Characteristics, Determinants, and Clinical Relevance of CD4 T Cell Recovery to <500 Cells/μL in HIV Type 1–Infected Individuals Receiving Potent Antiretroviral Therapy

Gilbert R. Kaufmann,[1,2] Hansjakob Furrer,[3] Bruno Ledergerber,[4] Luc Perrin,[5] Milos Opravil,[4] Pietro Vernazza,[6] Matthias Cavassini,[7] Enos Bernasconi,[8] Martin Rickenbach,[9] Bernard Hirschel,[10] Manuel Battegay,[1] and the Swiss HIV Cohort Study[a]

[1]Division of Infectious Diseases and Hospital Epidemiology, Department of Internal Medicine, and [2]Medical Outpatient Department, University Hospital Basel, Basel, [3]Division of Infectious Diseases, University Hospital Berne, Berne, [4]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Zurich, [5]Laboratory of Virology and [6]Division of Infectious Diseases, Geneva University Hospital, Geneva, [7]Department of Internal Medicine, Cantonal Hospital St. Gallen, St. Gallen, [8]Division of Infectious Diseases and [9]Data Center of the Swiss HIV Cohort Study, CHUV, Lausanne, and [10]Department of Internal Medicine, Regional Hospital Lugano, Lugano, Switzerland

(See the editorial commentary by Sasson et al. on pages 373–5)

Background. The CD4 T cell count recovery in human immunodeficiency virus type 1 (HIV-1)–infected individuals receiving potent antiretroviral therapy (ART) shows high variability. We studied the determinants and the clinical relevance of incomplete CD4 T cell restoration.

Methods. Longitudinal CD4 T cell count was analyzed in 293 participants of the Swiss HIV Cohort Study who had had a plasma HIV-1 RNA load <1000 copies/mL for ⩾5 years. CD4 T cell recovery was stratified by CD4 T cell count 5 years after initiation of ART (⩾500 cells/μL was defined as a complete response, and <500 cells/μL was defined as an incomplete response). Determinants of incomplete responses and clinical events were evaluated using logistic regression and survival analyses.

Results. The median CD4 T cell count increased from 180 cells/μL at baseline to 576 cells/μL 5 years after ART initiation. A total of 35.8% of patients were incomplete responders, of whom 47.6% reached a CD4 T cell plateau <500 cells/μL. Centers for Disease Control and Prevention HIV-1 disease category B and/or C events occurred in 21% of incomplete responders and in 14.4% of complete responders ($P > .05$). Older age (adjusted odds ratio [aOR], 1.71 per 10-year increase; 95% confidence interval [CI], 1.21–2.43), lower baseline CD4 T cell count (aOR, 0.37 per 100-cell increase; 95% CI, 0.28–0.49), and longer duration of HIV infection (aOR, 2.39 per 10-year increase; 95% CI, 1.19–4.81) were significantly associated with a CD4 T cell count <500 cells/μL at 5 years. The median increases in CD4 T cell count after 3–6 months of ART were smaller in incomplete responders ($P < .001$) and predicted, in conjunction with baseline CD4 T cell count and age, incomplete response with 80% sensitivity and 72% specificity.

Conclusion. Individuals with incomplete CD4 T cell recovery to <500 cells/μL had more advanced HIV-1 infection at baseline. CD4 T cell changes during the first 3–6 months of ART already reflect the capacity of the immune system to replenish depleted CD4 T lymphocytes.

The key feature of untreated HIV-1 infection is the progressive depletion of CD4 T lymphocytes. The major achievement of potent antiretroviral therapy (ART) consists of a durable suppression of viral replication, a steep increase in the CD4 T cell count, and a partial reversal of HIV-1–associated immunological alterations [1–7]. A complete and durable restoration of the CD4 T cell count and, particularly, of critical T cell subsets, such as naive cells, can be best achieved by very early initiation of ART, preferably during primary HIV-1 in

Received 12 December 2004; accepted 17 March 2005; electronically published 24 June 2005.

Reprints or correspondence: Dr. Manuel Battegay and Dr. Gilbert Kaufmann, Div. of Infectious Diseases, Dept. of Internal Medicine, University Hospital Basel, CH-4031 Basel, Switzerland (battegaym@uhbs.ch and kaufmanng@uhbs.ch).

Clinical Infectious Diseases 2005; 41:361–72

1058-4838/2005/4103-0015$15.00

Presented in part: 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, 2004 (abstract 557).

[a] Members of the study group are listed at the end of the text.

Table 1. Baseline characteristics for 293 HIV-1–infected, treatment-naive patients in the Swiss HIV Cohort Study.

Characteristic	All patients (n = 293)	All patients, by CD4 T cell response			Patients with an incomplete response, by CD4 T cell plateau		
		Complete (n = 188)	Incomplete (n = 105)	P	Present (n = 50)	Absent (n = 55)	P
Sex							
Male	216 (73.7)	136 (72.3)	80 (76.2)	.473	37 (74.0)	43 (78.2)	.615
Female	77 (26.3)	52 (27.7)	25 (23.8)		13 (26.0)	12 (21.8)	
Age, mean years ± SD	37.8 ± 9.3	36.5 ± 8.8	40.0 ± 9.7	.001	39.9 ± 9.7	40.1 ± 9.8	.936
Ethnicity							
White	257 (87.7)	159 (84.6)	98 (93.3)	.171	44 (88.0)	54 (98.2)	.163
Black	16 (5.5)	13 (6.9)	3 (2.9)		2 (4.0)	1 (1.8)	
Hispanic	5 (1.7)	5 (2.7)	0 (0.0)		0 (0.0)	0 (0.0)	
Asian	6 (2.0)	5 (2.7)	1 (1.0)		1 (2.0)	0 (0.0)	
Not available	9 (3.1)	6 (3.2)	3 (2.9)		3 (6.0)	0 (0.0)	
HIV transmission category							
Homosexual	127 (43.3)	81 (43.1)	46 (43.8)	.215	20 (40.0)	26 (47.3)	.842
Heterosexual	95 (32.4)	68 (36.2)	27 (25.7)		13 (26.0)	14 (25.5)	
Injection drug user	59 (20.1)	33 (17.6)	26 (24.8)		14 (28.0)	12 (21.8)	
Other/unknown	12 (4.2)	6 (3.2)	6 (5.8)		3 (6.0)	3 (5.5)	
Duration of HIV-1 infection, mean years ± SD	4.4 ± 4.4	3.8 ± 4.1	5.4 ± 4.7	.026	5.7 ± 4.6	5.1 ± 4.9	.430
CDC HIV-1 disease category							
A	147 (51.0)	116 (63.4)	31 (29.5)	<.001	18 (36)	13 (23.6)	.375
B	96 (33.3)	46 (25.1)	50 (47.6)		22 (44)	28 (50.9)	
C	45 (15.6)	21 (11.5)	24 (22.9)		10 (20)	14 (25.5)	
Year of antiretroviral therapy initiation							
1996	58 (19.8)	32 (17.0)	26 (24.8)	.215	10 (20.0)	16 (29.1)	.388
1997	185 (63.1)	125 (66.5)	60 (57.1)		32 (64.0)	28 (50.9)	
1998	50 (17.1)	31 (16.5)	19 (18.1)		8 (16.0)	11 (20.0)	
Baseline HIV-1 RNA load, $\log_{10}$ copies/mL	4.9 (4.3–5.4)	4.8 (4.2–5.3)	5.1 (4.6–5.6)	.001	5.1 (4.6–5.5)	5.1 (4.7–5.6)	.900
Baseline T cell count, cells/μL	1188 (810–1697)	1304 (970–1832)	960 (540–1348)	<.001	990 (545–1516)	931 (532–1194)	.357
Baseline CD4 T cell count, cells/μL	180 (60–311)	255 (127–355)	72 (29–153)	<.001	93 (48–197)	58 (25–98)	.021
Baseline CD8 T cell count, cells/μL	687 (420–987)	745 (450–1074)	595 (300–871)	.004	626 (326–978)	556 (298–832)	.590
Anti–hepatitis B virus surface antigen positive[a]	14 (5.8)	7 (4.4)	7 (8.6)	.185	2 (5.0)	5 (12.2)	.249
Anti–hepatitis C virus positive	85 (29.0)	44 (23.5)	41 (39.0)	.005	23 (46.0)	18 (32.7)	.164

NOTE Data are medians and interquartile ranges or proportions, unless otherwise indicated. See Methods for definitions of complete and incomplete CD4 T cell response and CD4 T cell plateau. CDC, Centers for Disease Control and Prevention.

[a] Data are for 240 patients.

fection [8, 9]. In chronic HIV-1 infection, the recovery of the CD4 T cell count is hindered by residual viral replication, impaired thymic function, advanced age, enhanced T cell activation and apoptosis, and, possibly, viral coinfection [7, 10–13]. As a consequence, a substantial proportion of treated individuals show incomplete or even poor CD4 T cell recovery [6, 14]. In some studies, CD4 T cell counts seemed to reach a plateau after the first 2–3 years of ART [7, 15, 16], whereas other studies found that, for selected groups of patients with a well-suppressed HIV-1 RNA load, there were continuous, albeit small increases in CD4 T cell counts even after 3–4 years of ART [11, 17]. Thus, long-term CD4 T cell recovery, including its modulating factors, needs further evaluation.

In this study, we addressed 3 important issues. First, we analyzed CD4 T cell and CD8 T cell counts during a minimum observation period of 5 years in a large, highly selected cohort of 293 HIV-1–infected individuals with continuously suppressed plasma HIV-1 RNA load, to characterize individual patterns of CD4 T cell recovery. Second, we evaluated the clinical relevance of incomplete CD4 T cell recovery to <500 cells/μL. Third, we studied potential determinants of CD4 T cell recovery, with the goal of predicting CD4 T cell responses during the first months of ART. We hypothesized that advanced immunodeficiency would limit CD4 T cell recovery and that CD4 T cell kinetics before initiation of ART might predict of the magnitude of CD4 T cell recovery during ART [7].

Table 2. Initial antiretroviral therapy (ART) regimen for 293 HIV-1–infected, treatment-naive patients in the Swiss HIV Cohort Study.

ART regimen	All patients (n = 293)	All patients, by CD4 T cell response		
		Complete (n = 188)	Incomplete (n = 105)	P
Protease inhibitor(s)				
Indinavir and ⩾2 NAs	130 (44.4)	81 (43.1)	49 (46.7)	.554
Nelfinavir and ⩾2 NAs	82 (28.0)	52 (27.7)	30 (28.6)	.868
Ritonavir and ⩾2 NAs	45 (15.4)	29 (15.4)	16 (15.2)	.966
Saquinavir-ritonavir and ⩾2 NAs	30 (10.2)	23 (12.2)	7 (6.7)	.132
Other protease or NNRTI	6 (2.0)	3 (1.6)	3 (2.8)	
NRTI combination				
Azidothymidine-lamivudine	160 (54.6)	96 (51.1)	64 (61)	.103
Stavudine-lamivudine	74 (25.3)	53 (28.2)	21 (20)	.122
Stavudine-didanosine	26 (8.9)	14 (7.4)	12 (11.4)	.250
Other NAs	33 (11.2)	25 (13.3)	8 (7.6)	

NOTE. Data are no. (%) of patients. See Methods for definitions of complete and incomplete CD4 T cell response. NA, nucleoside analogue; NNRTI, nonnucleoside analogue reverse-transcriptase inhibitor; NRTI, nucleoside analogue reverse-transcriptase inhibitor.

METHODS

Study design. We studied longitudinal CD4 T cell counts, CD8 T cell counts, and plasma HIV-1 RNA levels in 293 treatment-naive, HIV-1–infected persons in the Swiss HIV Cohort Study up to 4 years before and during a minimum follow-up period of 5 years after initiation of ART. Laboratory data were collected every 3–6 months. ART was defined as a combination of at least 3 antiretroviral drugs, including either 2 nucleoside analogue reverse-transcriptase inhibitors (NRTIs) in combination with a protease inhibitor or a non-NRTI (NNRTI), 2 protease inhibitors in combination with at least 1 NRTI, a combination of a protease inhibitor and an NNRTI with at least 1 NRTI, or a combination of 3 NRTIs.

Because the objective was to study the maximum regenerative capacity of the immune system, the analysis was restricted to patients who achieved and maintained plasma HIV-1 RNA loads of <1000 copies/mL during the entire 5-year observation period. The threshold was a trade-off between a reasonably good virologic response and a sufficiently large sample size that allowed a meaningful statistical analysis. A total of 3234 individuals were excluded; 802 had missing baseline values, 2200 had ⩾1 viral load measurement ⩾1000 copies/mL after 6 months, and 32 commenced ART with a CD4 T cell count ⩾500 cells/μL.

Data analysis. The primary end point was the recovery of the CD4 T cell count within 5 years after ART initiation. Complete and incomplete CD4 T cell responses were defined by CD4 T cell counts ⩾500 or <500 cells/μL, respectively, at 5 years. The threshold of 500 cells/μL was chosen because, for many laboratories, it represents the lower boundary of the normal range. Determinants of CD4 T cell responses were evaluated by means of a multivariate logistic regression model that evaluated demographic characteristics as well as HIV-specific variables. Calculation of the duration of HIV-1 infection was based on the date of the first documented positive HIV-1 serologic test result in a reference laboratory (for 76.2% of patients) or the date on which evidence of a previous positive HIV-1 serologic test result was recorded, as revealed by an analysis of patient medical histories (for 23.8% of patients). A receiver operating characteristics curve analysis was used to evaluate the accuracy of different models to predict incomplete CD4 T cell responses, using data for 2 different cohorts [6, 7].

The kinetics of the replenishment of the CD4 T cell pool was analyzed by fitting a mathematical model to individual patient data using a nonlinear regression routine (MatLab; MathWorks). CD4 T cell count at time t is given by $\lambda_1(1-e^{-\mu_1 * t}) + \lambda_2 e^{-\mu_2 * t}$. The model assumes that the regeneration of CD4 T lymphocytes occurs at a constant rate, whereas cells are eliminated in accordance with first-order kinetics. The second term accounts for the rapid redistribution of CD4 T cells from lymphoid tissue into peripheral blood at the time virus replication is suppressed [19]. The model was developed and tested in a different cohort of patients before it was applied in this study [6, 18].

New or relapsing HIV-1–related clinical events (Centers for Disease Control and Prevention [CDC] HIV disease categories B and C) that occurred after initiation of ART for individuals with complete and individuals with incomplete CD4 T cell

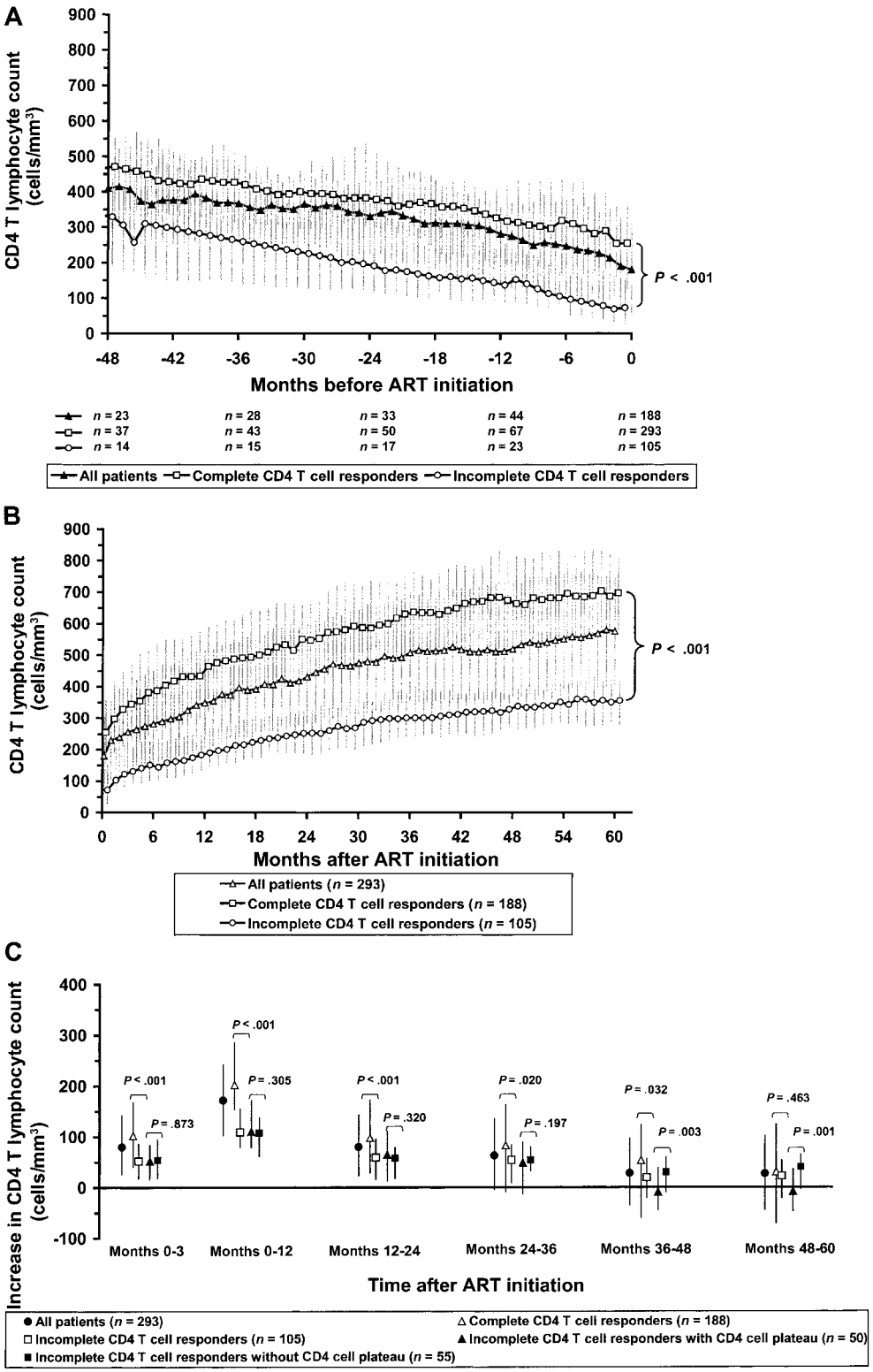

Figure 1. Time course of CD4 T cell count before *(A)* and after *(B)* initiation of antiretroviral therapy (ART). *C,* Median changes in CD4 T cell counts during consecutive time intervals after ART initiation. Data are medians and interquartile ranges. See Methods for definitions of complete and incomplete CD4 T cell response.

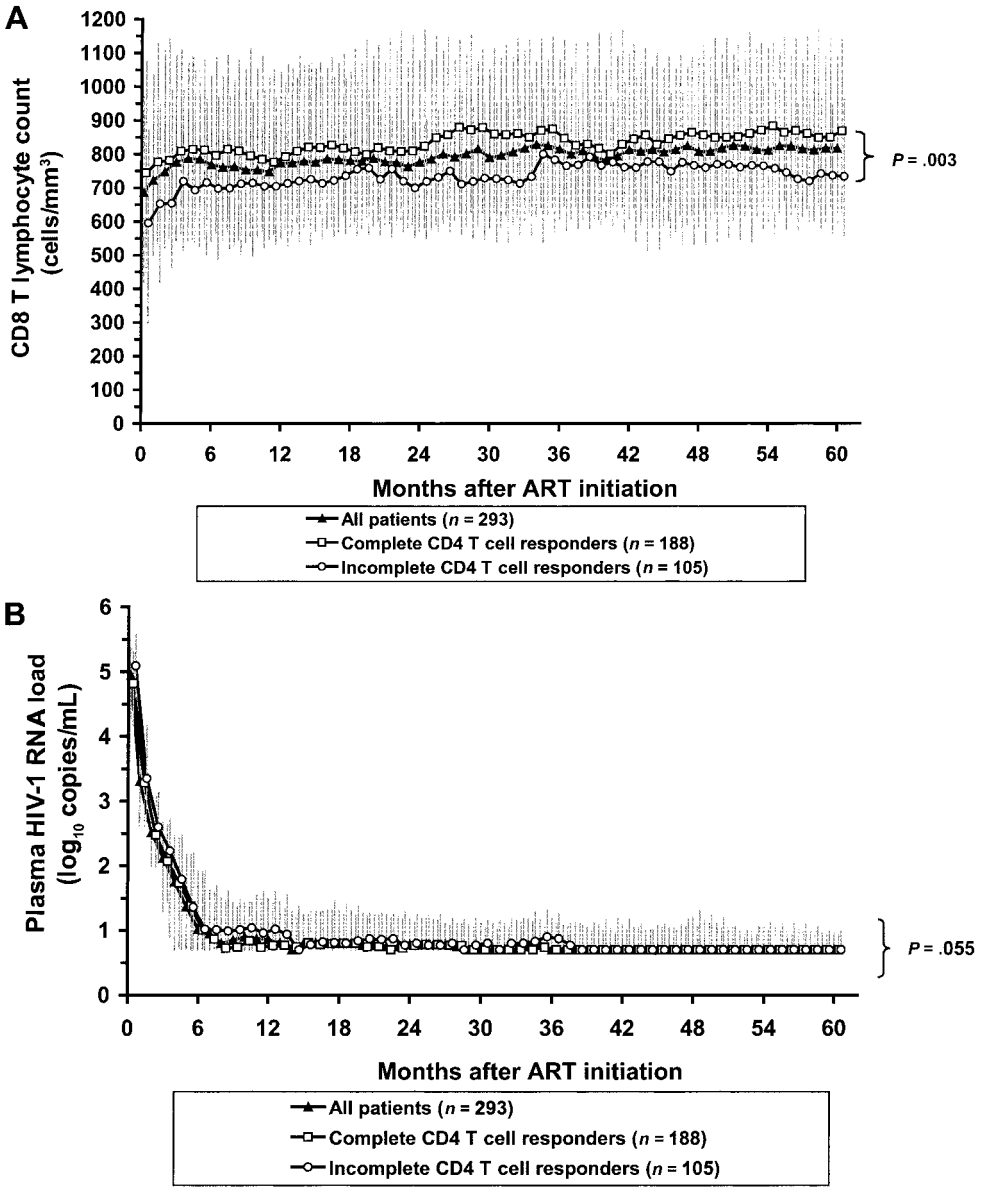

Figure 2. *A,* Time course of CD8 T cell count after antiretroviral therapy (ART) initiation. *B,* Time course of plasma HIV-1 RNA load after ART initiation. Data are medians and interquartile ranges. See Methods for definitions of complete and incomplete CD4 T cell response.

responses were compared using a Cox proportional hazards model. To account for possible immune reconstitution illness, early and late clinical events after initiation of ART ($\leq$12 and >12 months, respectively) were analyzed separately.

Continuous data for the groups with complete and incomplete CD4 T cell recovery and the groups that did and did not reach a CD4 T cell plateau were compared by means of a Mann-Whitney *U* test, whereas categorical data were compared by means of a χ^2 test. The relationship between continuous variables was analyzed with Spearman's rank-order correlation coefficient.

Continuous data are presented as medians (interquartile range), except for age and duration of HIV-1 infection, which are shown as means $\pm$ SD. All statistical analyses were performed using SPSS, version 11.0 (SPSS). A 2-sided *P* value <.05 was considered to be statistically significant.

RESULTS

Patient characteristics. The age of the patients was 37.8 $\pm$ 9.3 years; 73.7% were male, and 87.7% were white. The duration of HIV-1 infection was 4.4 $\pm$ 4.4 years. HIV-1 disease in 51.0% was classified as CDC category A. Additional baseline characteristics are shown in tables 1 and 2.

Time course of CD4 T lymphocyte count before initiation of ART. The CD4 T lymphocyte count decreased from 410

Table 3. Multivariate logistic regression analysis revealing determinants of an incomplete CD4 T cell response for 293 HIV-1–infected, treatment-naive patients in the Swiss HIV Cohort Study.

Parameter	Unadjusted OR (95% CI)	*P*	Adjusted[a] OR (95% CI)	*P*
Female sex	0.82 (0.47–1.42)	.473	1.07 (0.51–2.25)	.853
Age[b]	1.51 (1.16–1.96)	.002	1.71 (1.21–2.43)	.003
Duration of HIV-1 infection[c]	2.30 (1.28–4.15)	.005	2.39 (1.19–4.81)	.015
HIV transmission group				
Homosexual	1.0		1.0	
Heterosexual	0.70 (0.39–1.24)	.222	0.85 (0.40–1.80)	.670
Injection drug user	1.39 (0.74–2.60)	.307	0.74 (0.30–1.81)	.508
Anti–hepatitis C virus positive	2.08 (1.24–3.49)	.005	1.36 (0.66–2.79)	.401
Hepatitis B virus surface antigen positive	2.05 (0.70–6.07)	.193	2.75 (0.61–12.41)	.189
CDC HIV-1 disease category				
A	1.00		1.00	
B	4.07 (2.32–7.14)	<.001	1.09 (0.50–2.37)	.838
C	4.28 (2.11–8.67)	<.001	0.89 (0.35–2.28)	.805
Baseline HIV-1 RNA load[d]	1.49 (1.11–1.99)	.008	1.01 (0.73–1.40)	.964
Baseline CD4 T cell count[e]	0.37 (0.28–0.47)	<.001	0.37 (0.28–0.49)	<.001
Baseline CD8 T cell count[e]	0.93 (0.88–0.98)	.005	1.03 (0.96–1.10)	.425

NOTE. See Methods for definition of incomplete CD4 T cell response. CDC, Centers for Disease Control and Prevention.

[a] Adjusted for baseline CD4 T cell count, duration of HIV-1 infection, and age.
[b] Per 10-year increase in age.
[c] Per 1-year increase in duration.
[d] Per 1 log increase in the plasma HIV-1 RNA load.
[e] Per 100 cells/μL increase.

cells/μL (256–538 cells/μL) 4 years before the initiation of ART (for 37 patients) to 180 cells/μL (60–311 cells/μL) at baseline, when ART was initiated (for 293 patients). During the same period, the percentage of CD4 T lymphocytes decreased from 23% (19%–30%) 4 years before initiation of ART to 13% (6%–22%) at baseline (data not shown). The annual changes in the CD4 T lymphocyte count before the onset of ART were −43 cells/μL (−85 to +3 cells/μL) during the fourth year, −35 cells/μL (−85 to −2 cells/μL) during the third year, −55 cells/μL (−106 to −10 cells/μL) during the second year, and −68 cells/μL (−30 to −130 cells/μL) during the previous year. The annual changes in the CD4 T cell percentage during these intervals were −2% (−4.5% to 0%), −2% (−4.0% to 0%), −2% (−3.0% to 0%), and −3% (−6.0% to −1.0%), respectively.

Long-term recovery of CD4 T lymphocytes during ART. Absolute CD4 T lymphocyte counts increased from 180 cells/μL at time of ART initiation (60–311 cells/μL) to 576 cells/μL (401–743 cells/μL) 5 years later, whereas the percentage of CD4 T cells increased from 13% (6%–22%) to 30% (23%–37%). CD4 T cell counts increased to >200 cells/μL in 98.0% of patients, to >350 cells/μL in 82.6%, and to >500 cells/μL in 59.0%.

The analysis of CD4 T cell kinetics during the first 3 months after initiation of ART initiation revealed an increase in CD4 T cell count of 80 cells/μL (27–143 cells/μL). Increases during subsequent intervals gradually became smaller (172 cells/μL [103–243 cells/μL] during the first year of ART, 80 cells/μL [24–143 cells/μL] during the second year, 63 cells/μL [−4 to 136 cells/μL] during the third year, 28 cells/μL [−36 to 97 cells/μL] during the fourth year, and 27 cells/μL [−45 to 102 cells/μL] during the fifth year). Annual increases in the percentage of CD4 T cells during years 1–5 after ART initiation were 8% (5%–12%), 3% (1%–5%), 2% (0%–3%), 1% (0%–3%), and 1% (0%–3%). The decrease in the CD4 T cell count during the final 2 years before initiation of ART was significantly associated with increases in the CD4 T cell count during the first 3 and 6 months after ART initiation ($\rho = 0.41$ [$P = .003$] and $\rho = 0.399$ [$P = .004$], respectively) but not with changes >6 months after ART initiation.

The CD8 T cell count increased from 687 cells/μL (420–987 cells/μL) to 817 cells/μL (595–1096 cells/μL), whereas the percentage of CD8 T cells decreased from 60% (50%–69%) to 44% (37%–52%).

Characteristics of patients with incomplete CD4 T cell recovery. Patients with incomplete and patients with complete CD4 T cell responses (hereafter, "incomplete responders" and "complete responders," respectively) showed similar changes in CD4 T cell counts during the 2 years before the initiation of ART (−116 vs. −105 cells/μL; $P = .759$; figure 1*A*), but in-

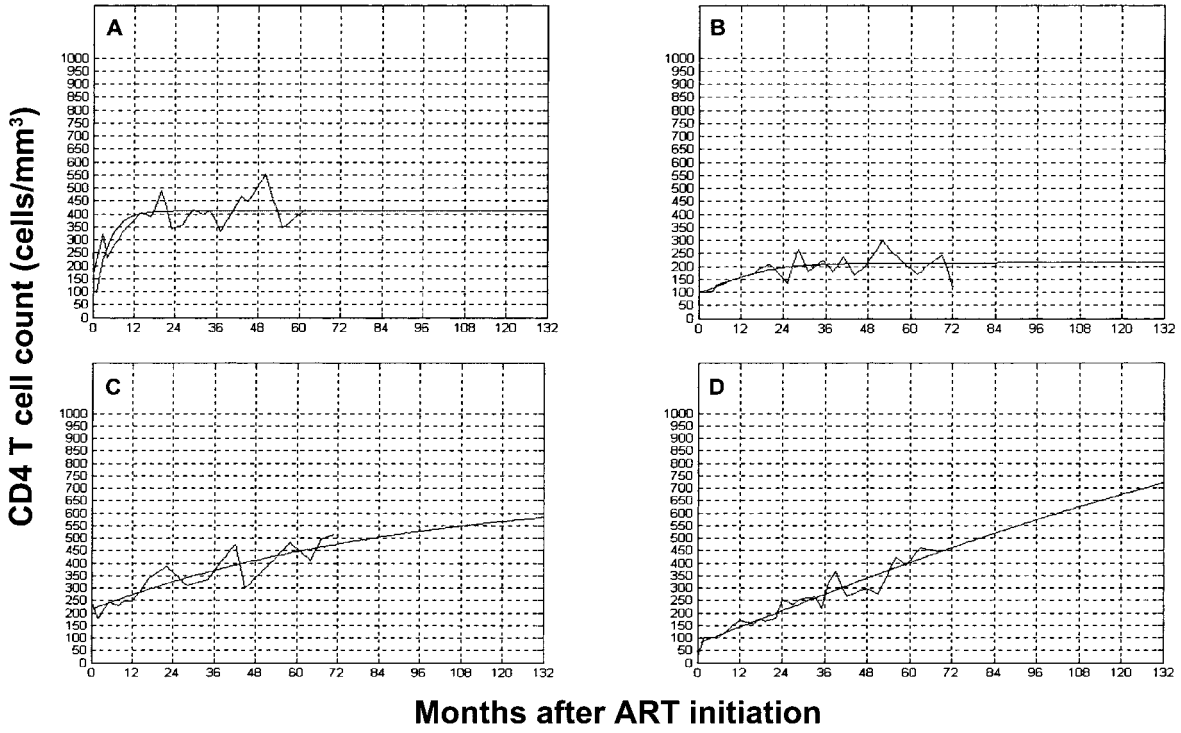

Figure 3. Distinct patterns of CD4 T cell recovery in 4 patients for whom the CD4 T cell count reached a plateau <500 cells/μL *(A* and *B)* or showed a slow, but steady increase *(C* and *D).*

complete responders commenced ART at lower CD4 T cell counts than did complete responders (72 vs 255 cells/μL; $P <$ .001). During the first 5 years after ART initiation, annual increases in the CD4 T cell count were significantly smaller for incomplete responders, compared with complete responders (109 vs. 203 cells/μL during the first year after ART initiation [$P <$ .001], 59 vs. 98 cells/μL during the second year [$P <$ .001], 54 vs. 83 cells/μL during the third year [$P = .020$], 19 vs. 54 cells/μL during the fourth year [$P = .032$], and 22 vs. 30 cells/μL during the fifth year [$P = .463$]; figure 1*B* and 1*C*). Even changes in the CD4 T cell count during the first 3 months after therapy differed significantly between incomplete and complete responders (52 vs. 103 cells/μL; $P <$ .001). This finding suggests that incomplete and complete responders may be distinguished on the basis of early differences in CD4 T cell kinetics.

Similarly, the increase in the CD4 T cell percentage during the first year of ART was significantly smaller in incomplete responders than in complete responders (7% vs. 8%; $P =$ .016). However, changes in CD4 T cell percentages during subsequent intervals were comparable (3% for nonresponders and 3% for responders during the second year, 2% and 2% during the third year, 1% and 1% during the fourth year, and 0% and 0% during the fifth year).

At all time points, absolute CD8 T cell counts and CD8 T lymphocyte percentages were significantly lower for incomplete responders than for complete responders (734 vs. 869 cells/μL [$P = .003$; figure 2*A*] and 50.0% vs. 41% [$P <$ .001], respectively, after 60 months of therapy). These findings most likely reflect the more advanced stage of HIV-1 infection in incomplete responders and are supported by the highly significant relationship between the baseline CD4 and CD8 T cell counts ($r = 0.499$; $P <$ .001)

Incomplete responders had higher plasma HIV-1 RNA loads at baseline, compared with complete responders (5.1 vs. 4.8 $\log_{10}$ copies/mL; $P = .001$), as well a larger decrease in the plasma HIV-1 RNA load during the first 3 months of ART (2.9 vs. 2.7 $\log_{10}$ copies/mL [$P = .02$]) and during the first 6 months of ART (3.8 vs. 3.4 $\log_{10}$ copies/mL [$P = .01$]) (figure 2*B*). There was also a trend toward a higher area under the plasma HIV-1 RNA curve for incomplete responders, compared with complete responders ($P = .055$).

Demographic and HIV-1–related variables at baseline differed significantly between complete and incomplete responders. Incomplete responders were older (40.0 vs. 36.5 years; $P = .001$), had HIV-1 infection for a longer period (5.4 vs. 3.8 years; $P = .026$), and had a higher prevalence of CDC category C disease (22.9% vs. 11.5%; $P <$ .001). In a multivariate logistic regression model, baseline CD4 T cell count (adjusted OR, 0.37 per 100-cell increase; 95% CI, 0.28–0.49; $P <$ .001), age (adjusted OR, 1.71 per 10-year increase; 95% CI, 1.21–2.43;

Table 4. Clinical events for 293 HIV-1–infected, treatment-naive patients in the Swiss HIV Cohort Study with a complete or incomplete CD4 T cell response.

Characteristic	CDC category B events			CDC category C events			CDC category B or C events			Patients with opportunistic infections	HIV-1–related events other than opportunistic infections	Events
	Overall	Early	Late	Overall	Early	Late	Overall	Early	Late			
Type of CD4 T cell response												
Complete (n = 188)	18 (9.6)	10 (5.3)	8 (4.3)	9 (4.8)	9 (4.8)	0 (0)	27 (14.4)	19 (10.1)	8 (4.3)	19 (10.1)	8 (4.3)	Bacterial pneumonia, cervical dysplasia (3), cytomegalovirus retinitis, esophageal candidiasis, herpes zoster (6), MAC infection, multiple events (2), NHL (2), oral candidiasis (2), oral hairy leukoplakia (5), PCP infection (2), peripheral neuropathy, thrombocytopenia (2), tuberculosis, vulvovaginal candidiasis (2)
Incomplete (n = 105)	14 (13.3)	6 (5.7)	8 (7.6)	8 (7.6)	7 (6.7)	1 (1.0)	22 (21.0)	13 (12.4)	9 (8.6)	15 (14.3)	7 (6.7)	Cervical dysplasia (4), cryptosporidiosis, cytomegalovirus retinitis, esophageal candidiasis (3), herpes zoster (4), KS, leukoencephalopathy, *M. kansasii* infection, multiple events (5), myelopathy, NHL, oral candidiasis (2), oral hairy leukoplakia (2), thrombocytopenia (3), toxoplasmosis, weight loss
Incomplete response, by CD4 T cell plateau												
Absent (n = 55)	5 (9.1)	…	…	6 (10.9)	…	…	11 (20)	…	…	9 (16.4)	2 (3.6)	Cervical dysplasia (2), cryptosporidiosis, esophageal candidiasis (3), herpes zoster (3), KS, *M. kansasii* infection, myelopathy, NHL, thrombocytopenia, toxoplasmosis, weight loss
Present (n = 50)	9 (18.0)	…	…	2 (4.0)	…	…	11 (22)	…	…	7 (14)	4 (8)	Cervical dysplasia (2), cytomegalovirus retinitis, herpes zoster, leukoencephalopathy, oral candidiasis, oral hairy leukoplakia (2), thrombocytopenia (2), toxoplasmosis

NOTE. Data are no. (%) of patients. Early events occurred during the first 12 months of antiretroviral therapy, whereas late events occurred after this time. See Methods for definitions of complete and incomplete CD4 T cell response and CD4 T cell plateau. CDC category, Centers for Disease Control and Prevention HIV-1 disease category; KS, Kaposi sarcoma; MAC, *Mycobacterium avium* complex; *M. kansasii, Mycobacterium kansasii;* NHL, non-Hodgkin lymphoma; PCP, *Pneumocystis jiroveci* pneumonia.

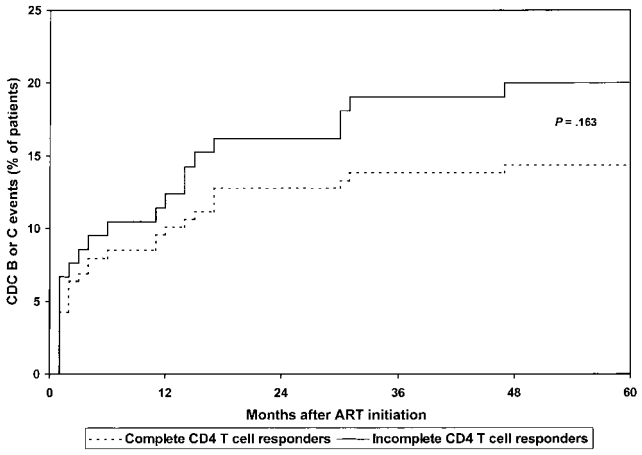

Figure 4. Proportions of complete CD4 T cell responders and incomplete T cell responders who had Centers for Disease Control and Prevention (CDC) HIV disease category B or C events. See Methods for definitions of complete and incomplete CD4 T cell response.

$P = .003$), and duration of HIV infection (adjusted OR, 2.39 per 10-year increase; 95% CI, 1.19–4.81; $P = .015$) independently predicted a CD4 T cell count <500 cells/μL 5 years after ART initiation (table 3).

Distinct patterns of incomplete CD4 T cell recovery. Almost one-half (47.6%) of incomplete responders reached a plateau in the CD4 T cell count (hereafter, "CD4 T cell plateau") that was <500 cells/μL, whereas the CD4 T cell count continued to increase steadily in the remaining patients (figure 3). Changes in CD4 T cell kinetics early after the initiation of ART were very similar for those who reached a CD4 T cell plateau and those who had a steady CD4 T cell count increase but differed significantly during the fourth and fifth years of ART (-9 cells/μL vs. 30 cells/μL [$P = .003$] and -8 vs. 40 cells/μL [$P = .001$], respectively). Thus, CD4 T cell kinetics early after ART initiation do not allow discrimination between individuals who reached a CD4 T cell plateau and individuals who had slow, but steady CD4 T cell count increases. The only significant difference between both groups was a higher CD4 T cell count for individuals who reached a CD4 T cell plateau <500 cells/μL (93 vs. 58 cells/μL; $P = .021$). The area under the virus load curve was not associated with a CD4 T cell plateau <500 cells/μL.

Estimation of the maximum CD4 T cell count. On the assumptions that ART use will continue indefinitely and that the plasma HIV-1 RNA load will permanently be <1000 copies/mL, model simulations suggest that the CD4 T cell count will reach a maximum of 650 cells/μL (466–883 cells/μL) after a treatment duration of 51 months (25–97 months). According to the model, 86.7% of individuals will reach a CD4 T cell count of $\geqslant$350 cells/μL, and 69.7% will reach a CD4 T cell count of $\geqslant$500 cells/μL.

Clinical relevance of incomplete CD4 T cell responses. CDC category B or C events occurred in 49 patients (16.7%) at a CD4 T cell count of 218 cells/μL (89–307 cells/μL; table 4). Eighteen complete responders (9.6%) experienced clinical CDC category B events, compared with 14 incomplete responders (13.3%). Similarly, fewer complete responders experienced CDC category C events (4.8% vs 7.6%). However, CDC category B and C events were not significantly more frequent among incomplete responders than among complete responders (21.0% vs. 14.4%; hazard ratio [HR], 1.49; 95% CI, 0.85–2.62; $P = .163$; figure 4). Of interest, the incidence of CDC category B and C events was similar in both groups during the first 12 months of ART (12.4% vs. 10.1%; HR, 1.27; 95% CI, 0.63–2.58; $P = .501$), whereas such events occurred more frequently among incomplete responders during years 2–5 after ART initiation (8.6% vs. 4.3%; HR, 2.04; 95% CI, 0.79–5.28). However, the difference between the 2 periods was not statistically significant ($P = .143$).

Prediction of incomplete CD4 T cell recovery. Increases in the CD4 T cell count early after ART initiation were smaller in incomplete responders, compared with complete responders (52 vs. 103 cells/μL 3 months after the start of ART; $P < .001$). On the basis of these significantly different increases, several models were tested to predict incomplete response. An increase of 99 cells/μL in the CD4 T cell count during the first 3 months after therapy was associated with an 80% sensitivity but only a 52% specificity to discriminate between complete and incomplete responders (figure 5*A*). On the basis of results of the logistic regression analysis, baseline CD4 T cell count and age were added to the model (baseline CD4 T cell count $\times$ 6 monthly CD4 T cell increases/age), which increased the specificity to 72% while maintaining a sensitivity of 80% as predictors of CD4 T cell response (figure 5*B*). The model predicted incomplete response in a different cohort with similar accuracy [6].

DISCUSSION

Influence of ART on CD4 T cells has been described in different settings and with regard to pathophysiology [19–24]. In this study, we addressed 3 major issues. First, we evaluated the capacity of the immune system to replenish the depleted pool of CD4 T cells in patients who had well-suppressed virus levels during long-term ART. We noted that approximately two-thirds of patients had reached a CD4 T cell count >500 cells/μL but that the remaining one-third showed impaired CD4 T cell recovery. Approximately one-half of patients with impaired CD4 T cell recovery had reached a CD4 T cell plateau, showing no evidence of further increases in CD4 T cell count. Secondly, we observed that a persistently low CD4 T cell count was associated more frequently with HIV-related CDC category B and C clinical events, although the difference between complete and

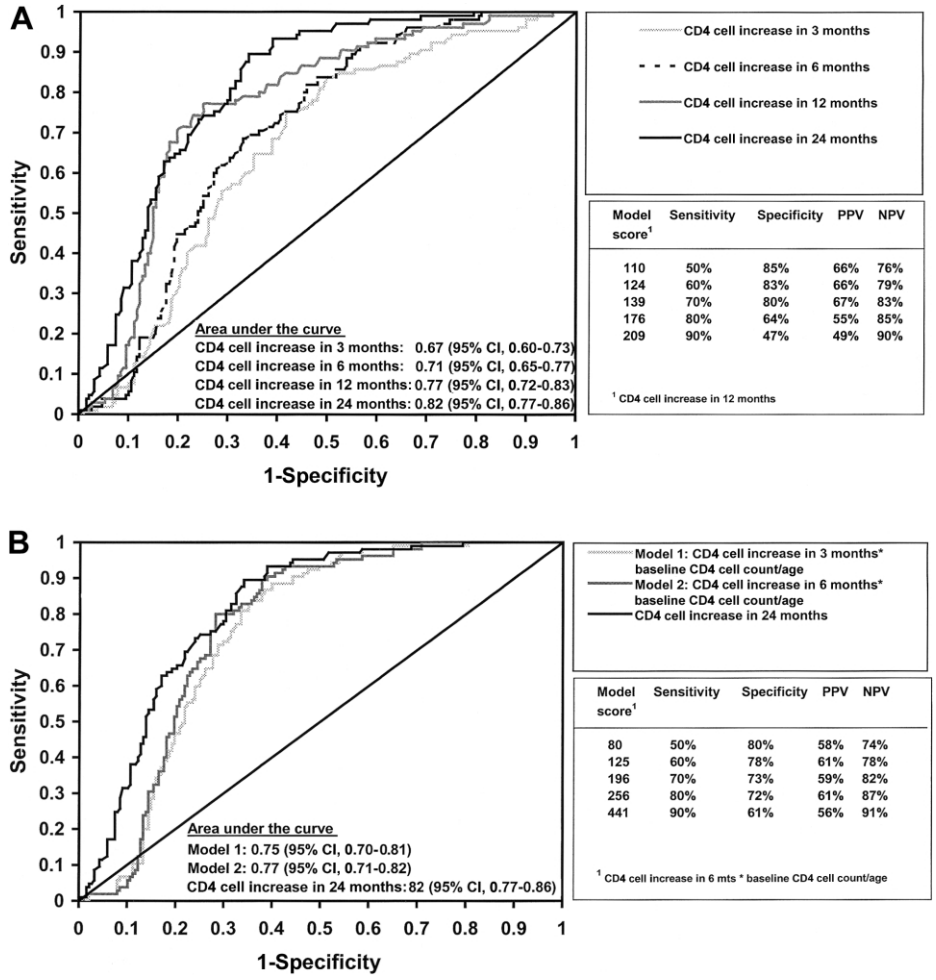

Figure 5. Receiver operating characteristic (ROC) curve analyses using baseline CD4 T cell count as the only predictor *(A)* or using a combination of baseline CD4 T cell count, early CD4 T cell increase, and age as predictors of CD4 T cell responses *(B)*. The curves shows the trade-off between sensitivity and specificity. An increase in sensitivity will be accompanied by a decrease in specificity. The accuracy of the prediction increases as the curve approaches the left-hand and top portions of the ROC space. The area under the curve is the percentage of randomly drawn pairs for which the prediction is true. The positive predictive value (PPV) is the proportion of patients with positive test results who had poor CD4 T cell responses. The negative predictive value (NPV) is the proportion of patients with negative test results who did not have poor CD4 T cell responses and is a measure of whether the prognosis of a poor CD4 T cell response can be ruled out.

incomplete responders was not statistically significant. Third, we developed a model that may be useful to identify individuals with incomplete CD4 T cell recovery early after initiation of ART.

Incomplete responders were characterized by older age and more advanced HIV infection (as revealed by lower baseline CD4 and CD8 T cell counts), had a higher rate of CDC category C events, had had HIV infection for a longer duration, and had higher baseline plasma HIV RNA levels, compared with complete responders. In a multivariate model, low CD4 T cell count, increased age, and a longer duration of HIV infection independently predicted an incomplete CD4 T cell response. Age has been previously reported to represent an independent risk factor for protracted CD4 T cell count restoration [25].

The relative decreases in CD4 T cell counts before ART initiation were parallel for incomplete and complete responders. This finding did not confirm our hypothesis that the kinetics associated with decreases in the CD4 T cell count before ART initiation would predict incomplete and complete CD4 T cell recovery. However, individuals with larger decreases in the CD4 T cell count before ART initiation had larger increases in the CD4 T cell count during the first 6 months of ART, as reported elsewhere [26]. In contrast, long-term CD4 T cell changes during ART were not associated with the natural course of CD4 T cell depletion in untreated HIV-1–infected persons before ART initiation.

Incomplete CD4 T cell responses had 2 main patterns: achievement of a CD4 T cell plateau <500 cells/μL or a slow

but steady increase in CD4 T cell count. The CD4 T cell kinetics associated with these patterns were similar early after ART initiation. However, after 3 years of ART, CD4 T cell kinetics began to differ. Baseline demographic data were comparable for both patterns, except for CD4 T cell count, which was slightly higher in patients who reached a CD4 T cell plateau. Thus, the 2 distinct patterns of CD4 T cell recovery seem to be difficult to predict.

Opravil et al. [27] reported that individuals who initiated ART with <350 CD4 T cells/μL experienced significantly more CDC category B or C events than did patients who initiated ART with higher CD4 T cell counts. In the present study, 22 (21.0%) of 105 incomplete responders had clinical CDC category B or C events; for 15 (68%), the events were opportunistic infections. However, in our study, the incidence of HIV-related events among incomplete responders was not statistically significantly different from that among complete responders. Starting ART late, in association with incomplete CD4 T cell response, may affect long-term prognosis, even in patients with good virologic control.

Many CDC category B and C events occurred early after initiation of ART, affecting incomplete and complete responders in similar proportions. This suggests that some opportunistic infections may have remained undetected before ART and were unmasked by immune restoration [28, 29]. However, approximately one-half of clinical events occurred after 1 year of ART, mainly consisting of new or relapsing infections.

Incomplete responders showed smaller CD4 T cell recovery during the first 3–6 months of ART. On the basis of these smaller changes, baseline CD4 T cell count, and age, incomplete CD4 T cell responses could be predicted with relatively high accuracy. The high negative predictive value suggests that the model can reliably rule out an incomplete CD4 T cell response for some patients. However, the validity of the model requires further confirmation in different HIV cohorts. In addition, the model does not yet account for patients with virologic failure.

Mathematical simulations for prediction of longitudinal CD4 T cell counts provided interesting estimations. They predicted a maximum CD4 T cell count of 650 cells/μL 51 months after ART initiation in this cohort. Furthermore, the model predicted that 87% of treated persons will eventually achieve a CD4 T cell count $\geqslant$350 cells/μL, which is likely to provide adequate protection against opportunistic infections. A total of 70% will even achieve a nearly normal CD4 T cell count $\geqslant$500 cells/μL. It has to be considered that these projections only apply to patients with good virologic responses who commence ART at similar baseline CD4 T cell counts.

A limitation of the study was the still relatively short follow-up period of 5 years. Only an extended observation time beyond 7–8 years will show whether predictions of the model were correct.

THE SWISS HIV COHORT STUDY

M. Battegay, E. Bernasconi, J. Böni, H. Bucher, Ph. Bürgisser, S. Cattacin, M. Cavassini, R. Dubs, M. Egger, L. Elzi, P. Erb, K. Fantelli, M. Fischer, M. Flepp, A. Fontana, P. Francioli (President of the Swiss HIV Cohort Study, Centre Hospitalier Universitaire Vaudois, CH-1011-Lausanne), H. Furrer (Chairman of the Clinical and Laboratory Committee), M. Gorgievski, H. Günthard, B. Hirschel, L. Kaiser, C. Kind, Th. Klimkait, B. Ledergerber, U. Lauper, M. Opravil, F. Paccaud, G. Pantaleo, L. Perrin, J.-C. Piffaretti, M. Rickenbach (Head of Data Center), C. Rudin (Chairman of the Mother and Child Substudy), P. Schmid, J. Schupbach, R. Speck, A. Telenti, A. Trkola, P. Vernazza (Chairman of the Scientific Board), R. Weber, and S. Yerly.

Acknowledgments

We thank Mark Bloch and Robert Finlayson for kindly providing the second data set to evaluate the model of CD4 T cell count kinetics.

Financial support. This study was financed in the framework of the Swiss HIV Cohort Study and was supported by the Swiss National Foundation (grant 3345–062041, project 414).

Potential conflicts of interest. All authors: no conflicts.

References

1. Egger M, May M, Chene G, et al. Prognosis of HIV-1–infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. Lancet **2002**; 360:119–29.
2. Autran B, Carcelain G, Li T, et al. Positive effects of combined antiretroviral therapy on $CD4^+$ T cell homeostasis and function in advanced HIV disease. Science **1997**; 277:112–6.
3. Kelleher AD, Carr A, Zaunders J, et al. Alterations in the immune response of human immunodeficiency virus (HIV)–infected subjects treated with an HIV-specific protease inhibitor, ritonavir. J Infect Dis **1996**; 173:321–9.
4. Ledergerber B, Egger M, Opravil M, et al. Clinical progression and virological failure on highly active antiretroviral therapy in HIV-1 patients: a prospective cohort study. Swiss HIV Cohort Study. Lancet **1999**; 353:863–8.
5. Pakker NG, Roos MT, van Leeuwen R, et al. Patterns of T-cell repopulation, virus load reduction, and restoration of T-cell function in HIV-infected persons during therapy with different antiretroviral agents. J Acquir Immune Def Syndr Hum Retrovirol **1997**; 16:318–26.
6. Kaufmann GR, Bloch M, Finlayson R, et al. The extent of HIV-1–related immunodeficiency and age predict the long-term CD4 T lymphocyte response to potent antiretroviral therapy. AIDS **2002**; 16: 359–67.
7. Kaufmann GR, Perrin L, Pantaleo G, et al. CD4 T-lymphocyte recovery in individuals with advanced HIV-1 infection receiving potent antiretroviral therapy for 4 years: the Swiss HIV Cohort Study. Arch Intern Med **2003**; 163:2187–95.
8. Carcelain G, Blanc C, Leibowitch J, et al. T cell changes after combined nucleoside analogue therapy in HIV primary infection. AIDS **1999**; 13: 1077–81.
9. Kaufmann GR, Zaunders JJ, Cunningham P, et al. Rapid restoration

of CD4 T cell subsets in subjects receiving antiretroviral therapy during primary HIV-1 infection. AIDS **2000**; 14:2643–51.
10. Greub G, Ledergerber B, Battegay M, et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. Lancet **2000**; 356:1800–5.
11. Hunt PW, Deeks SG, Rodriguez B, et al. Continued CD4 cell count increases in HIV-infected adults experiencing 4 years of viral suppression on antiretroviral therapy. AIDS **2003**; 17:1907–15.
12. Gougeon ML. Apoptosis as an HIV strategy to escape immune attack. Nat Rev Immunol **2003**; 3:392–404.
13. Lewin SR, Ribeiro RM, Kaufmann GR, et al. Dynamics of T cells and TCR excision circles differ after treatment of acute and chronic HIV infection. J Immunol **2002**; 169:4657–66.
14. Kaufmann G, Bloch M, Zaunders J, et al. Long-term immunological response in HIV-1 infected subjects receiving potent antiretroviral therapy. AIDS **2000**; 14:959–69.
15. Valdez H, Connick E, Smith KY, et al. Limited immune restoration after 3 years' suppression of HIV-1 replication in patients with moderately advanced disease. AIDS **2002**; 16:1859–66.
16. Tarwater PM, Margolick JB, Jin J, et al. Increase and plateau of CD4 T-cell counts in the 3(1/2) years after initiation of potent antiretroviral therapy. J Acquir Immune Defic Syndr **2001**; 27:168–75.
17. Opravil M, Hirschel B, Lazzarin A, et al. A randomized trial of simplified maintenance therapy with abacavir, lamivudine, and zidovudine in human immunodeficiency virus infection. J Infect Dis **2002**; 185: 1251–60.
18. Kaufmann GR, Zaunders J, Murray J, et al. Relative significance of different pathways of immune reconstitution in HIV type 1 infection as estimated by mathematical modeling. AIDS Res Hum Retroviruses **2001**; 17:147–59.
19. Bucy RP, Hockett RD, Derdeyn CA, et al. Initial increase in blood $CD4^+$ lymphocytes after HIV antiretroviral therapy reflects redistribution from lymphoid tissues. J Clin Invest **1999**; 103:1391–8.
20. de Oliveira Pinto LM, Lecoeur H, Ledru E, et al. Lack of control of T cell apoptosis under HAART: influence of therapy regimen in vivo and in vitro. AIDS **2002**; 16:329–39.
21. Estaquier J, Lelievre JD, Petit F, et al. Effects of antiretroviral drugs on human immunodeficiency virus type 1–induced $CD4^+$ T-cell death. J Virol **2002**; 76:5966–73.
22. Hunt PW, Martin JN, Sinclair E, et al. T cell activation is associated with lower $CD4^+$ T cell gains in human immunodeficiency virus–infected patients with sustained viral suppression during antiretroviral therapy. J Infect Dis **2003**; 187:1534–43.
23. Deeks SG, Hoh R, Grant RM, et al. $CD4^+$ T cell kinetics and activation in human immunodeficiency virus–infected patients who remain viremic despite long-term treatment with protease inhibitor–based therapy. J Infect Dis **2002**; 185:315–23.
24. Giovannetti A, Pierdominici M, Marziali M, et al. Persistently biased T-cell receptor repertoires in HIV-1–infected combination antiretroviral therapy–treated patients despite sustained suppression of viral replication. J Acquir Immune Defic Syndr **2003**; 34:140–54.
25. Teixeira L, Valdez H, McCune JM, et al. Poor CD4 T cell restoration after suppression of HIV-1 replication may reflect lower thymic function. AIDS **2001**; 15:1749–56.
26. Renaud M, Katlama C, Mallet A, et al. Determinants of paradoxical CD4 cell reconstitution after protease inhibitor–containing antiretroviral regimen. AIDS **1999**; 13:669–76.
27. Opravil M, Ledergerber B, Furrer H, et al. Clinical efficacy of early initiation of HAART in patients with asymptomatic HIV infection and CD4 cell count $>350 \times 10^6$/L. AIDS **2002**; 16:1371–81.
28. French MA, Lenzo N, John M, et al. Immune restoration disease after the treatment of immunodeficient HIV-infected patients with highly active antiretroviral therapy. HIV Med **2000**; 1:107–15.
29. Hirsch HH, Kaufmann G, Sendi P, et al. Immune reconstitution in HIV-infected patients. Clin Infect Dis **2004**; 38:1159–66.