Rapid progression hinders the recovery of CD4+ T-cells following initiation of cART

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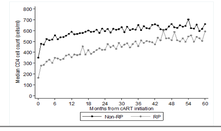
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Abstract

Background: We aimed to compare trends in CD4+ T-cell recovery after combination antiretroviral therapy (cART) initiation and proportion of patients achieving optimal CD4+ T-cell restoration (counts ≥500 cells/µl) after 12, 36 and 60 months of viral suppression between rapid (RP) and non-rapid progressors (non-RP).
Methods: We included HIV-1 seroconverters (SC) from CASCADE who initiated cART from naïve and achieved viral suppression within the first 6 months. Individuals were classified as RP if they experienced ≥1 CD4+<200 cells/µl within 12 months from SC before cART initiation, non-RP if not. We used piecewise linear mixed-models (slopes changes at months 1 and 18) to model trends in CD4+ T-cell counts and logistic regression to calculate Odds Ratios for optimal restoration. Models were adjusted for sex, risk group, geographical origin, age and HIV-RNA at cART initiation. To compare RP and non-RP with the same baseline CD4+ T-cell count, we applied a post-estimation adjustment procedure to the results of the multivariate linear mixed model and we also fitted multivariate logistic regression models which included an adjustment for CD4+ T-cell count at cART (<100, 100-199, ≥200) initiation.
Results: Of 4,197 individuals, 307 (7.3%) were classified as RP. Median CD4+ T-cell count profiles are shown in Figure 1. Comparison of RP and non-RP with the same baseline CD4+ T-cell count showed that RP experienced a faster CD4+ T-cell increase than non-RP in the first month [difference (95% CI) in mean CD4+ T-cell increase/month (square root scale): 1.87 (1.65; 2.10)], slightly slower increases in months 1-18 [-0.05 (-0.06; -0.03)] and no significant differences in 18-60 [0.001 (-0.010; 0.012)]. Percentage of patients achieving an optimal restoration was significantly lower in RP than non-RP at months 12 (29.0 versus 64.2%) and 36 (46.3% versus 73.2%) but not at month 60 (70.2% versus 72.3%), differences that disappeared after comparing patients with the same CD4+ T-cell count at start of cART: OR (95% CI) 0.79 (0.54; 1.15), 0.79 (0.34; 1.83) and 1.61 (0.58; 4.45) at months 12, 36 and 60, respectively.

Conclusion: Although RP experience faster initial increases of CD4+ T-cell counts that non-RP on suppressive therapy, they are less likely to achieve optimal CD4+ T-cell restoration during the first 36 months after cART, mainly due to their lower CD4+ T-cell counts at cART initiation .

Figure 1. Observed CD4+ T-cell counts in RP and non-RP



Background

- Accumulating evidence, coming from studies focused on extreme HIV phenotypes, suggests that a combination of viral and host factors are involved in protective immunity and virus control
- Studies on rapid progressors are limited to case reports or small cohorts given the difficulties in their definition and the identification of adequate numbers

Objective

To compare (i) trends in CD4+ T-cell recovery after combination antiretroviral therapy (cART) initiation and (ii) the proportion achieving optimal CD4+ T-cell restoration (counts ≥500 cells/ml) after 12, 36 and 60 months between rapid (RP) and non-rapid progressors (non-RP) achieving virological suppression

CASCADE collaboration
Steering Committee: Julia Del Amo (Chair), Laurence Meyer (Vice Chair), Heiner C. Bucher, Geneviève Chêne, Deenan Pillay, Maria Prins, Magda Rosinska, Caroline Sabin, Giota Touloumi. **Co-ordinating Centre**: Kholoud Porter (Project Leader), Sara Lodi, Kate Coughlin, Sarah Walker, Abdel Babiker, Janet Darbyshire.
Clinical Advisory Board: Heiner C. Bucher, Andrea De Luca, Martin Fisher, Roberto Muga
Collaborators: **Australia** Sydney AIDS Prospective Study and Sydney Primary HIV Infection cohort (John Kaldor, Tony Kelleher, Tim Ramacciotti, Linda Gelgor, David Cooper, Don Smith); **Canada** South Alberta clinic (John Gill); **Denmark** Copenhagen HIV Seroconverter Cohort (Louise Bruun Jørgensen, Claus Nielsen, Court Pedersen); **Estonia** Tartu Ülikool (Irja Lutsar); **France** Aquitaine cohort (Geneviève Chêne, Francois Dabis, Rodolphe Thiebaut, Bernard Masquelier), French Hospital Database (Dominique Costagliola, Marguerite Guiguet), Lyon Primary Infection cohort (Philippe Vanhems), French PRIMO cohort (Marie-Laure Chaix, Jade Ghosn), SEROCO cohort (Laurence Meyer, Faroudy Boufassa); **Germany** German cohort (Osamah Hamouda, Claudia Kucherer, Barbara Bartmeyer); **Greece** Greek Haemophilia cohort (Giota Touloumi, Nikos Pantazis, Angelos Hatzakis, Dimitrios Paraskevis, Anastasia Karafoulidou); **Italy** Italian Seroconversion Study (Giovanni Rezza, Maria Dorrucci, Claudia Balotta), ICONA cohort (Antonella d'Arminio Monforte, Alessandro Cozzi-Lepri, Andrea De Luca.) **Netherlands** Amsterdam Cohort Studies among homosexual men and drug users (Maria Prins, Ronald Geskus, Jannie van der Helm, Hanneke Schuitemaker); **Norway** Oslo and Ullevål Hospital cohorts (Mette Sannes, Oddbjorn Brubakk, Anne Eskild, Johan N Bruun); **Poland** National Institute of Hygiene (Magdalena Rosinska, Joanna Gniewosz); **Portugal** Universidade Nova de Lisboa (Ricardo Camacho); **Russia** Pasteur Institute (Tatyana Smolskaya); **Spain** Badalona IDU hospital cohort (Roberto Muga, Jordi Tor), Barcelona IDU Cohort (Patricia Garcia de Olalla, Joan Cayla), Madrid cohort (Julia Del Amo, Jorge del Romero), Valencia IDU cohort (Santiago Pérez-Hoyos); **Switzerland** Swiss HIV Cohort Study (Heiner C. Bucher, Martin Rickenbach, Patrick Francioli); **Uganda & Zimbabwe; Ukraine** Perinatal Prevention of AIDS Initiative (Ruslan Malyuta); **United Kingdom** Edinburgh Hospital cohort (Ray Brettle), Health Protection Agency (Valerie Delpech, Sam Lattimore, Gary Murphy, John Parry, Noel Gill), Royal Free haemophilia cohort (Caroline Sabin, Christine Lee), UK Register of HIV Seroconverters (Kholoud Porter, Anne Johnson, Andrew Phillips, Abdel Babiker, Janet Darbyshire, Valerie Delpech), University College London (Deenan Pillay), University of Oxford (Harold Jaffe). **African cohorts:** Genital Shedding Study (US: Charles Morrison, Family Health International, Robert Salata, Case Western Reserve University, Uganda: Roy Mugerwa, Makerere University, Zimbabwe: Tsungai Chipato, University of Zimbabwe; Early Infection Cohorts (Kenya, Uganda, Rwanda, Zambia, South Africa: Pauli Amornkul, International AIDS Vaccine Initiative).
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Methods

Study population

- HIV-1 seroconverters (SC) from CASCADE who initiated cART while naive and achieved viral suppression (HIV RNA ≤ 200 copies/ml) within the first 6 months of therapy
- Individuals were classified as RP if experienced ≥1 CD4 <200 cells/µl within 12 months from SC before ART initiation, and as Non-RP if all counts during this period remained ≥ 200 cells/µl

Statistical analyses

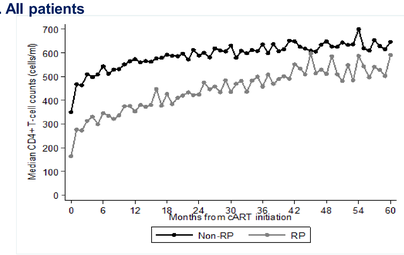
- Piecewise linear mixed-effects model with changes of slopes at months 1 and 18 (best Akaike criterion) to model trends in CD4+ T-cell counts
  - Initially adjusted for sex, age at cART initiation, risk group, geographical origin and log10 HIV-RNA levels at cART initiation
  - Then, correction to the parameter estimates to compare RP and non-RP with the same underlying CD4+ T-cell counts at start of cART
- Logistic regression to calculate Odds Ratios of achieving counts ≥ 500 cells/ml
  - Initially adjusted for the same factors as in the piecewise linear mixed-effects models (Model 1), and additionally adjusted for CD4+ T-cell count at cART initiation (<100, 100-199, ≥200)

Results

- The CASCADE database, updated in 2013 within EuroCoord (www.eurocoord.net) included data from 29,884 individuals. A total of 4,024 were included in the analyses, of which 294 (7.3%) were classified as RP
- RP were more likely than Non-RP to be women (17.7% vs. 11.2%), infected through sex between men and women (30.9% vs. 18.2%), 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)
- After initial adjustment, RP had faster initial and long term CD4+ T-cell increases than non-RP: 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 (0.02; 0.06, p<0.001) in 18-60 months. Applying the post-estimation adjustment procedure, RP experienced a faster CD4+ T-cell increase than non-RP 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 18-60 (-0,003, -0,01; 0,01, p=0.62)

Figure 1. Observed CD4+ T-cell counts in RP and non-RP

a. All patients



b. Patients starting cART with CD4+ T-cell counts <200 cells/µl

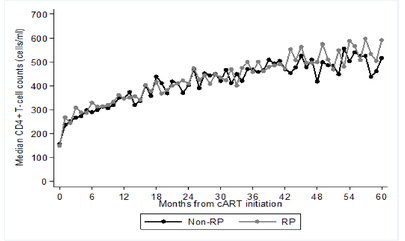
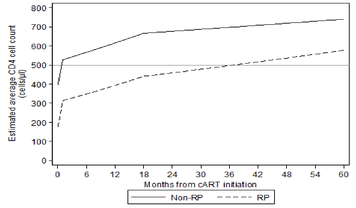


Figure 2. Predicted CD4+ T-cell counts in RP and non-RP

a. From an initial piecewise linear mixed model (men, MSM, non-SSA, 30 years old at start of cART and 5log10 HIV-RNA level at cART initiation)



b. After the post estimation adjustment procedure (men, MSM, non-SSA, 30 years old at start of cART and 5log10 HIV-RNA level at cART initiation and an underlying CD4+ T-cell count at cART initiation of 180 cells/ml)

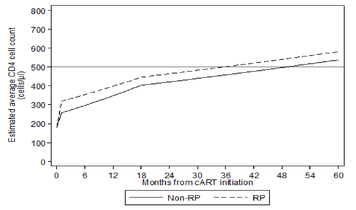


Table 1. CD4+ T-cell count restoration at 12, 36 and 60 months from cART initiation

		N	N (%) CD4 ≥500	Unadjusted analyses		Adjusted analyses			
						Model 1[1]		Model 1 + CD4 at cART initiation[2]	
				OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
12 months	non-RP	2,852	1,782 (62.5)	1.00		1.00		1.00	
	RP	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	non-RP	1,260	912 (72.4)	1.00		1.00		1.00	
	RP	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	non-RP	440	316 (71.8)	1.00		1.00		1.00	
	RP	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

Sensitivity analyses (i) using 100 and 350 as CD4 thresholds to define RP, (ii) using the first 6 months from SC to classify patients as RP and Non-RP, (iii) restricting to individuals who started cART with CD4 <200 cells/ml and (iv) restricting to patients with started cART after year 2000 provided similar results

Conclusions

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