CD4 T-Lymphocyte Recovery in Individuals With Advanced HIV-1 Infection Receiving Potent Antiretroviral Therapy for 4 Years

The Swiss HIV Cohort Study

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Background: Highly active antiretroviral therapy (HAART) for human immunodeficiency virus (HIV)-1 infection allows recovery of CD4 T lymphocytes. Few studies have explored the long-term T-lymphocyte responses to HAART.

Methods: Plasma HIV-1 RNA levels and CD4 and CD8 T-lymphocyte counts were longitudinally analyzed over 4 years in 2235 participants of the Swiss HIV Cohort, commencing HAART between 1996 and 1997. The CD4 T-lymphocyte count increase, the percentage of individuals with a CD4 T-lymphocyte count of 500/µL or greater and less than 200/µL, and the determinants of CD4 T-lymphocyte recovery were evaluated in individuals treated with continuous (CONT; n=985) and discontinuous (DISCONT; n=1250) HAART.

Results: At 4 years, 69.5% of subjects (CONT, 84.5%; DISCONT, 53.6%; $P<.001$) showed HIV-1 RNA levels below 400 copies/mL, while the median CD4 T-lymphocyte count increased from 190/µL to 423/µL (CONT, 486/µL; DISCONT, 343/µL; $P<.001$). Of the 2235 participants, 38.8% (CONT, 47.7%; DISCONT, 29.4%; $P<.001$) reached a CD4 T-lymphocyte count of 500/µL or greater, but in 15.6%, CD4 T-lymphocyte count remained below 200/µL (CONT, 5.9%; DISCONT, 25.9%; $P<.001$). Larger increases in CD4 T-lymphocyte count were associated with higher baseline HIV-1 RNA, a larger percentage of undetectable HIV-1 RNA levels, lower baseline CD8 T-lymphocyte count, and younger age. Individuals reaching a CD4 T-lymphocyte count of 500/µL or greater at 4 years were characterized by higher nadir and baseline CD4 T-lymphocyte counts and a more sustained reduction of HIV-1 RNA levels.

Conclusions: At 4 years, only 39% of individuals treated with HAART reached a CD4 T-lymphocyte count of 500/µL or greater, and 16% with CD4 T-lymphocyte counts less than 200/µL remained susceptible to opportunistic infections. Treatment interruptions, a poor virologic response, and older age were the major factors negatively affecting the recovery of CD4 T lymphocytes.

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HIGHLY ACTIVE antiretroviral therapy (HAART) has significantly improved the prognosis of individuals infected with human immunodeficiency virus (HIV)-1 and extended life expectancy.[1-5] The recovery of CD4 T lymphocytes in treated persons is usually accompanied by enhanced T-lymphocyte responses to antigens and mitogens,[6-8] providing adequate protection against opportunistic infections.[3,9-11] However, the immunological recovery shows a large variability from patient to patient.[12-16] A significant proportion of treated subjects experience only small increases in CD4 T-lymphocyte numbers despite optimum suppression of plasma HIV-1 viremia by HAART. In others, CD4 T-lymphocyte count rapidly rises despite modest reductions of plasma HIV-1 RNA levels.[17] The reasons for these different responses remain unknown. It has been suggested that differences in residual thymic function may play a role,[18] but additional factors may potentially affect the recovery of CD4 T lymphocytes, including age,[19] the degree of immunodeficiency before initiation of HAART,[20] residual viral activity,[21] viral coinfections such as hepatitis C or G,[22-24] and the susceptibility of CD4 T cells to HIV-1 infection, which depends in part on the expression of the viral coreceptor CCR5.[25-27]

Although the long-term recovery of CD4 T lymphocytes deserves particular attention because of its major clinical significance, few studies have addressed this issue. In this investigation, we have evaluated the long-term T-lymphocyte dynamics over 4 years in 2235 subjects enrolled in the Swiss HIV Cohort Study, who were infected with HIV-1, and commenced HAART between 1996 and 1997. In addition, potential predictors of CD4 T-lymphocyte re-

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A complete list of the members of the Swiss HIV Cohort Study Group appears in a box at the end of this article. The authors have no relevant financial interest in this article.

Table 1. Baseline Characteristics*

Characteristic	Continuous HAART (CONT; n = 985)	Discontinuous HAART (DISCONT; n = 1250)	*P* Value (CONT vs DISCONT)	All Subjects (N = 2235)
Sex				
Male	734 (74.5)	894 (71.5)	.11	1628 (72.8)
Female	251 (25.5)	356 (28.5)		607 (27.2)
Age, y	38.2 ± 9.0	37.7 ± 9.1	.12	37.9 ± 9.0
Ethnicity				
White	451 (87.4)	483 (86.1)		934 (86.7)
Black	37 (7.2)	54 (9.6)		91 (8.4)
Hispanic	13 (2.5)	17 (3.0)	.001	30 (2.8)
Asian	15 (2.9)	7 (1.2)		22 (2.0)
No information	469	689		1158
HCV antibody positive	300 (30.5)	506 (40.5)	<.001	806 (36.1)
HBs antigen positive	51 (5.2)	83 (6.6)	.07	134 (6.0)
Mode of HIV transmission				
Heterosexual	290 (29.4)	342 (27.4)		632 (28.3)
Homosexual	425 (43.1)	409 (32.7)		834 (37.3)
IV drug use	231 (23.4)	449 (35.9)	<.001	680 (30.4)
Blood products	15 (1.5)	17 (1.5)		32 (1.5)
Unknown/other sources	24 (2.4)	33 (2.6)		57 (2.6)
Duration of HIV-1 infection, y	6.8 ± 4.2	7.4 ± 4.1	.03	7.2 ± 4.1
CDC stage				
A	377 (38.3)	380 (30.4)		757 (33.9)
B	343 (34.8)	460 (36.8)	<.001	803 (35.9)
C	264 (26.8)	406 (32.5)		670 (30.0)
Pretreated	592 (60.1)	858 (68.6)		1450 (64.9)
Nucleoside analogues	569 (57.8)	833 (66.6)		1402 (62.7)
PI	22 (2.2)	24 (1.9)	<.001	46 (2.1)
NNRTI	1 (0.1)	1 (0.1)		2 (0.1)
Duration of pretreatment, mo	19.0 (9.0-39.2)	15.9 (7.0-39.9)	.06	17 (8.0-39.9)
Baseline HIV-1 RNA, $\log_{10}$ copies/mL	4.5 (3.7-5.1)	4.7 (4.0-5.2)	.001	4.6 (3.9-5.2)
Nadir CD4 T-lymphocyte count before HAART, cells/μL	149 (56-270)	127 (36-251)	.002	138 (45-259)
Baseline CD4 T-lymphocyte count, cells/μL	203 (85-342)	179 (68-326)	.02	190 (73-336)
Baseline CD8 T-lymphocyte count, cells/μL	740 (476-1048)	697 (425-1041)	.04	711 (445-1042)

Abbreviations: CDC, Centers for Disease Control and Prevention; HAART, highly active antiretroviral therapy; HBs, hepatitis B surface; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IV, intravenous; NNRTI, nonnucleoside analogue reverse transcriptase inhibitor; PI, protease inhibitor.

*Data are number (percentage), mean ± SD, or median (interquartile range [25th and 75th percentile]) unless otherwise specified. Groups were compared using a Mann-Whitney *U* or χ^2 test, as appropriate.

covery above the clinically relevant levels of 200/μL and 500/μL were analyzed, which represent the threshold of the occurrence of opportunistic infections and the lower limit of the physiological range.

METHODS

STUDY POPULATION

Individuals of the Swiss HIV Cohort Study were eligible if they had commenced HAART between January 1996 and December 1997. Highly active antiretroviral therapy was defined as (1) a combination of 2 nucleoside analogue reverse transcriptase inhibitors (NRTIs) in combination with a protease inhibitor or a nonnucleoside analogue reverse transcriptase inhibitor (NNRTI), (2) 2 protease inhibitors in combination with at least 1 NRTI, (3) a combination of a protease inhibitor and an NNRTI with at least 1 NRTI, or (4) a combination of 3 NRTIs. Data of 2235 individuals (73.9%) were used in the final analysis after excluding 786 individuals (26.0%) owing to missing baseline CD4 and CD8 T-lymphocyte counts or plasma HIV-1 RNA levels. The baseline value was defined as the last laboratory determination within a period of 3 months prior to the initiation of HAART.

Most individuals were male (72.8%) and white (86.8%). The mean±SD values for age and estimated duration of HIV-1 infection (based on the first positive HIV-1 test result) were 38±9 and 7.2±4.1 years, respectively. The cohort was in an advanced stage of HIV-1 infection. The median baseline CD4 T-lymphocyte count was 190/μL, and a third of patients met the criteria of Centers for Disease Control and Prevention (CDC, Atlanta, Ga) stage C. A large percentage of participants (65%) were pretreated with nucleoside analogue combinations. Additional baseline characteristics are given in **Table 1**.

In 1996 and 1997, potent antiretroviral therapy predominantly consisted of indinavir sulfate, ritonavir, or nelfinavir mesylate in combination with 2 nucleoside analogues (**Table 2**). During the study period, the proportion of subjects receiving double protease inhibitor therapy, NNRTI therapy, and combined protease inhibitor and NNRTI therapy increased.

DATA COLLECTION AND STATISTICAL ANALYSIS

Data were extracted from the January 2002 update of the Swiss HIV-1 Cohort database and included patient characteristics, treatment history, CD4 and CD8 T-lymphocyte counts, and plasma HIV-1 RNA levels. Laboratory values were determined irregularly at 1- to 6-month intervals, of which the 6-month values were calculated by linear interpolation. These calculations were based on a mean±SD number of 12.6±5.4 laboratory determinations per patient during the observation period. Although recently more sensitive assays have become

Table 2. Antiretroviral Therapy of Individuals Commencing HAART Between 1996 and 1997*

Therapy	Baseline	12 Months	24 Months	36 Months	48 Months
Indinavir sulfate + ≥2 nucleoside analogues	45.9	38.6	26.5	16.3	11.1
Ritonavir + ≥2 nucleoside analogues	22.6	13.2	8.5	5.5	5.2
Nelfinavir mesylate + ≥2 nucleoside analogues	13.1	19.8	21.6	26.0	20.1
Double PI + ≥1 nucleoside analogue	6.8	12.7	19.9	15.4	8.7
Saquinavir mesylate + ≥2 nucleoside analogues	6.9	2.2	0.8	0.4	0.4
PI + NNRTI + ≥1 nucleoside analogue	0.0	0.8	3.8	8.6	19.3
NNRTI + ≥2 nucleoside analogues	0.3	0.3	2.9	10.3	13.2
Triple nucleoside analogues	4.5	0.7	2.6	4.5	6.6
Other	0.0	4.4	4.0	3.0	4.3
Discontinued HAART	0.0	7.2	9.5	10.0	11.1

Abbreviations: HAART, highly active antiretroviral therapy; NNRTI, nonnucleoside analogue reverse transcriptase inhibitor; PI, protease inhibitor.
*Data are percentage of patients (N = 2235).

available, undetectable plasma HIV-1 RNA levels were defined as values below 400 copies/mL.

Longitudinal T-lymphocyte counts and HIV-1 RNA levels were separately analyzed in individuals who had continuously received HAART (CONT; n=985) and in subjects who discontinued HAART for at least 1 month (DISCONT; n=1250). In the CONT group, 725 individuals (73.6%) changed the HAART regimen, but only 51 (5.2%) were lost to follow-up, 10 of whom had died. In the DISCONT group, 458 (36.6%) individuals were lost to follow-up during the observation period, including 179 (14.3%) subjects who had died, 39 (3.1%) who had moved to another country, 28 (2.2%) who had discontinued participation in the Swiss Cohort study, and 212 (17.0%) who were lost to follow-up for unknown reasons. Of the 1250 subjects in the DISCONT group, 950 (76.0%) stopped antiretroviral therapy at least once for a median time of 3 (interquartile range, 1-10) months. The remaining 300 individuals (24.0%) were intermittently switched to non-HAART regimens for a median time of 4 (interquartile range, 1-12) months.

Three end points were evaluated and included absolute increases in CD4 T-lymphocyte count over 4 years, the percentage of subjects reaching a CD4 T-lymphocyte count of 500/µL or greater, and the percentage of individuals with a CD4 T-lymphocyte count less than 200/µL. Immunological end points and potential predictors of the immunological response were analyzed in individuals who had continuously received HAART (CONT; n=985). The following factors that could potentially affect the recovery of CD4 T lymphocytes were evaluated: sex, age, hepatitis C virus (HCV) serology (data available for 810 individuals), the duration of HIV-1 infection, the CDC stage, antiretroviral pretreatment before initiation of HAART, baseline HIV-1 RNA levels, baseline CD4 and CD8 T-lymphocyte counts, the number of therapy changes, and the percentage of HIV-1 RNA levels below 400 copies/mL.

The statistical analysis was performed using a general linear model and logistic regression. In the multivariate models, variables were entered stepwise in the order of strength of relationship found in the univariate model. A 2-sided *P* value less than .05 was considered statistically significant. All statistical calculations were performed using SPSS release 10.0 (SPSS Inc, Chicago, Ill).

RESULTS

PLASMA HIV-1 RNA AND T-LYMPHOCYTE DYNAMICS

In the entire cohort (N=2235), median plasma HIV-1 RNA declined from 4.6 $\log_{10}$ copies/mL to values below the limit of detection. At 48 months, 69.5% of treated individuals had undetectable plasma HIV-1 RNA levels (**Figure 1**A). During the observation period, the median CD4 T-lymphocyte count increased from 190/µL to 423/µL (Figure1B). Annual increases in CD4 T-lymphocyte count became gradually smaller over time. The percentage of individuals reaching CD4 T-lymphocyte counts of 500/µL or greater increased from 9.1% at baseline to 38.8% at 48 months. Of the 2235 subjects, 15.6% showed poor immunological responses and had persistently low CD4 T-lymphocyte counts below 200/µL.

In the CONT group, 84.5% showed HIV-1 RNA levels below 400 copies/mL at 48 months, whereas the median CD4 T-lymphocyte count increased from 203/µL to 486/µL (Figure1B). In 50.3%, CD4 T-lymphocyte count increased to 500/µL or greater, whereas in 26.8%, the number of CD4 T lymphocytes remained below 350/µL (Figure 1D). In this group, 264 individuals (6.1%) were classified as poor immunological responders (CD4 T-lymphocyte count <200/µL).

The percentage of patients reaching HIV-1 RNA levels below 400 copies/mL and the median CD4 T-lymphocyte count at 48 months was smaller in the DISCONT group than in the CONT group (53.6% vs 84.5%; 343/µL vs 486/µL, respectively; $P<.001$ for both comparisons). In addition, the percentage of individuals reaching CD4 T-lymphocyte counts of 500/µL or greater was smaller (29.4% vs 47.7%; $P<.001$) and the percentage of poor immunological responders was larger (25.9% vs 5.9%; $P<.001$). CD8 T lymphocytes showed smaller changes over time compared with CD4 T lymphocytes, increasing from 740/µL to 869/µL in the CONT group and from 697/µL to 872/µL in the DISCONT group (Figure1C).

DETERMINANTS OF CD4 T-LYMPHOCYTE COUNT INCREASES IN THE CONT GROUP

The potential factors associated with the recovery of CD4 T lymphocytes are given in **Table 3**. In the multivariate model, sex did not predict the recovery of CD4 T-lymphocyte count, although larger increases of CD4 T lymphocytes were observed in female study participants (323/µL vs 279/µL; Table 3). In contrast, younger age represented an independent predictor of larger rises in CD4 T-lymphocyte count ($P=.003$). The difference be-

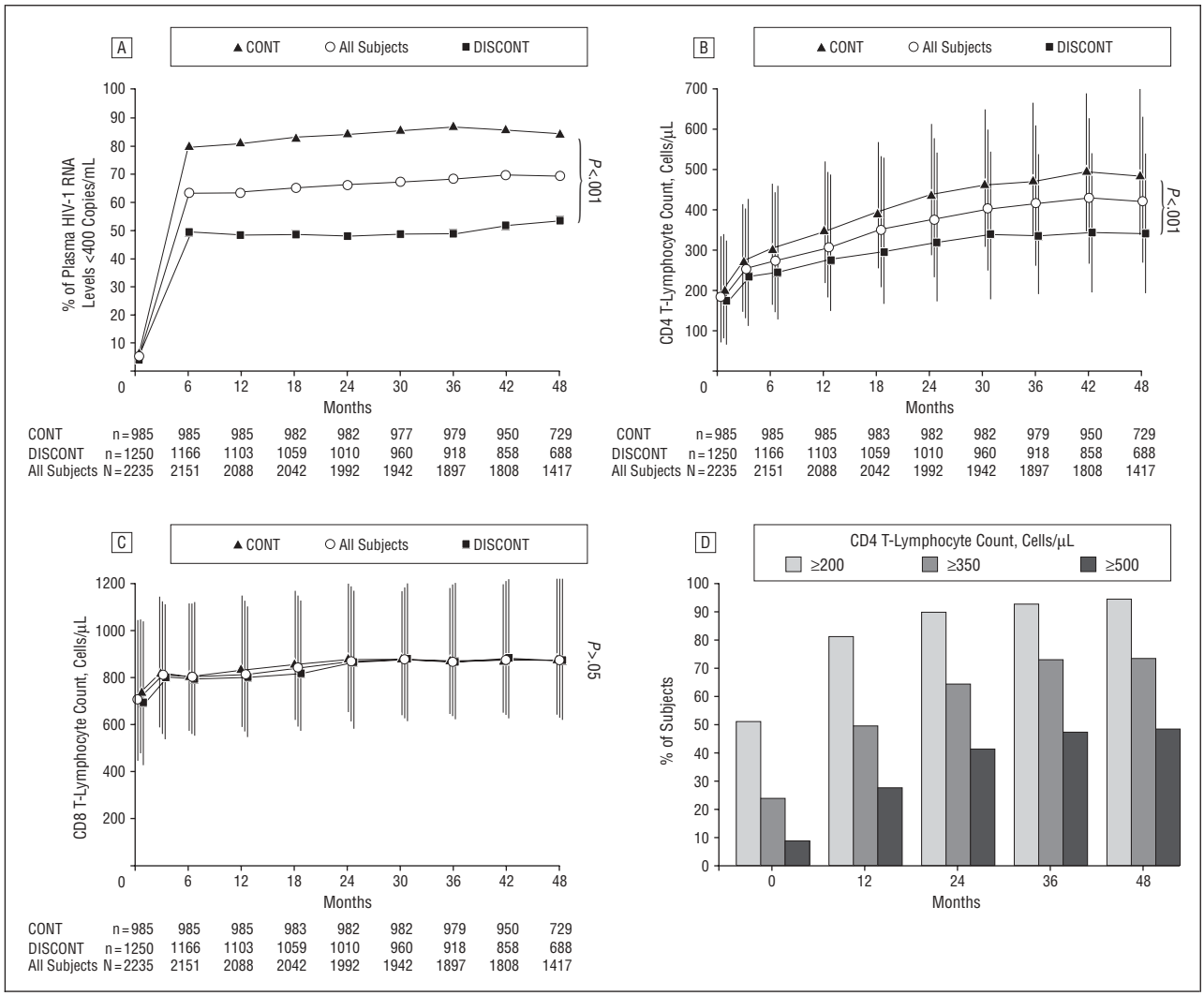

Figure 1. Time courses of the percentage of plasma human immunodeficiency virus–1 RNA levels below 400 copies/mL (A), CD4 T-lymphocyte count (B), and CD8 T-lymphocyte count (C) in the entire cohort (N=2235), in the group continuously receiving highly active antiretroviral therapy (HAART) (CONT; n=985), and in the group that intermittently discontinued HAART (DISCONT; n=1250). For B and C, data are median and interquartile range (25th and 75th percentiles). D, Percentage of subjects in the CONT group reaching clinically relevant thresholds of CD4 T-lymphocyte counts (≥200/µL, ≥350/µL, and ≥500/µL) during the observation period.

tween men and women regarding the increase in CD4 T-lymphocyte count may therefore be the result of the significantly younger age of female study participants (33 vs 37 years; $P<.001$).

The recovery of CD4 T lymphocytes showed no association with the mode of HIV transmission and was comparable in HCV-seropositive and -seronegative individuals. Nevertheless, significantly smaller rises in CD4 T-lymphocyte count were observed in HCV antibody–positive subjects in the first year of therapy (126/µL vs 151/µL at 1 year [$P=.005$] and 281/µL vs 294/µL at 48 months [$P=.34$]).

In the CONT group, 60.1% of individuals had been pretreated with antiretroviral agents for a median duration of 19 months. They showed smaller median increases in CD4 T-lymphocyte count than treatment-naive individuals (256/µL vs 335/µL at 48 months; $P<.001$). Nevertheless, in the multivariate model, pretreatment was not independently associated with the recovery of CD4 T lymphocytes ($P=.59$).

Importantly, baseline and nadir CD4 T-lymphocyte counts before initiation of HAART were not correlated with the recovery of CD4 T lymphocytes. Hence, the longitudinal time course of CD4 T lymphocytes in groups stratified by baseline CD4 T-lymphocyte count followed roughly parallel time courses (**Figure 2**A). As a consequence, the proportional increase of CD4 T-lymphocyte count from baseline was larger in individuals commencing HAART with lower baseline CD4 T-lymphocyte counts (Figure 2B). In contrast, lower baseline CD8 T-lymphocyte counts were independently associated with significantly larger rises in CD4 T-lymphocyte count ($P=.008$).

Higher baseline viral load was significantly associated with larger increases in CD4 T-lymphocyte count, both short term (3-6 months; $r=0.235$; $P<.001$) and long term (48 months; $r=0.218$; $P<.001$). In addition, more sustained suppression of HIV-1 viremia as measured by the percentage of plasma HIV-1 RNA values below 400 copies/mL during the observation period improved the recovery of CD4 T lymphocytes ($P<.001$; Figure 2C).

Table 3. Predictors of CD4 T-Lymphocyte Count Increase Over 48 Months*

Parameter	Baseline CD4 Cell Count, Cells/μL	CD4 T-Lymphocyte Count at 48 Months, Cells/μL	Increase in CD4 T-Lymphocyte Count Over 48 Months, Cells/μL	*P* Value	Multivariate *P* Value†
Sex					
Male	202 (85-348)	473 (336-691)	279 (165-419)	.02	.14
Female	206 (77-329)	520 (362-736)	323 (196-485)		
Age, y					
<34	227 (111-376)	523 (362-739)	304 (179-462)	.001	.003
34-40	170 (56-318)	486 (336-714)	303 (193-468)		
>40	210 (94-346)	469 (311-680)	264 (149-397)		
Transmission category					
Homosexual	221 (94-371)	493 (346-711)	291 (163-415)	.75	.67
Heterosexual	203 (89-339)	482 (335-683)	291 (172-466)		
IV drug use	174 (56-297)	447 (327-691)	284 (192-456)		
HCV antibody					
Negative	218 (91-349)	475 (333-690)	294 (167-428)	.86	.34
Positive	182 (64-311)	447 (337-687)	281 (191-460)		
CDC category					
A	317 (201-431)	609 (439-785)	303 (158-430)	.03	.05
B	190 (98-324)	446 (328-636)	266 (164-418)		
C	66 (25-167)	410 (293-608)	296 (196-481)		
Time from HIV-1 diagnosis to HAART, y					
<4.6	250 (103-385)	558 (421-690)	313 (172-415)	.23	.42
4.6-9.6	167 (76-290)	432 (292-706)	252 (179-420)		
>9.6	187 (55-296)	462 (339-711)	284 (156-456)		
Pretreatment					
No	192 (60-343)	550 (383-750)	335 (232-485)	<.001	.59
Yes	209 (100-342)	462 (324-671)	256 (158-411)		
Nadir CD4 T-lymphocyte count before initiation of HAART, cells/μL					
<90	49 (20-85)	368 (263-488)	302 (193-426)	.43	.92
90-220	193 (136-279)	508 (348-659)	258 (165-419)		
>220	382 (300-496)	723 (511-885)	307 (156-460)		
Baseline CD4 T-lymphocyte count, cells/μL					
<121	49 (20-85)	367 (263-505)	322 (201-464)	.009	.38
121-293	203 (160-250)	472 (349-662)	265 (170-421)		
>293	410 (342-511)	721 (522-886)	279 (125-417)		
Baseline CD8 T-lymphocyte count, cells/μL					
<560	98 (25-201)	421 (297-626)	303 (194-450)	.002	.008
560-926	254 (117-376)	515 (372-723)	294 (165-427)		
>926	277 (146-407)	524 (372-757)	269 (159-421)		
Baseline plasma HIV-1 RNA, $\log_{10}$ copies/mL					
<4.0	301 (183-406)	539 (371-716)	250 (124-394)	<.001	<.001
4.0-5.0	210 (103-341)	472 (322-726)	265 (175-455)		
>5.0	100 (36-231)	450 (331-676)	342 (218-477)		
No. of changes of therapy					
1	225 (84-361)	521 (362-733)	312 (195-477)	.06	.64
2	196 (89-341)	478 (341-699)	286 (160-443)		
>2	191 (83-325)	465 (327-669)	271 (171-410)		
Percentage of HIV-1 RNA values <400 copies/mL					
<90	176 (75-311)	412 (288-596)	220 (118-363)	<.001	<.001
90-97	185 (59-329)	505 (363-726)	345 (22-484)		
>97	263 (120-392)	548 (401-767)	307 (196-440)		

Abbreviations: CDC, Centers for Disease Control and Prevention; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IV, intravenous.

*Data are median and interquartile range (25th and 75th percentile) unless otherwise specified. A general linear model was used for the statistical evaluation using data of individuals who continuously have received HAART for at least 48 months (n = 728). Categories of continuous variables are based on equally sized groups.

†Adjusted for age, baseline CD8 cell count, baseline viral load, and the percentage of viral loads less than 400 copies/mL.

PREDICTORS OF GOOD (≥500/μL) AND POOR (<200/μL) IMMUNOLOGICAL RESPONSES IN THE CONT GROUP

Higher nadir CD4 T-lymphocyte count indicating the maximum extent of HIV-1–related immunodeficiency increased the likelihood of reaching CD4 T-lymphocyte counts of 500/μL or greater within 48 months (adjusted odds ratio [OR], 1.38 per 100-cell increase; **Table 4**). Similarly, the likelihood of reaching this CD4 T-lymphocyte count was higher in individuals with a larger number of CD4 T lymphocytes at baseline (adjusted OR, 2.04

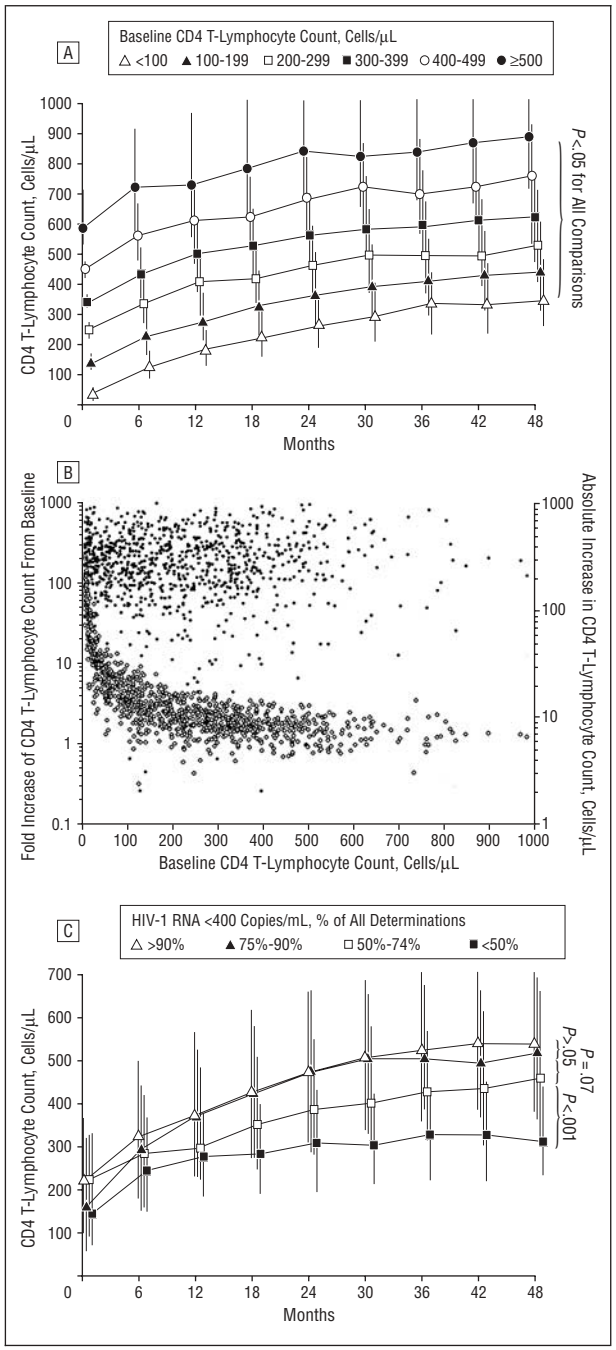

Figure 2. Baseline CD4 T-lymphocyte count, virologic response, and CD4 recovery. A, Time course of CD4 T lymphocyte count (medians and interquartile ranges) in groups with continuous highly active antiretroviral therapy (HAART) (CONT; n=985) stratified by baseline CD4 T-lymphocyte count. Of note, CD4 trajectories followed almost parallel time courses. Absolute increases in CD4 T-lymphocyte count were therefore in a similar range for all subgroups. B, However, fold-increase of CD4 T-lymphocyte count from baseline values was larger in individuals commencing HAART with lower CD4 T-lymphocyte counts. Dots represent absolute increases in CD4 T-lymphocyte count and open squares indicate the fold increase from baseline CD4 T-lymphocyte count. C, Time course of median CD4 T-lymphocyte count in the CONT group stratified by the reduction of plasma human immunodeficiency virus (HIV)-1 viremia.

per 100-cell increase). A baseline CD4 T-lymphocyte count ranging from 300/µL to 400/µL appeared thereby to represent a critical threshold. Almost 70% of subjects commencing HAART with a CD4 T-lymphocyte count of 300/µL to 400/µL reached the end point of a CD4 T-lymphocyte count of 500/µL or greater, whereas only 51% initiating HAART with a CD4 T-lymphocyte count of 200/µL to 300/µL and 40% with a count of 100/µL to 200/µL reached this target level (**Figure 3**A).

The virologic response was a further relevant predictor. Higher baseline plasma HIV-1 RNA levels (adjusted OR, 1.34 per 1-log increase) and a higher percentage of undetectable plasma HIV-1 RNA levels increased the likelihood of reaching a CD4 T-lymphocyte count of 500/µL at 48 months (adjusted OR, 1.27 per 10% increase; Figure 3B).

The risk of a poor recovery of CD4 T lymphocytes (<200/µL at 48 months) was significantly higher in subjects with lower baseline CD4 T-lymphocyte counts (adjusted OR, 0.26 per 100-cell increase; **Table 5**), lower baseline HIV-1 RNA levels (adjusted OR, 0.65 per 1-log increase), and a smaller percentage of undetectable plasma HIV-1 RNA levels during the observation period (adjusted OR, 0.75 per 10% increase).

COMMENT

In most HIV-1–infected individuals treated with HAART, CD4 T lymphocytes recover to levels above 200/µL, at which HIV-1–related clinical complications are exceedingly rare.[11] Nevertheless, many clinicians as well as patients aim at higher, more physiological levels of CD4 T lymphocytes, preferably above 500/µL. The percentage of individuals who ultimately reach this goal and the factors affecting the recovery of CD4 T lymphocytes were the focus of the present study.

At 4 years, only 39% of 2235 participants of the Swiss HIV Cohort reached CD4 T-lymphocyte counts above 500/µL and 16% had counts less than 200/µL, remaining susceptible to opportunistic infections. Higher baseline and nadir CD4 T-lymphocyte counts increased the likelihood of reaching a CD4 T-lymphocyte count of 500/µL within 4 years. Poor immunological responders failing to reach a CD4 T-lymphocyte count of 200/µL commenced HAART with a smaller number of CD4 T lymphocytes and showed poorer virologic responses. Larger absolute increases in CD4 T-lymphocyte count were observed in individuals who were younger, had higher baseline plasma HIV-1 RNA levels, lower CD8 T-lymphocyte counts, and a more sustained reduction of plasma HIV-1 viremia.

At 4 years, almost 70% of individuals commencing HAART with a CD4 T-lymphocyte count of 300/µL to 400/µL had CD4 T-lymphocyte counts of at least 500/µL. The percentage of subjects reaching this goal declined to 51% in individuals commencing HAART with a CD4 T-lymphocyte count less than 300/µL, which suggests that HAART should preferably be initiated before CD4 T-lymphocyte count has declined below 300/µL. This is in good agreement with current treatment guidelines that propose to commence HAART at a CD4 T-lymphocyte count of 350/µL.[28]

CD4 T lymphocytes showed a rapid increase in the first 3 months, followed by an almost linear rise in the subsequent 2 years. However, annual changes in CD4 T-lymphocyte count thereafter became gradually smaller,

Table 4. Predictors of CD4 T-Lymphocyte Count of 500/µL or Greater at 4 Years*

Parameter	Odds Ratio (95% CI)	*P* Value	Multivariate Analysis† Odds Ratio (95% CI)	*P* Value
Female sex	1.201 (0.851-1.697)	.30	1.423 (0.949-2.134)	.09
Age (per 10-y increase)	0.812 (0.685-0.963)	.02	0.819 (0.670-1.000)	.05
HCV antibody positive	0.970 (0.691-1.362)	.86	1.154 (0.772-1.725)	.49
Duration of HIV-1 infection (per 10-y increase)	0.501 (0.290-0.867)	.01	0.586 (0.307-1.115)	.10
CDC stage				
B	0.391 (0.274-0.558)	<.001	0.721 (0.476-1.091)	.12
C	0.289 (0.197-0.423)	<.001	0.992 (0.619-1.592)	.97
Pretreated	0.580 (0.426-0.788)	.001	0.710 (0.487-1.035)	.08
Nadir CD4 T-lymphocyte count before HAART (per 100/µL increase)	2.263 (1.949-2.629)	<.001	1.376 (1.044-1.814)	.02
Baseline CD4 T-lymphocyte count (per 100/µL increase)	1.898 (1.692-2.128)	<.001	2.036 (1.783-2.326)	<.001
Baseline CD8 T-lymphocyte count (per 100/µL increase)	1.045 (1.016-1.074)	.002	0.968 (0.935-1.002)	.07
Baseline HIV-1 RNA (per 1-log plasma HIV-1 RNA increase)	0.875 (0.768-0.997)	.046	1.337 (1.130-1.582)	.001
No. of therapy changes (per change of therapy)	0.864 (0.765-0.976)	.02	1.017 (0.876-1.180)	.83
Percentage of HIV-1 RNA levels <400 copies/mL (per 10% increase)	1.270 (1.187-1.360)	<.001	1.268 (1.174-1.368)	<.001

Abbreviations: CDC, Centers for Disease Control and Prevention; CI, confidence interval; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

*A logistic regression model was used for this analysis including only individuals who continuously had received HAART for at least 48 months (n = 728).

†Adjusted for baseline viral load, baseline CD4 cell count, and the percentage of viral loads less than 400 copies/mL.

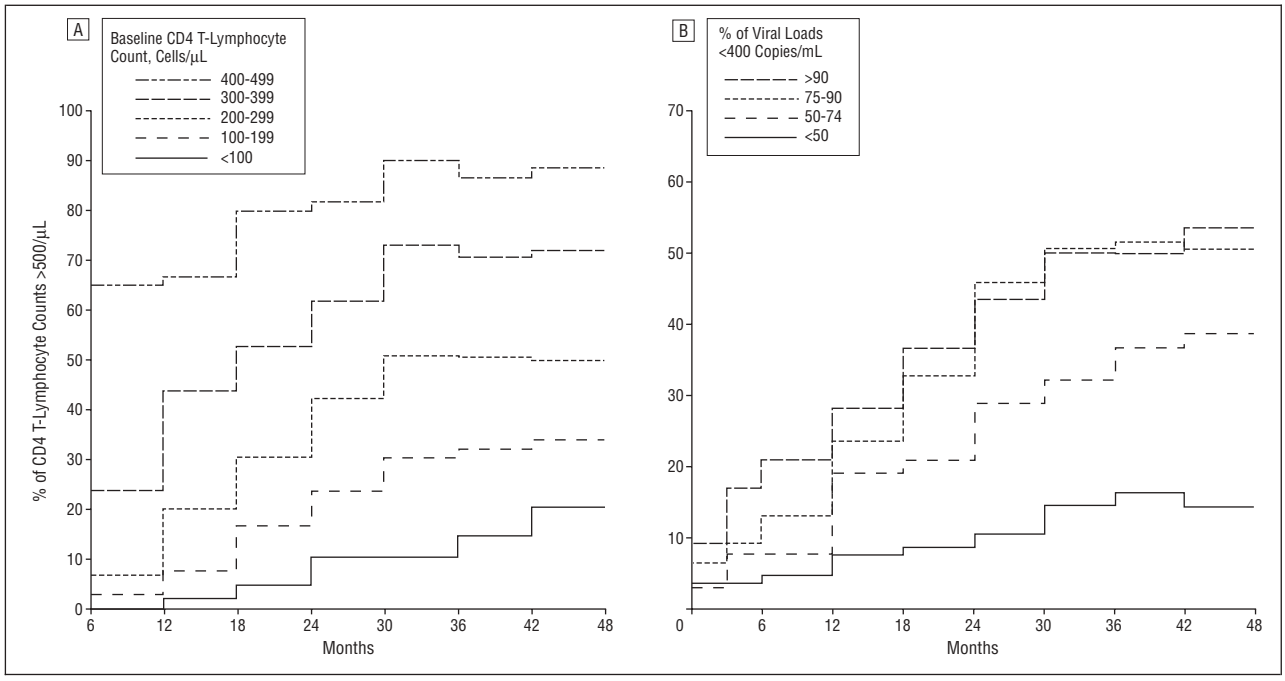

Figure 3. Predictors of CD4 T-lymphocyte counts of 500/µL or greater at 4 years. Percentages of individuals reaching a CD4 T-lymphocyte count of 500/µL or greater in groups with continuous highly active antiretroviral therapy (n=985) stratified by baseline CD4 T-lymphocyte count (A) and the percentage of viral loads below 400 copies/mL (B). *P*<.001 for all comparisons.

suggesting that the number of CD4 T lymphocytes may reach a plateau level. Therefore, a normalization of CD4 T-lymphocyte count does not appear feasible in all individuals or will require at least very long-term therapy. This is further supported by the fact that the increase of CD4 T lymphocytes did not depend on baseline values. The comparison of CD4 T lymphocytes of groups stratified by baseline CD4 T-lymphocyte count revealed that CD4 trajectories followed almost parallel time courses. Hence, individuals commencing HAART with a small number of CD4 T lymphocytes will reach, after the same observation period, on average lower CD4 T-lymphocyte counts than subjects who initiate HAART at higher CD4 T-lymphocyte numbers.

The delayed reconstitution of the CD4 T-cell compartment in elderly patients has previously been observed in smaller studies.[19,27] The thymus significantly contributes to the recovery of CD4 T lymphocytes,[29] but loses partly its functionality after physiological involution during puberty. This may provide an explanation for the poorer recovery of CD4 T lymphocytes in older patients.

Recovery of CD4 T lymphocytes was significantly associated with more sustained reduction of plasma HIV-1 viremia. However, we did not find a significant differ-

Table 5. Predictors of CD4 T-Lymphocyte Count Less Than 200/µL at 4 Years*

Parameter	Odds Ratio (95% CI)	*P* Value	Multivariate Analysis† Odds Ratio (95% CI)	*P* Value
Female sex	0.633 (0.276-1.449)	.28	0.594 (0.241-1.466)	.26
Age	1.342 (0.971-1.855)	.07	1.301 (0.887-1.909)	.18
HCV antibody positive	1.159 (0.580-2.315)	.68	1.223 (0.569-2.629)	.61
Duration of HIV-1 infection (per 10-y increase)	2.381 (0.858-6.608)	.10	2.358 (0.713-7.800)	.16
CDC stage				
B	1.829 (0.754-4.438)	.18	0.693 (0.250-1.921)	.48
C	3.514 (1.523-8.105)	.003	0.631 (0.224-1.776)	.38
Pretreated with nucleoside analogues	2.117 (0.999-4.486)	.05	1.307 (0.565-3.022)	.53
Nadir CD4 T-lymphocyte count before HAART (per 100/µL increase)	0.253 (0.147-0.435)	<.001	0.531 (0.181-1.561)	.25
Baseline CD4 T-lymphocyte count (per 100/µL increase)	0.362 (0.244-0.537)	<.001	0.264 (0.160-0.436)	<.001
Baseline CD8 T-lymphocyte count (per 100/µL increase)	0.952 (0.889-1.020)	.16	1.044 (0.971-1.122)	.25
Baseline HIV-1 RNA (per 1-log plasma HIV-1 RNA increase)	1.096 (0.823-1.461)	.53	0.652 (0.479-0.888)	.007
No. of therapy changes (per change of therapy)	1.321 (1.072-1.630)	.009	1.006 (0.779-1.299)	.96
Percentage of HIV-1 RNA values <400 copies/mL (per 10% increase)	0.764 (0.703-0.830)	<.001	0.754 (0.688-0.827)	<.001

Abbreviations: See Table 4 footnote for expansion of abbreviations.
*A logistic regression model was used for this analysis including only individuals who continuously have received HAART for at least 48 months (n = 728).
†Adjusted for baseline viral load, baseline CD4 cell count, and the percentage of viral loads less than 400 copies/mL.

ence regarding the increase in CD4 T-lymphocyte count between individuals with 75% to 90% and more than 90% undetectable viral loads during the observation period. In contrast, individuals with more than 25% detectable HIV-1 RNA levels showed a trend toward a poorer recovery of CD4 T lymphocytes. This observation supports the concept of a critical viral load threshold, which determines whether CD4 T lymphocytes recover or further decline.[30]

In the first year of HAART, HCV-seropositive individuals showed smaller increases in CD4 T-lymphocyte count than HCV-seronegative persons, which is in agreement with the results of a previous investigation of the Swiss HIV Cohort Study Group.[22] The negative effect of HCV infection on the recovery of CD4 T lymphocytes disappeared during the observation period. However, the CONT and DISCONT groups were not balanced for HCV infection. Most HCV-seropositive individuals were observed in the DISCONT group (41% vs 31%), but the analysis of predictors of CD4 T-lymphocyte recovery was based on data of the CONT group.

The substantial percentage (26%) of poor immunological responders in the DISCONT group indicates that a sizable proportion of individuals remains at risk for opportunistic infections over a lengthy period despite the availability of potent antiretroviral regimens. The substantial percentage of individuals who intermittently discontinued HAART also reflects the problems associated with currently available antiretroviral drug regimens such as frequent adverse events and poor adherence to the drug regimen.[31,32]

One limitation of this prospective cohort study is the follow-up pattern, which could have introduced bias. For example, patients with slow disease progression may have avoided outpatient visits, ultimately reducing the amount of information. This "walking well" phenomenon may have resulted in an underestimation of the recovery of CD4 T lymphocytes. Conversely, patients in more advanced stages of HIV-1 infection were more likely to discontinue HAART or to leave the study, which may have introduced a bias in the opposite direction.

CONCLUSIONS

This prospective observational cohort study shows that the recovery of CD4 T lymphocytes in treated HIV-1–infected individuals is slower than initially anticipated. Indeed, CD4 T-lymphocyte count failed to recover significantly in 16% of individuals, and more than 50% did not reach CD4 T-lymphocyte counts of 500/µL or greater after 4 years of HAART. Of further concern is the observation that the number of CD4 T lymphocytes appeared to reach a plateau level after 2 to 3 years. This suggests that CD4 T-lymphocyte count remains in a critically low range in a significant number of individuals. Therefore, HAART should not be deferred to late stages of HIV-1 infection, although the advantages of an earlier initiation of HAART have to be individually counterbalanced against potential adverse events and the rapid emergence of drug resistance.

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REFERENCES

1. Egger M, Hirschel B, Francioli P, et al. Impact of new antiretroviral combination therapies in HIV infected patients in Switzerland: prospective multicentre study: Swiss HIV Cohort Study. *BMJ*. 1997;315:1194-1199.
2. Palella FJ Jr, Delaney KM, Moorman AC, et al, HIV Outpatient Study Investigators. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med*. 1998;338:853-860.
3. Mocroft A, Vella S, Benfield T, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. *Lancet*. 1998;352:1725-1730.
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;353:863-868.
5. 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;360:119-129.
6. Angel JB, Kumar A, Parato K, et al. Improvement in cell-mediated immune function during potent anti-human immunodeficiency virus therapy with ritonavir plus saquinavir. *J Infect Dis*. 1998;177:898-904.
7. Komanduri KV, Viswanathan MN, Wieder ED, et al. Restoration of cytomegalovirus-specific CD4+ T-lymphocyte responses after ganciclovir and highly active antiretroviral therapy in individuals infected with HIV-1. *Nat Med*. 1998;4:953-956.
8. Li TS, Tubiana R, Katlama C, Calvez V, Ait Mohand H, Autran B. Long-lasting recovery in CD4 T-cell function and viral-load reduction after highly active antiretroviral therapy in advanced HIV-1 disease. *Lancet*. 1998;351:1682-1686.
9. Furrer H, Egger M, Opravil M, et al. Discontinuation of primary prophylaxis against *Pneumocystis carinii* pneumonia in HIV-1-infected adults treated with combination antiretroviral therapy: Swiss HIV Cohort Study. *N Engl J Med*. 1999;340:1301-1306.
10. Schneider MM, Borleffs JC, Stolk RP, Jaspers CA, Hoepelman AI. Discontinuation of prophylaxis for *Pneumocystis carinii* pneumonia in HIV-1-infected patients treated with highly active antiretroviral therapy. *Lancet*. 1999;353:201-203.
11. Ledergerber B, Egger M, Erard V, et al. AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy: the Swiss HIV Cohort Study. *JAMA*. 1999;282:2220-2226.
12. Piketty C, Castiel P, Belec L, et al. Discrepant responses to triple combination antiretroviral therapy in advanced HIV disease. *AIDS*. 1998;12:745-750.
13. Renaud M, Katlama C, Mallet A, et al. Determinants of paradoxical CD4 cell reconstitution after protease inhibitor-containing antiretroviral regimen. *AIDS*. 1999;13:669-676.
14. Kaufmann G, Bloch M, Zaunders J, Smith D, Cooper D. Long-term immunological response in HIV-1 infected subjects receiving potent antiretroviral therapy. *AIDS*. 2000;14:959-969.
15. Staszewski S, Miller V, Sabin C, et al. Determinants of sustainable CD4 lymphocyte count increases in response to antiretroviral therapy. *AIDS*. 1999;13:951-956.
16. Arno A, Ruiz L, Juan M, et al. Impact on the immune system of undetectable plasma HIV-1 RNA for more than 2 years. *AIDS*. 1998;12:697-704.
17. Kaufmann D, Pantaleo G, Sudre P, Telenti A. CD4-cell count in HIV-1-infected individuals remaining viraemic with highly active antiretroviral therapy (HAART): Swiss HIV Cohort Study. *Lancet*. 1998;351:723-724.
18. Lecossier D, Bouchonnet F, Schneider P, Clavel F, Hance AJ. Discordant increases in CD4+ T cells in human immunodeficiency virus-infected patients experiencing virologic treatment failure: role of changes in thymic output and T cell death. *J Infect Dis*. 2001;183:1009-1016.
19. Viard JP, Mocroft A, Chiesi A, et al. Influence of age on CD4 cell recovery in human immunodeficiency virus-infected patients receiving highly active antiretroviral therapy: evidence from the EuroSIDA study. *J Infect Dis*. 2001;183:1290-1294.
20. 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;14:2643-2651.
21. Zhang L, Ramratnam B, Tenner-Racz K, et al. Quantifying residual HIV-1 replication in patients receiving combination antiretroviral therapy. *N Engl J Med*. 1999;340:1605-1613.
22. 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;356:1800-1805.
23. Tillmann HL, Heiken H, Knapik-Botor A, et al. Infection with GB virus C and reduced mortality among HIV-infected patients. *N Engl J Med*. 2001;345:715-724.
24. Xiang J, Wunschmann S, Diekema DJ, et al. Effect of coinfection with GB virus C on survival among patients with HIV infection. *N Engl J Med*. 2001;345:707-714.
25. O'Brien TR, McDermott DH, Ioannidis JP, et al. Effect of chemokine receptor gene polymorphisms on the response to potent antiretroviral therapy. *AIDS*. 2000;14:821-826.
26. Guerin S, Meyer L, Theodorou I, et al. CCR5 delta32 deletion and response to highly active antiretroviral therapy in HIV-1-infected patients. *AIDS*. 2000;14:2788-2790.
27. Yamashita TE, Phair JP, Munoz A, et al. Immunologic and virologic response to highly active antiretroviral therapy in the Multicenter AIDS Cohort Study. *AIDS*. 2001;15:735-746.
28. Yeni PG, Hammer SM, Carpenter CC, et al. Antiretroviral treatment for adult HIV infection in 2002: updated recommendations of the International AIDS Society–USA Panel. *JAMA*. 2002;288:222-235.
29. Douek DC, McFarland RD, Keiser PH, et al. Changes in thymic function with age and during the treatment of HIV infection. *Nature*. 1998;396:690-695.
30. Deeks SG. Durable HIV treatment benefit despite low-level viremia: reassessing definitions of success or failure. *JAMA*. 2001;286:224-226.
31. Fellay J, Boubaker K, Ledergerber B, et al. Prevalence of clinical and laboratory adverse events associated with potent antiretroviral therapy: Swiss HIV Cohort Study. *Lancet*. 2001;358:1322-1327.
32. Hänsel A, Bucher H, Nüesch R, Battegay M. Durability and reasons for discontinuation of first highly active antiretroviral therapy (HAART) in a cohort of proteinase inhibitor naive HIV-infected patients. *J Acquir Immune Defic Syndr*. 2001;26:191-193.