Late presentation at entry into HIV care limits the impact of cART

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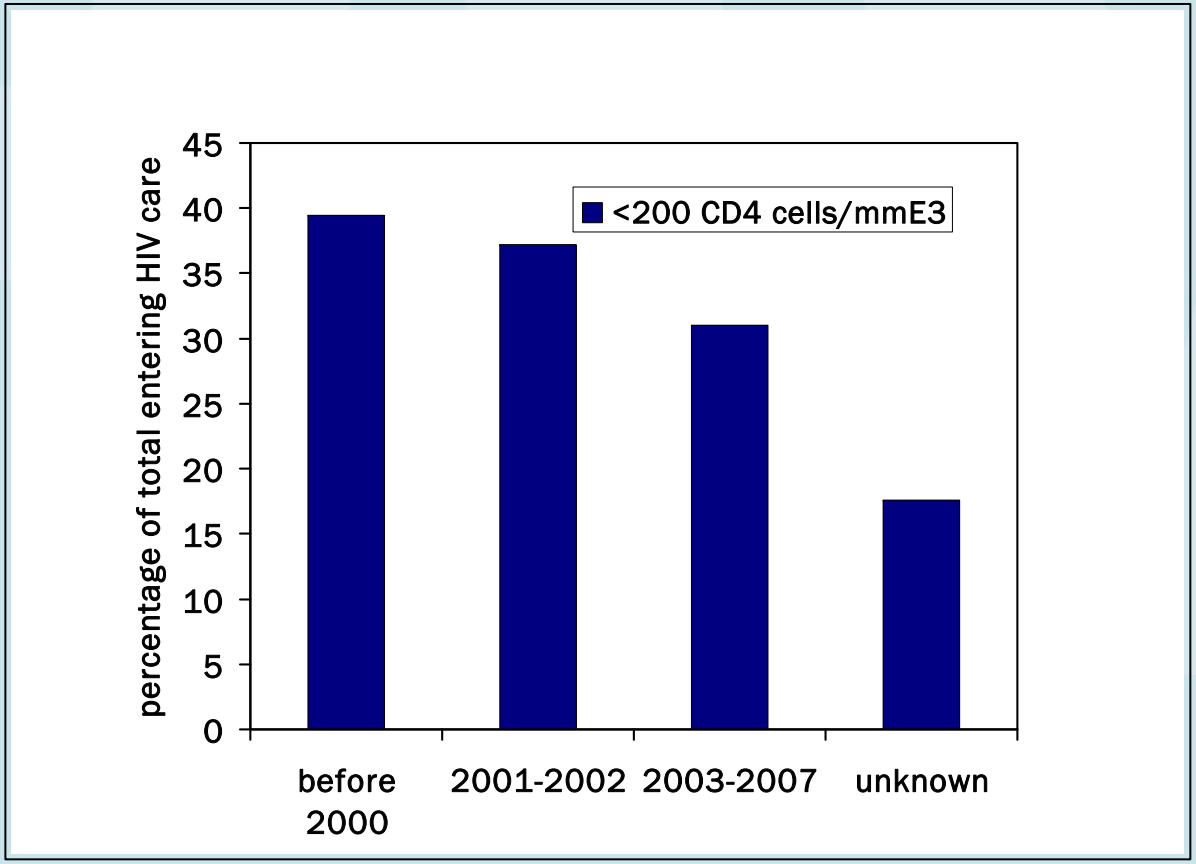
Related questions

- Late presentation = Late start of cART
- What are the risks of starting cART late?
- When to start cART?

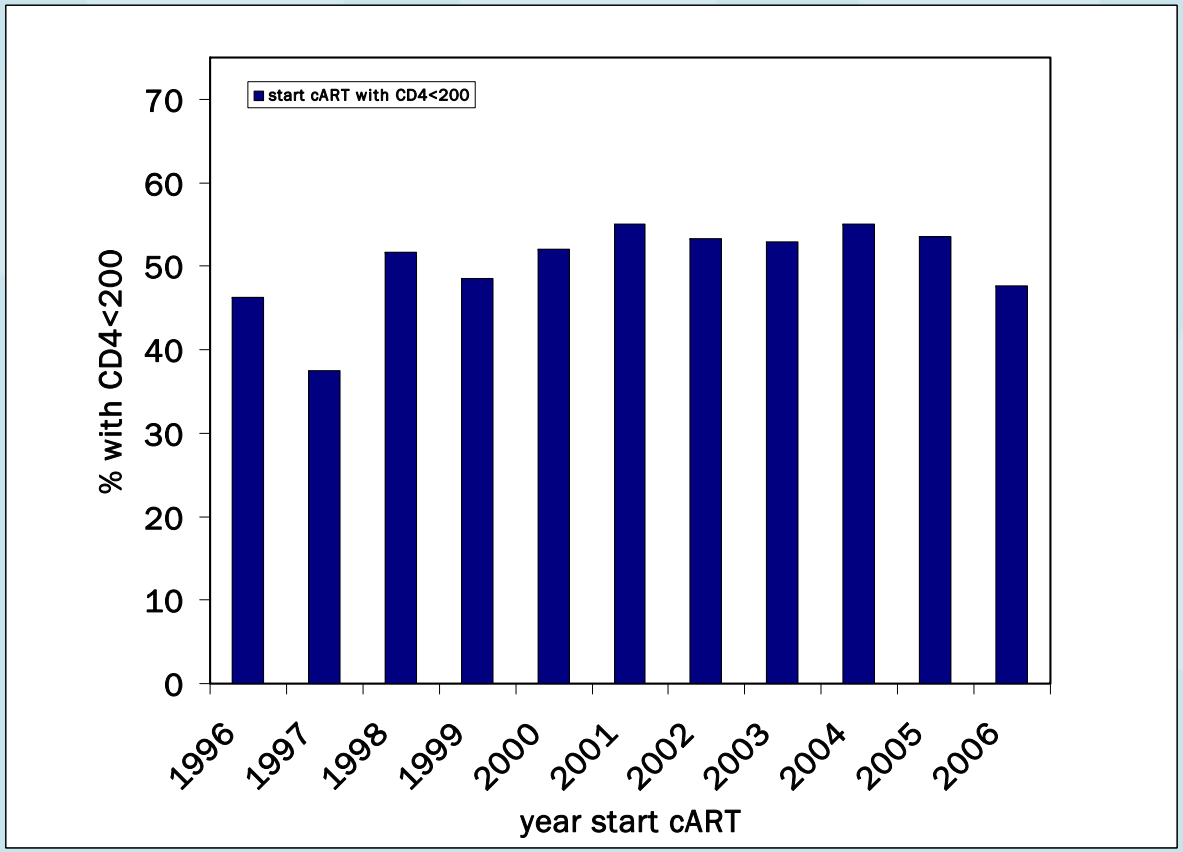
Patients presenting for care late



Patients presenting for care late

	At entry into care			
Characteristics	CD4 cells <200		Total population	
Total	2902	(34%)	8616	(100%)
Men	2204	(34%)	6515	(76%)
Women	698	(33%)	2101	(32%)
Average age (SD)	40	(±13)	38	(±12)
Average CD4 cell number/mmE3 (SD)	81	(±53)	349	(±281)
Symptomatic	1642	(53%)	3101	(36%)
Country/region of origin				
Netherlands + West Europe	1524	(30%)	5123	(59%)
Non Dutch/W-Europe	1378	(40%)	3471	(40%)
Transmission route				
MSM	1198	(27%)	4359	(51%)
Heterosexual contact + others	1704	(40%)	4257	(49%)

Patients starting cART late



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Patients starting cART late

	CD4 count at start cART (cell/mm3)					
	<200		≥200		total	
Total	3486	(50.5%)	3412	(49.5%)	6898	
Male	2711	(52.1%)	2493	(47.9%)	5204	
Female	775	(45.7%)	919	(54.3%)	1694	
Median log_{10} HIV RNA cps/ml (IQR)	4.77	(4.23-5.18)	5.09	(4.79-5.56)	5	(4.48-5.38)
Median age (yrs, IQR)	36.8	(30.7-44.0)	38.5	(32.7-45.8)	37.5	(31.5-44.8)
CDC-C diagnose at starting cART	1498	(80%)	374	(20%)	1872	
Transmission risk group						
MSM	1615	(46.9%)	1825	(53.1%)	3440	
Heterosexual a.o.	1871	(47.3%)	1587	(52.7%)	3458	
Region of origin						
Netherlands + West Europe	1990	(46.9%)	2220	(53.1%)	4210	
non Dutch/W-Europe	1496	(54.9%)	1192	(45.1%)	2688	

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HIV Care?

Background:

Comparing different HIV treatment centres is not straight forward.

Indicators of good patient management and successful treatment are influenced by patient characteristics and attributes of the centre.

Hypotheses:

1. the quality of treatment administered varies between the treatment centres;
2. more frequent patient monitoring in some centres generates better patient survival; or
3. patients entering care earlier in some centres generates better patient survival.

Methods

Treatment outcomes and patient profile

- Dutch homosexual (MSM) only were included to prevent socio-ethnicity status of the patients interfering with the comparison of the model.

- The risk of dying in the first 3 years on cART was estimated for each ATHENA HIV treatment centre, using a Cox-Proportional Hazards Model. The fraction of dying in the first three years of cART ranged from 0% to 8%.

- The risk of dying in each centre was then compared to that of the total HIV+ population in the Netherlands.

- 3 centres, A, B and C with widely varying mortality rates were selected for the comparison with the outcomes of a mathematical model. Their risk of dying compared to the national average:
  A) HR: 1.08; 95% confidence interval (CI): 0.51-2.29.
  B) no men died in the first three years of treatment
  C) HR: 2.22; 95% CI: 0.53-9.53

Mathematical model

A mathematical model representing patients entering care, being monitored for the need to start treatment and treatment outcomes was developed (PLOSMedicine 2008).
It includes:

- The decline in CD4 counts after seroconversion
- 3 years survival rates on cART, stratified by CD4 counts at initiation.

Data from the ATHENA cohort were used to estimate parameters of the natural history of HIV.

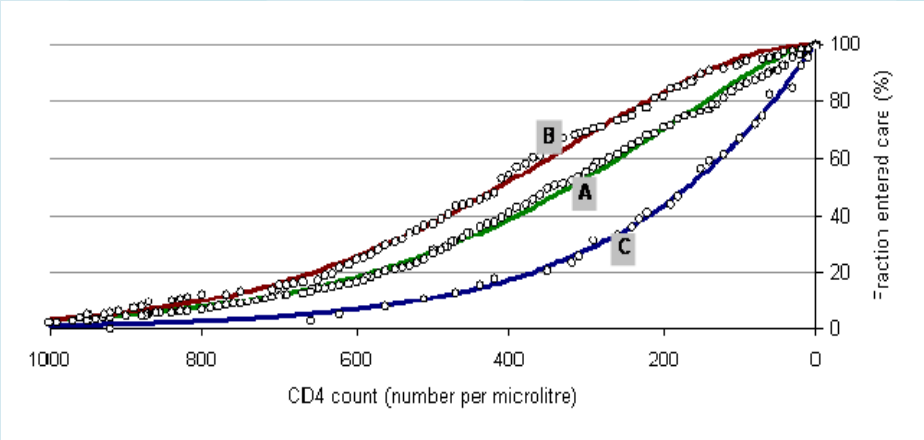
The model scenarios representing the 3 centres were differentiated by 3 parameters:

- age distribution of patients entering care
- average rate of clinic visits of the patients not on cART
- distribution of CD4 counts of patients first entering care.

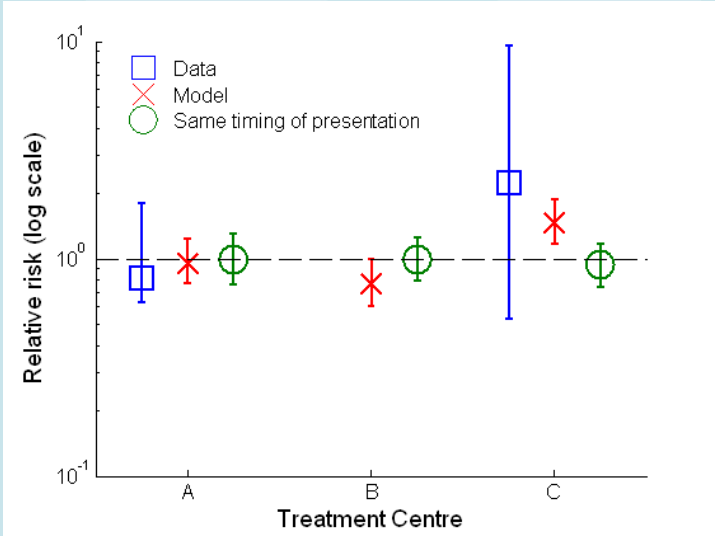
We investigated:

- whether the chance of individuals surviving on cART varied between treatment centres when patients are stratified by the initial CD4 cell count;
- whether the model could reproduce the observed variation in mortality between the three treatment centres when parameterised in this way; and,
- the relative influence of these treatment centre parameters on the predicted level of mortality on treatment.

Results



Distribution of CD4 count at presentation in three hospitals.



Observed and modeled risk of dying

The model captures the variation in observed mortality when parameterised using the age distribution, frequency of monitoring and the distribution of CD4 cell counts at entry to care observed in each of the three centres

When the same national average distribution of CD4 count at entry was used, the variation in predicted mortality between all centres was diminished.

Age-distribution of patients or the frequency of monitoring did not affect the model predictions.

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Conclusions

- Patients entering care with low CD4 counts are the main source of variation in the mortality rates between centres.
- When patients present with at least 400 CD4 cells/mm3, then the model predicts a reduction of the mortality in the first three years of cART by approximately 20%.
- Recruiting HIV-infected individuals to care earlier could lead to substantial improvements in cART outcomes.

CD4 Cell Counts of 800 Cells/mm^3 or Greater After 7 Years of Highly Active Antiretroviral Therapy Are Feasible in Most Patients Starting With 350 Cells/mm^3 or Greater

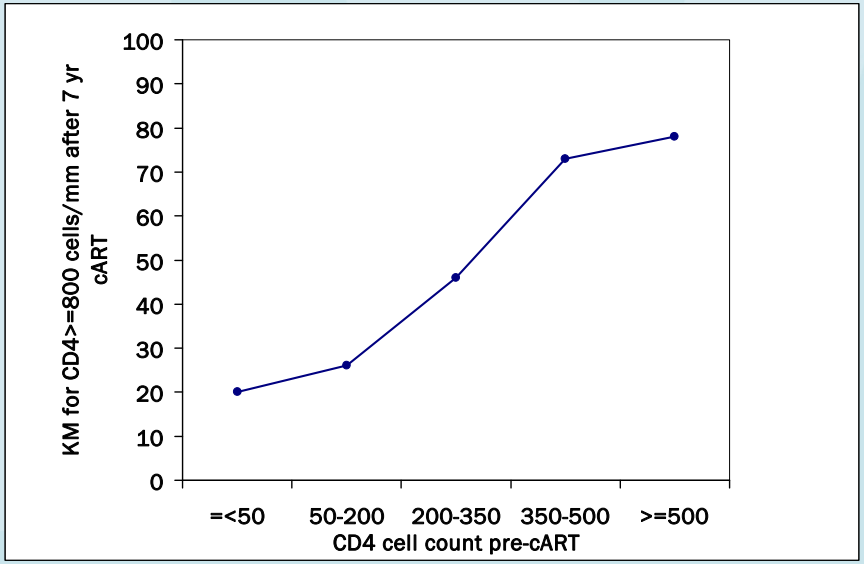
Lauk Gras J Aquir Immune Defic Syndr • Volume 45, Number 2, June 1, 2007

- Study the capacity of patients on long-term combination antiretroviral therapy cART to restore CD4 cell counts

- Time to CD4 cell counts ≥800/mm^3 in 5299 therapy naïve patients starting cART
- CD4 cell count changes over a 7 year uninterrupted cART in a subset of 544 patients
- CD4 cell changes in a subset of 366 virologically suppressed patients reaching a plateau of CD4 cell counts after 5 years of cART

Time to CD4 cell count ≥800 cells/mm^3

- The time required to restore CD4 counts to 800 cells/mm3 was associated with a higher pre-HAART CD4 cell count.



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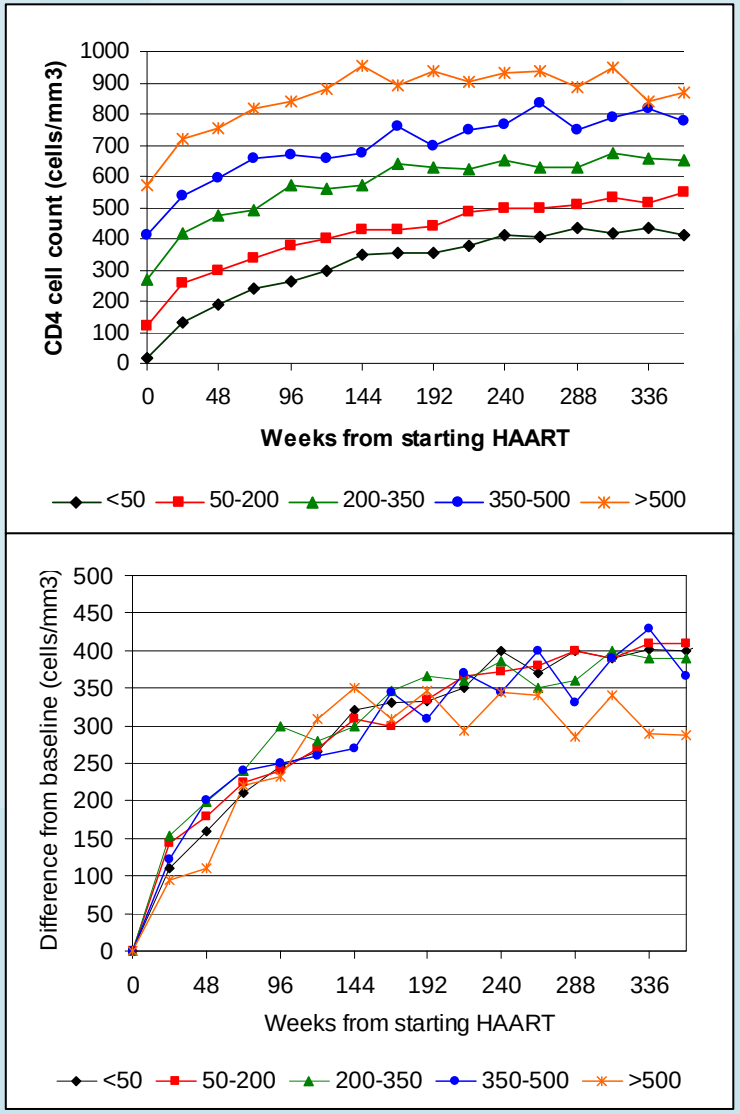
CD4 cell count in uninterrupted cART

- Patients continuously on HAART do show an increase of CD4 cells from median 221/mm^3 at start to 607/mm^3 after 7 years of treatment
- The highest increase is seen in the first 24 weeks and levels off thereafter
- The increase does not differ between baseline groups



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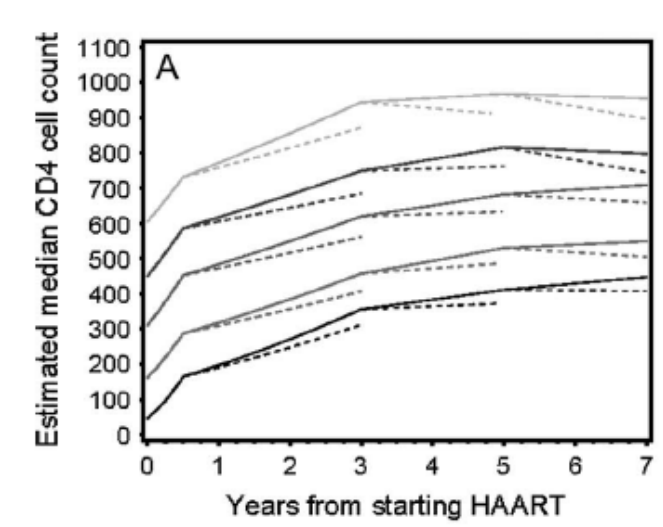
CD4 cell count in virologically suppressed patients

- In older patients and patients with viral rebounds after start of HAART the increase in CD4 cells is less.



Predictors of a plateauing CD4 cell count between 5 and 7 years after initiating cART in 366 patients with HIV RNA <500 cps/ml between 6 months and 5 years of uninterrupted cART

	HR	95% CI	p
CD4 cell count after 5 yrs			
CD4<400	1		
400-600	1.07	0.52-2.11	0.85
600-800	1.08	0.54-2.15	0.82
>=800	2.23	1.1-4.51	0.025
age at start cART			
<50	1		
>=50	3.01	1.6- 5.67	0.0006
vireamia between 5-7 years			
none	1		
at least once	4.69	1.66-13.19	0.003

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Conclusions

- Restoration of CD4 cell counts in HIV-infected persons to levels normally seen in uninfected individuals takes a long time an is not feasible within 7years in most patients who initiate cART with CD4 cell counts<350 cells/mm^3.
- Patients ≥ 50 years of age when starting cART and patients with episodes of vireamia (>500 HIV-RNA cps/ml) experience smaller increases and are more likely to reach a CD4 plateau earlier and at a lower level
- Given the better toxicity profiles of the currently used cART combinations, it may be beneficial to start cART earlier than current guidelines recommend.

Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected people: a collaborative analysis of 15 HIV cohort studies

- When to start or what's late?

- To establish a clear threshold: at what CD4 cell count should cART be initiated?
- Current threshold: start cART when below 350 cells/mm^3
- At present: Over 30% of the patients in the Netherlands start late.

- Ideal study: randomised trial (START)
- Second best: large observational study

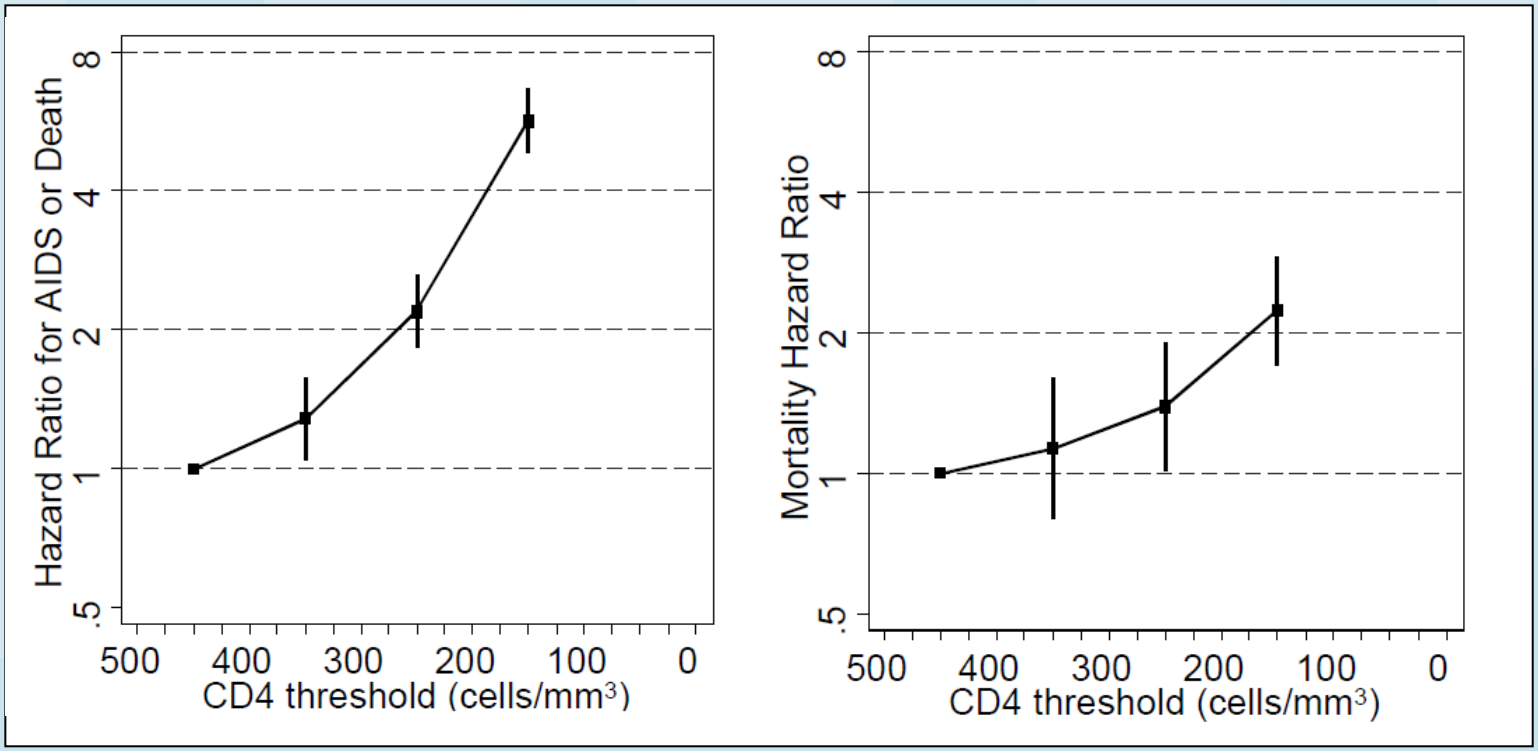
When to start study

- Compare pre-cART AIDS and death rates with on cART rates
- Use large numbers of patients that are AIDS-free at inclusion
- Large numbers in order to be able to distinguish between relatively small CD4 count strata (100 cells/mm^3)
- Estimate the time from the first CD4 measurement in the upper CD4 range to the upper threshold of the lower CD4 range
- Estimate the probability of progression to AIDS or death before reaching the upper threshold of the lower CD4 range

Pre-cART versus on cART cohorts

	pre-cART		on cART	
N	21247		24444	
Period of enrollment	1989-1995		1998-2006	
AIDS and death				
total follow-up (py)	68253		81071	
median years follow-up (IQR)	3.1	(1.9-4.5)	3.2	(1.5-5.3)
N (%) AIDS	5356	(25.2)	1860	(7.6)
N (%) death	3630	(17.1)	808	(3.3)
N (%) AIDS or death	5893	(27.7)	2366	(9.7)

CD4 threshold for starting cART



Deferring cART until CD4 cell counts are in the range 251-350 cells/mm^3 leads to increased rates of AIDS or death, compared with starting in the range of 351-450 cells/mm^3 (HR 1.28; 95% CI: 1.04-1.57)

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Conclusions

- Delayed entry into care is a major cause of late initiation of cART
  - Active HIV testing policies
- In addition, treatment is started late, even according to current guidelines
- Deferring cART results in higher AIDS and death rates
- The minimum threshold of starting cART is 350 CD4 cells/mm^3
  - Regular CD4 measurement: CD4 decline on average 80 cells/yr; twice a year?
- Episodes of viral production when on cART result in an increasing risk of AIDS or death
  - Regular HIV-RNA measurement

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