

# Maximum Capacity of Restoration of CD4 Counts Is Lower in HIV-1-infected Patients from Sub-Saharan Africa during the First Months of cART: the Athena Cohort

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## Background

Long term CD4 response according to gender and ethnicity has not been extensively studied. We investigated differences in the maximum capacity for immune restoration during 5 years of cART between male and female HIV-1 infected patients and between patients from different regions of origin.

## Methods

### Patients were selected from the Netherlands ATHENA cohort:

- Antiretroviral therapy naïve and starting cART ≥16 years of age between January 1996 and May 2005.
- Originating from W-Europe/N-America (**WES**), sub-Saharan Africa (**SSA**), South-East Asia (**SEA**) or Latin America / Caribbean (**LAC**).
- Included patients suppressed HIV RNA <400 copies/ml within 9 months following the start of cART.
- CD4 counts were censored at the first of two consecutive HIV RNA measurements ≥400 copies/ml.

### Statistical analyses

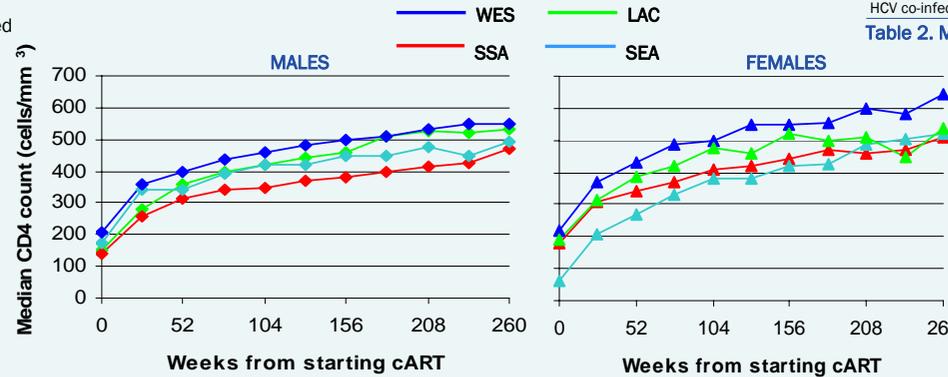
- Changes in long term CD4 response from start of cART (baseline) was analysed using mixed effect models with random slopes per patient.
- Changes in CD4 count were calculated separately for time periods 0-6, 6-36 and 36-60 months after starting cART.
- Multivariate analyses were adjusted for gender, age, baseline CD4 count and HIV RNA, HCV and/or HBV co-infection, transmission risk group, type of PI / NNRTI, type of NRTI, AIDS diagnosis (prior to start cART and between 0-6 months after starting cART) and region of origin.

## Results

- The majority of 4348 selected patients were males (80%) from WES (68%), 17% were from SSA, 4% from SEA and 11% from LAC (Table 1).
- Median follow-up after starting cART was 3.8 years.
- Median CD4 count at the start of cART was 210 cells/mm<sup>3</sup> in WES (ref), 160 in SSA (p<0.0001), 140 in SEA (p<0.0001), and 170 in LAC patients (p<0.0001).
- Median increase after 5 years was 360 cells/mm<sup>3</sup> (IQR 230-520) for WES (ref), 320 for SSA (210-450, p=0.004), 340 (240-490, p<0.87) for SEA and 360 (210-530, p=0.86) for LAC patients (Figure 1a and b).
- In the first six months after starting cART 299 patients were diagnosed with a new AIDS event, 6% amongst WES, 6% in SSA, 10% in SEA and 8% in LAC patients, (p=0.20).
- In total 56796 CD4 measurements were included in multivariate analyses.

	WES N (%)	SSA N (%)	SEA N (%)	LAC N (%)	p
Total	2970	751	157	470	
Male	2665 (90)	379 (50)	100 (64)	341 (73)	<0.0001
Prior AIDS diagnosis	721 (24)	206 (27)	54 (34)	129 (27)	0.01
Transmission risk group					
MSM	2061 (69)	30 (4)	74 (47)	195 (41)	<0.0001
Hetero	571 (19)	629 (84)	67 (43)	233(50)	
IDU	130 (4)	2 (0)	4 (3)	2 (0)	
Other	208 (7)	90 (12)	12 (8)	40 (9)	
Hepatitis B	222 (7)	82 (11)	18 (11)	41 (9)	0.009
Hepatitis C	286 (10)	38 (5)	12 (8)	15 (3)	<0.0001
Year start cART					
1996-2000	1420 (48)	202 (27)	63 (40)	162 (35)	<0.001
2001-2005	1550 (52)	549 (73)	94 (60)	308 (65)	
	<b>Median (IQR)</b>	<b>Median (IQR)</b>	<b>Median (IQR)</b>	<b>Median (IQR)</b>	
Nadir CD4 count (cells/mm <sup>3</sup> )	169 (70-260)	130 (50-210)	103 (29-200)	131 (40-230)	<0.0001
Age (yrs)	40 (34-47)	33 (28-38)	35 (30-43)	37 (32-42)	<0.0001
Plasma HIV RNA (log <sub>10</sub> c/ml)	5.0 (4.6-5.4)	5.0 (4.4-5.3)	4.9(4.6-5.3)	4.9 (4.5-5.3)	<0.0001

**Table 1. Baseline characteristics of 4348 patients who started cART between January 1996 and May 2005 and achieved HIV RNA <400 cps/ml within 9 months.**

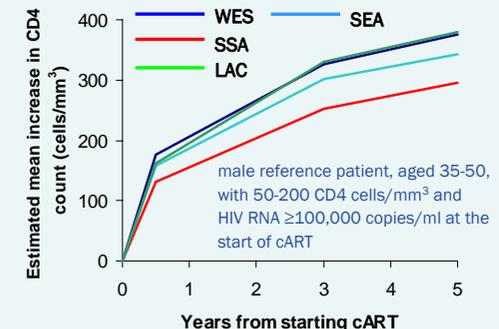


**Figure 1a and b: Median CD4 count in 3485 male and 863 female virologically suppressed patients.**

- The estimated mean increase in CD4 count was significantly higher in female compared to male patients: +27 cells/mm<sup>3</sup>/year between 0-6 months, p=0.04 and +11 cells/mm<sup>3</sup>/year between 6-36 months, p=0.001 (Table 2).
- The estimated mean change in CD4 count in patients from SSA was significantly lower compared to patients from WES: -93 CD4 cells/mm<sup>3</sup>/year (95% CI -121, -65, p<0.0001) between 0-6 months and -11 cells/mm<sup>3</sup>/year (-3, -18, p=0.008) between 6-36 months.
- No significant differences in CD4 increase between patients from SEA, LAC or WES origin were found. No interaction effect was found between region of origin and gender.
- Estimated mean CD4 counts increases on a boosted PI were 58 (95% CI 9, 107) and 36 (-12, 85) cells/mm<sup>3</sup>/year on a NNRTI containing regimen (p<0.0001 for difference).

	Annual changes in CD4 count		
	0-6 months	6 months-3 years	3-5 years
Female gender	27 (4, 55)	11 (6, 19)	2 (-8, 13)
Region of origin			
W-Europe / N-America	ref	ref	ref
Sub-Sahara Africa	-93 (-121, -65)	-11 (-18, -3)	-4 (-15, 8)
South-East Asia	-34 (-85, 15)	-8 (-16, 10)	-8 (-26, 10)
Latin America / Caribbean	-25 (-56, 6)	6 (-2, 14)	1 (-12, 14)
AIDS diagnosis prior to starting cART	3 (-20, 26)	12 (6, 18)	-1 (-10, 8)
AIDS diagnosis 0-6m after starting cART	-55 (-94, -15)	10 (-1, 20)	-7 (-22, 8)
Age			
<35	40 (14, 67)	1 (-6, 8)	-9 (-20, 1)
35-50	ref	ref	ref
≥50	-48 (-75, -21)	-15 (-22, -8)	-7 (-17, 3)
Baseline CD4 count (cells/mm <sup>3</sup> )			
<50	-77 (-108, -46)	14 (6, 22)	2 (-9, 14)
50-200	-27 (-51, -3)	7 (1, 13)	2 (-7, 11)
200-350	ref	ref	ref
350-500	-6 (-38, 26)	0 (-8, 8)	-9 (-20, 4)
>500	-148 (-185, -111)	5 (-5, 14)	-5 (-19, 9)
Baseline HIV RNA, (log <sub>10</sub> copies/ml)			
<4	-153 (-188, -118)	-2 (-11, 7)	2 (-11, 15)
4-5	-61 (-83, -40)	-2 (-8, 3)	-4 (-12, 4)
≥5	ref	ref	ref
HCV co-infection	-83 (-117, -48)	-16 (-25, -7)	-2 (-15, 11)

**Table 2. Multivariate analysis of CD4 count changes from baseline.**



**Figure 2: Estimated increases in CD4 count from baseline according to region of origin.**

## Conclusion

In patients achieving and maintaining viral suppression, changes in CD4 count during 5 year of cART were significantly lower in male patients and in patients from sub-Sahara African origin compared to W-European/N-American. This effect was independent of differences in baseline CD4 count and viral load and AIDS diagnosis prior or after starting cART. Differences in CD4 count increases were largest during the first 6 months of cART.