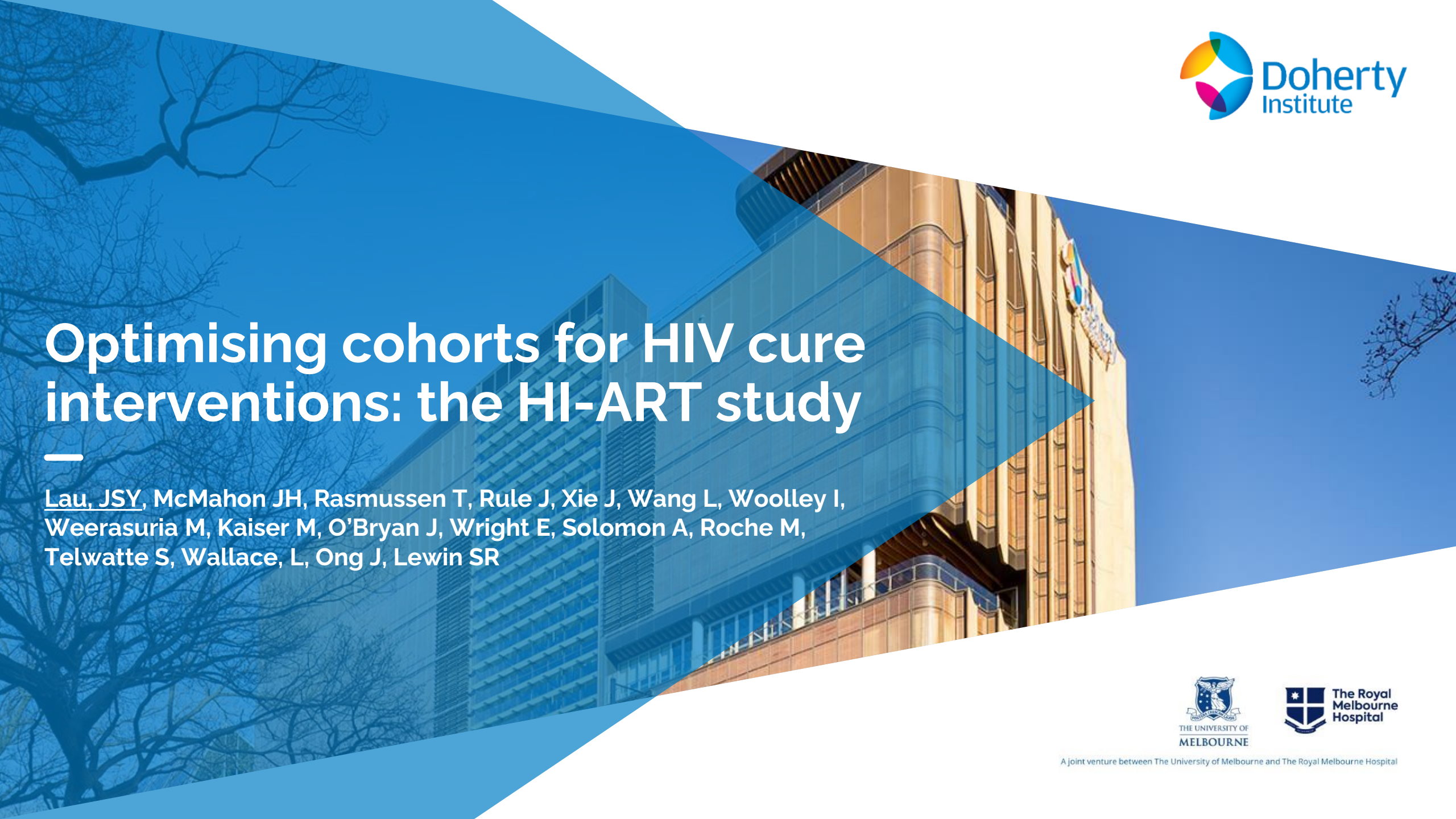

Optimising cohorts for HIV cure interventions: the HI-ART study

Lau, JSY, McMahon JH, Rasmussen T, Rule J, Xie J, Wang L, Woolley I, Weerasuria M, Kaiser M, O'Bryan J, Wright E, Solomon A, Roche M, Telwatte S, Wallace, L, Ong J, Lewin SR

Doherty Institute

THE UNIVERSITY OF MELBOURNE

The Royal Melbourne Hospital

A joint venture between The University of Melbourne and The Royal Melbourne Hospital

Disclosures

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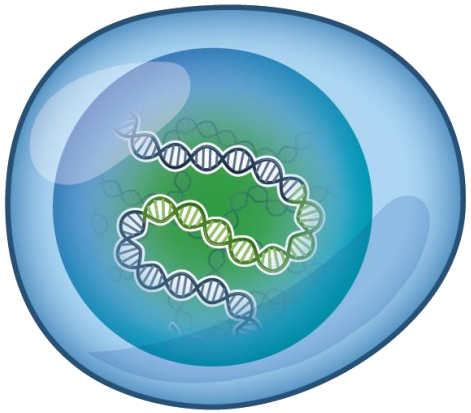
I have received honoraria for participation in Advisory Boards and consultancy roles for ViiV Healthcare and Gilead Sciences.

I would like to acknowledge the Traditional Owners of the land on which we meet today, the Kaurna People. I'd like to pay my respects to elders past and present and extend that respect to any Aboriginal and Torres Strait Islander people in the audience today.

The latent HIV reservoir is a major barrier to cure

- **Reservoir of integrated HIV DNA within infected cells**
- **Established early in infection, persists on ART[1]**
- **PWH with smaller reservoirs may be more likely to achieve cure[4]**
- **Small reservoirs observed in PWH[2] and animal models[3] of very early ART start but not enough to achieve cure[2]**
- **Difficult to determine exact time of infection**

- **Are there other ways to predict reservoir size?**



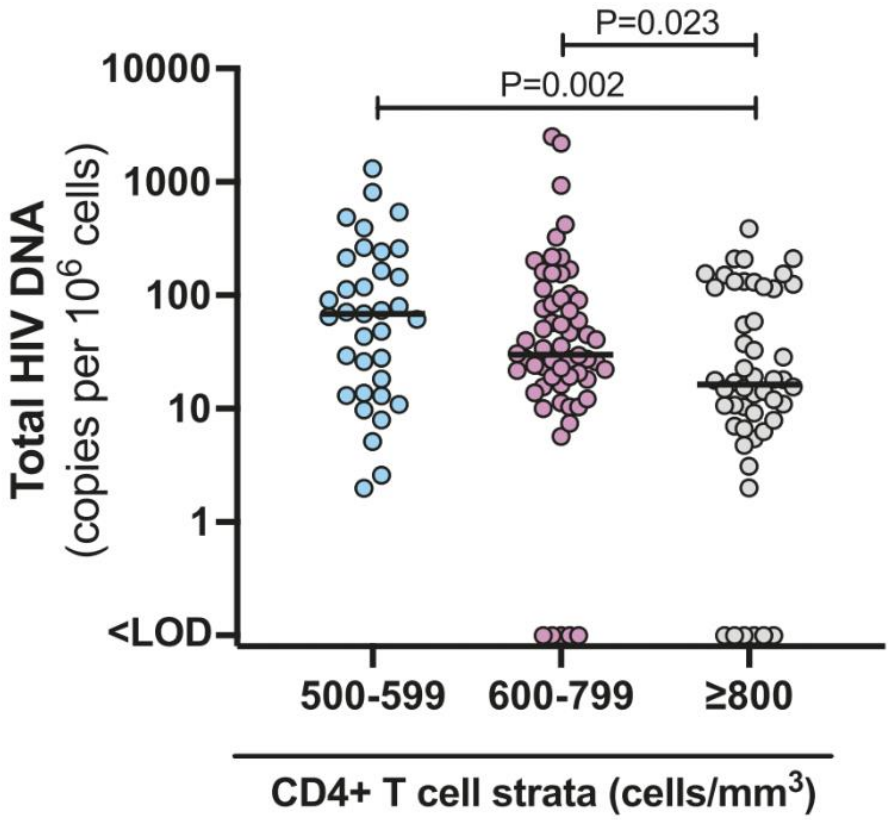
Latent infection

DNA positive
RNA negative
HIV protein negative
SURVIVAL

1)Finzi Science 1997; 2)Colby Nat Med 2018; 3)Whitney Nat Commun 2018; 4) Vanhamel JVE 2019

Higher CD4 count on ART initiation associated with smaller reservoir

- Sub-study of Strategic Timing of Antiretroviral Treatment (START)
- Peru, South Africa, and Uganda: participants commenced immediately on ART
- n=146, 60% female, majority commenced on NRTI/NNRTI
- Measured total HIV-DNA in peripheral blood CD4+ T cells after 36–44 months of ART
- CD4 > 800 associated with significantly lower total HIV DNA



Rasmussen, Clin Infect Dis, 2022

HI-ART pilot study

Hypothesis:

- PWH who start ART with very high CD4 counts (>800 cells) have smaller HIV reservoirs and lower immune activation compared to those who start with CD4 counts<800

Primary objective:

- Measure the frequency of CD4+ T cells containing HIV DNA in PWH with on ART who start antivirals at CD4>800

Secondary objective:

- Characterise reservoir by intact HIV DNA, transcriptional activity, proliferative capacity and immune activation in PWH on ART who start antivirals at CD4>800

Methods

Participants recruited from 2 tertiary hospitals in metropolitan Melbourne

Inclusion criteria

- >18 years old
- On suppressive ART for minimum 2 years
- Available data on CD4 count on ART initiation

HIV reservoir quantification

- Total HIV DNA by digital droplet PCR
- IPDA by digital PCR
- HIV RNA profiling by digital PCR

Analysis

- Comparative statistics with Mann-Whitney test and correlations with Spearmans r test on Prism, linear regression model to determine predictors of reservoir size

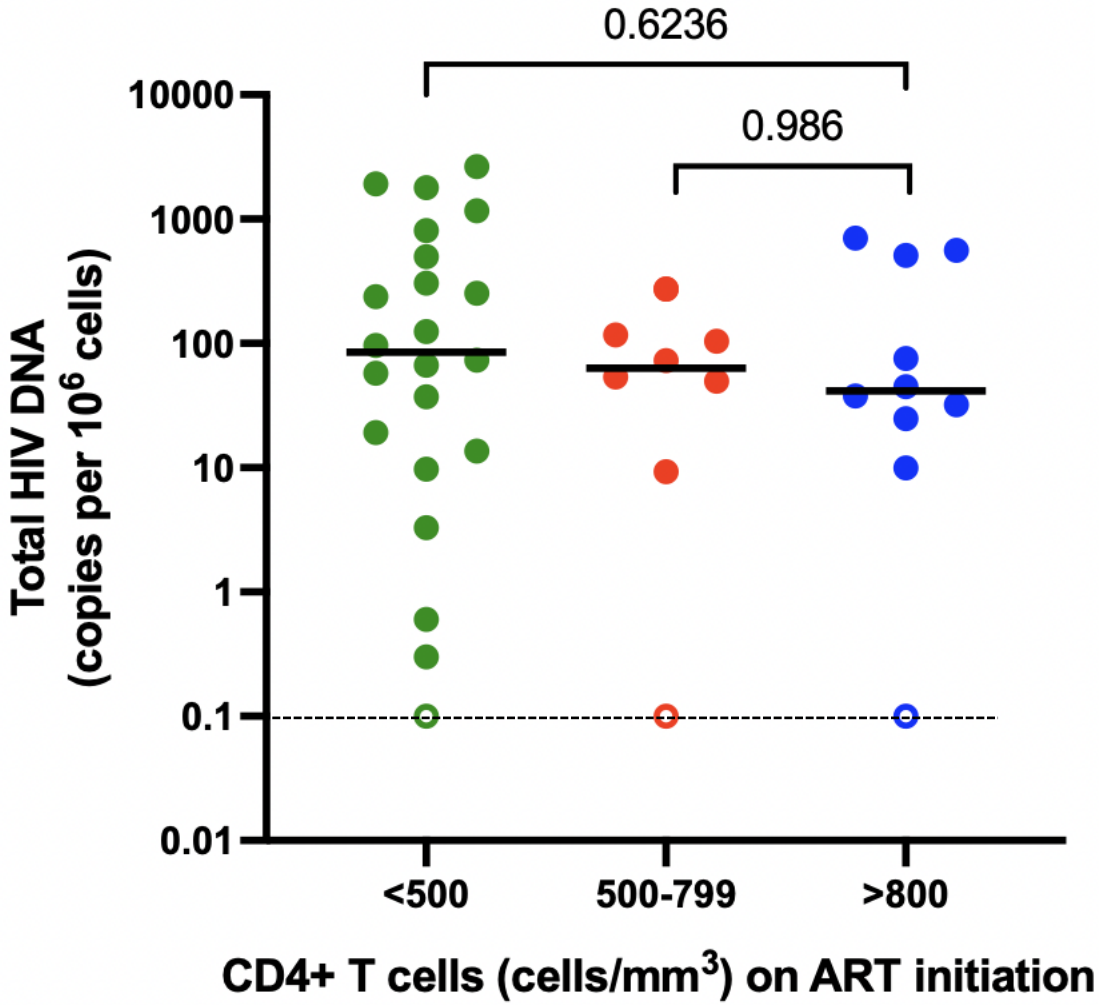
Results

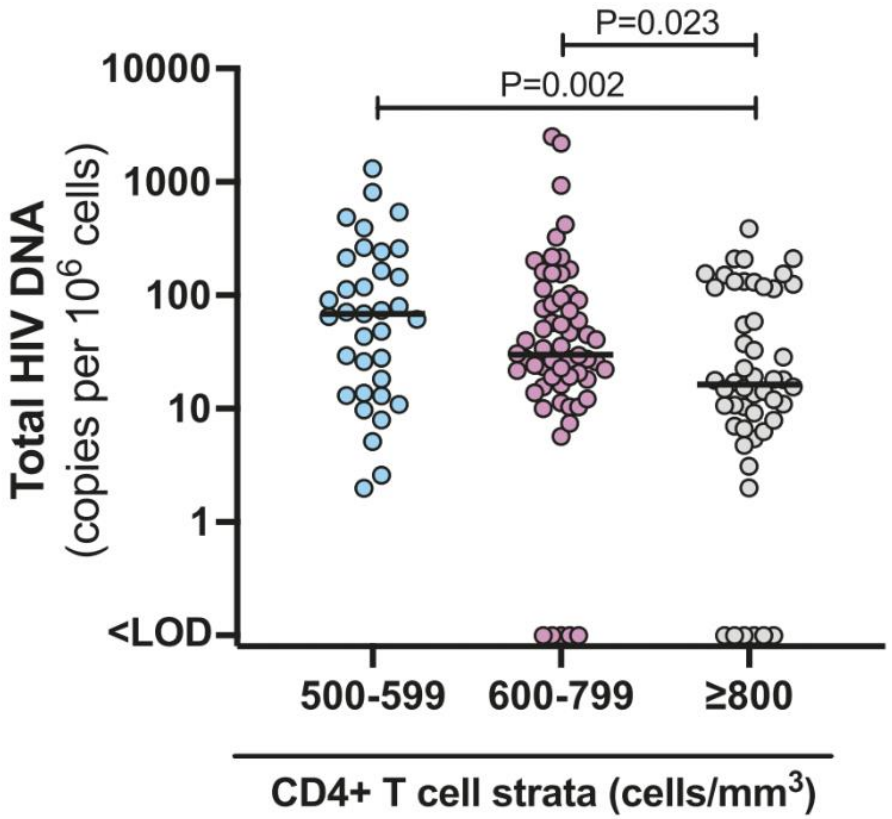
- **n=40 enrolled at 2 clinical sites from Feb '23 and Feb '24**
- **CD4 >800 n= 10**
- **CD4 500-799 n= 21**
- **CD4 <500 n= 9**

n (%)

	<500 n=9	500-799 n=21	>800 n=10
Age (median, IQR)	56 (48-62)	43 (38-55)	49 (38.5-60)
Gender			
Male	13 (61.9)	7 (77.8)	8 (80)
Non-male	8 (38.1)	2 (22.2)	2 (20)
Year of diagnosis			
Pre-2006	7 (33.3)	3 (33.3)	1 (10)
2006-2014	8 (38.1)	4 (44.4)	3 (30)
After 2014	6 (28.6)	2 (22.2)	6 (60)
Timing of ART from HIV diagnosis			
Acute infection (<6m)	11 (52.54)	8 (88.9)	9 (90)
Chronic infection (>6m)	10 (47.6)	1 (11.1)	1 (10)
HIV subtype			
AE	3 (14.3)	0 (0)	3 (30)
B	13 (61.9)	5 (55.6)	3 (30)
C	4 (19)	3 (33.3)	2 (20)
Unknown	1 (4.8)	1 (11.1)	2 (20)

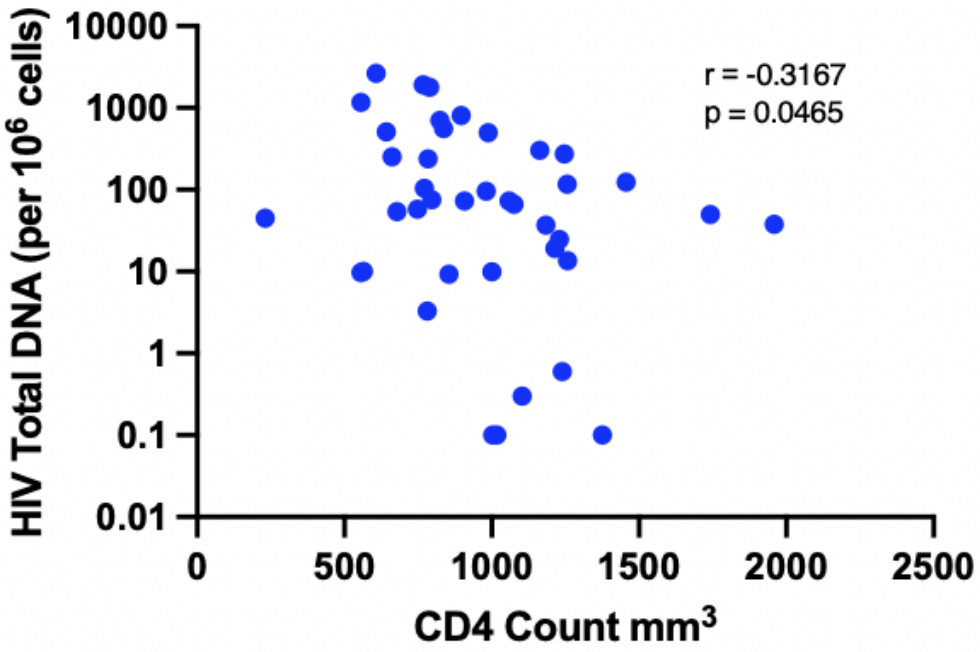
No significant difference in HIV reservoir between CD4 strata on ART initiation

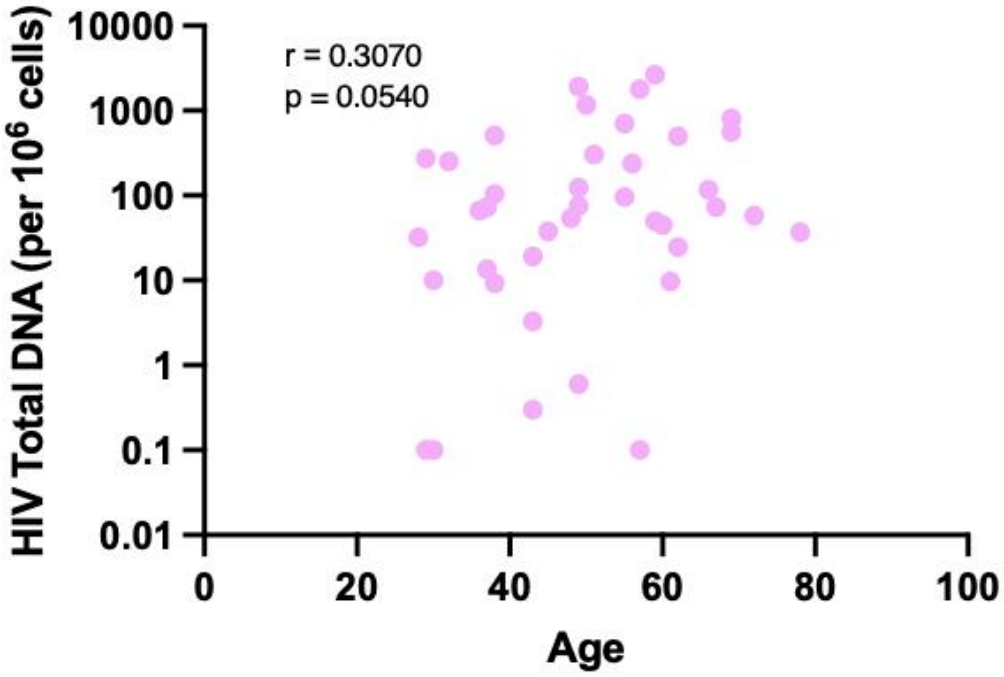




Black line: median, Mann-Whitney test

HIV DNA on ART is inversely correlated with CD4 and positively correlated with age





Spearman's r test

Smaller reservoir associated with diagnosis after 2014

Variable	Estimate	95% CI	p-value
Timing ART			
<6 months (ref)			
>6 months	0.3	0.03 – 2.51	0.25
Year of diagnosis:			
Prior to 2006 (ref)			
2006 – 2013	0.56	0.06 – 5.14	0.59
2014 or later	0.04	0.00 – 0.45	**0.01**
Age	1.02	0.97 – 1.08	0.35
ART:			
insti/nnrti (ref)			
insti/nrti	76.75	2.50 – 2354.44	**0.02**
insti/nrti + booster	1152.8	22.86 – 58145.78	**<0.01**
nrti	81.38	0.95 – 6997.23	**0.05**
nrti/nnrti	2.65	0.01 – 859.35	0.73
nrti/pi	1.19	0.02 – 83.17	0.93
AIDS defining illness:			
No (ref)			
AIDS defining illness: Yes	0.18	0.03 – 1.32	0.09

Linear regression model, estimates back-transformed

- **Lower HIV DNA associated with HIV diagnosis after 2014**
- **Higher HIV DNA associated with several ART regimens, but small numbers and wide CI**
- **CD4 on enrolment, CD4 nadir, and gender not associated with reservoir size (data not shown)**

Discussion

- No difference in HIV DNA in people who start ART with a CD4>800 compared to <800
- Potential reasons for different results from prior observations
  - Small sample size of pilot cohort
  - Different demographics ie MSM, fewer females
  - Different viral subtypes
  - Duration on ART – in previous study all participants were on ART for 36-44 months

- CD4 on study enrolment inversely correlated to reservoir size

- **Could recovery of CD4 count predict reservoir size?**

Clustering CD4 trajectory following ART initiation

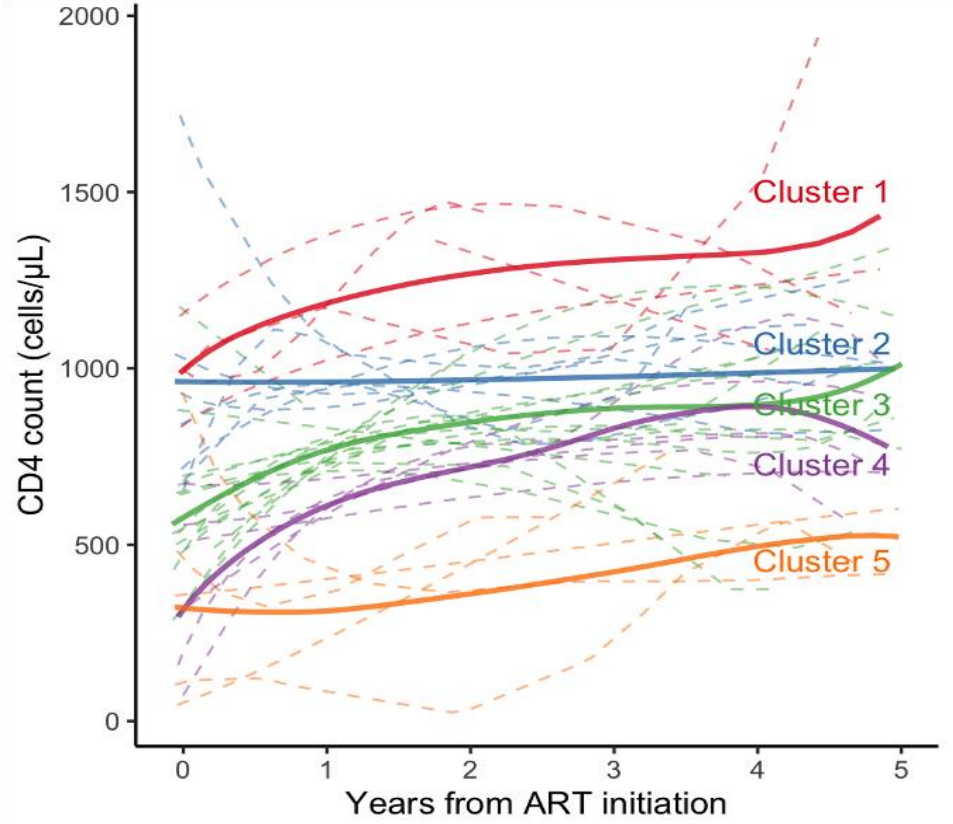
Clustering over the first 5 years from ART start

Clustering methods for longitudinal data:

- Include algorithm and model-based approaches
- Can model non-linear trajectories
- Depending on the approach, can work with data that is unequally spaced, and/or unequal number of measurements between participants

Algorithm-based approach using the Clustcurv package

Using K-medians – 5 clusters predicted

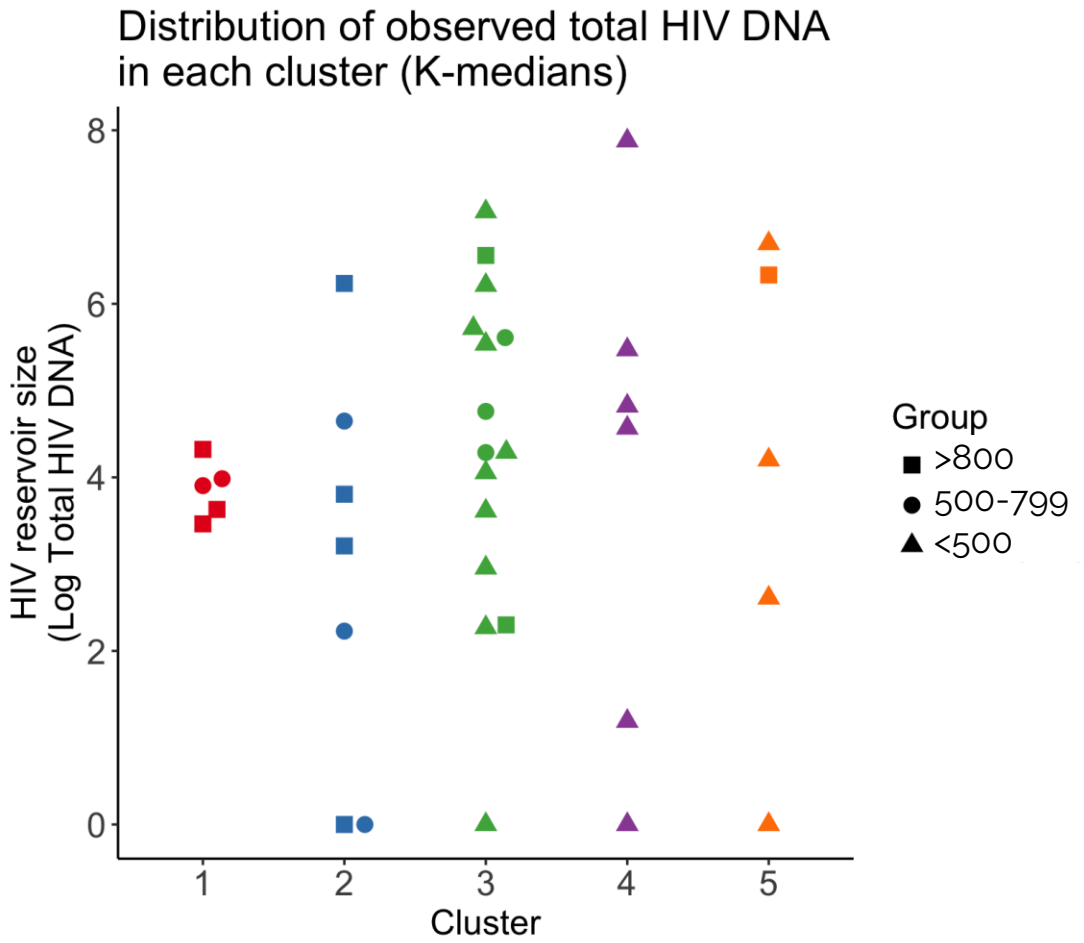


*only able to qualitatively describe clusters

Results

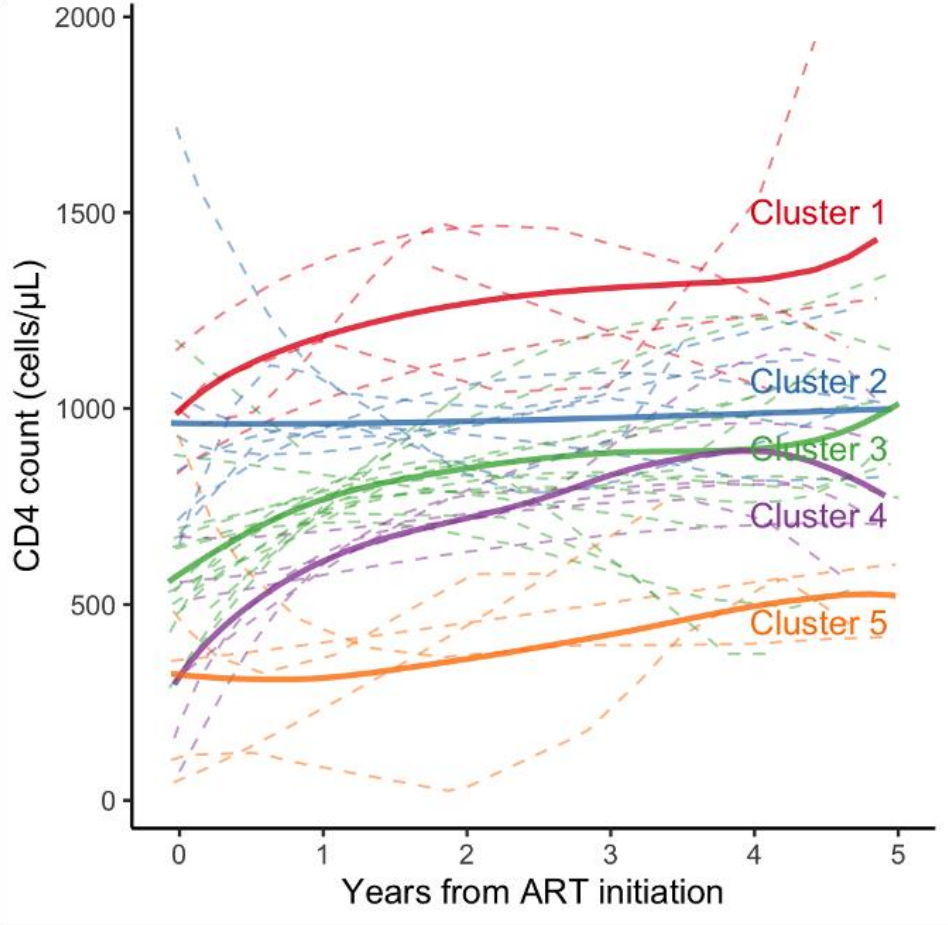
Estimated HIV reservoir size per cluster

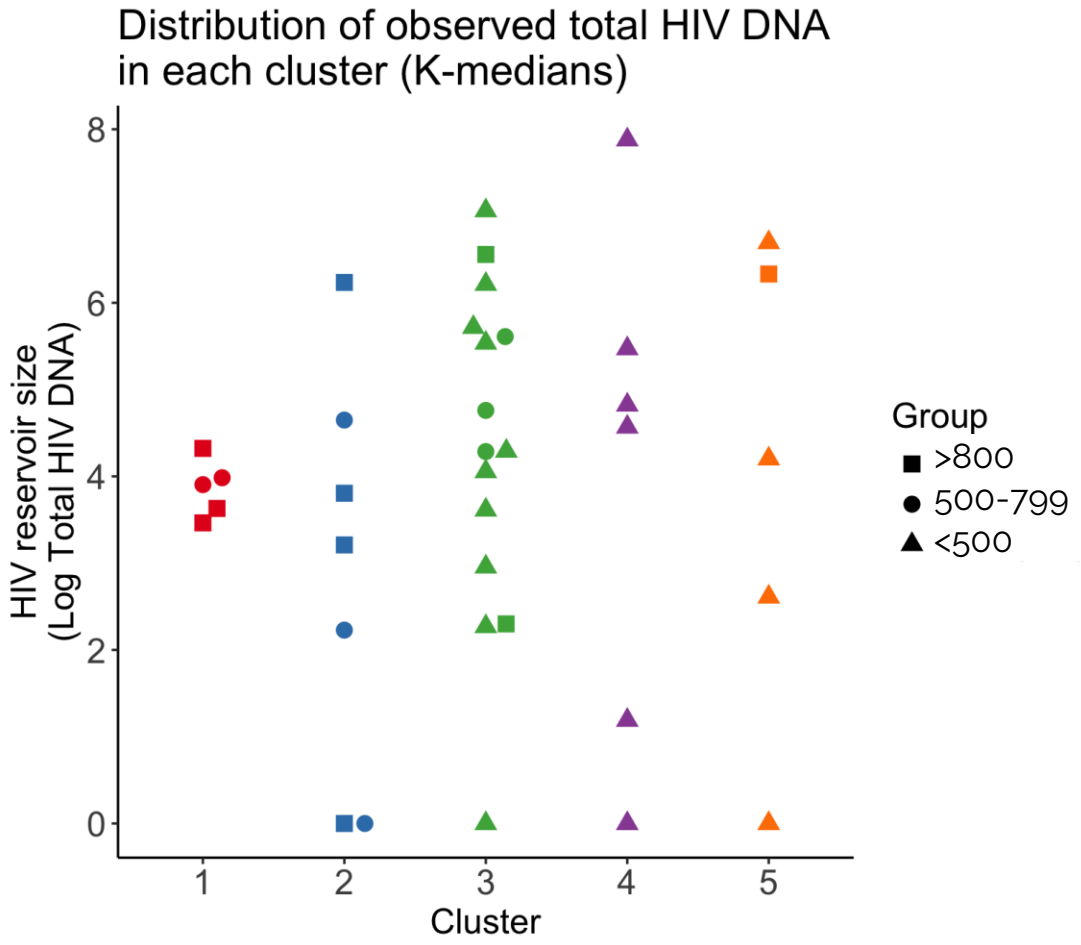
Cluster	Number of participants	Estimated log total HIV DNA	
		Mean estimate	95% CI
1	5	3.86	1.88 – 5.84
2	7	2.88	1.20 – 4.55
3	15	4.35	3.21 – 5.49
4	6	3.99	2.18 – 5.80
5	5	3.97	1.99 – 5.95



Results

Estimated HIV reservoir size per cluster





Conclusions

- In a cohort of primarily MSM in Australia on prolonged ART there were no differences in HIV DNA in people who started ART with CD4 >800 cells
  - In contrast to earlier work with PWH in LMIC on shorter duration of ART
- High CD4 count on enrolment associated with smaller reservoir
  - possibly indicating improved HIV specific immunity, or dilution of infected cells with T cell proliferation on ART
- Smaller reservoirs observed in people who start ART after 2014
  - Potential explanations include modern ART regimens and altered prescribing practices following the publication of the START study
- Further work will fully characterise the size and activity of the reservoir using IPDA and transcriptional profiling
- CD4 recovery can be classified by trajectories
  - Future work will define a quantitative slope or gradient to describe these trajectories, to determine if these can predict reservoir size

Summary slide

What was the purpose of this study? To determine if CD4 counts on treatment initiation could predict the size of the HIV reservoir.

What did we do? We collected blood samples from healthy people living with HIV and measured total HIV DNA. We then compared people with very high CD4 counts on treatment initiation with those who started with lower CD4 counts.

We also looked at CD4 recovery rates after treatment initiation to see if these could be clustered, and if these clusters could predict reservoir size

What were the results? In this small pilot study, did not find a clear association between CD4 counts on treatment initiation or CD4 recovery after treatment, and reservoir size.

How will these findings help people living with HIV? If we can predict reservoir using a commonly used clinical blood test, we may be able to identify people to prioritise for early clinical studies testing HIV cure interventions

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Kathryn Cisera

NAPWHA
John Rule

The people with HIV who participated in this study

HIV cure cross track session (11E)

Wednesday, 11:00 AM - 12:30 PM, Riverbank Room 7&8

Prof James McMahon

Clinical cure trials

Assoc. Prof Najla Nasr

Cure basic research

Jacqui

Participant in

HIV cure trial

Scott Harlum (NAPWHA)

Community perspectives

Panel discussion: Modern Day controversies and potential for cure research with speakers and a participant of a recent HIV cure clinical trial