

CD4⁺ T Cell Count Recovery in HIV Type 1–Infected Patients Is Independent of Class of Antiretroviral Therapy

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Background. In recent years, treatment options for human immunodeficiency virus type 1 (HIV-1) infection have changed from nonboosted protease inhibitors (PIs) to nonnucleoside reverse-transcriptase inhibitors (NNRTIs) and boosted PI–based antiretroviral drug regimens, but the impact on immunological recovery remains uncertain.

Methods. During January 1996 through May 2007, all patients in the Swiss HIV Cohort were included if they received the first combination antiretroviral therapy (cART) and had known baseline CD4⁺ T cell counts and HIV-1 RNA values ($n = 3293$). The mean (\pm SD) duration of follow-up was 26.8 ± 20.5 months. The follow-up time was limited to the duration of the first cART. CD4⁺ T cell recovery was analyzed in 3 different treatment groups: nonboosted PI, NNRTI, or boosted PI. The end point was the absolute increase of CD4⁺ T cell count in the 3 treatment groups after the initiation of cART.

Results. Two thousand five hundred ninety individuals (78.7%) initiated a nonboosted-PI regimen, 452 (13.7%) initiated an NNRTI regimen, and 251 (7.6%) initiated a boosted-PI regimen. Absolute CD4⁺ T cell count increases at 48 months were as follows: in the nonboosted-PI group, from 210 to 520 cells/ μ L; in the NNRTI group, from 220 to 475 cells/ μ L; and in the boosted-PI group, from 168 to 511 cells/ μ L. In a multivariate analysis, the treatment group did not affect the response of CD4⁺ T cells; however, increased age, pretreatment with nucleoside reverse-transcriptase inhibitors, serological tests positive for hepatitis C virus, Centers for Disease Control and Prevention stage C infection, lower baseline CD4⁺ T cell count, and lower baseline HIV-1 RNA level were risk factors for smaller increases in CD4⁺ T cell count.

Conclusion. CD4⁺ T cell recovery was similar in patients receiving nonboosted PI–, NNRTI–, and boosted PI–based cART.

The major aim of combination antiretroviral therapy (cART) is the reduction of HIV-1–related morbidity and mortality by suppression of plasma HIV-1 RNA,

with a subsequent increase in CD4⁺ T cell count [1–4]. The CD4⁺ T cell level reached during the first 5 years of cART strongly depends on baseline CD4⁺ T cell count, even among patients with completely suppressed plasma HIV-1 RNA [5, 6]. Other factors that have been shown to result in a better CD4⁺ T cell recovery are the absence of prior antiretroviral therapy (ART), lower baseline CD8⁺ T cell count, younger age, and cART that does not contain zidovudine (ZDV) [5, 7–9].

Several antiretroviral drugs have become available in the past few years, and strategies for treatment of HIV infection have changed [10–14]. The frequent dosing schedule, the high pill burden, and adverse events have led to a preference for a once-daily antiretroviral drug

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Table 1. Baseline demographic characteristics by combination antiretroviral therapy (cART) regimen.

Variable	All patients (n = 3293)	Nonboosted-PI cART (n = 2590)	NNRTI-containing cART (n = 452)	Boosted-PI cART (n = 251)
Sex				
Male	2367 (71.9)	1862 (71.9)	320 (70.8)	185 (73.7)
Female	926 (28.1)	728 (28.1)	132 (29.2)	66 (26.3)
Age, mean years \pm SD	38.2 \pm 9.5	37.9 \pm 9.2	38.5 \pm 10.4	40.7 \pm 10.0
Ethnicity				
White	2748 (83.4)	2179 (84.1)	356 (78.8)	213 (84.9)
Black	278 (8.4)	193 (7.5)	68 (15.0)	17 (6.8)
Hispanic	56 (1.7)	39 (1.5)	11 (2.4)	6 (2.4)
Asian	78 (2.4)	54 (2.1)	12 (2.7)	12 (4.8)
Other/no information	133 (4.0)	125 (4.8)	5 (1.1)	3 (1.2)
HIV transmission category				
MSM	1167 (35.4)	923 (35.6)	163 (36.1)	81 (32.3)
Heterosexual intercourse	1109 (33.7)	815 (31.5)	187 (41.4)	107 (42.6)
IDU	883 (26.8)	756 (29.2)	81 (17.9)	46 (18.3)
Other/unknown	134 (4.1)	96 (3.7)	21 (4.6)	17 (6.8)
Duration of HIV-1 infection, mean years \pm SD	5.4 \pm 4.6	5.6 \pm 4.4	4.7 \pm 5.3	4.6 \pm 5.6
CDC infection stage				
A	1480 (46.0)	1153 (44.5)	237 (52.4)	90 (35.9)
B	998 (31.0)	819 (31.6)	120 (26.5)	59 (23.5)
C	737 (22.9)	608 (23.5)	67 (14.8)	62 (24.7)
Unknown	78 (2.4)	10 (0.4)	28 (6.2)	40 (15.9)
Pretreated	1351 (41.0)	1262 (48.7)	57 (12.6)	32 (12.7)
Baseline HIV-1 RNA level, median log ₁₀ copies/mL (IQR)	4.8 (4.2–5.3)	4.7 (4.1–5.3)	4.9 (4.5–5.4)	5.3 (4.8–5.7)
Baseline CD4 ⁺ T cell count, median cells/ μ L (IQR)	201 (88–340)	201 (86–345)	220 (130–331)	168 (50–288)
Baseline CD8 ⁺ T cell count, median cells/ μ L (IQR)	733 (474–1090)	724 (467–1069)	803 (519–1215)	710 (445–1097)
Positive for HCV antibody	1052 (33.0)	903 (34.9)	95 (21.0)	54 (21.5)
Unknown	102 (3.1)	23 (0.9)	37 (8.2)	42 (16.7)
ZDV treatment	1792 (54.4)	1232 (47.6)	362 (80.1)	198 (78.9)

NOTE. Data are no. (%) of patients, unless otherwise indicated. CDC, Centers for Disease Control and Prevention; HCV, hepatitis C virus; IDU, injection drug use; IQR, interquartile range; MSM, men having sex with men; ZDV, zidovudine.

regimen consisting of 3 compounds, including a nonnucleoside reverse-transcriptase inhibitor (NNRTI) or a boosted protease inhibitor (PI) [15, 16]. However, direct comparisons of these antiretroviral drug regimens, with respect to the long-term recovery of CD4⁺ T cell count, are scarce. Importantly, this is particularly the case for follow-up studies that assess the first, unchanged cART. This issue may be particularly important for developing countries, where newer treatment options remain unavailable. Four large studies comparing ART in treatment-naïve patients using either an NNRTI- or a PI-based cART for a maximum follow-up of 32 months found comparable responses of CD4⁺ T cell count [17–20]. However, other studies found smaller increases in CD4⁺ T cell count in individuals using an NNRTI-based cART at 48 and 96 weeks [21–23]. In the present study, we analyzed the long-term CD4⁺ T cell recovery in 3293 patients of the Swiss HIV Cohort Study (SHCS) who received the first cART that included a nonboosted PI, NNRTI, or a boosted PI.

PATIENTS AND METHODS

Study participants. All patients of the SHCS who initiated their first cART during January 1996 through May 2007 were analyzed. The SHCS is a prospective, observational study of HIV-1-infected adults that was initiated in 1988, with clinical and laboratory follow-up documented every 6 months. Enrollment is independent of disease stage and treatment [24, 25]. cART was defined as a drug regimen containing a nucleoside reverse-transcriptase inhibitor (NRTI) backbone with a PI, NNRTI, or a ritonavir-boosted PI. Patients who had received prior treatment with NRTIs were also included. Laboratory values, including CD4⁺ and CD8⁺ T cell count and plasma HIV-1 RNA level, were monitored at 3–6-month intervals.

All patients with unknown baseline CD4⁺ T cell counts (1295 patients) or unknown plasma HIV-1 RNA values (195 patients) were excluded. In addition, all patients whose first cART duration was <3 months were excluded (790 patients).

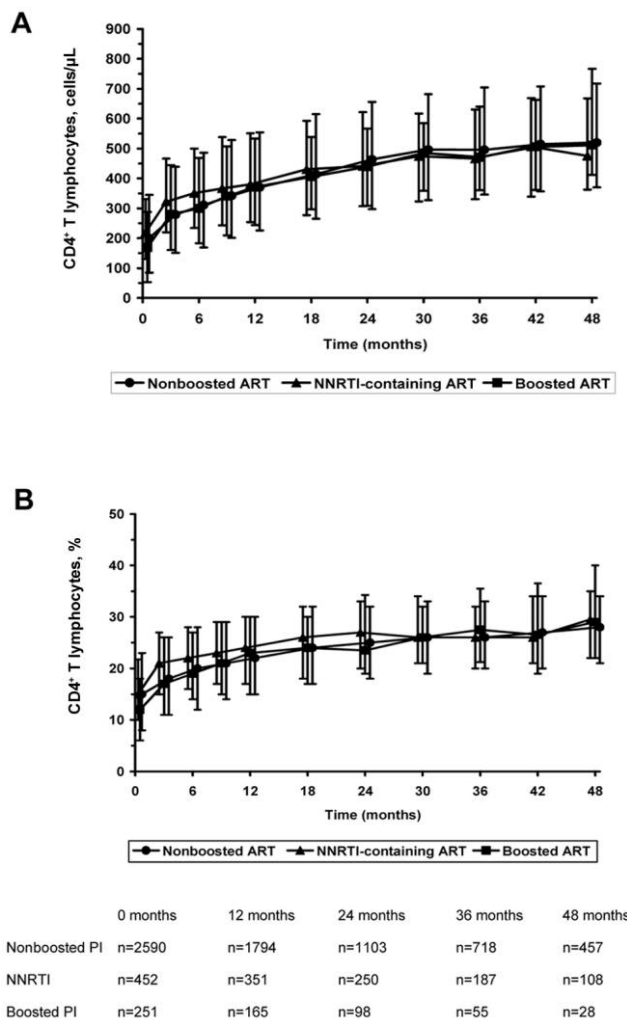


Figure 1. Absolute CD4⁺ T cell counts (A) and percentages (B) by treatment regimen. ART, antiretroviral therapy; NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

Study design. CD4⁺ T cell count increases were analyzed during the first cART until ART was stopped or switched to another cART regimen. The mean (\pm SD) follow-up was 26.8 ± 20.5 months. The reasons for discontinuation of ART could not be analyzed in detail, because these data were not collected for the SHCS database during the entire analyzed period. Treatment discontinuation was classified as virological failure if the prior 2 plasma HIV-1 RNA measurements were >400 copies/mL.

CD4⁺ T cell count increase was compared in 3 groups by type of ART. Group 1 consisted of patients receiving non-boosted PI-based drug regimens (2590 patients [78.7%]). These individuals commenced a drug regimen with indinavir (953 patients), ritonavir (357 patients), nelfinavir (992 patients), saquinavir (109 patients), and at least 2 NRTIs or a triple combination with saquinavir, ritonavir, and 1 NRTI (179 patients). Of the 2590 patients in this group, 2327 (89.8%) had

been receiving treatment at 6 months, 1794 (69.3%) had been receiving treatment at 12 months, 1103 (42.6%) had been receiving treatment at 24 months, 718 (27.7%) had been receiving treatment at 36 months, and 457 (17.6%) had been receiving treatment at 48 months.

Group 2 (452 [13.7%] of 3293 patients) received an NNRTI in combination with at least 2 NRTIs. Most patients received efavirenz (420 patients), and a small proportion of patients received nevirapine (32 patients). Of 452 patients treated with an NNRTI-containing regimen, 425 (94.0%) had been receiving treatment at 6 months, 351 (77.7%) had been receiving treatment at 12 months, 250 (55.3%) had been receiving treatment at 24 months, 187 (41.4%) had been receiving treatment at 36 months, and 108 (23.9%) had been receiving treatment at 48 months.

The third group received boosted PIs in combination with at least 2 NRTIs (251 [7.6%] of the 3293 patients). These patients received 100 mg ritonavir in combination with lopinavir (160 patients), saquinavir (29 patients), indinavir (60 patients), or atazanavir (2 patients). Of these 251 patients, 218 (86.9%) had been receiving treatment at 6 months, 165 (65.7%) had been receiving treatment at 12 months, 98 (39.0%) had been receiving treatment at 24 months, 55 (21.9%) had been receiving treatment at 36 months, and 28 (11.2%) had been receiving treatment at 48 months. cART containing nonboosted PI was more common during 1996–2000. cART containing NNRTIs and boosted PIs was more common after 2000.

Statistical analysis. The primary end point of the study was the absolute increase in CD4⁺ T cell count from baseline in the 3 different treatment groups. Absolute increases of CD4⁺ T lymphocyte count were analyzed using a Cox proportional hazards model. The potential factors for CD4⁺ T lymphocyte recovery were evaluated as follows: sex, age, duration of HIV-1 infection, pretreatment with NRTIs, Centers for Disease Control and Prevention (CDC) stage C infection, hepatitis C virus (HCV) coinfection, baseline HIV-1 RNA level, baseline CD4⁺ and CD8⁺ T cell counts, inclusion of ZDV in the antiretroviral drug regimen, year of initiation of cART, and the 3 groups of ART.

A 2-sided *P* value $<.05$ was considered to be statistically significant. All statistical analyses were performed with SPSS, version 14.0 (SPSS).

RESULTS

Patient characteristics. In total, 3293 individuals were included in the analysis, of whom 2367 (71.9%) were men. The mean age (\pm SD) was 38.2 ± 9.5 years. The percentage of injection drug users was smaller in the NNRTI group and the boosted-PI group than in the nonboosted-PI group (17.9% and 18.3% vs. 29.2%; *P* $<.001$ and *P* = .001, respectively). In addition, the proportion of untreated individuals was higher

Table 2. Determinants of patient CD4⁺ T cell count changes.

Variable	Unadjusted analysis		Adjusted analysis	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Female sex	1.14 (1.00–1.28)	.043	1.07 (0.94–1.22)	.304
Age ^a	0.83 (0.78–0.89)	<.001	0.84 (0.79–0.90)	<.001
Duration of HIV-1 infection ^b	0.96 (0.95–0.98)	<.001	1.00 (0.98–1.01)	.698
Treatment experienced	0.61 (0.54–0.69)	<.001	0.69 (0.61–0.79)	<.001
Positive for HCV antibody	0.79 (0.69–0.89)	<.001	0.79 (0.69–0.89)	<.001
CDC stage C infection	0.68 (0.59–0.79)	<.001	0.81 (0.69–0.95)	.009
Baseline HIV-1 RNA level ^c	1.14 (1.07–1.22)	<.001	1.21 (1.12–1.30)	<.001
Baseline CD4 ⁺ T cell count ^d	1.10 (1.08–1.13)	<.001	1.13 (1.10–1.16)	<.001
Baseline CD8 ⁺ T cell count ^d	1.00 (0.99–1.01)	.587	0.98 (0.97–0.99)	<.001
ZDV therapy	0.97 (0.87–1.09)	.597	0.85 (0.76–0.96)	.008
Year of cART ^b	1.05 (1.03–1.08)	<.001	1.00 (0.97–1.04)	.853
Nonboosted-PI versus NNRTI-containing regimen	1.16 (0.99–1.35)	.061	0.97 (0.82–1.15)	.709
Nonboosted PI versus boosted PI	1.26 (1.03–1.54)	.027	1.06 (0.84–1.33)	.648

NOTE. CD4⁺ T cell increases were >300 cells/ μ L. A Cox proportional hazards model was used for this analysis. cART, combination antiretroviral therapy; CDC, Centers for Disease Control and Prevention; HCV, hepatitis C virus; NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; ZDV, zidovudine.

^a Per 10-year increase.

^b Per 1-year increase.

^c Per 1-log plasma HIV-1 RNA level increase.

^d Per 100-cell increase.

(87.4% and 87.3% vs. 51.3%; $P < .001$ for both comparisons), and the duration of HIV-1 infection was shorter (4.7 and 4.6 vs. 5.6 years; $P < .001$ for both comparisons). In the NNRTI-containing cART group, fewer patients had CDC stage C infection (14.8% vs. 23.5%; $P < .001$). On the other hand, median baseline CD4⁺ T cell count was lower in the boosted-PI cART group than in the nonboosted-PI cART group (168 vs. 201 cells/ μ L; $P = .002$), probably reflecting the tendency of physicians to start treatment with a double PI-containing regimen in patients with low CD4⁺ T cell counts. In the nonboosted-PI group, 34.9% of patients had a positive HCV antibody test result, whereas those percentages were statistically significantly lower in the other 2 groups (21.0% and 21.5%; $P < .001$ and $P = .006$, respectively). Patients who received treatment with a nonboosted PI-containing cART had a statistically significantly lower proportion of individuals receiving ZDV. Further baseline characteristics are shown in table 1.

Response of CD4⁺ T lymphocytes to cART. In the nonboosted-PI group, CD4⁺ T lymphocytes increased from a median of 210 cells/ μ L (interquartile range [IQR], 86–370 cells/ μ L) to 520 cells/ μ L (IQR, 350–717 cells/ μ L) at 48 months, whereas similar increases of CD4⁺ T lymphocytes were observed in the NNRTI group (220 cells/ μ L [IQR, 130–331 cells/ μ L] to 475 cells/ μ L [IQR, 362–668 cells/ μ L]) and in the boosted-PI group (168 cells/ μ L [IQR, 50–288 cells/ μ L] to 511 cells/ μ L [IQR, 412–767 cells/ μ L]) at 48 months. The increase in CD4⁺ T cell count of the 3 groups was not statistically significantly different ($P > .01$) (figure 1A).

In a multivariate analysis, patients who achieved an increase

over the threshold of 300 CD4⁺ T cells/ μ L were investigated. In this analysis, adjusted for confounding variables, higher age, previous NRTI treatment, a test result positive for HCV antibody, CDC stage C infection, and therapy with ZDV showed a statistically significantly smaller increase of CD4⁺ T lymphocytes, whereas a higher baseline CD4⁺ T cell count and higher baseline HIV-1 RNA value resulted in a better recovery of these cells. However, the antiretroviral treatment regimen did not statistically significantly affect absolute increases in the CD4⁺ T cell count (table 2).

The changes of CD4⁺ T cell percentages were similar in all 3 groups. In the nonboosted group, median percentages increased from 15% (IQR, 8–23 cells/ μ L) to 28% (IQR, 21–34 cells/ μ L) at 48 months; in the NNRTI group, percentages increased from 15% (IQR, 10–21.75 cells/ μ L) to 29% (IQR, 22–35 cells/ μ L); and in the boosted group, percentages increased from 12% (IQR, 6–18 cells/ μ L) to 29% (IQR, 23–36 cells/ μ L) (figure 1B).

Virological response. Patients with nonboosted cART initiated ART at a median plasma HIV-1 RNA value of 4.75 log₁₀ copies/mL. Individuals who received NNRTI initiated cART at a slightly higher value, 4.94 log₁₀ copies/mL ($P < .001$), whereas patients who received boosted cART commenced ART at the highest HIV-1 RNA value, 5.26 log₁₀ copies/mL ($P < .001$) (figure 2A). A statistically significant decrease in the HIV-1 RNA level was achieved in all treatment groups after 6 months. In the NNRTI treatment group and in the boosted cART group, HIV-1 RNA level decreased statistically significantly faster than in the nonboosted cART group ($P < .001$). Median HIV-1 RNA

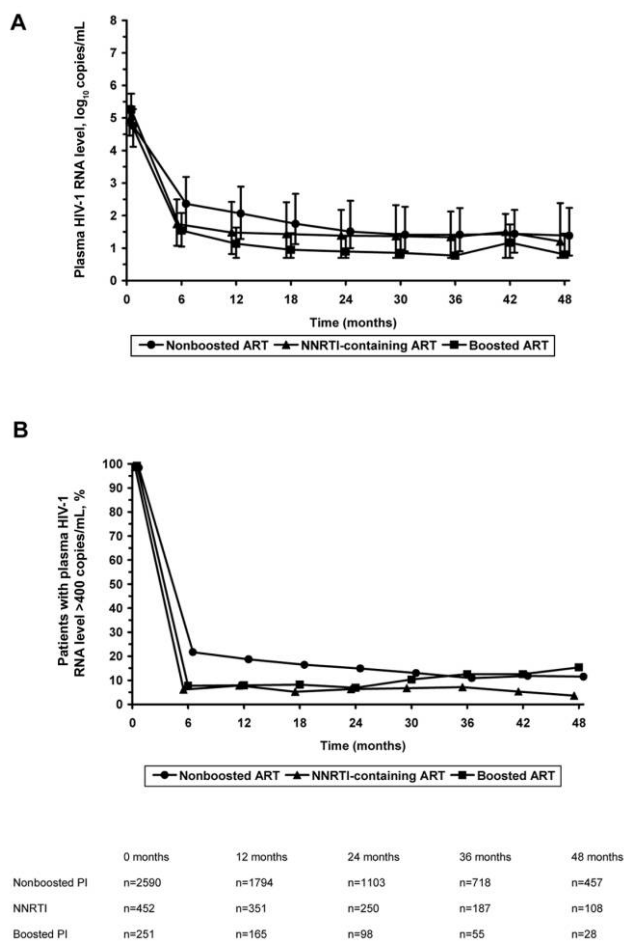


Figure 2. A, HIV-1 RNA levels by treatment regimen. B, Percentages of patients with HIV-1 RNA levels >400 copies/mL, by treatment regimen. ART, antiretroviral therapy; NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

level at 6 months was 2.36 \log_{10} copies/mL (IQR, 1.49–3.19 copies/mL) in the nonboosted group, 1.74 \log_{10} copies/mL (IQR, 1.01–2.50 copies/mL) in the NNRTI group, and 1.54 \log_{10} copies/mL (IQR, 1.05–2.08 copies/mL) in the boosted group.

The proportion of HIV-1 RNA values <400 copies/mL was initially higher in the NNRTI-containing group and in the boosted-PI group, but the proportion remained only slightly higher in the NNRTI group ($P = .04$) (figure 2B).

At discontinuation of first cART, 28.7% of the nonboosted-PI group experienced virological failure, whereas virological failure was observed less frequently in the other 2 groups (NNRTI group, 11.1%; boosted-PI group, 10.0%).

CD4⁺ T cell increases in patients with HIV-1 RNA levels <400 copies/mL. After 6 months of treatment, 2159 patients (65.6%) had undetectable HIV-1 RNA values (i.e., <400 copies/mL), and viral load remained suppressed for the entire observation period. The increase of median absolute CD4⁺ T cell

count of these patients was statistically significantly higher than those of patients with 1 plasma HIV-1 RNA test result >400 copies/mL after 6 months (322 cells/ μ L [IQR, 218–462 cells/ μ L] vs. 212 cells/ μ L [IQR, 103–413 cells/ μ L]; $P < .001$) (figure 3).

In the group that received nonboosted treatment, median absolute CD4⁺ T cell counts increased from 224 cells/ μ L (IQR, 100–372 cells/ μ L) to 546 cells/ μ L (IQR, 388–750 cells/ μ L) in patients with all HIV-1 RNA values <400 copies/mL after 6 months, whereas these cell counts increased in patients with at least 1 test showing an HIV-1 RNA level >400 copies/mL after 6 months, from 167 cells/ μ L (IQR, 70–290 cells/ μ L) to 491 cells/ μ L (IQR, 336–648 cells/ μ L; $P = .017$).

In the group receiving NNRTI-containing treatment, a similar pattern was observed. The CD4⁺ T lymphocyte count increased from a median of 218 cells/ μ L (IQR, 131–327 cells/ μ L) to 492 cells/ μ L (IQR, 338–711 cells/ μ L; $P = .328$) in patients with all HIV-1 RNA values <400 copies/mL after 6 months, whereas in patients with ≥ 1 HIV-1 RNA value >400 copies/mL, these cell counts increased only from 243 cells/ μ L (IQR, 122–370 cells/ μ L) to 361 cells/ μ L (IQR, 288–414 cells/ μ L; $P = .062$).

In the group that received boosted-PI treatment, CD4⁺ T lymphocyte counts increased from 170 cells/ μ L (IQR, 52–288 cells/ μ L) to 563 cells/ μ L (IQR, 425–973 cells/ μ L; $P = .162$) in patients with all HIV-1 RNA test results <400 copies/mL after 6 months, whereas in patients with ≥ 1 HIV-1 RNA value >400 copies/mL, these cell counts increased from 139 cells/ μ L (IQR, 46–245 cells/ μ L) to 460 cells/ μ L (IQR, 180–512 cells/ μ L; $P = .199$).

CD4⁺ T cell increases according to baseline CD4⁺ T cell count.

CD4⁺ T cell count was stratified into 3 groups according to baseline CD4⁺ T cell count: 0–149 cells/ μ L, 150–299 cells/ μ L, and

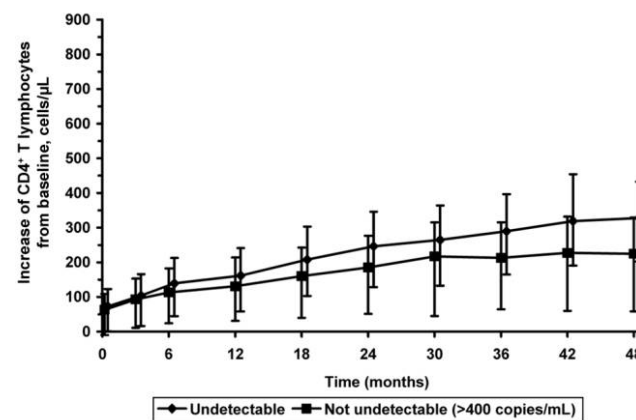


Figure 3. Increase of absolute CD4⁺ T cell counts from baseline for all patients by undetectable HIV-1 RNA level (≤ 400 copies/mL; 2159 patients) and detectable HIV-1 RNA level (> 400 copies/mL; 1134 patients) over 48 months.

≥ 300 cells/ μL . The increase in CD4⁺ T cell count was similar in all strata in all 3 treatment groups (figure 4A–4C).

CD4⁺ T cell increases, excluding patients pretreated with nucleosides. In a subanalysis, all patients who were pretreated with NRTIs were excluded ($n = 1351$). In a multivariate analysis, the CD4⁺ T cell count in the boosted-PI group was slightly higher than that in the nonboosted-PI group (median, 568 cells/ μL [IQR, 431–973 cells/ μL] vs. 547 cells/ μL [IQR, 396–740 cells/ μL]; $P = .03$). A boosted-PI regimen may, therefore, result in slightly better CD4⁺ T cell responses in treatment-naïve patients, compared with patients who had received previous treatment. However, the number of patients with a follow-up of 48 months was very small (9 patients). The boosted-PI group was, therefore, not analyzed at all, and the results presented here should be interpreted with caution.

CD4⁺ T cell increases in patients receiving ZDV. We observed a trend toward a larger increase in CD4⁺ T cell count among patients who did not receive ZDV than among individuals who did receive ZDV as a component of the drug regimen. The median CD4⁺ T cell count increased from 206 cells/ μL (IQR, 83–349 cells/ μL) to 544 cells/ μL (IQR, 382–734 cells/ μL) in the ZDV-naïve group and from 200 cells/ μL (IQR, 93–335 cells/ μL) to 494 cells/ μL (IQR, 363–689 cells/ μL) in the ZDV-treated group. In the multivariate model, the difference in CD4⁺ T cell increase reached statistical significance ($P = .008$) (table 2).

Response of CD8⁺ T lymphocytes to cART. The changes in CD8⁺ T lymphocytes showed a similar pattern in the 3 groups. In the nonboosted-PI group, median absolute CD8⁺ T cell counts increased from 724 cells/ μL (range, 467–1069 cells/ μL) to 843 cells/ μL (range, 633–1171 cells/ μL); in the NNRTI-group, counts increased from 803 cells/ μL (range, 519–1215 cells/ μL) to 809 cells/ μL (range, 612–1033 cells/ μL ; $P = .141$); and in the boosted group, counts increased from 710 cells/ μL (range, 445–1097 cells/ μL) to 747 cells/ μL (range, 621–1003 cells/ μL ; $P = .319$). The median CD8⁺ T cell percentages increased to comparable values in all 3 groups ($P > .05$).

DISCUSSION

In this study, we compared the impact of 3 major strategies of ART on CD4⁺ T cell recovery for first unchanged cART in a large number of participants of the SHCS. In the first years of cART, patients received a nonboosted-PI regimen or an NNRTI in combination with NRTIs. More recently, ritonavir-boosted PI-containing regimens were applied as well. The main finding of this study suggests that all 3 treatment strategies result in a similar recovery of CD4⁺ T cells.

In other studies, the comparison of NNRTI-containing regimens and PI-based regimens, with regard to CD4⁺ T cell recovery, had contradictory results. In the Atlantic Study, a nonboosted-PI regimen with indinavir resulted in a larger increase

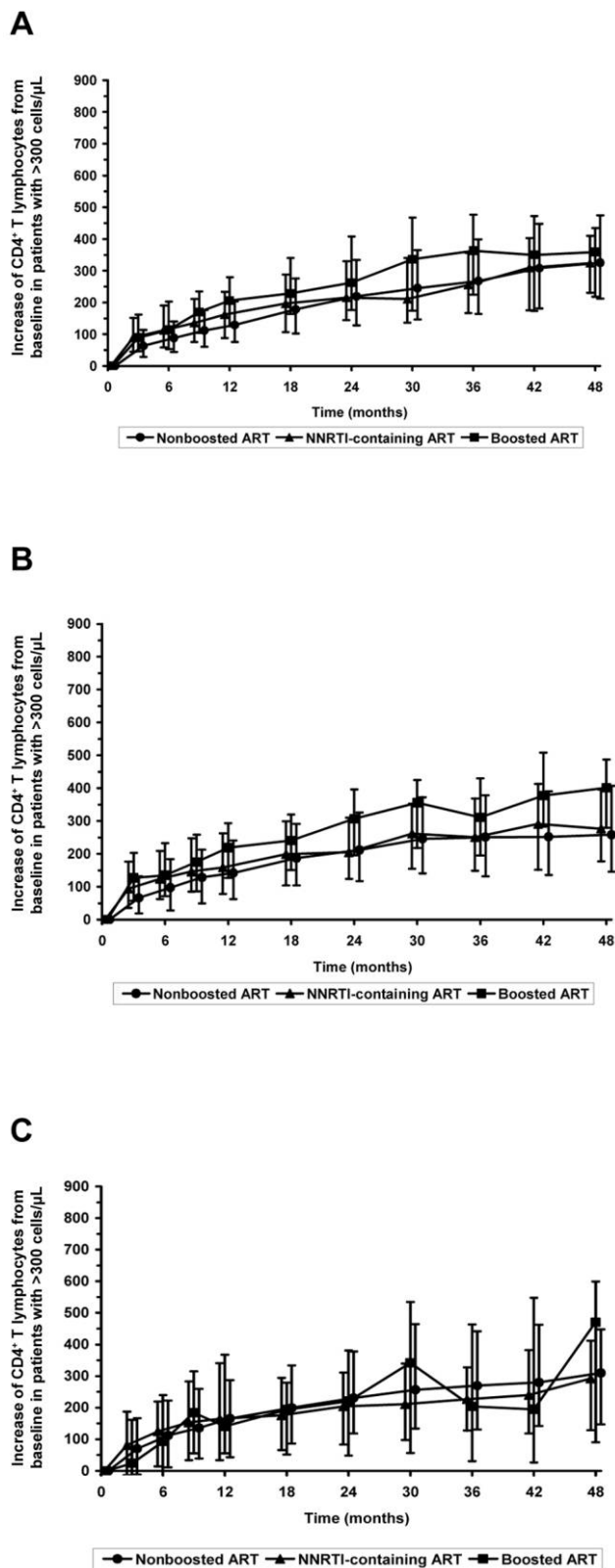


Figure 4. Absolute CD4⁺ T cell count with baseline CD4⁺ T cell count of 0–149 cells/ μL (A), 150–299 cells/ μL (B), and ≥ 300 cells/ μL (C) by treatment regimen. ART, antiretroviral therapy; NNRTI, nonnucleoside reverse-transcriptase inhibitor.

in the CD4⁺ T cell count than did an ART that was based on nevirapine and 2 nucleoside analogues [21]. This finding was also supported by a meta-analysis that found an improvement of the virological response, immunological recovery, and a reduced progression to AIDS or death among patients receiving PIs [26]. However, a limiting factor of the meta-analysis was the large number of NRTI-pretreated patients, whose treatment might have induced NNRTI resistance. In contrast, an additional meta-analysis including only treatment-naive patients demonstrated a better immunological and virological outcome of NNRTI-based regimens, without any influence on clinical outcomes [27]. Several other studies, including ours, did not find any difference in the immunological recovery between patients who received nonboosted-PI and NNRTI treatment [18, 19, 28].

Only a few studies, which investigated immunological recovery, compared boosted PI-based regimens with NNRTI-containing regimens. In one study, an efavirenz-based regimen was compared with a lopinavir-ritonavir-containing regimen. No difference in CD4⁺ T cell count recovery was found, including among patients with low baseline CD4⁺ T cell levels [29]. In another randomized, double-blind, controlled trial involving treatment-naive patients, results of a once-daily atazanavir-containing therapy were compared with those of an efavirenz-based regimen over 48 weeks [30]. The study found a comparable virological response and CD4⁺ T cell count increase [30]. Nevertheless, this contrasts a recently published study that compared results of lopinavir-ritonavir plus 2 NRTIs, efavirenz plus 2 NRTIs, and lopinavir-ritonavir plus efavirenz in 753 treatment-naive patients over 96 weeks [31]. In that study, the 2 PI-based therapies resulted in statistically significantly higher CD4⁺ T cell count increases than did the efavirenz-based treatment. However, the time to virological failure was significantly shorter in the lopinavir-ritonavir group [31].

Studies comparing results of nonboosted and boosted PI-based regimens are scarce. In one study, no difference in CD4⁺ T cell count increase could be demonstrated in comparison of lopinavir-ritonavir with nelfinavir at 1-year follow-up [32]. Our study showed similar CD4⁺ T cell count increases in the 2 treatment groups. Because of the significant imbalance of the number of patients, especially those in the nonboosted-PI group who had received prior ART, a subanalysis was performed that either excluded all pretreated individuals or used a similar number of randomly chosen patients for each treatment group. If pretreated patients were excluded, a slightly better CD4⁺ T cell increase was found among patients in the boosted-PI group. However, the reduction of the number of observations in the nonboosted-PI group had no impact on the results.

In the present study, 3 major groups of antiretroviral therapeutic regimens were analyzed, but the effect of individual compounds was not assessed in detail. Therefore, we cannot exclude

the possibility that individual drugs had a slightly better effect on CD4⁺ T cell recovery than did others. Because of the extended number of possible antiretroviral combinations and the limited number of long-term observations on 1 specific treatment, a more detailed analysis was not performed. However, we did not find an indication that major antiretroviral drug regimens including indinavir, efavirenz, or lopinavir-ritonavir would show different CD4⁺ T cell count responses.

A total of 24.8% of all patients who discontinued cART had 2 test results indicating a plasma HIV-1 RNA level >400 copies/mL. The percentage was higher in the nonboosted-PI group than in the 2 other groups (28.7% vs. 11.1% and 10.0%). This observation may indicate that many patients in the nonboosted-PI group were pretreated and were therefore more likely to experience ART failure.

We confirmed the findings of previous studies that patients with undetectable HIV-1 RNA level, younger age, and higher CD4⁺ T cell count at baseline enhance CD4⁺ T cell recovery [5, 7, 8, 33]. In particular, many patients with CD4⁺ T cell counts <300 cells/ μ L did not achieve CD4⁺ T cell counts >500 cells/ μ L. Therefore, to achieve good immunological recovery, cART should not be deferred until late stages of HIV-1 infection. We showed additional and less common factors influencing CD4⁺ T cell recovery. In the multivariate analysis, a positive HCV status, usually the case for injection drug users, limited the recovery of CD4⁺ T cell count. An impaired CD4⁺ T cell increase in HCV seropositive patients over 36 months, including those with well-suppressed HIV-1 RNA level, was reported elsewhere for the SHCS [34]. Whether coinfection with HCV or a poorer adherence to ART in this group of primarily injection drug users is responsible for this observation remains to be shown. Lastly, we confirmed previously published data that treatment with ZDV hinders CD4⁺ T cell recovery [9].

Limitations of the study are inherent to all observational cohort studies in which patients are not randomized. Therefore, different numbers of patients were observed in each treatment group, and there was an especially higher number in the nonboosted-PI group. Moreover, patients received treatment for a different amount of time; therefore, confounding data cannot be excluded.

In summary, the increase in the CD4⁺ T cell count was similar among recipients of nonboosted PI- and NNRTI- and ritonavir-boosted PI-based regimens. However, treatment-naive patients showed a statistically significantly better CD4⁺ T cell recovery if they were in early CDC infection stages, were young, were HCV negative, and had not received ZDV.

SWISS HIV COHORT

The members of the Swiss HIV Cohort Study are M. Battegay, E. Bernasconi, J. Böni, H. C. Bucher, P. Bürgisser, A. Calmy, S. Cattacin, M. Cavassini, R. Dubs, M. Egger, L. Elzi, P. Erb,

M. Fischer, M. Flepp, A. Fontana, P. Francioli (President of the SHCS, Centre Hospitalier Universitaire Vaudois, Lausanne), H. Furrer (Chairman of the Clinical and Laboratory Committee), C. Fux, M. Gorgievski, H. Günthard (Chairman of the Scientific Board), H. Hirsch, B. Hirschel, I. Hösli, C. Kahlert, L. Kaiser, U. Karrer, C. Kind, T. Klimkait, B. Ledergerber, G. Martinetti, B. Martinez, N. Müller, D. Nadal, M. Opravil, F. Paccaud, G. Pantaleo, A. Rauch, S. Regenass, M. Rickenbach (Head of the Data Center), C. Rudin (Chairman of the Mother & Child Substudy), P. Schmid, D. Schultze, J. Schüpbach, R. Speck, P. Taffé, P. Tarr, A. Telenti, A. Trkola, P. Vernazza, R. Weber, and S. Yerly.

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