Curtin University

Factors affecting affect cardiovascular health in Indonesian HIV patients beginning ART

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- **Vascular pathology:**

Well described in older HIV patients in Western settings

? systemic inflammation before ART & metabolic factors on ART.

- **Altered cardiac function:**

Diastolic dysfunction and high LVMI described in HIV patients on ART

? myocarditis/pericarditis before ART & autoimmunity/drug toxicities on ART.

Eg:…..cardiovascular risk in HIV patients on ART is more effectively predicted by the D:A:D algorithm than by Framingham scores

However…….abacavir has been phased out.

Piconi *et al. AIDS.* 2013; 27:381-9.
Ettorre *et al. AIDS Res Ther.* 2016; doi: 10.1186/s12981-016-0105-z.
Reinsch *et al. Am J Cardiovasc Dis.* 2011; 1:176-84.
Hsue *et al. Circ Heart Fail.* 2010; 3:132-9.

JakCCANDO

Cohort study of the recovery of immune function and the role of cytomegalovirus (CMV) in patients recruited and monitored in Indonesia.

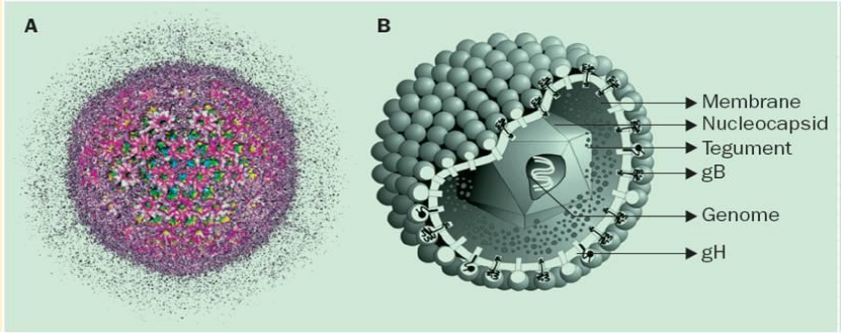
Antibody responses to CMV are extremely high in Indonesian patients with a significant (but undocumented) burden of disease.

82 patients recruited and tested.

Evidence of repeated CMV reactivation (the "footprint" of CMV) correlated with...
a) immune activation and altered T-cell and NK cell profiles
b) clinical outcomes previously associated with CMV (ocular, cardiovascular, neurological)

Why CMV?

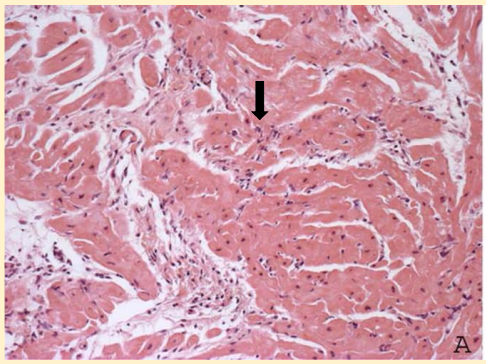
- CMV is a herpes virus with a stable DNA genome
- It replicates in fibroblasts, monocytes and endothelial cells
- It can become latent and persist for a lifetime
- A subset of its genes are expressed in latently infected cells
- >80% of people in this room are CMV seropositive

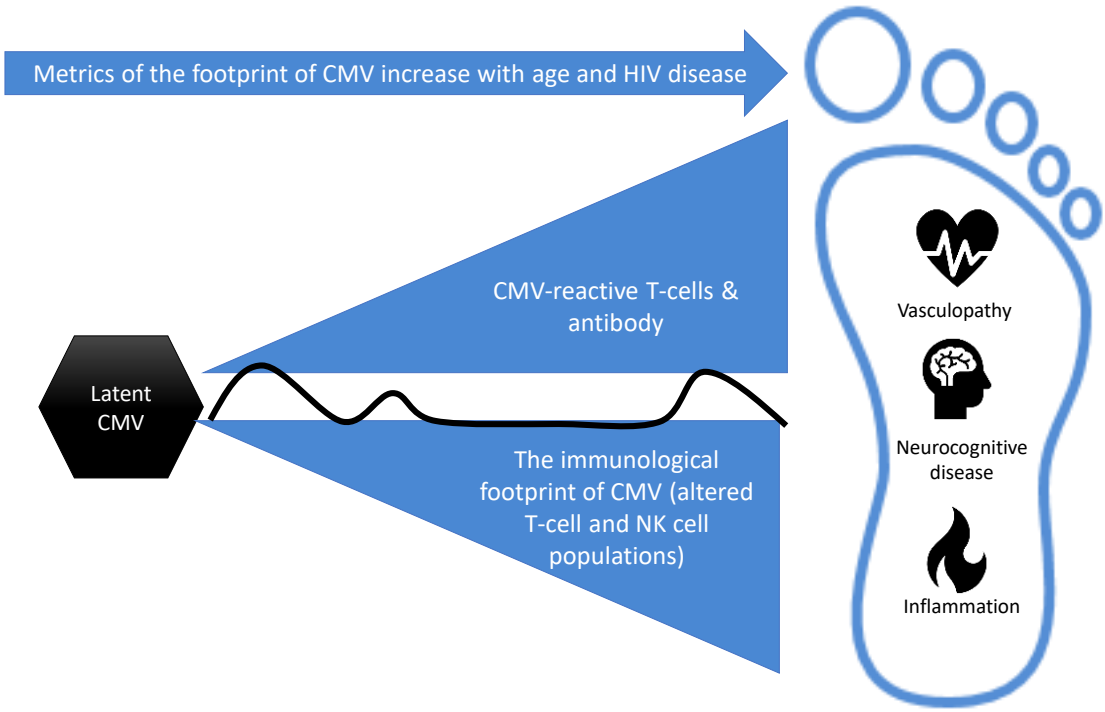


And…….

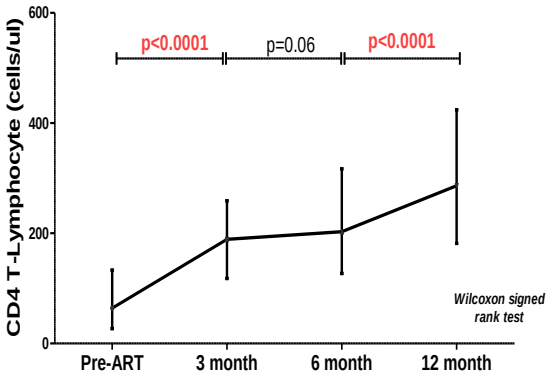
CMV causes a lot of inflammation for a small amount of virus

This is from a patient with CMV myocarditis

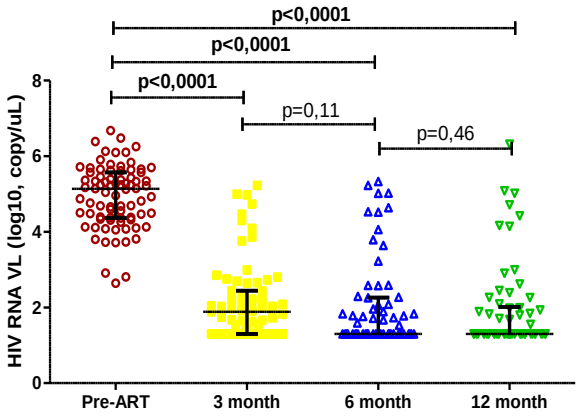




ART-naïve HIV patients [31(19-48) years] in JakCCANDO were followed for I year

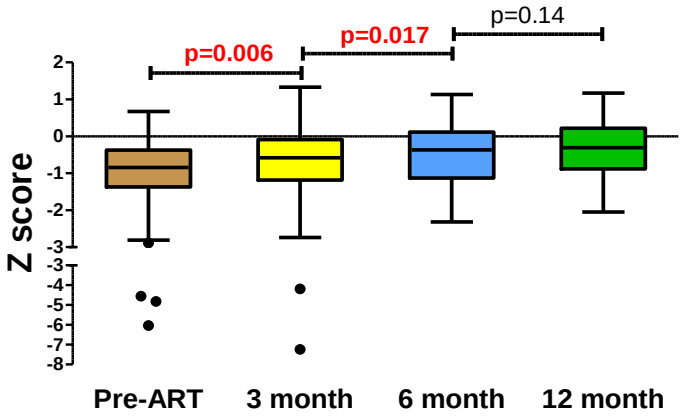


CD4 T cells count increased on ART



HIV RNA decreased on ART

Neurocognitive function improved on ART



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Cardiovascular health may decline over one year on ART
…..but remains similar to controls

	Pre-ART	3-months	6-months	12-months	Healthy controls
n	67	60	54	55	11
BMI (kg/m²)	19.6 (13-37)	20.5 (15-40)	**21.7(16-40)**	**23.0(13-40)**	
EF (%)	68 (51-84)[c]	69 (50-83)	70 (61-80)	**70 (50-79)**	71 (53-77)
E/A ratio	1.3 (0.6-4.7)[c]	1.3 (0.8-1.9)	1.3 (0.8-1.9)	1.3 (1.1-1.8)	1.4 (1.0-1.9)
LVMI	94 (30-177)	99 (52-187)	**100 (57-217)**	**102 (47-222)**	83 (48-125)
cIMT (right)	0.58(0.39-0.64)	0.58(0.38-0.77)	0.57(0.45-0.90)	**0.70(0.46-1.0)**	0.58(0.39-0.83)
cIMT (left)	0.57(0.32-0.89)	0.57(0.39-0.77)	0.51(0.32-0.89)	**0.65(0.45-0.96)**	0.58(0.45-0.70)

Echocardiography [EF%, E/A ratio & LVMI] and carotid doppler ultrasonography [cIMT]

Demographic factors and inflammatory biomarkers had no predictive power

No clear distinctions based on age and gender

No measures of HIV disease or CVD were influenced by smoking in males (n=24; $p > 0.19$).

The 51% of patients with pulmonary tuberculosis had higher baseline HIV RNA [p=0.05] and lower BMI [p=0.02]. Cardiovascular parameters were unaffected

Plasma CRP levels stayed high but were not associated with cardiovascular disease ($p > 0.10$).

HIV disease parameters poorly predictive of vascular change

Systolic blood pressures on ART correlated inversely with the HIV RNA load at V0 (r = -0.24 to -0.35), but not later……so viral set point may be important.

cIMT increased at V12 (p<0.0001), but did not correlate with CD4 T-cell counts or HIV RNA.

	Pre-ART	3-months	6-months	12-months	Healthy controls
cIMT (right,mm)	0.58(0.39-0.64)	0.58(0.38-0.77)	0.57(0.45-0.90)	**0.70(0.46-1.0)**	0.58(0.39-0.83)
cIMT (left,mm)	0.57(0.32-0.89)	0.57(0.39-0.77)	0.51(0.32-0.89)	**0.65(0.45-0.96)**	0.58(0.45-0.70)

HIV disease parameters weakly predict adverse cardiac function

EF values began low than healthy controls (p = 0.03) and increased (p = 0.04) by V12

-not correlated with CD4 T-cell counts or HIV RNA levels at any time.

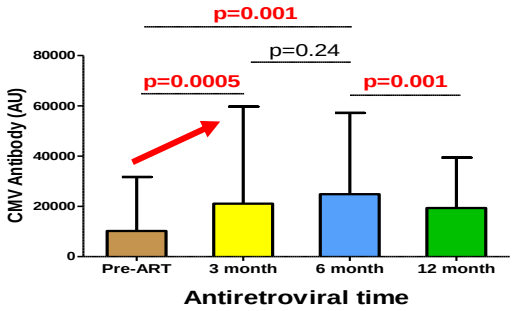
	Pre-ART	3-months	6-months	12-months	Healthy controls
EF (%)	**68 (51-84)**	**69 (50-83)**	**70 (61-80)**	**70 (50-79)**	**71 (53-77)**
LVMI	94 (30-177)	99 (52-187)	**100 (57-217)**	**102 (47-222)**	83 (48-125)

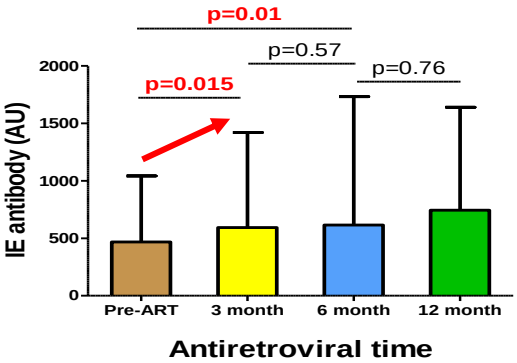
LVMI values high in patients and increased above controls by V6 (p<0.05)

– values at V3 correlated with CD4 T-cell counts at all times (r=0.27 - 0.42, p=0.03 - 0.002)

Perhaps CMV is more important than residual HIV
…….but how do we assess CMV burden?

The rise in levels of CMV-reactive antibodies on ART suggests that **the level seen before ART underestimates the true burden of CMV in an individual.**





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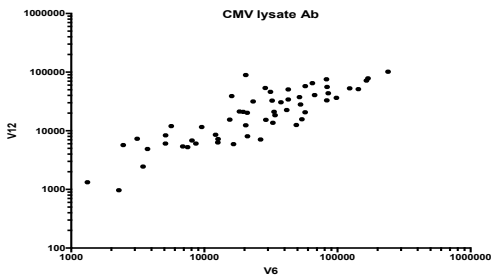
Levels of antibody reactive with CMV lysate **rise with age**, whilst CMV IE-1 antibody reflect low baseline CD4 T-cell counts.

		CMV lysate antibody				CMV IE-1 antibody			
		V0	**V3**	**V6**	**V12**	**V0**	**V3**	**V6**	**V12**
Age		**0.28**	**0.23**	**0.25**	**0.27**	0.10	0.11	0.15	0.14
CD4 T-cells	V0	0.18	-0.17	-0.23	-0.19	-0.19	**-0.34**	**-0.35**	**-0.40**
	V3	0.04	-0.09	-0.10	-0.08	-0.15	-0.15	0.01	0.02
	V6	0.10	-0.01	-0.05	-0.02	-0.13	-0.13	-0.24	**-0.26**
	V12	0.09	-0.07	-0.05	0.01	-0.10	-0.13	-0.04	-0.10



Levels of CMV antibodies measured at each time point were tightly correlated => a stable measure of the CMV burden

CMV DNA detected in buffy coats (neutrophils) at V0 in 30/64 patients.

All CMV DNA^{neg} patients were CMV seropositive

CMV DNA^{+} patients had slightly lower CD4 T-cells & higher CMV IE Abs pre-ART

CMV DNA→	Positive	Negative	P
CD4 T-cells/uL	53 (2-196)	74 (4-199)	***0.05***
HIV RNA	5.24 (2.6-6.68)	4.92 (3.7-6.4)	0.74
CMV lysate Ab	10.3 (1.4-1049)	11.9 (1.6-77)	0.24
CMV IE Ab	0.61 (0.5-6.5)	0.32 (0.05-11.6)	0.09

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CMV DNA did not affect any markers of cardiovascular health except…….

E/A ratios

- *low E/A ratios indicate poor ventricular filling between contractions and so mark an increased risk of diastolic heart failure.*

- slightly lower in CMV DNA^{pos} patients [1.20 *vs* 1.36; p=0.03] at V0 and similar at V3.
- increased in CMV DNA^{pos} patients by V6, becoming similar to the CMV DNA^{neg} group.

- may reflect transient ill health, CMV myocarditis or mycobacterial pericarditis

Levels of CMV antibodies did not correlate with E/A ratios, EF or LVMI values

Levels of CMV Ab correlated inversely with the diameter of the right carotid artery at V6 and V12 and **directly** with right cIMT values.

		CMV lysate antibody				CMV IE-1 antibody			
		V0	**V3**	**V6**	**V12**	**V0**	**V3**	**V6**	**V12**
Diam Right	V0	0.03	-0.03	-0.06	-0.21	-0.14	-0.18	-0.11	-0.25
	V3	0.11	0.11	-0.10	-0.27	**-0.28**	**-0.27**	**-0.30**	**-0.46**
	V6	0.00	-0.15	**-0.27**	**-0.32**	-0.09	-0.12	-0.13	-0.16
	V12	0.02	-0.18	**-0.31**	**-0.29**	0.04	-0.12	-0.22	-0.19
cIMT Right	V0	0.08	0.17	0.18	0.21	-0.03	0.10	**0.27**	**0.31**
	V3	**0.27**	0.15	0.14	0.12	0.11	0.10	0.10	0.16
	V6	0.18	0.21	0.23	0.21	0.07	0.14	**0.29**	**0.30**
	V12	0.00	-0.06	-0.02	0.07	0.06	0.03	**0.21**	**0.26**
Diam Left	V0	0.07	0.01	-0.06	-0.14	-0.10	-0.21	-0.21	-0.27
	V3	-0.08	0.01	-0.01	-0.08	-0.10	-0.14	0.01	-0.06
	V6	-0.03	-0.16	-0.24	-0.17	0.02	0.02	-0.12	-0.01
	V12	0.08	-0.07	-0.06	-0.06	0.05	0.03	-0.05	-0.10
cIMT Left	V0	-0.12	0.02	0.16	0.10	-0.11	0.01	**0.23**	0.16
	V3	0.14	0.03	0.03	0.02	0.02	-0.07	-0.12	-0.02
	V6	-0.09	0.07	0.10	0.15	0.10	0.08	0.11	0.19

Summary

- Markers of adverse cardiovascular prognosis [LVMI, EF, cIMT] were similar to healthy controls, but increased at V12.
- Internal diameters of the carotid arteries and systolic blood pressure correlated with HIV disease severity at V0, but cardiac parameters and cIMT did not.

The severity of HIV disease and the response to ART have only subtle effects on cardiovascular health in this young Asian population.

- E/A ratios (left ventricular diastolic function) were lower in patients with CMV DNA at V0, but this effect waned by V6

CMV replication before ART may have a transient effect on cardiac health - CMV myocarditis, TB pericarditis ?

- Levels of antibody reactive with CMV correlated directly with the right cIMT on ART

Antibody reactive with CMV may mark a high persistent CMV burden with cumulative effects on the carotid artery.

The JakCCANDO team !

Shelley Waters &
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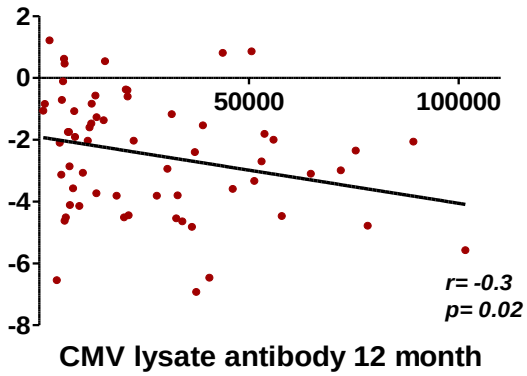
CMV lysate Ab correlated with Memory function but not with total Z score



- Subjects with low score of Z-memory pre-ART tend to have higher CMV lysate Ab level
- CMV IE Ab also correlate with fluency and motor speed (CMV-IE)

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Selective associations between CMV antibodies and right carotid arteries may reflect the young age of the cohort

- Left cIMT values are higher than the right in healthy adults >40 years old
- High left cIMT may reflect intimal hyperplasia or medial hypertrophy, due to increased haemodynamic stress.
- Atherosclerotic progression faster on the left, and linked to deposition of triglycerides
- Hemorrhage, lipid deposition and fibrosis more prevalent in plaques of the left artery
- Plaques in the right artery were more frequently calcified and stable in an older cohort

Denarie et al. *Atherosclerosis,* 2000; 148:297–302
Rodríguez *et al*. *Hypertension.* 2003; 42:56-60.
De Blois *et al*. *Clin Physiol Funct Imag* 2012; 32:400-3
Selwaness *et al. Stroke.* 2014; 45:3226-30.

Most individuals in JakCCANDO were <40 years old, so their left cIMT was not higher.

No studies of CMV in HIV patients present the right and left arteries separately, but two studies where values were averaged could not link CMV antibody levels with cIMT.

Parrinello *et al. J Infect Dis.* 2012; 205:1788-96.
Goulenok *et al*. *AIDS.* 2015; 29:287-93.

No clear picture from demographics…….

Gender

Male and female patients did not differ in cIMT.

Males had slightly lower (worse) EF percentages than females - marginal at V6 (p=0.11) and significant at V12 [0.67 *vs* 0.72, p=0.05].

Males had slightly higher (worse) LVMI values than females - significant at V0 [98 *vs* 83, p=0.03], waning by V3 (p=0.10), and not evident thereafter.

Age

Increasing age was associated with higher cIMT values - weak at V0 (? influence of HIV), but consistent thereafter [V6, Right: r = 0.36, p = 0.01].

Accordingly, E/A ratios (left ventricular function) declined with age - negative correlations at V0 - V6 (r = -0.25 to -0.3).

Smoking

24 males & 1 female were current smokers.

No measures of HIV disease or CVD were influenced by smoking in males ($p > 0.19$).

Tuberculosis

51% of patients had pulmonary tuberculosis before ART.

They had slightly higher baseline HIV RNA levels [p=0.05] and lower BMI [p=0.02].

Cardiovascular parameters were unaffected, but the diameter of the carotid artery was lower at V0 in patients with tuberculosis [p=0.06-0.0007], with smaller changes thereafter.

Systemic inflammation

Plasma CRP levels were elevated relative to healthy controls and unchanged on ART.

Levels were not associated with any parameters of cardiovascular disease ($p > 0.10$).