

Longer time on virological successful cART is independently associated with decreasing CD4 cell count in patients with <500 CD4 cells/mm<sup>3</sup>

Luuk Gras, Colette Smit, Steven van Lelyveld, Anouk Kesselring, Ard van Sighem, Frank de Wolf for the ATHENA national observational cohort

# Background

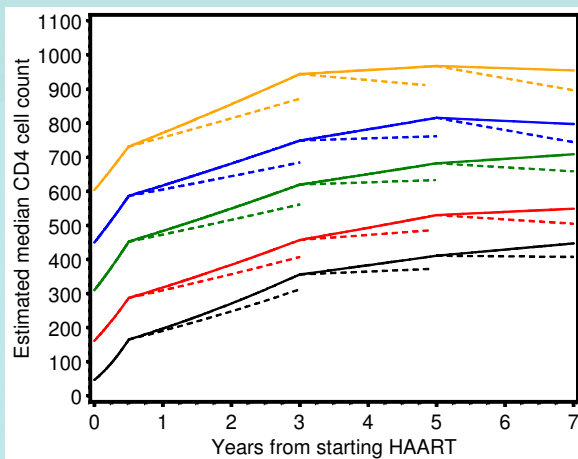


- ~90% of HIV-1 infected individuals starting cART manage to suppress plasma viral load to below detectable levels.
- A minority (10-35%) of virologically successfully treated HIV-1 infected individuals remain at low CD4 cell counts.
- Even if CD4 cell counts do increase, return to levels seen in HIV-negative individuals ( $\sim 800$  cells/mm<sup>3</sup>) may take years, and may not be feasible in some.

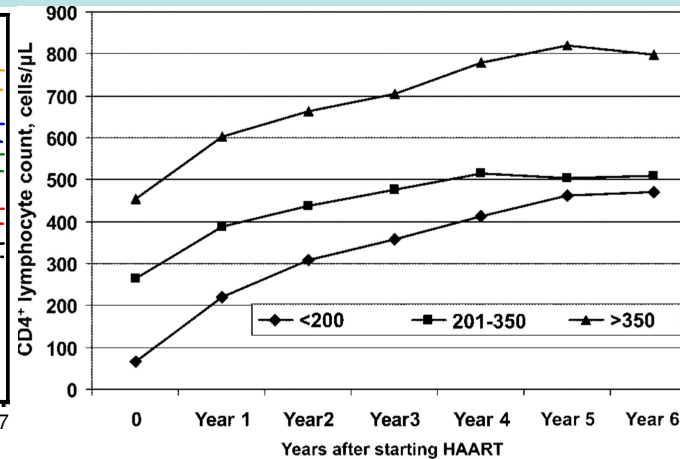
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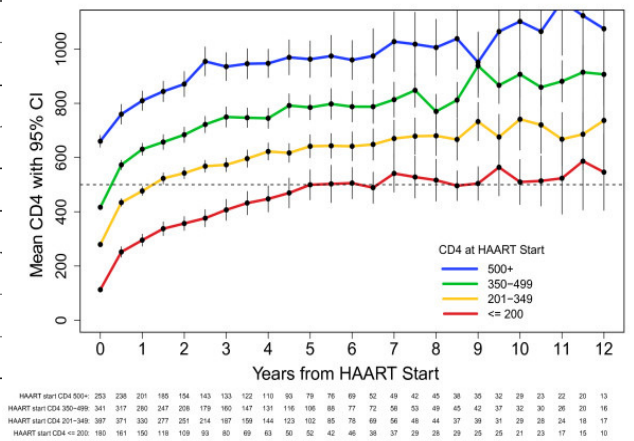
Median CD4+ lymphocyte count over time, stratified by baseline CD4+ cell count.  
In patients with virological suppression below detection limit.



Gras L, Kesselring A et al. JAIDS 2007



Moore R D, Keruly J C Clin Infect Dis. 2007

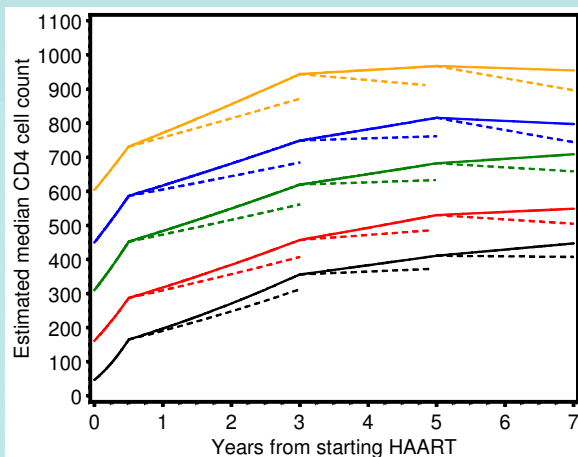


Lifson, Krantz et al. AIDS Research and Therapy 2011

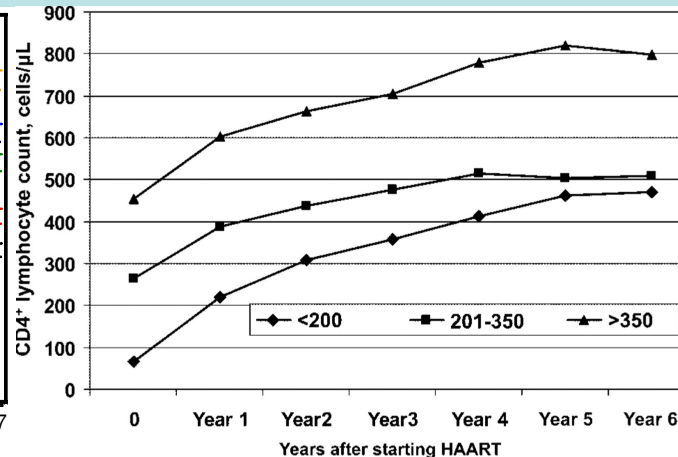
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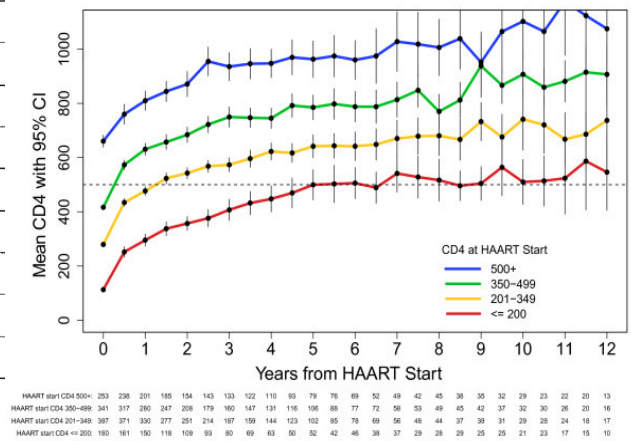
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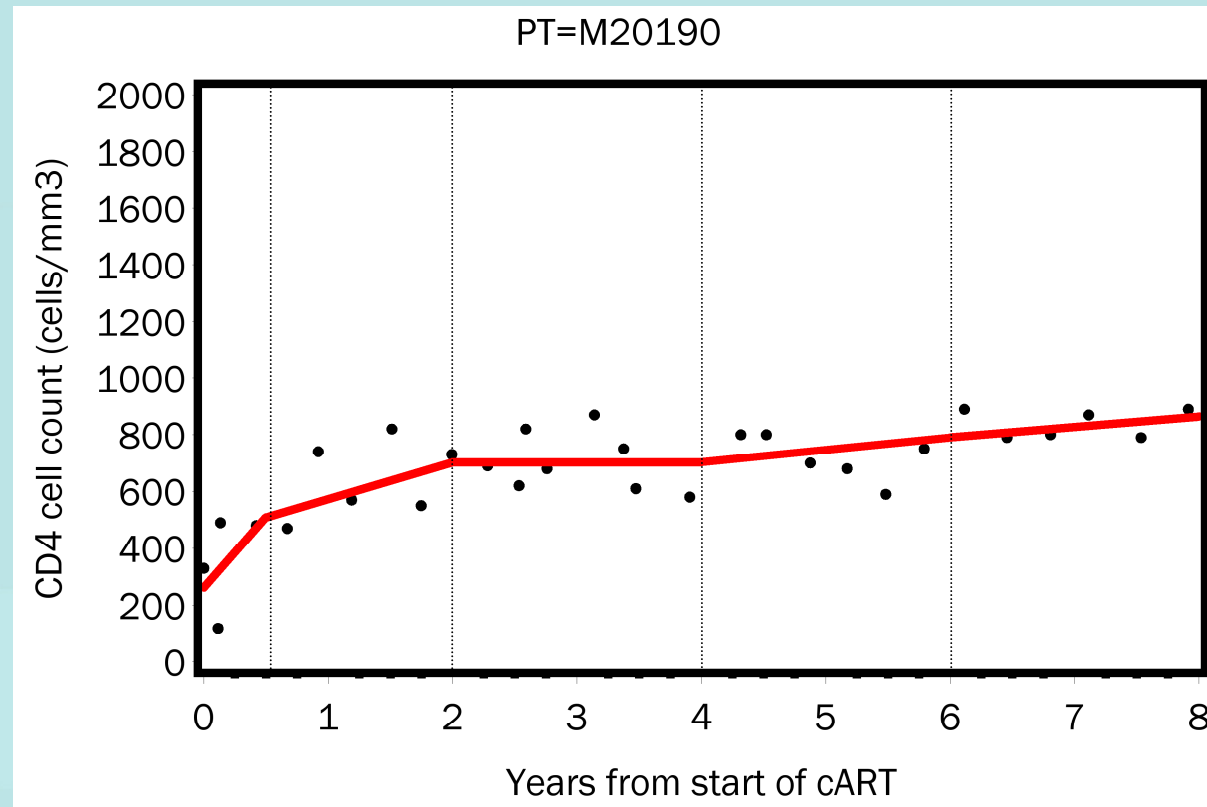
- Unclear whether a plateau is eventually reached or that CD4 cell counts keep increasing over time.
- In longitudinal studies mean increase / decrease is modeled. If there is a plateau approx. 50% of patients will have decreasing CD4 cell counts.
- Difficult to quantify the number of patients with decreasing CD4 cell counts from longitudinal CD4 plots.

# Background



- Objective:
  - Quantify the number of patients with episodes of decreasing CD4 cell counts during virological successful cART.
  - Identify risk factors for episodes with decreasing CD4 cell counts.

# Methods - decreasing CD4 cell count



- Follow-up divided into episodes: 0.5-2 2-4 4-6 and 6-8 yrs on virological successful cART.
- Slope determined using mixed effect modelling of CD4 cell count. Random intercept and slopes for each patient.
- Definition: Slope  $<0$  during each episode.

# Methods



Patients selected from the ATHENA cohort who were

- $\geq 16$  years of age at HIV diagnosis
- start cART in or after 2000
- ART-naive at start cART
- plasma HIV RNA  $< 50$  copies/ml within 9 months from start
- $\geq 2$  years virologically successfully cART treated

## Outcome

- Episodes of decreasing CD4 cell count during viral suppression.

CD4 cell counts at or after first of 2 consecutive pVL  $> 50$  copies/ml were censored.

# Methods – statistical analysis



- Episodes of decreasing CD4 cell count (yes/no) analysed using logistic regression models including a GEE correlation structure.
- Included variables:
  - Time on successful cART (0.5-2, 2-4, 4-6, 6-8 year),
  - gender, region of birth, transmission risk group, year of starting cART, CD4 cell count at the start of each period (<500, 500-800 and  $\geq 800$  cells/mm<sup>3</sup>), duration of known HIV infection, age at the start of cART.



# Results

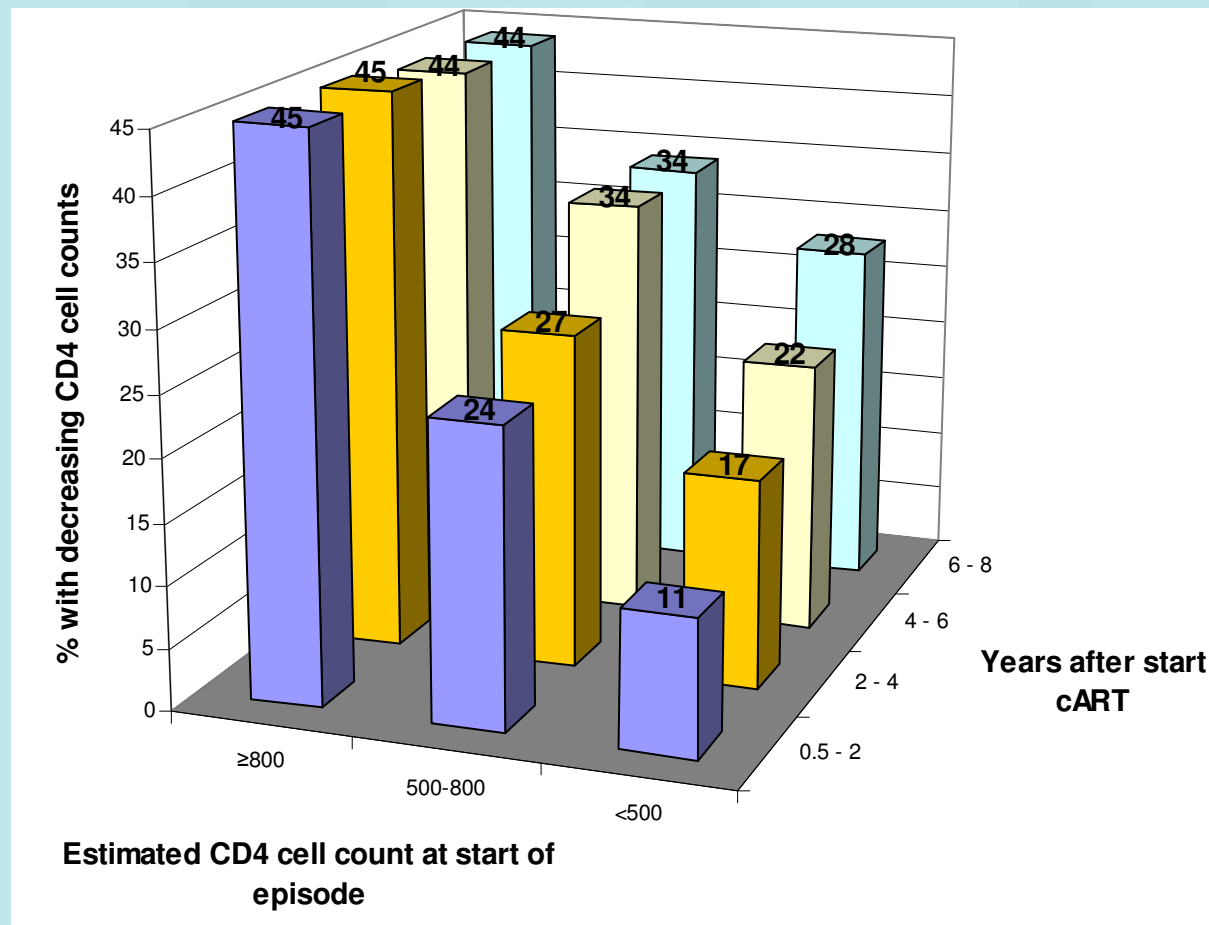


Characteristics at start cART		N	%
Total		3550	100
Gender	<i>Male</i>	2821	79
Risk group	<i>MSM</i>	1956	55
	<i>Heterosexual</i>	1194	34
	<i>Other</i>	400	11
Region of origin	<i>W-Europe/N-America</i>	2202	64
	<i>Sub Sahara Africa</i>	663	19
	<i>Caribbean/S-America</i>	405	11
		median	IQR
Age at start cART	<i>years</i>	39.4	33.2-46.1
CD4 cell count	<i>cells/mm<sup>3</sup></i>	190	80-270
HIV RNA	<i>log<sub>10</sub> copies/ml</i>	5.0	4.6-5.4
Known HIV infection	<i>years</i>	0.3	0.1-2.0

# Results



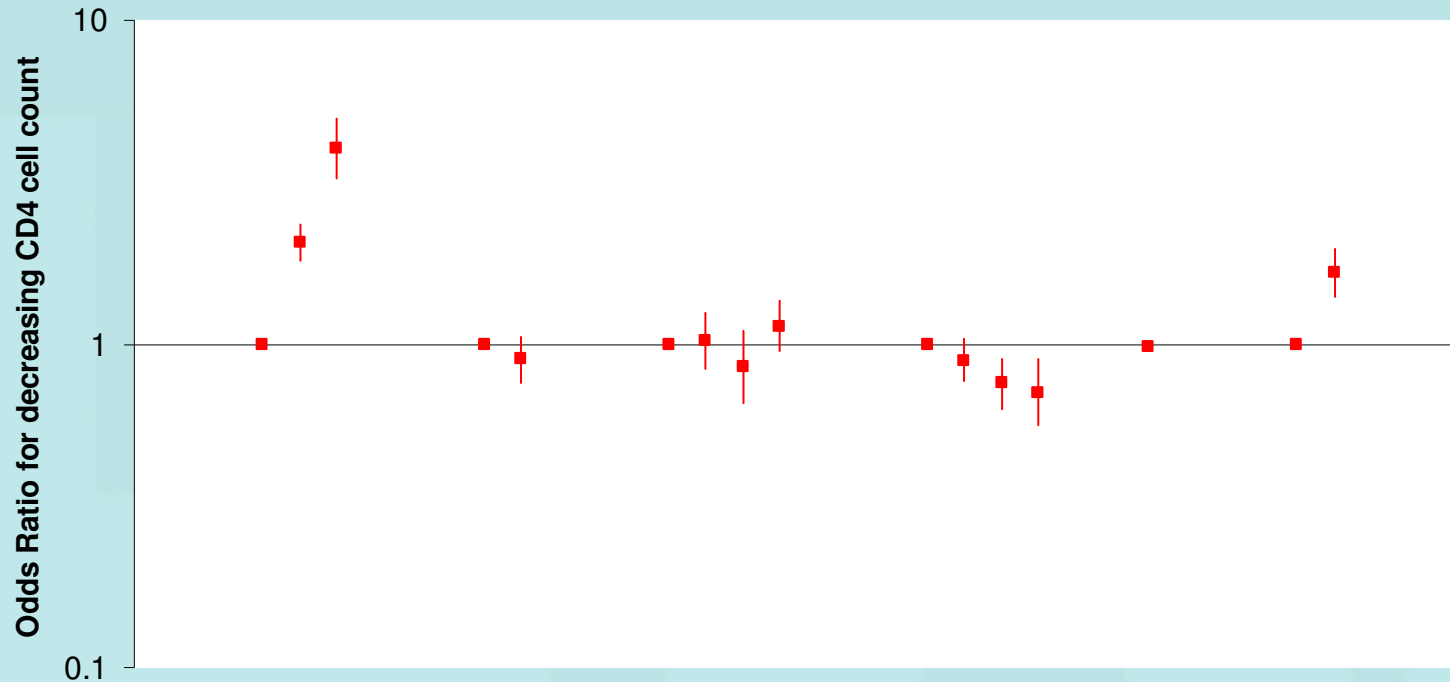
Decreasing CD4 cell counts by years on successful cART and CD4 cell count at start of each episode.



Out of 3550 patients, 1188 (33%) experienced at least 1 episode of decreasing CD4 cell count.

Median estimated decline in each episode between -43 and -54 cells/mm<sup>3</sup>

# Results **adjusted**



CD4 cell count at start episode

Region of birth

Year of start cART

Age

CD4 slope in previous period

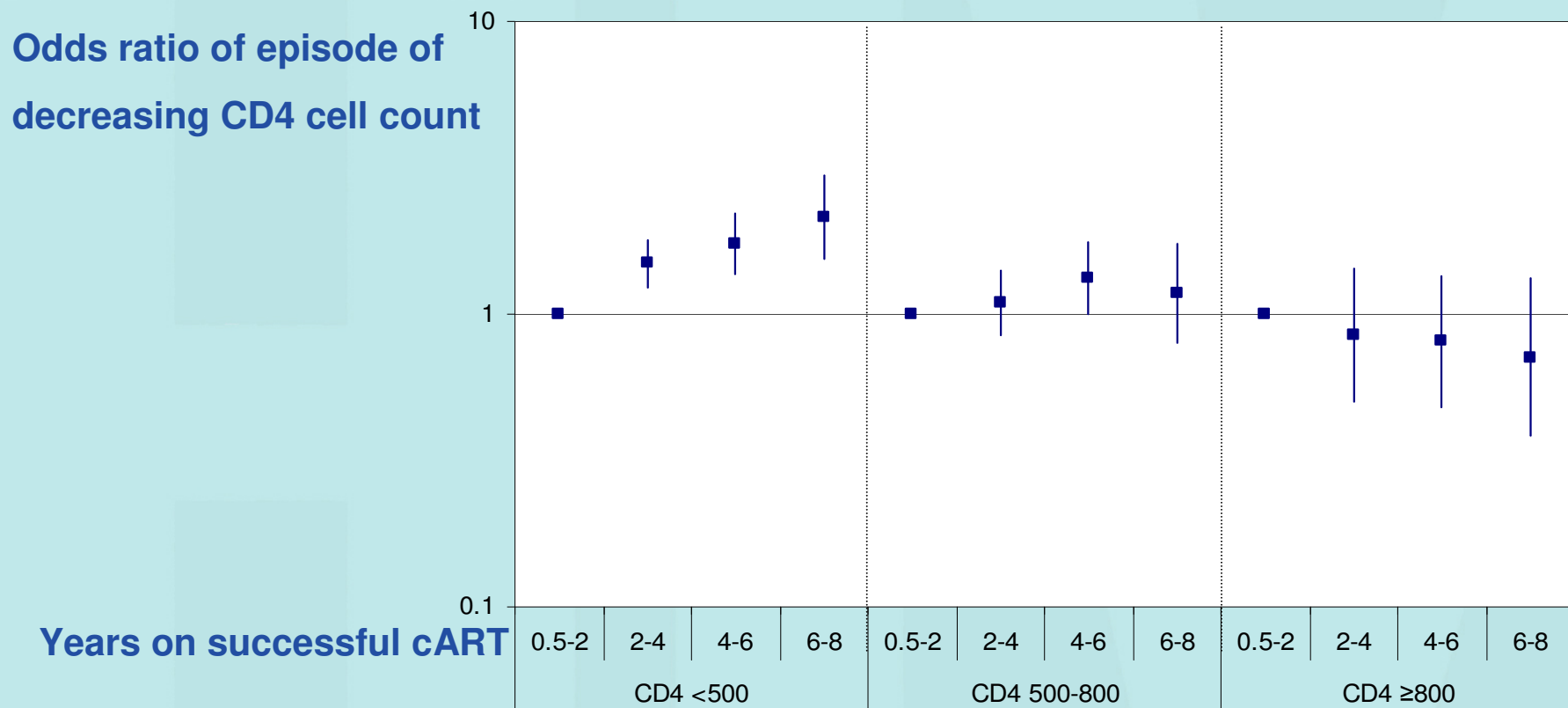
Pos

Neg

# Results



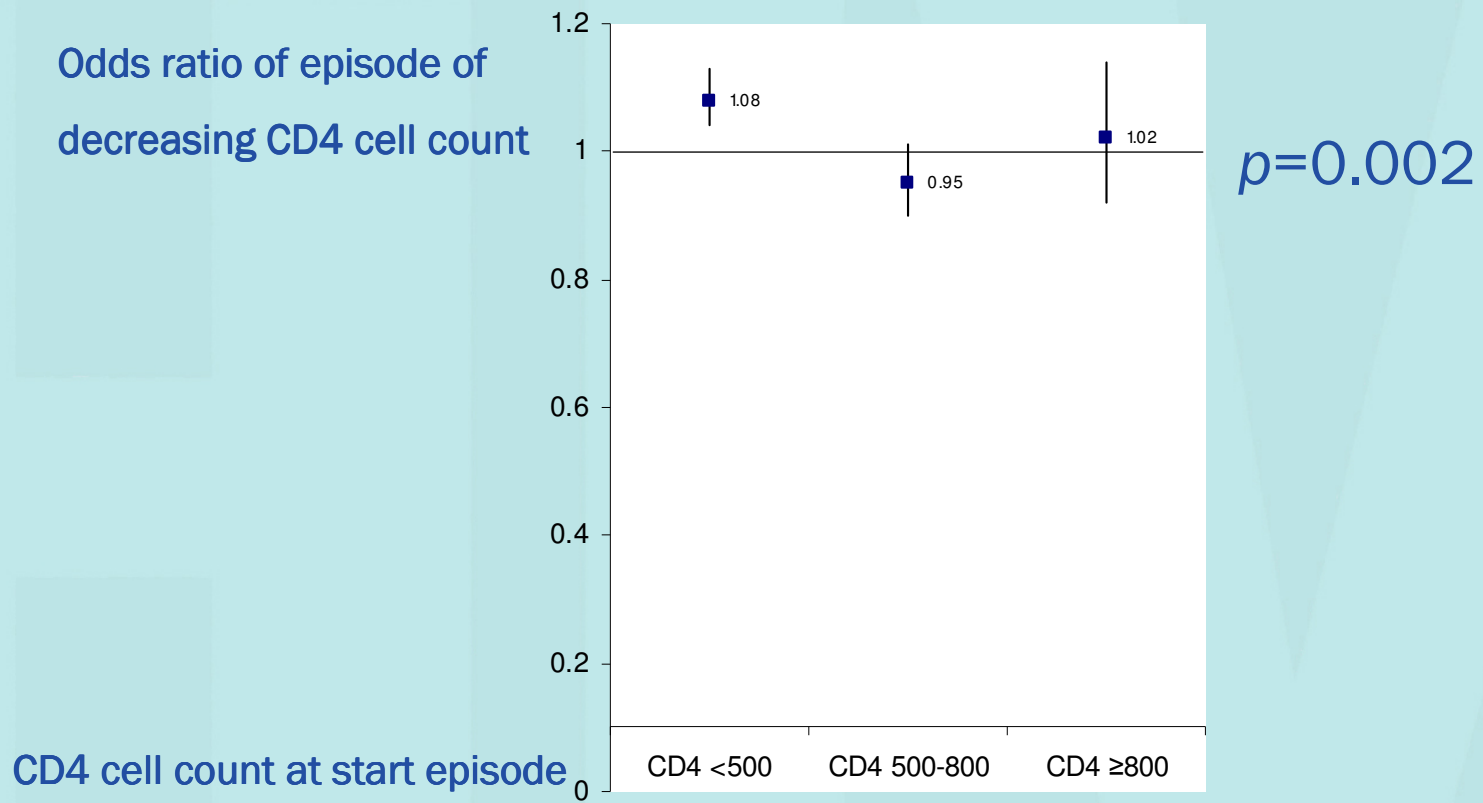
interaction CD4 cell count at start of episode and years on successful cART,  $p=0.007$



# Results



interaction CD4 cell count and years of known HIV infection (per 2 yr longer)



# Conclusion



- Episodes of decreasing CD4 cell counts were common among patients on virological successful cART,
  - Especially at high CD4 cell counts.
- Probability of episode of decreasing CD4 cell counts higher in earlier calendar years of starting cART.
- At  $<500$  CD4 cells/mm<sup>3</sup> increasing probability of episodes of decreasing CD4 cell counts
  - with longer time on successful cART
  - with longer duration of known HIV infection.



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