

HIV patients beginning ART with <200 CD4 T-cells/ μ l retain a high burden of cytomegalovirus for at least 5 years

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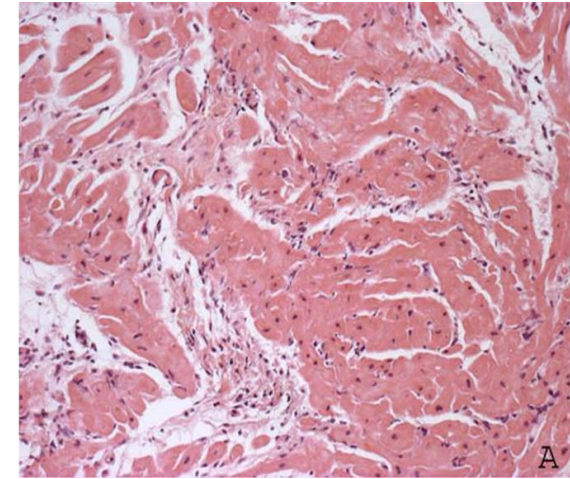
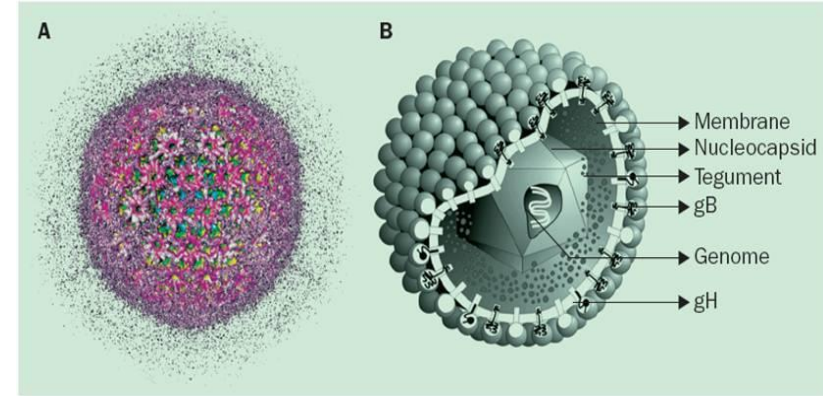
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Basic facts about CMV

- CMV is a herpes virus with a large DNA genome
- It replicates in small numbers of fibroblasts, monocytes and endothelial cells *and causes a lot of inflammation for a small amount of virus*
- CMV becomes latent and persist for life
- Genes that can modify the host's immune system may be expressed during latency (eg: *US28*)

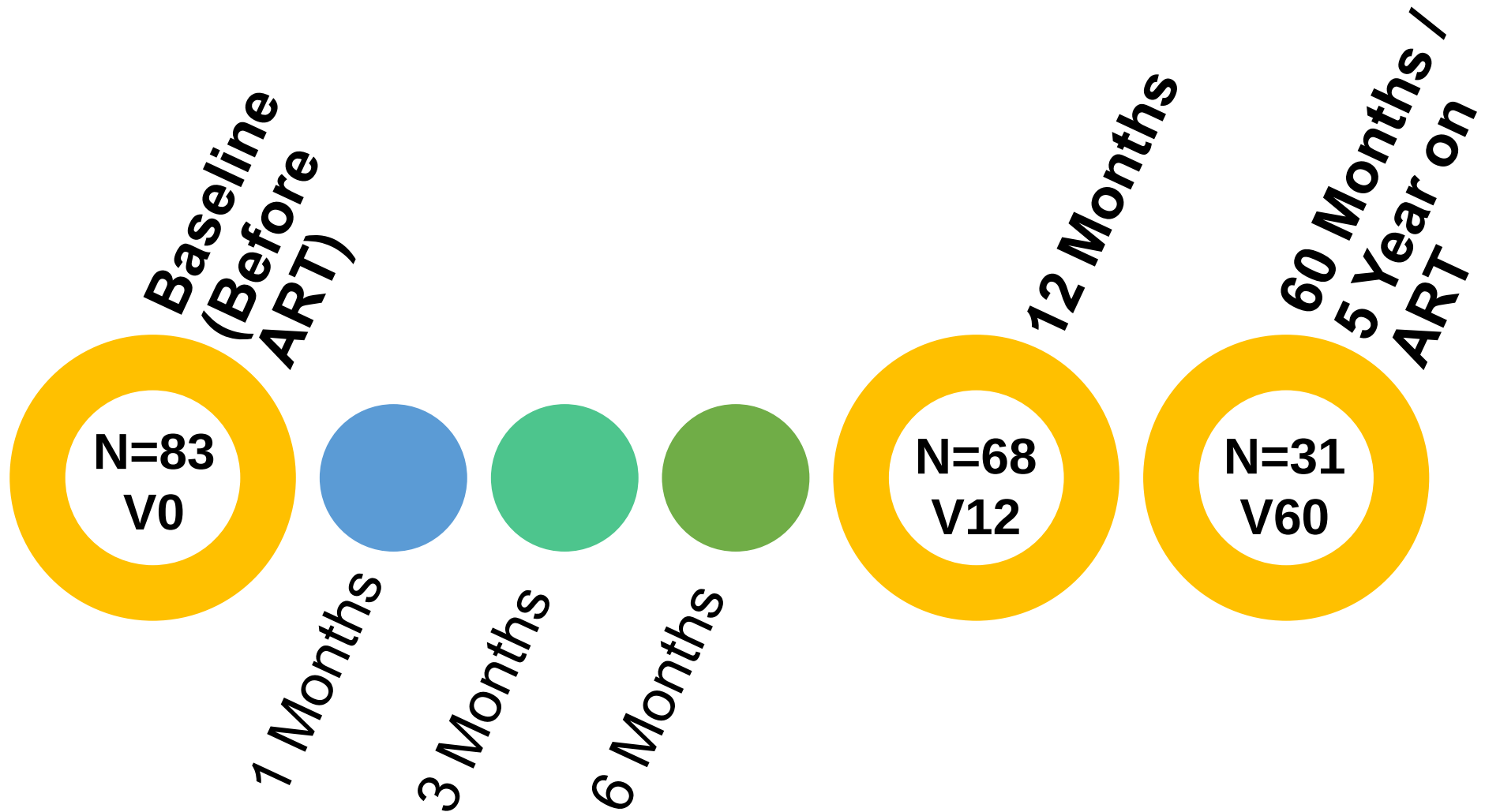


~83% of the global population are CMV seropositive [Zuhair, Rev Med Virol. 2019; 29(3):e2034]

- Causes retinitis in patients with advanced HIV disease

JakCCANDO Study - Cohort

Jakarta CMV Cardiovascular Antiretroviral Neurology
Dentistry Ophthalmology



CMV antibody (in-house assay)

- 1. CMV lysate (lab strain AD169) – Dilutions (1:10000)**
- 2. Glycoprotein B (gB) protein (1:10000)**
- 3. Immediate Early-1 (IE-1) protein (1:3000)**

Results presented in Arbitrary Unit (AU)

- HIV Viral load, CD4 & CD8 T cells assessed by Cipto Mangunkusumo Hospital Clinical Pathology Laboratory

Clinical data 1 year on ART

- Assessed by the..
 - Neurologist (Cognitive Function)
 - Ophthalmologist (Retinitis – 0 case and Retinal Artery Caliber)
 - Cardiologist (cIMT, Flow mediated dilatation, & Artery Diameter)

Immunology

- T cells profiles 1 year on ART

CMV DNA ASSAY

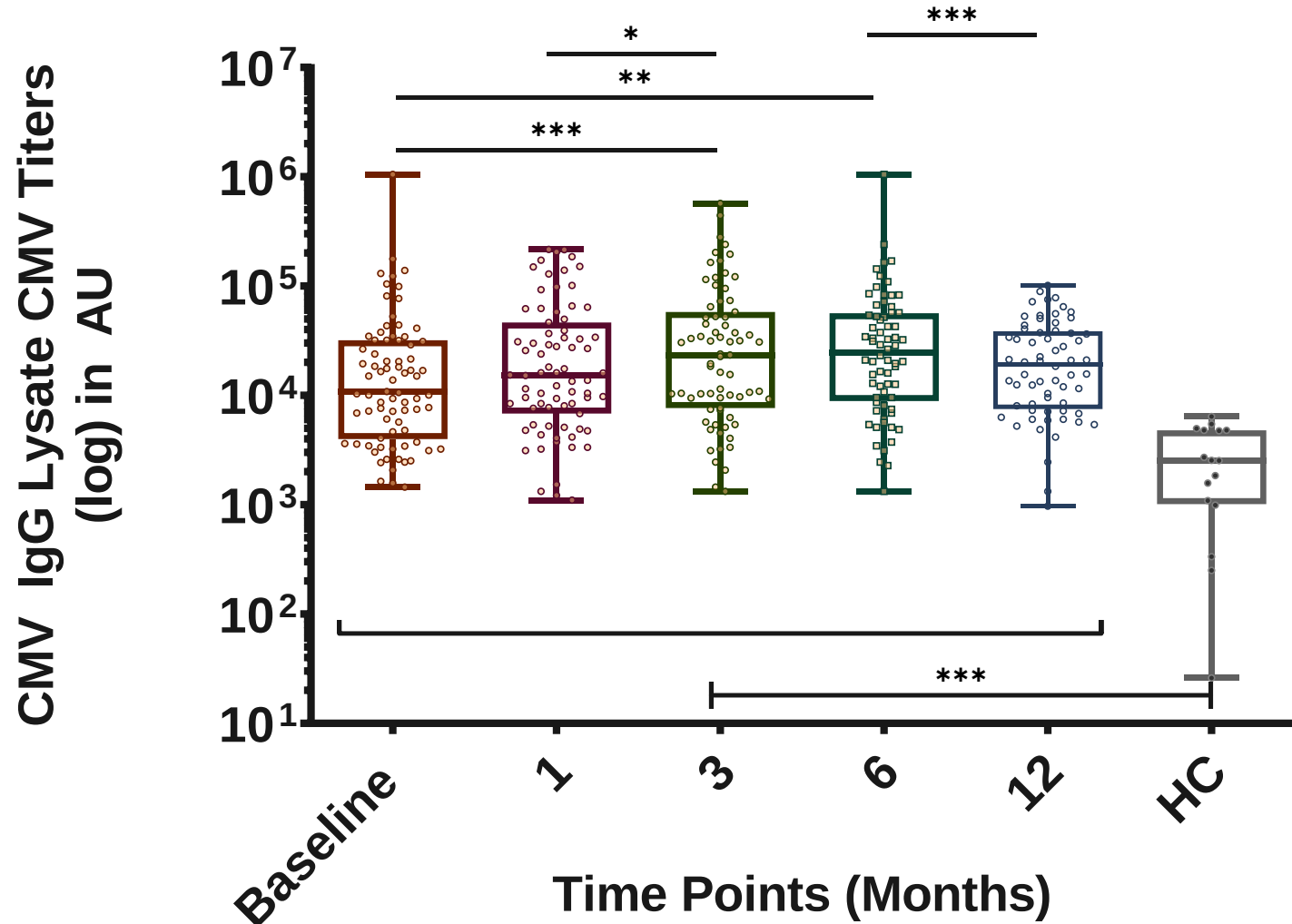
V0
(Before)
N=82

V60
(5 YEAR)
N=31

CMV DNA (in-house qPCR)

- DNA Extracted from buffy coat
- qPCR performed using UL54 (DNA Polymerase) Primer pairs and Probe (*Designed by Andrew Davidson, Birmingham University*).
- Then normalized with unit of Housekeeping Genes ($\beta 2$ Globulin)
- Results presented in Arbitrary Unit (AU)

HIV patients starting ART have higher antibodies to CMV than healthy controls in the first year...and levels rose and then declined



Links with CMV antibodies in the first year on ART in JakCCANDO patients

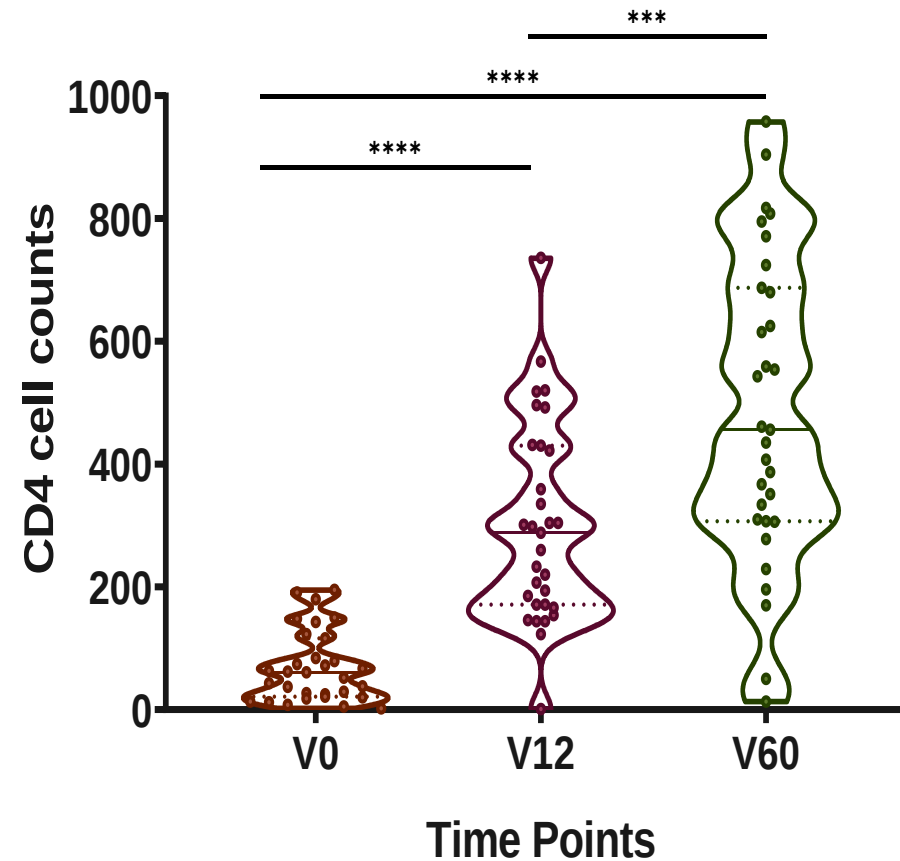
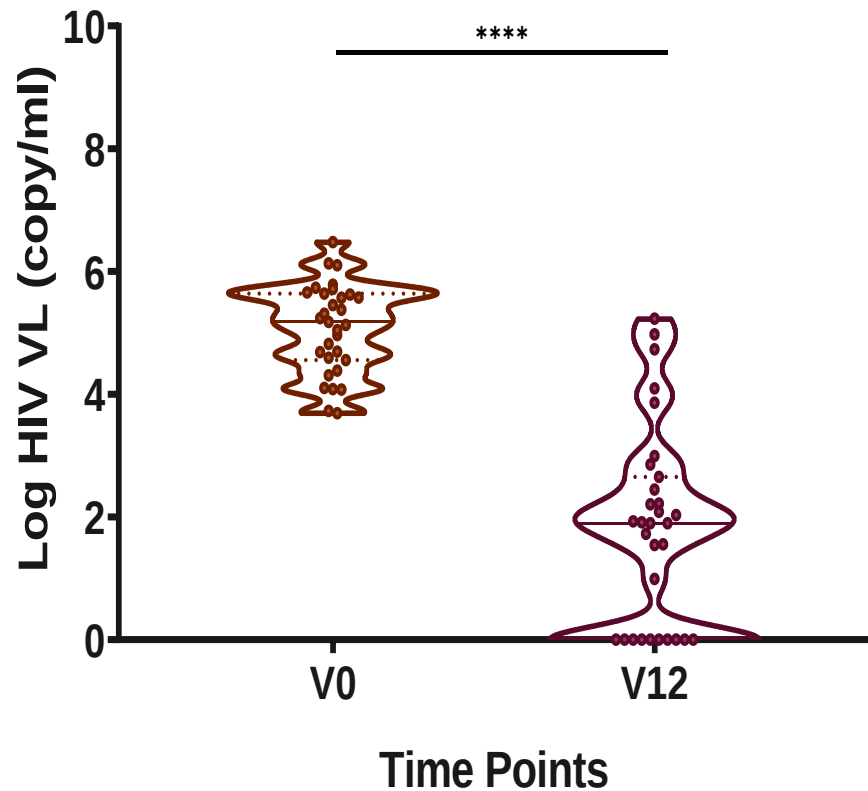
- Reactive antibody to CMV IE-1 (Immediate Early antigen) correlated with increased cIMT. (Karim *et al*, AIDS Res & Ther 2017)
- The decline of right eye Retinal Artery Caliber (RAC) correlated with CMV IE-1 antibodies (Edwar *et al*, AIDS Re Hum Retro 2019)
- CMV lysate antibody correlated inversely with cognitive (memory) function. (Estiasari *et al*, J Neurovirol 2019)

We can see that CMV antibodies may rise and fall during ART, so which time point should we use to assess the burden of CMV? Are there other ways to assess this?

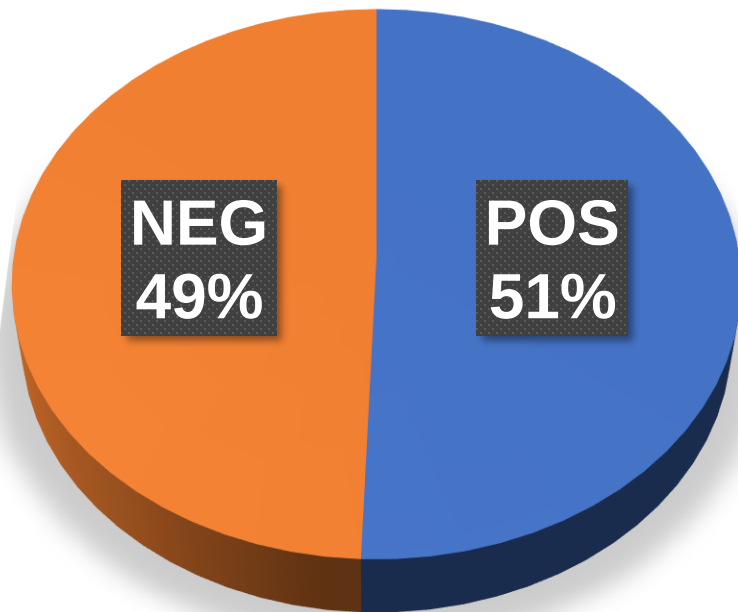
So what happens after 5 years?

- ✓ CD4 T cells recovery
- ✓ CMV DNA in peripheral blood
- ✓ CMV antibody levels

Decreased HIV RNA & CD4 T cells recovery on ART

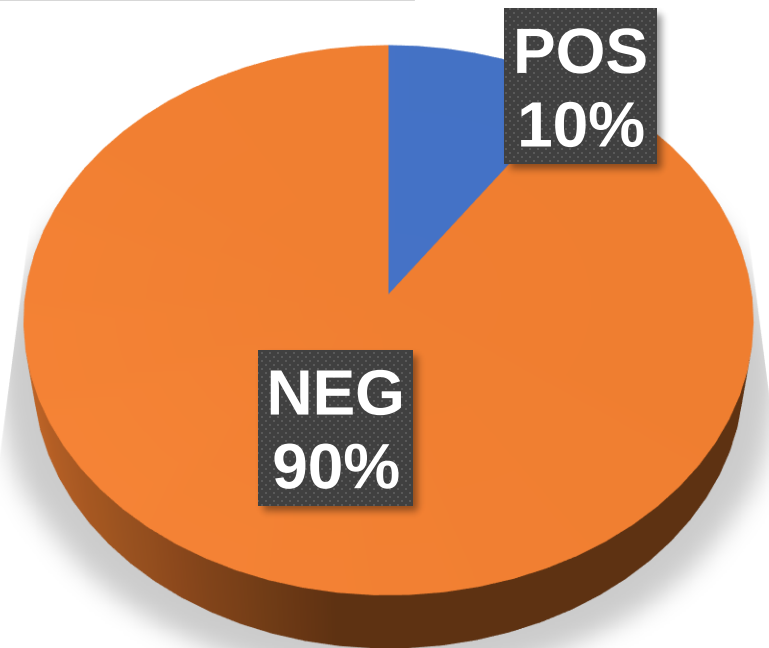


Percentage of CMV DNA positive very high at baseline with some remaining positive after 5 years



Pre – ART (V0)

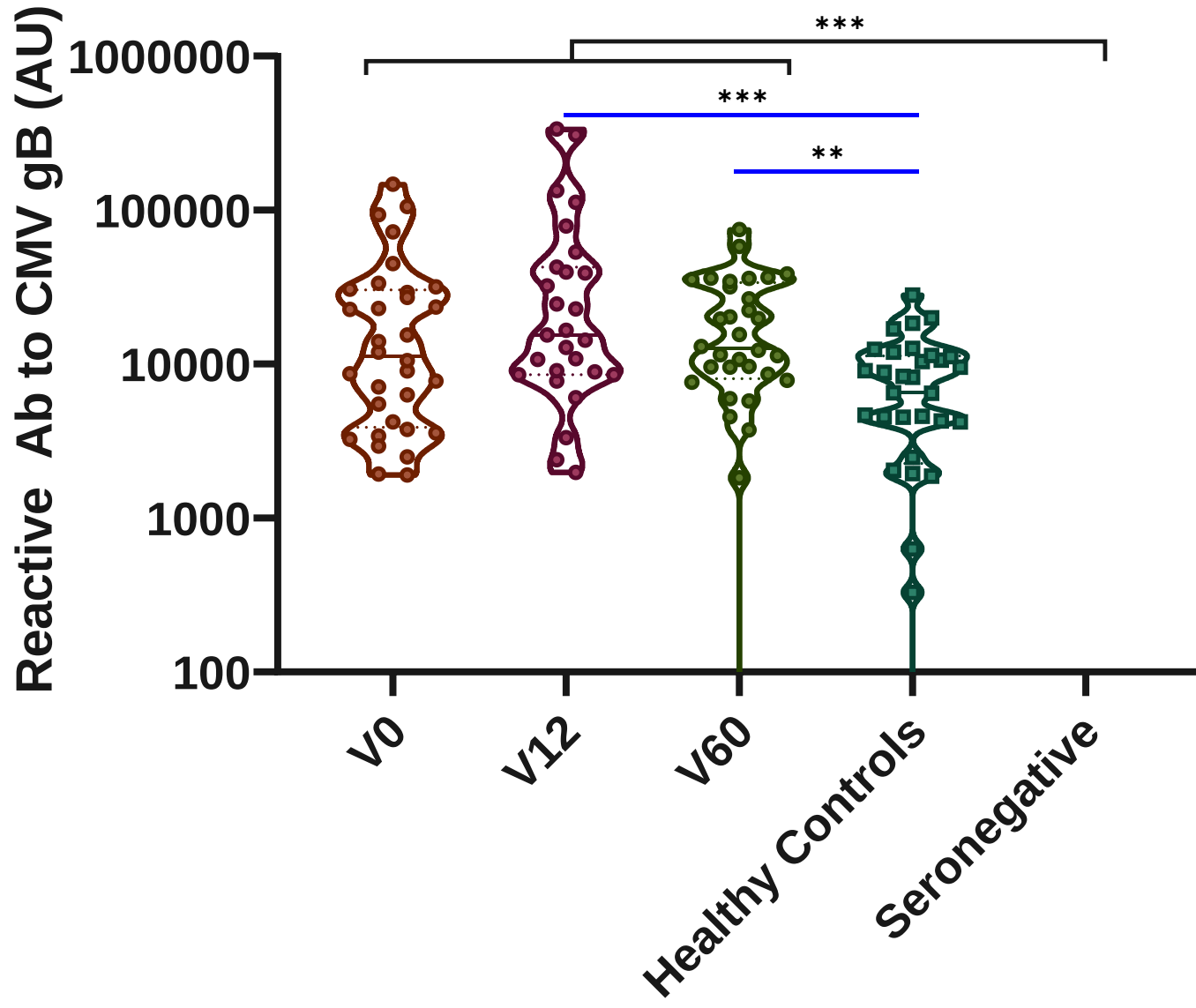
N = 81



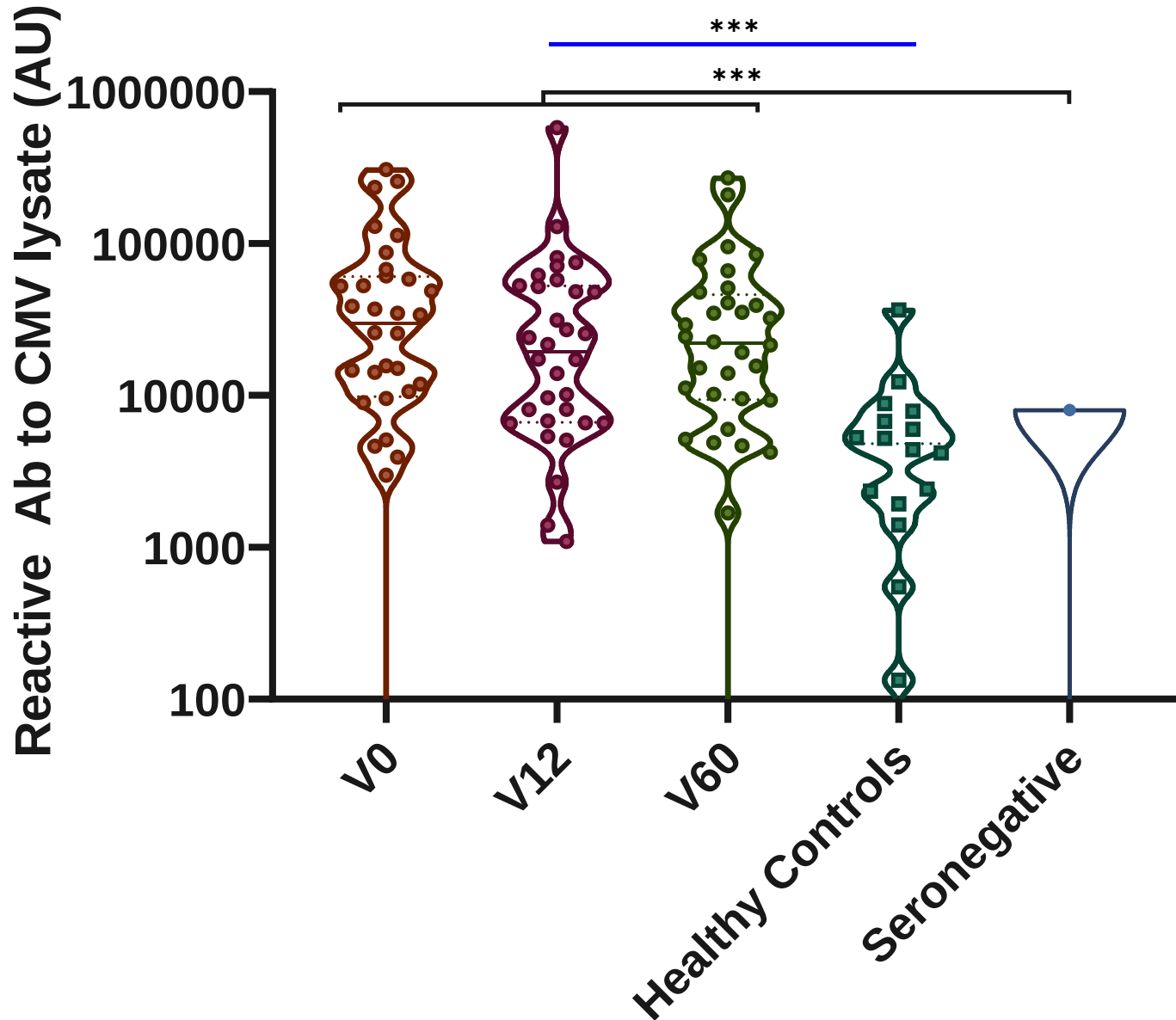
5 year on ART (V60)

N = 31

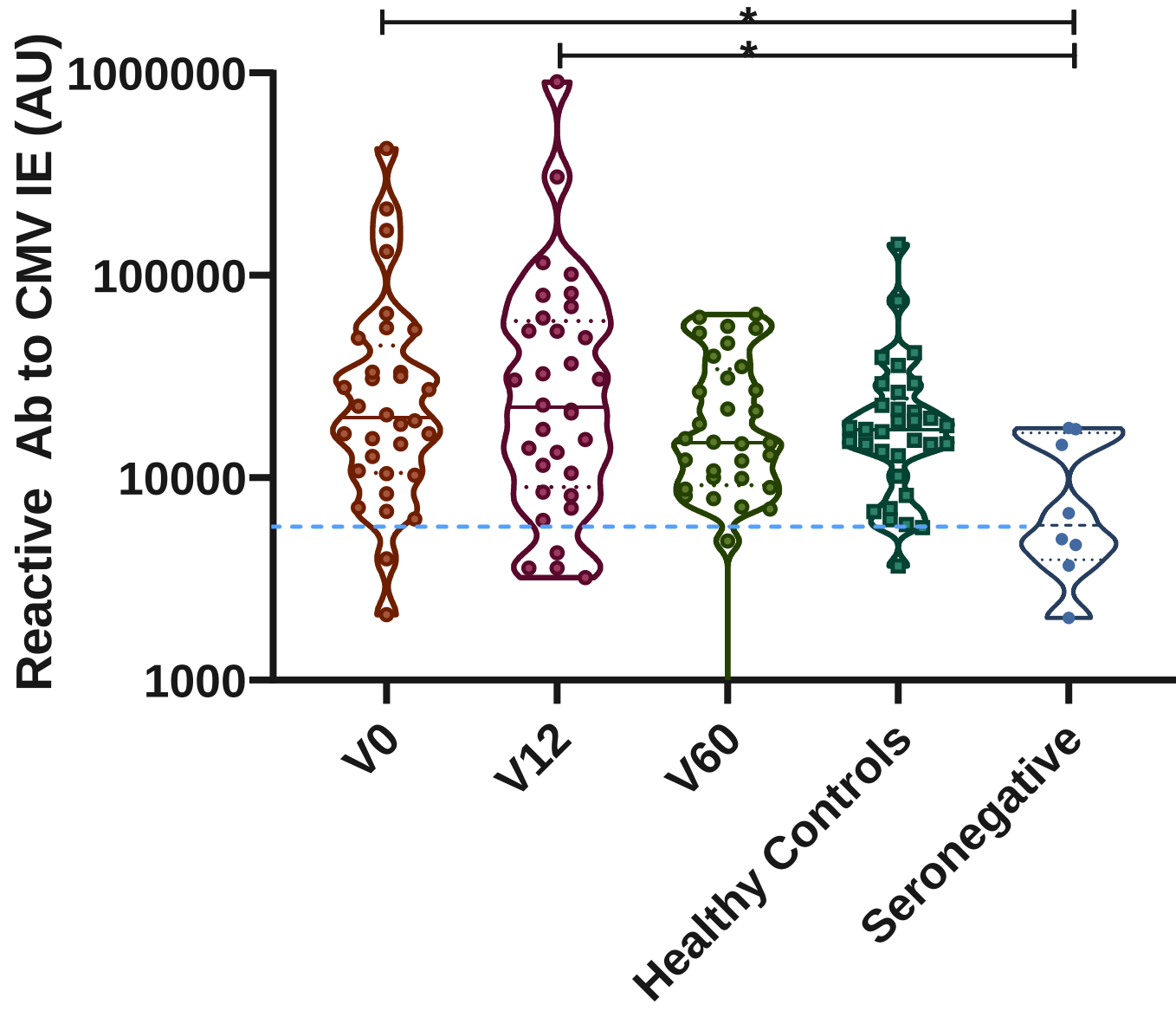
Antibodies to CMV gB are high in all patients and persist on ART



Antibodies to CMV Lysate are high in all patients and persist on ART



Levels of antibodies to CMV IE-1 are stable on ART



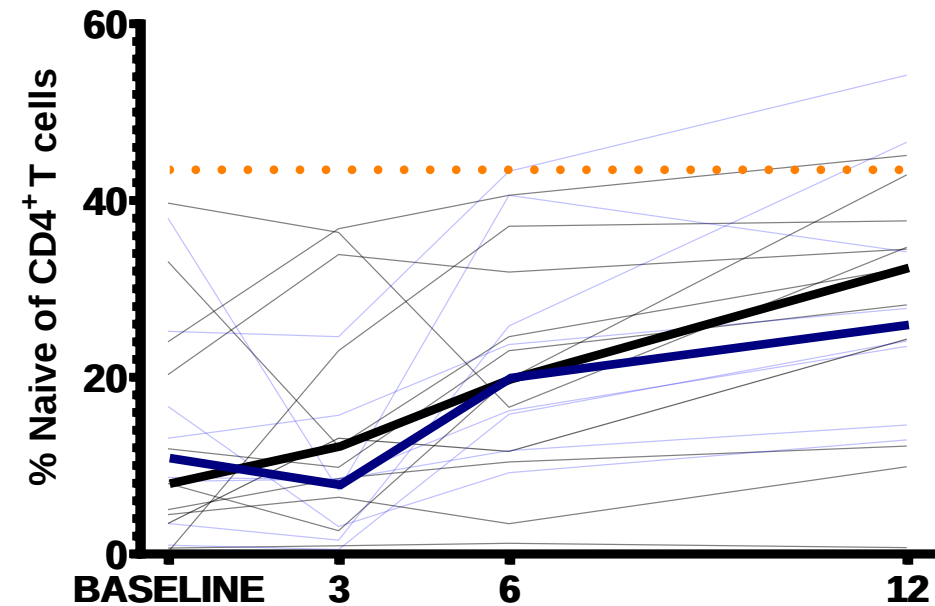
How does this high burden of CMV affect the immune system?

Could this have long term consequences?

I can present a detailed analysis of the first year on ART, plus CD4/CD8 T cell ratios at year 5

T-cells were analysed in a sub-set of the cohort (n=19)

Naive CD4 and CD8 T-cells remained depressed

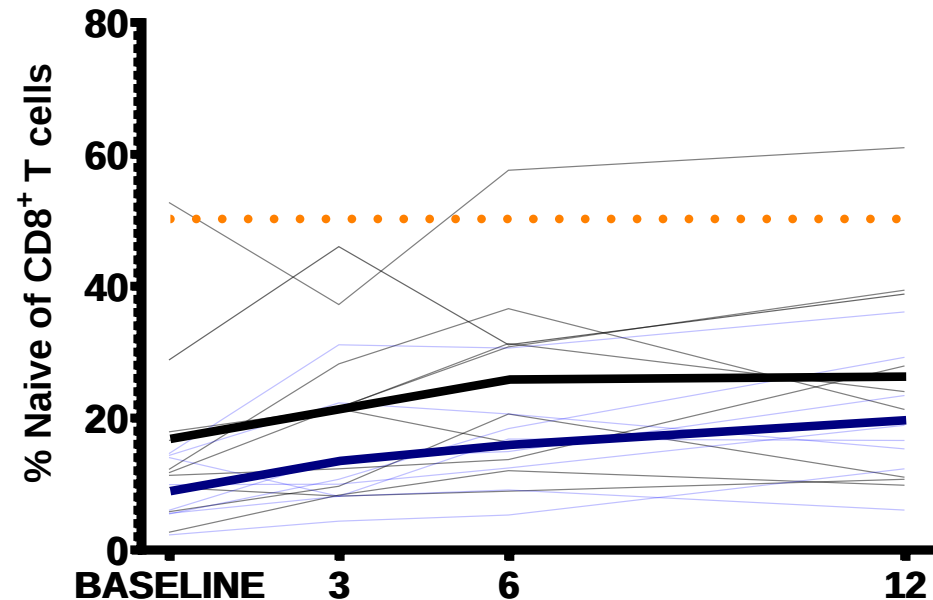


Median of HIV Group

CMV DNA+

CMV DNA-

Healthy Control



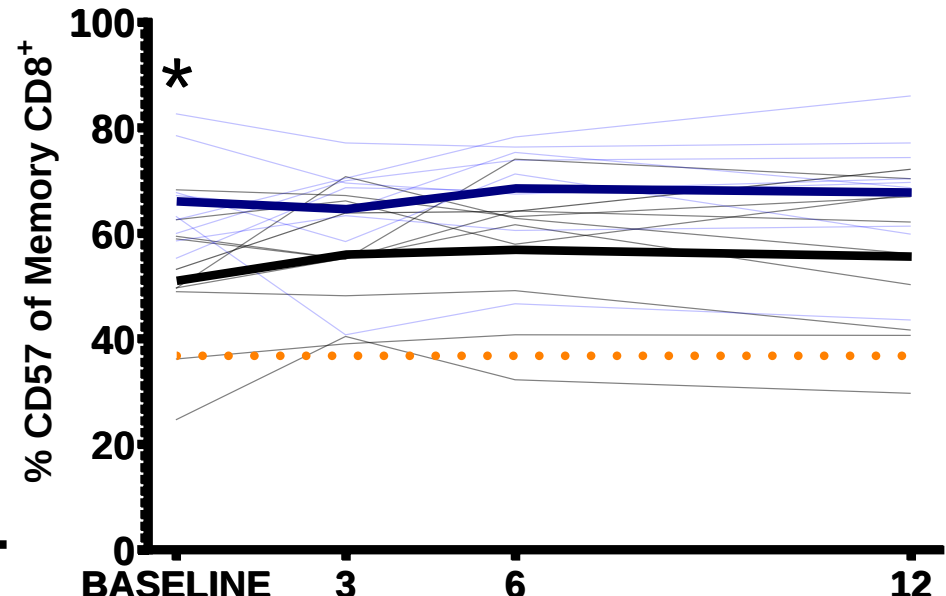
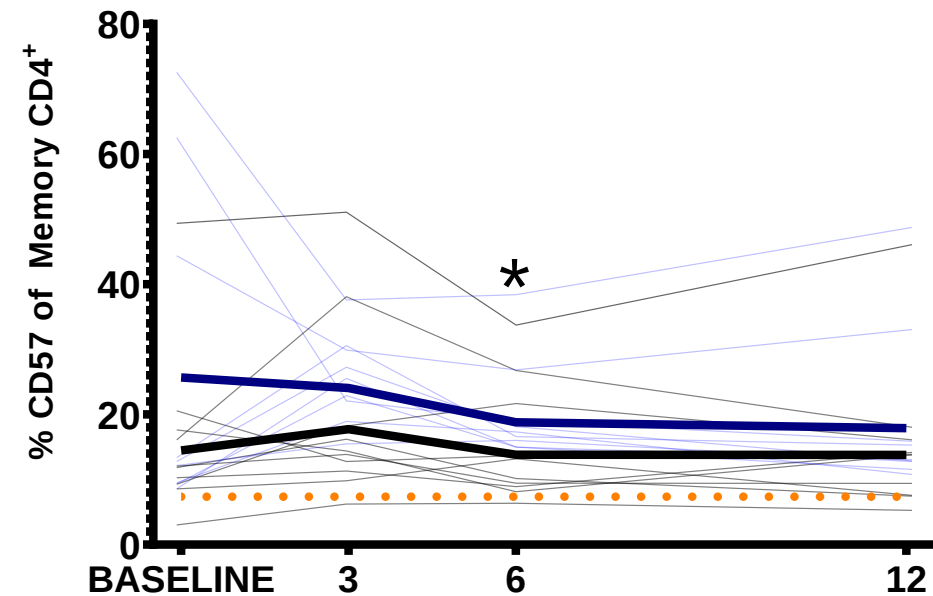
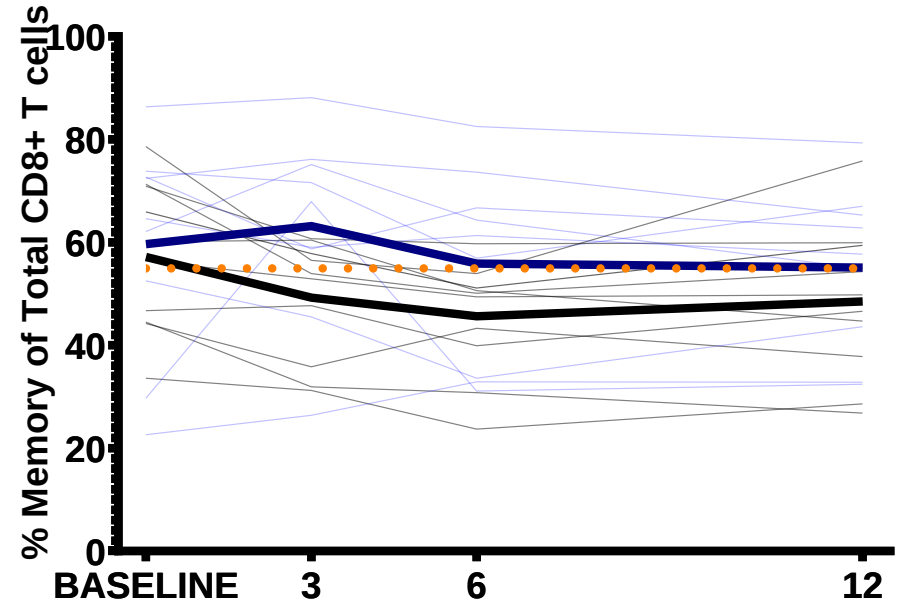
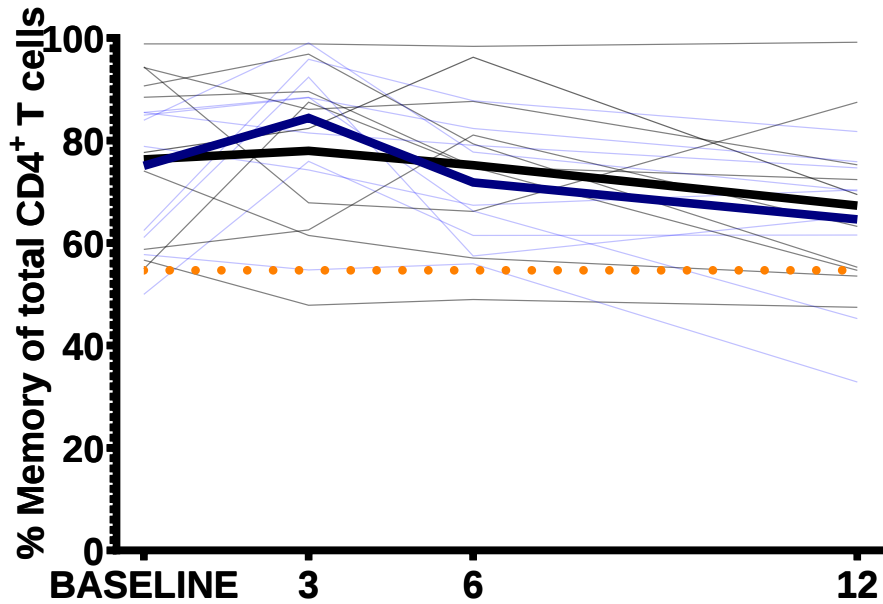
Individual Value

CMV DNA+

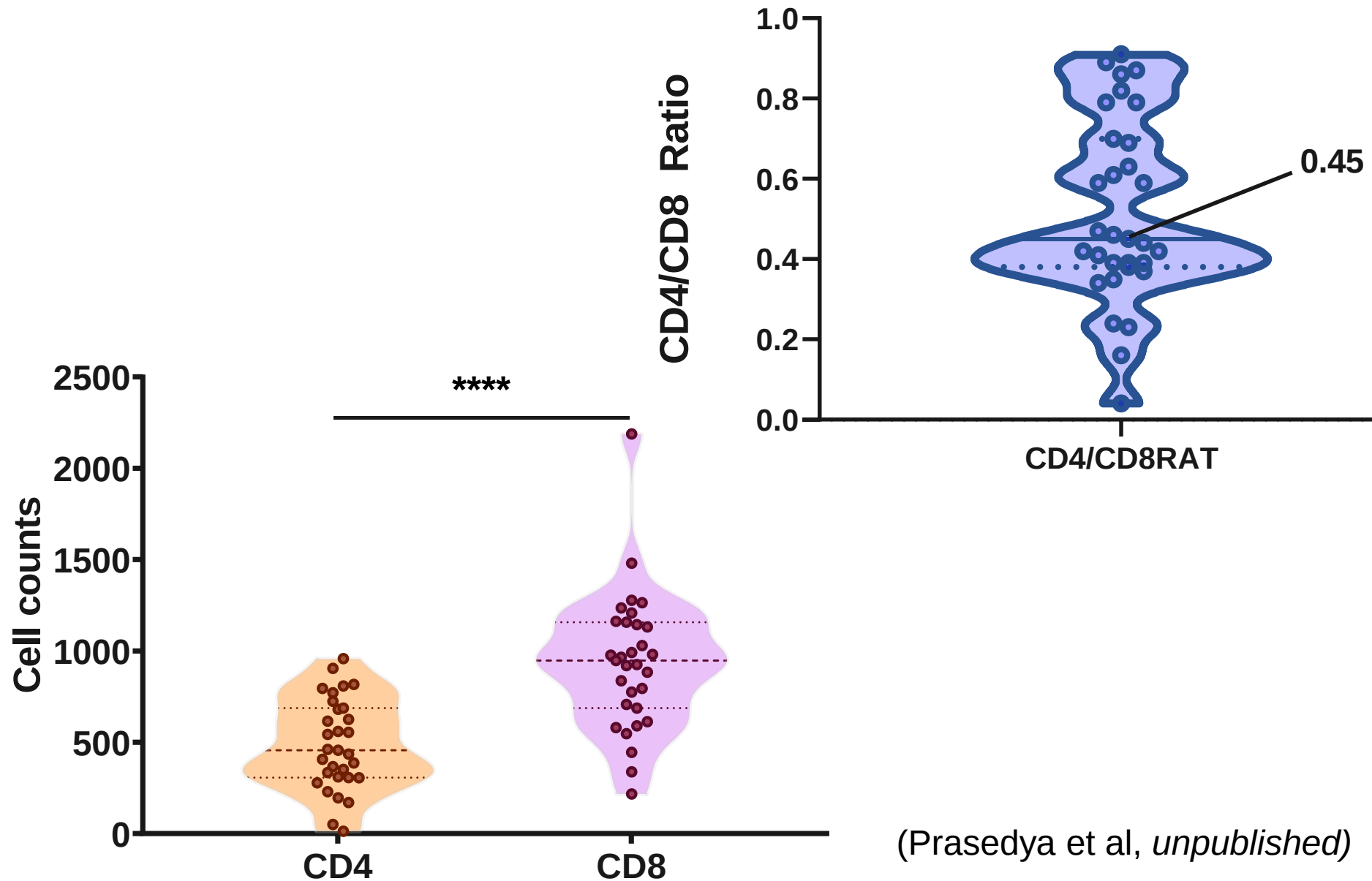
CMV DNA-

(Ariyanto *et al*, Viral Immunol, 2017)

Populations of memory and CD57+ memory T cells were expanded... as seen in CMV seropositive older healthy adults



After 5 years of ART, 81% of patients retain a CD4/8 T cells ratio < 0.8



Conclusions

- Indonesian HIV patients begin ART with a high burden of CMV evidenced by the detection of CMV DNA and by high levels of antibodies to CMV proteins.
- CMV replication is less common after 5 years, but levels of antibodies are maintained.
- This suggests a high burden of CMV and consequently may associate with high CD8 T cell counts, increased proportion of memory T-cells and possibly associated with clinical outcomes. This work continues.



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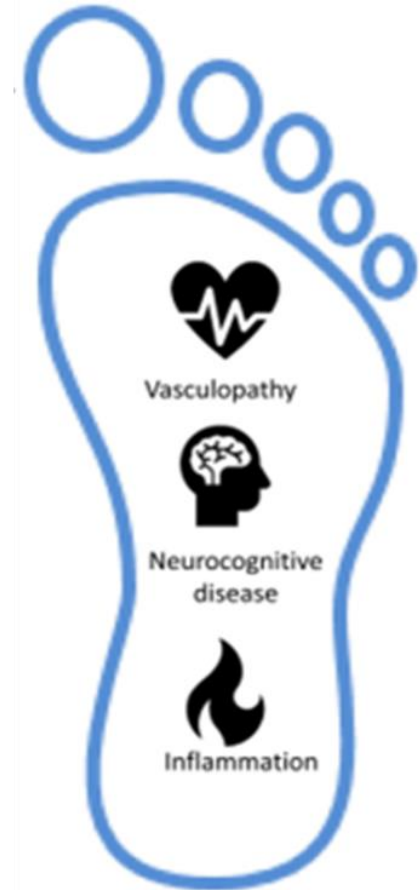
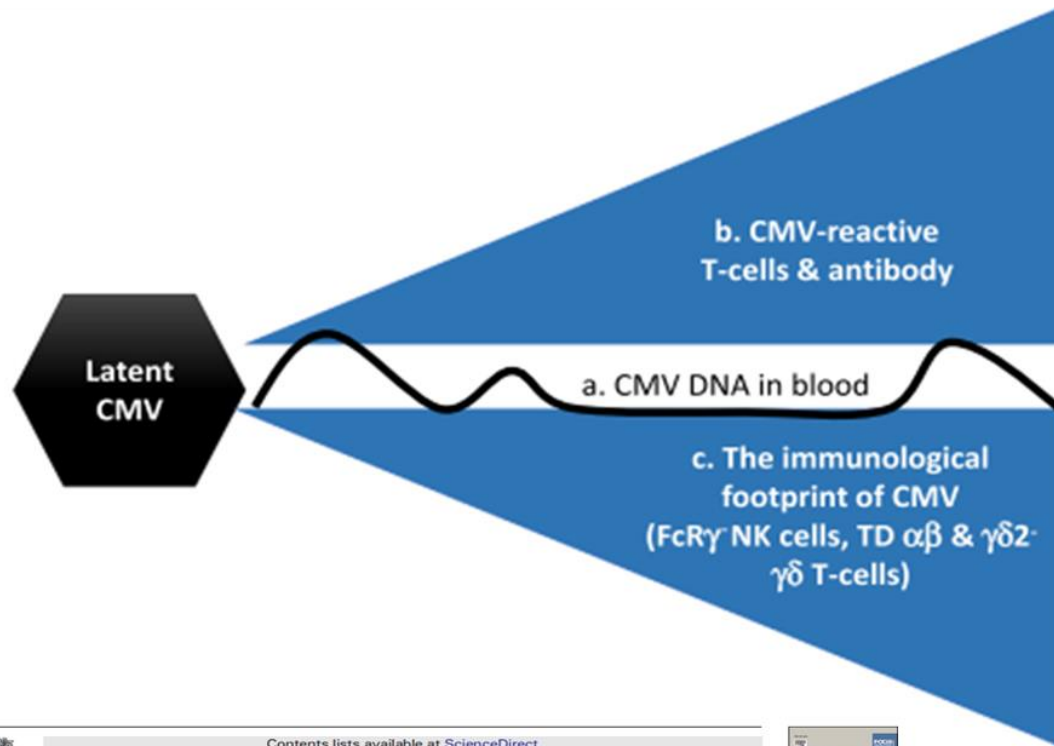
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Collaboration Grants

Ongoing study linked CMV footprint to Clinical Status

d. Metrics of the footprint of CMV increase with age and HIV disease



Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim



Review Article

HIV patients, healthy aging and transplant recipients can reveal the hidden footprints of CMV

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CMV Footprint

Links between CMV antibodies and cardiovascular disease

- CMV antibodies are risk factors for Cardiovascular Disease in older people in the general population. (Simanek *et al*, 2013)
- High CMV antibodies associate with reduced blood vessel elasticity and increase blood pressure in younger participants. (Harala *et al*, 2013)
- CMV DNA detected in aortic smooth muscle removed from patients suffering from abdominal aortic aneurysm. (Gredmark-Russ, *et al*. J Mol Med 2009)

Is there a link between CMV & CVD in PLWH?

- Higher CMV IgG levels associated with artery stiffness in HIV infected woman (Traditional risk factors excluded).
(Parinello *et al*, 2012)
- LARGE Cohort in Italy (ICONA Study): CMV IgG status of people living with HIV is an independent risk factor. (Lictner *et al*, 2015)
- Reactive antibody to CMV IE-1 (Immediate Early antigen) correlated with increased cIMT in HIV+ young Indonesian adults (JakCCANDO). (Karim *et al*, 2017)