Association of CD4:CD8 ratio with non-AIDS morbidity in cART treated individuals

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IWHOD 2015, Catania, 27 March

HIV Monitoring

Background

- Low CD4:CD8 ratio in HIV-negative elderly has been associated with mortality.
- Low CD4:CD8 ratio in HIV-infection has been associated with risk of AIDS, non-AIDS mortality and morbidity, and lung cancer, when CD4 cell counts ≥350 or ≥500. Serrano-Villar PLOS Pathogens 2014, May CROI 2015, Sigel CROI 2015.
- CD4:CD8 ratio correlates with markers of immune senescence.
- CD4:CD8 slowly improves during virological successful cART; Reaching ≥1.0 may take very long. Pantazis, poster 105.

Goal: To investigate the independent association between the CD4:CD8 ratio and ***specific non-AIDS morbidity*** in HIV-1 infected individuals after starting cART.

HIV Monitoring

Methods

- HIV-1 infected individuals starting cART or on cART at baseline were selected from the ATHENA cohort.

- Baseline: date of the start of cART, June 2000 (start of routine data collection of non-AIDS morbidity endpoints), or the date CD4:CD8 ratios were first available, whichever came last.

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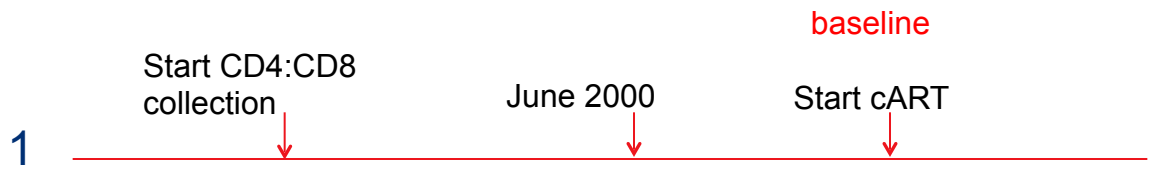

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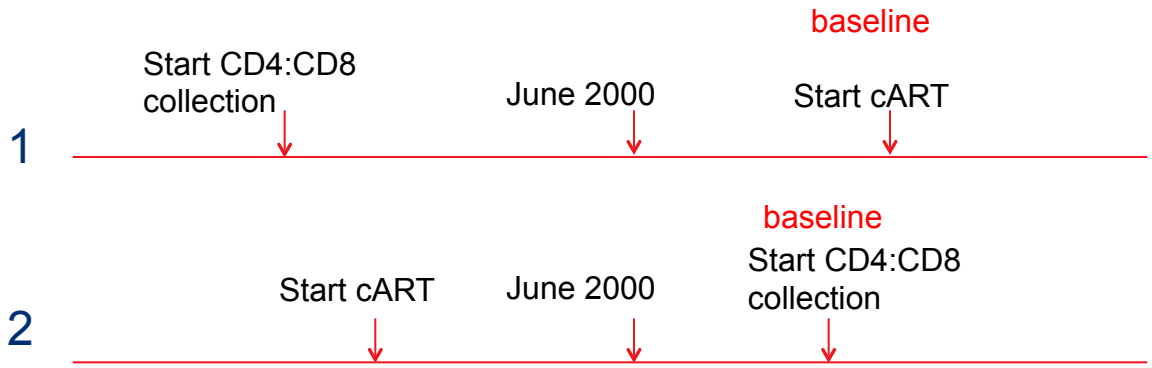

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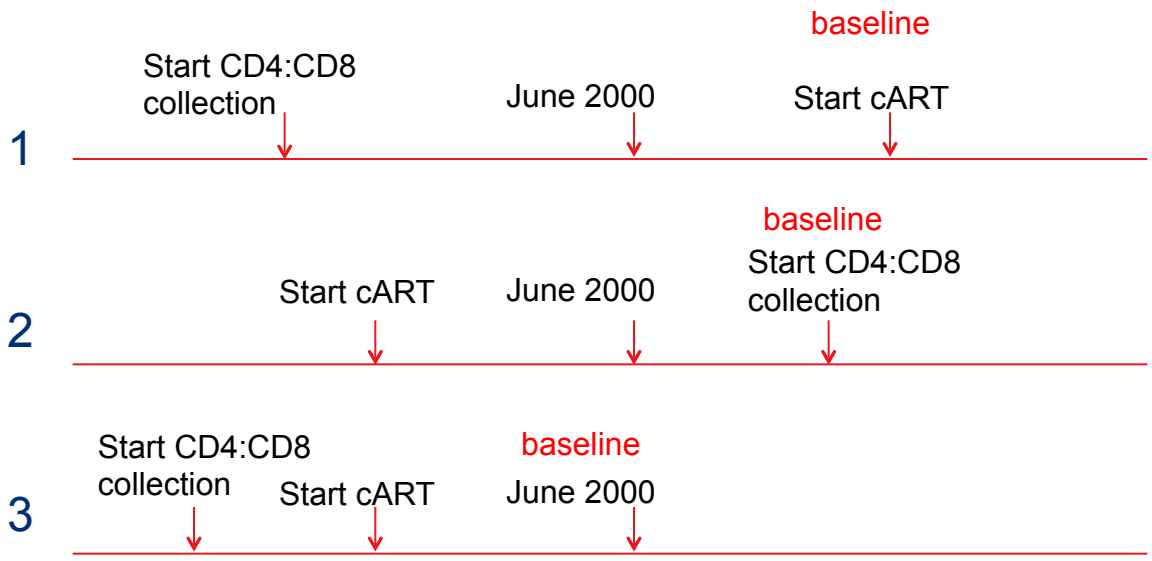

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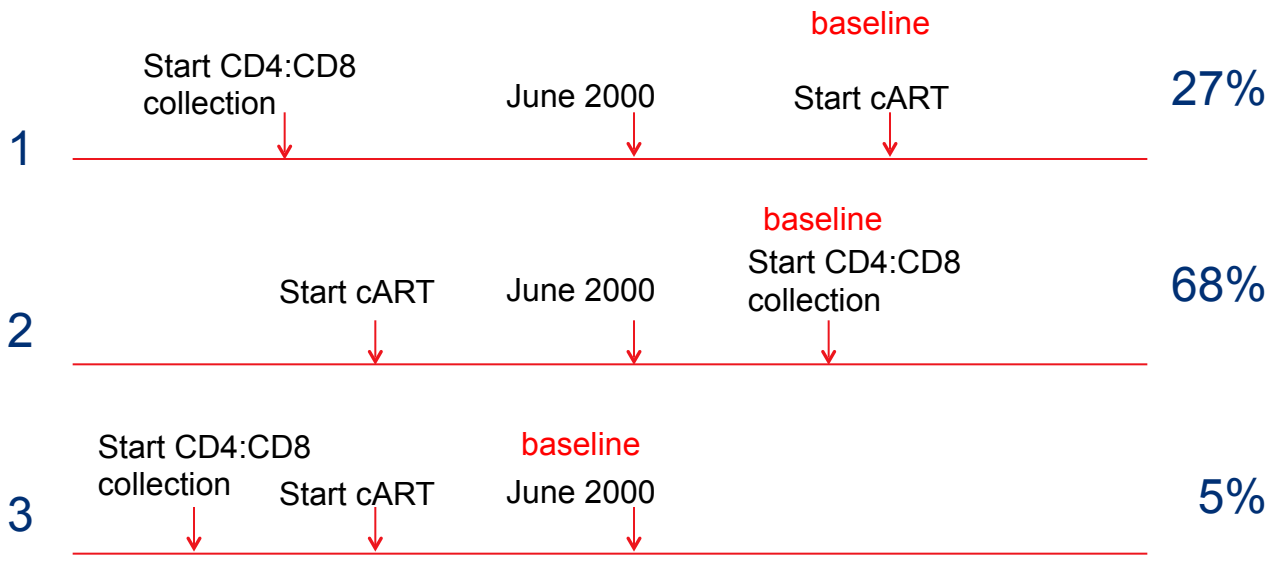


N=11,216

Methods

- Endpoints:
  1. non-AIDS malignancies (excl. precancerous stages of anal cancer, basal-cell carcinoma, and squamous-cell carcinoma of the skin; incl. Castleman's disease).*
  2. cardiovascular disease (myocardial infarction, stroke and coronary artery by-pass grafting, coronary angioplasty or stenting and carotid endarterectomy)*.
  3. diabetes mellitus*.
  4. combined endpoint (first of any of 1, 2 or 3).

- Patients with endpoints prior to baseline were excluded from that particular analysis.

* Using the criteria established by the D:A:D: Study

Methods

- Follow-up time after baseline divided into 3-monthly periods.

- For each endpoint 3 Poisson regression models were fitted:
  1. Only including latest available CD4:CD8 ratio***, lagged by 3 months*** (<0.3, 0.3-0.5, 0.5-1.0, and ≥1.0).

  2. Adjusted for: time updated CD4 cell count, gender, region of birth, HIV-1 transmission risk group, time-updated age, known time spent with <200 CD4 cells/mm^3, known time spent with HIV RNA >1000 copies/ml, last available viral load, time updated AIDS, hypertension, HBV and HCV co-infection, smoking and time-updated cumulative exposure to various antiretroviral drugs and drug classes (depending on the endpoint).

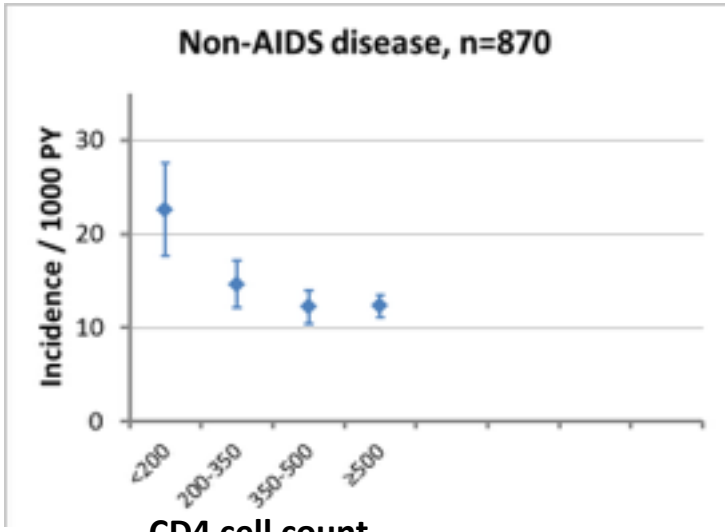
  3. As under 2, but also interaction between CD4:CD8 ratio and CD4 cell count.

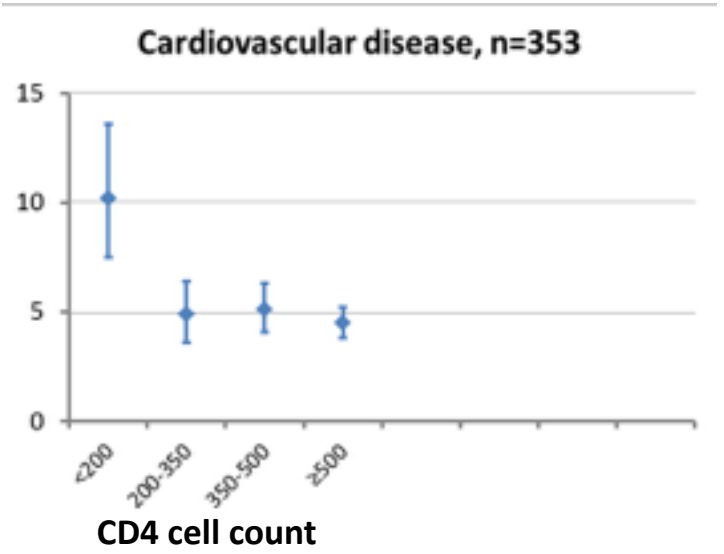
Characteristics at baseline, n=11,216

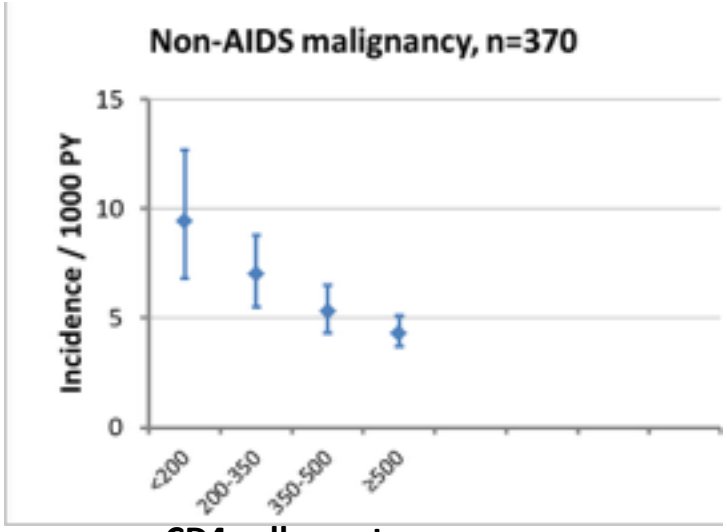
Therapy naïve when cART was started, %		87.8
Age, years, median (IQR)		40.8 (34.3-47.8)
Gender, %	Male	82.3
Region of origin, %	W-Europe/N-America	65.9
	Sub Sahara Africa	14.0
Risk group, %	MSM	62.8
	Heterosexual	29.1
HCV +*, %		3.7
HBV +** , %		5.6
CD4 cell count, cells/mm^3, median (IQR)		390 (260-550)
CD8 cell count, cells/mm^3, median (IQR)		990 (700-1370)
CD4:CD8 ratio, median (IQR)		0.40 (0.24-0.60)
Year of starting ART, median (IQR)		2005 (1999-2010)
pVL, % <400 among those >1yr after start cART		86.9
Current smoker, %		38.6

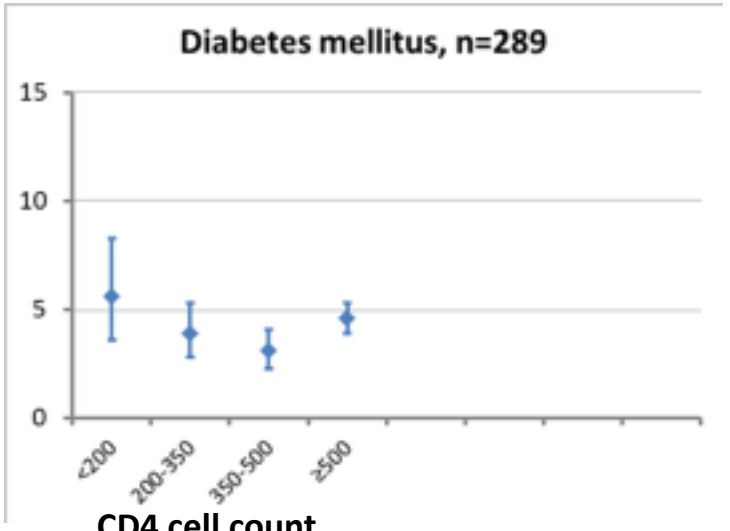
* HCV: positive HCV RNA, if not available positive Ab; ** HBV: positive hepatitis B surface antigen,

Crude incidence of non-AIDS morbidity by CD4 cell count

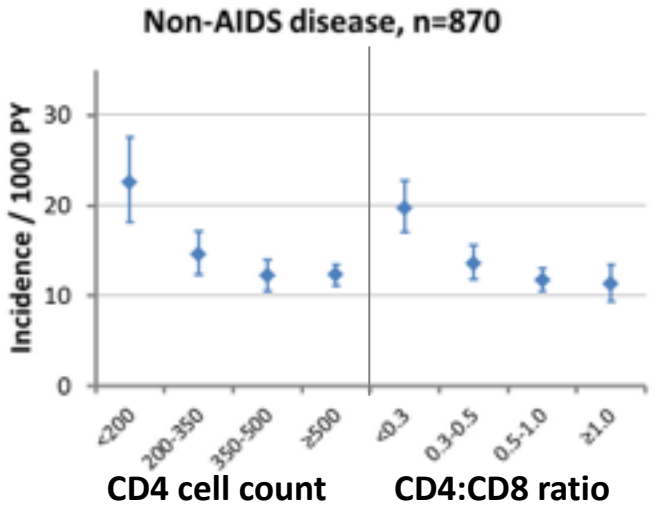


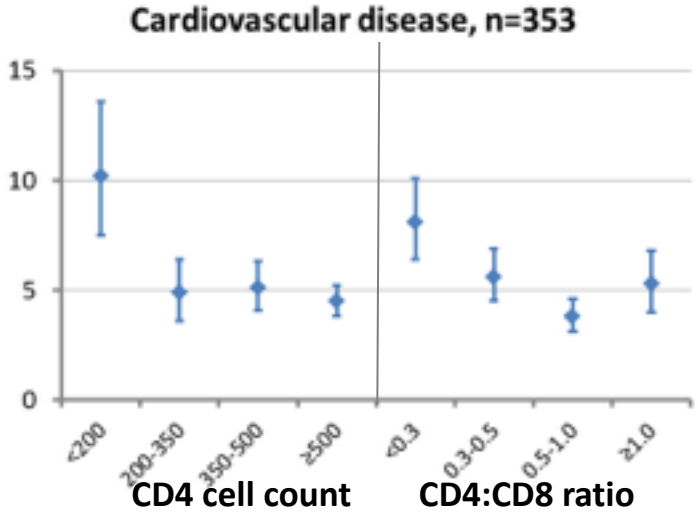


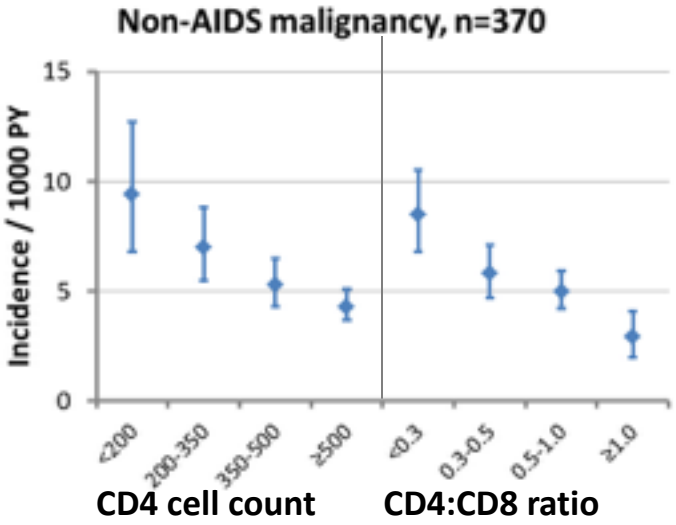


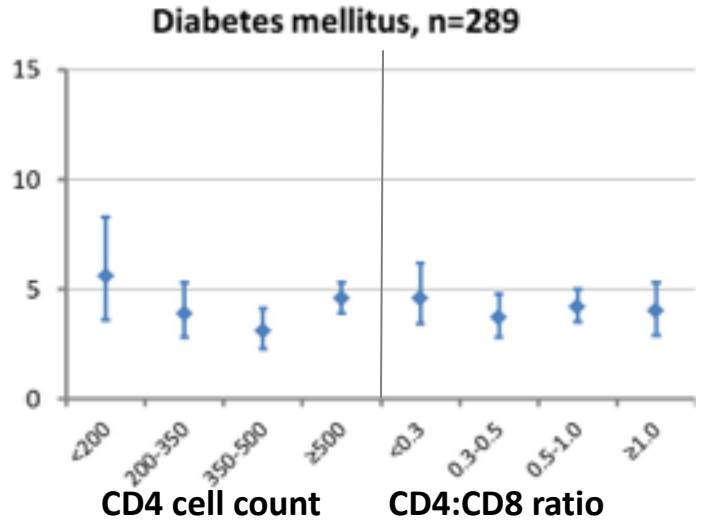


Crude incidence of non-AIDS morbidity by CD4 cell count and CD4:CD8 ratio



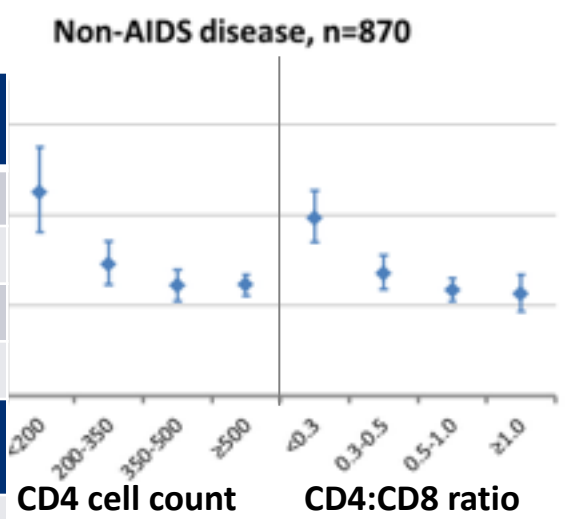


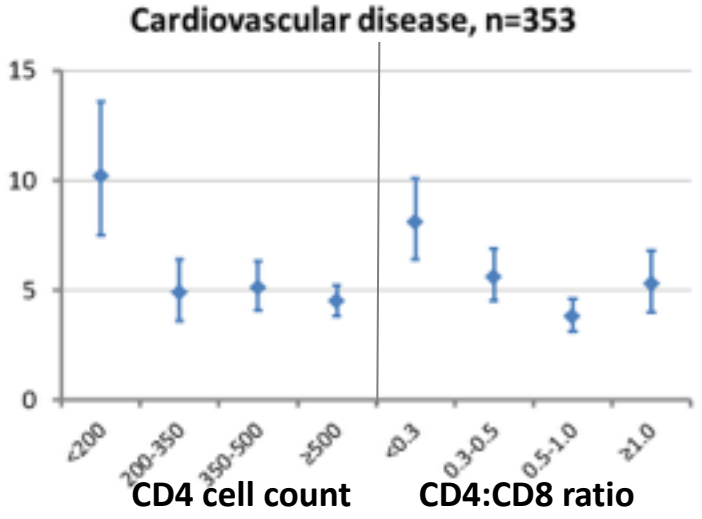


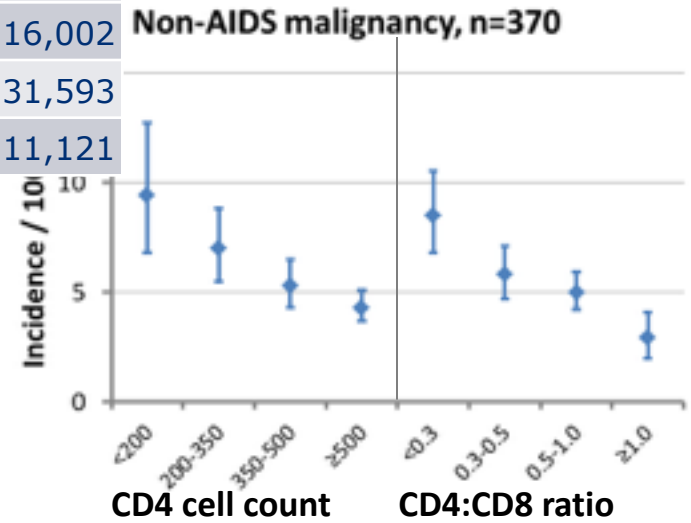


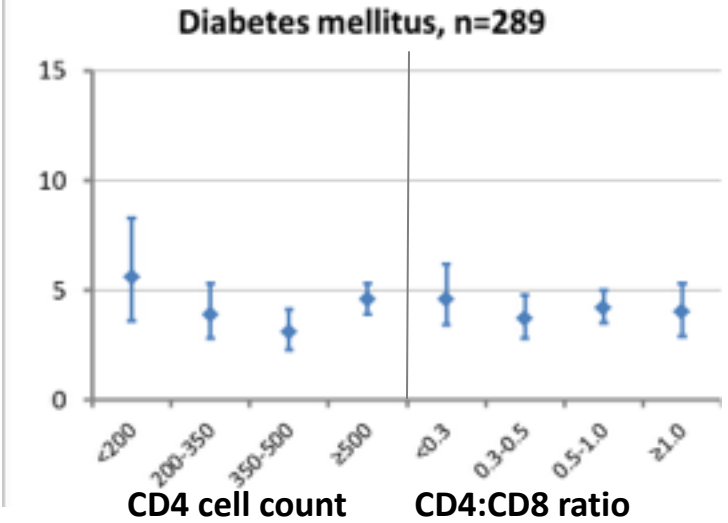
Crude incidence of non-AIDS morbidity by CD4 cell count and CD4:CD8 ratio

CD4 cell count	PY follow-up
<200	4,453
200-350	10,533
350-500	16,288
≥500	36,452
CD4:CD8 ratio	
<0.3	9,763
0.3-0.5	16,002
0.5-1.0	31,593
≥1	11,121

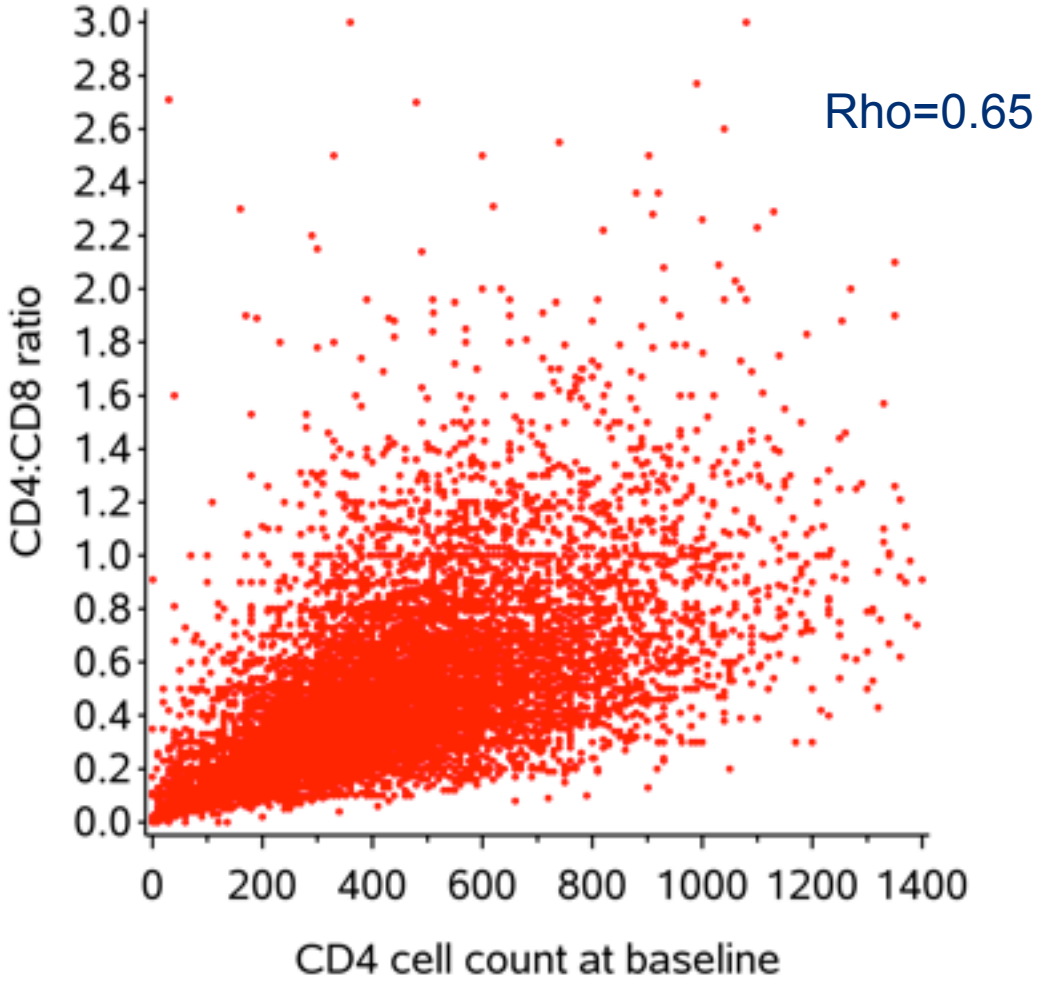






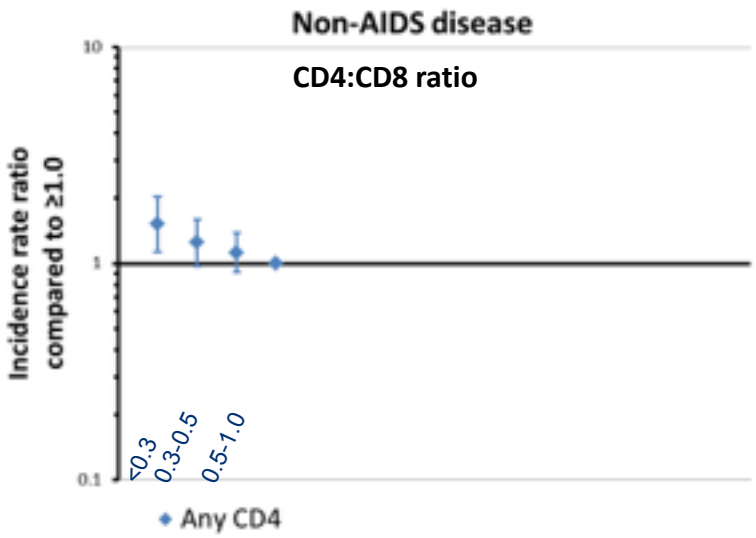


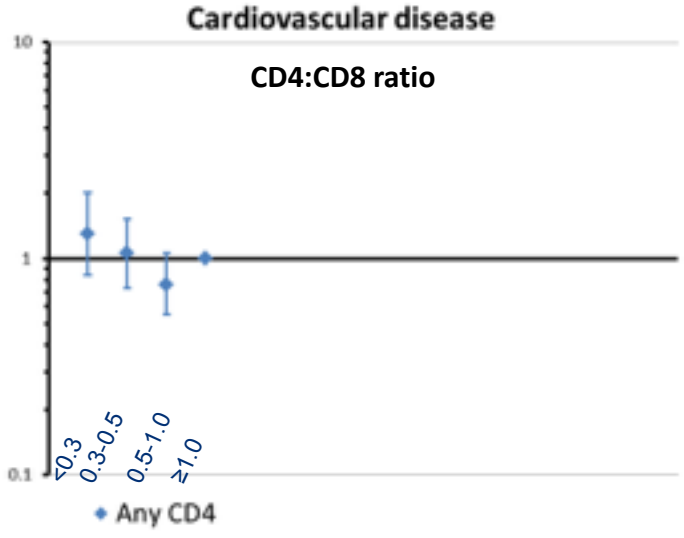
Correlation between CD4 cell count and CD4:CD8 ratio at baseline

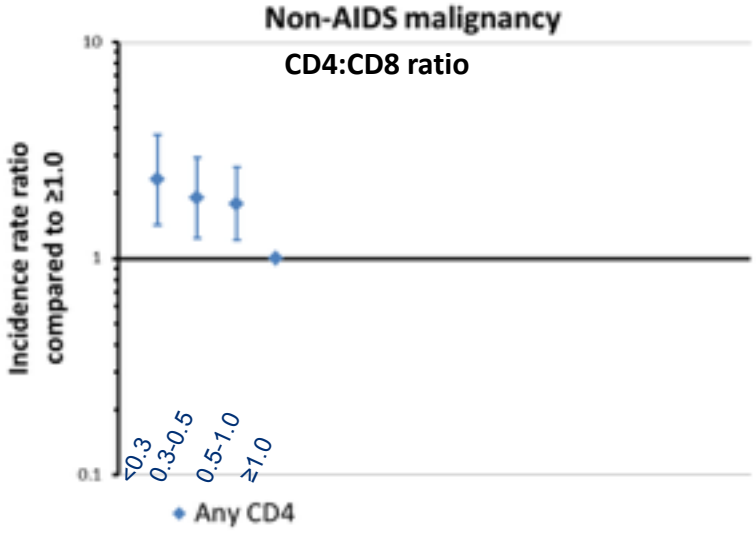


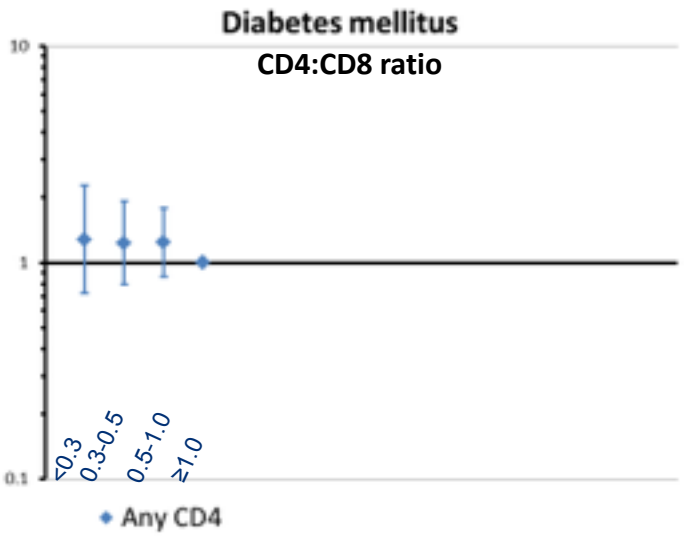
Poster 106 Adam Trickey

Association of time-updated CD4:CD8 ratio with non-AIDS diseases, adjusted for CD4 cell count and other risk factors









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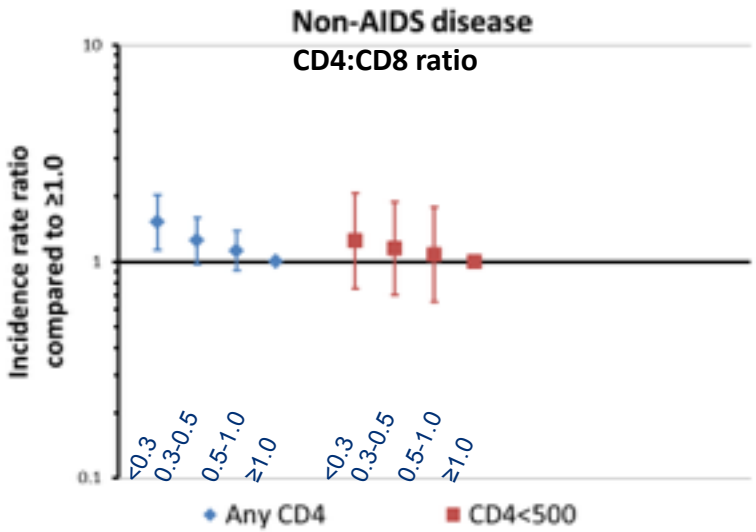

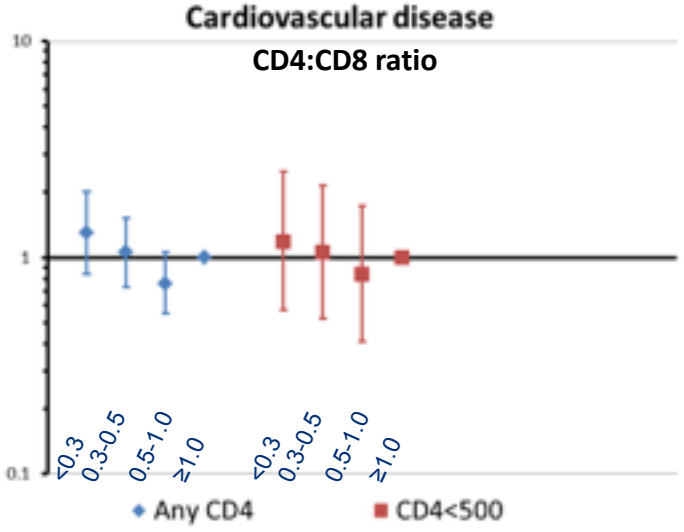

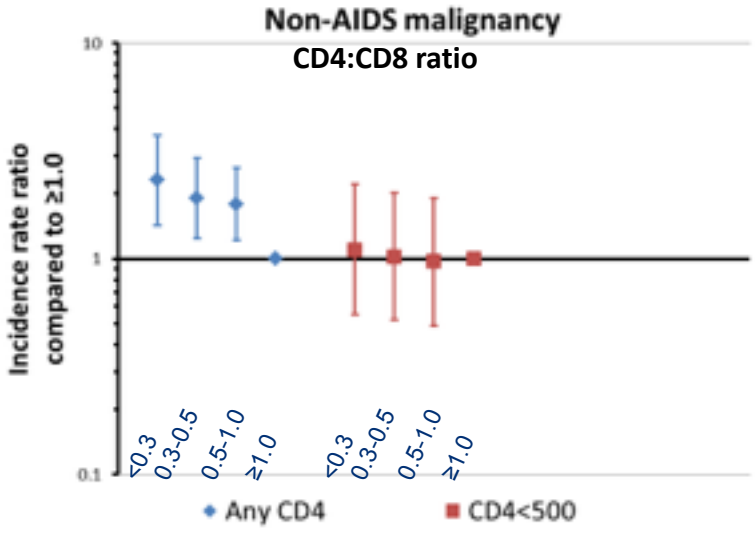

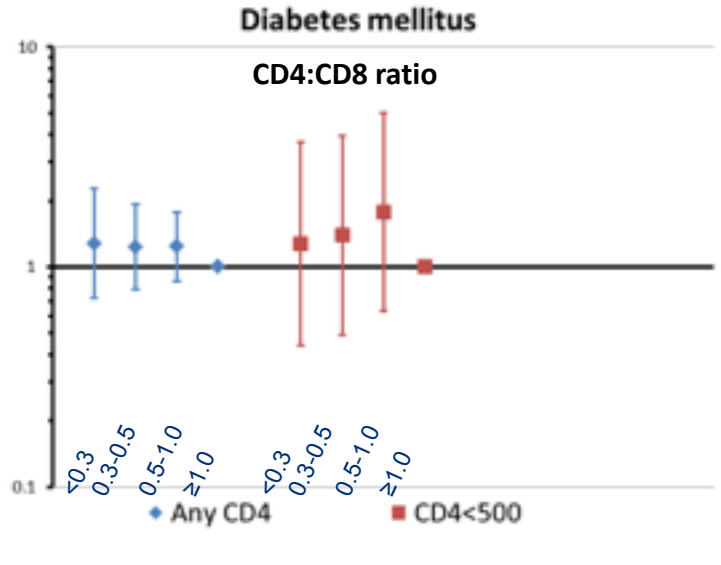

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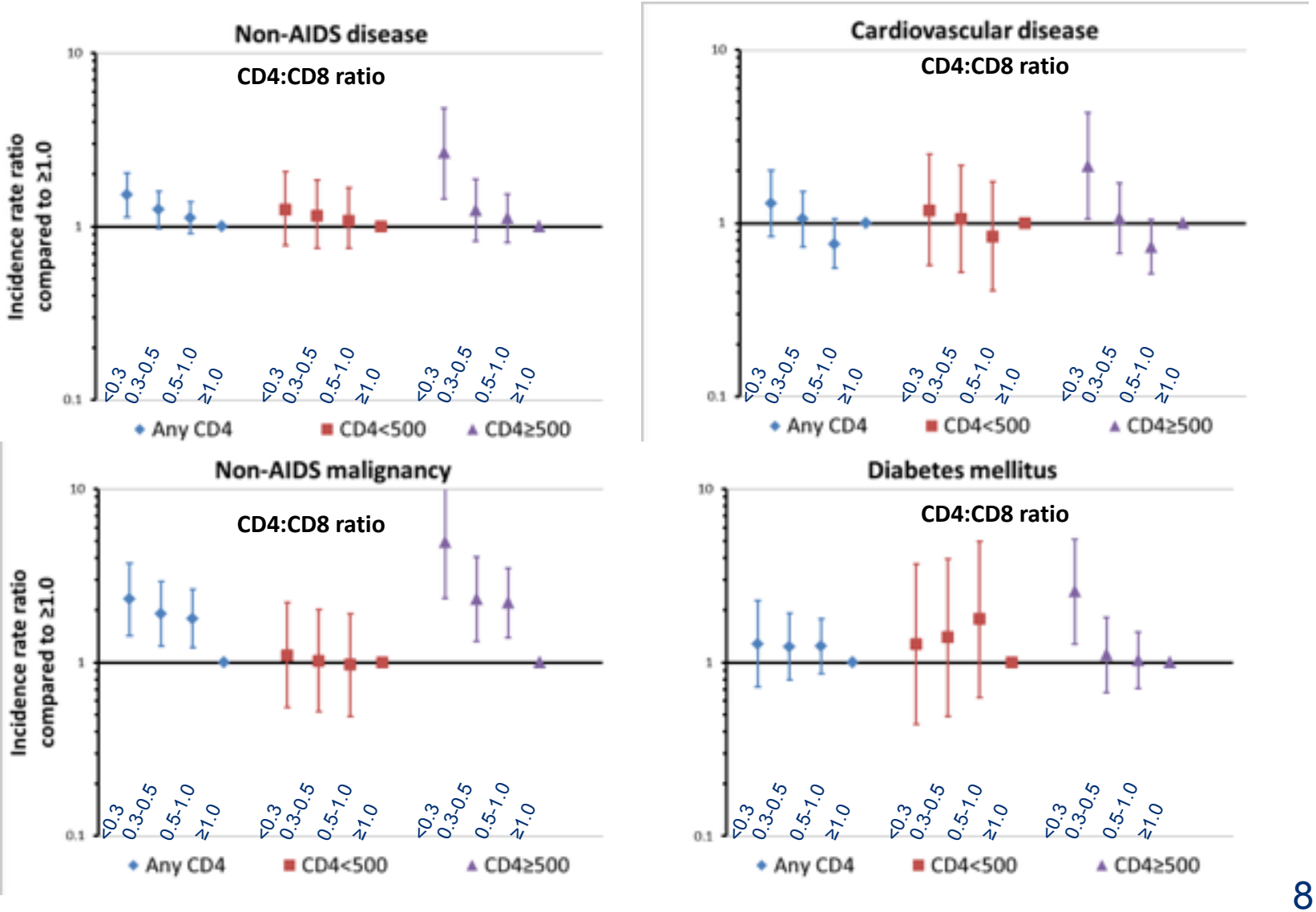
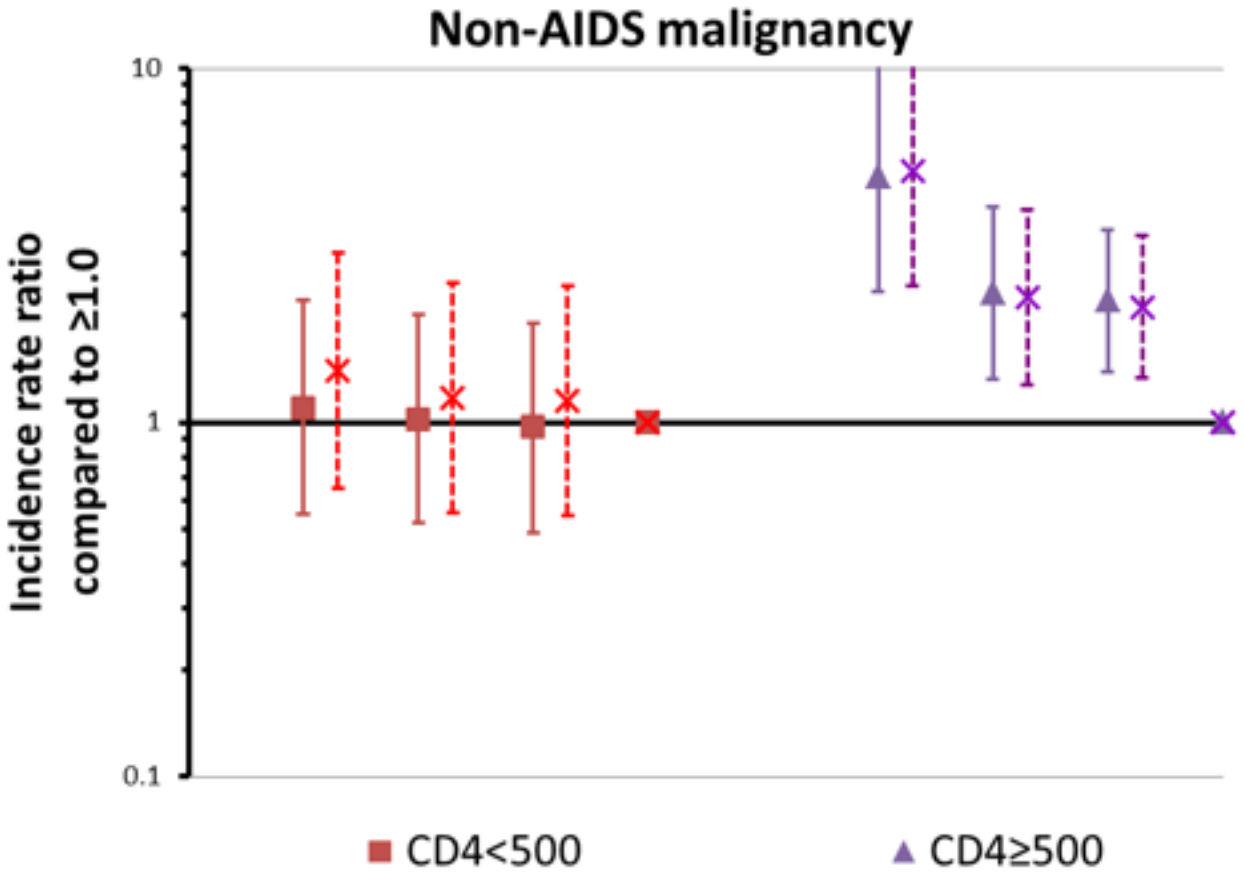
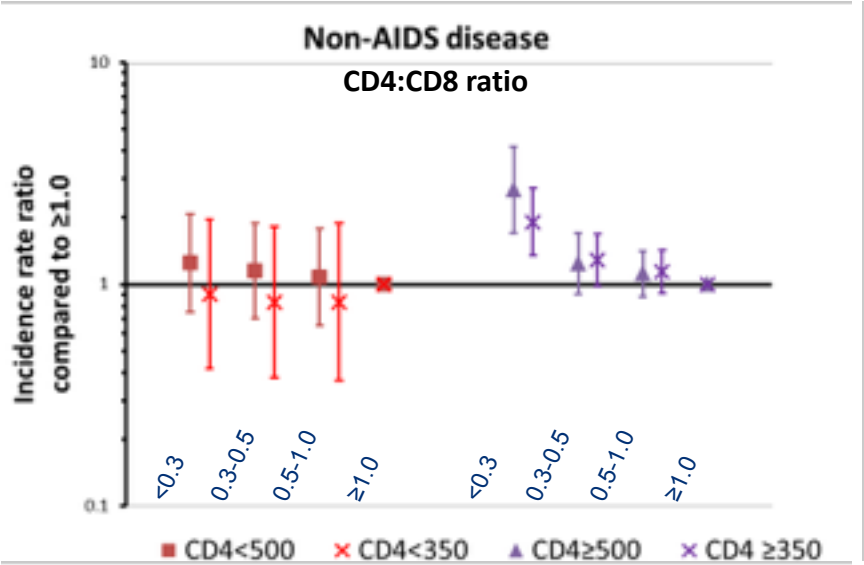


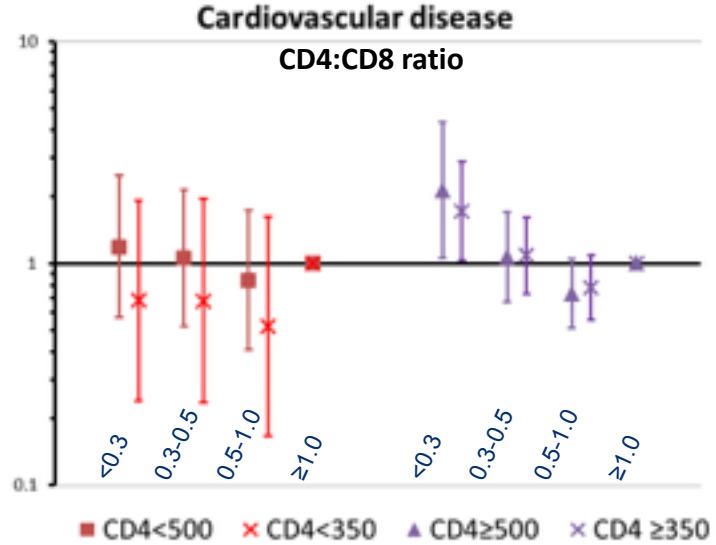
Sensitivity analysis
Excluding 18 liver related malignancies

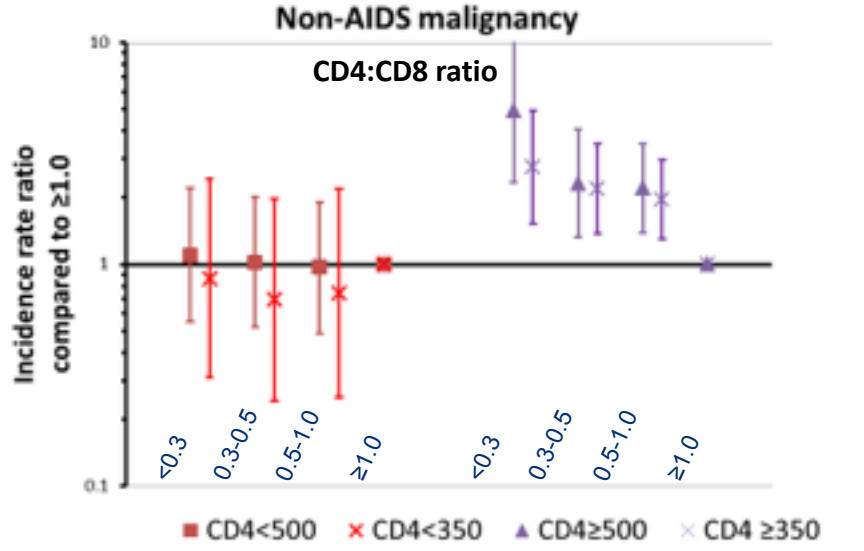


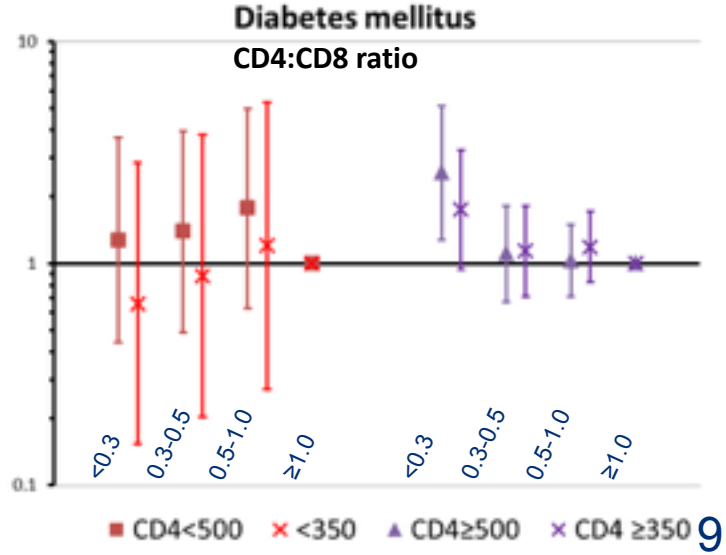
Sensitivity analysis

CD4 cell count cutoff of 350 (instead of 500 cells/mm³)

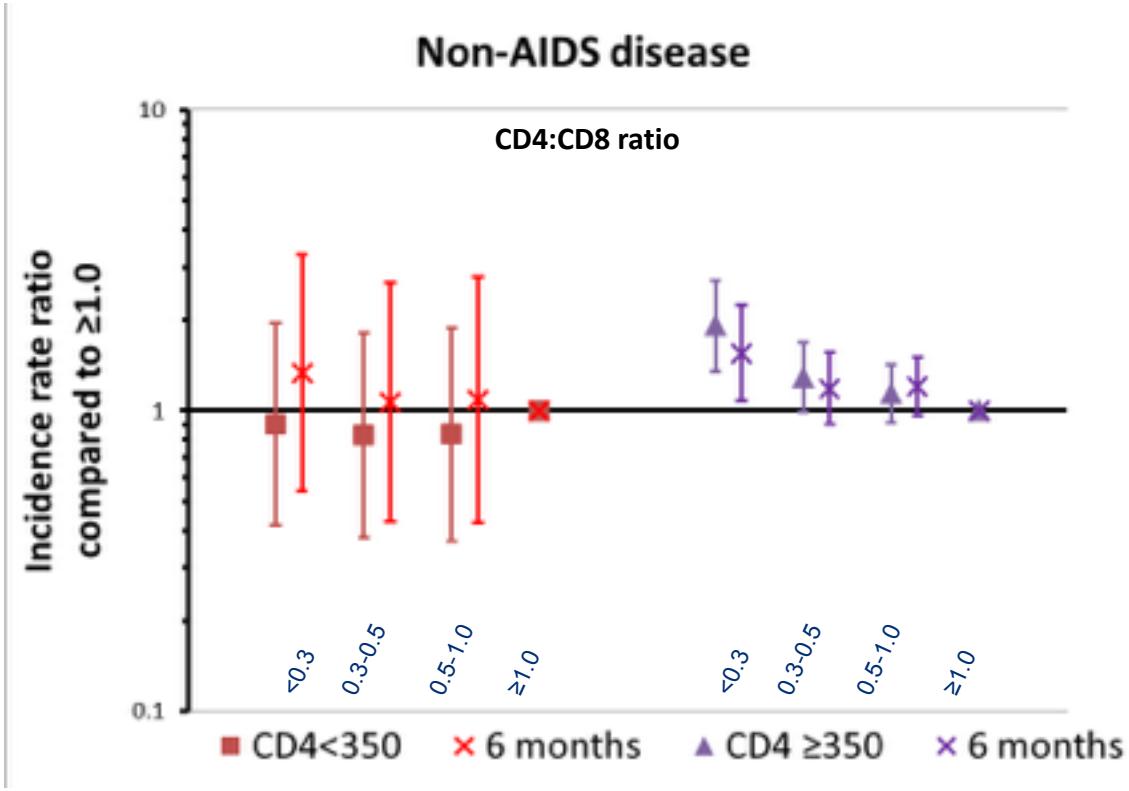








Sensitivity analysis
Time updated variables lagged 6 months (instead of 3)



Limitations

- Association ≠ causality
- Wide confidence intervals; results need validation in a larger cohort

Conclusion

- Having a CD4:CD8 ratio <0.3 whilst having ≥500 CD4 cells/mm^3 was associated with a significantly increased risk of cardiovascular disease, non-AIDS malignancies and diabetes mellitus when compared to having a ratio ≥1.0.

- The CD4:CD8 ratio may be useful in identifying a subset of patients with adequate CD4 responses on treatment who may benefit most from novel anti-inflammatory/immune-based interventions aimed at further reducing the risk of these morbidities.

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Future work:

- Associations in virological suppressed patients?
- At which CD4 cell count and CD4:CD8 ratio thresholds does the risk of non-AIDS morbidity increase?

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