Antiretroviral Therapy Reduces Markers of Endothelial and Coagulation Activation in Patients Infected with Human Immunodeficiency Virus Type 1

Katja Wolf,[1,a] Dimitrios A. Tsakiris,[2,a] Rainer Weber,[4] Peter Erb,[3] and Manuel Battegay,[1] for the Swiss HIV Cohort Study[b]

[1]Basel Center for HIV Research, Outpatient Department of Internal Medicine, and [2]Haemostasis Laboratory, Department of Central Laboratories, University Hospital Basel, and [3]Institute of Medical Microbiology, University of Basel, Basel, and [4]Division of Infectious Diseases, University Hospital Zurich, Zurich, Switzerland

We investigated the effect of antiretroviral therapy on vascular activation in 41 human immunodeficiency (HIV)–infected patients receiving a regimen that included either at least 1 protease inhibitor (PI; $n = 21$) or a nonnucleoside reverse-transcriptase inhibitor (NNRTI; $n = 20$). A control group of 21 healthy subjects was included for comparison. Levels of endothelial markers (soluble vascular cell adhesion molecule [sVCAM]–1, soluble intercellular adhesion molecule–1, and von Willebrand factor) were higher in HIV-infected persons before treatment than in control subjects and decreased significantly after 5–13 months of treatment. Levels of sVCAM-1 and von Willebrand factor correlated significantly with initial virus load. D-dimer concentrations also decreased significantly after initiation of treatment. PI- and NNRTI-containing regimens had similar effects. Therapy did not reduce levels of the soluble platelet (sP) activation markers sP-selectin and CD40 ligand. The inhibition of markers of vascular activation may counterbalance sequelae of therapy-induced dyslipidemia and potentially prevent development of atherosclerosis in HIV-infected patients.

Since highly active antiretroviral therapy (HAART) was introduced into clinical practice in 1995–1996, the morbidity and mortality associated with human immunodeficiency virus (HIV) infection has drastically decreased [1–3]. However, protease inhibitors (PIs) cause long-term side effects, such as dyslipidemia and, in particular, hypercholesterolemia, which is known to be an important risk factor for cardiovascular disease [4, 5]. On the other hand, infectious agents themselves (e.g., viruses or bacteria) may play an important role in the etiology of the atherosclerosis, thrombosis, and intimal thickening that occur after arterial injury [6]. Possible mechanisms involve replication of a pathogen within human endothelial cells and expression of endothelial cell markers such as vascular cell adhesion molecule (VCAM)–1 and intercellular adhesion molecule (ICAM)–1 [7, 8].

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All patients enrolled in the study gave informed consent approved by the Cantonal ethical review board of the University Hospital Basel and Zurich.

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[a] K.W. and D.A.T. contributed equally to this work.

[b] Study group members are listed after the text.

Reprints or correspondence: Prof. Manuel Battegay, Outpatient Dept. of Internal Medicine, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland (mbattegay@uhbs.ch).

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Various biological markers of endothelial dysfunction, such as VCAM-1, ICAM-1, von Willebrand factor, and thrombomodulin, have been described [9]. These markers indicate chronic endothelial activation and subsequent dysfunction of the endothelium in atherosclerosis. Marked increases in circulating levels of adhesion molecules were observed in patients with hyperlipidemia, hypertension, diabetes mellitus, oxidative stress, changes in hormone metabolism, and a history of cigarette smoking [10]. Hence, measuring the levels of these molecules in blood may identify early vascular changes. In earlier studies, we and others [11–14] found that levels of biological markers of endothelial or platelet activation are increased in patients with arterial disease and are associated with progression of atherosclerosis. Endothelial activation may promote inflammatory reactions and thereby trigger activation of coagulation mechanisms and induction of a hypercoagulable state [10]. This process can be monitored by measurement of coagulation markers. The thrombin–antithrombin III complex is a marker of intravital thrombin generation. Thrombin and antithrombin III have very short half-lives (5–7 min) and are produced whenever the coagulation cascade is sufficiently activated. D-dimers are fibrin-degradation products, and levels of D-dimers are elevated whenever cross-linked fibrin is produced as a result of coagulation activation followed by secondary fibrinolysis. Whenever thrombin is generated or endothelial cells are stimulated, platelets may be activated. Activated platelets, in turn, can stimulate endothelial cells and induce up-regulation of various cell adhesion molecules [15].

HIV infection may cause coagulation disorders, most frequently HIV-associated thrombocytopenia [16, 17], but it may also induce production of antiphospholipid antibodies [18] or

cause other abnormalities associated with a prothrombotic state [19]. Endothelial dysfunction or damage, hypercoagulability, hypertriglyceridemia, and abnormal coronary artery pathology have all been associated with HIV infection [16, 20, 21]. Levels of soluble endothelial activation markers (sVCAM-1, sICAM-1, and von Willebrand factor) are elevated in HIV-infected patients, and this elevation may be associated with a hypercoagulable state [22]. Circulating activated platelets also have been found in the plasma of HIV-infected patients [23] and add to a hypercoagulable state. The degree of hypercoagulability may be proportional to the virus load [22], and elevated levels of sICAM-1 have been associated with disease progression [24]. Reversal of vascular activation after initiation of antiviral therapy has been investigated and was demonstrated only for von Willebrand factor and platelet activation [22, 23]. To assess vascular activation in patients with HIV infection, we investigated changes in levels of various endothelial, coagulation, and platelet activation markers. These were investigated before and after initiation of HAART (after virus load had decreased substantially, to <400 copies/mL) in 2 groups of patients receiving 2 different antiretroviral regimens and were compared with levels in healthy control subjects.

Patients and Methods

Patients and control subjects. We selected our patients from the group of adult patients (age, >16 years) participating in the Swiss HIV Cohort Study (SHCS) in Basel and Zurich who were about to start a therapeutic regimen that included either at least 1 PI ($n = 21$) or a nonnucleoside reverse-transcriptase inhibitor (NNRTI; $n = 20$). Of 115 adult patients who were about to begin receiving HAART, we excluded 41 who changed therapy before blood samples were obtained, 4 who were known to be nonadherent to the therapeutic regimen, and 29 who did not respond well to therapy (a good response was defined as a virus load <400 copies/mL). Within the SHCS, patients are followed up at 6-month intervals (±1 month). We obtained blood samples at the first follow-up appointment, 6 months (±1 month) after initiation of HAART, or, for patients who missed the 6-month consultation or had a virus load ⩾400 copies/mL at 6 months, at the 12-month follow-up appointment. The earliest follow-up appointment was at month 5, and the latest was at month 13. Hence, all patients had information from 1 follow-up appointment. Age, sex, HIV disease stage (according to the Centers for Disease Control and Prevention classification [25]), and CD4 cell count were not used as inclusion or exclusion criteria. The mean age in our group of patients was higher than that in the SHCS group overall (41 vs. 36 years) [26]. The proportion of women was very similar (nonsignificant difference). With regard to pretherapy parameters, our group had a lower mean virus load (4.3 vs. 5.01 $\log_{10}$ copies/mL) and a higher mean CD4 cell count (245 vs. 181 cells/μL). Patients who had primary HIV infection or ongoing opportunistic infections were excluded, because these diseases can interfere with hemostasis. We excluded patients whose medical history raised suspicion of hereditary coagulation disorders, such as hemophilia or hereditary thrombophilia. Clinical information, including age, sex, HIV disease stage, virus load, CD4 cell count, and platelet count before initiation of therapy and, thereafter, at follow-up were prospectively collected by cohort questionnaires and obtained from review of medical files. Twenty-one healthy HIV-negative blood donors made up the control group.

Blood sampling. Stored plasma samples from HIV-infected patients were obtained before and at least 5 months after initiation of HAART. Blood was drawn in 0.11 *M* sodium citrate (9/1, vol/vol; used as an anticoagulant) in a Vacutainer CPT system (Becton Dickinson). After a 2-step centrifugation, plasma was stored at −80°C for further use. Specimens from control subjects were obtained and processed in the same manner as specimens from HIV-infected patients but were only frozen for a few weeks. Recently published data about the stability of the parameters we tested indicate that coagulation proteins remain stable for at least 18–24 months when stored in frozen plasma at −74°C [27]. If a degradation of coagulation proteins were to occur during a longer period of freezing, it would result in lower levels of markers in samples from HIV-infected patients but not in samples from control subjects and therefore would strengthen, rather than weaken, our results.

Laboratory tests. CD4 lymphocyte counts were analyzed by flow cytometry. For HIV quantification, plasma samples were processed according to the published protocols of the Roche HIV-1 Monitor test kit (Roche Diagnostics), with a modification of the ultrasensitive assay [28].

Levels of biological endothelial activation markers (sVCAM-1, sICAM-1, von Willebrand factor, and thrombomodulin) were measured by ELISA (R&D Systems Europe and Diagnostica Stago). Levels of coagulation activation markers (D-dimers and thrombin–antithrombin III complex) were also assayed by ELISA (Roche Diagnostics and Behring Diagnostics). Platelet activation was determined by measurement of soluble platelet (sP) activation markers (sP-selectin and soluble CD40 ligand), using ELISA (R&D Systems Europe and Bender Medical Systems).

Statistical analysis. Nonparametric tests were used for statistical comparison, because some parameters did not show a normal distribution. Two-group comparisons were done with the Mann-Whitney *U* test and the Bonferroni correction for multiple testing and were confirmed using a 1-way analysis of variance (Scheffé test for post hoc multiple comparisons). Paired comparisons were made with the Wilcoxon rank sum test. Bivariate correlations were calculated with the Spearman rank correlation. $P \leqslant .05$ was considered to be significant.

Results

Demographic and laboratory data for case patients and control subjects are given in table 1. Of 41 case patients, 21 received antiretroviral therapy that included 2 nucleoside reverse-transcriptase inhibitors (NRTIs) and 1 or 2 PIs, and 20 received therapy that included 2 NRTIs and 1 NNRTI. According to the eligibility criteria for this investigation, all patients had an HIV load <400 copies/mL of plasma after initiation of HAART. This was the case after a mean duration of 9.7 months of antiretroviral therapy (5–13 months). Twenty-three patients (56%) had a virus load <50 copies/mL of plasma at the first follow-up ap-

Table 1. Demographic characteristics and laboratory results for human immunodeficiency virus (HIV)–infected patients involved in a study of the effects of highly active antiretroviral therapy (HAART) on vascular activation.

Characteristic	All patients (n = 41)	Patients receiving PIs (n = 21)	Patients receiving NNRTIs (n = 20)	Control subjects (n = 21)
Age, mean years (±SD)	41 (11)	40 (11)	41 (11)	46 (14)[a]
Male sex, no. (%)	31 (76)	19 (90)	12 (60)	16 (76)
HIV disease stage,[b] no. (%)				
A	18 (44)	7 (33)	11 (55)	
B	16 (39)	10 (48)	6 (30)	
C	7 (17)	4 (19)	3 (15)	
Antiviral therapy, no.				
2 NRTIs, ritonavir, and saquinavir	15	15		
2 NRTIs and ritonavir	2	2		
2 NRTIs and indinavir	4	4		
2 NRTIs and efavirenz	16		16	
2 NRTIs and nevirapine	4		4	
Length of treatment, mean months (±SD)	9.7 (2.5)	9.6 (2.5)	9.9 (2.6)	
Virus load, mean $\log_{10}$ copies/mL (±SD)				
At baseline	4.3 (1.1)	4.7 (0.9)	3.9 (1.3)	
After initiation of HAART[c]	1.4 (0.8)	1.8 (0.5)	0.9 (0.8)	
CD4 T cell count, median cells/μL (range)				
At baseline	210 (19–640)	192 (19–640)	315 (80–582)	
After initiation of HAART	482 (53–977)	411 (53–972)	500 (79–977)	

NOTE. PI, protease inhibitor; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor.
[a] Nonsignificant statistical difference (Mann-Whitney U test).
[b] HIV disease stages are from the Centers for Disease Control and Prevention classification [25].
[c] Virus load was <400 copies/mL in all patients; virus load was <50 copies/mL in 23 patients.

pointment. During the study period, the virus load dropped by a mean ± SD of 2.9 ± 1.41 $\log_{10}$ copies/mL (range, 4.3 ± 1.1 to 1.4 ± 0.8 $\log_{10}$ copies/mL). Simultaneously, median CD4 cell counts increased from 210 cells/mL before to 482 cells/mL after initiation of therapy (table 1). Patients treated with an NNRTI had smaller baseline and follow-up virus loads. As is shown in table 1, the decrease in virus load in the 2 treatment groups was almost identical. Disease characteristics in the 2 treatment groups were also similar. As expected, all control subjects had negative results of testing for hepatitis C virus (HCV), whereas 11 (27%) of the case patients were HCV positive.

Endothelial activation. Levels of sVCAM-1, sICAM-1, and von Willebrand factor were significantly higher in HIV-infected patients before initiation of antiretroviral treatment than in healthy control subjects ($P < .01$). Levels of sVCAM-1, sICAM-1, and von Willebrand factor, but not of thrombomodulin, decreased significantly after 5 months of treatment (figure 1), regardless of whether treatment included PIs or an NNRTI (table 2). The results of treatment with PIs were very similar to the results of treatment with an NNRTI, as is shown in figure 1. In addition, levels of sVCAM-1 correlated significantly with levels of both sICAM-1 ($\rho = 0.66$; $P < .001$) and von Willebrand factor ($\rho = 0.59$; $P < .001$), and levels of sICAM-1 correlated with levels of von Willebrand factor ($\rho = 0.49$; $P = .001$). These correlations were significant before and after initiation of antiretroviral treatment. To test whether initial virus load influenced levels of endothelial markers, we investigated the association of baseline virus load with the markers examined in the study. Levels of sVCAM-1 ($\rho = 0.49$; $P < .001$) and von Willebrand factor ($\rho = 0.34$; $P < .03$), but not of sICAM-1, correlated significantly with virus load. These results demonstrate that marked endothelial activation was reduced during therapy.

Coagulation activation. To evaluate whether a procoagulant state existed in our patients, we measured levels of markers of coagulation activation such as thrombin–antithrombin III complexes and D-dimers before and after initiation of HAART. Levels of D-dimers decreased significantly in both treatment groups (figure 1 and table 2) after initiation of treatment. Levels of thrombin–antithrombin III complex did not increase or decrease significantly during therapy (table 2). Interestingly, levels of D-dimers correlated significantly with levels of von Willebrand factor ($\rho = 0.38$; $P < .02$), thrombomodulin ($\rho = 0.52$; $P < .01$), and sVCAM-1 ($\rho = 0.32$; $P < .05$) before initiation of treatment. After treatment with PIs or NNRTIs, the correlations between levels of von Willebrand factor and sVCAM-1 diminished. Levels of D-dimers also correlated highly with the virus load ($\rho = 0.51$; $P < .001$). In summary, these results demonstrate that coagulation markers were activated, but to a lesser degree than were endothelial markers, by HIV infection. Therapy had a less marked but still obvious effect on coagulation markers.

Platelet activation. To examine whether production of platelets was stimulated by treatment with PIs or NNRTIs, we measured soluble markers of platelet activation, such as soluble CD40 ligand and sP-selectin. We found that platelet activation

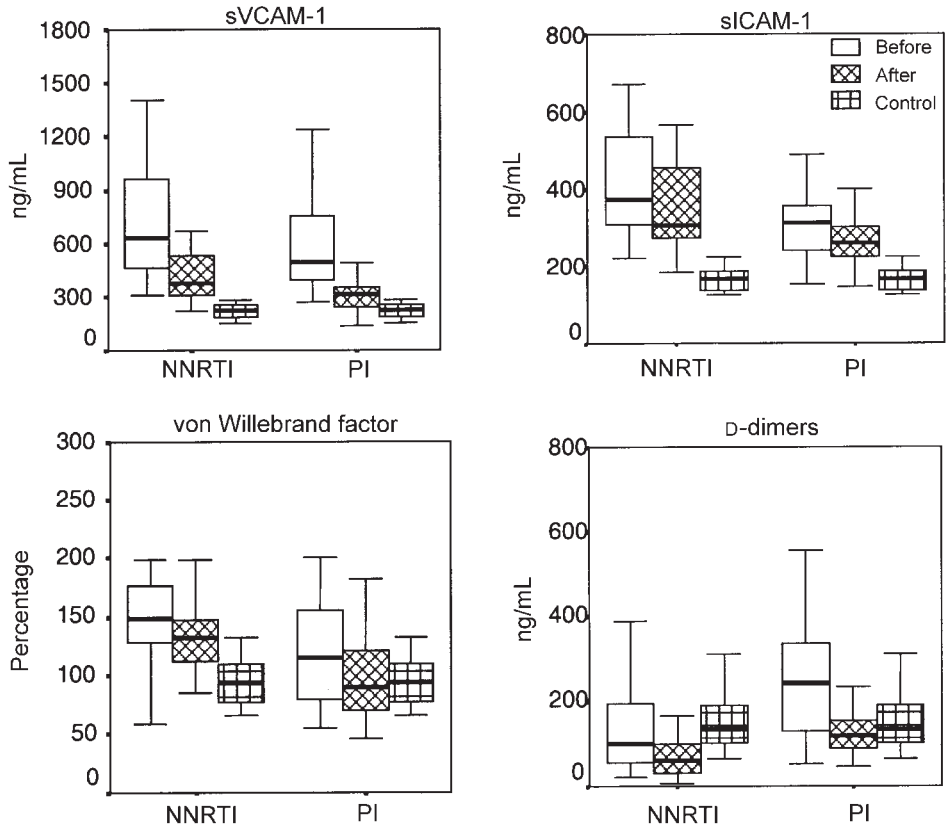

Figure 1. Plasma levels of soluble vascular cell adhesion molecule (sVCAM)–1, soluble intercellular adhesion molecule (sICAM)–1, von Willebrand factor, and D-dimers in human immunodeficiency virus (HIV)–infected patients who received treatment with protease inhibitors (PIs; $n = 21$) or a nonnucleoside reverse-transcriptase inhibitor (NNRTI; $n = 20$), before and after initiation of treatment, compared with levels in healthy, HIV-negative control subjects ($n = 21$).

markers were significantly higher in HIV-infected patients than in control subjects but did not decrease after initiation of therapy (table 2). The mean platelet count ± SD in control subjects was not significantly different from that in HIV-infected patients ($[202 \pm 89] \times 10^9$ vs. $[206 \pm 32] \times 10^9$ platelets/L). Plasma levels of soluble CD40 ligand correlated significantly with levels of sP-selectin ($\rho = 0.93$; $P < .001$). Levels of sP-selectin also correlated well with levels of thrombomodulin ($\rho = 0.40$; $P < .02$) before initiation of treatment, a correlation that diminished after initiation of treatment with PIs or NNRTIs. In summary, levels of platelet activation markers were significantly higher in HIV-infected patients than in healthy control subjects and did not decrease in response to therapy.

Discussion

In this study, we demonstrated that HIV infection with ongoing viral replication leads to a significant elevation of endothelial, platelet, and, to a lesser extent, coagulation activation markers. We also showed that therapy substantially decreases but does not completely normalize the endothelial activation state.

Levels of endothelial activation markers are elevated in HIV-infected patients and are sometimes associated with a hypercoagulable state [22]. Activated endothelial cells promote platelet activation, inflammatory reactions, and progression of atherosclerosis [12]. In combination with other humoral factors, these effects can lead to a prethrombotic state. Indeed, a predisposition to thrombosis has been described in AIDS patients and was attributed to changes in various hemostatic balances [19]. In our patients, levels of biological endothelial markers (sVCAM-1, sICAM-1, and von Willebrand factor) were high before treatment; they decreased significantly after initiation of treatment but were still higher than levels in control subjects. This might be due to persistence of viral replication; concomitant infections, such as hepatitis C; or differences in smoking history. Interestingly, levels of sVCAM-1 and von Willebrand factor correlated significantly with levels of D-dimers, which implies that an association exists between endothelial stimulation and activation of the coagulation cascade. This correlation diminished after treatment, probably because levels of endothelial activation markers decreased.

The levels of markers of platelet activation (soluble CD40 ligand and sP-selectin) were high among HIV-infected patients

Table 2. Levels of endothelial, coagulation, and platelet activation markers in human immunodeficiency virus (HIV)–infected patients receiving protease inhibitors (PIs) or nonnucleoside reverse-transcriptase inhibitors (NNRTIs), compared with levels in HIV-negative control subjects.

	Patients receiving PIs (n = 21)		Patients receiving NNRTIs (n = 20)		
Activation marker	Before initiation of treatment	After initiation of treatment	Before initiation of treatment	After initiation of treatment	Control subjects (n = 21)
Endothelial, mean (±SD)					
sVCAM-1, ng/mL	595 (266)[a]	381 (98)[a,b]	790 (442)[a]	515 (324)[a,b]	223 (42)
sICAM-1, ng/mL	313 (125)[a]	267 (86) [a,b]	444 (218)[a]	401 (249)[a,b]	168 (30)
von Willebrand factor, %	120 (45)	99 (39)[b]	149 (35)[a]	129 (33)[a,b]	98 (28)
Thrombomodulin, ng/mL	78 (16)[a]	77 (14)	46 (16)[a]	47 (17)[a]	67 (11)
Coagulation, mean (±SD)					
D-dimers, ng/mL	311 (248)	224 (320)[b]	141 (118)	74 (57)[b]	153 (68)
Thrombin–antithrombin III complex, g/L	4.9 (7.7)	3.5 (2.6)	5.5 (5.7)	13 (18.3)[a]	3.2 (0.6)
Platelet, mean (±SD)					
sP-selectin, ng/mL	79 (84)[a]	67 (16)	49 (32)	58 (44)	34 (9)
Soluble CD40 ligand, ng/mL	2.3 (2.3)[a]	1.9 (0.7)[a]	2.3 (3.0)	3.1 (3.4)[a]	0.7 (0.3)

NOTE. sICAM, soluble intercellular adhesion molecule; sP, soluble platelet; sVCAM, soluble vascular cell adhesion molecule.
[a] Statistically significantly higher than that of the control group (calculated using 1-way analysis of variance, Scheffé test, and Bonferroni correction; $P < .05$).
[b] Statistically significantly lower than values before initiation of treatment (calculated using paired Wilcoxon rank sum test; $P < .01$).

with platelet counts comparable to those of control subjects. Both markers normally reside inside the platelet and are expressed on the surface only after activation and release. CD40 ligand can also be found on macrophages or activated T cells. Induction of tissue factor expression on macrophages [29] or endothelial cells [30] by the receptor CD40 and its ligand has been described. In HIV-infected patients, binding of CD40 ligand to its receptors on CD4 cells or endothelial cells may lead to an increase in the inflammatory reaction, up-regulation of cell adhesion molecules, and, potentially, a hypercoagulant effect [15, 30]. In our study, 22% of the case patients but none of the control subjects presented with thrombocytopenia (platelet count $<150 \times 10^9$ platelets/L). If platelet counts had been higher, levels of activation might have been even higher, strengthening our comparison of levels of platelet activation in HIV-infected patients with levels in control subjects. In our case patients, levels of increased soluble CD40 ligand correlated strongly with levels of sP-selectin, which indicates that these markers have in common either platelet origin or an event causing stimulation of platelets and T cells in parallel. CD40 ligand is expressed on activated T cells, macrophages, mast cells, and basophils, as well as on the platelet surface after platelet activation [15, 29, 30]. CD40 ligand plays an important role in HIV disease progression. CD40 ligand is expressed on activated T cells and may contribute to the control of viral replication at the initial stages of HIV infection by stimulating the expression of chemokines that have an anti-HIV effect [31]. On the other hand, CD40 ligand activates dendritic cells or macrophages later in the progression of HIV disease, thereby stimulating activity of helper T cells and replication of HIV [31].

Our results demonstrate that endothelial stimulation may result in activation of coagulation and fibrinolysis in HIV-infected patients. Levels of sVCAM-1 correlated well with levels of D-dimers and von Willebrand factor. In addition, levels of sVCAM-1, D-dimers, and von Willebrand factor correlated well with the virus load before initiation of treatment in our study, indicating that an association exists between the stimulation of endothelium and coagulation mechanisms and the effects of HIV infection. Promotion of bleeding tendency in HIV-infected hemophiliac, as well as nonhemophiliac, patients by PIs has been described [32]. This effect has been attributed to a reduction in levels of platelet activation or possible hypofibrinolysis [23]. One might speculate that fast reversion of endothelial activation and elevation of cholesterol levels lead to endothelial destabilization.

In our study, the results of treatment with PIs and NRTIs were consistent with the results of treatment with an NNRTI and NRTIs. This may demonstrate that reversion of endothelial activation is mediated via control of viral replication and not via mechanisms associated with drug class. In addition, the decrease of virus load was almost identical in the 2 treatment groups (table 1). An alternative hypothesis would be that the effects of therapy are mediated by the NRTIs, which were part of both regimens.

Our study was not designed to define differences between the results of treatment with PIs and the results of treatment with NNRTIs; its primary goal was to assess whether any difference is seen in levels of endothelial, coagulation, and platelet activation markers in HIV-infected patients before and after initiation of HAART. However, results in patients treated with PIs and patients treated with NNRTIs show the same trends. Whether the effects of such treatment reduce the risk of clinically relevant atherosclerosis, as has been demonstrated in pilot studies involving patients treated with anti-*Chlamydia* antibiotics [33], remains to be proven.

Are the changes found in this study in endothelial, coagulation, and platelet activation biologically relevant? Several studies confirm that elevated plasma levels of endothelial markers, such as sVCAM-1 and sICAM-1, may serve as molecular

markers for atherosclerosis and are independent risk factors for the development of coronary heart disease [34, 35]. In addition, elevated plasma levels of D-dimers are independently associated with myocardial infarction, and reduction of levels of von Willebrand factor might protect patients from myocardial infarction [36, 37]. The degree of platelet activation found in our patients may represent a biologically and clinically significant risk factor for thrombotic events [23, 38]. The degree of elevation of levels of the investigated factors in HIV-infected patients is similar to or even greater in magnitude than changes reported to be a risk factor for cardiovascular disease. One study reports that patients with incident coronary heart disease or carotid artery atherosclerosis had mean ICAM-1 levels of 289 ng/mL and 284 ng/mL, respectively, compared with 244 ng/mL in healthy control subjects [39]. This is in keeping with the findings of another study, in which the mean ICAM-1 level was measured at 320 ng/mL in patients with coronary heart disease and at 275 ng/mL in control subjects [40].

Unlike the authors of other studies, we did not observe a decrease in levels of platelet activation markers in patients who were receiving antiretroviral treatment [23]. This may be due to the short observation period that we used and the low mean virus load found in our patients before initiation of antiretroviral therapy. In our study, cholesterol levels increased after initiation of antiretroviral therapy in patients who received PIs (data not shown), which strengthens the interpretation of our results. Higher cholesterol concentrations are associated with endothelial, coagulation, and platelet activation [41, 42]. Our patients had less-pronounced viral activity and higher CD4 cell counts than other patients in the SHCS [26]. It may be that the differences in levels before and after initiation of HAART would be even more pronounced in patients who have more-advanced disease.

Our study may have limitations. For example, differences in HCV positivity might explain some of the differences seen between patients and control subjects; infection with pathogens other than HIV could lead to elevated levels of endothelial and coagulation markers. However, it can be assumed that antiretroviral therapy had a negligible impact on activity of HCV. Therefore, differences seen in levels of markers before and after initiation of HAART should not be influenced by HCV infection. Smoking history was not assessed, but smoking might have influenced the levels of endothelial and coagulation activation in patients and control subjects. However, changes in the parameters we investigated that occurred after initiation of therapy would not be influenced by this, because smoking cessation was probably rare in HIV-infected patients during the follow-up period.

Several questions remain unanswered (e.g., what is the molecular mechanism of this effect?). Although our study needs confirmation from larger trials, our results indicate that antiretroviral treatment in HIV-infected patients that is associated with decreased endothelial and coagulation activation may reduce inflammation and, thereby, the risk of atherosclerosis. Whether the observed effects reduce the risk of atherosclerosis in HIV-infected individuals treated with HAART who present with associated dyslipidemia remains to be proven. Certainly, such mechanisms are not sufficient to prevent all atherosclerotic development; premature lesions of the carotid vessels have been observed in HIV-infected patients treated with PIs [43]. Nevertheless, the beneficial effects might postpone clinical manifestations of atherosclerosis, such as coronary artery disease or stroke.

Swiss HIV Cohort Study Members

The members of the Swiss HIV Cohort Study Group are M. Battegay (chairman of the Scientific Board), M.-C. Bernard, E. Bernasconi, H. Bucher, P. Bürgisser, M. Egger, P. Erb, W. Fierz, M. Flepp (chairman of the Clinical and Laboratory Committee), P. Francioli (president of the Swiss HIV Cohort Study), H. J. Furrer, M. Gorgievski, H. Günthard, P. Grob, B. Hirschel, C. Kind, T. Klimkait, B. Ledergerber, U. Lauper, M. Opravil, F. Paccaud, G. Pantaleo, L. Perrin, J.-C. Piffaretti, M. Rickenbach (head of the Data Center), C. Rudin (chairman of the Mother and Child Substudy), J. Schupbach, A. Telenti, P. Vernazza, T. Wagels, and R. Weber.

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