



# Prognosis of patients treated with cART from 36 months after initiation of therapy, according to current and previous CD4 cell count

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## Abstract

**Background:** Current CD4 count predicts mortality in patients treated with combination antiretroviral therapy (cART). It is unclear whether, in pts treated for some years, there is additional prognostic value in CD4 measurements at initiation of treatment.  
**Methods:** Data from 15 HIV cohort studies in Europe and N. America were combined. Eligible pts were aged >15 and antiretroviral-naïve when they started cART before 2002. We used Cox models to estimate mortality hazard ratios (HR) from 36 mo after initiation of cART according to CD4 at 0, 6 and 36 mo, among pts still followed up at this time.  
**Results:** CD4 at 36 mo was measured in 17159 pts (median 462/mm<sup>3</sup>, IQR 320-683). Median 36 mo CD4 was 279, 319, 334, 400, 512, 639 & 780 in pts starting cART with 0-24, 25-49, 50-99, 100-199, 200-349, 350-499 & >500/mm<sup>3</sup> respectively. The table shows mortality HR from 36 mo, according to CD4 at the 3 time points. CD4 at 36 mo was highly prognostic for subsequent mortality. In unadjusted models, pts with baseline CD4 <200 cells/mL had higher mortality from 36 mo, and CD4 at 6 mo was moderately prognostic. In the adjusted model, CD4 at 6 mo was no longer prognostic. Given pts' CD4 at 36 mo, there was a negative association with CD4 at initiation because, given CD4 at 36 mo, pts with higher baseline CD4 will tend to be those whose rise in CD4 over 36 months is lower; e.g. because of non-adherence or treatment failure.  
**Conclusions:** CD4 count at 36 mo is strongly related to CD4 count at initiation of cART. At 36 mo after starting cART, current CD4 count is strongly prognostic for subsequent mortality. Additionally, pts whose CD4 increase is below average have worse prognosis.

## Background

- The ART Cohort Collaboration was established with the aim of providing estimates of the probability of progression to a new AIDS event or death for drug naïve patients starting combination antiretroviral therapy (cART)
- CD4 cell count is the dominant prognostic factor at the time patients start cART<sup>1</sup>
- Current CD4 cell count is strongly prognostic for short term risk of AIDS and death, in patients on cART<sup>2</sup>
- A number of studies have shown that differences in CD4 cell count at the time of starting cART are maintained for some years after starting cART
- In previous analyses<sup>2</sup> we showed that baseline CD4 cell count was not strongly prognostic from 6 months after starting cART, after adjusting for CD4 cell count 6 months<sup>3</sup>
- The ART Cohort Collaboration dataset was recently updated to include data on more than 40,000 patients from 16 cohort studies. Measurements of CD4 cell count at around 36 months after starting HAART were included in this update

## Aim

- To establish the relative prognostic importance, for AIDS and death from 36 months after the start of cART, of CD4 cell count at 0, 6 and 36 months after starting cART

## Methods

- Data from 16 HIV cohort studies in Europe and N. America were combined (see box for list of contributing cohorts)
- Eligible patients were aged >15 and antiretroviral-naïve when they started cART (with at least three antiretrovirals and HIV-1 RNA > 1,000 copies per mL at treatment initiation), and first started antiretroviral therapy after 1 January 1996 and before 2002.
- We used Cox proportional hazards models to estimate hazard ratios (HR) for AIDS and death from 36 months after initiation of cART according to CD4 at 0, 6 and 36 months, among patients followed up for at least this length of time. All analyses were stratified by cohort.

## References

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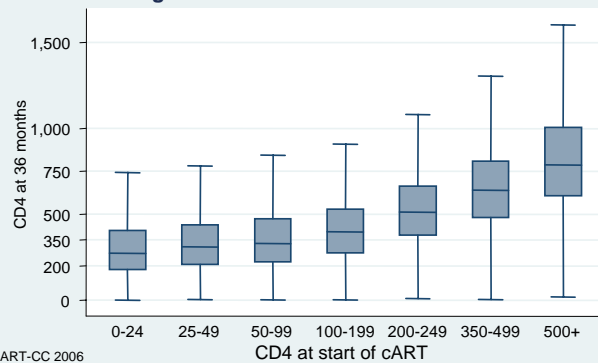
## ART-CC Steering Committee

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## Results

- The figure below shows that differences in CD4 cell count at the time of initiating cART were reflected in CD4 cell counts at 36 months

CD4 distribution at 36 months after start of cART according to CD4 count at initiation of treatment



- The table below shows crude and mutually adjusted hazard ratios for death from 36 months after initiation of cART, by CD4 count at 0, 6 and 36 months after start of cART. The reference category is CD4>500

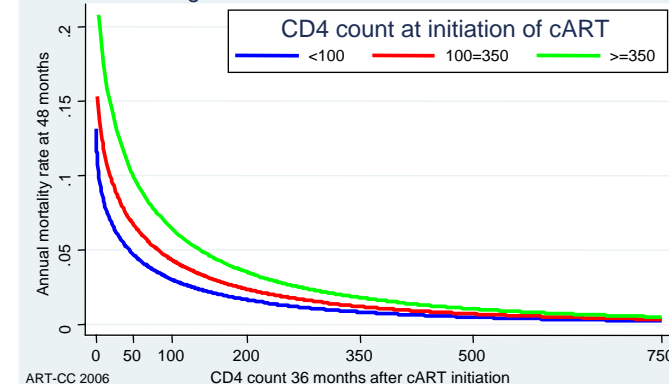
CD4 count	No. of subjects (N = 18018)	No. (%) deaths (N=532)	Mortality hazard ratio (95% CI) from 36 months after starting cART for CD4 at other time points	
			Unadjusted	Adjusted for CD4 at other time points
<b>At initiation of cART</b>				
0-24	1741	79 (4.5)	1.97 (1.40 - 2.76)	0.52 (0.31 - 0.86)
25-49	1079	36 (3.3)	1.57 (1.04 - 2.38)	0.48 (0.28 - 0.82)
50-99	1762	63 (3.6)	1.57 (1.10 - 2.24)	0.54 (0.33 - 0.87)
100-199	3166	110 (3.5)	1.58 (1.15 - 2.17)	0.68 (0.45 - 1.05)
200-349	4794	116 (2.4)	1.06 (0.78 - 1.45)	0.69 (0.47 - 1.00)
350-499	3175	69 (2.2)	0.90 (0.64 - 1.28)	0.73 (0.51 - 1.05)
>500 (reference)	2313	59 (2.6)	1	1
<b>6 months after initiation</b>				
0-24	170	15 (8.8)	4.75 (2.75 - 8.20)	0.85 (0.42 - 1.73)
25-49	284	24 (8.5)	4.61 (2.95 - 7.20)	1.62 (0.88 - 2.97)
50-99	1084	50 (4.6)	2.43 (1.73 - 3.41)	0.98 (0.58 - 1.65)
100-199	2944	110 (3.7)	1.98 (1.51 - 2.59)	1.11 (0.72 - 1.72)
200-349	4440	142 (3.2)	1.73 (1.35 - 2.24)	1.31 (0.91 - 1.88)
350-499	3967	87 (2.2)	1.14 (0.85 - 1.51)	1.13 (0.81 - 1.56)
>500 (reference)	5141	104 (2.0)	1	1
<b>36 months after initiation</b>				
0-24	174	53 (30.5)	18.17 (13.13 - 25.14)	25.86 (17.21 - 38.85)
25-49	117	23 (19.7)	10.88 (6.96 - 17.00)	13.35 (8.13 - 21.90)
50-99	285	35 (12.3)	6.54 (4.50 - 9.51)	7.78 (5.12 - 11.83)
100-199	1249	80 (6.4)	3.78 (2.87 - 4.98)	4.52 (3.26 - 6.26)
200-349	3488	111 (3.2)	2.02 (1.57 - 2.58)	2.30 (1.71 - 3.08)
350-499	4192	85 (2.0)	1.25 (0.96 - 1.63)	1.32 (0.98 - 1.76)
>500 (reference)	8525	145 (1.7)	1	1

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- The table, and the figure below show that, after accounting for CD4 count at 36 months, there is a *negative* association of CD4 at initiation with subsequent prognosis.
- This *does not* imply that it is better to initiate cART at lower CD4 cell counts!

Annual mortality rate 48 months after cART initiation according to CD4 count at 36 months and at initiation



- In univariable analyses, CD4 counts at 36 months after initiation and at 6 months after initiation are each prognostic for mortality from 36 months after initiation of cART
- In univariable analyses, CD4 count at initiation of cART was weakly prognostic for mortality from 36 months after initiation of cART
- After accounting for CD4 at initiation of HAART and CD4 at 36 months, CD4 at 6 months is not prognostic for mortality from 36 months. The counterintuitive negative association of CD4 at initiation with subsequent prognosis is seen only after adjusting for CD4 at 36 months
- This negative association arises because, for a given CD4 at 36 months, patients with higher CD4 at initiation have benefited less from cART. This reduced benefit is associated with worse subsequent prognosis

## Interpretation and conclusions

- In considering the prognosis of patients who have been on cART for some years, physicians should be aware that CD4 at the time of initiation of HAART has prognostic value additional to that provided by current CD4 cell count
- In future work, we will provide prognostic models from 36 months that account for all relevant information

## ART-CC Contributing Cohorts

**Alabama:** UAB 1917 Clinic Cohort, University of Alabama at Birmingham, US  
**Aquitaine:** Bordeaux University Hospital and four other public hospitals in the Aquitaine region, France  
**ATHENA:** (AIDS Therapy Evaluation Project Netherlands); 23 HIV treatment centres including 25 hospitals in The Netherlands  
**BCCFE:** British Columbia Centre for Excellence in HIV/AIDS  
**CHORUS:** 4 clinics in the United States (Nashville, New York, San Francisco and Los Angeles)  
**EUROSIDA:** 82 hospitals in 29 European countries and Argentina  
**Frankfurt:** Klinikum der JW Goethe-Universität Frankfurt  
**FHDH:** (French Hospital Database on HIV): National cohort study based on 69 hospitals in France  
**ICONA:** (Italian Cohort of Antiretroviral-Naïve Patients): cohort of treatment-naïve patients based in 65 clinics in Italy  
**Köln/Bonn:** Departments of Internal Medicine at University of Cologne and Bonn, Germany  
**PISCIS:** Proyecto para la Información del Seguimiento Clínico-epidemiológico de la Infección por HIV y SIDA. Catalonia and Balearic Islands, Spain. 10 regional hospitals in Barcelona, Mallorca and Girona.  
**Royal Free:** Ian Charleson Centre at the Royal Free Hospital London, UK  
**South Alberta:** Southern Alberta Clinic, Canada  
**Swiss:** Swiss HIV Cohort Study (7 centres in Switzerland)  
**VACS:** Observational cohort study of HIV-positive and matched HIV-negative veterans based on the Veterans Health Administration, USA  
**Vancouver:** St. Paul's Hospital in Vancouver, Canada  
**Washington:** University of Washington Harborview Medical Center, USA

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