when on EFV. In the SENSE study [25], both total cholesterol and LDL-C were lower in patients on ETR as compared with patients on EFV (number of patients with grade 3 or 4 elevation of total cholesterol was 1% vs. 8%). In the C227 trial [26], exploring two treatment regimens (ETR + 2NRTI or boosted PI + 2NRTI) after an NNRTI first-line failure, lipid and bilirubin elevations were less frequent in the ETR arm. These observations can be applied in a clinical pragmatic intervention to reduce lipid levels and therefore cardiovascular risk.

The so-called neutral effect on lipids of ETR has been showed in studies using placebo [27], and this may explain its favourable profile compared with antiretroviral drugs known for their unwanted effect on lipids. This effect is usually measured at 24 weeks in clinical trial, but seems to start earlier, as in our study.

Our study focused on numerous cardiovascular risk biomarkers, including active factors of atherogenesis previously investigated in both high-risk populations as well as patients with HIV [10,28]. The levels of these mediators in the present study were similar to those observed in previous studies [29]. Serum levels of IL-6, TNF-alpha and D-dimer were confirmed to be very low in patients with HIV as well as in other subjects with elevated cardiovascular risk [10,28]. These results indicate that despite their promise in other cohorts [19], these mediators might not be useful in patients with HIV. Alternatively, our data might also suggest the need for methods providing a higher sensitivity for investigating these biomarkers in patients with HIV infection. During the 4 weeks following statin interruption, no significant modification in any of these biomarkers was seen, in contradiction to previous studies that showed that statins lower serum CRP levels [30,31]. The discrepancy could be due to the relatively short follow-up; 4 weeks might not be

Table 3 The association between baseline characteristics and the absence of indication for statin treatment at study completion

| Factors | Univariate OR (95% CI) | P value | Multivariate OR (95% CI) | P value |
|---|------------------------|---------|--------------------------|---------|
| Age (in year) | 1.13 (1.01–1.27) | 0.028 | 1.18 (1.02–1.37) | 0.028 |
| Sex | | | | |
| Male | 1 | | | |
| Female | 0.91 (0.15–5.58) | 0.918 | | |
| Time since HIV diagnosis: | | | | |
| ≤ 10 years | 1 | | | |
| > 10 years | 1.29 (0.26–6.27) | 0.756 | | |
| CD4 count, cells/mm ³ | | | | |
| ≤ 500 | 0.91 (0.15–5.58) | | | |
| > 500 | 1 | 0.918 | | |
| Statin half-life | | | | |
| Short acting statin | 1 | | | |
| Long acting statin | 0.63 (0.14–2.89) | 0.548 | | |
| Baseline ART treatment | | | | |
| NNRTI (efavirenz) | 1 | | | |
| Protease inhibitor | 0.61 (0.11–3.49) | 0.582 | | |
| Known hypertension | 3.10 (0.47–19.67) | 0.240 | | |
| Active smoker | 0.48 (0.10–2.23) | 0.346 | | |
| LDL-C value (mM) at week 4 | 0.32 (0.09–1.17) | 0.085 | 0.17 (0.02–1.36) | 0.094 |
| 8-week percentage change of laboratory marker TIMP-1 | 1.01 (1.00–1.03) | 0.079 | 1.02 (1.00–1.01) | 0.092 |
| 8-week percentage change of laboratory marker MCP1-CCL2 | 1.01 (0.98–1.04) | 0.481 | | |
| 8-week percentage change of laboratory marker sICAM | 0.99 (0.95–1.02) | 0.451 | | |
| 8-week percentage change of laboratory marker CCL5/RANTES | 1.00 (0.98–1.01) | 0.488 | | |

LDL-C, low-density lipoprotein cholesterol; MCP, monocyte chemoattractant protein; NNRTI, non-nucleoside reverse transcriptase inhibitor; OR, odds ratio; RANTES, regulated upon activation, normal T-cell expressed and secreted; sICAM, serum soluble intercellular adhesion molecule; TIMP, tissue inhibitor of metalloproteinase.

enough time to observe an inflammatory rebound due to statin cessation.

The switch to ETR was associated with a protective decrease in sICAM (a marker of endothelial activation) and MCP1/CCL2 (a pro-atherosclerotic chemokine), and a beneficial increase in TIMP-1. These changes indicate a potential direct cardiovascular protection induced by ETR that may improve endothelial activation, protect from the deleterious activities of MMP and reduce atherosclerotic inflammation (via MCP1/CCL2-mediated pathways). The weak association between lipid profile and biomarkers (only shown for TGs and MCP1/CCL2) suggests that ETR might reduce the cardiovascular risk

not only via improvement in the lipid profile, but also via biomarkers.

A study in healthy volunteers [32] showed no effect of ETR on inflammatory biomarkers and endothelial function and finally on CV risk. ETR was introduced over 28 days with no significant changes, but the study population was very different: not only patients had no HIV infection but they had also a normal lipid profile, making comparisons difficult. In addition, the ETR exposure was only of 28 days that could be a too short period to observe changes.

We also found a weak but statistically significant increase in the serum levels of the chemokine CCL5/RANTES in patients

with HIV infection on ETR. This chemokine was recently shown to activate both circulating leucocytes and platelets and potentially increase cardiovascular vulnerability [28,33]. Considering the design and low number of patients enrolled in our study, we might only speculate that results on this marker merit additional investigations. In addition, we cannot conclude whether ETR-associated increase in CCL5 levels is limited to the first 8 weeks of treatment, or sustained over time.

Our study has several limitations. It was not a randomized design, and bias in selection of participants cannot be excluded. The lack of a control group prevents the clear attribution of the effect of the intervention, but previous studies' results and the appearance of the effect after ETV introduction make the relation plausible. Recruitment varied by centre depending on the number of patients already receiving statin treatment. Fewer patients were receiving statin treatment than expected, while many patients were excluded because of previous cardiovascular disease and/or documented drug mutations. Pill burden and refusal to change regimens were the main reasons for nonparticipation, especially for patients receiving a once daily fixed-dose combination such as Atripla[®]. As a result of insufficient recruitment, the desired sample size of 40 included patients was not achieved, thereby reducing the power of the study and the possibility to study additional predictive factors.

The criteria for the initial indication of statin treatment were not known and probably differed widely across study sites, which adds possible confounding factors not considered in our analysis. The study has a short follow-up period, which does not allow evaluation of the long-term effect of the proposed treatment strategy, but in a previously reported clinical trial, the effect of switch to ETR on lipid profile could be maintained over the follow-up period of 48 weeks [34]. We did not collect information on nutrition or physical activities, which may have contributed to the lipid changes over the study period.

In conclusion, although surrogate experimental biomarkers of CV risk have been widely investigated, their clinical use requires further validation in this population. Our preliminary results demonstrating the lowering effect of ETR on circulating pro-inflammatory markers cannot yet be considered as a relevant reduction in CV risk for patients with HIV. Combination of serum inflammatory biomarkers with other validated and classical parameters (i.e. LDL cholesterol) remains essential when assessing the CV risk. Additional larger trials are needed to clarify the role of some biomarkers such as CCL2 to further improve the CV risk assessment of patients with HIV infection.

While indications for statin use in primary prevention of cardiovascular disease are controversial [16–18], the present study indicates that out of the 27 patients with HIV infection who switched to ETR for 8 weeks, 10–15 patients (depending on the

guideline used) or 37–56% no longer required statin treatment. In view of the importance of this finding for the management of patients with HIV, further investigations, including prospective, large-scale, randomized studies with a longer follow-up period, are required to justify the switch to ETR and removal of statins from the treatment regimen in patients with HIV with a low-to-moderate Framingham risk score.

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Appendix

The members of the Swiss HIV Cohort Study are as follows:

V Aubert, M Battegay, E Bernasconi, J Böni, HC Bucher, C
Burton-Jeangros, A Calmy, M Cavassini, M Egger, L Elzi, J Fehr,
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Speck, P Tarr, A Telenti, A Trkola, P Vernazza, R Weber, S Yerly.

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