RIVER

Research In Viral Eradication of HIV Reservoirs

The impact of vorinostat & therapeutic vaccine on gut HIV DNA
The RIVER gut study

Presented by Dr John Thornhill

on behalf of the RIVER study team and investigators

NHS National Institute for Health Research

BHIVA British HIV Association

CHERUB

Imperial College London

MRC Medical Research Council

UNIVERSITY OF CAMBRIDGE

MRC Clinical Trials Unit

UCL

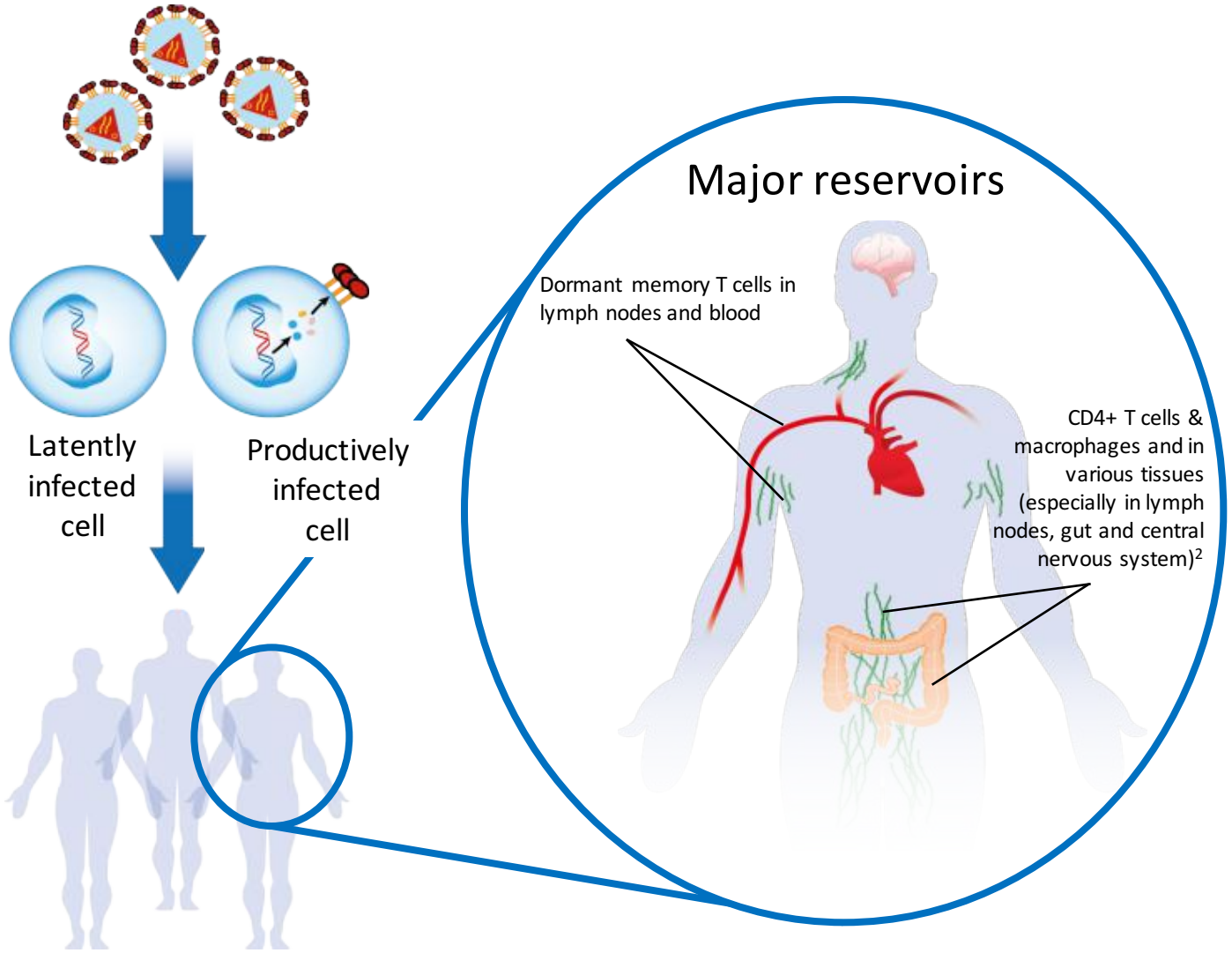
UNIVERSITY OF OXFORD

Barriers to HIV cure: viral latency and reservoirs

HIV infects CD4+ cells

Some become resting memory cells; 'reservoir' [1]

Gut associated lymphoid tissue is the largest collection of CD4+ cells in the body [2]

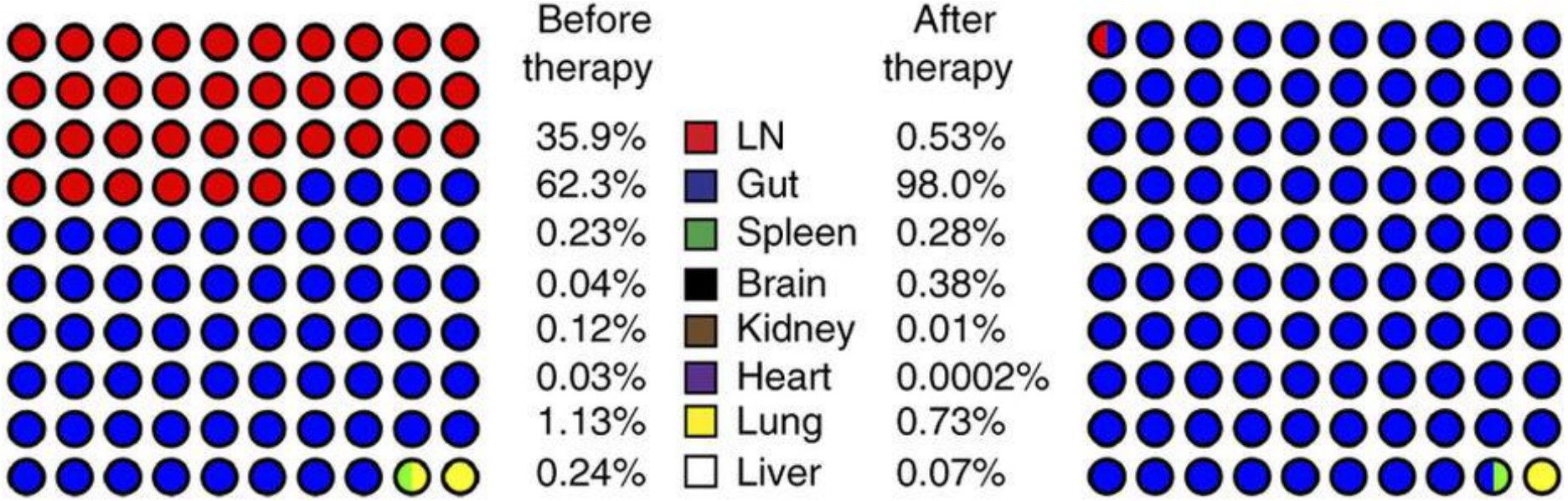


1. Finzi D et al Science 1997; 278: 1295-300
2. Mowat AM, Viney JL. . Immunological reviews 1997; 156: 145-166.

Figure adapted from Coiras M, et al. Nat Med 2009;7:798–812

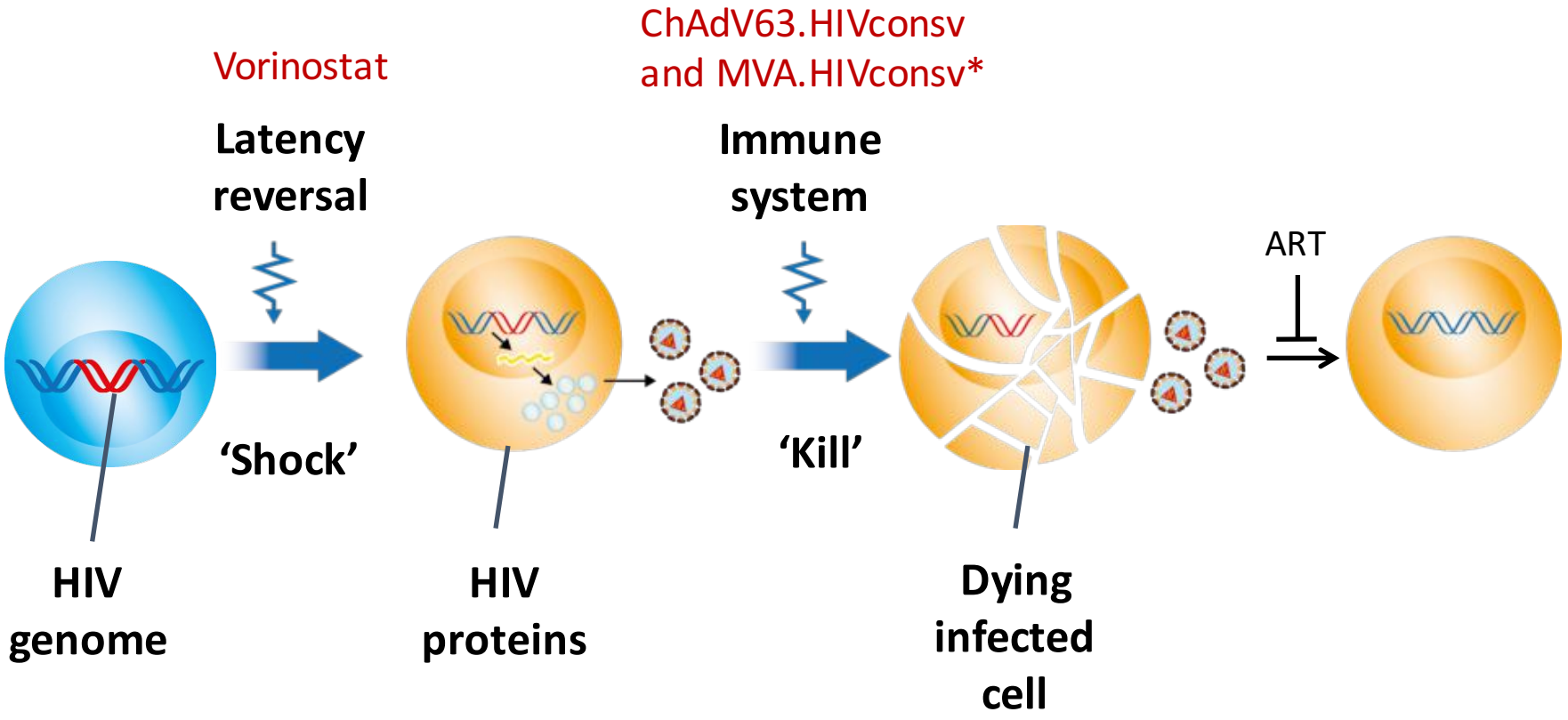
On ART – Gut-associated lymphoid tissue (GALT) is a key site of HIV persistence

Graphical representation of the proportion of vRNA^{+} cells in each organ system before and during suppressive ART.



Estes et al. Nature Medicine 2017

The RIVER study investigated the HIV Cure approach "Kick and Kill"



1. Deeks SG. Nature 2012;487:439–40. 2. Walker-Sperling VE, et al. J Virol 2015;89:9631–8.

RIVER study design

- **Cohort - Treated Primary HIV infection**:
  - lowest reservoirs, preserved immune responses
- **The Kick:**
  - HDAC inhibitor Vorinostat
- **The Kill:**
  - ChAdV63.HIVconsv and MVA.HIVconsv*
- **Design:**
  - Randomised control comparison with ART alone
- **Primary endpoint:**
  - Total HIV DNA in peripheral blood CD4+ T-cells at weeks 16 & 18 post randomisation

The RIVER gut study compared HIV DNA, markers of immune activation & exhaustion in GALT, and microbial translocation in subset of RIVER participants by study arm.

*Letourneau S Plos One 2007

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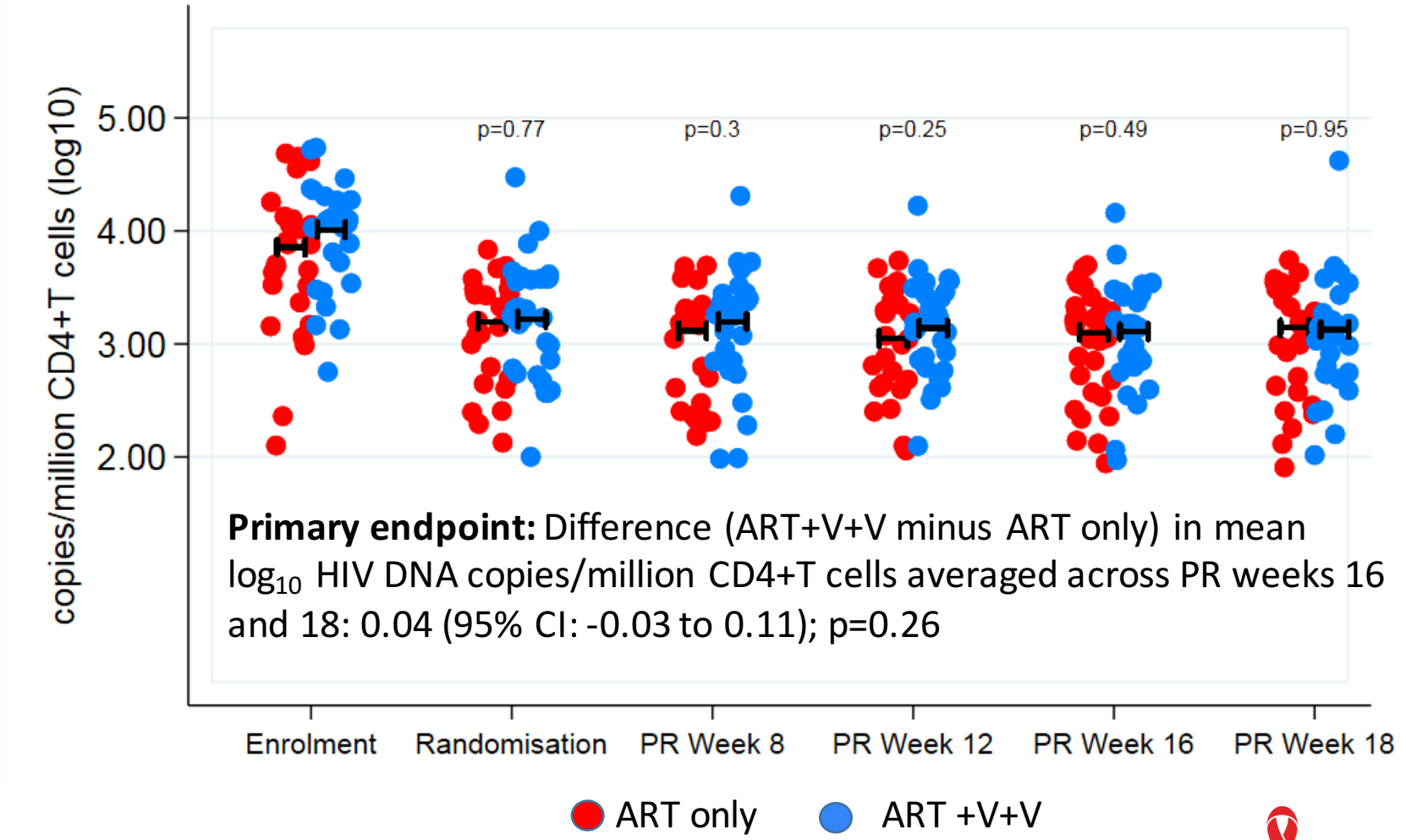
The RIVER RCT – Main Study Results



Primary endpoint: Difference (ART+V+V minus ART only) in mean $\log_{10}$ HIV DNA copies/million CD4+T cells averaged across PR weeks 16 and 18: 0.04 (95% CI: -0.03 to 0.11); p=0.26

Fidler et al. 22nd IAC, 23-27th July 2018, the Netherlands

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Methods

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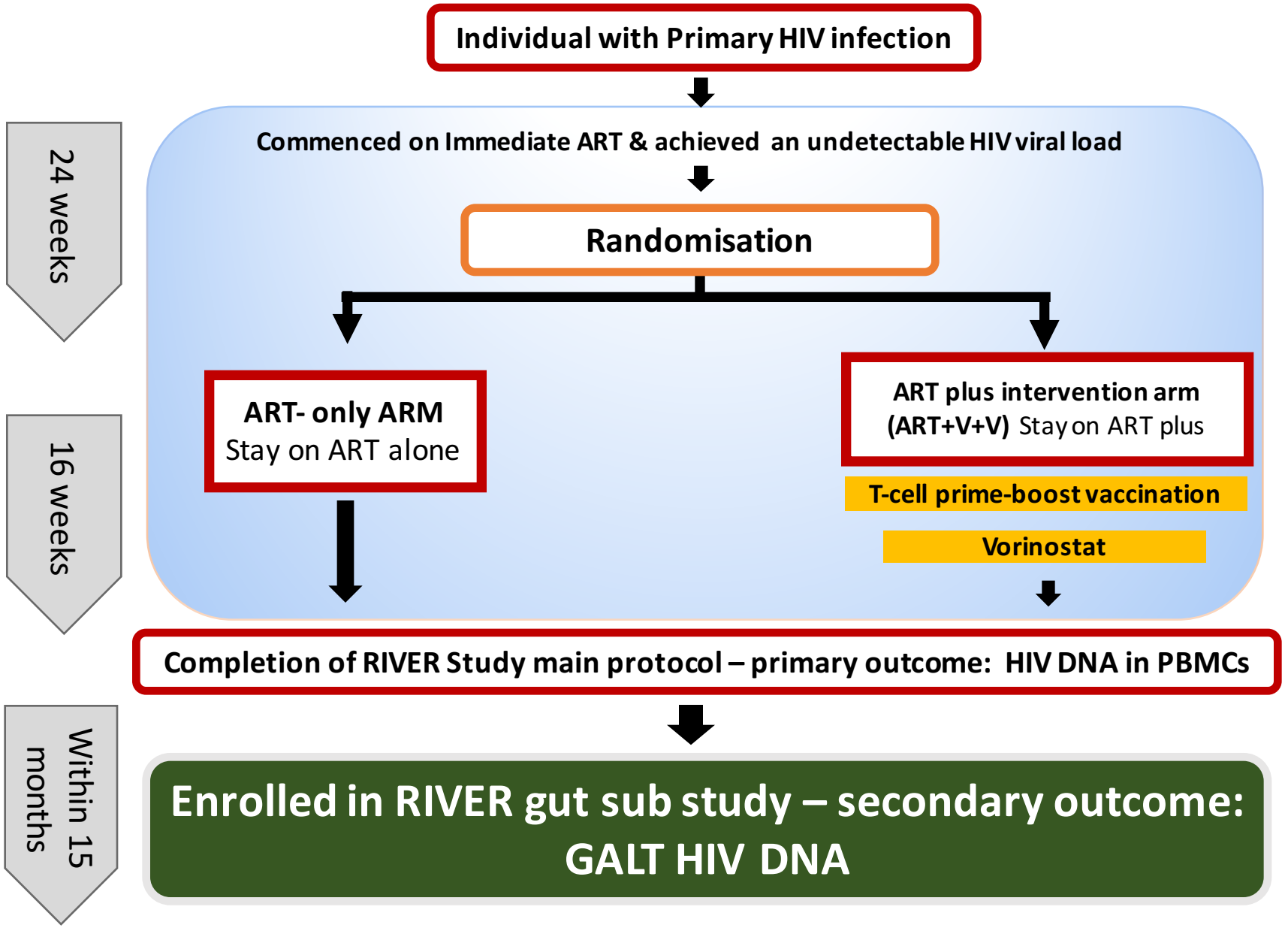
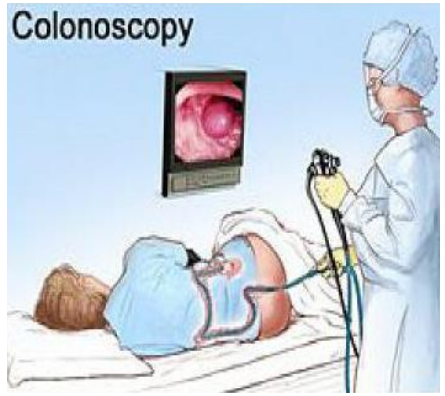
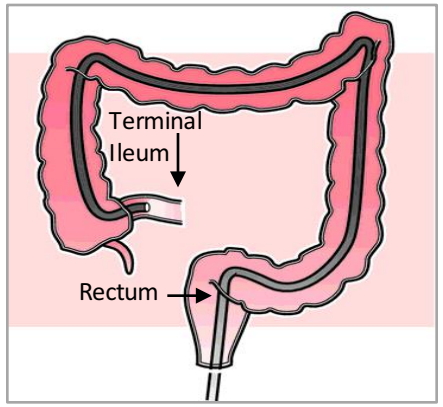
RIVER gut study design



RIVER Gut study - methods

RIVER study participants who completed the main study protocol enrolled at 2 London sites





1. Gut Biopsies
- Rectum
- Terminal Ileum

2. Blood Samples
- PBMCs
- Plasma

Laboratory assays

HV Reservoir
- Total HIV DNA qPCR assay

Tissue p24 levels
- p24 measured in activated tissue supernatants

Immune Activation & Immune exhaustion in gut
- HLA-DR, CD38 & PD-1 expression measured on CD4+ cells by flow cytometry

Marker of bacterial translocation
- **sCD163 & sCD14 was measured in plasma**

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Results

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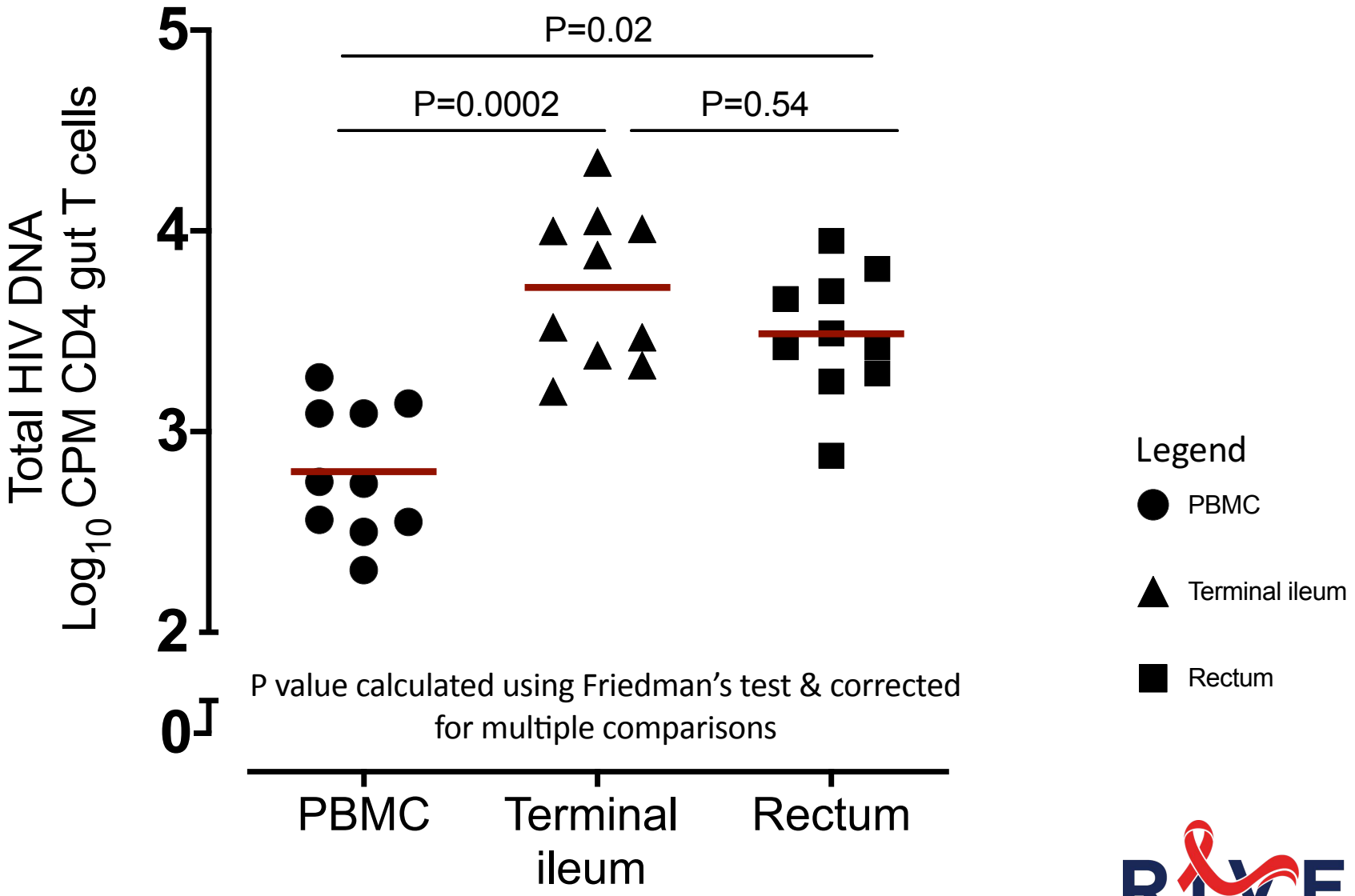
RIVER Gut study – participant characteristics

	ART-plus-intervention Arm (n=6)	ART-only Arm (n=5)	P value
Age	37 (27-46)	33 (27-35)	0.62
Results at Enrolment*:			
HIV viral load, Log_{10} CPM	4.1 (3.9-5.3)	4.9 (4.6-5.6)	0.38
CD4 count cells/mm^3	492 (435-561)	543 (449-548)	
CD4/CD8 ratio	0.55 (0.35-0.90)	0.54 (0.49-0.58)	0.97
Median (IQR) time from:			
EDI to ART start, days	75 (31-86)	65 (25-97)	0.93
Completed RIVER protocol to biopsy, months	9 (3-14)	6 (6-14)	0.69
ART start to biopsy	22 (21-24)	17 (16-22)	0.42
Results at time of Biopsy:			
CD4 count cells/mm^3	669 (618-920)	1058 (809-1186)	0.06
CD4/CD8	1.40 (1.18-1.5)	1.60 (1.28-2.13)	0.51
HIV viral load	<20	<20	

Values given represent n (%) categorical variables and median (interquartile range) for continuous variables. * refers to measure closest to serconversion. Abbreviations: EDI, estimated date of infection; RITA, recent infection testing algorithm. EDI, estimated date of HIV infection

Gut HIV DNA levels, all participants



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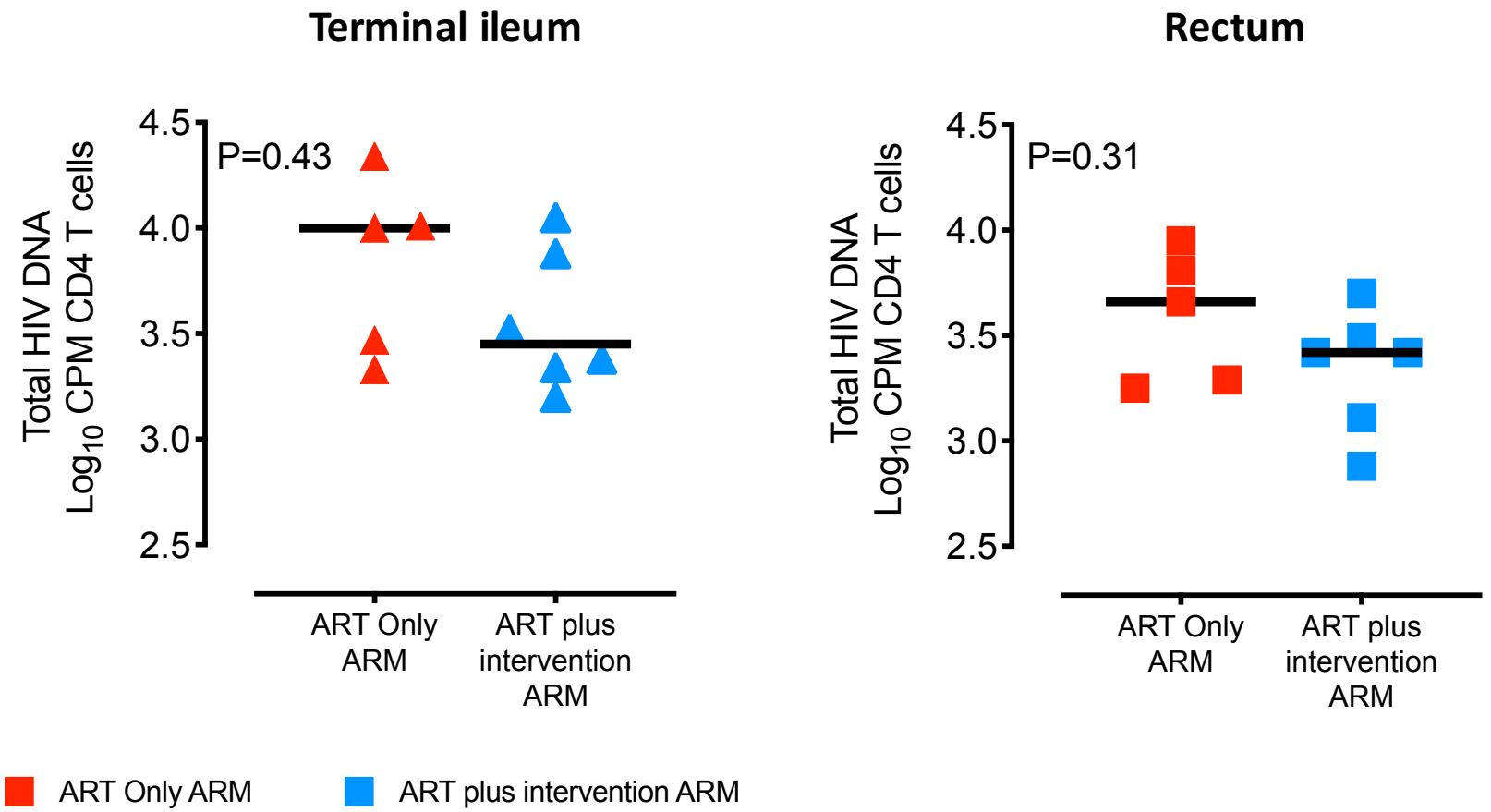
HIV DNA level in Gut-Associated Lymphoid Tissue (GALT), by study arm



No Difference in measures of HIV reservoir in GALT between study arms

P values calculated using a Mann-Whitney test

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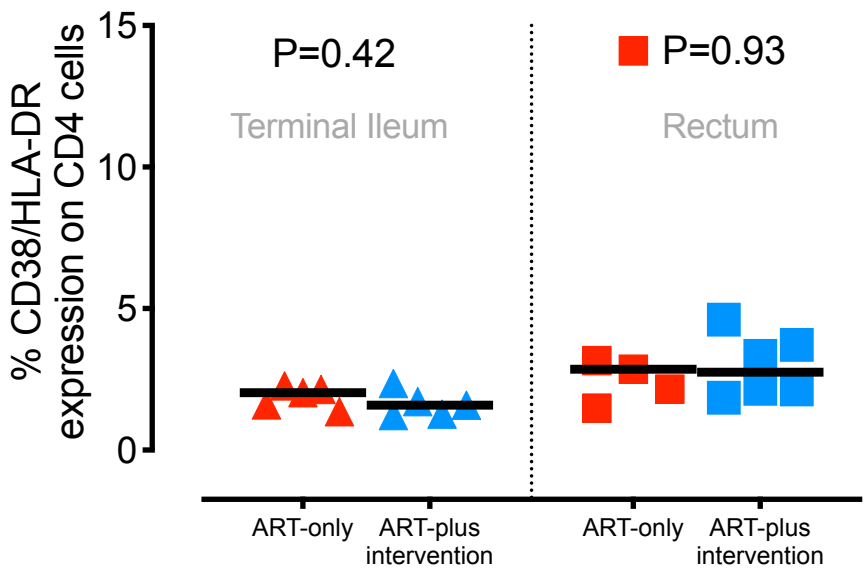
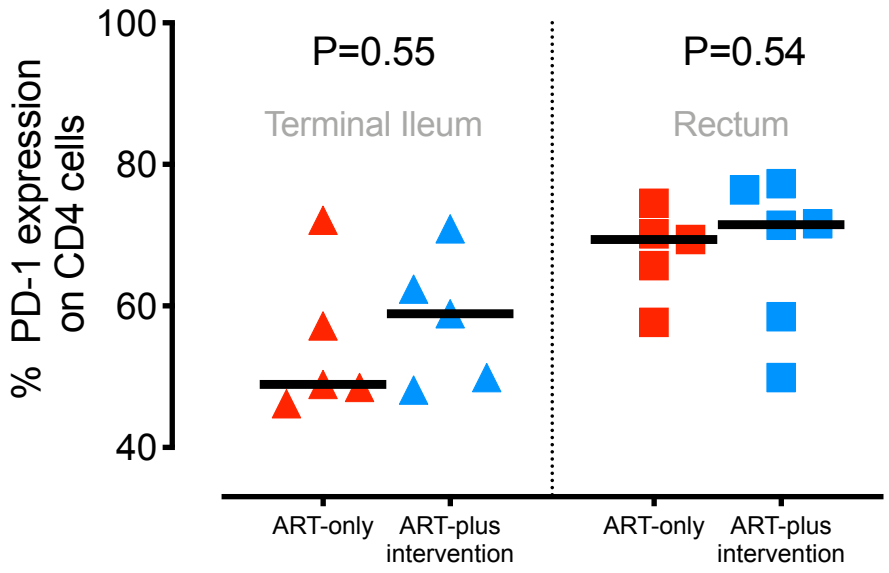
Immune activation & exhaustion in GALT, by study arm

CD38⁺/HLA-DR⁺ expression on CD4+ cells



PD-1 expression on CD4+ cells



ART Only ARM ART plus intervention ARM

No Difference in immune activation or exhaustion in GALT between study arms

P values calculated using a Mann-Whitney test

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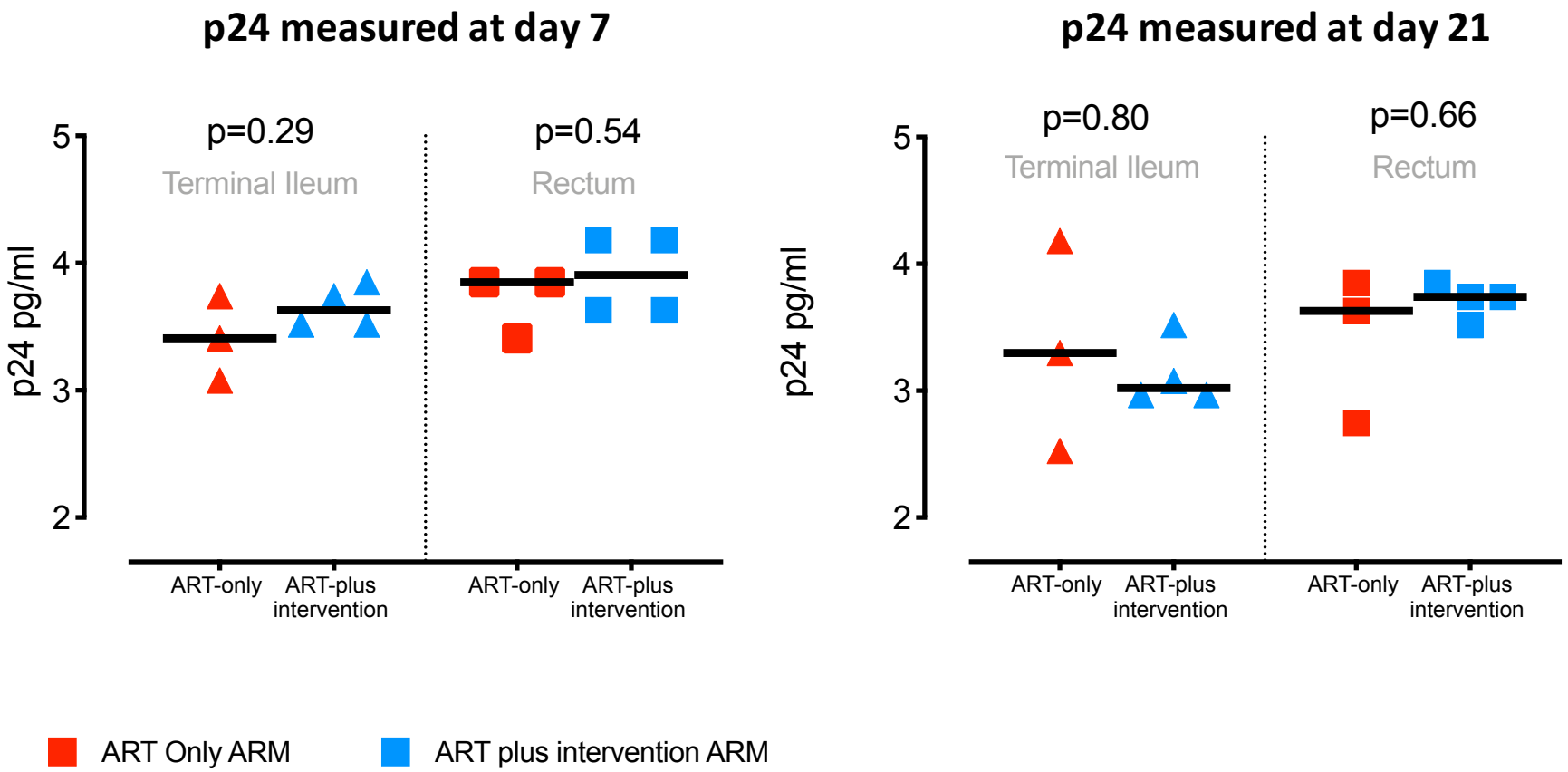
p24 measured in tissue cultures, by study arm



No Difference in p24 production at day 7 or day 21 post activation, between study arms

P values calculated using a Mann-Whitney test

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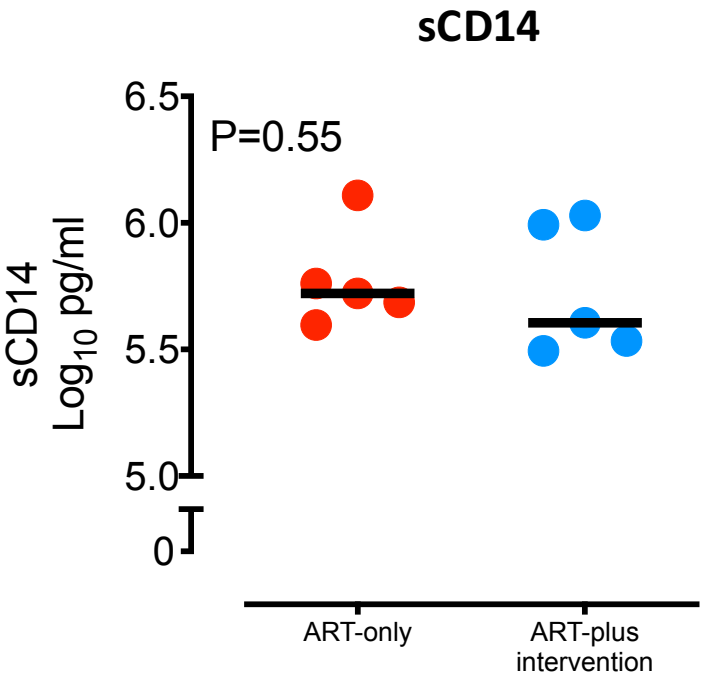
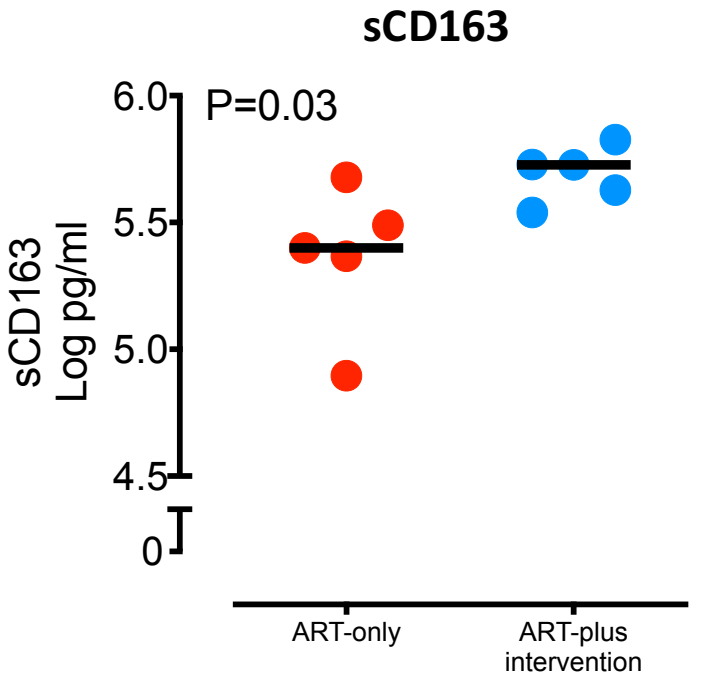
Bacterial Translocation, by study arm





ART Only ARM ART plus intervention ARM

No Difference in sCD14 but higher levels of sCD163 were observed in the ART plus intervention arm

P values calculated using a Mann-Whitney test

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Limitations

- Unlike the main RIVER study which examined HIV DNA in PBMCs, this sub study had a small sample size and the findings should be interpreted with caution

- However, tissue data is lacking from most studies of HIV cure and this data adds important insights in to the impact of cure interventions on HIV tissue reservoir

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Conclusions

- These data suggest that vorinostat in combination with a T-cell prime-boost-vaccine during PHI did not impact the GALT HIV reservoir
- Similarly measures of immune exhaustion & activation on GALT CD4+ T-cells were not impacted by the intervention
- Measures of bacterial translocation appear to be increased in ART plus intervention compared to ART-only arm warranting further investigation in a larger cohort

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Funding

Thank you to BHIVA and the MRC for their funding of the RIVER gut study

- BHIVA research award
- MRC clinical research training fellowship

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British HIV Association

MRC Medical Research Council

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All the RIVER gut study participants

RIVER Chief Investigator: Sarah Fidler
RIVER co-investigator and laboratory lead: John Frater
RIVER Gut Study Collaborators: Jonathan Hoare, Heather Lewis & Simon Peake
RIVER statisticians: Abdel Babiker, Wolfgang Stöhr

RIVER laboratory investigators: Lucy Dorrell, Tom Hanke, Andrew Lever, Myra McClure, Steve Kaye, Matt Pace, Axel Fun, Mikaila Bandara, Maryam Khan, Andrew Lovell, HongBing Yang, Jakub Kopycinski, Natalia Olejniczak, Helen Brown, Nicola Robinson, Otto Erlwein, Alison Crook

RIVER trial management team: Rachel Bennett, Michelle Gabriel, Fleur Hudson, Aminata Sy, Adam Gregory, Mary Rauchenberger, Yinka Sowunmi, Shaadi Shidfar, Dominic Hague, Hanna Box, Cherry Kingsley, Katie Topping, Gemma Wood, Charlotte Russell, Sarah Pett

RIVER clinical investigators: Sarah Fidler, Sabine Kinloch, Sarah Pett, Julie Fox, Amanda Clarke, Mark Nelson, Margaret Johnson

RIVER Trial Steering Committee (TSC): Independent Members: Eric Sandström , Janet Darbyshire, Frank Post, Chris Conlon, Jane Anderson, Mala Maini

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King's College London Guy's and St Thomas' NHS
Imperial College London Imperial College Healthcare NHS
University of Cambridge Oxford Radcliffe Hospitals NHS
Cambridge University Hospitals NHS

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Community of people living with HIV: Simon Collins, Damian Kelly

CHERUB collaboration

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