



# Associations between Markers of Immunosuppression and the Risk of Cardiovascular Disease (CVD): the D:A:D Study

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## BACKGROUND

The evidence for a potential role of immune suppression in the development of cardiovascular disease (CVD) is conflicting. Whilst some studies have reported a higher risk of CVD in those with a low CD4 count<sup>1,2</sup>, others have not<sup>3</sup>. Whilst such an association, if present, could suggest an inflammatory effect of untreated HIV infection, it may also reflect bias resulting from increased monitoring frequency in those with low CD4 counts or residual confounding.

## AIM OF THE STUDY

We considered associations between the latest and nadir CD4 count, and time spent with a CD4 count <200 cells/mm<sup>3</sup> ('duration of immunosuppression'), and the following centrally validated outcomes:

- I. Myocardial infarction (MI)
- II. Coronary heart disease (CHD): MI, sudden cardiac death or invasive coronary procedure
- III. Stroke
- IV. CVD: first CHD or stroke event

## METHODS

- The D:A:D Study is an observational study of >49,000 HIV-positive patients from 11 cohorts from Europe, Australia, and the United States. The primary study aim is to investigate associations between use of antiretroviral drugs and risk of CVD and other major disease events.
- Data are collected prospectively during routine clinic visits; the standardised dataset includes information on socio-demographic factors, AIDS events and deaths, known risk factors for CVD, laboratory markers for monitoring HIV (including CD4 count and HIV RNA) and CVD, antiretroviral treatment and treatments that influence CVD risk.
- All incident cases of MI and stroke are reported to the study co-ordinating centre for validation and coding using criteria applied in the WHO MONICA Study<sup>4</sup>; reported MIs are classified as definite, possible, or unclassifiable, strokes are classified as definitive or possible.

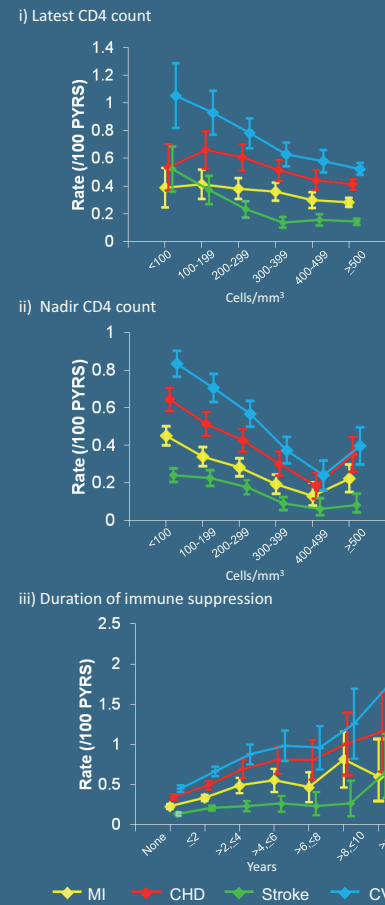
## STATISTICAL METHODS

- Individuals recruited to cohorts I and II of the D:A:D Study (n=33,301) were followed from study entry to the earliest of an endpoint, death, 1<sup>st</sup> February 2010 or 6 months after the last clinic visit.
- Analyses were performed using Poisson regression with the latest CD4, nadir CD4 and duration of immune suppression as time-updated covariates
- Multivariable models included adjustment for potential confounders: sex, age, previous CVD, body mass index, smoking status (all events), hypertension (stroke event only), cohort, HIV exposure, ethnicity, family history of CVD, calendar year, cumulative/recent exposure to antiretrovirals (MI, CHD, CVD events)
- As ongoing cytomegalovirus (CMV) infection has been reported to be associated with an increased risk of CVD in the general population<sup>5</sup>, analyses investigated a possible modifying effect of CMV disease, as a surrogate for CMV infection, on the reported associations with immune suppression; to investigate whether any association with CMV may be explained by bias due to increased monitoring frequency in those with an opportunistic infection, sensitivity analyses also considered the potential modifying effect of an other, non-CMV, AIDS-defining opportunistic infection.

**Table 1:** Number of events, event rate and 95% confidence interval

Event	No. events	Person-years	Event rate (/100 PYRS)	95% CI
MI	716	223,242	0.321	0.297, 0.344
CHD	1056	222,290	0.475	0.446, 0.504
Stroke	407	224,224	0.182	0.164, 0.199
CVD	1374	221,203	0.621	0.588, 0.654

**Figure 1:** Incidence of each endpoint (with 95% CI) stratified by (i) latest CD4 count, (ii) nadir CD4 count, or (iii) duration of immunosuppression



## RESULTS

- Over the study period, the individuals in the D:A:D Study experienced 716 MI, 1056 CHD, 407 stroke and 1374 CVD events (Table 1).
- In unadjusted analyses, individuals with latest or nadir CD4 counts <350 cells/mm<sup>3</sup> tended to experience higher rates of all four endpoints (Figure 1(i) and (ii)). After controlling for potential covariates, however, there was no strong evidence that this higher risk remained (Table 2). Stroke and CVD rates did, however, remain substantially higher in those with a latest CD4 <100 cells/mm<sup>3</sup>.
- All events occurred less frequently in individuals who had never experienced immune suppression, although evidence for a strong linear association between each event and duration of immune suppression was weak (Figure 1(iii), Table 2).
- The latest CD4 count was independently associated with both stroke (relative rate: 0.79 [0.72, 0.88])/2-fold higher, p=0.0001) and CVD (0.90 [0.84, 0.95])/2-fold higher, p=0.0001) after adjustment for the nadir count and duration of immune suppression, neither of which remained associated with either event in adjusted models.
- Additional adjustment for prior CMV disease, which was significantly associated with CVD risk but not stroke did not modify the associations between the latest CD4 count and risk of either event (Table 3). A previous non-CMV, AIDS-defining opportunistic infection was associated with an increased risk of both events although, as with CMV, adjustment for these infections did not modify the reported associations with the latest CD4 count.

## CONCLUSIONS

- Whilst no associations were seen between the measures of immunosuppression and MI or CHD, the latest CD4 count was associated with stroke and CVD. Thus, stroke appears to be the event that is driving the association with immune suppression and comparisons of results from studies that utilise different cardio- or cerebrovascular endpoints should be made with caution.
- Of note, whilst MI and stroke risk is determined by the underlying risk of the individual, the decision to undergo an invasive cardiovascular procedure is largely clinician-dependent and may be affected by knowledge of an individual's HIV and treatment status.
- The association between CMV infection and MI risk, reported in the general population, does not, in this study, at least appear to be specific for CMV. Thus in our setting, the identification of patients with opportunistic infections may simply identify a group of individuals with advanced immune suppression that cannot be captured by our current CD4 count markers. Of note, the D:A:D Study does not capture information on CMV serostatus, only CMV disease; analyses of CMV serostatus may reach different conclusions.
- Further research is needed to establish whether these associations are causal in those with HIV or reflect bias/unmeasured confounding.

## REFERENCES

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**Table 2:** Relative rates (95% CI) for progression to each endpoint

	MI	CHD	Stroke	CVD
<b>Latest CD4 count</b>				
<100	1.07 [0.71, 1.64]	0.96 [0.68, 1.37]	2.39 [1.58, 3.61]	1.44 [1.11, 1.88]
100-199	0.98 [0.71, 1.36]	1.00 [0.78, 1.30]	1.48 [1.02, 2.15]	1.09 [0.87, 1.36]
200-299	Ref.	Ref.	Ref.	Ref.
300-399	1.03 [0.79, 1.34]	0.91 [0.73, 1.13]	0.64 [0.44, 0.94]	0.86 [0.71, 1.04]
400-499	0.88 [0.66, 1.16]	0.80 [0.64, 1.01]	0.79 [0.55, 1.14]	0.82 [0.67, 1.00]
≥500	0.90 [0.71, 1.14]	0.83 [0.68, 1.00]	0.82 [0.60, 1.11]	0.83 [0.70, 0.98]
/doubling	0.95 [0.89, 1.02]	0.95 [0.89, 1.00]	0.80 [0.74, 0.86]	0.88 [0.84, 0.93]
<b>Nadir CD4 count</b>				
<100	1.15 [0.93, 1.43]	1.13 [0.94, 1.34]	1.09 [0.82, 1.43]	1.11 [0.95, 1.29]
100-199	0.96 [0.76, 1.21]	0.96 [0.80, 1.16]	1.07 [0.81, 1.43]	1.00 [0.85, 1.18]
200-299	Ref.	Ref.	Ref.	Ref.
300-399	0.79 [0.57, 1.09]	0.81 [0.63, 1.05]	0.56 [0.36, 0.88]	0.74 [0.58, 0.92]
400-499	0.62 [0.38, 1.01]	0.61 [0.41, 0.92]	0.42 [0.21, 0.85]	0.56 [0.39, 0.80]
≥500	1.11 [0.75, 1.63]	1.20 [0.88, 1.64]	0.61 [0.33, 1.11]	0.98 [0.73, 1.30]
/50 cells/mm <sup>3</sup>	0.97 [0.95, 1.00]	0.98 [0.96, 1.00]	0.94 [0.90, 0.98]	0.97 [0.95, 0.99]
<b>Duration of immune suppression</b>				
None	Ref.	Ref.	Ref.	Ref.
≤2	1.09 [0.91, 1.31]	1.06 [0.91, 1.24]	1.20 [0.95, 1.53]	1.12 [0.98, 1.28]
>2, ≤4	1.33 [1.04, 1.70]	1.29 [1.05, 1.58]	1.24 [0.88, 1.74]	1.28 [1.07, 1.54]
>4, ≤6	1.33 [0.98, 1.81]	1.34 [1.04, 1.73]	1.25 [0.81, 1.92]	1.27 [1.01, 1.60]
>6, ≤8	0.86 [0.54, 1.35]	1.04 [0.74, 1.48]	1.03 [0.56, 1.90]	1.00 [0.73, 1.37]
>8, ≤10	1.61 [1.01, 2.57]	1.27 [0.84, 1.93]	1.11 [0.51, 2.44]	1.28 [0.88, 1.87]
>10	1.13 [0.61, 2.13]	1.38 [0.87, 2.19]	2.55 [1.35, 4.83]	1.64 [1.12, 2.41]
/year	1.02 [0.99, 1.05]	1.03 [1.00, 1.05]	1.03 [1.00, 1.06]	1.02 [1.01, 1.04]

**Table 3:** Additional impact of adjusting for CMV disease and other AIDS-defining opportunistic infections

Endpoint	Not adjusted for CMV or other OI		Model including CMV		Model including other OI	
	Covariate	RR [95% CI]	P	RR [95% CI]	P	RR [95% CI]
<b>CVD</b>						
Prior CMV/OI*	n/a		1.47 [1.13, 1.92]	0.005	1.21 [1.07, 1.37]	0.003
Latest CD4 count (per doubling)	0.90 [0.84, 0.95]	0.0001	0.89 [0.85, 0.93]	0.0001	0.90 [0.85, 0.94]	0.0001
<b>Stroke</b>						
Prior CMV/OI*	n/a		1.25 [0.74, 2.10]	0.41	1.33 [1.06, 1.66]	0.01
Latest CD4 count (per doubling)	0.79 [0.72, 0.88]	0.0001	0.80 [0.74, 0.86]	0.0001	0.81 [0.75, 0.88]	0.0001

\*Effect shown is parameter estimate for either CMV infection (in model that includes CMV) or other AIDS-defining OI (in model that includes other OI). Models also include adjustment for all factors listed in Statistical Methods section.



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