

Relations among CD4 Lymphocyte Count Nadir, Antiretroviral Therapy, and HIV-1 Disease Progression: Results from the EuroSIDA Study

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Background: The effect of previous CD4 cell count nadir on clinical progression in patients with increases in CD4 cell counts has not been investigated.

Objective: To assess risk for progression of HIV disease in patients with CD4 counts of at least 200 cells/mm³ (stratified by the lowest previous CD4 count) and compare the rate of progression in patients with CD4 counts less than 50 cells/mm³ with that in patients whose CD4 counts rebounded from less than 50 cells/mm³ to at least 200 cells/mm³.

Design: Prospective, observational multicenter study.

Setting: 52 HIV outpatient clinics in Europe.

Patients: Two groups were identified: those with CD4 counts of at least 200 cells/mm³ (group A) and those with CD4 counts less than 50 cells/mm³ (group B). Group A was stratified according to the lowest previous CD4 count: at least 150 cells/mm³ (stratum 1), 100 to 149 cells/mm³ (stratum 2), 50 to 99 cells/mm³ (stratum 3), and 1 to 50 cells/mm³ (stratum 4).

Measurements: Patients were followed until a progression event occurred (first AIDS-defining event, new AIDS-defining event, or death) or until the CD4 count decreased to less than 200 cells/mm³ (group A) or increased to more than 50 cells/mm³ (group B). Incidence rates were based on a patient-years analysis and reported as events per 100 patient-years of follow-up; the relative hazards for progression were based on Cox proportional hazards models.

Results: The overall rate of disease progression in group A was 3.9 per 100 patient-years (95% CI, 3.5 to 4.3 per 100 patient-years), whereas in group B it was much higher (72.9 per 100 patient-years [CI, 69.0 to 76.8 per 100 patient-years]). In group A, the rate increased in patients with previous low CD4 cell count nadirs, resulting in a significant increase in the relative hazard for progression. The relative hazards for strata 2, 3, and 4 were 2.29 (CI, 1.30 to 4.03), 3.65 (CI, 1.94 to 6.85), and 2.94 (CI, 1.44 to 6.00), respectively.

Conclusions: Increases in CD4 counts from very low levels to at least 200 cells/mm³ are associated with a much reduced rate of disease progression. However, a previously low CD4 cell count nadir remains associated with a moderately higher risk for disease progression among patients with CD4 counts of at least 200 cells/mm³.

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* For members of the EuroSIDA Study Group, see Appendix.

The availability and widespread use of highly active antiretroviral therapy have led to marked decreases in the incidence of AIDS-defining illnesses and death (1–3). Highly active antiretroviral therapy substantially increases CD4 lymphocyte counts (4–6) and T-cell function (7–9). Speculation exists about the immune reconstitution and complete recovery of patients infected with HIV (10). The potential for immune reconstitution after severe immunodeficiency is of clinical significance because it may change the need for primary and secondary prophylaxis (11) and will ultimately help to determine the well-being of the patient.

Viral load and CD4 cell counts have independently predicted HIV-1 disease progression (12). Clinical trials (13–15) have demonstrated that therapy-related changes in surrogate markers were associated with clinical benefit. However, the effect of a previous CD4 cell count nadir on clinical benefit in patients experiencing increases in CD4 cell count has not been addressed. In addition, an analysis of clinical benefit in patients whose CD4 cell counts have rebounded from very low levels compared with benefit in patients who do not experience such a rebound has not been reported. This information may be difficult to obtain through clinical trials and may be accessible only through large, standardized, monitored observational databases. We explored the relations among CD4 lymphocyte count, antiretroviral treatment, and clinical disease progression through an analysis of the EuroSIDA cohort study, which follows 7333 European patients infected with HIV-1.

Our first objective was to investigate the effect of a previous CD4 cell count nadir on prognosis (rate of disease progression and relative hazard for disease progression) in patients who have a CD4 count of at least 200 cells/mm³. We wanted to determine whether HIV-1 disease progresses at the same rate in two types of patients: 1) patients whose previously low CD4 counts have increased to and remain greater than 200 cells/mm³ and 2) patients whose CD4 counts have never decreased to less than 150 cells/mm³ (Figure). Our second objective was to investigate the effect of a rebound in CD4 cell count after a patient has experienced severe immunosup-

pression. We did this by comparing the rate of disease progression in patients with current CD4 counts of at least 200 cells/mm³ who had a previous nadir of 50 cells/mm³ or less (group A, stratum 4) with the rate of progression in patients with current CD4 cell counts of 50 cells/mm³ or less (group B) (Figure). In addition, we investigated the effect of type of antiretroviral treatment on disease progression in both patient groups.

Methods

The EuroSIDA study is a prospective, observational study of HIV-infected patients in 52 outpatient clinics across Europe (Appendix) (2, 16). Individual centers enrolled between 24 and 323 patients (13 centers enrolled >200 patients, 18 centers enrolled between 100 and 200 patients, and 21 centers enrolled <100 patients). Consecutive patients who made a regular appointment at least 2 weeks before recruitment were enrolled. Eligible patients were at least 16 years of age and had had a CD4 count less than 500 cells/mm³ in the previous 4 months. The EuroSIDA study has enrolled a total of 7333 patients who were recruited at three separate time points: May 1994 (cohort I; *n* = 3121), December 1995 (cohort II; *n* = 1369), and February 1997 (cohort III; *n* = 2843).

Information was collected on a standardized data collection form at baseline and every 6 months thereafter. This information included CD4 cell counts, starting and ending dates of each antiretroviral treatment, use of prophylaxis against opportunistic infections, and dates of diagnosis of all AIDS-defining diseases (according to the 1993 clinical definition of AIDS as determined by the Centers for Disease Control and Prevention). Members of the EuroSIDA coordinating office visited all centers to ensure that patients were selected correctly and that accurate data were provided.

Statistical Analysis

We identified two groups of patients. Patients in group A had CD4 counts of 200 cells/mm³ or greater; patients in group B had CD4 counts less than 50 cells/mm³. For example, a patient in group A who had a previous CD4 cell count nadir less than 50 cells/mm³ while enrolled in the study would have contributed data to group B for the period that the CD4 cell count was less than 50 cells/mm³. A single patient could thus contribute data to both groups, depending on the profile of CD4 cell counts. At recruitment, information on the four most recent CD4 counts was collected; these data were included in the analyses. Information on all CD4 cell counts measured after recruitment was also collected.

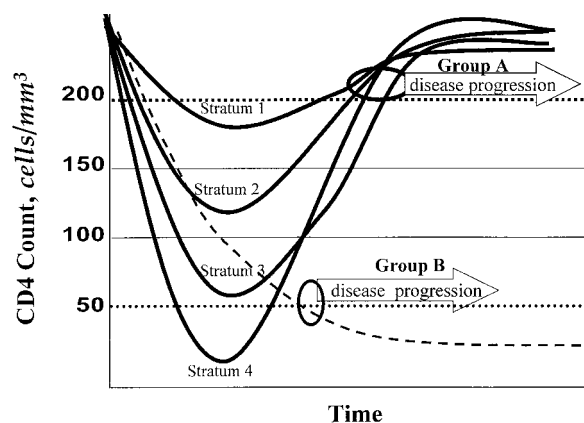


Figure. Study design. Disease progression for patients in group A was measured when CD4 count first reached a value of at least 200 cells/mm³. Patients were stratified according to the previous CD4 cell nadir (solid-line graphs). Follow-up for patients in group B began when the CD4 count first decreased to less than 50 cells/mm³ (broken-line graph). Dotted lines indicate the limits (≥ 200 cells/mm³ or < 50 cells/mm³) used to define patient group A and group B.

We used a patient-years method of analysis to calculate incidence of AIDS-defining illness or death, unadjusted for potential confounding variables. We calculated 95% CIs using a normal approximation or a Poisson distribution when the number of events was small. For the analysis of events in group A (patients with CD4 counts ≥ 200 cells/mm³), patient follow-up was from the date on which the first CD4 count of at least 200 cells/mm³ was obtained (referred to as baseline) until the CD4 count decreased to less than 200 cells/mm³ or the patients progressed to death or to an AIDS-defining illness. For patients who had AIDS at baseline, follow-up was continued until development of a new AIDS-defining illness (recurrences of disease were not included). Patients whose CD4 cell count did not decrease to less than 200 cells/mm³ and who did not experience an event were censored at their last follow-up visit. This analysis was stratified according to the minimum CD4 cell count experienced before baseline. Four strata were defined: CD4 cell count nadirs of 150 cells/mm³ or greater (stratum 1), 100 to 149 cells/mm³ (stratum 2), 50 to 99 cells/mm³ (stratum 3), and 1 to 50 cells/mm³ (stratum 4).

The incidence of disease in patients from group B (CD4 counts < 50 cells/mm³) was calculated in the same way. Patient follow-up began at the date on which the first CD4 count less than 50 cells/mm³ was obtained and ended when the CD4 count increased above this level, when the patient died, or when HIV-1 disease progressed. If none of these events occurred, follow-up ended at the last office visit.

To further investigate the relative hazard of disease progression according to CD4 cell count nadir in group A patients, we used Cox proportional hazards models. We investigated the relation between disease progression and such demographic factors

as age, exposure category, sex, and ethnicity. In addition, we considered the following factors at baseline: CD4 cell count, treatment regimen (no treatment, monotherapy, dual combination therapy, combination therapy with three or more drugs, or highly active antiretroviral therapy [defined as a minimum of one protease inhibitor or non-nucleoside reverse transcriptase inhibitor in combination with a minimum of two nucleoside reverse transcriptase inhibitors]), and whether AIDS had been diagnosed in a patient. With the exception of age, demographic factors were not related to disease progression in univariate models and were therefore not included in multivariate models. Variables were included in the multivariate model as fixed covariates. When measurements of CD4 cell count before recruitment to EuroSIDA were included, the analysis was left-censored at the date of recruitment. In the multivariate analysis, we also adjusted for calendar time (because of the strong relation between calendar time and the introduction of more effective therapies) and stratified by study center. We also adjusted for use of prophylaxis against *Pneumocystis carinii* pneumonia.

All analyses were done by using SAS software, version 2 (SAS Institute, Inc., Cary, North Carolina), with one exception: The CIs were calculated on a hand calculator with the use of tables for the Poisson distribution when the number of events was small.

Role of the Funding Source

The sponsors of the EuroSIDA study did not influence the organization or execution of the study in general; were not involved in the design, execution, and interpretation of this analysis; and had no role in the decision to publish these findings.

Results

The patient samples on which the analyses are based are described in **Table 1**. Of a total of 7333 EuroSIDA patients, 5352 had a CD4 count of at least 200 cells/mm³ (group A) and 2514 patients had CD4 cell counts of 50 cells/mm³ or less (group B). Group A patients were stratified according to CD4 cell count nadir: Those in stratum 1 had a nadir of at least 150 cells/mm³; those in stratum 2 had a nadir of 100 to 149 cells/mm³; those in stratum 3 had a nadir of 50 to 99 cells/mm³; and those in stratum 4 had a nadir of less than 50 cells/mm³. When we compared patients from these four strata, the median baseline CD4 cell count was significantly higher in patients from stratum 1. Baseline viral loads were available for a subset of patients only. Median baseline values were greater for patients from stratum 4 and group B.

Table 2 lists the number of events, patient-years of follow-up, and incidence rates for each patient

Table 1. Patient Characteristics

Characteristic	All Patients	Group A: CD4 Cell Count \geq 200 cells/mm ³ (Stratified by CD4 Cell Count Nadir)				Group B: CD4 Count <50 cells/mm ³
		\geq 150 cells/mm ³	100–149 cells/mm ³	50–99 cells/mm ³	<50 cells/mm ³	
All, n (%)	5352 (100)	4230 (79.0)	375 (7.0)	348 (6.5)	399 (7.5)	2514 (100)
Sex, n (%)						
Male	4172 (78.0)	3258 (77.0)	305 (81.3)	269 (77.3)	340 (85.2)	2139 (85.1)
Female	1177 (22.0)	970 (22.9)	70 (18.7)	79 (22.7)	58 (14.5)	375 (14.9)
Cohort, n (%)						
I	2054 (38.4)	1777 (42.0)	90 (24.0)	69 (19.8)	118 (29.6)	1506 (59.9)
II	991 (18.5)	734 (17.4)	66 (17.6)	80 (23.0)	111 (27.8)	472 (18.8)
III	2307 (43.1)	1719 (40.6)	219 (58.4)	199 (57.2)	170 (42.6)	538 (21.4)
Risk factor, n (%)						
Homosexual contact	2484 (46.4)	1916 (45.3)	186 (49.6)	156 (44.8)	226 (56.6)	1276 (50.7)
Intravenous drug use	1297 (24.2)	1066 (25.2)	89 (23.7)	75 (21.6)	67 (16.8)	604 (24.0)
Heterosexual contact	1256 (23.5)	998 (23.6)	81 (21.6)	93 (26.7)	84 (21.1)	467 (18.6)
Other	315 (5.9)	250 (5.9)	19 (5.1)	24 (6.9)	22 (5.5)	169 (6.7)
Ethnicity, n (%)						
White	4738 (88.5)	3754 (88.8)	324 (86.4)	296 (85.1)	364 (91.2)	2320 (92.3)
Other	614 (11.5)	476 (11.3)	51 (13.6)	52 (14.9)	35 (8.8)	196 (7.8)
Region, n (%)						
Southern Europe	1812 (33.9)	1488 (35.2)	114 (30.4)	106 (30.5)	104 (26.1)	848 (33.7)
Central Europe	1718 (32.1)	1328 (31.4)	129 (34.4)	116 (33.3)	145 (36.3)	718 (28.6)
Northern Europe	1822 (34.0)	1414 (33.4)	132 (35.2)	126 (36.2)	150 (37.6)	950 (37.8)
Age, y*	35.3	36.6	37.8	37.8	37.0	36.1
CD4 count, cells/mm ³ *	300 (240–397)	321 (254–420)	238 (215–278)	231 (210–272)	245 (210–297)	30 (15–40)
Viral load, log ₁₀ HIV-1 RNA copies/mL*	4.23 (3.07–5.04)	4.24 (3.20–4.90)	3.99 (2.87–5.02)	4.11 (2.77–4.96)	4.52 (3.07–5.27)	4.93 (4.00–5.42)
Patients with baseline viral load data available, %	29.6	17.3	60.0	80.5	87.0	16.4

* Median values at baseline (interquartile ranges).

Table 2. Incidence Rates and Duration of Follow-up*

Patients	CD4 Cell Count Category	Events	Duration of Follow-up	Median Follow-up	Incidence Rate (95% CI)†
	cells/mm ³	n	patient-years	mo	
Group A	>200				
All		348	8839.7	16	3.9 (3.5–4.3)
Stratum 1	≥150 (nadir)	306	8202.3	19	3.7 (3.3–4.1)
Stratum 2	100–149 (nadir)	15	248.1	6	6.0 (3.4–10.0)
Stratum 3	50–99 (nadir)	15	184.6	4	8.1 (4.5–13.4)
Stratum 4	<50 (nadir)	12	204.6	5	5.9 (3.0–10.2)
Group B	<50	1323	1813.8	6	72.9 (69.0–76.8)

* The incidence rates presented are unadjusted for any other variable; thus, differences in incidence rates among the four CD4 cell count nadir groups may be caused by various factors.
† Incidence rate expressed as the number of events per 100 patient-years of follow-up.

group and stratum. For patients in group A, the overall median duration of follow-up was 16 months; follow-up times decreased sharply as the nadir decreased. Patients in group B had a median follow-up duration of 6 months. The overall incidence for patients with CD4 counts of at least 200 cells/mm³ was 3.9 events per 100 patient-years of follow-up (95% CI, 3.5 to 4.3 events); within the four strata, patients from stratum 1 had the lowest incidence (3.7 events) and patients from strata 2, 3, and 4 had a higher incidence (6.0, 8.1, and 5.9 events, respectively). The incidence for patients from group B was 18-fold higher (72.9 events per 100 patient-years of follow-up [CI, 69.0 to 76.8 events]) than that for patients from group A. Patients in group A were censored if their CD4 count decreased to less than 200 cells/mm³, and patients in group B were censored if their CD4 count increased to more than 50 cells/mm³; therefore, all events occurred while CD4 cell counts were maintained at the respective designated levels.

Because patients who never had a CD4 count less than 150 cells/mm³ had a higher median baseline CD4 count, we repeated the analysis including only patients in stratum 1 with baseline CD4 counts of 300 cells/mm³ or less; this yielded a comparable incidence of 4.3 events per 100 patient-years (CI, 3.5 to 5.1 events).

We did not have sufficient data to stratify group A by viral load. However, patients whose disease was not progressing (median incidence, 4.22 events per 100 patient-years) did not differ significantly from patients whose disease was progressing (median incidence, 4.58 events).

Of the 348 events that occurred in group A, 17.2% were deaths, 71.3% were first AIDS-defining illnesses, and 11.5% were progressions to a new AIDS-defining illness. Seventy-four percent of events were confirmed diagnoses. The distribution of type of event differed significantly among the four strata: In strata 1 and 2, first AIDS-defining illnesses predominated (76.5% and 66.7%, respectively), whereas in strata 3 and 4, death (40% and 58.3%, respectively) and new AIDS-defining illnesses (40% and

33.3%, respectively) predominated ($P < 0.001$). Esophageal candidiasis was most common (19.6%), followed by Kaposi sarcoma (12.8%), *P. carinii* pneumonia (12.8%), pulmonary tuberculosis (8.7%), and non-Hodgkin lymphoma (7.6%). No diagnosis occurred significantly more frequently as a first AIDS-defining event ($P > 0.2$), and no relation existed between diagnosis and previous minimum CD4 cell count ($P > 0.2$) or between diagnosis and time to diagnosis ($P > 0.2$).

The four strata in group A also differed significantly in terms of time to the occurrence of an event. The overall median time to an event was 13 months (75% [range, 5.0 to 26.0 months]). Patients from strata 3 and 4 progressed the most rapidly (median, 3.0 and 2.0 months, respectively, compared with 15.0 months for patients in stratum 1; $P < 0.001$). With respect to type of event, patients experiencing a new AIDS-defining illness progressed the most rapidly (median, 4 months; $P < 0.001$).

We next examined the influence of type of antiretroviral treatment regimen on incidence of disease in both patient groups. **Table 3** shows the number of patients in each group and strata according to the number of drugs in the antiretroviral regimen and whether highly active antiretroviral therapy was used. Group A patients from strata 3 and 4 were more likely to be receiving combinations of three or more drugs at baseline than patients from stratum 1 (76.7% and 84.7%, respectively, compared with 10.7%) and were more likely to have received highly active antiretroviral therapy (55.0% and 58.1%, respectively, compared with 8.3%). In contrast, only 15.4% of patients with CD4 counts that remained less than 50 cells/mm³ were receiving a regimen of three drugs or more and only 10.9% were receiving highly active antiretroviral therapy.

Table 3 also shows the incidence rates for group A and group B. The incidence of disease progression decreased in both groups as the number of drugs in the antiretroviral regimen increased. This decrease was especially marked in patients from group B. Compared with the overall incidence of 72.9 events per 100 patient-years (CI, 69.0 to 76.8

events), the incidence in untreated patients was 99.6 events (CI, 90.3 to 108.9 events); the incidence among patients receiving regimens of three or more drugs was 34.8 events (CI, 26.3 to 43.3 events). Compared with patients not receiving highly active antiretroviral therapy (incidence, 76.4 events per 100 patient-years of follow-up [CI, 72.2 to 80.6 events]), potent antiretroviral treatment reduced the incidence of disease to 25.8 events (CI, 16.8 to 34.8 events). Thus, although more potent antiretroviral treatment considerably reduced the event rate in patients with very low CD4 cell counts, these rates nevertheless remained significantly higher than the rates in patients who experienced rebounds in CD4 cell counts.

The incidence rates presented in **Tables 2** and **3** are unadjusted for any other variable; thus, differences in incidence rates among the strata in group A may be due to such factors as age, sex, differences in treatment centers, or differences in antiretroviral regimen (as illustrated by the effect of the type of antiretroviral regimen). We therefore calculated the increased risk for disease progression according to CD4 cell count nadir using a proportional hazards model that allowed us to adjust for potential confounding variables (**Table 4**). In a univariate analysis, CD4 cell count nadir (in strata 2 and 3), age, baseline CD4 cell count, and previous diagnosis of AIDS were all significantly associated with a higher risk for disease progression. Antiretroviral treatment with two- or three-drug combinations was associated with a significantly lower risk.

The multivariate model indicates that a lower CD4 cell count nadir remains independently associated at a highly significant level with risk for disease progression among patients in strata 2, 3, and 4. Patients who had a nadir between 100 and 149 cells/

mm³ had a relative hazard of 2.29, patients who had a nadir between 50 and 99 cells/mm³ had a relative hazard of 3.65, and patients who had a nadir less than 50 cells/mm³ had a relative hazard of 2.94 (**Table 4**). The increase in rate of disease progression according to decreasing CD4 cell nadir is low compared with the increase in rate of disease progression for patients not experiencing rebounds in CD4 cell count; however, patients with previous low nadirs have a threefold higher risk for progression than those without previous low nadirs.

We performed a series of additional analyses to test the robustness of our findings. Consistent results were obtained when we adjusted for CD4 cell count as a time-dependent covariate, limited patients included in stratum 1 to those with CD4 counts less than 300 cells/mm³, limited the analysis to definitive diagnosis only, and limited the analysis to prospective data only. A proportional hazards model restricted to patients receiving therapy with at least two drugs yielded relative hazards values for strata 2 and 3 that were slightly higher than those reported in **Table 4**.

Discussion

In this analysis of disease progression, we have shown that for patients with current CD4 counts of at least 200 cells/mm³, a previous low CD4 cell nadir remains associated with a higher rate of disease progression and a higher relative hazard for progression compared with a CD4 count that never decreased to less than 150 cells/mm³. The threefold increase in risk was independent of antiretroviral treatment, age, baseline CD4 cell count, and previous diagnosis of AIDS. However, the rate of disease

Table 3. Distribution of Antiretroviral Treatment and Incidence Rates*

Treatment at Baseline	Distribution of Antiretroviral Treatments				Group B: CD4 Count < 50 cells/mm ³	Incidence Rate (95% CI)†	
	Group A: CD4 Count > 200 cells/mm ³ (Stratified by CD4 Cell Count Nadir)					Group A	Group B
	≥150 cells/mm ³	100–149 cells/mm ³	50–99 cells/mm ³	<50 cells/mm ³			
	←————— n (%) —————→						
Antiretroviral drugs							
All	4230 (79.0)	375 (7.0)	348 (6.5)	399 (7.5)	2516 (100)	3.9 (3.5–4.3)	72.9 (69.0–76.8)
0	1967 (46.5)	22 (5.9)	8 (2.1)	11 (2.8)	695 (27.6)	4.0 (3.4–6.7)	99.6 (90.3–108)
1	936 (22.1)	57 (15.2)	23 (6.6)	10 (2.5)	803 (31.9)	4.7 (3.7–5.7)	75.6 (69.1–82)
2	874 (20.7)	87 (23.2)	50 (14.4)	40 (10.0)	631 (25.1)	2.6 (1.8–3.4)	59.5 (52.7–66.3)
≥3	453 (10.7)	209 (55.7)	267 (76.7)	338 (84.7)	387 (15.4)	2.7 (1.6–3.8)	34.8 (26.3–43)
Highly active antiretroviral therapy‡							
No	3880 (91.7)	220 (58.7)	156 (44.8)	167 (41.9)	2241 (89.1)	4.0 (3.6–4.4)	76.4 (72.2–80)
Yes	350 (8.3)	155 (41.3)	192 (55.2)	232 (58.1)	275 (10.9)	3.0 (1.7–4.3)	25.8 (16.8–34)

* Sufficient data were unavailable to stratify the incidence rates by treatment regimen and CD4 cell nadir. The incidence rates presented are unadjusted for any other variable; thus, differences in incidence rates among the four CD4 cell nadir groups may be caused by various factors.

† Incidence rate expressed as number of events per 100 patient-years of follow-up.

‡ Minimum of one protease inhibitor or non-nucleoside reverse transcriptase inhibitor plus two nucleoside reverse transcriptase inhibitors.

Table 4. Relative Hazard of Disease Progression for Patients in Group A*

Variable	Univariate Analysis		Multivariate Analysis	
	Relative Hazard (95% CI)	P Value	Relative Hazard (95% CI)	P Value
CD4 cell nadir†				
≥150 cells/mm ³	1.00	—	1.00	—
100–149 cells/mm ³	1.61 (0.95–2.72)	0.078	2.29 (1.30–4.03)	0.0042
50–99 cells/mm ³	2.16 (1.27–3.66)	0.0045	3.65 (1.94–6.85)	<0.001
<50 cells/mm ³	1.56 (0.86–2.80)	0.14	2.94 (1.44–6.00)	0.0031
Age‡	1.12 (1.01–1.25)	0.040	1.19 (1.06–1.34)	0.0033
Baseline CD4 cell count (per 50% lower)	1.25 (1.01–1.55)	0.042	1.24 (0.99–1.57)	0.065
AIDS	1.61 (1.19–2.17)	0.0019	1.48 (1.05–2.09)	0.024
Antiretroviral drug therapy				
No antiretroviral drugs	1.00	—	1.00	—
1 antiretroviral drug	1.08 (0.84–1.39)	>0.2	0.89 (0.67–1.74)	>0.2
2 antiretroviral drugs	0.58 (0.41–0.83)	0.0026	0.54 (0.36–0.80)	0.0024
≥3 antiretroviral drugs	0.57 (0.37–0.88)	0.012	0.20 (0.07–0.58)	0.0032
Highly active antiretroviral therapy§				
No	1.00	—	1.00	—
Yes	0.72 (0.45–1.14)	0.16	1.70 (0.57–5.01)	>0.2

* Estimates are the relative hazard of disease progression. The model has also been adjusted for the logarithm (base 2) of the first CD4 lymphocyte count ≥ 200 cells/mm³ and whether AIDS had been diagnosed by this date. At the date of first CD4 count ≥ 200 cells/mm³, the number of concurrent antiretroviral drugs being taken by each patient was calculated and adjusted for (reference category, 0); whether a patient was receiving highly active antiretroviral therapy at the date of first CD4 count ≥ 200 cells/mm³ was also adjusted for. The model remains censored and has been stratified for center and adjusted for calendar time and use of *Pneumocystis carinii* pneumonia prophylaxis. Demographic variables, such as sex, ethnicity, and exposure group, were of no significance in the univariate analysis and are not included in the final multivariate model.

† Reference group: ≥ 150 cells/mm³.

‡ Per 10-year age difference.

§ Defined as a minimum of one protease inhibitor or non-nucleoside reverse transcriptase inhibitor plus two nucleoside reverse transcriptase inhibitors.

progression in patients experiencing a rebound in CD4 count from very low levels (<50 cells/mm³) was 12-fold lower than in patients whose CD4 count decreased to and remained less than 50 cells/mm³.

These results suggest that an almost complete recovery from immunosuppression as measured by disease progression is possible, but patients who experienced profound immunosuppression remain at a disadvantage. This is, to our knowledge, the first analysis that addresses the question of the prognostic value of a CD4 cell count in patients experiencing increases in CD4 cell counts. Of additional interest is the finding that multidrug combination therapies were associated with a significantly reduced rate of disease progression in both patient groups and with a significantly reduced hazard for progression in patients with CD4 counts of at least 200 cells/mm³, regardless of CD4 cell count nadir.

The effect of improved antiretroviral treatment on disease progression was recently addressed in two other cohorts of patients infected with HIV. Brodt and coworkers (1) reported a decrease in the incidence of AIDS-related events that was paralleled by an increase in use of multidrug combination therapy and protease inhibitors; however, an association between these variables was not investigated. Palella and colleagues (3) reported on the decrease in morbidity and mortality and a reduction in the risk for disease progression in patients receiving protease inhibitors. We previously reported (2) that the decrease in deaths observed in the EuroSIDA study could be explained by the use of protease inhibitors and combination therapy. Our present data are consistent with these reports. We

show that CD4 cell count nadir is associated with a significantly higher risk for progression, independent of the number and type of drugs used in treatment. The overall disease incidence that we observed for patients in groups A and B is similar to that described for other cohorts.

Our analysis is based on a cohort study; all the caveats about the limitations and sensitivity of these types of studies apply. The data originate from 52 treatment centers with potential regional and temporal differences in the availability of antiretroviral agents and in treatment practices. We used center stratification to attempt to adjust for some of these differences. In addition, we performed a series of sensitivity analyses and obtained highly consistent results.

An additional limitation of our study is that we could not differentiate the groups in terms of viral loads. This is partially due to the fact that EuroSIDA recruitment was initiated in 1994, when viral load was not measured routinely. However, the available baseline viral loads do not indicate a bias for higher viral load in patients with lower CD4 cell nadirs. In fact, patients in group A, stratum 1—patients with the lowest incidence—had viral loads higher than patients from strata 2 and 3. This probably reflects the fact that patients in stratum 1 were more likely to be untreated. In addition, patients whose disease progressed did not have higher viral load values than patients whose disease did not progress. With continued follow-up in EuroSIDA, we hope to establish the relations among viral load, CD4 cell count, and disease progression in patients with therapy-induced increases in CD4 cell counts.

Our data have implications for antiretroviral

treatment strategies. Although patients who recover from severe immunodeficiency are much better off than patients who remain severely immunosuppressed, immunodeficiency should be avoided in the first place. The effect of multidrug combinations on reducing incidence rates in both patient groups indicates that more aggressive treatments may provide benefit independent of their effect on CD4 cell count and supports the use of combinations of three or more drugs for antiretroviral therapy. The safety of discontinuation of prophylaxis in patients responding immunologically to potent antiretroviral therapy is being discussed. Although our data could be used as an argument against such an approach, individual diseases in various therapeutic scenarios should be further analyzed to determine the risk-benefit ratio of prophylaxis discontinuation compared with continued use of such drugs.

We have observed an increased risk for disease progression among patients with previously low CD4 lymphocyte counts. This risk, however, was very small compared with the risk among patients in whom CD4 cell counts had not recovered. It is possible that as the management and monitoring of antiretroviral therapy improve, the differences in disease progression will be minimized. As follow-up of patients in the EuroSIDA study continues, the effect and significance of changes in viral load under different treatment regimens and their relation to CD4 lymphocyte count can be investigated further.

Appendix: The Multicentre Study Group on EuroSIDA

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