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Does rapid HIV disease progression prior to combination antiretroviral therapy hinder optimal CD4$^+$ T-cell recovery once HIV-1 suppression is achieved?

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Objective: This article compares trends in CD4$^+$ T-cell recovery and proportions achieving optimal restoration ($\geq$500 cells/μl) after viral suppression following combination antiretroviral therapy (cART) initiation between rapid and nonrapid progressors.

Methods: We included HIV-1 seroconverters achieving viral suppression within 6 months of cART. Rapid progressors were individuals experiencing at least one CD4$^+$ less than 200 cells/μl within 12 months of seroconverters before cART. We used piecewise linear mixed models and logistic regression for optimal restoration.

Results: Of 4024 individuals, 294 (7.3%) were classified as rapid progressors. At the same CD4$^+$ T-cell count at cART start (baseline), rapid progressors experienced faster CD4$^+$ T-cell increases than nonrapid progressors in first month [difference (95% confidence interval) in mean increase/month (square root scale): 1.82 (1.61; 2.04)], which reversed to slightly slower increases in months 1–18 [−0.05 (−0.06; −0.03)] and no significant differences in 18–60 months [−0.003 (−0.01; 0.01)]. Percentage achieving optimal restoration was significantly lower for rapid progressors than nonrapid progressors at months 12 (29.2 vs. 62.5%) and 36 (47.1 vs. 72.4%) but not at month 60 (70.4 vs. 71.8%). These differences disappeared after adjusting for baseline CD4$^+$ T-cell count: odds ratio (95% confidence interval) 0.86 (0.61; 1.20), 0.90 (0.38; 2.17) and 1.56 (0.55; 4.46) at months 12, 36 and 60, respectively.

Conclusion: Among people on suppressive antiretroviral therapy, rapid progressors experience faster initial increases of CD4$^+$ T-cell counts than nonrapid progressors, but are less likely to achieve optimal restoration during the first 36 months after cART, mainly because of lower CD4$^+$ T-cell counts at cART initiation.

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Introduction

Humans show a remarkable variation in clinical outcomes following HIV-1 infection. Although some individuals are able to control HIV replication for long periods (elite controllers), others experience rapid $CD4^+$ T-cell loss after seroconversion (rapid progressors) in the absence of combination antiretroviral therapy (cART) [1–2]. Over the last few years, many studies have focused on these extreme HIV phenotypes in a search for clues relating to viral pathogenesis. Accumulating evidence suggests that a combination of viral and host factors play a role in HIV disease outcomes [3–7].

Rapid HIV progression is defined by a decay of $CD4^+$ T-cell counts below a threshold ranging between 100 and 350 cells/μl in a time frame from 6 months to 3 years [2,5] after seroconversion. Studies of rapid progressors have been limited by small numbers [7–9] and by the heterogeneity of definitions used for rapid progressors. Both a documented seroconversion date and a narrow seroconversion window are generally required to characterize these uncommon phenotypes. Indeed, Muñoz *et al.* [10] reported frequency of the rapid progressors to be under 10% in the MACS, and Rotger *et al.* [5] reported that approximately 8% of seroconverters in the Swiss cohort were rapid progressors. Recently, Olson *et al.* [2] showed that 2.8, 7.3 and 24.9% of seroconverters in the Concerted Action of Seroconversion to AIDS and Death in Europe (CASCADE) Collaboration experienced at least one $CD4^+$ cell count less than 100, 200 and 350 cells/μl, respectively, within 1 year of seroconverters.

Rapid progression could be clinically relevant for immune restoration after cART initiation as poorer $CD4^+$ T-cell recovery has been associated with low $CD4^+$ T-cell counts at the initiation of therapy in a cross-sectional study [11]. However, the link between rapid progression and immune recovery is unknown.

The CASCADE Collaboration has previously reported that individuals with steeper precART $CD4^+$ T-cell decline are more likely to experience greater $CD4^+$ T-cell increases after cART [12] but did not examine if these responses varied among those who are virologically suppressed. Several studies have revealed a substantial prevalence of immunological nonresponders among patients who are virologically suppressed on cART, with rates ranging from 17 to 40%, depending on the study criteria and the population [13–15]. Compared with concordant responders (i.e. those with a good $CD4^+$ T-cell response while virally suppressed on cART), these nonconcordant responders are at increased risk of clinical progression to AIDS-related and non–AIDS-related illnesses and death [11,13,16–23].

We hypothesized that rapid progression before cART initiation predicts poor $CD4^+$ T-cell recovery in virologically suppressed individuals and hinders optimal $CD4^+$ T-cell restoration. The objective of this analysis was, therefore, to compare trends in $CD4^+$ T-cell recovery after cART initiation and the proportion achieving counts at least 500 cells/μl after 12, 36 and 60 months between rapid and nonrapid progressors achieving virological suppression.

Methods

Ethics statement

All collaborating cohorts received approval from their respective or national ethics review boards. Ethics approval for CASCADE collaborating cohorts within EuroCoord has been granted by the committees detailed in the 'Acknowledgements' section.

Study population

We used data from CASCADE, updated in 2013 within EuroCoord (www.EuroCoord.net), which consists of 29 884 individuals with well estimated dates of HIV seroconversion (seroconverters) from 28 cohorts across Europe, Canada, Australia and Sub-Saharan Africa [24]. Individuals followed-up in the two African cohorts were excluded as both $CD4^+$ T-cell count evolution during natural history and treatment guidelines applied to these populations differ from those in high-income countries [25]. We also excluded individuals infected through a route other than injecting drug use or sexual intercourse (i.e. haemophilia, transfusion, other and unknown) to avoid other clinical complications that affect HIV disease progression. Eligible individuals were patients initiating their first cART regimen from naive and who achieved viral suppression (plasma HIV-RNA level $\leq$200 copies/ml) within the first 6 months of therapy and maintained it thereafter until their censoring date. Patients had to have both $CD4^+$ T-cell counts and HIV-RNA measurements available at start of cART (i.e. within the last 6 months prior to cART initiation). Individuals with a viral load less than 1000 copies/ml at the time of starting cART were excluded as they may have been misclassified as treatment naïve. Furthermore, to be able to classify patients as rapid or nonrapid progressors, we required that seroconversion dates were estimated in one of three ways: as the midpoint between the last negative and first positive HIV antibody test dates with an interval of less than 12 months between tests, as the date of laboratory evidence of acute seroconversion (PCR positivity in the absence of HIV antibodies or antigen positivity with fewer than four bands on Western blot), or as the date of seroconversion illness for individuals with a test interval of 12 months or less. Patients also had to have at least one $CD4^+$ T-cell count within the first 12 months of seroconversion in the absence of antiretroviral therapy (ART).

Individuals were classified as rapid progressors if there was at least one determination of CD4$^+$ T-cell counts less than 200 cells/μl within 12 months from seroconverters before ART initiation, and as nonrapid progressors otherwise. Additional definitions were also tested [2], and more details are provided in the sensitivity analyses section.

Follow-up time started at cART initiation and was censored at the first of the following dates: the first of two consecutive occasions when the plasma HIV-RNA level increased above 200 copies/ml (considered to be treatment failure), the first of two consecutive HIV-RNA measurements separated by more than 12 months (considered to be lost to follow-up) or at the last date when an HIV-RNA measurement was available within 60 months of starting therapy. Patients who modified their cART regimens were not censored at date of modification, provided plasma HIV-RNA levels remained 200 copies/ml or less.

CART was defined as a protease inhibitor-based, nonnucleoside reverse transcriptase inhibitor (NNRTI), or fusion inhibitor-based regimen, in combination with at least two nucleoside or nucleotide reverse transcriptase inhibitors, or a triple nucleotide reverse transcriptase inhibitor regimen including abacavir or tenofovir.

Statistical analysis

Differences in sociodemographic and clinical characteristics between rapid and nonrapid progressors were assessed through the nonparametric Mann–Whitney test for continuous variables and the χ^2 test for independence for categorical variables.

Trends in CD4$^+$ T-cell counts after cART initiation were modelled using a piecewise linear mixed-effects model (to take into account the correlation between measurements in the same individual) with three slopes (including random effects for the intercept and the three slopes); the best model (Akaike criterion) obtained allowed for changes of slopes at months 1 and 18. The square root transformation of the CD4$^+$ T-cell counts was used to fulfil the model assumptions.

As an initial approach, multivariable piecewise linear mixed-effects models were initially adjusted for sex, age at cART initiation, risk group (MSM, sex between men and women, IDUs), geographical origin (non-sub-Saharan Africa, migrants from sub-Saharan Africa, unknown) used as a proxy for HIV subtype and $\log_{10}$ HIV-RNA levels at cART initiation. However, as CD4$^+$ T-cell count at cART initiation is known to be a strong predictor of immunological outcome and is significantly lower in rapid progressors, this initial approach was confounded by the CD4$^+$ T-cell counts at cART initiation. As attempting to remove this confounding by including the observed CD4$^+$ T-cell counts at cART initiation as a covariate in a model for later measurements is likely to introduce bias, we used a method based on first following the initial approach and then applying a correction to the parameter estimates to compare rapid and nonrapid progressors with the same underlying CD4$^+$ T-cell counts at start of cART [26].

We calculated the proportion of patients who experienced an optimal CD4$^+$ T-cell restoration, defined as achieving CD4$^+$ T-cell counts of at least 500 cells/μl, at 12, 36 and 60 (±3) months from cART initiation and used logistic regression models to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for association between rapid progressors status and optimal CD4$^+$ T-cell count restoration. Multivariate logistic regression models were initially adjusted for the same factors as in the piecewise linear mixed-effects models, and additionally adjusted for CD4$^+$ T-cell count at cART initiation ($<$100, 100–199, $\geq$200).

A set of sensitivity analyses was undertaken. Analyses were repeated using 100 and 350 as CD4$^+$ T-cell thresholds to define rapid progressors; considering the first 6 months from seroconverters to classify patients as rapid and nonrapid progressors; defining an optimal CD4$^+$ T-cell restoration as achieving CD4$^+$ T-cell counts of at least 600 cells/μl; restricting to individuals who started cART with CD4$^+$ T-cell counts less than 200 cells/μl; restricting to patients who started cART after year 2000 when boosted protease inhibitors became widely available and allowing patients to achieve viral suppression within the first 12 months of therapy as patients with high viral loads and those on protease inhibitor-based regimen may not suppress by 6 months yet nonetheless by 12 months.

All statistical analyses were performed by using Stata software (version 13.1; StataCorp, College Station, Texas, USA).

Results

Study population characteristics

Of 29 884 individuals, 25 860 were excluded from analyses as follows: 916 followed-up in two African cohorts, 1520 who were infected through a route other than injecting drug use or sexual intercourse (157 haemophilia, 44 transfusion, 184 other and 1135 unknown), 9716 who never initiated cART, 5347 who were ART experienced at cART initiation, 4009 who did not achieve viral suppression within the first 6 months of therapy, 691 as CD4$^+$ T-cell count and/or HIV-RNA measurements at cART initiation were not available, 485 who had a viral load at cART initiation less than 1000 copies/ml, 2680 for whom seroconversion date was above 12 months after the last negative test and 496 as CD4$^+$ T-cell count within 12 months from seroconverters in the absence of ART was not available.

Of 4024 individuals included in the analyses, 294 (7.3%) were classified as rapid progressors, who were more likely than nonrapid progressors to be women (17.7 vs. 11.2%), infected through sex between men and women (30.9 vs. 18.2%), migrants originating from sub-Saharan Africa (12.6 vs. 3.9%) and, when they subsequently started cART, did so at with higher $\log_{10}$ HIV-RNA levels (5.1 vs. 4.8) and lower $CD4^+$ T-cell counts (164 vs. 350) (Table 1).

Trends in $CD4^+$ T-cell counts after combination antiretroviral therapy initiation

A total of 40 893 $CD4^+$ T-cell count measurements were available post-cART initiation, 3451 among rapid progressors and 37 442 among nonrapid progressors. The median number of $CD4^+$ T-cell counts measurements per individual was 10 [interquartile range (IQR): 6; 16] for rapid progressors and 9 (IQR: 5; 14) for nonrapid progressors with a median interval of 2.8 (IQR: 2.3; 3.5) and 2.9 (2.2; 3.6) months between consecutive determinations for rapid and non-rapid progressors, respectively.

Median $CD4^+$ T-cell count profiles for rapid and nonrapid progressors, overall and among individuals who started cART with $CD4^+$ T-cell counts less than 200 cells/μl, are shown in Fig. 1. Unadjusted and adjusted trends in $CD4^+$ T-cell counts after cART initiation from the piecewise linear mixed-effects model at 0–1, 1–18 and more than 18 months are given in Table 2. After initial adjustment for sex, risk group, geographical origin, age and $\log_{10}$ HIV-RNA level at cART initiation, rapid progressors had faster initial and long-term $CD4^+$ T-cell increases than nonrapid progressors: differences in mean $CD4^+$ increase/month (square root scale) were 1.34 (95% CI: 0.95; 1.72, $P < 0.001$) in 0–1 months, 0.03 (−0.001; 0.05, $P = 0.063$) in 1–18 months and 0.04 (95% CI: 0.02; 0.06, $P < 0.001$) in 18–60 months. Applying the postestimation adjustment procedure [26] to compare rapid and nonrapid progressors with the same underlying $CD4^+$ T-cell counts at cART initiation, we found that rapid progressors experienced a faster $CD4^+$ T-cell increase than nonrapid progressors in 0–1 months (1.82, 95% CI: 1.61; 2.04, $P < 0.001$), which reversed to slightly slower increases in months 1–18 (−0.05, −0.06; −0.03, $P < 0.001$) and no significant differences in months 18–60 (−0.003, 95% CI: −0.01; 0.01, $P = 0.62$) (Table 2).

Figure 2a depicts the evolution of $CD4^+$ T-cell counts for rapid and nonrapid progressors MSM of 30 years of age, of non-sub-Saharan African origin who started cART at 5 $\log_{10}$ HIV-1 RNA. It shows how rapid progressors, in spite of steeper initial $CD4^+$ T-cell counts increases, fail to reach the threshold of 500 cells/μl until month 36. Figure 2b illustrates the same changes comparing rapid and nonrapid progressors who start cART at $CD4^+$ T-cell count of 180 cells/μl. Figure 2b also shows rapid progressors having steeper initial $CD4^+$ T-cell count increases but given that nonrapid progressors are now 'forced' to start cART at the same $CD4^+$ T-cell count, rapid progressors maintain higher values to month 60.

Analyses using 100 and 350 cells/μl as $CD4^+$ T-cell thresholds to define rapid progressors led to results consistent with those of the main analyses although differences in mean $CD4^+$ increase/month between rapid and nonrapid progressors were attenuated when considering 350 cells/μl as the $CD4^+$ T-cell threshold. Similar results were also obtained when the first 6 months from seroconverters were used to classify patients as rapid and nonrapid progressors, when analyses were restricted to individuals who started cART after year 2000. Restricting analyses to individuals who initiated cART with $CD4^+$ T-cell counts less than 200 cells/μl yielded results similar to those obtained when using an adjustment procedure [26]. Allowing patients to achieve viral suppression within the first 12 months of therapy yielded results consistent with those of the main analyses.

$CD4^+$ T-cell count restoration (≥500 cells/μl) following suppressive combination antiretroviral therapy

Among 4024 eligible patients, a total of 3092, 1379 and 484 were available for $CD4^+$ T-cell analyses at 12, 36 and 60 months, respectively. Patients with missing data were more likely than persons with available measurements to be younger at cART initiation, infected through injecting drug use and to have started cART in more recent years with higher $CD4^+$ T-cell counts. The percentage of patients experiencing optimal restoration of $CD4^+$ T-cell counts of at least 500 cells/μl was significantly lower among rapid than nonrapid progressors at months 12 (29.2 vs. 62.5%) and 36 (47.1 vs. 72.4%) but no differences were found at month 60 (70.4 vs. 71.8%). After initial adjustment for sex, risk group, geographical origin, age and $\log_{10}$ HIV-RNA level at cART initiation, rapid progressors remained less likely to achieve counts of at least 500 cells/μl at months 12 (OR: 0.21, 95% CI: 0.13; 0.36, $P < 0.001$) and 36 (OR: 0.30, 95% CI: 0.11; 0.87, $P = 0.03$), a difference that disappeared at month 60 (OR: 0.79, 95% CI: 0.30; 2.09, $P = 0.63$). Additional adjustment for $CD4^+$ T-cell counts at cART initiation (<100, 100–199, ≥200), however, showed no differences between rapid and nonrapid progressors at 12 (OR: 0.86, 95% CI: 0.61; 1.20, $P = 0.36$), 36 (OR: 0.90, 95% CI: 0.38; 2.17, $P = 0.82$) or 60 months (OR: 1.56, 95% CI: 0.55; 4.46, $P = 0.40$) (Table 3). Similar results were obtained when using 600 as a cutoff to define optimal $CD4^+$ T-cell restoration (data not shown).

Analyses defining an optimal $CD4^+$ T-cell restoration as achieving $CD4^+$ T-cell counts of at least 600 cells/μl led to results consistent with those of the main analyses. In addition, performing the other procedures of sensitivity analyses mentioned earlier yielded results consistent with those of the main analysis (data not shown).

Table 1. Sociodemographic and clinical characteristics at start of combination antiretroviral therapy for 4024 individuals by precombination antiretroviral therapy progressor status.

	Nonrapid progressors 3730 (92.7)	Rapid progressors 294 (7.3)	*P* value
Sex			0.001
Men	3312 (88.8)	242 (82.3)	
Women	418 (11.2)	52 (17.7)	
Age at cART (years)			
Median (IQR[a])	36 (30; 42)	35 (29; 42)	0.66
<30	928 (24.9)	74 (25.2)	0.89
30–39	1501 (40.2)	122 (41.5)	
40–49	887 (23.8)	64 (21.8)	
≥50	414 (11.1)	34 (11.6)	
Transmission category			<0.001
Sex between men	2887 (77.4)	187 (63.6)	
Sex between men and women	679 (18.2)	91 (31.0)	
IDU	164 (4.4)	16 (5.4)	
Geographical origin			<0.001
Non sub-Saharan Africa	2729 (73.2)	195 (66.3)	
Migrants from sub-Saharan Africa	145 (3.9)	37 (12.6)	
Unknown	856 (22.9)	62 (21.1)	
Ethnic group			0.001
White	1800 (48.3)	118 (40.1)	
Black	111 (2.9)	17 (5.8)	
Other	45 (1.2)	8 (2.7)	
Unknown	1774 (47.6)	151 (51.4)	
Higher education ever attained			0.001
Preprimary or primary education	88 (2.4)	13 (4.4)	
Secondary education	527 (14.1)	45 (15.3)	
Postsecondary education	503 (13.5)	18 (6.1)	
Unknown	2612 (70.0)	218 (74.2)	
Acute infection[b]			0.11
No	2504 (67.1)	184 (62.6)	
Yes	1226 (32.9)	110 (37.4)	
Date of SC [median (IQR[a])]	05 March (00 December; 08 June)	05 August (02 March; 08 September)	0.04
Date of cART initiation [median (IQR[a])]	08 February (03 March; 10 July)	06 September (02 November; 09 June)	<0.001
cART based on			0.48
NNRTI	1656 (44.4)	120 (40.8)	
PI	1544 (41.4)	128 (43.5)	
3 class/other	530 (14.2)	46 (15.7)	
CD4$^+$ T-cell counts at cART (cells/μl)			
Median (IQR[a])	350 (270; 473)	164 (120; 196)	<0.001
<200	276 (7.4)	234 (79.6)	<0.001
200–350	1602 (42.9)	53 (18.0)	
>350	1852 (49.7)	7 (2.4)	
Log_{10} HIV-RNA at cART initiation			
Median (IQR[a])	4.8 (4.3–5.3)	5.1 (4.6–5.7)	<0.001
<4	502 (13.5)	26 (8.8)	<0.001
4–5	1728 (46.3)	102 (34.7)	
>5	1500 (40.2)	166 (56.5)	
AIDS diagnosis at cART			0.005
No	3589 (96.2)	272 (92.5)	
Yes	137 (3.7)	22 (7.5)	
Unknown	4 (0.1)	0	
Hepatitis C virus antibodies at cART			0.93
No	2013 (54.0)	160 (54.4)	
Yes	163 (4.4)	14 (4.8)	
Unknown	1554 (41.6)	120 (40.8)	
Hepatitis B surface antigen			0.47
No	1949 (52.2)	159 (54.1)	
Yes	73 (2.0)	3 (1.0)	
Unknown	1708 (45.8)	132 (44.9)	
Time from SC to cART initiation (months)			
Median (IQR[a])	16 (4; 38)	6 (3; 9)	<0.001
<6	1118 (30.0)	142 (48.3)	<0.001
6–12	507 (13.6)	106 (36.0)	
≥12	2105 (56.4)	46 (15.7)	

cART, combination antiretroviral therapy; IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SC, seroconversion.
[b]Acute infection is defined as having laboratory evidence of acute seroconversion or an HIV test interval of less than 30 days.

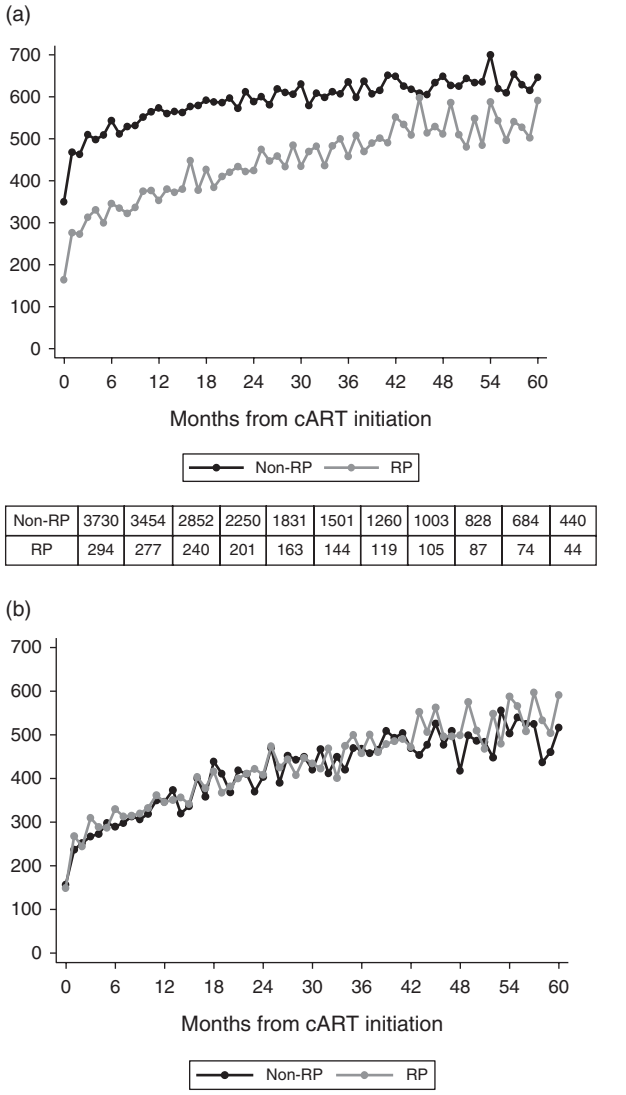

Fig. 1. Observed CD4$^+$ T-cell counts in rapid and nonrapid progressors. (a) All patients. (b) Patients starting combination antiretroviral therapy with CD4$^+$ T-cell counts less than 200 cells/μl.

Discussion

Rapid progression prior to cART initiation hinders optimal CD4$^+$ T-cell recovery once HIV-1 suppressive response to cART is achieved. Although rapid progressors experience faster initial increases in CD4$^+$ T-cells than nonrapid progressors, they are less likely to achieve CD4$^+$ T-cell counts of at least 500 cells/μl during the first 36 months after cART. These outcomes are largely explained by their lower CD4$^+$ T-cell counts at cART initiation.

Our current work builds on previous work conducted by the CASCADE Collaboration showing that individuals

Table 2. Immunological outcome following combination antiretroviral therapy according to the rapid progressors status from linear mixed-effects model in the univariate and multivariate analyses.

			Unadjusted analyses		Adjusted analyses			
					Model 1[a]		Model 1 + postestimation adjustment procedure[b]	
Months from cART initiation	Nonrapid progressors	Rapid progressors	Rapid vs. nonrapid progressors	*P* value	Difference (95% CI) in mean increase in CD4$^+$ T-cell count per month (square root scale)	*P* value	Difference (95% CI) in mean increase in CD4$^+$ T-cell count per month (square root scale)	*P* value
	Mean (95% CI) increase in CD4$^+$ T-cell count per month (square root scale)		Difference (95% CI) in mean increase in CD4$^+$ T-cell count per month (square root scale)					
0–1	2.94 (2.84; 3.05)	4.55 (4.17; 4.92)	1.60 (1.21; 1.99)	<0.001	1.34 (0.95; 1.72)	<0.001	1.82 (1.61; 2.04)	<0.001
1–18	0.17 (0.16; 0.17)	0.20 (0.17; 0.22)	0.03 (0.004; 0.06)	0.024	0.03 (−0.001; 0.05)	0.063	−0.05 (−0.06; −0.03)	<0.001
18–60	0.04 (0.03; 0.04)	0.07 (0.06; 0.09)	0.04 (0.02; 0.05)	<0.001	0.04 (0.02; 0.06)	<0.001	−0.003 (−0.01; 0.01)	0.62

CI, confidence interval; cART, combination antiretroviral therapy.
[a]From an initial piecewise linear mixed model including rapid progressors status, sex, age at cART initiation, risk group (MSM, sex between men and women, IDUs), geographical origin (migrants from sub-Saharan Africa, non-sub-Saharan Africa, unknown) used as a proxy of subtype and $\log_{10}$ HIV-RNA levels at cART initiation.
[b]After the postestimation adjustment procedure to provide an estimate of the difference for patients with the same underlying CD4$^+$ T-cell count at cART initiation.

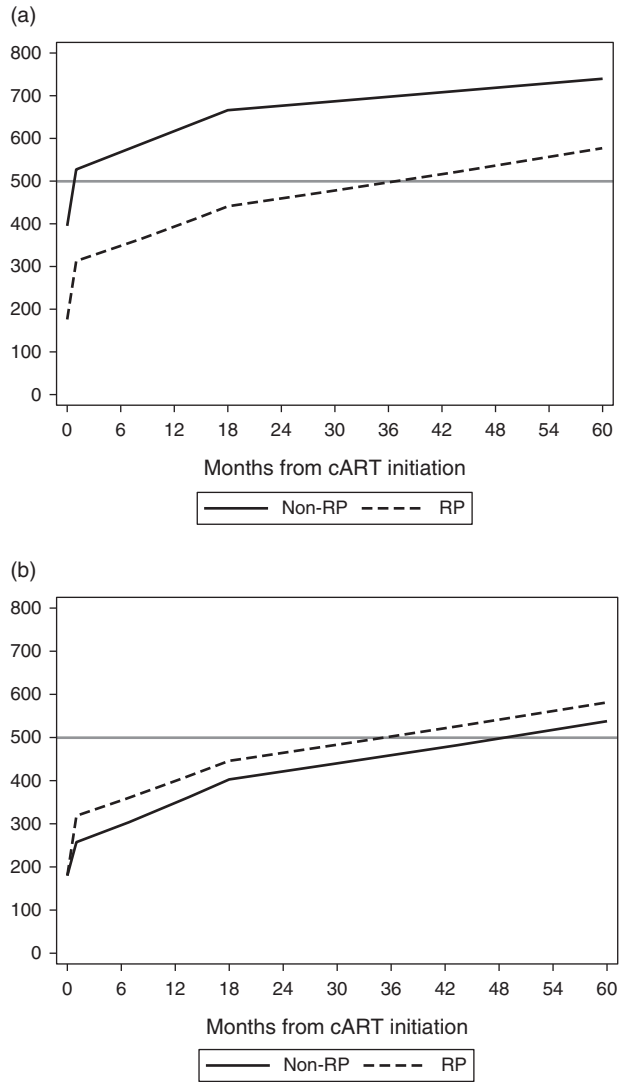

Fig. 2. Predicted CD4$^+$ T-cell counts in rapid and nonrapid progressors. (a) From an initial piecewise linear mixed model (men, MSM, non-SSA, 30 years old at start of cART and 5 $\log_{10}$ HIV-RNA level at cART initiation). (b) After the postestimation adjustment procedure (men, MSM, non-SSA, 30 years old at start of cART, 5 $\log_{10}$ HIV-RNA level at cART initiation and an underlying CD4$^+$ T-cell count at cART initiation of 180 cells/μl). cART, combination antiretroviral RP, rapid progressors; SSA, sub-Saharan Africa.

with a faster rate of CD4$^+$ T-cell loss precART tended to experience faster immune reconstitution once they started cART, independently of baseline CD4$^+$ T-cell count and plasma HIV-RNA value [12]. We show that rapid progressors who achieve suppressive response to cART experience delays in achieving optimal CD4$^+$ count recovery during the first 36 months after cART, which puts them at a higher risk of developing immunodeficiency-related complications. That this may happen in a nonnegligible proportion of the population is of concern. In our study, 7.3% of HIV-1 seroconverters fulfilled the criteria of rapid progression, a similar percentage to that previously reported in other studies [2,5,10], although study populations were not strictly comparable.

When comparing the outcomes of these rapid progressors with patients whose progression was not rapid, but whose CD4$^+$ T-cell count at cART was similar, the differences in CD4$^+$ T-cell responses largely disappeared. Nevertheless, steeper CD4$^+$ T-cell responses were still experienced by the rapid progressors suggesting that a prior faster decline may allow mounting enhanced responses. It could be that the rapid loss of CD4$^+$ T cells from the peripheral blood observed in rapid progressors is secondary to cell redistribution in lymph nodes in a higher proportion than in nonrapid progressors, as well as to cellular death. Thus, recovery is bound to be more rapid once HIV viral replication is suppressed and thus the cause of the redistribution is eliminated [27,28]. This suggests that not only the absolute CD4$^+$ T-cell value but also the time to reach that value influences responses to cART in virally suppressed individuals; cART may elicit better CD4$^+$ T-cell responses in a time window before deep immunological damage has been caused.

These data confirm the potency of current cART regimes in their ability to reduce viremia and thus facilitate subsequent immune recovery of CD4$^+$ T cells, even among those who had experienced rapid progression to low CD4$^+$ count prior to starting cART. However, the similar dynamics in the recovery of CD4$^+$ T cells after the first month of therapy prevents rapid progressors from fully recovering from their profound initial loss of cells.

This study has some limitations. First, the high proportion of patients with missing data made it difficult to assess CD4$^+$ T-cell count restoration at 12, 36 and, especially, 60 months after cART initiation. However, as missingness appeared not related to status of the rapid progressors, there is no reason to believe that this should influence our results. Second, in 3.7% of seroconverters (1.7% in rapid progressors and 3.8% in nonrapid progressors), seroconversion date was estimated as the date of seroconversion illness, which has been associated with faster disease progression [29]. However, in sensitivity analyses excluding these patients, results were consistent with those of the main analyses. Third, although our work is based on HIV-1 seroconverters who are unlikely to be comparable with the general HIV-infected population in a number of ways, it has been recently shown that there are no major differences in HIV disease progression between seroconverters and seroprevalent individuals [30] suggesting that our results are generalizable to the HIV-positive population.

Our findings have implications for public health policy, clinical management and basic science research. Ideally, cART should be started as soon as possible after HIV-1 diagnosis regardless of the CD4 T-cell count (START

Table 3. CD4$^+$ T-cell count restoration at 12, 36 and 60 months from combination antiretroviral therapy initiation.

				Unadjusted analyses		Adjusted analyses			
						Model 1[a]		Model 1 + CD4$^+$ at cART initiation[b]	
		N	*N* (%) CD4$^+$ cell count ≥500	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
12 months	Nonrapid progressors	2852	1782 (62.5)	1.00		1.00		1.00	
	Rapid progressors	240	70 (29.2)	0.25 (0.14; 0.42)	<0.001	0.21 (0.13; 0.36)	<0.001	0.86 (0.61; 1.20)	0.36
36 months	Nonrapid progressors	1260	912 (72.4)	1.00		1.00		1.00	
	Rapid progressors	119	56 (47.1)	0.34 (0.11; 1.05)	0.06	0.30 (0.11; 0.87)	0.03	0.90 (0.38; 2.17)	0.82
60 months	Nonrapid progressors	440	316 (71.8)	1.00		1.00		1.00	
	Rapid progressors	44	31 (70.4)	0.94 (0.37; 2.36)	0.89	0.79 (0.30; 2.09)	0.63	1.56 (0.55; 4.46)	0.40

CI, confidence interval; cART, combination antiretroviral therapy; OR, odds ratio.
[a]Adjusted for sex, age at cART initiation, risk group (MSM, sex between men and women, IDUs), geographical origin (migrants from sub-Saharan Africa, non-sub-Saharan Africa, unknown) used as a proxy of subtype and $\log_{10}$ HIV-RNA levels at cART initiation.
[b]Adjusted for sex, age at cART initiation, risk group (MSM, sex between men and women, IDUs), geographical origin (sub-Saharan Africa, non-sub-Saharan Africa, unknown) used as a proxy of subtype, $\log_{10}$ HIV-RNA levels at cART initiation and CD4$^+$ T cells at cART initiation (<100, 100–199, ≥200 cells/μl).

study: http://www.niaid.nih.gov/news/newsreleases/Archive/2011/Pages/START.aspx).

However, in clinical settings wherein cART is not widely available, our results would support strategies that promote frequent testing to reduce the proportion of patients initiating cART at low CD4$^+$ T-cell counts, which is largely secondary to delayed HIV-1 diagnoses. For those testing early, we suggest frequent CD4$^+$ T-cell count monitoring close to the time of HIV diagnoses to establish the rapid progressors phenotype in order to avoid unnecessary CD4$^+$ T-cell count decay among rapid progressors. Finally, elucidating the immunopathological bases of rapid progression should help to improve individual clinical outcome and limit its impact in the global HIV-1 pandemics.

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Conflicts of interest

There are no conflicts of interest.

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