MAJOR ARTICLE

Predictors of Immunological Failure after Initial Response to Highly Active Antiretroviral Therapy in HIV-1–Infected Adults: A EuroSIDA Study

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Background. Factors that determine the immunological response to highly active antiretroviral therapy (HAART) are poorly defined.

Objective. Our aim was to investigate predictors of immunological failure after initial $CD4^+$ response.

Methods. Data were from EuroSIDA, a prospective, international, observational human immunodeficiency virus (HIV) type 1 cohort.

Results. Of 2347 patients with an increase in $CD4^+$ cell count $\geqslant$100 cells/μL within 6–12 months of the initiation of HAART, 550 (23%) subsequently experienced immunological failure ($CD4^+$ count less than or equal to the pre-HAART value). The incidence of failure was 11.6 incidences/100 person-years of follow-up (95% confidence interval [CI], 10.2–13.4) during the first 12 months and decreased significantly over time ($P < .0001$). Independent predictors of immunological failure were pre-HAART $CD4^+$ cell count (per 50% higher; relative hazard [RH], 2.05; 95% CI, 1.83–2.31; $P < .0001$), time-updated virus load (per 1 $\log_{10}$ higher; RH, 1.77; 95% CI, 1.64–1.92; $P < .0001$), and HIV-1 risk behavior ($P = .047$ for a global comparison of risk groups).

Conclusion. The risk of immunological failure in patients with an immunological response to HAART diminishes with a longer time receiving treatment and is associated with pretreatment $CD4^+$ cell count, ongoing viral replication, and intravenous drug use.

In patients infected with HIV-1, the primary treatment goal of highly active antiretroviral therapy (HAART) is to suppress the HIV-1 RNA level in plasma (i.e., the plasma virus load [pVL]) to below the level of detection [1, 2]. In both cohort studies and randomized clinical trials (RCTs), a lower pVL has been associated with a reduction in HIV-1–related morbidity and mortality [3–5]. The results of recent cohort studies and RCTs have, however, suggested that baseline and time-updated $CD4^+$ cell counts are better predictors of HIV-1 disease progression than are pVLs [6–8].

Discordant virological and immunological responses have been observed during HAART [9–11]. Similarly, virological and immunological failure has been observed to occur independently during HAART [12]. This suggests a complex interaction between the virological response to HAART and the resulting change in $CD4^+$ cell count. In the results of a previous study from the EuroSIDA cohort, older age and being naive for antiretroviral therapy (ART) were identified as predictors of a sustained virological response during HAART [13]. Furthermore, younger age, being naive for ART, and having a lower baseline pVL and $CD4^+$ cell count were shown to be independent predictors of virological failure in the APROCO cohort [14]. The identification of predictors of immunological failure after the initial response to HAART, which may be different from predictors of virological failure, may have implications for the treatment of patients. To our knowledge, such data have not previously been reported from a large international HIV-1 cohort.

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PATIENTS AND METHODS

Patients. The EuroSIDA study is a prospective observational study of HIV-1–infected patients from 70 centers in 27 countries across Europe, plus Israel and Argentina. For analysis, countries have been grouped into the following regions: central (Austria, Belgium, France, southern Germany, Luxembourg, and Switzerland), east (Hungary, Poland, Czech Republic, Slovakia, Estonia, Latvia, Lithuania, and Romania), north (Denmark, Finland, northern Germany, Ireland, Norway, Sweden, The Netherlands, and the United Kingdom), south (Greece, Israel, Italy, Portugal, and Spain), and Argentina. Details of the study have been published elsewhere [15]. In brief, centers provided data on consecutive patients seen in outpatient clinics from 2 May 1994 until a predefined number of patients was enrolled at each center. This cohort of 3116 patients was defined as the EuroSIDA 1 cohort. In December 1995, enrollment began for the EuroSIDA 2 cohort ($n = 1365$ patients). In April 1997, a further 2839 patients were enrolled (the EuroSIDA 3 cohort). The EuroSIDA 4 cohort, which consisted of 1225 patients, was enrolled starting in April 1999, and the EuroSIDA 5 cohort, which consisted of 1258 patients, was enrolled starting in November 2001. For cohorts 1–3, eligible patients were those with a $CD4^+$ cell count <500 cells/L during the preceding 4 months, a scheduled clinic appointment, and age >16 years at the time of enrollment. The $CD4^+$ cell-count restriction was removed for cohorts 4 and 5. Information was provided on a standardized data-collection form at baseline and every 6 months thereafter. Follow-up continued until spring 2003, with information from up to 17 forms available for cohort 1, up to 12 forms for cohort 2, up to 9 forms for cohort 3, up to 6 forms for cohort 4, and up to 2 forms for cohort 5. At each follow-up visit, details on all $CD4^+$ cell counts measured since the last follow-up visit and pVL measurements were obtained. For each patient, the date of starting and stopping each antiretroviral drug was recorded. Dates of diagnosis of all AIDS-defining diseases were also recorded, including those diagnoses made subsequent to the initial diagnosis, using the 1993 clinical definition of AIDS from the Centers for Disease Control and Prevention [16]. An extensive quality-assurance program was established that included data control at the coordinating center as well as site visits to check selection of patients and perform source verification. The information used in the present analysis included demographic data (age, ethnic origin, sex, country of origin, and risk group) and clinical factors (hemoglobin level, $CD4^+$ cell count, pVL, start and stop dates of each ART regimen, and dates and type of AIDS-defining diseases).

Patients were included in the analysis if they initiated HAART and had at least 1 $CD4^+$ cell count done within 6 months before starting HAART (i.e., any combination of $\geq$3 antiretroviral drugs, including at least 1 protease inhibitor [PI], 1 nonnucleoside reverse-transcriptase inhibitor [NNRTI], or abacavir). The last available $CD4^+$ cell count before the start of HAART was termed the pre-HAART $CD4^+$ cell count. Patients with an increase from the pre-HAART $CD4^+$ cell count of at least 100 cells/μL 6–12 months after the initiation of HAART were identified as immunological responders. Patients without this increase in $CD4^+$ cell count were excluded from further analysis (immunological nonresponders). The level and date of the first $CD4^+$ cell count that was $\geq$100 cells/μL higher than the pre-HAART $CD4^+$ cell count was chosen as the baseline $CD4^+$ cell count and date. Patients were monitored from baseline until they had immunological failure or, if they did not have immunological failure, until the last recorded $CD4^+$ cell count. Patients whose $CD4^+$ cell count dropped to or below the pre-HAART $CD4^+$ cell count were considered to have experienced immunological failure, in our analyses. To qualify as an immunological response or failure, only 1 $CD4^+$ cell count measurement that met the failure criteria was necessary.

Statistical methods. As a simple summary measure, the changes in $CD4^+$ cell count and proportion of patients with a pVL <400 copies/mL between starting HAART and the end of the study were calculated. During each calendar month, patients with either a $CD4^+$ cell count or a pVL recorded in that month contributed to analyses in that month. Changes in $CD4^+$ cell count between starting HAART and baseline were expressed relative to pre-HAART levels. Patients were included in the analysis until they had achieved an immunological response for 6–12 months. After the initial immunological response, changes in $CD4^+$ cell count were estimated relative to baseline levels. A lower limit of detection for pVL of 400 copies/mL was chosen because of the wide range of assays used across centers.

Kaplan-Meier survival curves were used to describe the median time to the modification of therapy or to immunological failure. Person-years of follow-up (PYFU) and Poisson regression were used to determine whether the rate of immunological failure changed over time. Cox proportional-hazards models were used to determine the factors associated with immunological failure; all Cox models were stratified by center. Variables fitted in Cox models included all available demographic variables (sex, risk behavior, ethnic origin, and age), whether a diagnosis of AIDS had been made before baseline, and the date of starting HAART. The ART history before starting HAART included ART-naive patients, number of ART drugs in the HAART regimen (3 or $\geq$4), the cumulative number of ART drugs each patient had been exposed to before starting HAART, the drugs in HAART regimen started, and the number of new ART drugs started at the date of starting HAART. The models were also adjusted for immunological and virological factors, including nadir $CD4^+$ cell count, change in $CD4^+$ cell count (i.e., baseline $CD4^+$ cell count minus nadir $CD4^+$ cell count), pre-HAART $CD4^+$ cell count, time from nadir $CD4^+$ cell count to starting HAART, change in $CD4^+$ cell count between starting

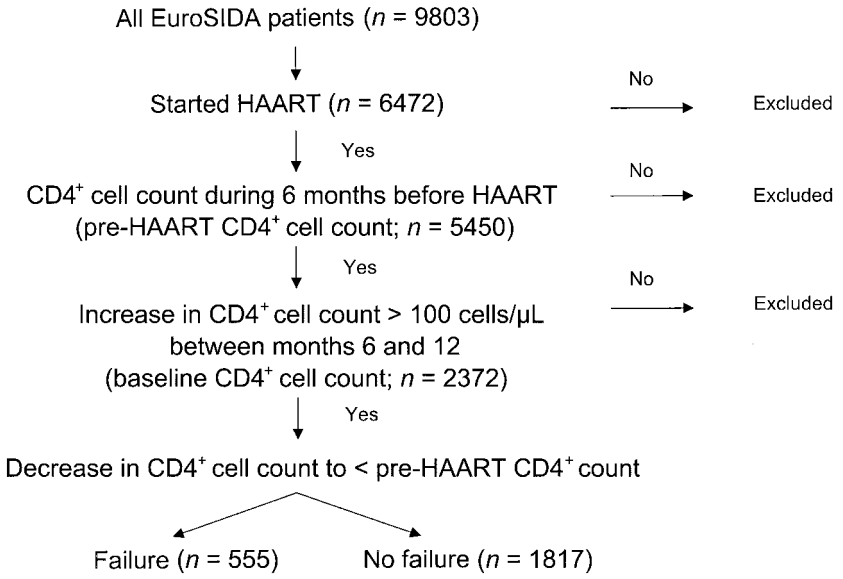

Figure 1. Selection of patients for analysis

HAART and baseline, and pVL (included in multivariate models as both a fixed and a time-dependent covariate). Variables that were not significant in univariate analyses ($P > .10$) were excluded from multivariate analyses. Various additional analyses were performed to determine the sensitivity of the results to small changes in the assumptions. All analyses were performed using Statistical Analysis Software (version 6.12; SAS Institute); all significance tests were 2-sided.

RESULTS

As of spring 2003, the EuroSIDA database contained follow-up data on 9803 patients, of whom 6472 had initiated HAART. A pre-HAART $CD4^+$ cell count was available from 5450 patients. Of these, 2372 showed an increase in $CD4^+$ cell count $\geq$100 cells/μL 6–12 months after the initiation of HAART (baseline $CD4^+$ cell count) and, thus, were eligible for the present analysis (figure 1). There was a median of 12 $CD4^+$ cell-count measurements after baseline/patient (interquartile range [IQR], 5–19 measurements/patient) at a median time apart of 3 months (IQR, 2–4 months). There was a median of 11 pVL measurements/patient (IQR, 5–18 measurements/patient) at a median time apart of 3 months (IQR, 2–4 months). The rate of loss to follow-up in EuroSIDA was ~10%.

Patient characteristics. Eighty-eight percent of patients were white, 78% were men, 48% had male homosexual HIV-1 risk behavior, and the median age was 37.4 years (IQR, 32.7–44.7 years) (table 1). Of 621 patients who had received a diagnosis of AIDS at or before baseline, 412 (66%) had 1 new AIDS-defining disease, 144 had 2 (23%), and 65 had $\geq$3 (11%). The median pre-HAART $CD4^+$ cell count was 200 cells/μL (IQR, 84–315 cells/μL), and the median pVL, measured during the 6 months before starting HAART, was 4.57 $\log_{10}$ copies/mL (IQR, 3.79–5.19 $\log_{10}$ copies/mL)—this measurement was available for 1893 patients (79.8%). The median time between the pre-HAART $CD4^+$ cell count and starting HAART was 1 month (IQR, 0–2 months). Most patients (74%) initiated a single PI-based HAART regimen, and 12% initiated a NNRTI-based HAART regimen. Seven percent initiated a mixed regimen, and only 38 patients (<2% of total) started a triple-nucleoside regimen that contained abacavir.

Response to HAART. At 3 and 6 months after the initiation of HAART, the median increase in the $CD4^+$ cell count since the start of HAART was 88 and 120 cells/μL, respectively. The proportion of patients with a pVL <400 copies/mL increased rapidly during the months after starting HAART (figure 2) and reached ~55% by month 6 after starting HAART. After baseline, this proportion remained fairly steady at ~60%–70%. In contrast, the $CD4^+$ cell count initially decreased by a very small amount and then slowly began to increase again. The median increase in $CD4^+$ cell count from pre-HAART to baseline was 171 cells/μL (IQR, 130– 241 cells/μL). Significant differences in the increase in $CD4^+$ cell count from the pre-HAART level to baseline, according to patient characteristics, were seen, of which the most pronounced was the difference between patients who had a nadir $CD4^+$ cell count <50 cells/μL versus those who had a nadir $CD4^+$ cell count $\geq$250 cells/μL, who had increases of 153 and 202 cells/μL, respectively ($P < .0001$, Wilcoxon test).

The median baseline pVL was 2.60 $\log_{10}$ copies/mL (IQR, 1.70–3.00 $\log_{10}$ copies/mL), the median baseline $CD4^+$ cell count was 393 cells/μL (IQR, 260–544 cells/μL), and the median nadir $CD4^+$ cell count was 150 cells/μL (IQR, 55 251 cells/μL). The median change in $CD4^+$ cell count was 216 cells/μL (IQR, 152–312 cells/μL); this variable was very strongly correlated with the baseline

Table 1. Patient characteristics at the time of inclusion.

Parameter	Percentage of patients (N = 2372)
Sex	
Female	21.9
Male	78.1
Risk behavior	
Heterosexual contact	19.6
Homosexual contact	47.9
Intravenous drug use	25.4
Other	7.1
Region	
Central	25.7
East	10.3
North	34.3
South	28.5
Argentina	1.1
Age, years	
<30	14.0
30–39	45.9
⩾40	40.1
Nadir CD4$^+$ cell count, cells/μL	
<50	22.8
50–149	26.7
150–249	24.8
⩾250	25.7
Prior diagnosis of AIDS	
No	73.8
Yes	26.2
ART naive	
No	62.5
Yes	37.5
HAART	
Single PI based	73.8
Dual PI based	6.8
NNRTI based	12.4
Mixed	7.0

NOTE. ART, antiretroviral therapy; HAART, highly active antiretroviral therapy; NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

CD4$^+$ cell count (correlation coefficient, 0.94; $P < .00001$). The median time between the nadir CD4$^+$ cell count and starting HAART was 3 months (IQR, 1–14 months), and the median follow-up time since baseline was 40 months (IQR, 15–57 months), with a total of 7329 PYFU.

Modification to HAART. Modification to the HAART regimen during follow-up was seen in 1769 patients (75%) , 1720 of whom stopped taking at least 1 drug and 1664 of whom started taking at least 1 new drug. Between the initiation of HAART and baseline, 627 (26%) started at least 1 new drug, and a further 1037 patients (44%) started at least 1 new drug after baseline. During the same follow-up periods, 657 (28%) and 1063 (45%) stopped taking at least 1 drug. The median time to any modification of HAART was 20 months (IQR, 19–22 months); this was significantly shorter among patients who had both a lower baseline CD4$^+$ cell count ($P < .0001$, log rank test) and a higher pVL ($P = .0071$, log rank test). Six hundred ninety-nine patients continued the original HAART regimen throughout the study—that is, until the time of the last CD4$^+$ cell count or immunological failure, and all 2372 patients were receiving ART at that time.

Immunological failure. Of the 2372 immunological responders, 555 (23%) subsequently had immunological failure (i.e., had at least 1 CD4$^+$ cell count that was less than or equal to the pre-HAART CD4$^+$ cell count). At 12 months after the initial immunological success, 11.1% of patients were estimated to have had immunological failure (95% CI, 9.8–12.4, Kaplan-Meier estimate). In addition, there was a gradual and significant decrease in the rate of immunological failure over time (table 2). For example, during the first 12 months after the initial response to HAART, the incidence of failure was 11.6 incidences/100 PYFU (95% CI, 10.2–13.0); this decreased to 5.0 incidences/100 PYFU 24–36 months after the initial immunological response (95% CI, 3.8–6.2). The test for trend over time showed a 28% decrease in the rate of immunological failure with each additional year since the initial immunological success (95% CI, 22%–33%; $P < .0001$, Poisson regression). The median CD4$^+$ cell count at the time of immunological failure, for those who experienced failure, was 240 cells/μL (IQR, 136–357 cells/μL).

Predictors of immunological failure. Cox models were constructed to investigate the factors associated with immunological failure. All models were stratified by center (table 3). Factors associated with immunological failure in the univariate model were HIV-1 risk behavior ($P = .047$ for global comparison of risk groups), age, nadir CD4$^+$ cell count at the start of HAART (per 50% higher), time since nadir CD4$^+$ cell count at the start of HAART (per 6 months more), pre-HAART CD4$^+$ cell count (per 50% higher), any change to the HAART regimen (yes/no), HAART regimen started, date of starting HAART (per 6 months more), number of drugs the patient had ever been exposed to (per drug), and most recent pVL (per 1 $\log_{10}$ higher). The pVL at baseline was also significant in a univariate model. Compared with ART-experienced patients, ART-naive patients were less likely to experience failure. In the multivariate model that used time-updated covariates, 3 factors remained significantly associated with an increased risk of immunological failure: pre-HAART CD4$^+$ cell count (RH, 2.05; 95% CI, 1.83–2.31; $P < .0001$), time-updated pVL (RH, 1.77; 95% CI, 1.64–1.92; $P < .0001$), and HIV-1 risk group, with all risk groups having a significantly decreased risk of immunological failure, compared with intravenous drug users. In addition, a change to the HAART regimen was of marginal statistical significance (RH, 1.21; 95% CI, 0.98–1.48; $P = .063$).

The analyses were repeated using baseline pVL and only changes to HAART that occurred before baseline; similar results

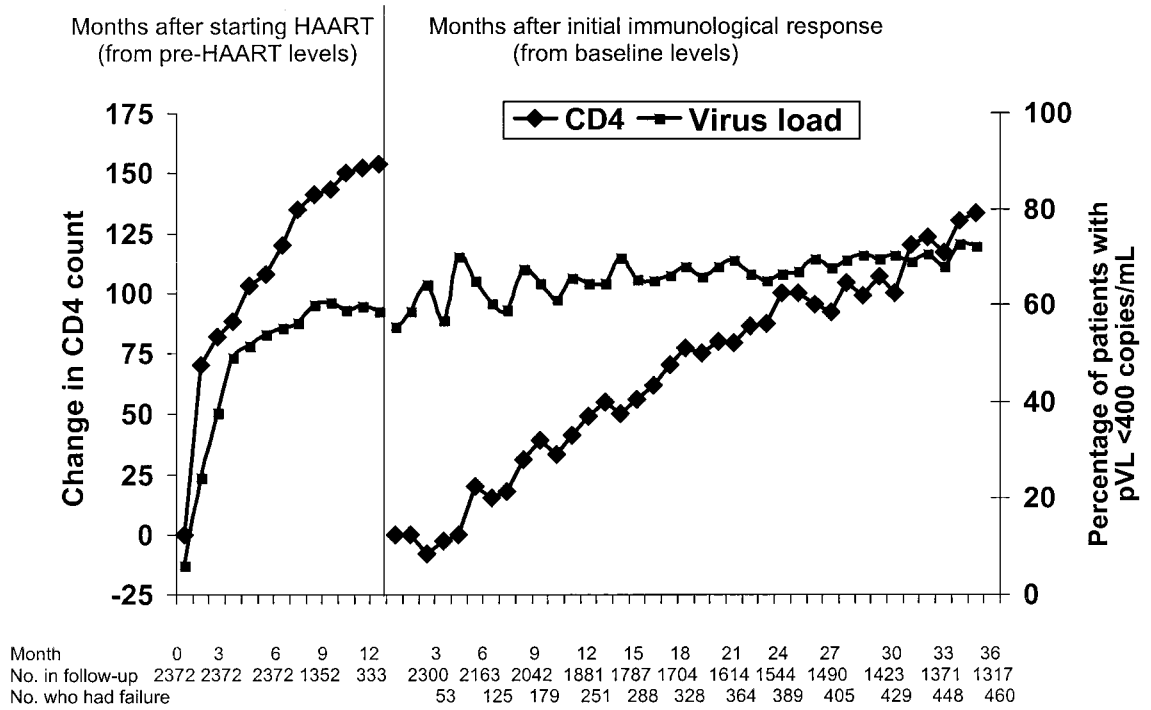

Figure 2. Changes in $CD4^+$ cell count and plasma virus load (pVL) after the initiation of highly active antiretroviral therapy (HAART)

were found, although, in this analysis, the baseline pVL was not associated with the risk of immunological failure (RH, 0.99; 95% CI, 0.89–1.09; $P = .84$), which suggests that it is more changes in pVL, rather than the initial pVL, that drive the immunological response.

The analyses were also repeated using a more strict definition of failure, in which patients were required to have a confirmatory $CD4^+$ cell count at or below the pre-HAART $CD4^+$ cell count. This reduced the number of events to 241 (10.1%), but the results were almost identical to those shown in table 3. In addition, the analyses were repeated using a definition of failure of a decrease of 100 cells/μL from the baseline $CD4^+$ cell count (thus, both the inclusion and failure criteria were defined using absolute $CD4^+$ cell counts). In this analysis, 11.5% of patients had immunological failure, but the results were almost identical to the previous findings, except that the association between a higher pre-HAART $CD4^+$ cell count and failure was even stronger. In this analysis, patients with pre-HAART $CD4^+$ cell counts <100 cells/μL were excluded (by definition, they could not experience failure). In addition, the analyses were repeated using an inclusion criteria of a 25% increase in $CD4^+$ cell counts after the initiation of HAART and a 25% decrease to below the pre-HAART $CD4^+$ cell count (thus, both the inclusion and exclusion criteria were defined using percentages). The results were, again, very similar.

DISCUSSION

In the present study of immunological failure in HIV-1–infected patients initiating HAART, 2372 patients from the EuroSIDA cohort were included, of whom 11.1% had immunological failure within 12 months of an initial immunological response to HAART. A higher pre-HAART $CD4^+$ cell count, higher time-updated pVL, and intravenous drug use were found to be independent predictors of immunological failure.

The study confirmed findings by Deeks et al. [12] that patients with a high pre-HAART $CD4^+$ cell count are at an increased risk of immunological failure. One reason for this finding could lie in the difference in actual numbers of $CD4^+$ cells at the time of failure, between patients with high and those with low pre-HAART $CD4^+$ cell counts. For instance, by use of our definition of immunological failure (a decrease in the $CD4^+$ cell count to or below the pre-HAART $CD4^+$ cell count),

Table 2. Rate of immunological failure over time.

Months of follow-up	PYFU	Immunological failures	Incidence (95% CI)
⩽12	2161.6	251	11.6 (10.2–13.0)
>12–24	1705.1	137	8.0 (6.7–9.3)
>24–36	1429.7	72	5.0 (3.8–6.2)
>36	2033.0	95	4.7 (3.8–5.6)

NOTE. CI, confidence interval; PYFU, person-years of follow-up.

Table 3. Factors associated with immunological failure.

	Univariate analysis			Multivariate analysis		
Factor	RH	95% CI	*P*	RH	95% CI	*P*
Risk behavior						
Intravenous drug use	1.00	…	…	1.00	…	…
Homo-/bisexual contact	0.75	0.58–0.96	.021	0.65	0.49–0.87	.0031
Heterosexual contact	0.83	0.64–1.08	.17	0.66	0.49–0.90	.0072
Other	0.59	0.38–0.92	.020	0.62	0.39–1.00	.050
Antiretroviral naive						
No	1.00	…	…	1.00	…	…
Yes	0.71	0.57–0.88	.016	0.94	0.69–1.30	.72
HAART regimen						
Single PI	1.00	…	…	1.00	…	…
Dual PI	1.30	0.90–1.88	.16	1.40	0.95–2.07	.088
Single NNRTI	1.91	1.46–1.91	<.0001	1.29	0.94–1.77	.19
Mixed regimen	1.24	0.82–1.88	.31	0.87	0.54–1.41	.58
Pre-HAART nadir $CD4^+$ cell count, per 50% higher	1.24	1.17–1.31	<.0001	0.96	0.91–1.02	.18
Pre-HAART $CD4^+$ cell count, per 50% higher	1.78	1.63–1.94	<.0001	2.05	1.83–2.31	<.0001
Plasma virus load,[a] per 1 $\log_{10}$ higher	1.52	1.42–1.63	<.0001	1.77	1.64–1.92	<.0001
Change to HAART[a]	1.27	1.04–1.54	.0023	1.21	0.98–1.48	.063
Total no. of ART drugs,[b] per ART	1.07	1.01–1.12	.017	1.09	0.96–1.13	.31
Time from nadir $CD4^+$ cell count,[c] per 6 months	1.09	1.06–1.12	<.0001	1.02	0.99–1.06	.15
Age, per 10 years older	0.92	0.84–1.02	.10	0.95	0.86–1.05	.34
Date started HAART, per 6 months later	1.20	1.11–1.30	<.0001	1.06	0.94–1.19	.38

NOTE. ART, antiretroviral therapy; CI, confidence interval; HAART, highly active antiretroviral therapy; NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; RH, relative hazard.

[a] Time-dependent covariate.
[b] Total no. of ART drugs ever exposed to.
[c] Time from HAART to baseline.

for a patient with a pre-HAART $CD4^+$ cell count of 500 cells/μL and an increase to 600 cells/μL (immunological response), immunological failure would be a $CD4^+$ cell count $\leqslant$500 cells/μL (a 17% decrease); in comparison, for a patient with a pre-HAART $CD4^+$ cell count of 50 cells/μL and an increase to 150 cells/μL, immunological failure would be a $CD4^+$ cell count $\leqslant$50 cells/μL (a 67% decrease). However, we found similar results when both immunological response and failure were defined as an increase and decrease in actual numbers and in percentages. Furthermore, we do not think that clinical practice is guided by changes in percentages. We hypothesize that the reason why patients with higher pre-HAART $CD4^+$ cell counts were found to be at increased risk of immunological failure, compared with those who had lower pre-HAART $CD4^+$ cell counts, is that the latter group of patients is at an increased risk of developing opportunistic diseases (ODs); thus, clinicians have a lower threshold for the modification of therapy in these patients, which thereby prevents or delays the development of immunological failure. This is supported by the significantly shorter time to modification of treatment seen in patients with lower pre-HAART $CD4^+$ cell counts and higher pVLs. Another explanation could be that patients with higher $CD4^+$ cell counts had lower adherence to or stopped receiving therapy at a time when the risk of developing an OD was less. In the example given above, even though a patient with a high $CD4^+$ cell count has a substantial numerical decrease in $CD4^+$ cell count, the $CD4^+$ cell count at the time of immunological failure is still well above any critical level, from a clinical point of view. Hence, despite immunological failure, patients with higher pre-HAART $CD4^+$ cell counts would be at less immediate risk of disease progression. In support of this, the median $CD4^+$ cell count at the time of immunological failure was found to be 240 cells/μL. Also, if patients with higher baseline $CD4^+$ cell counts were more likely to not be receiving treatment at the time of immunological failure, one would expect the patients to have a rebound in pVL. However, we found a higher baseline $CD4^+$ cell count to be predictive of failure independently of time-updated pVL.

Variability in $CD4^+$ cell measurements could potentially influence the rate of immunological failure. Such variability is, however, not likely to have had any significant effect on the outcome of the present study: we found similar results when a more strict definition of failure was used in which patients were required to have a confirmatory $CD4^+$ cell count.

The time-updated pVL was also found to predict immunological failure. This finding is in accordance with those of

previous studies. In a cohort of patients starting a PI regimen who subsequently had virological failure, Deeks et al. [12] found changes in pVL from pre–PI therapy levels and a high pVL to be associated with immunological failure. We also identified intravenous drug use to be a predictor of immunological failure. This is in accordance with previous results of cohort studies that have shown this risk group to have smaller increases in $CD4^+$ cell counts and an excess rate of progression of disease and death during HAART [7, 17].

The results of previous cohort studies have shown the use of nucleoside reverse-transcriptase inhibitors before HAART to be predictive of failure [18, 19]. In the present study, being naive for ART was found to be significantly associated with a diminished risk of immunological failure in the univariate, but not in the multivariate, model. In a previous study from the EuroSIDA cohort, Paredes et al. [13] found virological failure in ~37% of patients 12 months after they had achieved viral suppression. In the present study, ~11% of patients had immunological failure 12 months after an initial response to HAART. This difference is to be expected if patients are treated according to current treatment guidelines, which aim to suppress pVL rather than increase $CD4^+$ cell counts—treatment is changed shortly after virological failure rather than after immunological failure. No data exist about which treatment strategy is better, the maximal and durable suppression of pVL, as stated in current treatment guidelines, or a strategy to maintain the $CD4^+$ cell count above a certain level where the development of ODs is infrequent [1, 2]. An international RCT (the SMART study) is currently investigating this question. Should the SMART study show the superiority of a treatment strategy driven by $CD4^+$ cell count, the identification of predictors of a sustained immunological response could prove to be of clinical significance.

In a large international HIV-1 cohort, we have found that the risk of immunological failure in patients with an immunological response to HAART diminishes with a longer time receiving treatment. Immunological failure was associated with the pre-HAART $CD4^+$ cell count, the rate of ongoing viral replication, and intravenous drug use. These findings may have implications for the clinical treatment of HIV-1–infected patients.

THE EUROSIDA STUDY GROUP

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