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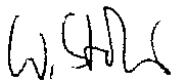
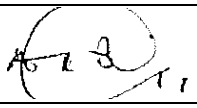
FINAL STATISTICAL REPORT

Version 1.0

28. March 2019

Author	**Position**	**Signature**	**Date**
Wolfgang Stöhr	Trial Statistician		28.3.2019
Approved by	**Position**	**Signature**	**Date**
Abdel Babiker	Project Lead & Statistician		28.3.2019
Sarah Fidler	Chief Investigator		28.3.2019

Revision History

Version	Author	Date	Reason for Revision
0.1	W Stöhr	22-Oct-2018	First full draft
0.2	W Stöhr	31-Oct-2018	Reviewed by R Bennett
0.3	W Stöhr	22-Nov-2018	Reviewed by S Pett, A Babiker, S Fidler, J Frater, L Dorrell.
0.4	W Stöhr	02-Feb-2019	Final edits
1.0	W Stöhr	28-Mar-2019	Approved version

TABLE OF CONTENTS

1 ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse Event
AEB	Average amount of enzyme per bead
ANCOVA	Analysis of covariance
ART	Antiretroviral therapy
cART	Combination Antiretroviral Therapy
CRF	Case Report Form
CTU	Clinical Trials Unit
DNA	Deoxyribonucleic acid
ECG	Electrocardiography
eGFR	Estimated Glomerular Filtration Rate
HDACi	Histone deacetylase inhibitors
HIV	Human Immunodeficiency Virus
IMP	Investigational medicinal product
ITT	Intention to Treat
IUPM	Infectious Units per Million cells
MRC	Medical Research Council
MRC CTU	Medical Research Council Clinical Trials Unit at UCL
PBMC	Peripheral blood mononucleated cell
PHI	Primary HIV-1 infection
PR	Post-Randomisation
QTc	Corrected QT interval (ECG)
RITA	Recent Infection Testing Algorithm
RIVER	Research In Viral Eradication of HIV Reservoirs
RNA	Ribonucleic acid
SAE	Serious Adverse Event
uPCR	Urine protein to creatinine ratio
ULN	Upper Limit of Normal
VL	HIV viral load

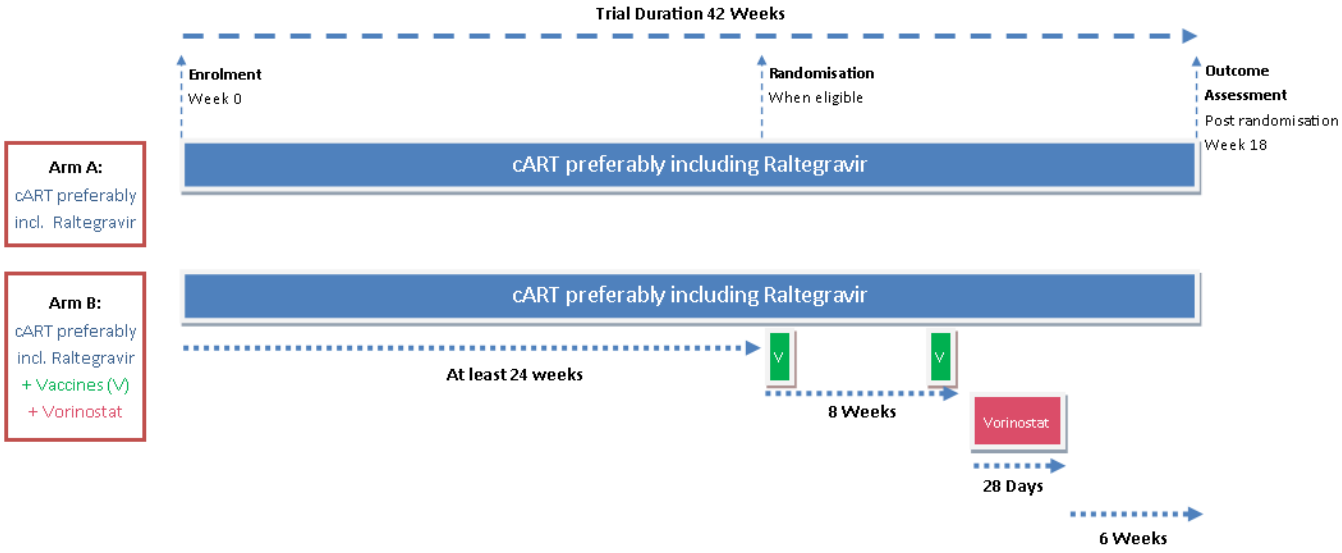
2 OVERVIEW OF RIVER

2.1 SUMMARY

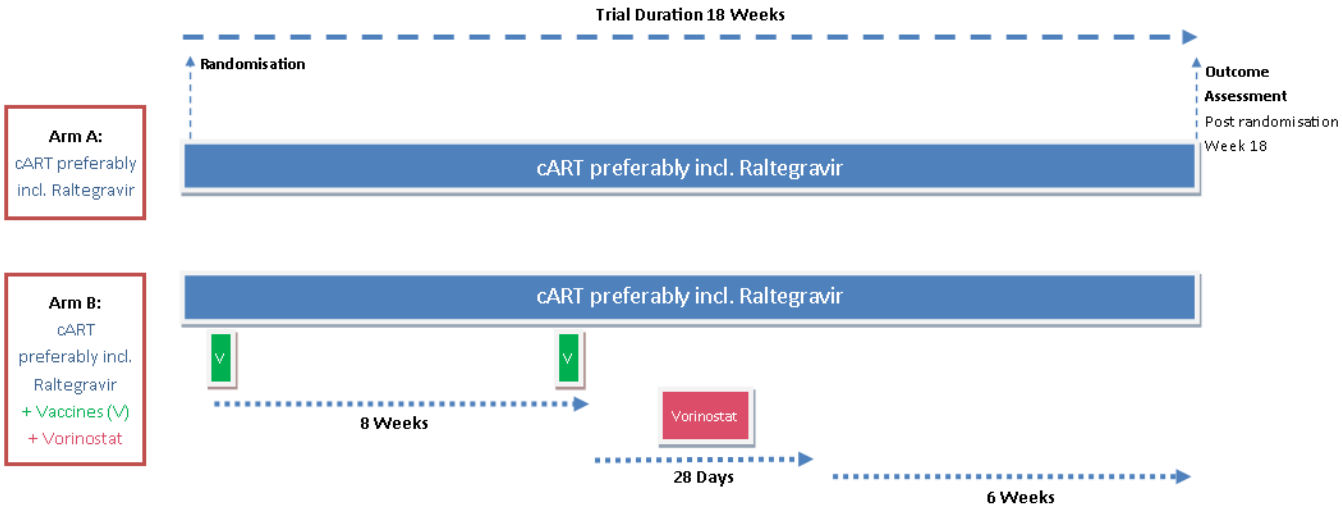
TRIAL NAME	RIVER (RESEARCH IN VIRAL ERADICATION OF HIV RESERVOIRS)
Interventions to be compared	This study is a two-arm prospective randomised controlled trial comparing: **ART only:** 4-drug cART including raltegravir (control) **ART +V+V:** 4-drug cART including raltegravir plus ChAdV63.HIVconsv prime and MVA.HIVconsv boost vaccines; followed by a 28-day course of vorinostat (10 doses in total).
Study Hypothesis	In primary HIV infection, a combination of immediate cART, immunisation and latency reactivation using the HDACi vorinostat will confer a significant reduction in the reservoir when compared with cART alone.
Participants	The study aims to enrol 60 individuals across 6 UK collaborating clinical centres, from two different strata: Stratum I: Recently diagnosed with primary HIV-1 infection [see protocol for definition]. Participants must be enrolled within 4 weeks of a confirmed diagnosis of primary HIV-1 infection. Eligible participants are enrolled at week 0 when combination ART (cART) begins. Randomisation of participants occurs after assessment of eligibility at week 22. **Stratum II:** Previously diagnosed with primary HIV-1 infection. Confirmed diagnosis of primary HIV-1 infection must be within a maximum of 2 years prior to randomisation. Participants must have started at least 3-drug ART within 4 weeks of a confirmed diagnosis of primary HIV-1 infection and remained on ART since starting. Randomisation of participants occurs within 2 weeks of the assessment of eligibility at screening.
Randomisation	The participants enrolled in the trial are randomised in a 1:1 ratio to one of two intervention arms, with randomisation stratified by the two strata defined above.

2.2 TRIAL SCHEMA

Stratum I - Recently diagnosed



Stratum II - Previously diagnosed



2.3 OUTCOME MEASURES

2.3.1 PRIMARY OUTCOME MEASURE

The primary outcome measure is total HIV DNA from CD4 T-cells averaged across post-randomisation weeks 16 and 18.

2.3.2 SECONDARY OUTCOME MEASURES

- Clinical and laboratory adverse events, all grades, including SAE
- Further assessment of the HIV reservoir e.g. HIV integrated DNA; HIV cell associated RNA; plasma HIV RNA measured with an ultra-low copy assay i.e. with a threshold of <1 copy/ml, viral outgrowth assays
- Studies of immune function including measuring the latently-infected resting memory T-cells and HIV-specific T cell responses (in protocol vs 5.0: cytotoxic immune responses)
- Changes in inflammatory biomarkers

2.4 SAMPLE SIZE

The sample size calculation is based on the primary endpoint which will be analysed on a $\log_{10}$-scale. The following assumptions are made:

- The combination intervention will confer a 50% reduction in total HIV DNA when compared with cART alone. On a $\log_{10}$-scale this corresponds to a difference between the two arms of $\log_{10}$ (2) (approximately 0.3). The effect is assumed to be the same in both strata (recently and previously diagnosed patients).
- Standard deviation (SD) is 0.4 for a single measurement in both arms based on two publications:
    - Reported on data from 31 participants treated with HAART at PHI in the French PRIMO study. The median (IQR) at 6 and 12 months after starting treatment were 2.30 (2.10, 2.70) and 2.10 (1.80, 2.40) $\log_{10}$ DNA copies/10^6 PBMC respectively suggesting a SD of 0.45 at both time points[57].
    - Reported on 8 participants with PHI. At week 52, the median (IQR) was 494 (250 - 694) for total HIV-1 DNA copies/10^6 CD4+ T-cells suggesting a SD (in log scale) of 0.33[49].
- 1:1 allocation of participants in the two study arms.
- Method of analysis: comparing the treatment arms in terms of absolute HIV total DNA level at post-randomisation weeks 16 and 18 adjusted for baseline (here: randomisation) level (analysis of covariance; ANCOVA); one baseline measurement and two follow-up measurements (at PR16 and 18) will be taken for an individual participant.
- A correlation coefficient of 0.5 between a baseline measurement and a PR 16/18 measurement, and a correlation coefficient of 0.7 for measurements at PR 16 and 18.
- Two-sided $\alpha = 0.05$ for the null hypothesis that there is no difference between the two arms in the primary endpoint.

Under the above assumptions, a sample size of 52 individuals would provide 94% power to detect a 50% reduction in HIV total DNA (86% power for a 45% reduction).

Assuming that some individuals enrolled will not reach visits PR 16/18 (due to failing the eligibility criteria for randomisation in stratum I, or withdrawal) it is planned to enrol a total of 60 individuals overall (both strata combined).

2.5 DATES OF DATA FREEZE

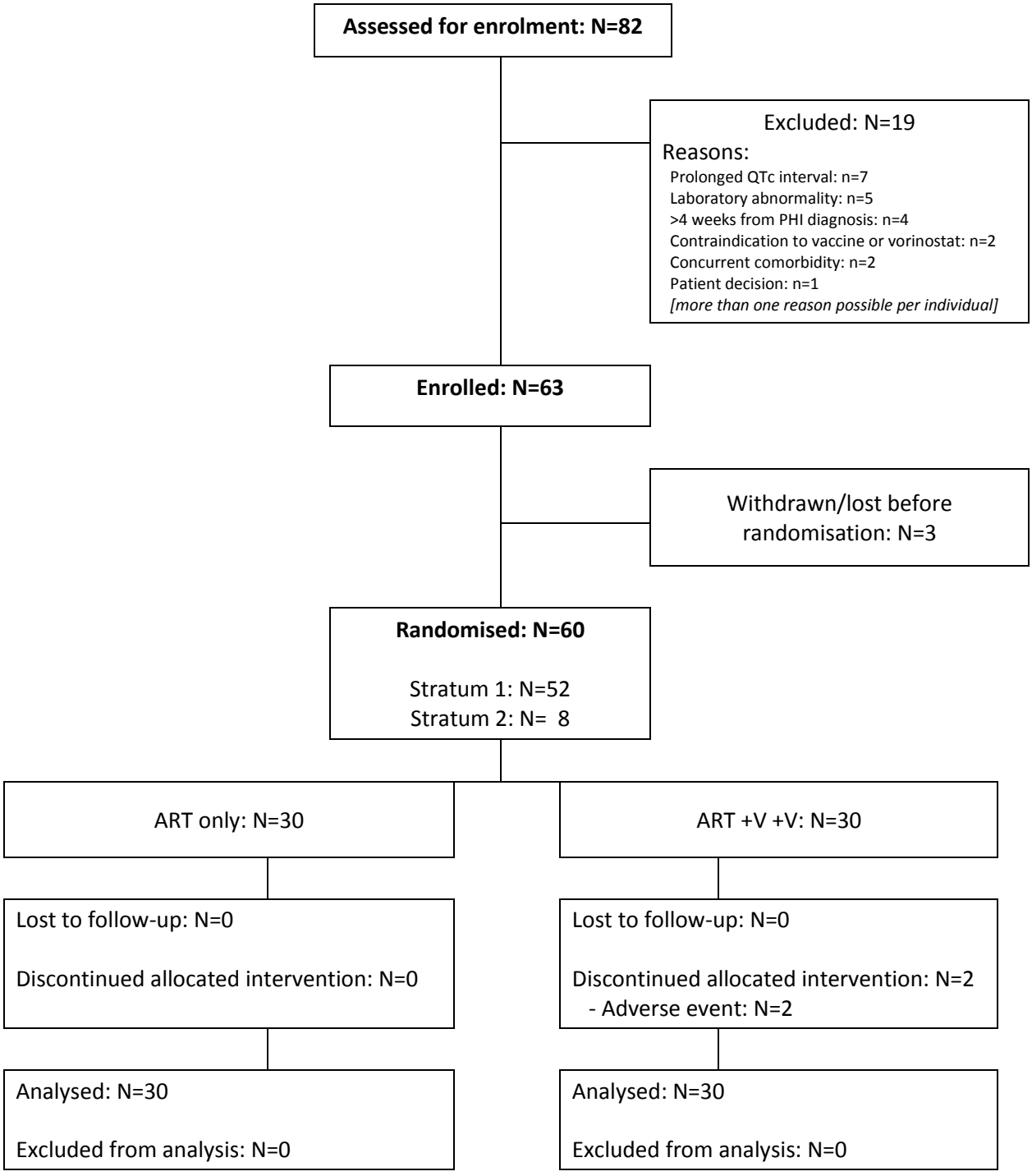
2.5.1 INTERIM ANALYSES

Date of download	Date if IDMC meeting	Meeting
27-11-2016	06-12-2016	1st IDMC meeting
26-03-2017	03-2017	2nd IDMC review (no meeting/call; report reviewed by email)
03-09-2017	12-09-2017	3rd IDMC meeting

2.5.2 FINAL ANALYSIS

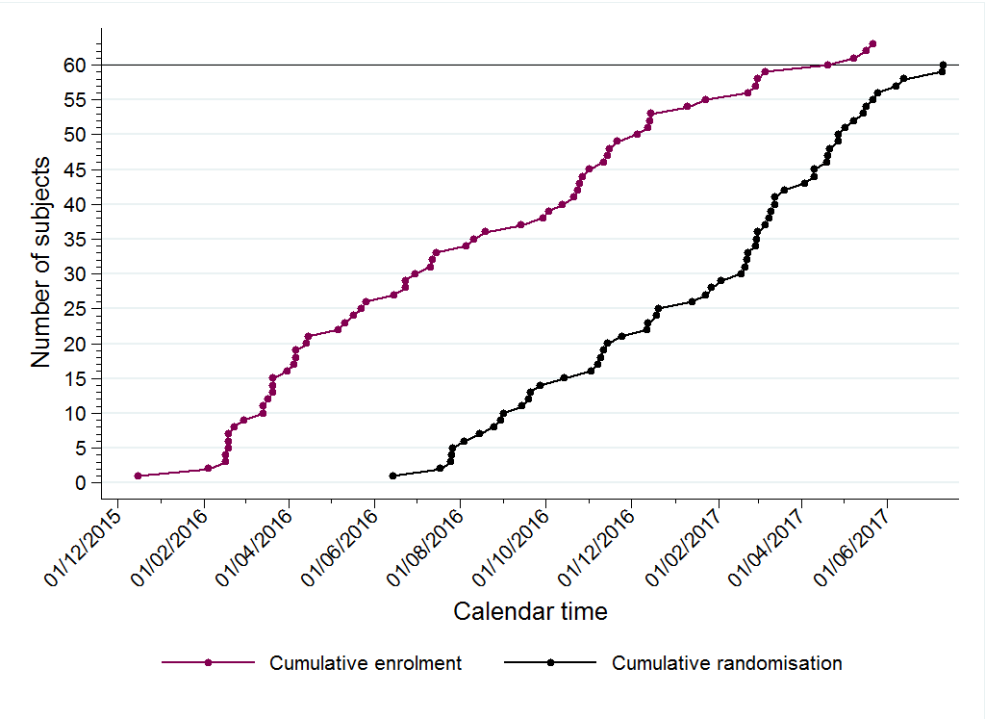
Date of data download and freeze: 08-07-2018

3 CONSORT FLOW DIAGRAM



4 ENROLMENT AND RANDOMISATION

4.1 ENROLMENT AND RANDOMISATION FIGURE



Note: 3 participants withdrew before randomisation

4.2 SCREENING AND ENROLMENT

4.2.1 DESCRIPTION OF SCREENINGS AND ENROLMENTS, BY SITE AND STRATUM

Centre	N screened	First screening	N enrolled	First enrolment	Last enrolment	N enrolled in stratum 1	N enrolled in stratum 2
Brighton	13	28/01/2016	11	04/02/16	20/04/17	9	2
Mortimer Market	9	16/03/2016	7	21/03/16	17/05/17	5	2
St. Mary's	23	08/12/2015	16	16/12/15	22/05/17	13	3
Chelsea & Westm.	18	19/04/2016	13	11/05/16	14/12/16	13	
Royal Free	3	14/03/2016	3	14/03/16	19/08/16	3	
St. Thomas	16	08/02/2016	13	16/02/16	01/03/17	12	1
Total	82	08/12/2015	63	16/12/15	22/05/17	55	8

4.2.2 REASONS FOR NOT BEING ENROLLED

Criterion	Number failed
Prolonged QTc interval	7
>4 weeks from PHI diagnosis	4
eGFR <90 ml/min/1.73m^2	3
Platelets <150x10^9/L	2
Concurrent comorbidity	2
Drugs contraindicated with vorinostat	1
History of anaphylaxis or severe adverse reaction to vaccines	1
Patient decision	1
Total	19

Note: more than one reason per participant possible

4.2.3 ELIGIBILITY CRITERIA FOR ENROLMENT

	N=63
Aged ≥18 to ≤60 years old	63 (100%)
Enrolled within 4 weeks from PHI diagnosis	63 (100%)
Adequate haemoglobin	63 (100%)
Weight ≥50kg	63 (100%)
No Hep B co-infection	63 (100%)
No Hep C co-infection	63 (100%)
QTc interval normal	63 (100%)
eGFR appropriate	63 (100%)
uPCR ≤30mg/mmol	63 (100%)
Platelet count ≥150x10^9/L	63 (100%)

Note: no violation against eligibility criteria.

4.3 RANDOMISATION

4.3.1 DESCRIPTION OF RANDOMISATIONS, BY SITE AND STRATUM

Centre	N randomised	First randomisation	Last randomisation	N randomised in stratum 1	N randomised in stratum 2	ART only	ART +V+V
Brighton	10	18/07/16	20/04/17	8	2	6	4
Mortimer Market	7	01/09/16	07/06/17	5	2	2	5
St. Mary's	16	14/06/16	22/05/17	13	3	8	8
Chelsea & Westminster	11	07/11/16	13/06/17	11		6	5
Royal Free	3	03/02/17	21/02/17	3		1	2
St. Thomas	13	27/07/16	11/07/17	12	1	7	6
Total	60	14/06/16	11/07/17	52	8	30	30

4.3.2 RANDOMISATION OUTCOME BY STRATUM

	Stratum 1 N=52	Stratum 2 N=8	Total N=60
Randomisation arm			
ART only	26 (50%)	4 (50%)	30 (50%)
ART +V+V	26 (50%)	4 (50%)	30 (50%)

4.4 PATIENT CHARACTERISTICS

4.4.1 BASELINE CHARACTERISTICS, BY RANDOMISATION ARM

	ART only N=30	ART +V+V N=30	Total N=60
Age (years), median (IQR)	31 (30, 38)	35 (28, 44)	32 (29, 40)
Sex			
Male	30 (100%)	30 (100%)	60 (100%)
Ethnicity			
White	16 (53%)	26 (87%)	42 (70%)
South Asian	0 (0%)	1 (3%)	1 (2%)
South East Asian	1 (3%)	0 (0%)	1 (2%)
Hispanic/Latino	3 (10%)	2 (7%)	5 (8%)
Black Caribbean/American	2 (7%)	0 (0%)	2 (3%)
Black African	2 (7%)	0 (0%)	2 (3%)
Mixed ethnic group	5 (17%)	1 (3%)	6 (10%)
Other	1 (3%)	0 (0%)	1 (2%)
Mode of HIV infection			
MSM	26 (87%)	29 (97%)	55 (92%)
MSW	1 (3%)	1 (3%)	2 (3%)
Unknown	1 (3%)	0 (0%)	1 (2%)
MSM+IDU	2 (7%)	0 (0%)	2 (3%)
CD4 cell count (cells/mm^3), median (IQR)	694 (561, 844)	710 (579, 759)	708 (568, 788)
CD4/CD8 ratio, median (IQR)	1.09 (0.77, 1.42)	1.07 (0.91, 1.46)	1.08 (0.87, 1.43)
HIV RNA (copies/ml)			
<50	29 (97%)	30 (100%)	59 (98%)
50 - <200	1 (3%)	0 (0%)	1 (2%)
eGFR (mL/min/1.73 m^2), median (IQR)	106 (99, 119)	111 (105, 120)	110 (100, 120)
Weeks since PHI diagnosis (at enrolment)			
<=1 week	1 (3%)	0 (0%)	1 (2%)
>1 - 2 weeks	3 (10%)	3 (10%)	6 (10%)
>2 - 3 weeks	7 (23%)	7 (23%)	14 (23%)
>3 - 4 weeks	15 (50%)	16 (53%)	31 (52%)
>4 weeks	4 (13%)	4 (13%)	8 (13%)
Weeks since PHI diagnosis (at randomisation), median (IQR)	28 (27, 41)	28 (27, 34)	28 (27, 36)

Note: MSM=men who have sex with men; MSW=men who have sex with women; IDU=Injection Drug Use.

4.4.2 BASELINE CHARACTERISTICS, BY STRATUM

	Stratum 1 N=52	Stratum 2 N=8	Total N=60
Age (years), median (IQR)	32 (29, 40)	35 (27, 44)	32 (29, 40)
Sex			
Male	52 (100%)	8 (100%)	60 (100%)
Ethnicity			
White	37 (71%)	5 (63%)	42 (70%)
South Asian	1 (2%)	0 (0%)	1 (2%)
South East Asian	1 (2%)	0 (0%)	1 (2%)
Hispanic/Latino	4 (8%)	1 (13%)	5 (8%)
Black Caribbean/American	2 (4%)	0 (0%)	2 (3%)
Black African	2 (4%)	0 (0%)	2 (3%)
Mixed ethnic group	5 (10%)	1 (13%)	6 (10%)
Other	0 (0%)	1 (13%)	1 (2%)
Mode of HIV infection			
MSM	48 (92%)	7 (88%)	55 (92%)
MSW	2 (4%)	0 (0%)	2 (3%)
Unknown	1 (2%)	0 (0%)	1 (2%)
MSM+IDU	1 (2%)	1 (13%)	2 (3%)
CD4 cell count (cells/mm^3), median (IQR)	708 (571, 792)	668 (480, 737)	708 (568, 788)
CD4/CD8 ratio, median (IQR)	1.09 (0.77, 1.42)	1.07 (0.91, 1.46)	1.08 (0.87, 1.43)
HIV RNA (copies/ml)			
<50	51 (98%)	8 (100%)	59 (98%)
50 - <200	1 (2%)	0 (0%)	1 (2%)
eGFR, median (IQR)	110 (101, 118)	108 (94, 121)	110 (100, 120)
Weeks since PHI diagnosis (at enrolment)			
<=1 week	1 (2%)	0 (0%)	1 (2%)
>1 - 2 weeks	6 (12%)	0 (0%)	6 (10%)
>2 - 3 weeks	14 (27%)	0 (0%)	14 (23%)
>3 - 4 weeks	31 (60%)	0 (0%)	31 (52%)
>4 weeks	0 (0%)	8 (100%)	8 (13%)
Weeks since PHI diagnosis (at randomisation), median (IQR)	28 (27, 30)	59 (46, 76)	28 (27, 36)

4.4.3 METHOD OF PHI DIAGNOSIS, BY RANDOMISATION ARM AND STRATUM

	ART only	ART +V+V	Total	Stratum 1	Stratum 2
	N=30	N=30	N=60	N=52	N=8
Positive HIV-1 serology within <=12 weeks of a documented negative test	4 (13%)	3 (10%)	7 (12%)	6 (12%)	1 (13%)
Positive p24 result and negative HIV antibody test	4 (13%)	7 (23%)	11 (18%)	11 (21%)	0 (0%)
Negative antibody test with either detectable HIV RNA or proviral DNA	2 (7%)	1 (3%)	3 (5%)	3 (6%)	0 (0%)
Weakly reactive or equivocal 4th generation HIV antibody antigen test	3 (10%)	0 (0%)	3 (5%)	3 (6%)	0 (0%)
Equivocal or reactive antibody test with <4 bands on western blot	1 (3%)	0 (0%)	1 (2%)	1 (2%)	0 (0%)
RITA test algorithm reported as 'Incident' only	20 (67%)	20 (67%)	40 (67%)	33 (63%)	7 (88%)

4.4.4 GENOTYPE AND BASELINE RESISTANCE

	ART only	ART +V+V		Total	Stratum 1	Stratum 2
	N=30	N=30	p-value	N=60	N=52	N=8
Genotype			1.00			
not available	3 (10%)	3 (10%)		6 (10%)	4 (8%)	2 (25%)
available	27 (90%)	27 (90%)		54 (90%)	48 (92%)	6 (75%)
Clade			0.32			
B	20 (67%)	20 (67%)		40 (67%)	34 (65%)	6 (75%)
A	0 (0%)	1 (3%)		1 (2%)	1 (2%)	0 (0%)
F	3 (10%)	0 (0%)		3 (5%)	3 (6%)	0 (0%)
recombinant	3 (10%)	6 (20%)		9 (15%)	9 (17%)	0 (0%)
not known	4 (13%)	3 (10%)		7 (12%)	5 (10%)	2 (25%)
Resistance test			1.00			
not available	3 (10%)	3 (10%)		6 (10%)	4 (8%)	2 (25%)
available	27 (90%)	26 (87%)		53 (88%)	48 (92%)	5 (63%)
test failed	0 (0%)	1 (3%)		1 (2%)	0 (0%)	1 (13%)
Any major mutation			1.00			
no	25 (93%)	25 (96%)		50 (94%)	45 (94%)	5 (100%)
Yes	2 (7%)	1 (4%)		3 (6%)	3 (6%)	0 (0%)
Major PI mutations						
No	27 (100%)	26 (100%)		53 (100%)	48 (100%)	5 (100%)
Major NRTI mutations			1.00			
No	26 (96%)	26 (100%)		52 (98%)	47 (98%)	5 (100%)
Yes	1 (4%)	0 (0%)		1 (2%)	1 (2%)	0 (0%)
Major NNRTI mutations			1.00			
No	26 (96%)	25 (96%)		51 (96%)	46 (96%)	5 (100%)
Yes	1 (4%)	1 (4%)		2 (4%)	2 (4%)	0 (0%)

Note: mutations defined as major if causing intermediate or high-level resistance according to the HIV drug resistance database (Stanford); affected patients: R01211B (ART +V+V) and R03811B (ART only), both with K103N mutation causing high-level resistance to efavirenz & nevirapine. R03808W (ART only): M184I mutation causing highlevel resistance to lamivudine and emtricitabine.

4.4.5 PROTECTIVE HLA CLASS I B ALLELES

	ART only N=30	ART +V+V N=30	p-value	Total N=60
HLA class B			0.49	
not available	2 (7%)	0 (0%)		2 (3%)
available	28 (93%)	30 (100%)		58 (97%)
HLA-B*5701			0.42	
No	26 (93%)	25 (83%)		51 (88%)
Yes	2 (7%)	5 (17%)		7 (12%)
HLA-B*2705			1.00	
No	27 (96%)	28 (93%)		55 (95%)
Yes	1 (4%)	2 (7%)		3 (5%)
HLA-B*5801			1.00	
No	26 (93%)	28 (93%)		54 (93%)
Yes	2 (7%)	2 (7%)		4 (7%)
HLA-B*81				
no	28 (100%)	30 (100%)		58 (100%)
Any protective HLA			0.36	
no protective	23 (82%)	21 (70%)		44 (76%)
protective	5 (18%)	9 (30%)		14 (24%)

Note: PCR failed for B alleles in two participants: R01214L & R04405W (both ART only)

4.4.6 ART PRE RANDOMISATION, BY ARM AND STRATUM

	ART only	ART +V+V	Total	Stratum 1	Stratum 2
	N=30	N=30	N=60	N=52	N=8
Weeks from PHI diagnosis to ART start, median (IQR)	2 (0, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (-1, 3)
before PHI diagnosis	7 (23%)	3 (10%)	10 (17%)	7 (13%)	3 (38%)
<=1 week	4 (13%)	4 (13%)	8 (13%)	8 (15%)	0 (0%)
1-2 weeks	7 (23%)	5 (17%)	12 (20%)	11 (21%)	1 (13%)
2-3 weeks	3 (10%)	8 (27%)	11 (18%)	9 (17%)	2 (25%)
3-4 weeks	9 (30%)	10 (33%)	19 (32%)	17 (33%)	2 (25%)
Weeks from ART start to randomisation, median (IQR)	26 (24, 38)	26 (24, 34)	26 (24, 34)	25 (24, 30)	58 (50, 74)
[min - max]	[22-80]	[23-82]	[22-82]	[22-54]	[40-82]
Number of ART changes between enrolment and randomisation					
None	25 (83%)	27 (90%)	52 (87%)	44 (85%)	8 (100%)
1	4 (13%)	1 (3%)	5 (8%)	5 (10%)	0 (0%)
2	1 (3%)	1 (3%)	2 (3%)	2 (4%)	0 (0%)
3	0 (0%)	1 (3%)	1 (2%)	1 (2%)	0 (0%)

4.4.7 ART AT RANDOMISATION, BY ARM AND STRATUM

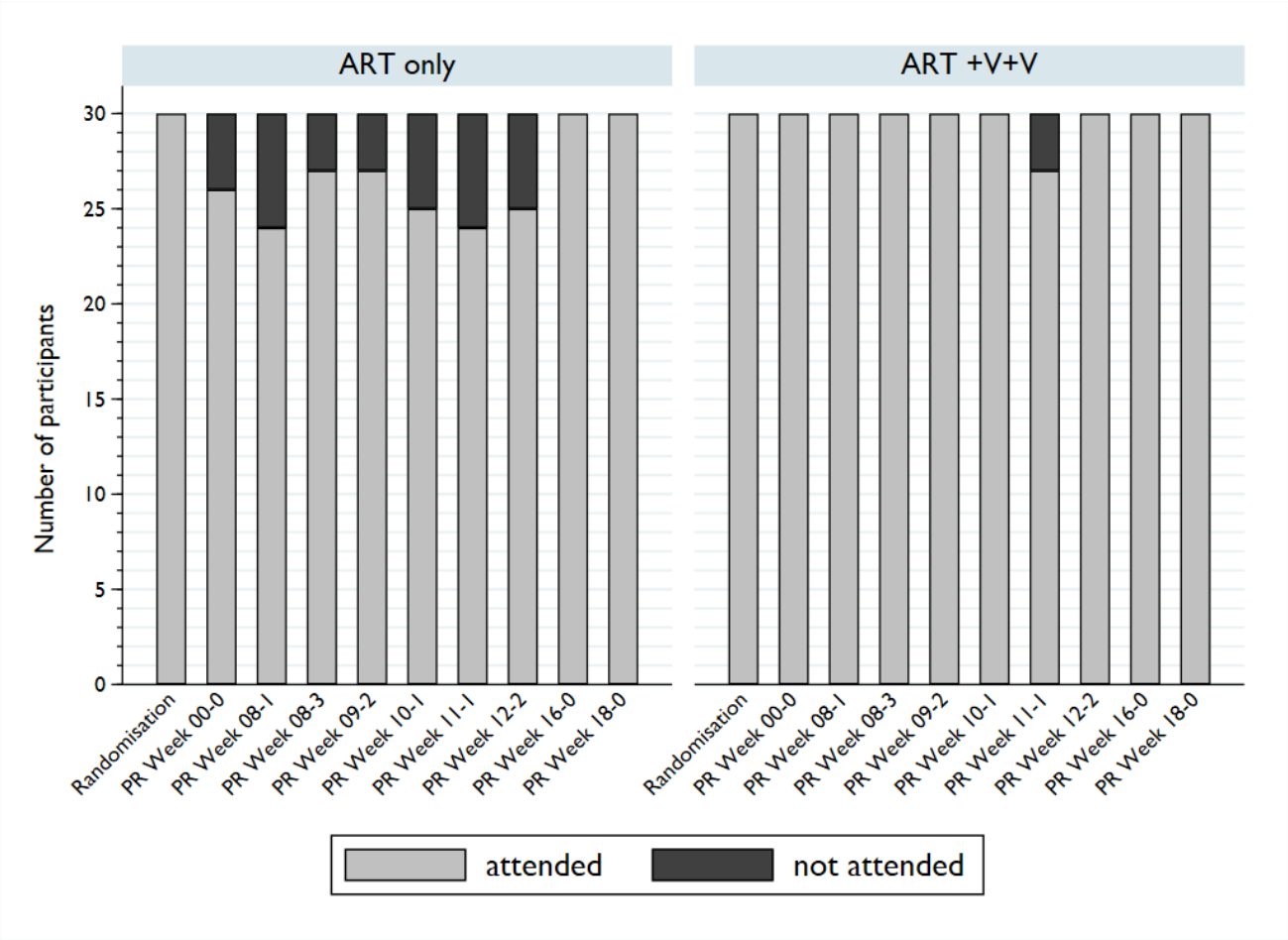
	ART only	ART +V+V	Total	Stratum 1	Stratum 2
	N=30	N=30	N=60	N=52	N=8
Number of drugs					
3	6 (20%)	7 (23%)	13 (22%)	6 (12%)	7 (88%)
4	24 (80%)	23 (77%)	47 (78%)	46 (88%)	1 (13%)
On Integrase Inhibitor					
no	0 (0%)	2 (7%)	2 (3%)	1 (2%)	1 (13%)
yes	30 (100%)	28 (93%)	58 (97%)	51 (98%)	7 (88%)
ART at randomisation					
ABC 3TC DOL	2 (7%)	1 (3%)	3 (5%)	0 (0%)	3 (38%)
FTC DRV/r RAL	0 (0%)	1 (3%)	1 (2%)	1 (2%)	0 (0%)
FTC TDF DRV/c	0 (0%)	1 (3%)	1 (2%)	1 (2%)	0 (0%)
FTC TDF DRV/c DOL	1 (3%)	0 (0%)	1 (2%)	1 (2%)	0 (0%)
FTC TDF DRV/c RAL	7 (23%)	6 (20%)	13 (22%)	13 (25%)	0 (0%)
FTC TDF DRV/r RAL	15 (50%)	16 (53%)	31 (52%)	31 (60%)	0 (0%)
FTC TDF EFV	0 (0%)	1 (3%)	1 (2%)	0 (0%)	1 (13%)
FTC TDF EFV RAL	0 (0%)	1 (3%)	1 (2%)	1 (2%)	0 (0%)
FTC TDF ELV	0 (0%)	1 (3%)	1 (2%)	0 (0%)	1 (13%)
FTC TDF RAL	4 (13%)	2 (7%)	6 (10%)	4 (8%)	2 (25%)
FTC TDF RPV RAL	1 (3%)	0 (0%)	1 (2%)	0 (0%)	1 (13%)

5 FOLLOW-UP

5.1.1 FOLLOW-UP POST RANDOMISATION

	ART only N=30	ART +V+V N=30	Total N=60
Withdrawal or lost after randomisation	0	0	0
Follow-up since randomisation (weeks), median (IQR); [min - max]	19 (18, 20) [17-27]	19 (18, 20) [17-22]	19 (18, 20) [17-27]
Last visit PR Week 18-0	30 (100%)	30 (100%)	60 (100%)
Date of last visit: min-max	24/11/2016- 15/11/2017	08/11/2016- 20/10/2017	08/11/2016- 15/11/2017

5.1.2 ATTENDANCE OF POST-RANDOMISATION VISITS, BY ARM



5.1.3 NUMBER OF MISSED VISITS PER PARTICIPANT

	ART only	ART +V+V	Total
	N=30	N=30	N=60
# missed visits			
0	19 (63%)	27 (90%)	46 (77%)
1	4 (13%)	3 (10%)	7 (12%)
2	3 (10%)	0 (0%)	3 (5%)
5	2 (7%)	0 (0%)	2 (3%)
6	2 (7%)	0 (0%)	2 (3%)

6 TREATMENT

6.1 ANTIRETROVIRAL THERAPY

6.1.1 ART CHANGES POST RANDOMISATION

	ART only N=30	ART +V+V N=30	Total N=60
Number of post-randomisation ART changes			
None	28 (93%)	29 (97%)	57 (95%)
1	2 (7%)	0 (0%)	2 (3%)
2	0 (0%)	1 (3%)	1 (2%)

Overall, three participants changed ART post randomisation. The reasons were as follows:

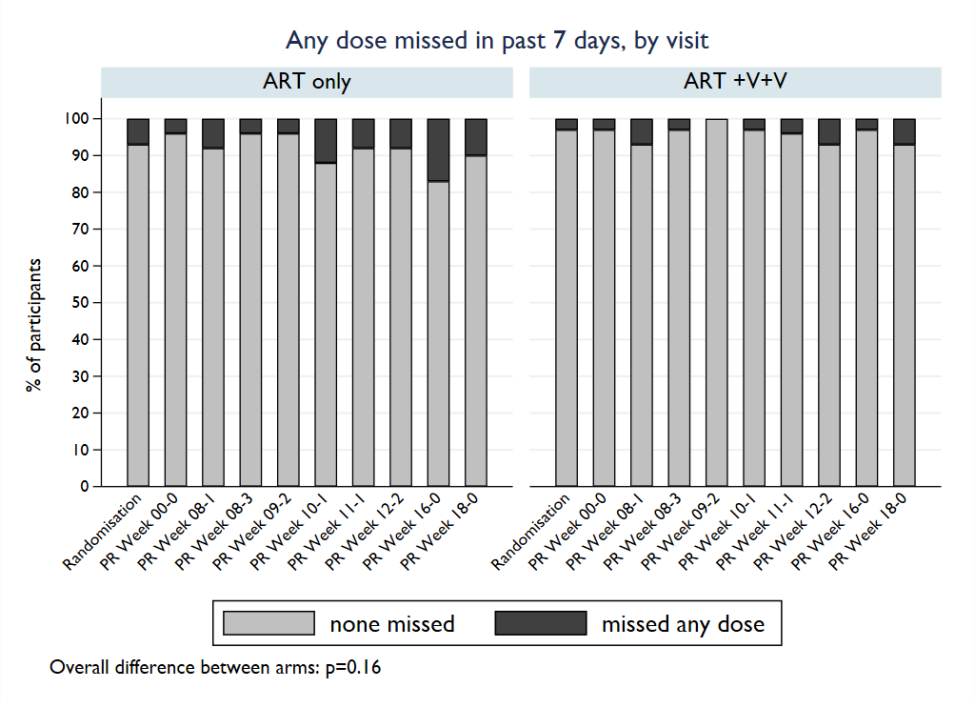
ART only:

- raised LFTs (n=1): ABC 3TC DOL -> FTC TDF DOL
- declining renal function (n=1): FTC TDF DRV/c RAL -> FTC TAF DRV/c

ART +V+V:

- nausea and vomiting (n=1): FTC TDF EFV RAL -> FTC TDF DRV/r RAL (and back)

6.1.2 ADHERENCE TO ART



6.1.3 EVER MISSED A DOSE

	ART only N=30	ART +V+V N=30	Total N=60
Ever missed a dose			
no	12 (40%)	17 (57%)	29 (48%)
yes	18 (60%)	13 (43%)	31 (52%)

Note: difference between the arms: p=0.196

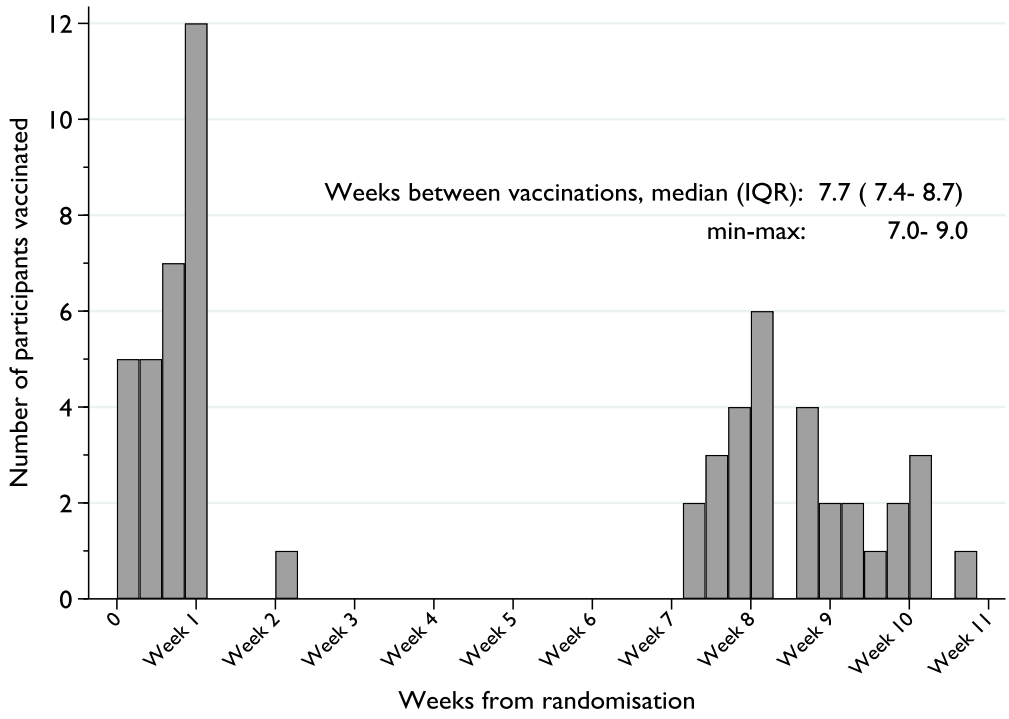
6.2 VACCINATION

The section only includes participants randomised to ART +V+V.

6.2.1 VACCINATIONS

	ART +V+V N=30
Vaccinated with ChAdV63.HIVconsv	30 (100%)
Vaccinated with MVA.HIVconsv	30 (100%)

6.2.2 TIME OF VACCINATION



6.3 VORINOSTAT

The section only includes participants randomised to ART +V+V.

	ART +V+V (n=30)
Completion of vorinostat course as scheduled	
Yes	27 (90%)
No	3 (10%)
Reason for non-completion	
Ineligible to start vorinostat	1
Discontinued vorinostat before schedule	1
Missed vorinostat doses intermittently	1

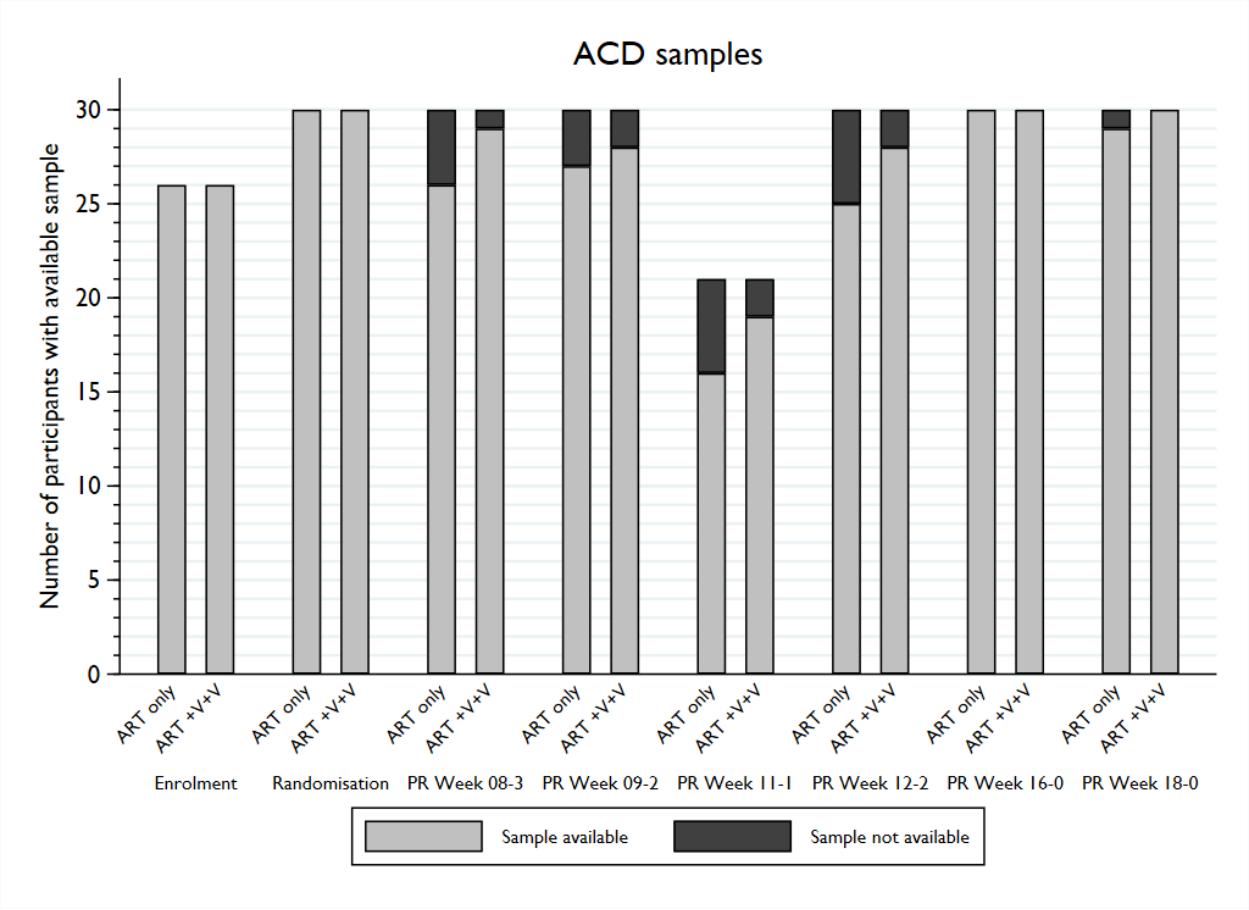
R01211B: Ineligibility to start vorinostat: ALT >5xULN due to hepatitis

R04402N: Discontinued vorinostat before schedule after 5 doses due to nausea & vomiting

R05510Q: Missed three vorinostat doses (doses 4,5,6) out of confusion over schedule; no evidence of an AE

7 SAMPLES

7.1 ACD SAMPLES TAKEN AND PROCESSED



Note: Collection of post randomisation week 11-1 samples only started part way through the trial therefore several patients had already passed this time point and the sample could not be collected.

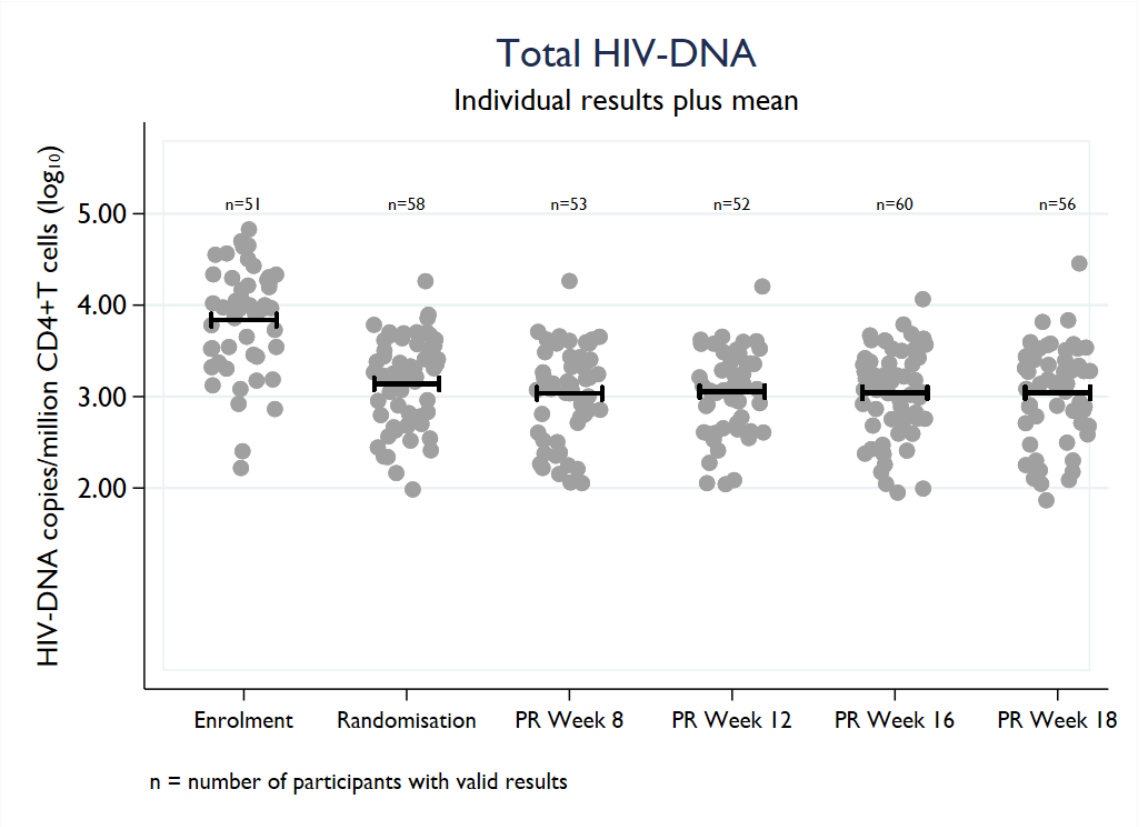
8 PRIMARY ENDPOINT: TOTAL HIV DNA

8.1 AVAILABILITY OF TOTAL HIV-DNA RESULTS

	ART only N=30	ART +V+V N=30	Total N=60
Enrolment			
Sample not taken	4 (13%)	4 (13%)	8 (13%)
Sample taken Result not valid	0 (0%)	1 (3%)	1 (2%)
Sample taken Result valid	26 (87%)	25 (83%)	51 (85%)
Randomisation			
Sample taken Result not valid	2 (7%)	0 (0%)	2 (3%)
Sample taken Result valid	28 (93%)	30 (100%)	58 (97%)
PR Week 08-3			
Sample not taken	5 (17%)	1 (3%)	6 (10%)
Sample taken Result not valid	0 (0%)	1 (3%)	1 (2%)
Sample taken Result valid	25 (83%)	28 (93%)	53 (88%)
PR Week 12-2			
Sample not taken	5 (17%)	1 (3%)	6 (10%)
Sample taken Result not valid	1 (3%)	1 (3%)	2 (3%)
Sample taken Result valid	24 (80%)	28 (93%)	52 (87%)
PR Week 16-0			
Sample taken Result valid	30 (100%)	30 (100%)	60 (100%)
PR Week 18-0			
Sample not taken	1 (3%)	0 (0%)	1 (2%)
Sample taken Result not valid	1 (3%)	2 (7%)	3 (5%)
Sample taken Result valid	28 (93%)	28 (93%)	56 (93%)
Primary endpoint samples			
PR-16 & PR-18, missing baseline	2 (7%)	0 (0%)	2 (3%)
Baseline & one of PR-16 / PR-18	2 (7%)	2 (7%)	4 (7%)
Baseline, PR-16 AND PR-18	26 (87%)	28 (93%)	54 (90%)

Note: no enrolment sample available for stratum 2 patients.

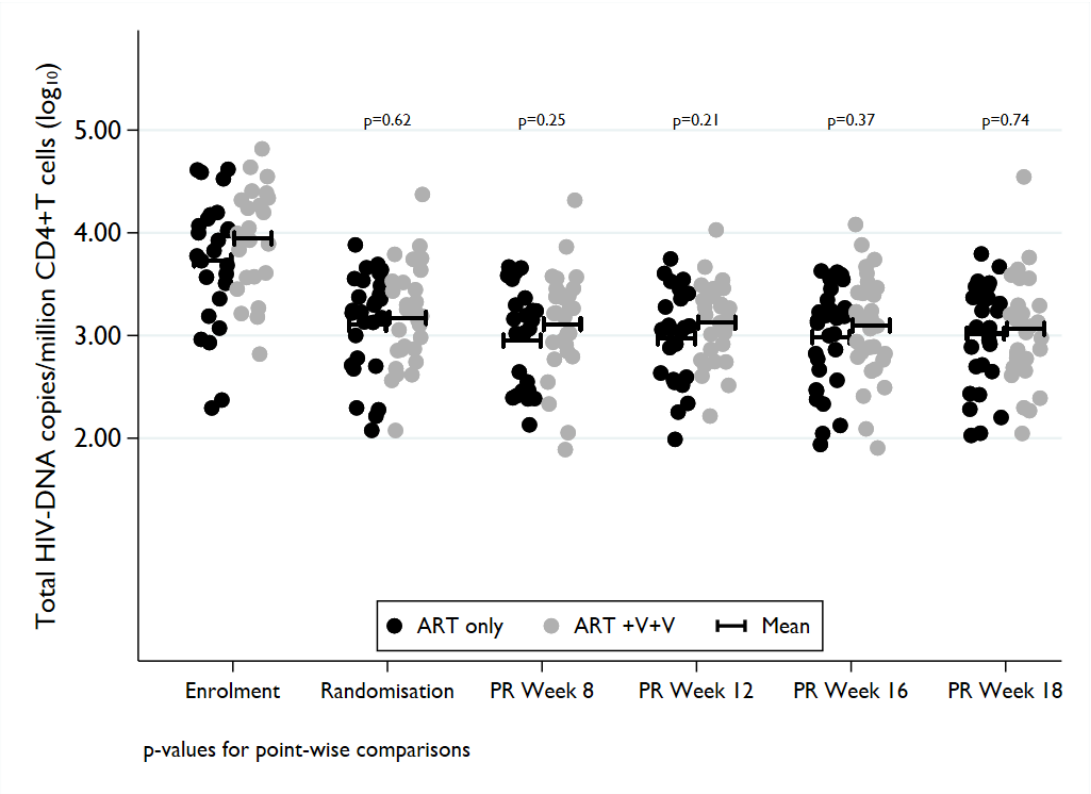
8.2 TOTAL HIV-DNA: INDIVIDUAL RESULTS PLUS MEAN OVER TIME



Note: Enrolment results only available for Stratum 1.

8.3 TOTAL HIV-DNA: SUMMARY STATISTICS, BY TIME-POINT

Visit	HIV-DNA copies/million CD4+T cells (log_{10})				HIV-DNA copies/million CD4+T cells	
	mean	95% CI	sd (min-max)	change from enrolment (95% CI)	Geom. mean	95% CI
Enrolment	3.84	(3.67 - 4.00)	0.58 (2.17-4.80)	0	6862	(4705 - 10006)
Randomisation	3.14	(3.01 - 3.27)	0.49 (2.00-4.38)	-0.63 (-0.72 to -0.55)	1378	(1027 - 1849)
PR Week 08-3	3.03	(2.90 - 3.17)	0.50 (2.00-4.25)	-0.73 (-0.87 to -0.58)	1083	(790 - 1484)
PR Week 12-2	3.05	(2.93 - 3.18)	0.44 (2.13-4.16)	-0.71 (-0.81 to -0.62)	1135	(858 - 1501)
PR Week 16-0	3.04	(2.91 - 3.17)	0.49 (2.00-4.10)	-0.73 (-0.82 to -0.64)	1098	(818 - 1474)
PR Week 18-0	3.04	(2.91 - 3.18)	0.51 (2.00-4.52)	-0.71 (-0.81 to -0.62)	1101	(803 - 1510)
Average PR Weeks 16/18	3.04	(2.92-3.17)	0.49 (2.00-4.31)	-0.73 (-0.76 to -0.69)	1131	(845 – 1513)



8.3.1 ART ONLY

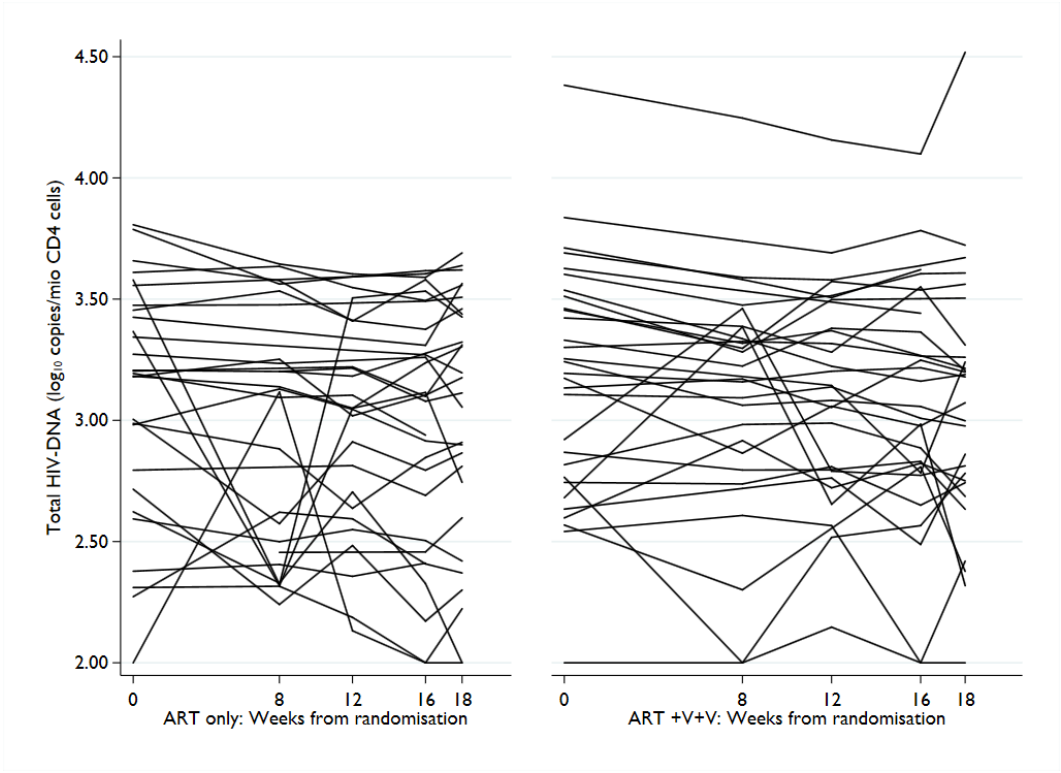
Visit	HIV-DNA copies/million CD4+T cells (log_{10})				HIV-DNA copies/million CD4+T cells	
	mean	95% CI	sd (min-max)	change from enrolment (95% CI)	Geom. mean	95% CI
Enrolment	3.73	(3.47 - 3.99)	0.65 (2.17-4.65)		5380	(2936 - 9860)
Randomisation	3.11	(2.92 - 3.29)	0.49 (2.00-3.81)	-0.61 (-0.74 to -0.48)	1276	(827 - 1968)
PR Week 08-3	2.95	(2.75 - 3.15)	0.49 (2.24-3.64)	-0.77 (-1.03 to -0.51)	892	(559 - 1426)
PR Week 12-2	2.97	(2.79 - 3.16)	0.44 (2.13-3.60)	-0.71 (-0.87 to -0.55)	938	(611 - 1439)
PR Week 16-0	2.98	(2.80 - 3.17)	0.50 (2.00-3.62)	-0.73 (-0.85 to -0.61)	963	(625 - 1482)
PR Week 18-0	3.02	(2.82 - 3.22)	0.52 (2.00-3.69)	-0.71 (-0.84 to -0.57)	1044	(658 - 1658)
Average PR Weeks 16/18	2.95	(2.76 - 3.15)	0.50 (2.00-3.64)	-0.73 (-0.78 to -0.68)	989	(643 - 1520)

8.3.2 ART +V +V

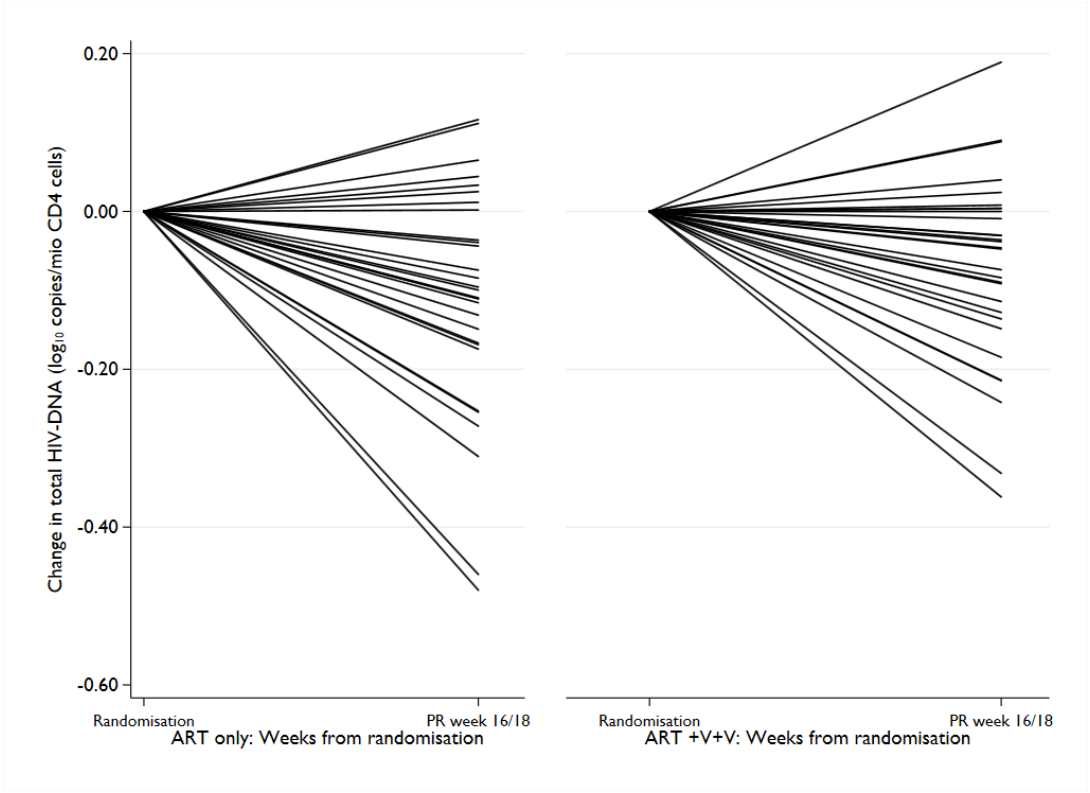
Visit	HIV-DNA copies/million CD4+T cells (log_{10})				HIV-DNA copies/million CD4+T cells	
	mean	95% CI	sd (min-max)	change from enrolment (95% CI)	Geom. mean	95% CI
Enrolment	3.95	(3.74 - 4.15)	0.49 (2.87-4.80)	0	8837	(5545 - 14083)
Randomisation	3.17	(2.99 - 3.35)	0.49 (2.00-4.38)	-0.66 (-0.78 to -0.54)	1481	(970 - 2261)
PR Week 08-3	3.11	(2.92 - 3.30)	0.50 (2.00-4.25)	-0.69 (-0.86 to -0.53)	1286	(826 - 2004)
PR Week 12-2	3.13	(2.96 - 3.29)	0.43 (2.15-4.16)	-0.72 (-0.84 to -0.60)	1336	(912 - 1957)
PR Week 16-0	3.10	(2.92 - 3.28)	0.49 (2.00-4.10)	-0.73 (-0.87 to -0.58)	1253	(823 - 1908)
PR Week 18-0	3.06	(2.86 - 3.26)	0.52 (2.00-4.52)	-0.72 (-0.86 to -0.58)	1161	(733 - 1840)
Average PR Weeks 16/18	3.06	(2.88 - 3.26)	0.49 (2.00-4.31)	-0.72 (-0.77 to -0.67)	1293	(855 - 1955)

8.4 TOTAL HIV-DNA: INDIVIDUAL TRAJECTORIES FROM RANDOMISATION

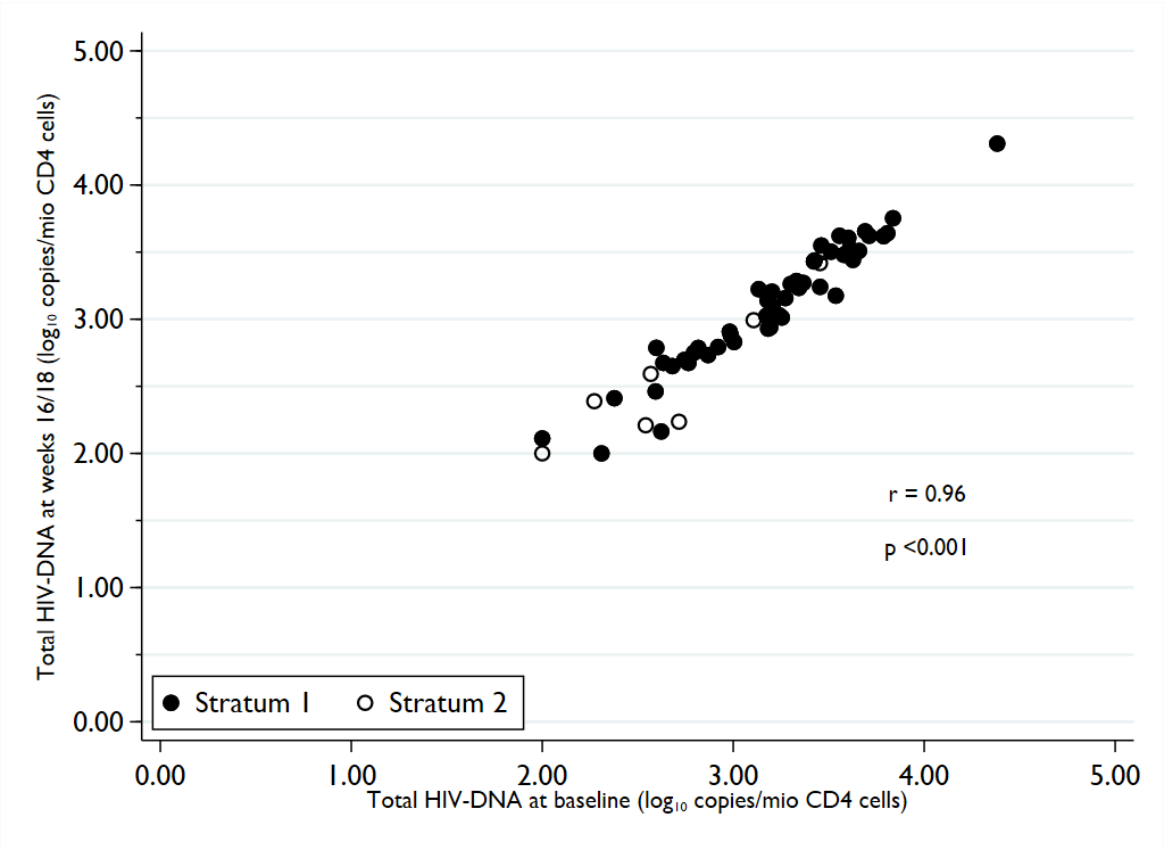
8.4.1 ABSOLUTE VALUES (LOG_{10})



8.4.2 CHANGE FROM RANDOMISATION TO PR WEEK 16 AND 18 (LOG_{10})



8.5 TOTAL HIV-DNA: CORRELATION BETWEEN BASELINE AND MEAN OF WEEK 16 & 18 (LOG_{10})



8.6 ANALYSIS OF THE PRIMARY ENDPOINT

8.6.1 PRIMARY ANALYSIS

From the Statistical Analysis Plan:

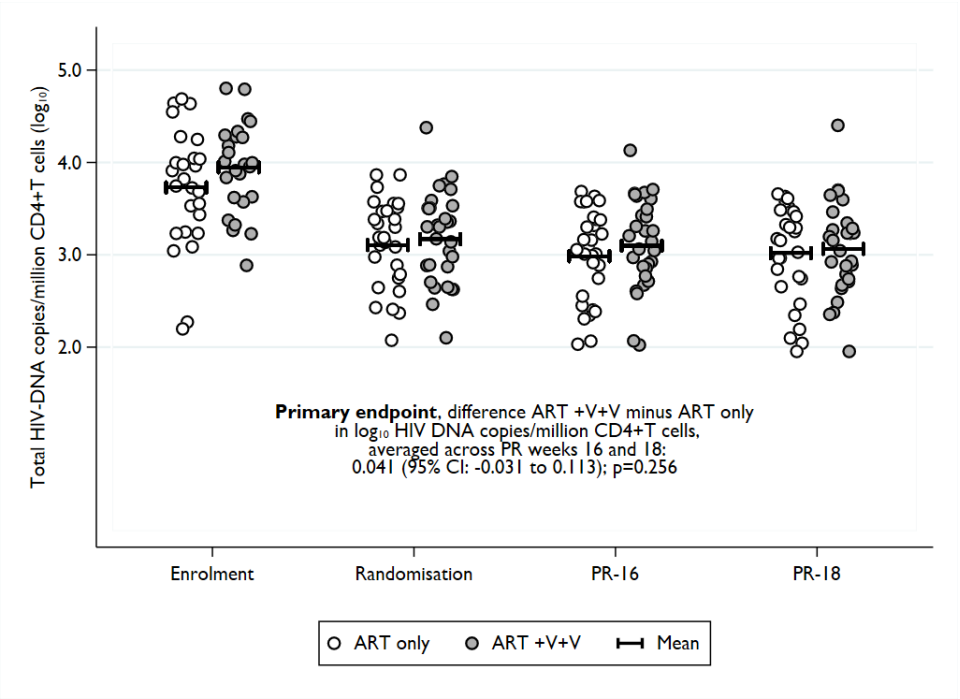
"The primary endpoint is total HIV-DNA averaged across post-randomisation weeks 16 and 18. It will be analysed on a log_{10}-scale. Treatment arms will be compared in terms of absolute total HIV DNA levels at post-randomisation weeks 16 and 18 adjusted for the baseline (i.e. randomisation) level and by stratum using analysis of covariance.

If either the PR week 16 result or the PR week 18 result is entirely missing but not both, the primary endpoint consists of the single available result. If total HIV DNA is missing at both PR-16 or PR-18, or at baseline, an imputation method will be used to estimate missing values. Predictors may include stratum, total HIV-DNA from previous time-points and other factors associated with total HIV DNA."

Baseline results were missing in 2 participants. Results were imputed using stratum and mean total HIV-DNA from PR week 16 and 18. Therefore, the primary analysis of the primary endpoint included all 60 randomised participants.

	Estimate	SE	95% CI	p-value
Difference in log_{10} total HIV-DNA at weeks 16/18: ART +V+V vs ART only *	0.041	0.036	(-0.031- 0.113)	0.256
Change in log_{10} total HIV-DNA from randomisation to weeks 16/18:				
ART only	-0.11	0.03	(-0.17 to -0.06)	<0.001
ART +V +V	-0.07	0.02	(-0.12 to -0.02)	0.005
Overall	-0.09	0.02	(-0.13 to -0.06)	<0.001

Note: * ART +V+V minus ART only; a result of 0.041 means a higher total HIV DNA in the ART +V+V arm. Results are adjusted for baseline value and stratum.



8.6.2 SENSITIVITY ANALYSES OF THE PRIMARY ENDPOINT

Model	N	Difference in log_{10} total HIV-DNA at weeks 16/18: ART +V+V minus ART only	SE	95% CI	p-value
a. unadjusted	60	0.107	0.128	(-0.148-0.363)	0.404
b. Adjusted for baseline total HIV-DNA	58	0.039	0.035	(-0.032-0.109)	0.279
c. Adjusted for baseline total HIV-DNA & stratum	58	0.039	0.036	(-0.033-0.110)	0.282
d. as c), excluding patients with incomplete intervention	55	0.039	0.037	(-0.035-0.113)	0.292

Note: Results from linear regression models. All analyses without imputation of missing results.

9 SECONDARY ENDPOINTS: EFFICACY

9.1 REPLICATION COMPETENCE (VIRAL OUTGROWTH ASSAY)

9.1.1 AVAILABILITY OF RESULTS

	ART only N=30	ART +V+V N=30	Total N=60
Randomisation			
available	25 (83%)	26 (87%)	51 (85%)
invalid assay	3 (10%)	2 (7%)	5 (8%)
no blood draw	2 (7%)	2 (7%)	4 (7%)
PR Week 16			
available	29 (97%)	27 (90%)	56 (93%)
invalid assay	1 (3%)	3 (10%)	4 (7%)
Valid result available			
Randomisation only	1 (3%)	3 (10%)	4 (7%)
PR-16 only	5 (17%)	4 (13%)	9 (15%)
Both randomisation AND PR-16	24 (80%)	23 (77%)	47 (78%)

Note: Due to a temporary problem with an assay reagent (PHA), nine samples that were collected between mid-December and end of January did not give valid results and could not be used for the statistical analysis.

9.1.2 UNDETECTABLE VIRAL OUTGROWTH

	ART only	ART +V+V	Total
Undetectable at Randomisation			
No	13 (52%)	18 (69%)	31 (61%)
Yes	12 (48%)	8 (31%)	20 (39%)
Undetectable at PR Week 16			
No	17 (59%)	21 (78%)	38 (68%)
Yes	12 (41%)	6 (22%)	18 (32%)
Cambridge assay results			
Undetectable at both time-points	6 (25%)	2 (9%)	8 (17%)
Undetectable at Randomisation only	5 (21%)	6 (26%)	11 (23%)
Undetectable at PR-16 only	5 (21%)	4 (17%)	9 (19%)
Detectable at both time-points	8 (33%)	11 (48%)	19 (40%)

Note: denominators include available and valid results only.

9.1.3 PRIMARY ANALYSIS 1: UNDETECTABLE VIRAL OUTGROWTH AT PR WEEK 16

Model	N	Odds Ratio: ART +V+V vs ART only	SE	95% CI	p-value
a. Unadjusted	56	0.40	0.24	0.13 - 1.30	0.130
b. Adjusted for stratum	56	0.40	0.24	0.13 - 1.31	0.131
c. Adjusted for stratum & baseline undetectable	47	0.43	0.27	0.12 - 1.49	0.182
d. As c), with imputed missing baseline results *	56	0.41	0.25	0.13 - 1.35	0.145
e. As b), excluding patients with incomplete intervention	53	0.38	0.24	0.11 - 1.29	0.119
f. As c), excluding patients with incomplete intervention	45	0.38	0.25	0.10 - 1.39	0.142

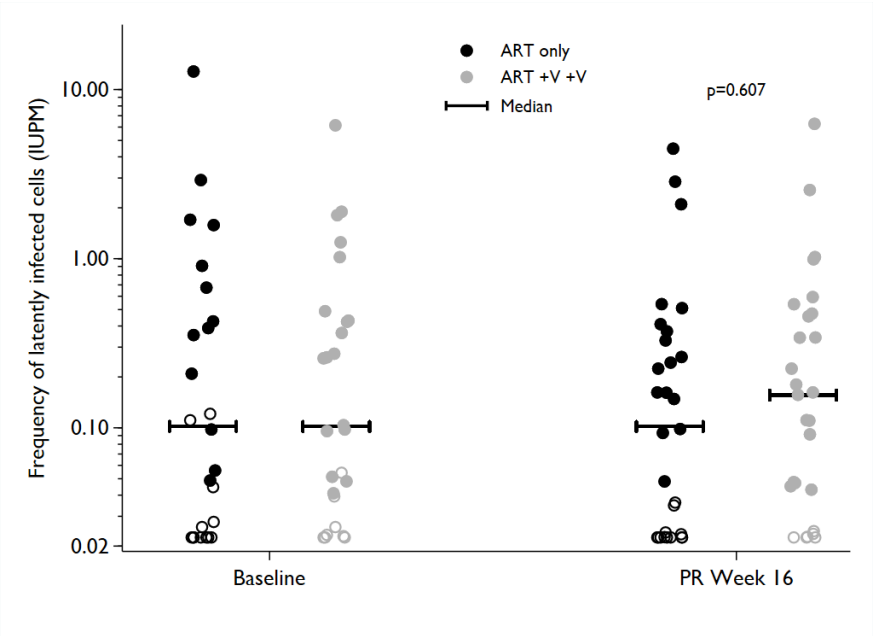
Note: * missing baseline results imputed separately for each arm using multiple imputation based on stratum and PR week 16 results.

9.1.4 PRIMARY ANALYSIS 2: COMPARISON OF IUPM IN PATIENTS WITH "POSITIVE" RESULTS

Model	N	IUPM at week 16: ART +V+V minus ART only	SE	95% CI	p-value
a. Unadjusted	38	-0.04	0.16	-0.36 - 0.28	0.783
b. Adjusted for stratum	38	-0.04	0.16	-0.37 - 0.29	0.788
c. Adjusted for stratum & baseline undetectable (y/n)	30	0.04	0.36	-0.69 - 0.77	0.905
d. As c), with imputed missing baseline results *	38	0.05	0.16	-0.28 - 0.39	0.758
e. As b), excluding patients with incomplete intervention	36	-0.07	0.15	-0.37 - 0.22	0.628
f. As c), excluding patients with incomplete intervention	29	0.04	0.36	-0.70 - 0.78	0.910

Note: Comparison of IUPM using median regression with bootstrapped standard error (*sqreg command in Stata*). Patients with a "negative" PR-16 result were excluded from this analysis.

9.1.5 VIRAL OUTGROWTH: INDIVIDUAL RESULTS (IUPM)



Note: Hollow circles represent values below the limit of detection (LDL/2); p-value derived from interval regression, adjusted for stratum and viral outgrowth detectable/undetectable at baseline.

9.1.6 SECONDARY ANALYSIS: COMPARISON OF IUPM IN ALL PATIENTS WITH PR WEEK 16 RESULT

Model	N	Log_{10} IUPM at week 16: ART +V+V minus ART only	SE	95% CI	p-value
a. Unadjusted	56	0.19	0.22	-0.25 - 0.62	0.401
b. Adjusted for stratum	56	0.19	0.22	-0.25 - 0.62	0.402
c. Adjusted for stratum & baseline undetectable (y/n)	47	0.13	0.26	-0.38 - 0.65	0.607
d. As b), excluding patients with incomplete intervention	53	0.13	0.22	-0.30 - 0.55	0.567
e. As c), excluding patients with incomplete intervention	45	0.12	0.26	-0.39 - 0.62	0.652

Note: Comparison of IUPM using a linear model appropriate for left-censored data (interval regression; *intreg command in Stata*). This analysis included all patients with a valid PR-16 result, "positive" or "negative".

9.2 HIV INTEGRATED DNA

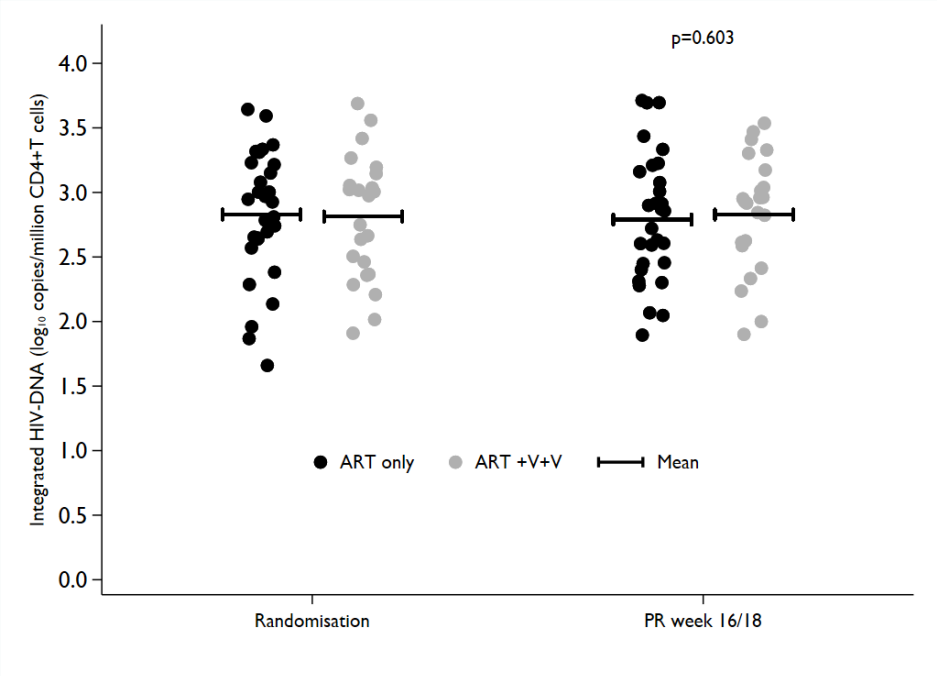
9.2.1 INTEGRATED HIV DNA: AVAILABILITY OF RESULTS

	ART only N=30	ART +V+V N=30	Total N=60
Results			
none	1 (3%)	7 (23%)	8 (13%)
Randomisation + PR-16	2 (7%)	0 (0%)	2 (3%)
Randomisation + PR-18	27 (90%)	23 (77%)	50 (83%)

9.2.2 INTEGRATED HIV DNA AT RANDOMISATION AND PR WEEKS 16/18 (COPIES PER MIO CELLS)

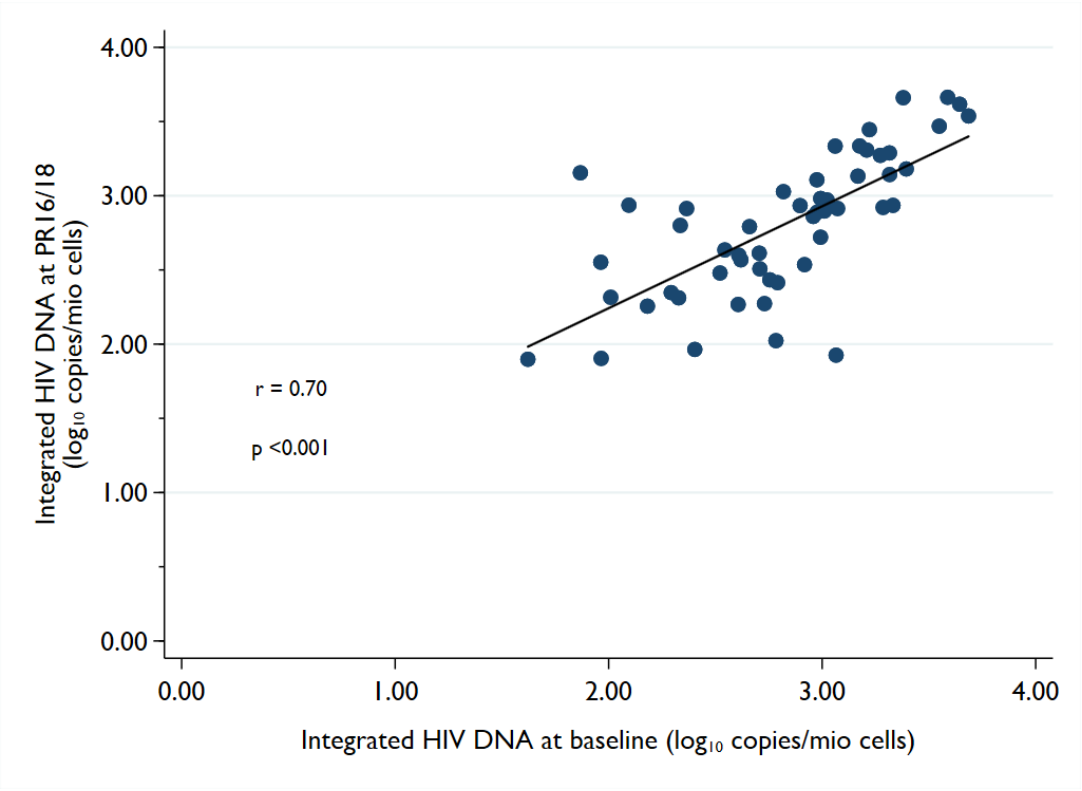
Time-point	statistics	ART only	ART +V+V	TOTAL
Randomisation	median (IQR) [min-max]	788 (407 - 1665) [42 - 4406]	945 (232 - 1471) [92 - 4851]	808 (341 - 1558) [42 - 4851]
	log_{10}: mean (SD) [min-max]	2.83 (0.51) [0.51 - 3.64]	2.81 (0.48) [0.48 - 3.69]	2.82 (0.49) [0.49 - 3.69]
PR Week 16/18	median (IQR) [min-max]	725 (260 - 1428) [79 - 4604]	789 (356 - 1356) [80 - 3448]	781 (286 - 1409) [79 - 4604]
	log_{10}: mean (SD) [min-max]	2.79 (0.51) [0.51 - 3.66]	2.83 (0.45) [0.45 - 3.54]	2.81 (0.48) [0.48 - 3.66]

9.2.3 INTEGRATED HIV DNA (LOG_{10}): DOT PLOT PLUS MEAN

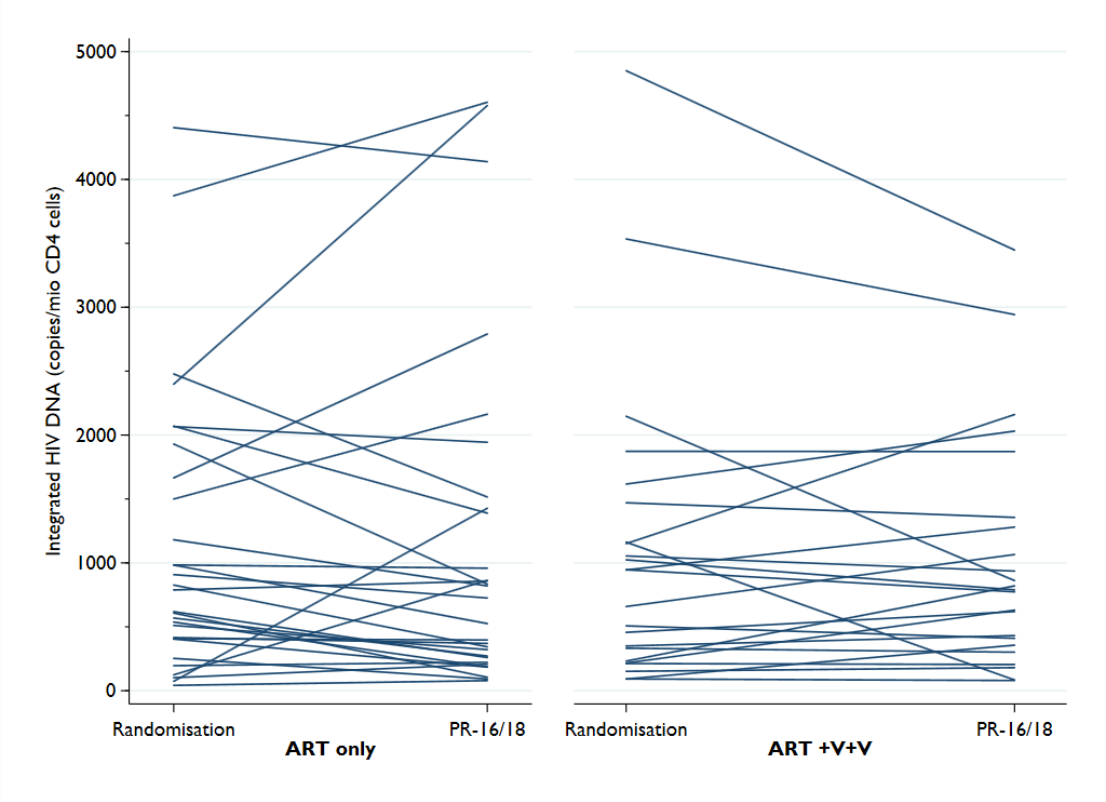


Note: p-value derived from linear regression, adjusted for stratum and baseline level.

9.2.4 CORRELATION OF LOG_{10} INTEGRATED HIV DNA AT BASELINE AND AT PR WEEKS 16/18



9.2.5 CHANGE IN INTEGRATED HIV DNA FROM RANDOMISATION TO PR WEEK 16/18, BY PARTICIPANT



9.2.6 REGRESSION ANALYSIS: LOG$_{10}$ INTEGRATED HIV DNA AT PR WEEK 16/18

N=52	Estimate	SE	95% CI	p-value
Difference in log$_{10}$ integrated HIV-DNA at weeks 16/18: ART +V+V vs ART only *	0.05	0.10	-0.15 - 0.25	0.603
Change in log$_{10}$ integrated HIV-DNA from randomisation to weeks 16/18:				
ART only	-0.04	0.06	-0.17 to 0.09	0.562
ART +V +V	0.01	0.07	-0.13 to 0.16	0.856
Overall	-0.02	0.05	-0.11 to 0.08	0.754

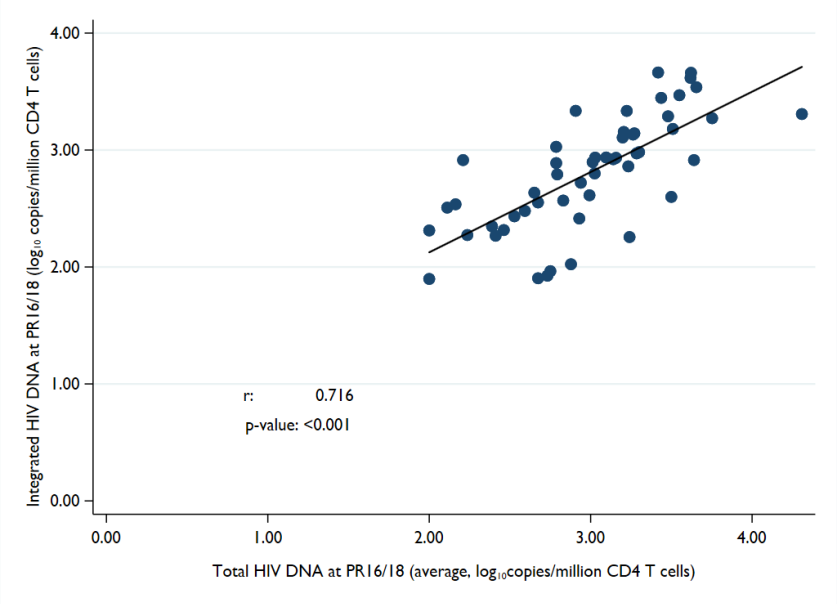
Note: * ART +V+V minus ART only; a result of 0.05 means a higher integrated HIV DNA in the ART +V+V arm. Results are from linear regression adjusted for baseline value and stratum. N=52

9.2.7 REGRESSION ANALYSIS: LOG$_{10}$ INTEGRATED HIV DNA AT PR WEEK 16/18, EXCLUDING ART +V+V PARTICIPANTS WHO DID NOT RECEIVE ALL 10 SCHEDULED DOSES OF VORINOSTAT

N=50	Estimate	SE	95% CI	p-value
Difference in log$_{10}$ integrated HIV-DNA at weeks 16/18: ART +V+V vs ART only *	0.10	0.09	-0.08 - 0.28	0.284

Note: Results are from linear regression adjusted for baseline value and stratum. N=50.

9.2.8 CORRELATION BETWEEN TOTAL HIV DNA AND INTEGRATED HIV DNA AT WEEK 16 & 18.



9.3 HIV CELL ASSOCIATED RNA

9.3.1 HIV CELL ASSOCIATED RNA: ANY DATA AVAILABLE

	ART only N=30	ART +V+V N=30	Total N=60
Data available			
No	3 (10%)	6 (20%)	9 (15%)
Yes	27 (90%)	24 (80%)	51 (85%)

9.3.2 HIV CELL ASSOCIATED RNA: AVAILABILITY, BY VISIT

	Pre vorinostat only	Pre & post vorinostat
Number of results	N=138	N=31
Visit		
Randomisation	50	0
PR Week 08-3	0	11
PR Week 09-2	0	10
PR Week 12-2	0	10
PR Week 16-0	49	0
PR Week 18-0	39	0

9.3.3 HIV CELL ASSOCIATED RNA: AVAILABILITY, BY VISIT AND ARM

	ART only N=27	ART +V+V N=24	Total N=51
Randomisation	27	23	50
PR Week 08-3		11	11
PR Week 09-2		10	10
PR Week 12-2		10	10
PR Week 16-0	27	22	49
PR Week 18-0	21	18	39

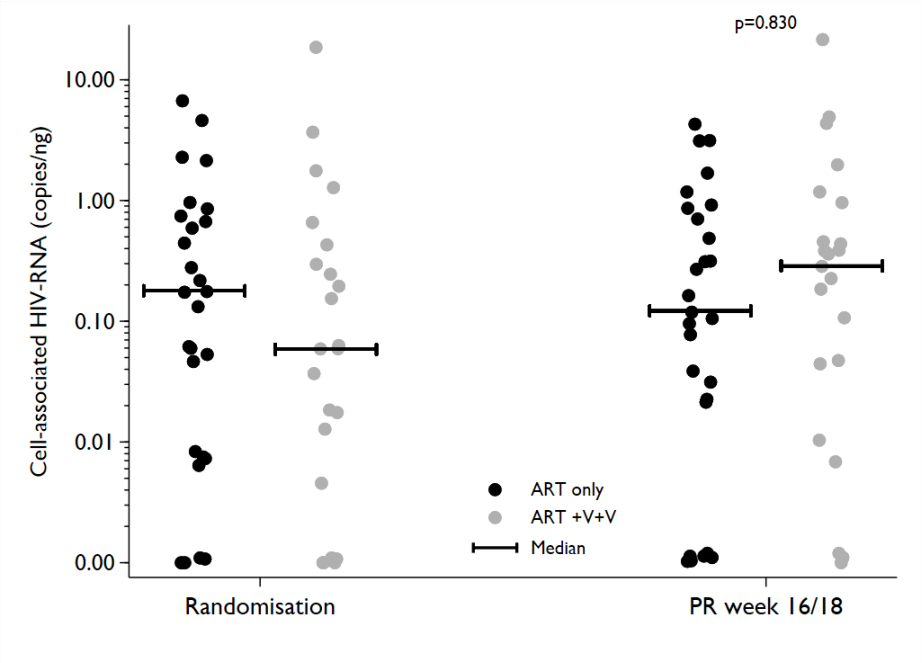
	ART only N=30	ART +V+V N=30	Total N=60
Primary samples			
Baseline & one of PR-16 / PR-18	6 (20%)	6 (20%)	12 (20%)
Baseline, PR-16 AND PR-18	21 (70%)	17 (57%)	38 (63%)
none of baseline, PR-16 or PR-18	3 (10%)	7 (23%)	10 (17%)

9.3.4 HIV CELL ASSOCIATED RNA AT RANDOMISATION AND PR WEEKS 16/18 (COPIES PER NG)

Time-point	ART only	ART +V+V	Total
Randomisation	0.18 (0.01 - 0.74) [0.00 - 6.79]	0.06 (0.00 - 0.50) [0.00 - 21.24]	0.10 (0.01 - 0.66) [0.00 - 21.24]
PR Week 16	0.07 (0.00 - 0.57) [0.00 - 5.01]	0.26 (0.01 - 0.93) [0.00 - 22.66]	0.15 (0.00 - 0.57) [0.00 - 22.66]
PR Week 18	0.23 (0.01 - 0.68) [0.00 - 6.21]	0.16 (0.00 - 1.45) [0.00 - 20.40]	0.19 (0.00 - 1.08) [0.00 - 20.40]

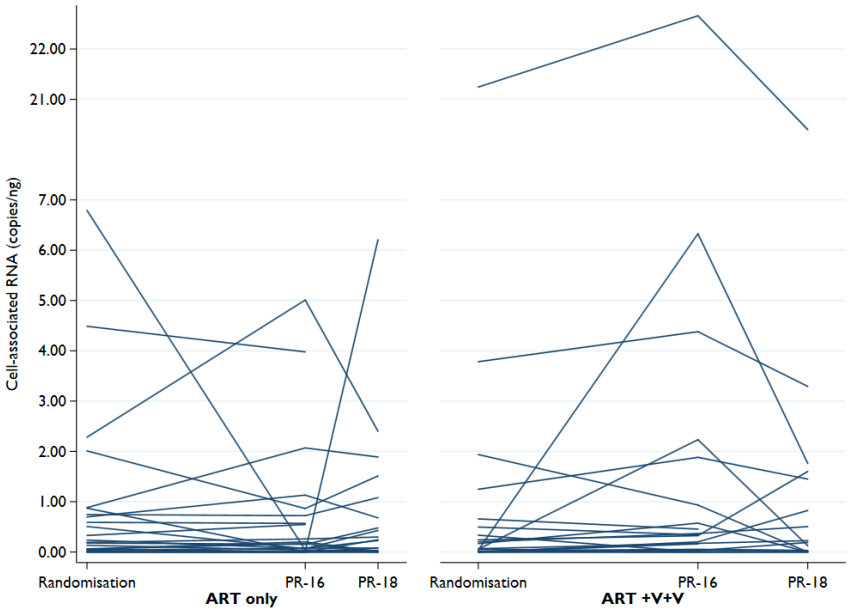
Note: Median (IQR) [min-max]

9.3.5 HIV CELL ASSOCIATED RNA: DOT PLOT PLUS MEDIAN



Note: p-value derived from median regression, adjusted for stratum and baseline level.

9.3.6 CHANGE IN HIV CELL ASSOCIATED RNA FROM RANDOMISATION TO PR WEEK 16/18, BY PARTICIPANT



9.3.7 REGRESSION ANALYSIS: HIV CELL ASSOCIATED RNA AT PR WEEK 16/18

N=50	Estimate	SE	95% CI	p-value
Difference in cell-associated HIV-RNA at weeks 16/18: ART +V+V vs ART only *	0.02	0.11	-0.19 - 0.24	0.830

Note: * ART +V+V minus ART only; a result of 0.02 means a higher cell-associated HIV RNA in the ART +V+V arm. Results are from median regression with bootstrapped standard error (Stata command *bsqreg*), adjusted for baseline value and stratum.

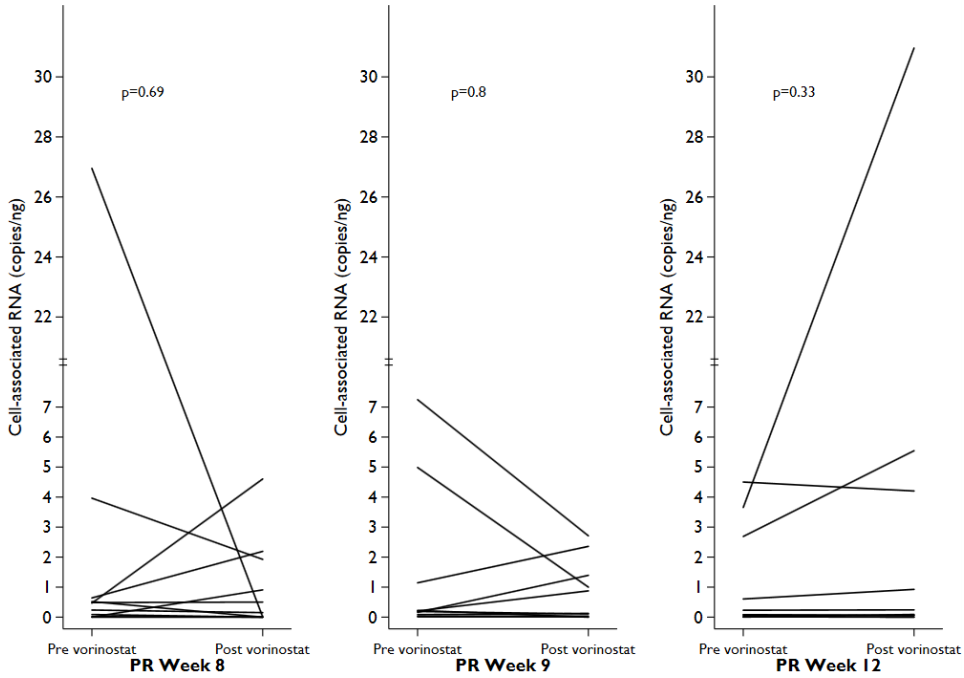
9.3.8 REGRESSION ANALYSIS: HIV CELL ASSOCIATED RNA AT PR WEEK 16/18, EXCLUDING ART +V+V PARTICIPANTS WHO DID NOT RECEIVE ALL 10 SCHEDULED DOSES OF VORINOSTAT

N=48	Estimate	SE	95% CI	p-value
Difference in cell-associated HIV-RNA at weeks 16/18: ART +V+V vs ART only	0.11	0.12	-0.14 - 0.35	0.379

Note: Results are from median regression with bootstrapped standard error (Stata command *bsqreg*), adjusted for baseline value and stratum.

9.3.9 HIV CELL ASSOCIATED RNA PRE AND POST VORINOSTAT, BY PARTICIPANT

Number of participants with pre-post results: n = 17



9.3.10 ART +V +V ONLY: COMPARISON OF PRE AND POST VORINOSTAT RESULTS

	PR Week 08-3	PR Week 09-2	PR Week 12-2
N	11	10	10
Pre vorinostat	0.47 (0.02-0.64) [0 – 26.95]	0.20 (0.08-1.14) [0.01 – 16.99]	0.16 (0.01-2.69) [0 – 15.65]
Post vorinostat	0.15 (0-1.93) [0 – 4.61]	0.50 (0.03-2.36) [0 – 13.00]	0.17 (0.06-4.20) [0 – 30.96]
p-value	*0.69*	*0.80*	*0.33*

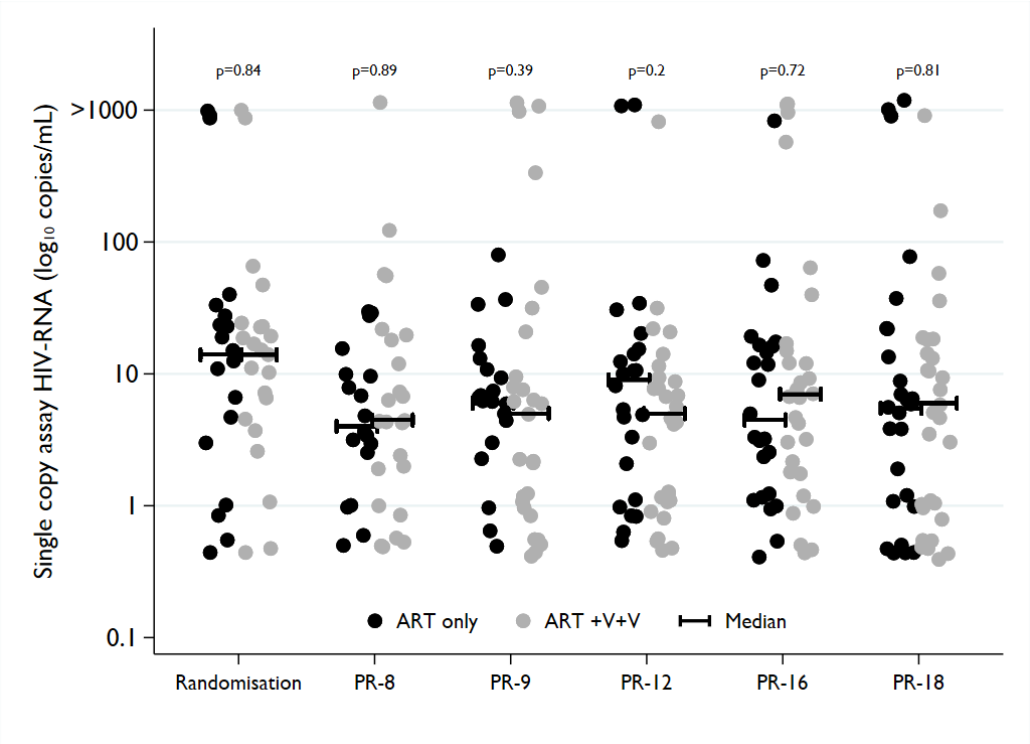
Note: A total number of 17 participants provided pre-post vorinostat results. Numbers are median (IQR) [min-max]; p-values from Wilcoxon rank-sum test.

9.4 PLASMA HIV RNA MEASURED WITH AN SINGLE COPY ASSAY

9.4.1 AVAILABILITY OF RESULTS

No of samples	Assay valid N=317	Assay failure N=33	Total N=350
Visit			
Enrolment	28	3	31
Randomisation	41	12	53
PR Week 08-3	42	8	50
PR Week 09-2	47	4	51
PR Week 12-2	51	3	54
PR Week 16-0	53	3	56
PR Week 18-0	55	0	55

9.4.2 SINGLE COPY ASSAY HIV-RNA OVER TIME, BY ARM



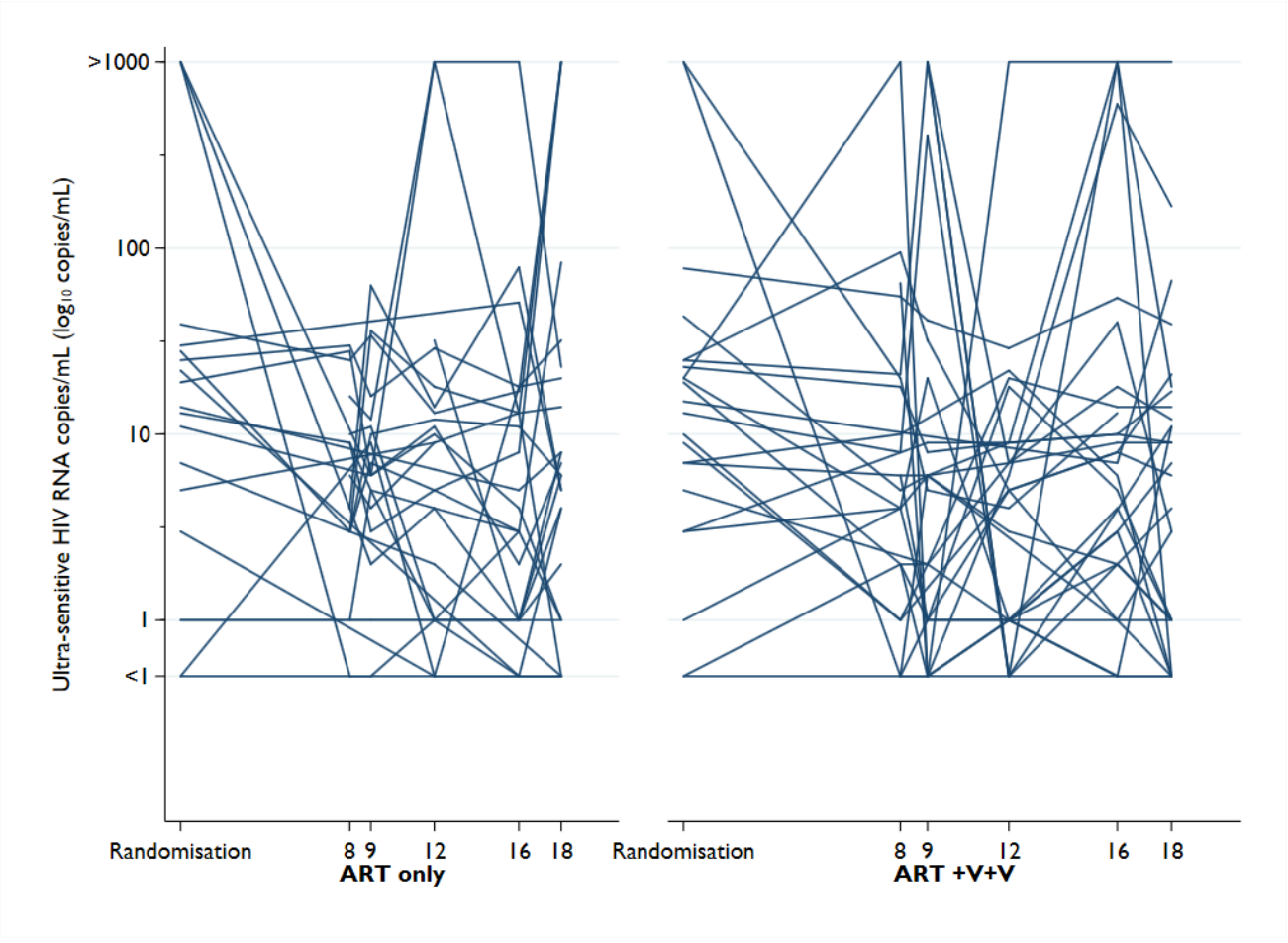
Note: point-wise p-values from rank tests.

9.4.3 SINGLE COPY ASSAY HIV-RNA OVER TIME, BY ARM

Statistics	Time-point	ART only	ART +V+V	*p-value*
Median (IQR) [min-max]	Enrolment	383 (59 - >1000) [8 - >1000]	447 (17 - >1000) [0 - >1000]	*0.39*
copies/mL	Randomisation	14 (3 - 30) [0 - >1000]	14 (5 - 25) [0 - >1000]	*0.84*
	PR Week 8	4 (3 - 10) [0 - 30]	5 (2 - 19) [0 - >1000]	*0.89*
	PR Week 9	6 (4 - 12) [0 - 63]	5 (1 - 20) [0 - >1000]	*0.39*
	PR Week 12	9 (1 - 14) [0 - >1000]	5 (1 - 9) [0 - >1000]	*0.20*
	PR Week 16	5 (1 - 15) [0 - >1000]	7 (2 - 14) [0 - >1000]	*0.72*
	PR Week 18	6 (1 - 20) [0 - >1000]	6 (1 - 14) [0 - >1000]	*0.81*
Median (IQR) [min-max]	Enrolment	2.58 (1.77 - 3.00) [0.90 - >3.00]	2.65 (1.23 - 3.00) [-0.30 - >3.00]	
$\log_{10}$ copies/mL	Randomisation	1.15 (0.48 - 1.48) [-0.30 - >3.00]	1.15 (0.70 - 1.40) [-0.30 - >3.00]	
	PR Week 8	0.60 (0.48 - 1.00) [-0.30 - 1.48]	0.65 (0.15 - 1.28) [-0.30 - >3.00]	
	PR Week 9	0.78 (0.54 - 1.06) [-0.30 - 1.80]	0.70 (0.00 - 1.30) [-0.30 - >3.00]	
	PR Week 12	0.95 (0.00 - 1.15) [-0.30 - >3.00]	0.70 (0.00 - 0.95) [-0.30 - >3.00]	
	PR Week 16	0.65 (0.00 - 1.17) [-0.30 - >3.00]	0.85 (0.30 - 1.15) [-0.30 - >3.00]	
	PR Week 18	0.74 (0.00 - 1.30) [-0.30 - >3.00]	0.78 (0.00 - 1.15) [-0.30 - >3.00]	

Note: $\log_{10}(0.5)$ assumed if copies/mL=0.

9.4.4 CHANGE IN SINGLE COPY ASSAY HIV-RNA FROM RANDOMISATION, BY PARTICIPANT



9.4.5 ART +V +V ARM: AVAILABILITY OF PRE AND POST VORINOSTAT RESULTS

Factor	PR Week 08-3	PR Week 09-2	PR Week 12-2
N	29	29	29
Pre/post vorinostat			
no result	3 (10%)	0 (0%)	0 (0%)
pre only	2 (7%)	7 (24%)	7 (24%)
post only	2 (7%)	2 (7%)	1 (3%)
pre & post	22 (76%)	20 (69%)	21 (72%)

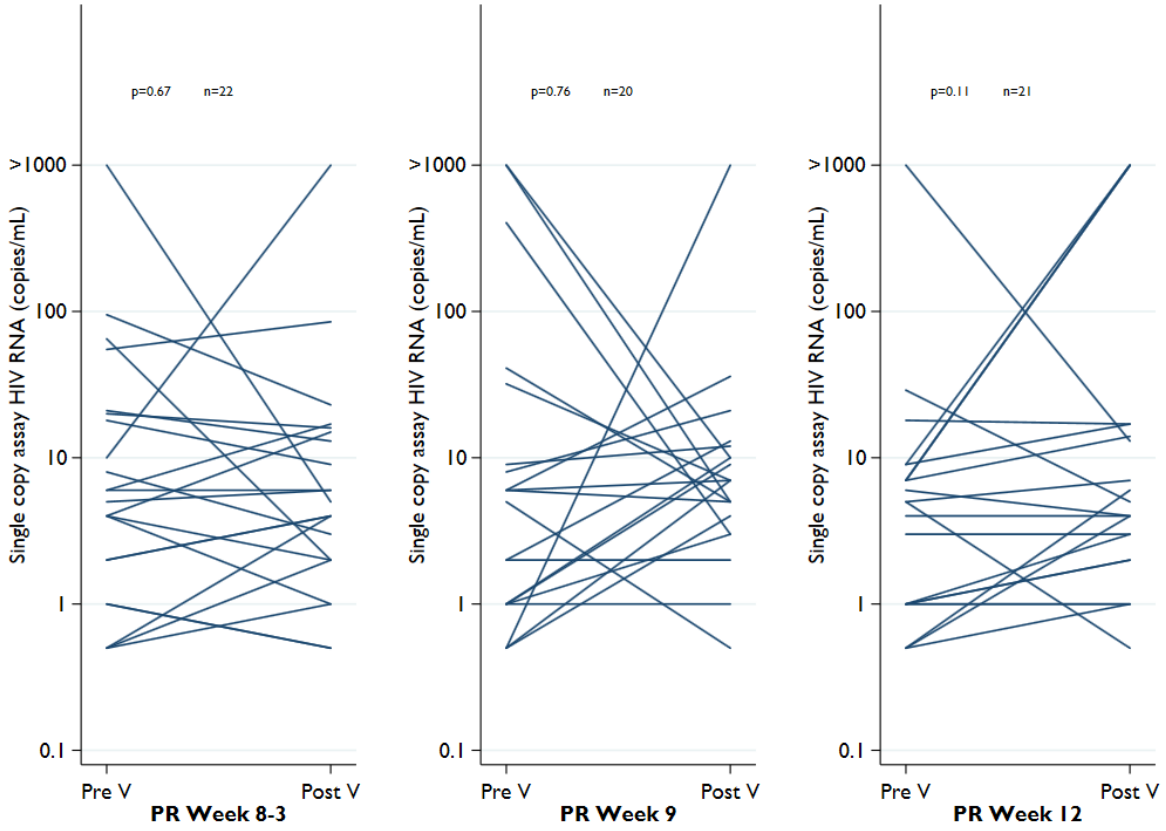
Note: excluding one participant randomised who did not start vorinostat

9.4.6 ART +V +V ARM: COMPARISON OF PRE AND POST VORINOSTAT RESULTS

	PR Week 08-3	PR Week 09-2	PR Week 12-2
Pre vorinostat	5.5 (2-20) [0 - >1000]	5.5 (1-20.5) [0 - >1000]	5 (1-7) [0 - >1000]
Post vorinostat	4.5 (2-15) [0 - >1000]	7 (3.5-11) [0 - >1000]	4 (2-14) [0 - >1000]
p-value	*0.67*	*0.76*	*0.11*

Note: Numbers are median (IQR) [min-max] for participants with results pre and post vorinostat; p-values from Wilcoxon rank-sum test. Number of patients with at least on pre/post vorinostat results pair: n=28.

9.4.7 SINGLE COPY ASSAY HIV-RNA PRE AND POST VORINOSTAT, BY PARTICIPANT



9.5 HIV-SPECIFIC T CELL RESPONSES (BOTH CD8+ AND CD4+ T CELL RESPONSES)

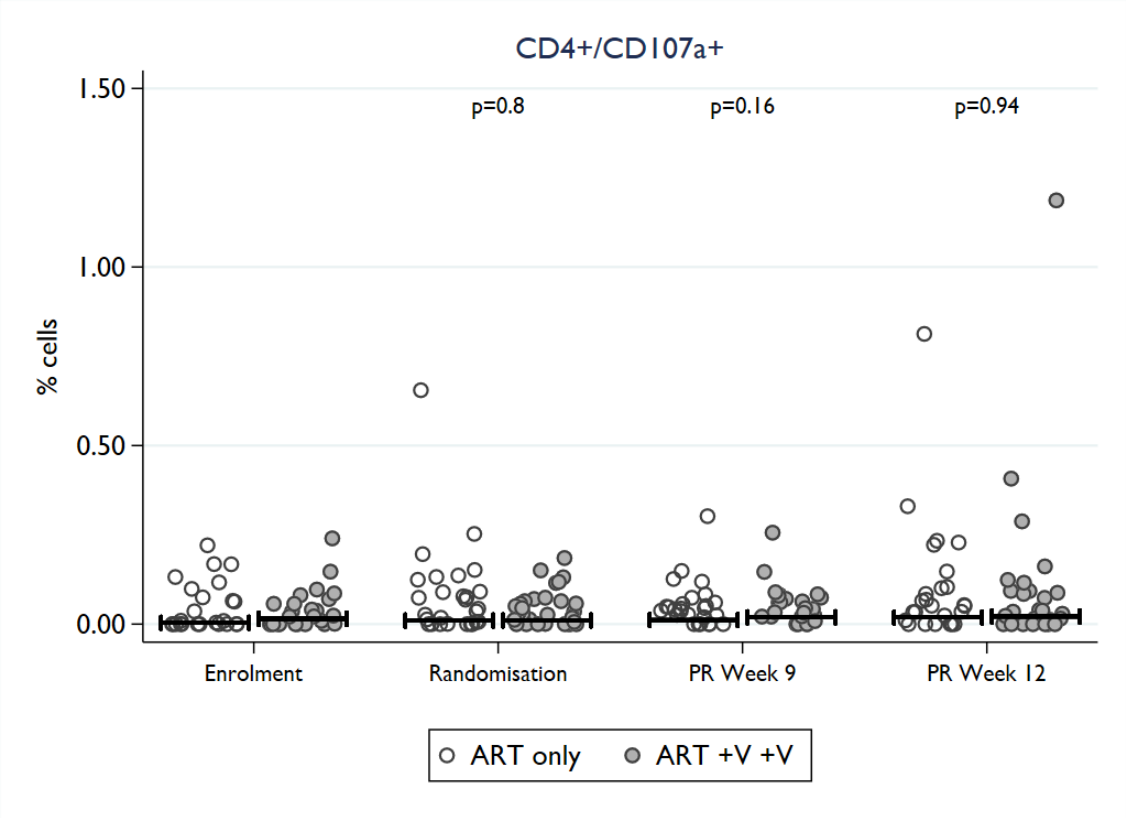
9.5.1 AVAILABILITY OF RESULTS

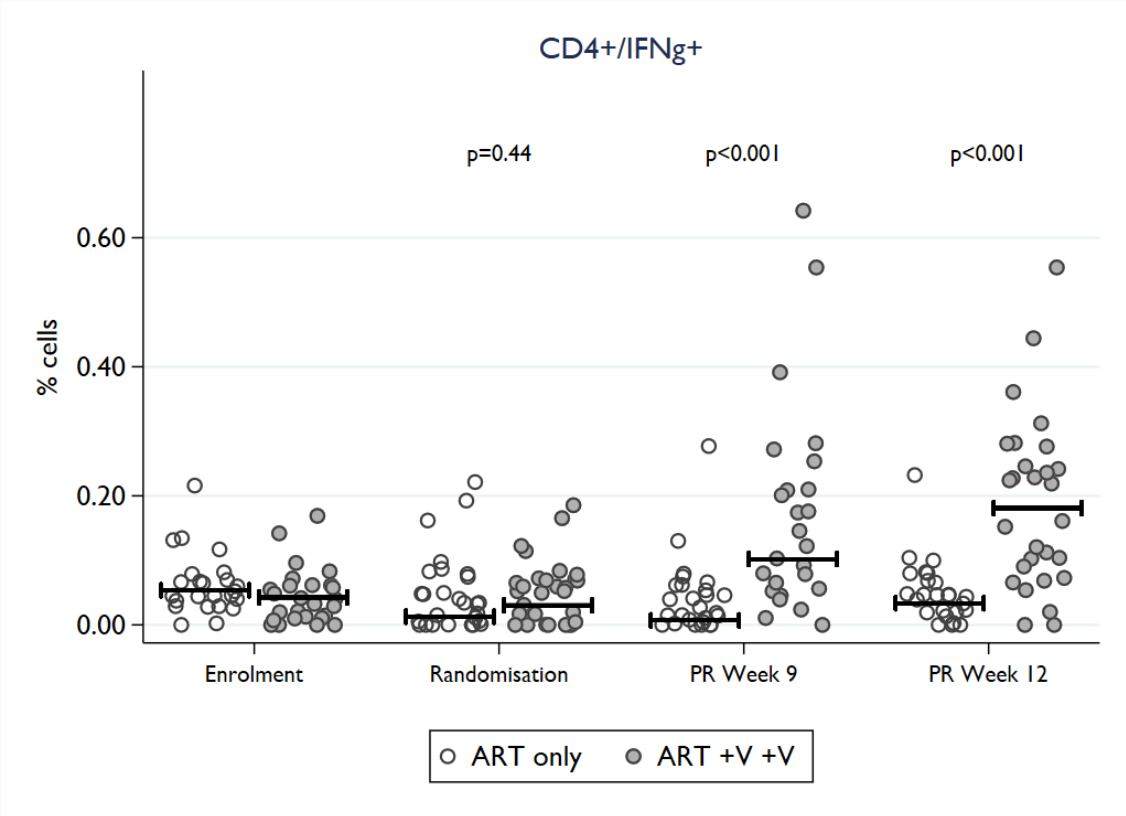
		ART only N=27	ART +V+V N=30	Total N=60
Enrolment:	CD4	24	26	50
	CD8	24	26	50
Randomisation:	CD4	27	30	57
	CD8	26	30	56
	CD8 invalid	1	0	1
PR-9:	CD4:	26	25	51
	CD8	26	24	50
	CD8 invalid	0	1	1
PR-12:	CD4	25	28	53
	CD8	25	28	53

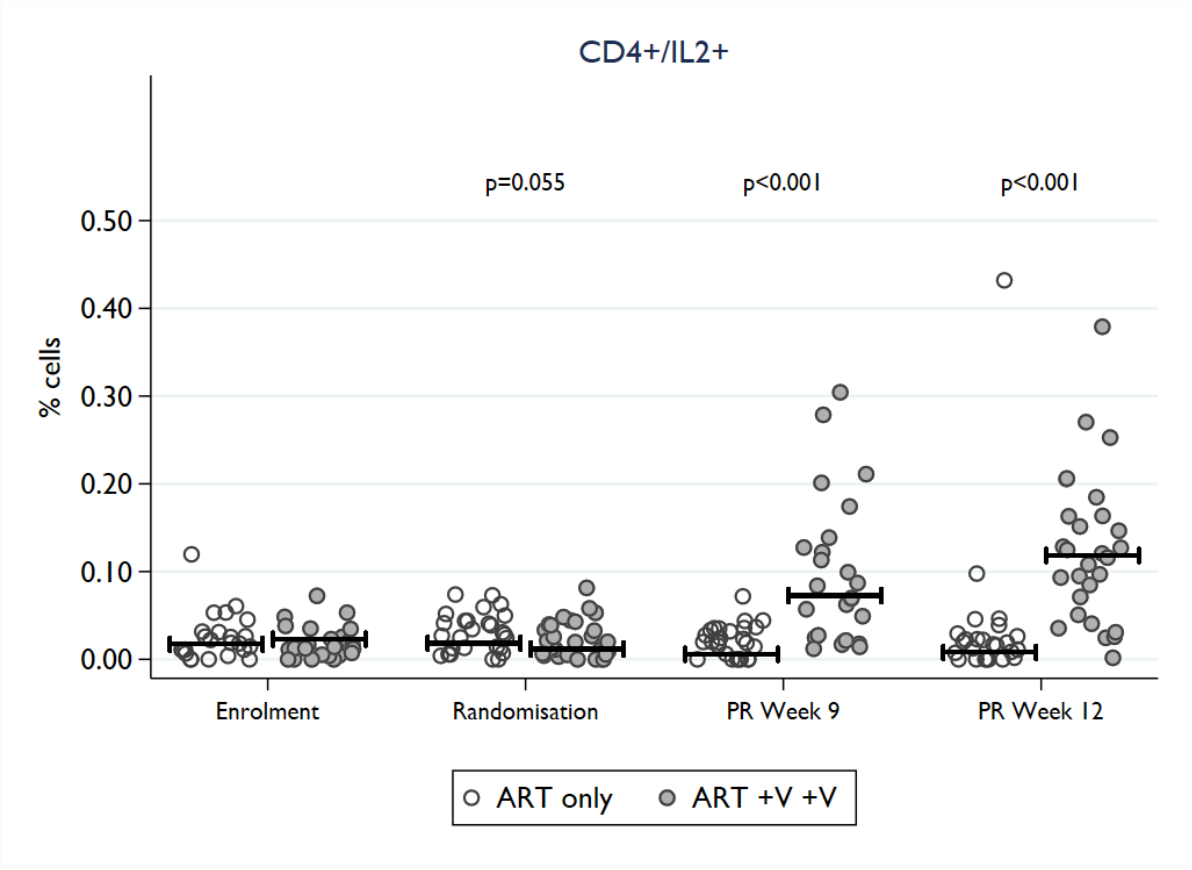
Notes on missing results:

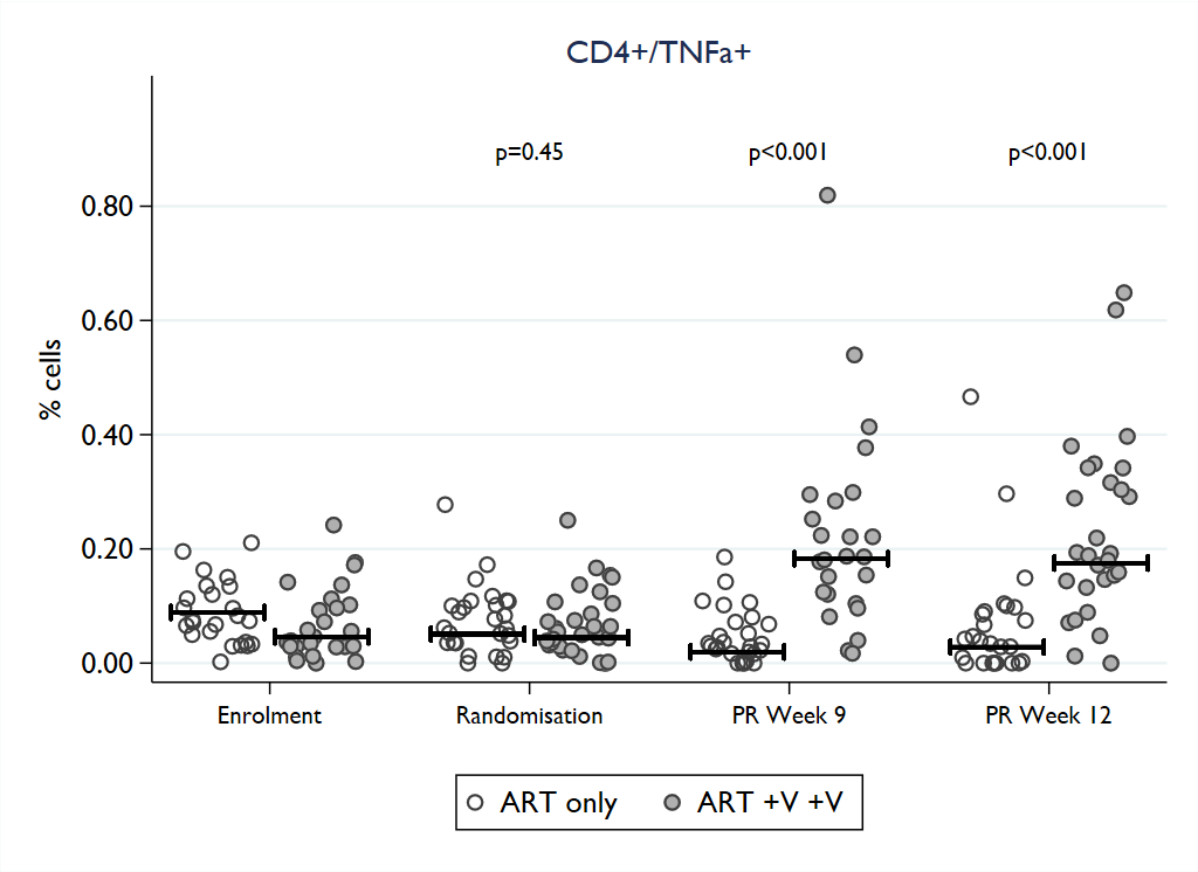
- Three of 30 participants in ART only arm (R01214L, R04405W, R05501S) missed both PR-9 and PR-12 visits, and it was decided not to run ICS assays on their enrolment/randomisation samples
- No enrolment sample taken in 8 participants from stratum 2.
- The remaining missingness was due to missed visits, samples not taken, or samples taken but not processed

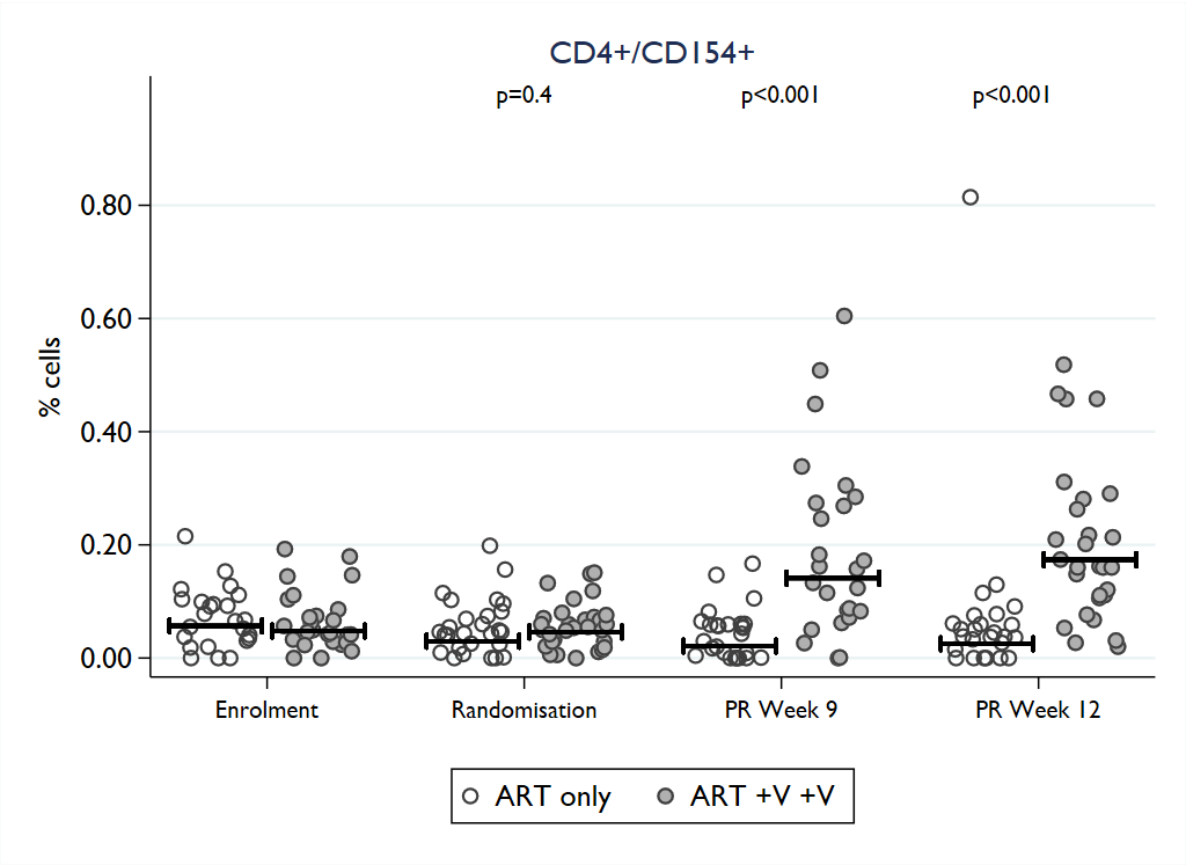
9.5.2 CD4+ T CELL RESPONSES






CD4+/IL2+
p=0.055
p<0.001
p<0.001
0.50
0.40
0.30
0.20
0.10
0.00
% cells
Enrolment
Randomisation
PR Week 9
PR Week 12
ART only
ART +V +V

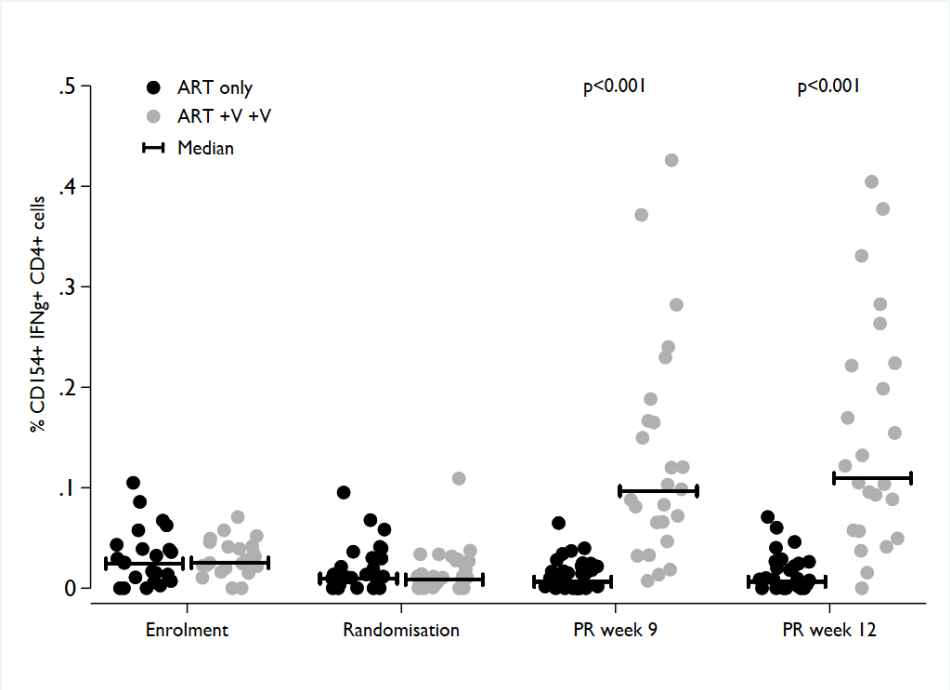

CD4+/TNFa+
p=0.45
p<0.001
p<0.001
0.80
0.60
0.40
0.20
0.00
% cells
Enrolment
Randomisation
PR Week 9
PR Week 12
ART only
ART +V +V



CD4+		ART only N=27	ART +V+V N=30	p-value
% CD107a$^+$:	Randomisation	0.010 (0.000, 0.096)	0.010 (0.000, 0.043)	0.80
	Visit PR-9	0.011 (0.000, 0.030)	0.019 (0.006, 0.056)	0.16
	Visit PR-12	0.019 (0.000, 0.061)	0.021 (0.000, 0.068)	0.94
% CD154$^+$:	Randomisation	0.030 (0.011, 0.073)	0.046 (0.015, 0.062)	0.40
	Visit PR-9	0.021 (0.001, 0.037)	0.141 (0.065, 0.256)	<0.001
	Visit PR-12	0.025 (0.011, 0.049)	0.174 (0.118, 0.257)	<0.001
% IFNγ$^+$:	Randomisation	0.013 (0.000, 0.077)	0.030 (0.001, 0.060)	0.44
	Visit PR-9	0.007 (0.000, 0.042)	0.102 (0.051, 0.235)	<0.001
	Visit PR-12	0.034 (0.007, 0.061)	0.181 (0.070, 0.266)	<0.001
% IL2$^+$:	Randomisation	0.018 (0.009, 0.036)	0.012 (0.003, 0.020)	0.055
	Visit PR-9	0.006 (0.000, 0.024)	0.073 (0.022, 0.132)	<0.001
	Visit PR-12	0.008 (0.000, 0.019)	0.118 (0.069, 0.158)	<0.001
% TNFα$^+$:	Randomisation	0.051 (0.032, 0.089)	0.045 (0.015, 0.082)	0.45
	Visit PR-9	0.020 (0.002, 0.051)	0.183 (0.104, 0.274)	<0.001
	Visit PR-12	0.028 (0.011, 0.059)	0.175 (0.128, 0.300)	<0.001

Note: Numbers are median (IQR); p-values from Wilcoxon rank-sum test

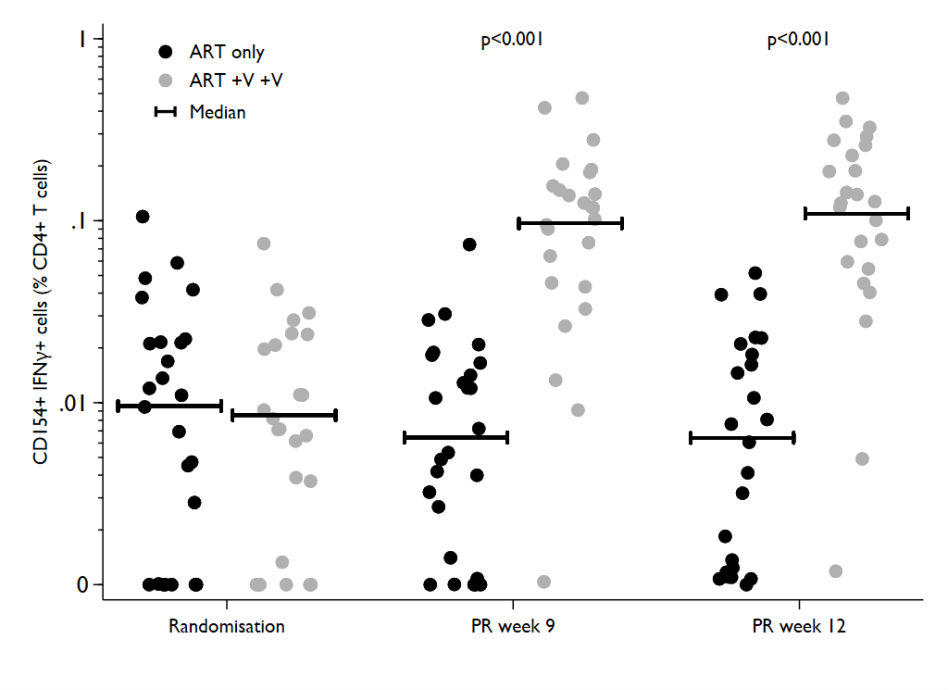
9.5.3 CD4+ T CELL RESPONSES, POLYFUNCTIONAL



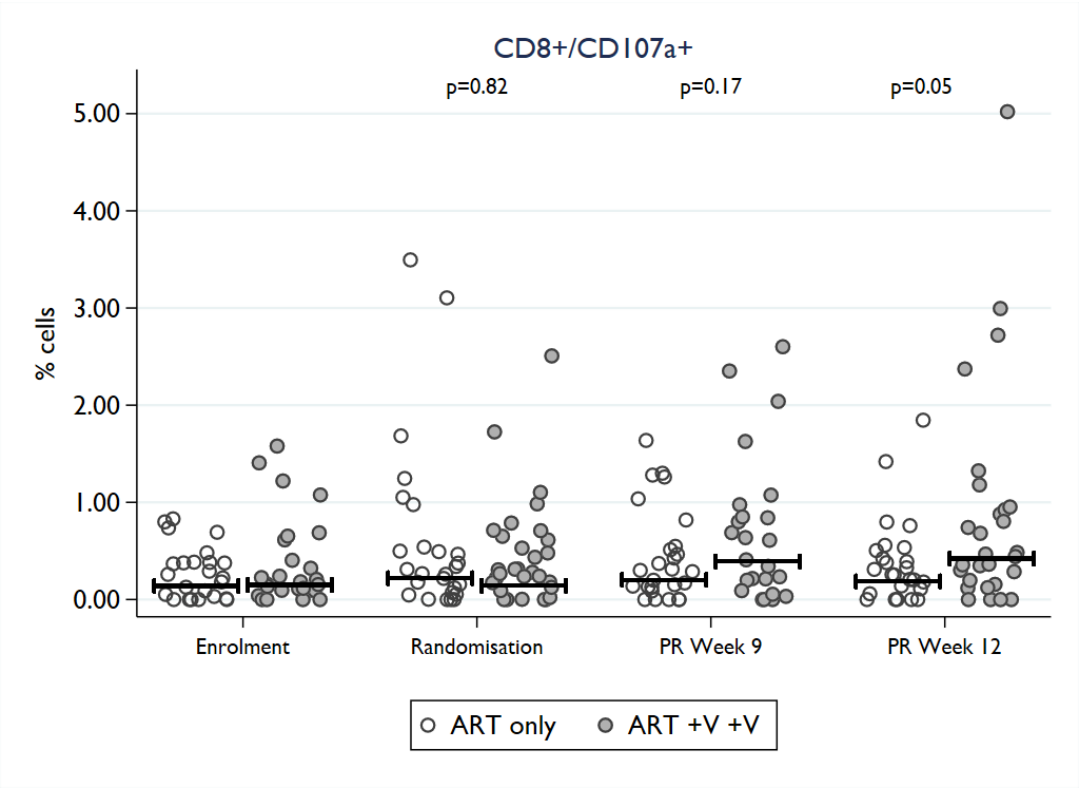
% CD4+ CD154+ IFNγ+	ART only N=27	ART +V+V N=30	p-value
Randomisation	0.010 (0.000, 0.024)	0.009 (0.000, 0.020)	0.67
Visit PR-9	0.006 (0.000, 0.015)	0.097 (0.043, 0.161)	<0.001
Visit PR-12	0.006 (0.000, 0.015)	0.109 (0.050, 0.214)	<0.001

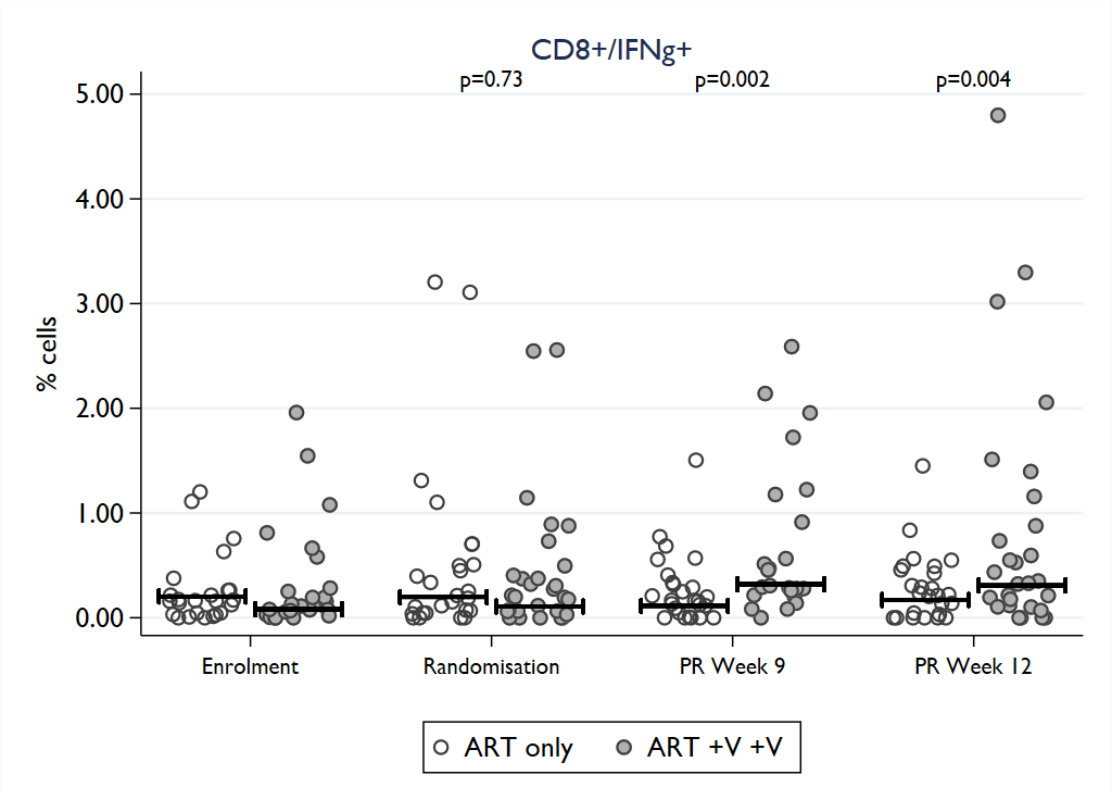
Note: Numbers are median (IQR); p-values from Wilcoxon rank-sum test.

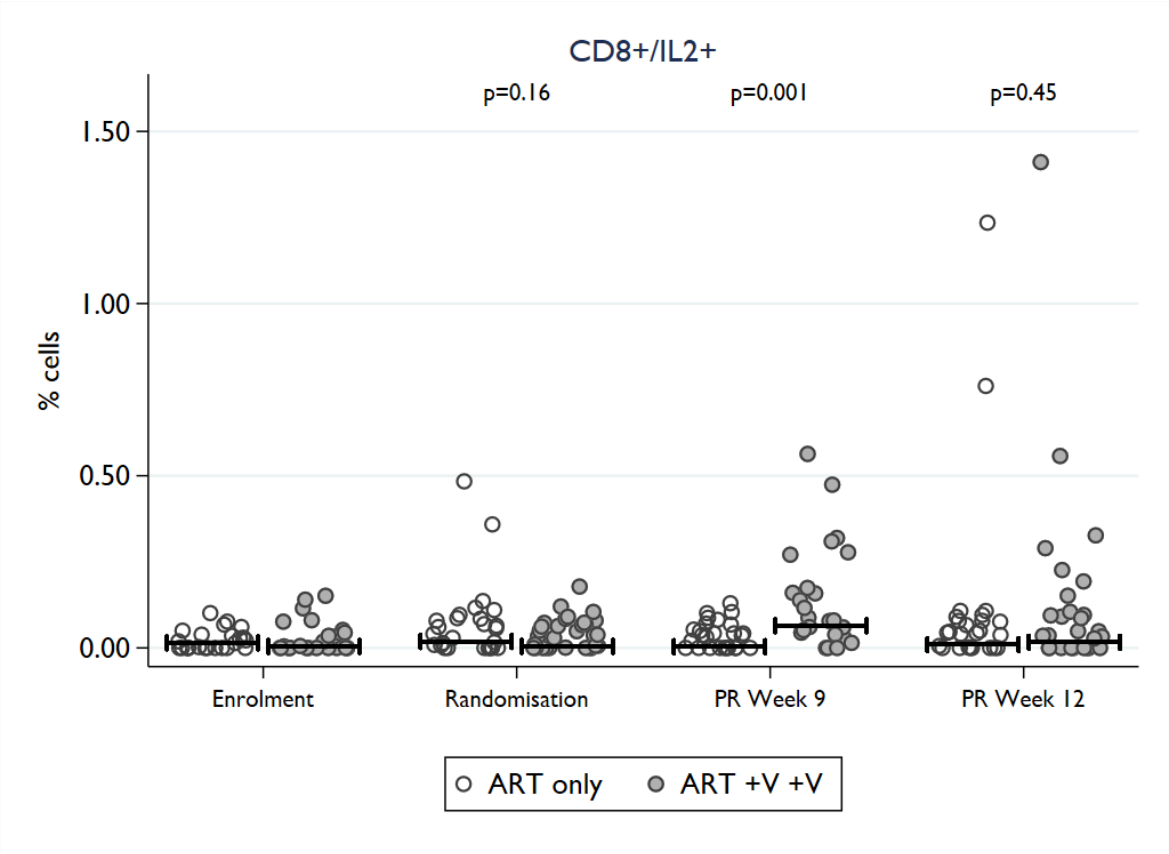
As above, with y axis on log scale

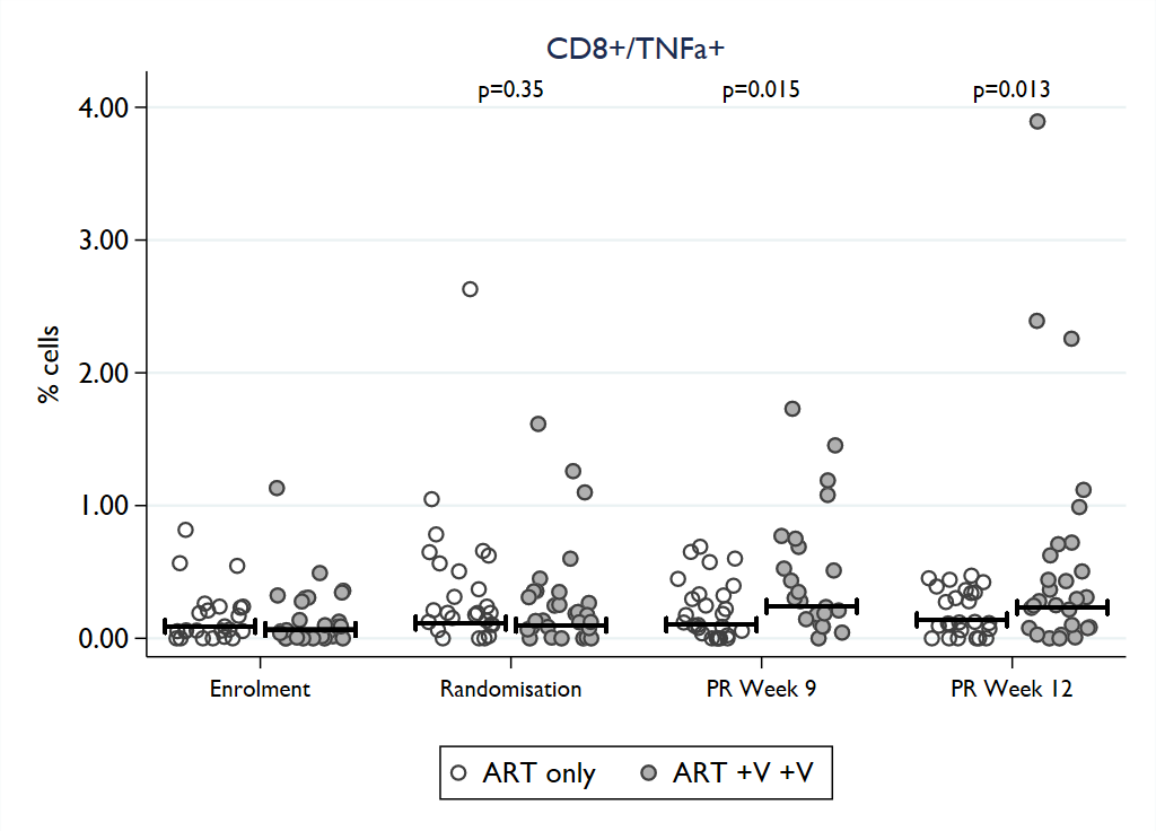


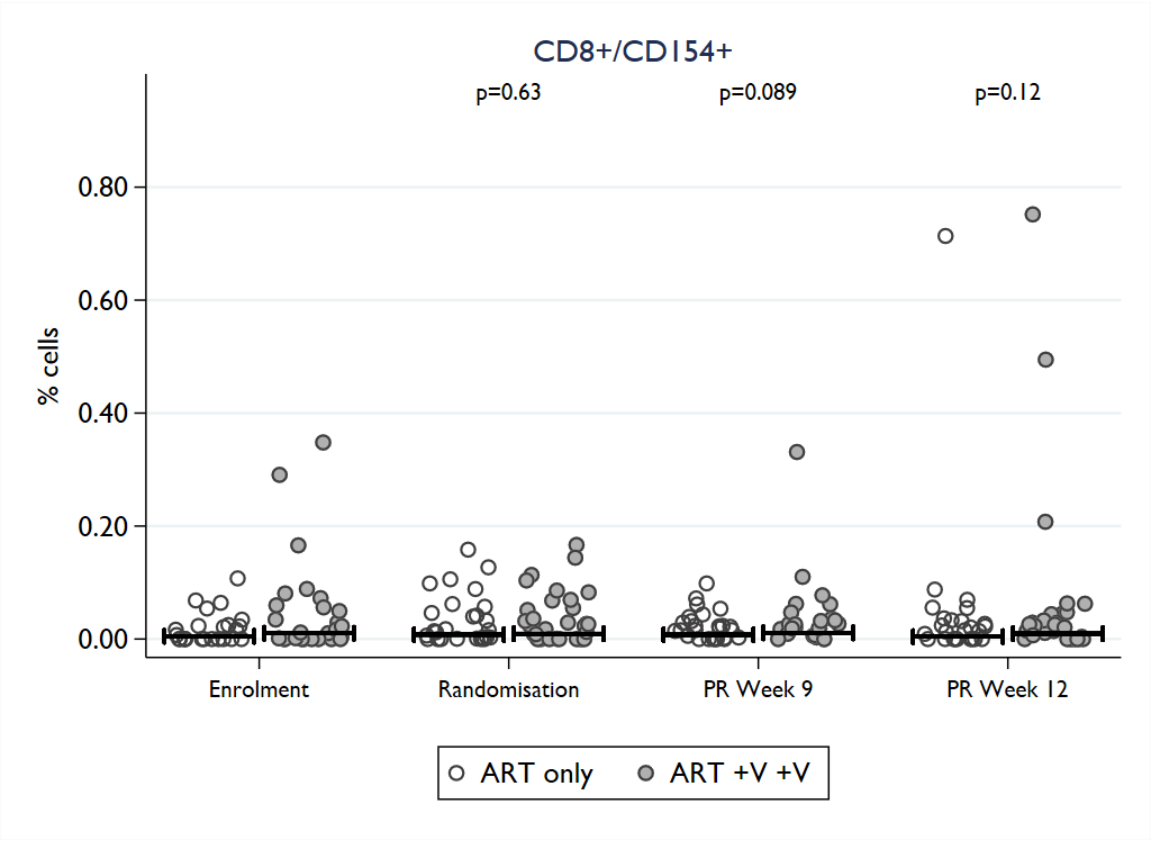
9.5.4 CD8+ T CELL RESPONSES






CD8+/IL2+
p=0.16
p=0.001
p=0.45
1.50
1.00
0.50
0.00
% cells
Enrolment
Randomisation
PR Week 9
PR Week 12
ART only
ART +V +V

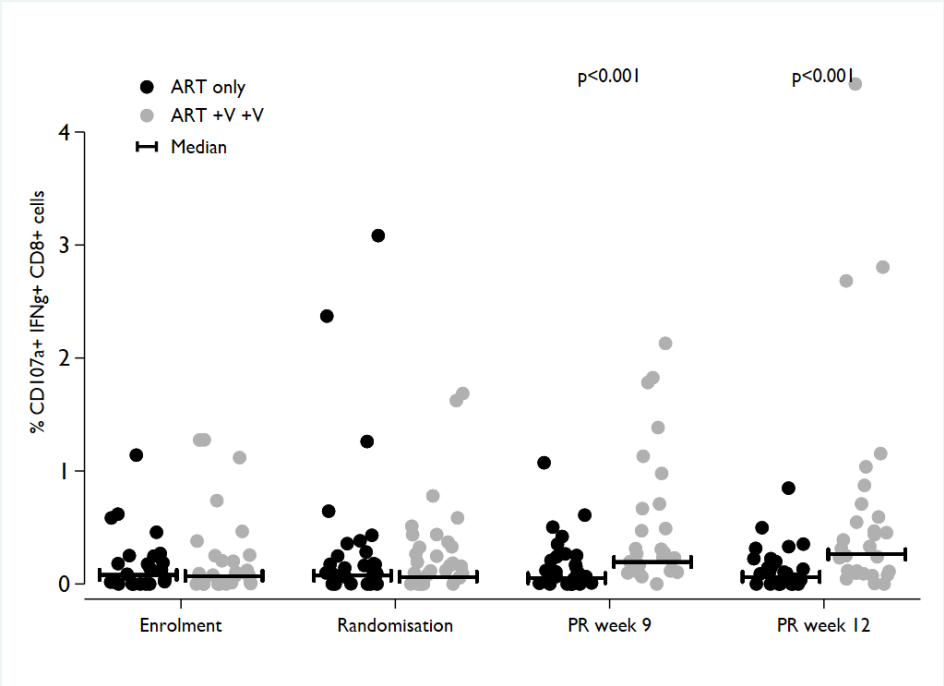

CD8+/TNFa+
p=0.35
p=0.015
p=0.013
4.00
3.00
2.00
1.00
0.00
% cells
Enrolment
Randomisation
PR Week 9
PR Week 12
ART only
ART +V +V



CD8+		ART only N=27	ART +V+V N=30	p-value
% CD107$^+$a:	Randomisation	0.220 (0.032, 0.465)	0.141 (0.054, 0.604)	0.82
	Visit PR-9	0.202 (0.027, 0.732)	0.391 (0.155, 0.829)	0.17
	Visit PR-12	0.187 (0.082, 0.384)	0.421 (0.141, 1.038)	0.050
% CD154$^+$:	Randomisation	0.008 (0.000, 0.041)	0.009 (0.003, 0.034)	0.63
	Visit PR-9	0.008 (0.000, 0.017)	0.011 (0.006, 0.036)	0.089
	Visit PR-12	0.004 (0.000, 0.010)	0.009 (0.002, 0.040)	0.12
% IFNγ$^+$:	Randomisation	0.197 (0.011, 0.525)	0.107 (0.040, 0.428)	0.73
	Visit PR-9	0.114 (0.036, 0.307)	0.320 (0.195, 0.942)	0.002
	Visit PR-12	0.170 (0.057, 0.279)	0.309 (0.177, 1.061)	0.004
% IL2$^+$:	Randomisation	0.019 (0.000, 0.063)	0.005 (0.000, 0.021)	0.16
	Visit PR-9	0.004 (0.000, 0.015)	0.065 (0.010, 0.190)	0.001
	Visit PR-12	0.010 (0.000, 0.032)	0.017 (0.000, 0.105)	0.45
% TNFα$^+$:	Randomisation	0.115 (0.055, 0.524)	0.098 (0.011, 0.280)	0.35
	Visit PR-9	0.104 (0.033, 0.207)	0.240 (0.102, 0.645)	0.015
	Visit PR-12	0.139 (0.018, 0.255)	0.232 (0.102, 0.585)	0.013

Note: Numbers are median (IQR); p-values from Wilcoxon rank-sum test

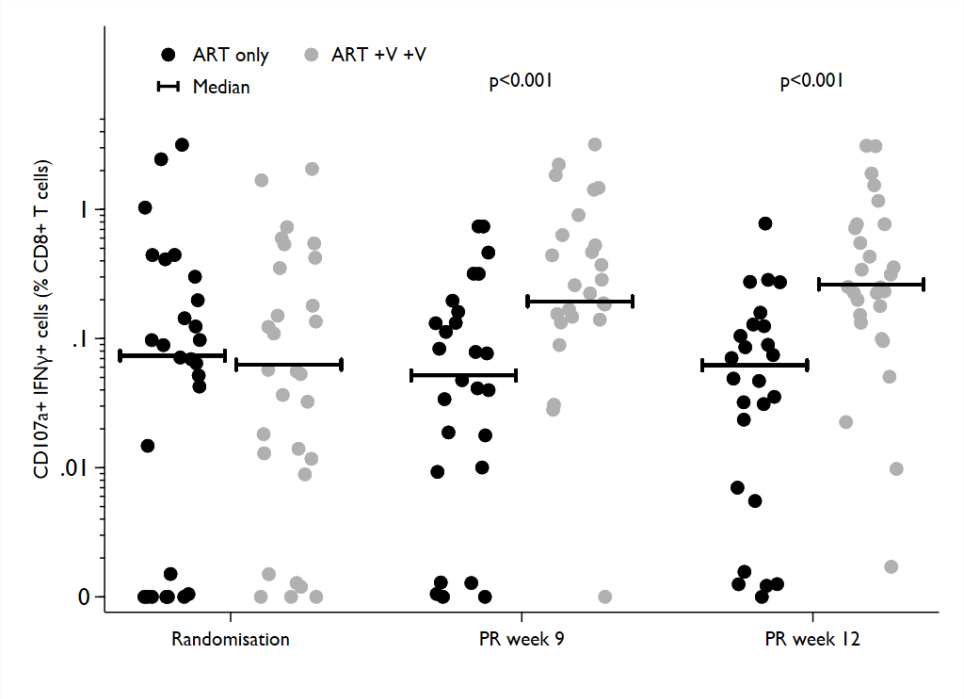
9.5.5 CD8+ T CELL RESPONSES, POLYFUNCTIONAL



% CD8+ CD107a+ IFNγ+	ART only N=27	ART +V+V N=30	p-value
Randomisation	0.074 (0.000, 0.262)	0.063 (0.010, 0.289)	0.82
Visit PR-9	0.052 (0.014, 0.142)	0.194 (0.142, 0.722)	<0.001
Visit PR-12	0.062 (0.008, 0.106)	0.263 (0.105, 0.620)	<0.001

Note: Numbers are median (IQR); p-values from Wilcoxon rank-sum test.

As above, with y axis on log scale



9.6 CD8+ T CELL ANTIVIRAL ACTIVITY (VIRAL INHIBITION)

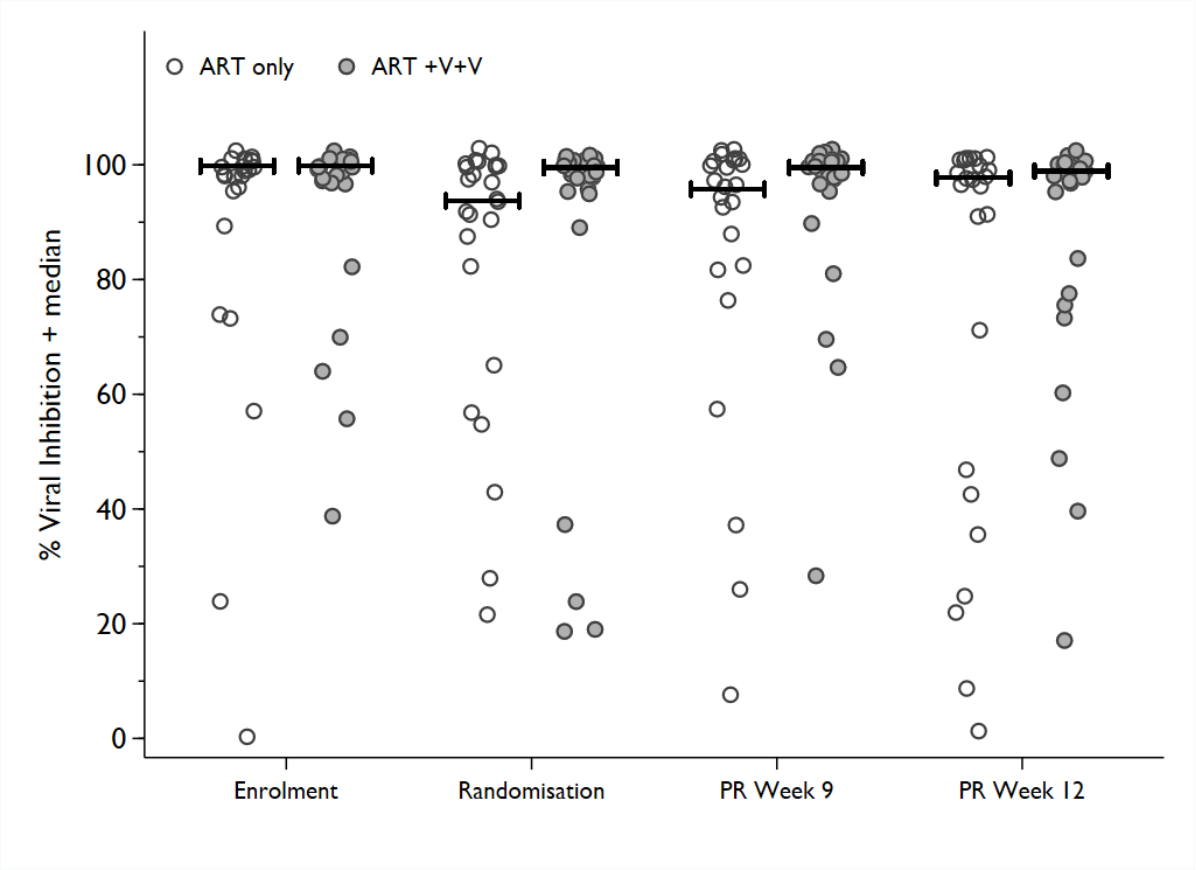
9.6.1 AVAILABILITY OF VALID RESULTS

	ART only N=30	ART +V+V N=30	Total N=60
Availability of results			
None	4 (13%)	3 (10%)	7 (12%)
Baseline, PR-9 AND PR-12	22 (73%)	24 (80%)	46 (77%)
Baseline AND PR-9	2 (7%)	1 (3%)	3 (5%)
Baseline AND PR-12	1 (3%)	2 (7%)	3 (5%)
PR-12 only	1 (3%)	0 (0%)	1 (2%)

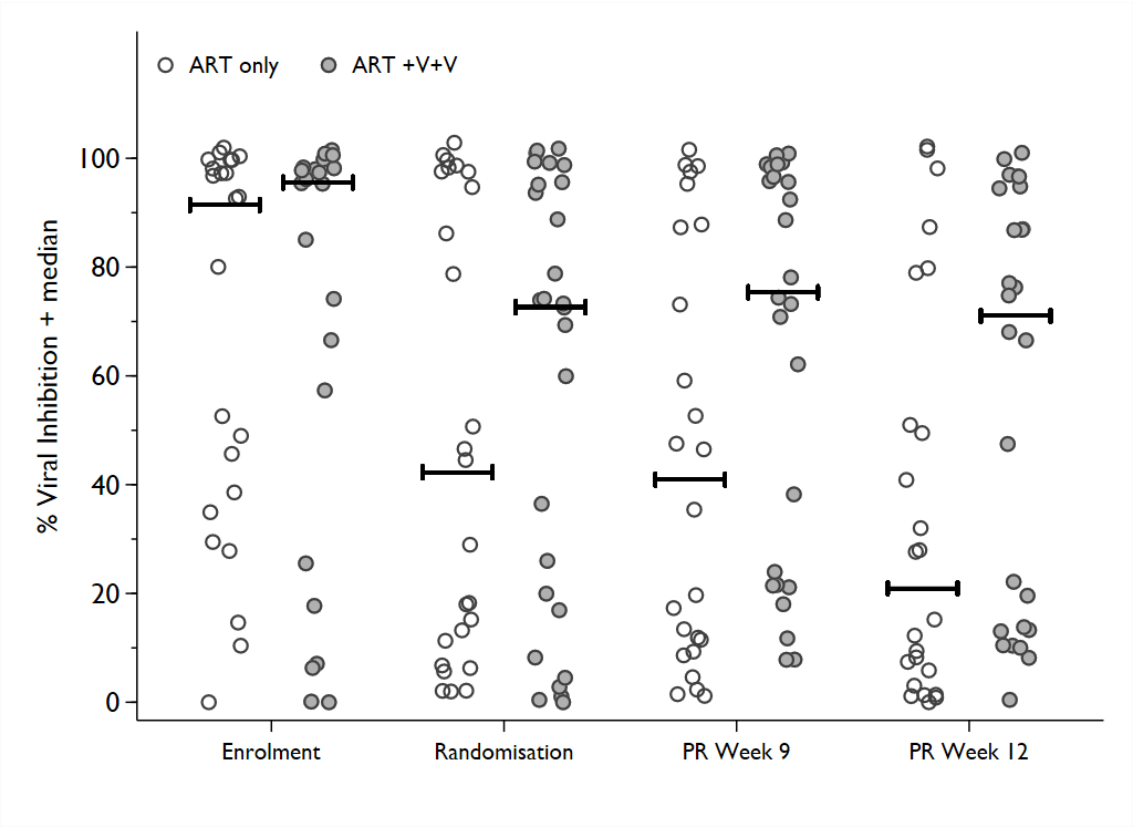
Notes on missing results:

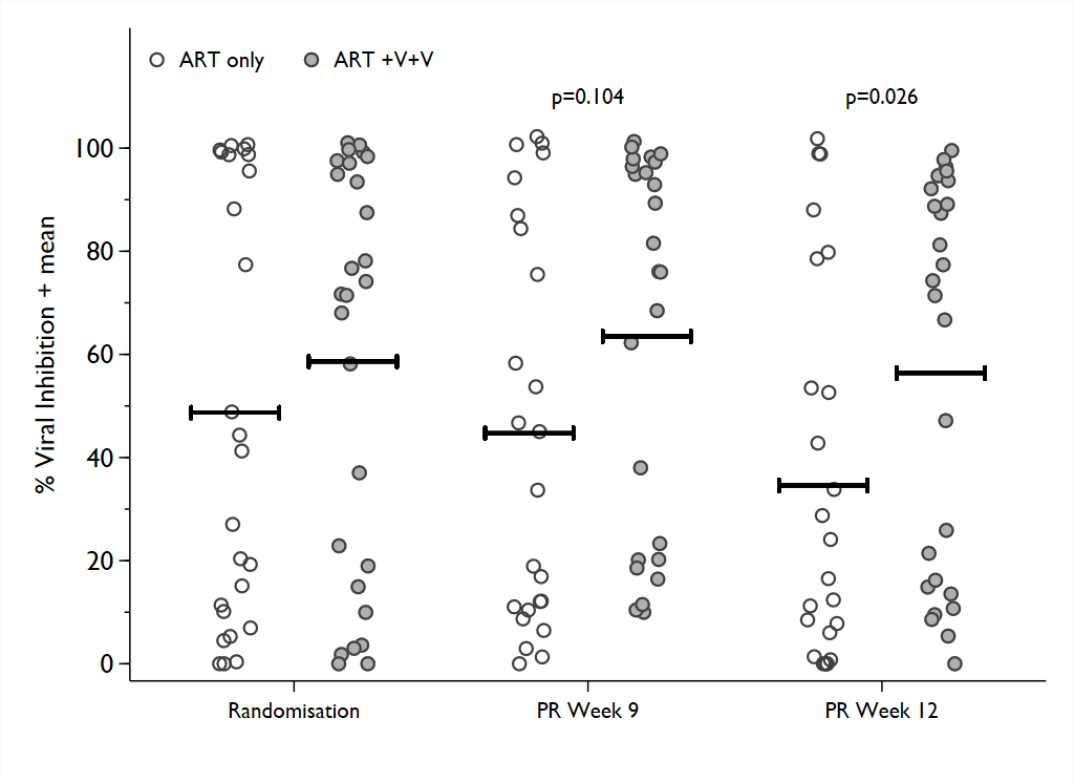
- 4 assays in 3 patients (n=2 ART only: R03306S, R03618N; n=1 ART +V +V: R04403H) performed were not valid; in addition, 1 patient (R03601J, ART +V+V) had invalid 1:1 ratio assay at enrolment.
- the remainder had no visit/sample

9.6.2 INDIVIDUAL RESULTS, BY TIME-POINT AND ARM: CD4:CD8 1:1



9.6.3 INDIVIDUAL RESULTS, BY TIME-POINT AND ARM: CD4:CD8 10:1





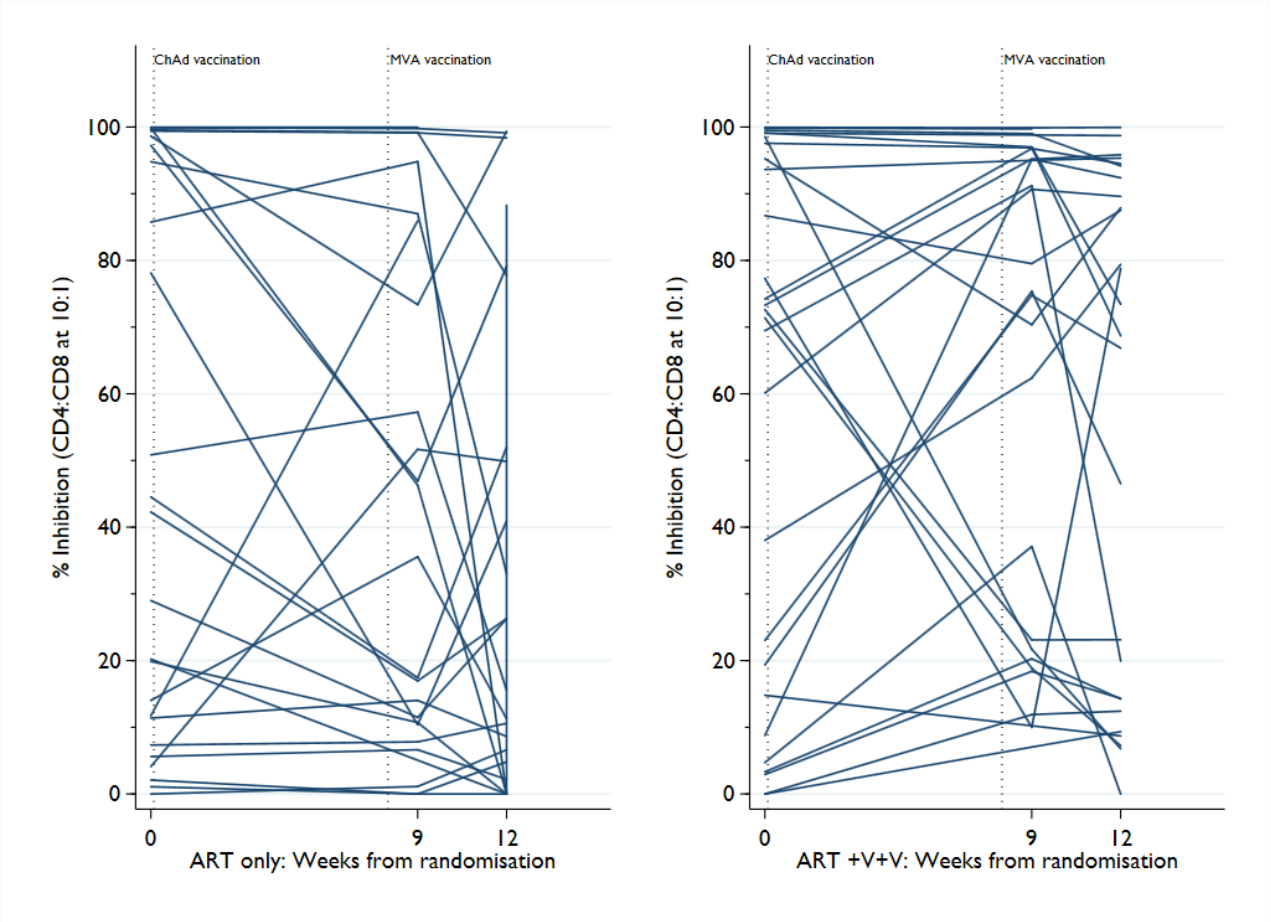
Note: p-value derived from linear regression, adjusted for stratum and baseline level.

9.6.4 VIRAL INHIBITION: DESCRIPTION OF RESULTS (10:1 RATIO)

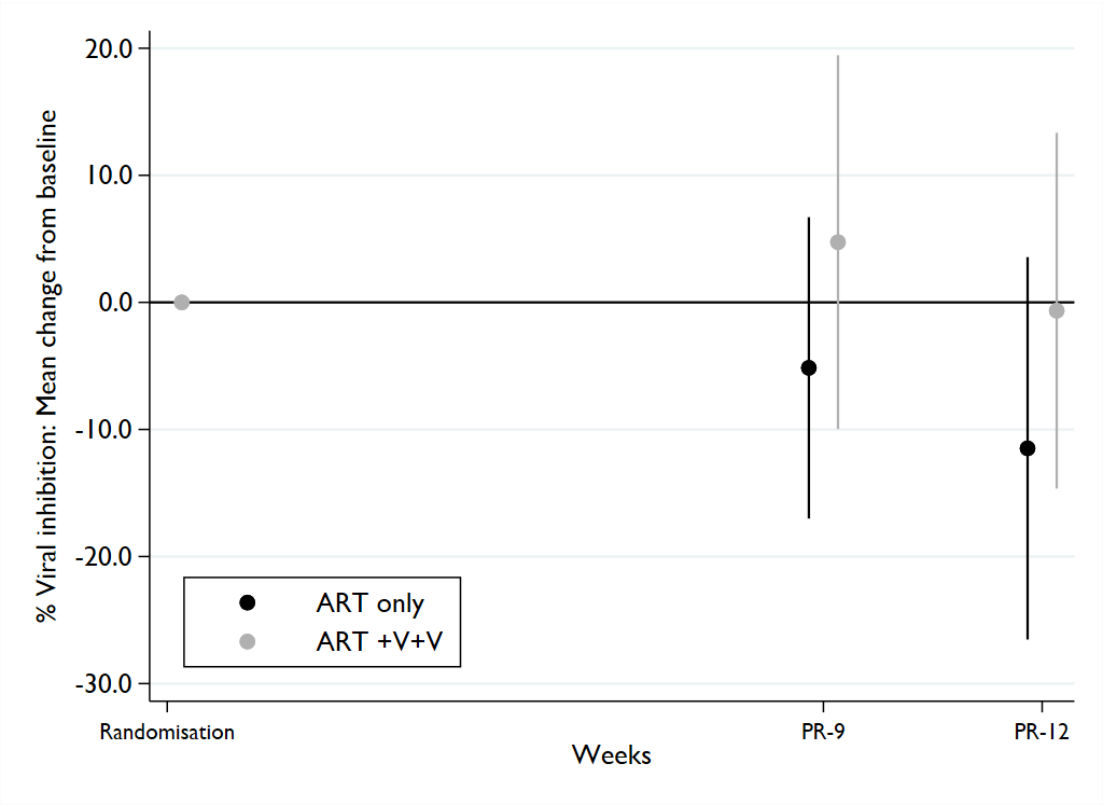
% inhibition	ART only N=27	ART +V+V N=30	p-value
Enrolment	91 (35-99) [0-100]	96 (27-100) [0-100]	0.81
Randomisation	42 (11-97) [0-100]	73 (15-98) [0-100]	0.67
Visit PR-9	41 (11-86) [0-100]	75 (22-95) [7-100]	0.072
Visit PR-12	21 (4-65) [0-99]	71 (14-92) [0-100]	0.046

Note: Point-wise p-values derived from rank tests.

9.6.5 VIRAL INHIBITION: INDIVIDUAL TRAJECTORIES FROM RANDOMISATION



9.6.6 VIRAL INHIBITION: CHANGE FROM RANDOMISATION, 10:1 RATIO



Regression results: change from randomisation and difference between randomisation arms

		Change	SE	95% CI	p-value
Change to PR week 9	**ART only**	-7.39	6.11	-19.70 to 4.92	0.233
	ART +V +V	6.89	5.99	-5.16 to 18.95	0.256
	Difference between arms	14.29	8.61	-3.06 to 31.64	0.104
Change to PR week 12	**ART only**	-18.25	5.66	-29.65 to -6.85	0.002
	ART +V +V	1.50	6.34	-11.28 to 14.27	0.815
	Difference between arms	19.75	8.61	2.42 to 37.08	0.026

Notes: linear regression, adjusted for baseline result and stratum

9.7 HISTONE H4 ACETYLATION (ART +V +V ARM ONLY)

9.7.1 AVAILABILITY OF RESULTS

Factor	PR Week 08-3	PR Week 09-2	PR Week 12-2
N	28	20	27
Samples			
Pre vorinostat only	12	7	12
Post vorinostat only	0	3	0
Pre & post vorinostat	16	10	15

Note: Twenty-two patients in the ART +V+V arm provided a total of 41 pre/post vorinostat results.

9.7.2 RESULTS PRE AND POST VORINOSTAT

	PR Week 08-3	PR Week 09-2	PR Week 12-2	Overall
fmol/million PBMCs				
Pre vorinostat (geom. mean + 95% CI)	10.1 (7.4 to 13.7)	7.4 (4.7 to 11.7)	8.0 (5.9 to 10.9)	8.6 (7.1 to 10.4)
Post vorinostat (geom. mean + 95% CI)	27.8 (20.8 to 37.2)	29.7 (18.8 to 46.9)	32.2 (22.0 to 47.3)	29.8 (24.9 to 35.7)
Fold increase	2.94	3.43	3.32	3.19
(95% CI)	(1.65 to 5.21)	(1.70 to 6.93)	(1.81 to 6.09)	(2.42 to 4.22)
p-value	*0.001*	*0.005*	*<0.001*	*<0.001*

Note: point-wise p-values from paired t-test; Overall estimates and p-value derived from GEE models.
P-value for difference between time-points: 0.9299.

9.8 P24 ASSAY

9.8.1 AVAILABILITY OF RESULTS

Factor	Randomisation	PR Week 11-1	PR Week 16-0
N	57	35	60
Randomisation arm			
ART only	29	16	30
ART +V+V	28	19	30

Note: Post randomisation week 11 sample only introduced at a later stage during the trial.

9.8.2 DETECTABLE P24 (AEB > 0.02)

	ART only N=30	ART +V+V N=30	*p-value*	Overall N=60
Randomisation				
No	28 (97%)	28 (100%)		56 (98%)
Yes	1 (3%)	0 (0%)	*1.0*	1 (2%)
PR-11				
No	15 (94%)	19 (100%)		34 (97%)
Yes	1 (6%)	0 (0%)	*0.46*	1 (3%)
PR-16				
No	29 (97%)	29 (97%)		58 (97%)
Yes	1 (3%)	1 (3%)	*1.0*	2 (3%)

Note: AEB = average amount of enzyme per bead.

9.8.3 RESULTS (AEB) BY ARM AND BY TIME-POINT (UNADJUSTED)

	ART only	Arm +V +V	*p-value*	Overall
Randomisation	0.0135 (0.0124 - 0.0147)	0.0127 (0.0118 - 0.0136)	*0.45*	0.0131 (0.0124 - 0.0138)
PR Week 11	0.0121 (0.0106 - 0.0138)	0.0123 (0.0116 - 0.0146)	*0.23*	0.0126 (0.0115 - 0.0136)
PR Week 16	0.0130 (0.0112 - 0.0151)	0.0134 (0.0117 - 0.0154)	*0.24*	0.0122 (0.0113 - 0.0133)

Note: Numbers are geom. mean (%95 CI); AEB = average amount of enzyme per bead; p-value: rank-test.

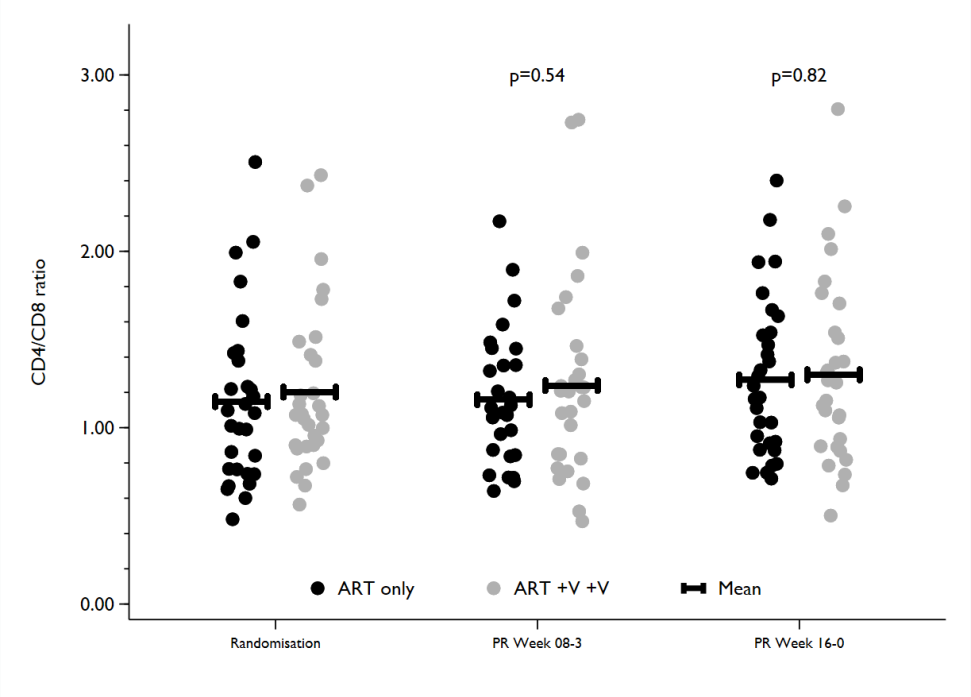
9.8.4 RESULTS (AEB) BY ARM AND BY TIME-POINT (ADJUSTED)

	ART only	ART +V +V	*p-value*
PR week 11	0.0120 (0.0107 - 0.0132)	0.0129 (0.0117 - 0.0145)	*0.249*
PR week 16	0.0126 (0.0112 - 0.0141)	0.0135 (0.0120 - 0.0151)	*0.434*

Notes: AEB = average amount of enzyme per bead; adjusted for baseline result and stratum (point-wise linear regression model on $\log_{10}$-transformed AEB); results back-transformed to original scale.

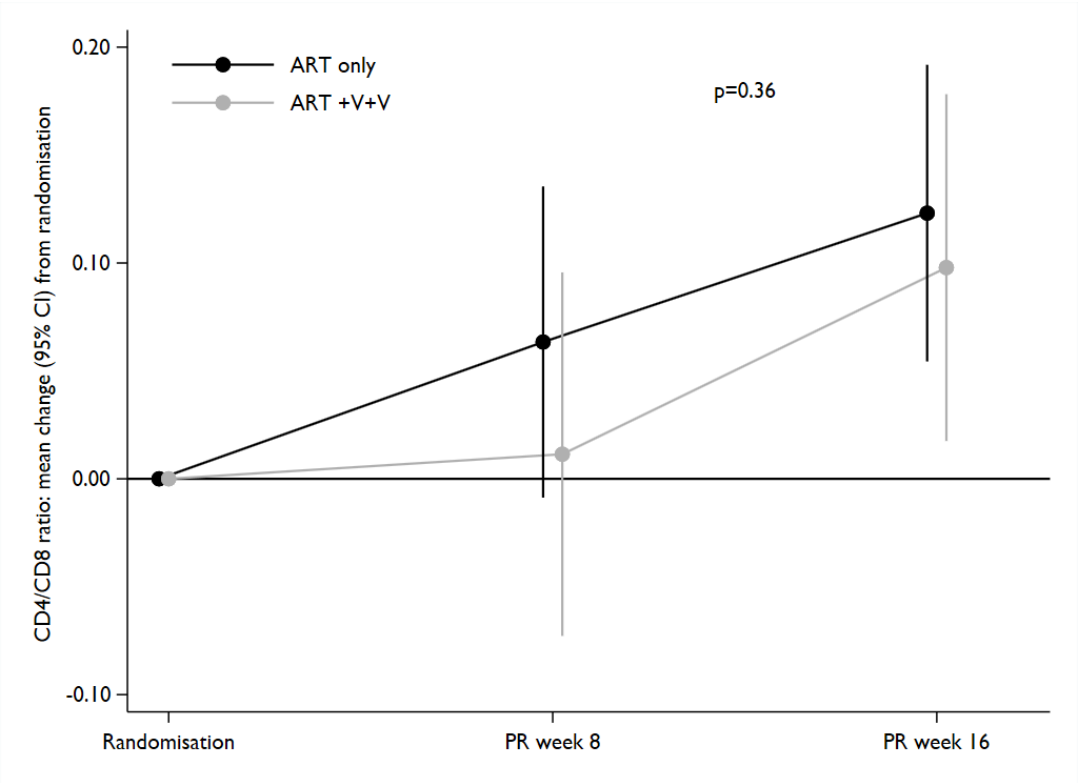
9.9 INFLAMMATORY BIOMARKERS

9.9.1 CD4/CD8 RATIO



Note: N at randomisation, PR week 8, and PR week 16 were 30, 27, 30, and 30, 28, 30 in ART only and ART +V+V, respectively.

Time-point	ART only	ART +V+V	Total
CD4/CD8 ratio: median (IQR) [min-max]			
Screening	0.64 (0.44 - 0.96) [0.15 - 2.13]	0.71 (0.54 - 1.02) [0.15 - 1.75]	0.67 (0.47 - 1.00) [0.15 - 2.13]
Week 04	0.89 (0.68 - 1.20) [0.49 - 2.29]	0.86 (0.81 - 1.24) [0.50 - 2.62]	0.87 (0.70 - 1.22) [0.49 - 2.62]
Week 12	1.01 (0.69 - 1.34) [0.46 - 2.07]	0.98 (0.88 - 1.37) [0.57 - 2.56]	0.99 (0.82 - 1.37) [0.46 - 2.56]
Week 22	1.12 (0.92 - 1.39) [0.46 - 2.38]	1.12 (1.02 - 1.65) [0.59 - 2.46]	1.12 (0.97 - 1.44) [0.46 - 2.46]
Randomisation	1.09 (0.77 - 1.42) [0.49 - 2.52]	1.07 (0.91 - 1.46) [0.60 - 2.42]	1.08 (0.87 - 1.43) [0.49 - 2.52]
PR Week 08-3	1.08 (0.84 - 1.41) [0.63 - 2.18]	1.16 (0.82 - 1.42) [0.47 - 2.79]	1.12 (0.84 - 1.41) [0.47 - 2.79]
PR Week 16-0	1.18 (0.89 - 1.53) [0.71 - 2.36]	1.27 (0.93 - 1.50) [0.46 - 2.79]	1.23 (0.92 - 1.52) [0.46 - 2.79]
CD4/CD8 ratio (log_{10}): mean (SD) [min-max]			
Screening	-0.19 (0.26) [0.26 - 0.33]	-0.18 (0.27) [0.27 - 0.24]	-0.19 (0.26) [0.26 - 0.33]
Week 04	-0.04 (0.16) [0.16 - 0.36]	-0.01 (0.18) [0.18 - 0.42]	-0.03 (0.17) [0.17 - 0.42]
Week 12	-0.00 (0.18) [0.18 - 0.32]	0.04 (0.15) [0.15 - 0.41]	0.02 (0.16) [0.16 - 0.41]
Week 22	0.03 (0.16) [0.16 - 0.38]	0.09 (0.15) [0.15 - 0.39]	0.06 (0.16) [0.16 - 0.39]
Randomisation	0.03 (0.17) [0.17 - 0.40]	0.05 (0.15) [0.15 - 0.38]	0.04 (0.16) [0.16 - 0.40]
PR Week 08-3	0.04 (0.14) [0.14 - 0.34]	0.05 (0.19) [0.19 - 0.45]	0.05 (0.16) [0.16 - 0.45]
PR Week 16-0	0.08 (0.15) [0.15 - 0.37]	0.08 (0.17) [0.17 - 0.45]	0.08 (0.16) [0.16 - 0.45]



Note: global p-value for difference between randomisation arms: p=0.36; GEE model adjusted for stratum. P-value for time: p=0.0016.

9.10 EX VIVO VORINOSTAT STIMULATION

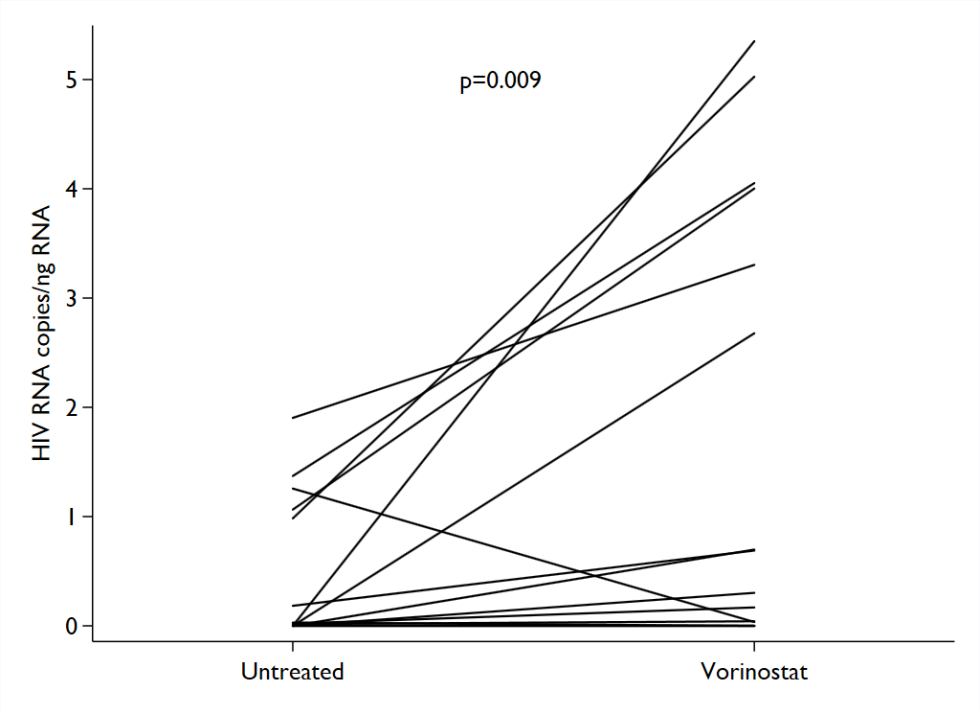
16 ART+V+V arm patient samples from PR week 8 visit 3 pre-vorinostat were used to examine *in vitro* vorinostat stimulation.

9.10.1 DESCRIPTION OF RESULTS

Time-point	Untreated	Vorinostat stimulation	*p-value*
Undetectable			
No	9 (56%)	13 (81%)	*0.125*
Yes	7 (44%)	3 (19%)	
HIV RNA (copies/ng RNA)			
Excluding undetectables	0.98 [0.02-1.90]	0.70 [0.00-5.35]	*0.066*
All samples (Undetectables = zero)	0.02 [0.00-1.90]	0.50 [0.00-5.35]	*0.009*

Note: Results are number (%) or median [min-max]. P-values from exact McNemar test or sign-rank test.

9.10.2 INDIVIDUAL TRAJECTORIES



10 SECONDARY ENDPOINTS: SAFETY

10.1 SAES

10.1.1 ANY SAE POST-RANDOMISATION

	ART only N=30	ART +V+V N=30	Total N=60
SAE post-randomisation			
No	30 (100%)	29 (97%)	59 (98%)
Yes	0 (0%)	1 (3%)	1 (2%)

Note: Difference between the arms: p=1.0

One participant in the ART +V+V arm developed a vasovagal syncope likely secondary to venesection for the large blood draw at the randomisation visit. It was classified as grade 1, and not related to any IMP. After discussions with members of the Safety Group at MRC CTU it was decided to categorise this event as a SAE, 'Other important medical condition'. The participant (R01206H) proceeded with vaccinations and vorinostat dosing as scheduled.

10.1.2 SAES PRE-RANDOMISATION

ID	Diagnosis	Event week post enrolment	Grade	SAE type	Relationship to trial medication	Action taken
R01207B	Fractured neck of femur	3	3	Hospitalisation	Not related	None
R01207B	Periprosthetic fracture	17	3	Hospitalisation	Not related	None
R05504A	Gastroenteritis Shigella	20	3	Hospitalisation	Not related	None
R05504A	Diarrhoea	25	3	Hospitalisation	Not related	None

Two participants reported two SAEs pre-randomisation each, which were unrelated to ART. Both proceeded to randomisation and completed follow-up and interventions as scheduled.

10.2 NOTABLE EVENTS

Notable events in RIVER were defined as:

- Pregnancy in a partner
- Cancer
- Particular vaccine related adverse events defined by GSK (owners of the ChAd vector) which are listed in the RIVER Protocol Appendices.

10.2.1 ANY NOTABLE EVENT POST RANDOMISATION

	ART only	ART +V+V	Total
	N=30	N=30	N=60
Notable event post-randomisation			
No	30 (100%)	30 (100%)	60 (100%)

None of these were reported post-randomisation.

10.2.2 NOTABLE EVENTS PRE RANDOMISATION

There was one notable event in a participant (R01208W) reported before randomisation, a papillary bladder tumour. This participant withdrew before prior to randomisation.

10.3 CLINICAL ADVERSE EVENTS PRE RANDOMISATION

Pre randomisation, only grade 3 or 4 events needed to be reported, and only in stratum 1 participants (n=55 enrolled).

10.3.1 ANY CLINICAL ADVERSE EVENT PRE RANDOMISATION

	N=55
Any grade 3 pre-randomisation AE?	
no	54 (98%)
yes	1 (2%)

There was one grade 3 or 4 event in one participant (R03610F) reported before randomisation, tonsillitis, grade 3. This participant proceeded to randomisation and completed follow-up and interventions as scheduled.

10.4 CLINICAL ADVERSE EVENTS POST RANDOMISATION

Post randomisation, clinical adverse events of any grade needed to be reported.

10.4.1 ANY CLINICAL ADVERSE EVENT POST RANDOMISATION

	ART only	ART +V+V	Total
	N=30	N=30	N=60
Any post-randomisation AE?			
no	8 (27%)	1 (3%)	9 (15%)
yes	22 (73%)	29 (97%)	51 (85%)

Note: difference between the arms: p=0.026

10.4.2 MAXIMUM GRADE OF ANY CLINICAL ADVERSE EVENT POST RANDOMISATION

	ART only	ART +V+V	Total
	N=30	N=30	N=60
Maximum grade			
0	8 (27%)	1 (3%)	9 (15%)
mild	10 (33%)	21 (70%)	31 (52%)
moderate	6 (20%)	7 (23%)	13 (22%)
severe	6 (20%)	1 (3%)	7 (12%)

Note: difference between the arms (rank test): p=0.023

10.4.3 NUMBER OF CLINICAL ADVERSE EVENTS POST RANDOMISATION PER PARTICIPANT

	ART only	ART +V+V	Total
	N=30	N=30	N=60
N of post-randomisation AEs			
0	8 (27%)	1 (3%)	9 (15%)
1	8 (27%)	4 (13%)	12 (20%)
2	7 (23%)	5 (17%)	12 (20%)
3	3 (10%)	10 (33%)	13 (22%)
4	3 (10%)	2 (7%)	5 (8%)
5	1 (3%)	2 (7%)	3 (5%)
6	0 (0%)	2 (7%)	2 (3%)
7	0 (0%)	2 (7%)	2 (3%)
8	0 (0%)	1 (3%)	1 (2%)
11	0 (0%)	1 (3%)	1 (2%)
N of post-randomisation AEs, median (IQR)	1 (0, 2)	3 (2, 5)	2 (1, 3)

Note: difference between the arms (rank test): p<0.001

10.4.4 TOTAL NUMBER OF POST RANDOMISATION CLINICAL ADVERSE EVENTS REPORTED IN RIVER

	ART only	ART +V+V	Total
	N=48	N=107	N=155
Grade			
1	32	91	123
2	10	15	25
3	6	1	7

Note: across all participants

Overall, seven participants had a grade 3 clinical adverse event, 6 in ART only, and 1 in ART +V+V:

- Four participants (all ART only) had a grade 3 infection: acute hepatitis A (n=1), influenza (n=1), proctitis herpes (n=1), shingles (n=1).
- One participant (ART only) had a grade 3 injury: Wrist injury (n=1)
- Two participants (one in each arm) had a musculoskeletal and connective tissue disorder: back pain (n=2)

None of these events were related to ART, vaccines or vorinostat.

10.4.5 CLINICAL ADVERSE EVENTS: NUMBER OF EVENTS PER SYSTEM ORGAN CLASS, PART 1

SOC	ART only n	ART +V+V n	Total n	Diagnosis	ART only n	ART +V+V n	Total n
Cardiac Disorders:	0	1	1	AV Block		1	1
Gastrointestinal Disorders:	12	23	35	Acute Gastroenteritis	1		1
				Anal Fissure	1		1
				Anal Warts	1		1
				Constipation		1	1
				Diarrhoea	3	9	12
				Dry Mouth		3	3
				Epigastric Pain	1		1
				Gastroenteritis	1		1
				Heartburn	1		1
				Loose Stools	1	1	2
				Nausea		5	5
				Proctitis	1		1
				Rectal Bleeding	1		1
				Vomiting		4	4
General Disorders And Administration Site Conditions:	1	27	28	Administration Site Rash		1	1
				Excessive Thirst		1	1
				Fatigue		11	11
				Flu-Like Symptoms		2	2
				General Malaise		1	1
				Injection Site Muscle Pain		1	1
				Injection Site Pain		2	2
				Night Sweats	1		1
				Tiredness		1	1
				Vaccination Site Induration		1	1
				Vaccination Site Pain		6	6
Infections And Infestations:	18	21	39	Acute Hepatitis A	1	1	2
				Acute Upper Respiratory Tract Infection	1		1
				Cold	1	3	4
				Cold Sore	1		1
				Common Cold		1	1
				Coryzal Illness	1		1
				Coryzal Symptoms		2	2
				Eye Infection	1		1
				Flu Symptoms		1	1
				Folliculitis	1		1
				Fungal Infection		1	1
				Furuncle	1		1
				Gingivitis		1	1
				Gonorrhoea	2	3	5
				Helicobacter Pylori Infection	1		1
				Influenza	1		1
				Influenza B Virus Infection	1		1
				Lymphogranuloma Venereum		1	1
				Pharyngeal Gonococcal Infection		1	1
				Proctitis Herpes	1		1
				Ringworm Of Body		1	1
				Salmonella Gastroenteritis		1	1
				Shingles	1		1
				Syphilis		2	2
				Tonsillitis	1		1
				Tooth Abscess	1		1
				Upper Respiratory Tract Infection	1	2	3

10.4.6 CLINICAL ADVERSE EVENTS: NUMBER OF EVENTS PER SYSTEM ORGAN CLASS, PART 2

SOC	ART only n	ART +V+V n	Total n	Diagnosis	ART only n	ART +V+V n	Total n
Injury, Poisoning And Procedural Complications:	3	1	4	Head Injury	1		1
				Insect Bite Nos		1	1
				Soft Tissue Injury	1		1
				Wrist Injury	1		1
Metabolism And Nutrition Disorders:	0	2	2	Glucose Tolerance Impaired		1	1
				Vitamin D Deficiency		1	1
Musculoskeletal And Connective Tissue Disorders:	4	3	7	Achilles Tendonitis	1		1
				Back Pain	1	1	2
				Low Back Pain	1		1
				Muscle Swelling		1	1
				Musculoskeletal Pain	1		1
				Pain In Arm		1	1
Neoplasms Benign, Malignant And Unspecified:	0	1	1	Skin Tags		1	1
Nervous System Disorders:	1	9	10	Dizziness		1	1
				Forgetfulness	1		1
				Headache		4	4
				Light Headedness		1	1
				Sleepiness		3	3
Psychiatric Disorders:	2	5	7	Anxiety		2	2
				Low Mood	2	1	3
				Panic Attack		1	1
				Vivid Dreams		1	1
Renal And Urinary Disorders:	2	0	2	Haematuria	1		1
				Urethral Irritation	1		1
Respiratory, Thoracic And Mediastinal Disorders:	2	5	7	Cough		2	2
				Hay Fever	1	1	2
				Nasal Congestion		1	1
				Sore Throat	1	1	2
Skin And Subcutaneous Tissue Disorders:	3	9	12	Eczema		2	2
				Epidermal Cyst	1		1
				Erythematous Rash		2	2
				Folliculitis		1	1
				Foot Callus	1		1
				Itchy Rash		1	1
				Night Sweats		1	1
				Seborrhoeic Dermatitis	1		1
				Skin Rash		1	1
				Tinea Corporis		1	1

Note: Multiple events per participant possible.

10.5 VACCINE RELATED EVENTS

10.5.1 CLINICAL ADVERSE EVENTS RELATED TO VACCINES

	ChAd N=30	MVA N=30	Total N=30
Ever event related to vaccine			
no	26 (87%)	15 (50%)	14 (47%)
yes	4 (13%)	15 (50%)	16 (53%)
Maximum grade of vaccine-related event			
0	26 (87%)	15 (50%)	14 (47%)
1	3 (10%)	13 (43%)	13 (43%)
2	1 (3%)	2 (7%)	3 (10%)

Notes: Events reported as possibly, probably or definitely related.

10.5.2 NUMBER OF CLINICAL ADVERSE EVENTS RELATED TO VACCINES, BY SYSTEM ORGAN CLASS

	Grade 1	Grade 2
Gastrointestinal Disorders		
Diarrhoea	1	
Dry Mouth	1	
Loose Stools	1	
Nausea	2	
General Disorders And Administration Site		
Administration Site Rash	1	
Fatigue	2	
Flu-Like Symptoms	1	
General Malaise	1	
Tiredness		1
Vaccination Site Induration	1	
Vaccination Site Pain	7	1
Infections And Infestations		
Coryzal Symptoms	1	
Musculoskeletal And Connective Tissue Disease		
Muscle Swelling	1	
Nervous System Disorders		
Headache	1	
Light Headedness	1	
Skin And Subcutaneous Tissue Disorders		
Erythematous Rash	1	1
Skin Rash	1	

10.5.3 AVAILABILITY OF PARTICIPANT COMPLETED SYMPTOM DIARY

	ART +V+V N=30
Dairy post ChAd	
not available	1 (3%)
available	29 (97%)
Dairy post MVA	
not available	4 (13%)
available	26 (87%)

10.5.4 SOLICITED GENERAL SYMPTOMS AND INJECTION SITE REACTIONS

	Post ChAd N=30	Post MVA N=30	Difference between vaccines: p-value	Total N=30
Any symptom post vaccination				
No	4 (13%)	2 (7%)	0.50	2 (7%)
Yes	26 (87%)	28 (93%)		28 (93%)
Maximum grade post vaccination				
0	4 (13%)	2 (7%)		2 (7%)
Grade 1	17 (57%)	15 (50%)	0.27	11 (37%)
Grade 2	7 (23%)	10 (33%)		13 (43%)
Grade 3	2 (7%)	3 (10%)		4 (13%)

Note: Symptoms and reactions reported in clinic on the CRF and the participant completed symptom diary, from day of vaccination daily until day 3 post vaccination.

Overall, 4 participants reported at least one grade 3 event, all on the participant completed diary card:

1. R03305X reported pain grade 3 one day after the MVA vaccination. Pain then decreased and was grade 2 on day 2, grade 1 on day 3, and not present on the 72h follow-up call.
2. R03802D reported chills grade 3 and tiredness grade 3 on the same day after the ChAd vaccination. No chills of any grade were reported on days 1-3, and no tiredness from day 2.
   The same patient also reported a single day of grade 3 tiredness 2 days after the MVA vaccination.
3. R03302P reported grade 3 itching one day after ChAd vaccination but no itching on any other time point.
4. R03309A reported several events in the three days after MVA with maximum grade 3 for headache, grade 3 for chills and grade 3 for pain. During the same period, diarrhoea was present as well.

One participant reported an additional event on the diary: bowel motion and watery stool after the ChAd vaccination, which was given grade 2 for severity.

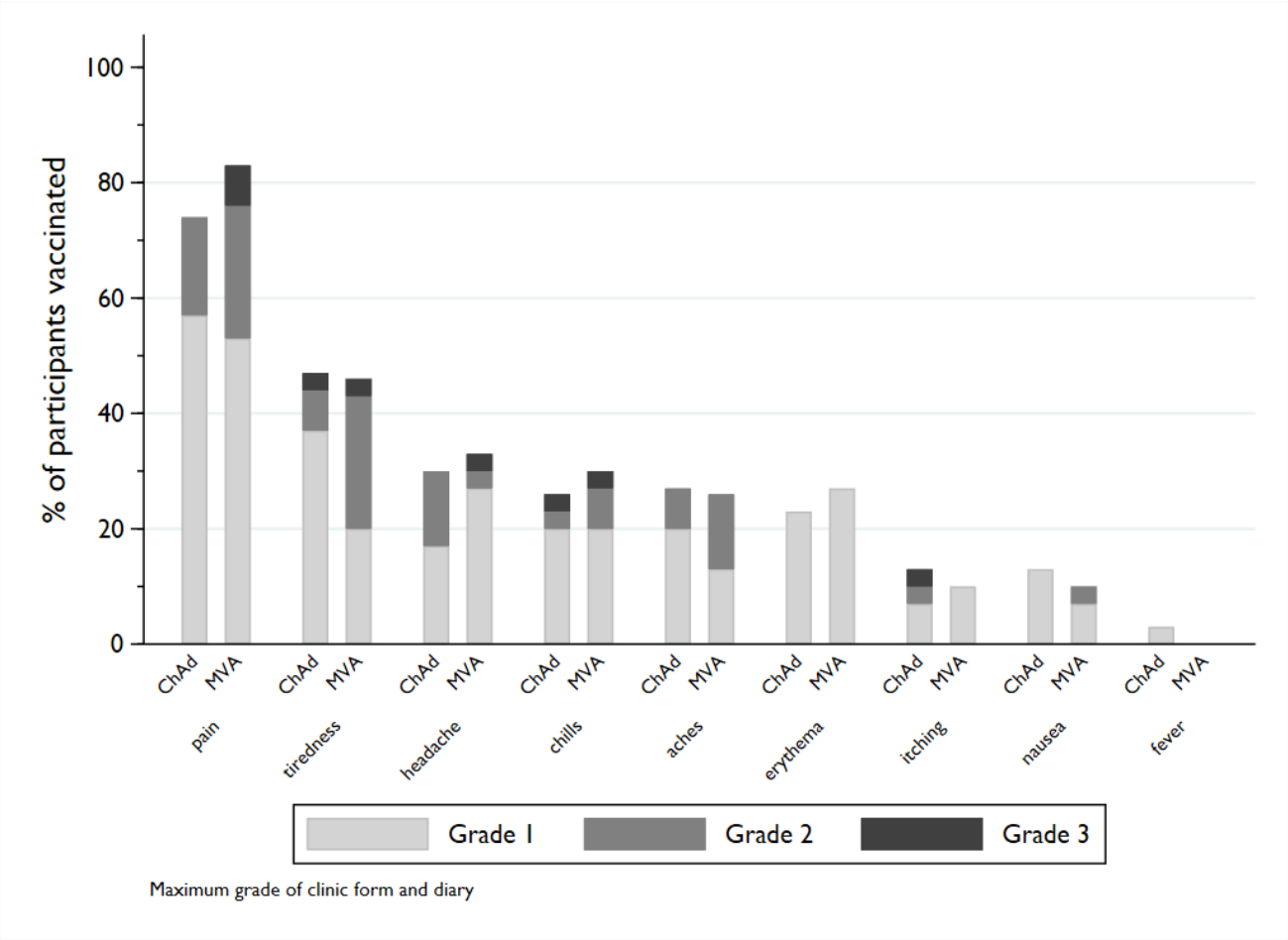
10.5.5 SOLICITED GENERAL SYMPTOMS AND INJECTION SITE REACTIONS: MAXIMUM GRADE BY VACCINE AND EVENT

	Post ChAd N=30	Post MVA N=30	Total N=30
Pain:			
0	8 (27%)	5 (17%)	4 (13%)
Grade 1	17 (57%)	16 (53%)	14 (47%)
Grade 2	5 (17%)	7 (23%)	10 (33%)
Grade 3	0 (0%)	2 (7%)	2 (7%)
Itching:			
0	26 (87%)	27 (90%)	23 (77%)
Grade 1	2 (7%)	3 (10%)	5 (17%)
Grade 2	1 (3%)	0 (0%)	1 (3%)
Grade 3	1 (3%)	0 (0%)	1 (3%)
Erythema:			
0	23 (77%)	22 (73%)	16 (53%)
Grade 1	7 (23%)	8 (27%)	14 (47%)
Temperature:			
0	29 (97%)	30 (100%)	29 (97%)
Grade 1	1 (3%)	0 (0%)	1 (3%)
Chills:			
0	22 (73%)	21 (70%)	16 (53%)
Grade 1	6 (20%)	6 (20%)	9 (30%)
Grade 2	1 (3%)	2 (7%)	3 (10%)
Grade 3	1 (3%)	1 (3%)	2 (7%)
Tiredness:			
0	16 (53%)	16 (53%)	10 (33%)
Grade 1	11 (37%)	6 (20%)	12 (40%)
Grade 2	2 (7%)	7 (23%)	7 (23%)
Grade 3	1 (3%)	1 (3%)	1 (3%)
Muscle/joint aches:			
0	22 (73%)	22 (73%)	17 (57%)
Grade 1	6 (20%)	4 (13%)	7 (23%)
Grade 2	2 (7%)	4 (13%)	6 (20%)
Headache:			
0	21 (70%)	20 (67%)	16 (53%)
Grade 1	5 (17%)	8 (27%)	9 (30%)
Grade 2	4 (13%)	1 (3%)	4 (13%)
Grade 3	0 (0%)	1 (3%)	1 (3%)
Nausea:			
0	26 (87%)	27 (90%)	24 (80%)
Grade 1	4 (13%)	2 (7%)	5 (17%)
Grade 2	0 (0%)	1 (3%)	1 (3%)

Note: This table combines symptoms reported in clinic and in the participant completed diary, taking the maximum grade of each per event. There was no significant difference between the vaccinations in any event.

One participant (R03609Q) reported an additional non-solicited event in the participant completed diary post ChAd: bowel motion and watery stool, grade 2.

10.5.6 FIGURE OF SOLICITED GENERAL SYMPTOMS AND INJECTION SITE REACTIONS: MAXIMUM GRADE BY VACCINE AND EVENT



Note: sorted by event frequency.

10.6 VORINOSTAT RELATED EVENTS

10.6.1 CLINICAL ADVERSE EVENTS RELATED TO VORINOSTAT

	N=29
Ever event related to vorinostat	
no	20 (69%)
yes	9 (31%)
Maximum grade of vorinostat-related event	
1	16 (73%)
2	6 (27%)

Notes: Events reported as possibly, probably or definitely related. Only patients who started vorinostat are included.

10.6.2 NUMBER OF CLINICAL ADVERSE EVENTS RELATED TO VORINOSTAT, BY SYSTEM ORGAN CLASS

	Grade 1	Grade 2
Gastrointestinal Disorders		
Constipation	1	
Diarrhoea	6	1
Dry Mouth		2
Nausea	4	
Vomiting	2	
General Disorders and Administration Site		
Excessive Thirst	1	
Fatigue	7	2
Tiredness		1
Infections And Infestations		
Common Cold	1	
Coryzal Symptoms	1	
Metabolism And Nutrition Disorders		
Glucose Tolerance Impaired		1
Neoplasms Benign, Malignant And Unspecific		
Skin Tags	1	
Nervous System Disorders		
Headache	2	
Sleepiness	1	
Psychiatric Disorders		
Anxiety	1	
Low Mood	1	
Panic Attack	1	
Sleepiness	2	

	Grade 1	Grade 2
Respiratory, Thoracic And Mediastinal Disorders		
Cough	1	
Sore Throat	1	
Skin And Subcutaneous Tissue Disorders		
Itchy Rash	1	
Night Sweats		1

10.7 LABORATORY EVENTS

10.7.1 MAXIMUM GRADE IN ANY LABORATORY PARAMETER POST RANDOMISATION

	ART only N=30	ART +V+V N=30	Total N=60
Maximum lab grade per participant			
0	8 (27%)	7 (23%)	15 (25%)
mild	18 (60%)	17 (57%)	35 (58%)
moderate	2 (7%)	4 (13%)	6 (10%)
severe	1 (3%)	1 (3%)	2 (3%)
potentially life-threatening	1 (3%)	1 (3%)	2 (3%)

Note: Difference between the arms: p = 0.58

10.7.2 LIST OF ALL LAB ABNORMALITY POST-RANDOMISATION WITH SEVERE OF HIGHER GRADE

Patient ID	Randomisation arm	Event week post randomisation	Parameter	Result	Unit	Grade
R03623H	ART only	8	AST	214	U/L	severe
R03805N	ART only	16	Glucose	1.8	mmol/L	severe
R03623H	ART only	8	CK	9102	U/L	pot. life-threatening
R01211B	ART +V+V	8	Bilirubin	104.0	µmol/L	severe
R05502M	ART +V+V	12	CK	2556	U/L	severe
R01211B	ART +V+V	7	ALT	2179	U/L	pot. life-threatening
R01211B	ART +V+V	8	ALT	559	U/L	pot. life-threatening
R01211B	ART +V+V	8	AST	837	U/L	pot. life-threatening
R01211B	ART +V+V	7	AST	1888	U/L	pot. life-threatening
R01211B	ART +V+V	8	Bilirubin	215.0	µmol/L	pot. life-threatening

Note: AST (aspartate transaminase), CK (creatine kinase), ALT (alanine transaminase).

Four participants had at least one severe or potentially life-threatening lab event:

R03623H, ART only: One single value of severe AST, and simultaneously a single potentially life-threatening value of creatine kinase at PR 08-03. AST was mildly elevated 6 days later, and normal subsequently. CK was in the normal range at all other measurements.

R03805N, ART only: One single severe value of low glucose (fasted) at PR-16. This was preceded by a moderately lowered glucose but a normal value followed at PR-18.

R01211B, ART +V+V: Several severe or potentially life-threatening lab events due to acute hepatitis A.

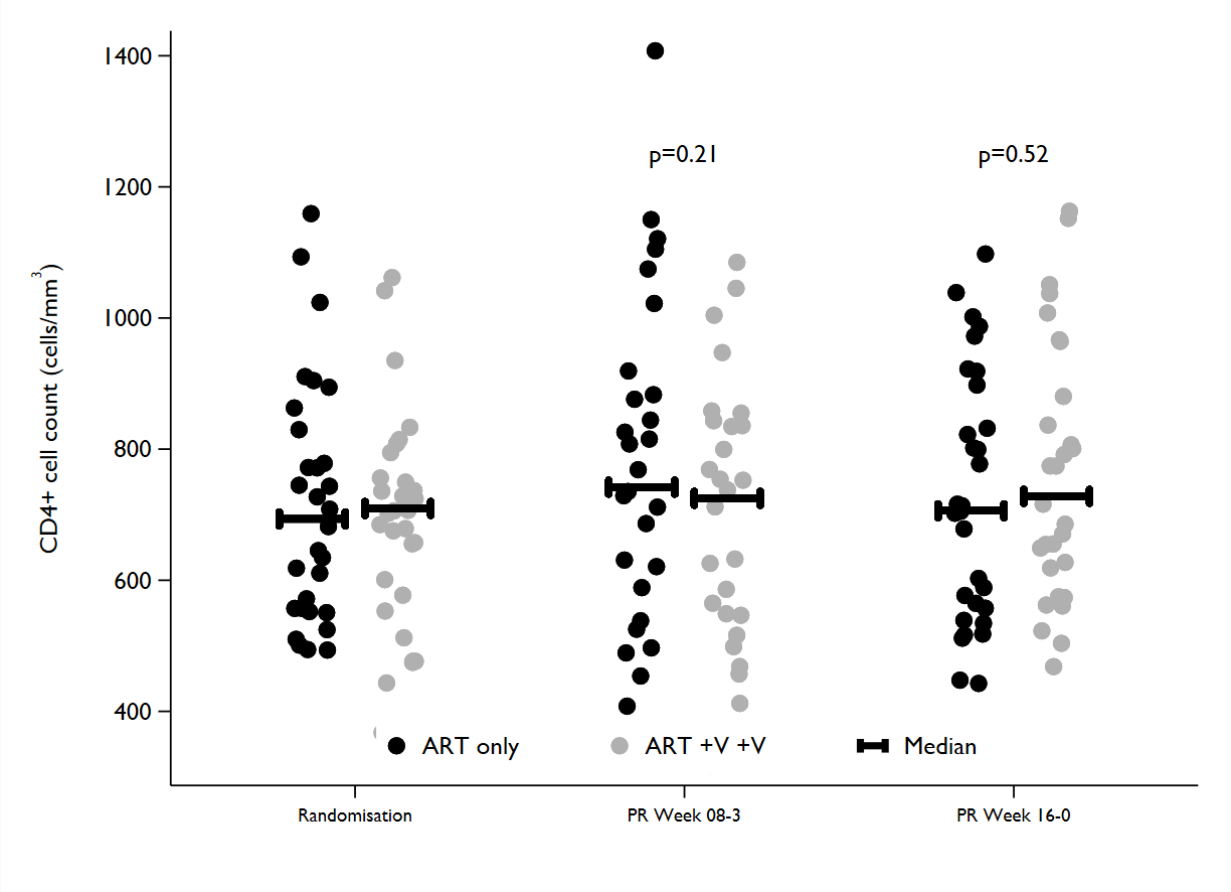
R05502M, ART +V+V: One single severe value of CK at PR-12. This was followed by a normal creatine kinase result at the next measurement at PR-16.

11 OTHER ENDPOINTS

11.1 CD4 CELL COUNT

Time-point	ART only	ART +V+V	TOTAL
Screening			540 (464 - 669) [263 - 1158]
Week 04			658 (532 - 832) [344 - 1120]
Week 12			710 (580 - 919) [411 - 1106]
Week 22			707 (571 - 835) [334 - 1401]
Randomisation	694 (561 - 844) [480 - 1137]	710 (579 - 759) [369 - 1056]	708 (568 - 788) [369 - 1137]
PR Week 08-3	742 (609 - 920) [394 - 1408]	725 (512 - 835) [317 - 1102]	742 (538 - 849) [317 - 1408]
PR Week 16-0	706 (543 - 889) [450 - 1090]	728 (602 - 871) [464 - 1166]	706 (562 - 880) [450 - 1166]

Note: numbers are median (IQR) [min-max] in cells/mm^3.



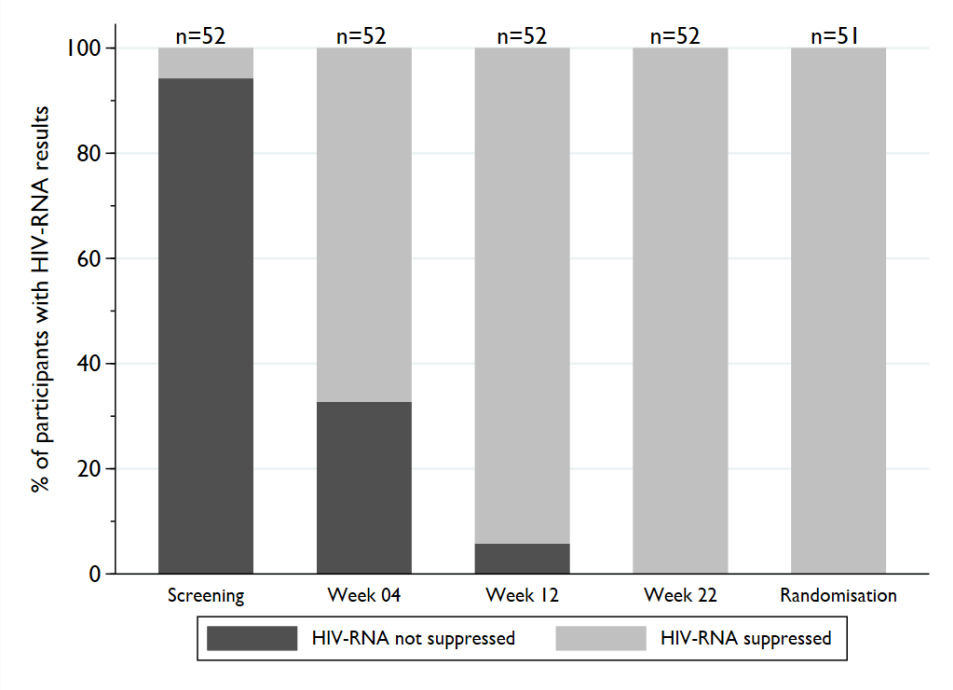
11.2 HIV-RNA

Conventional HIV-RNA assay. Suppressed plasma HIV RNA is defined <200 copies/mL for the Taqman Roche 2.0 assay, and as <50 copies/mL for all other assays.

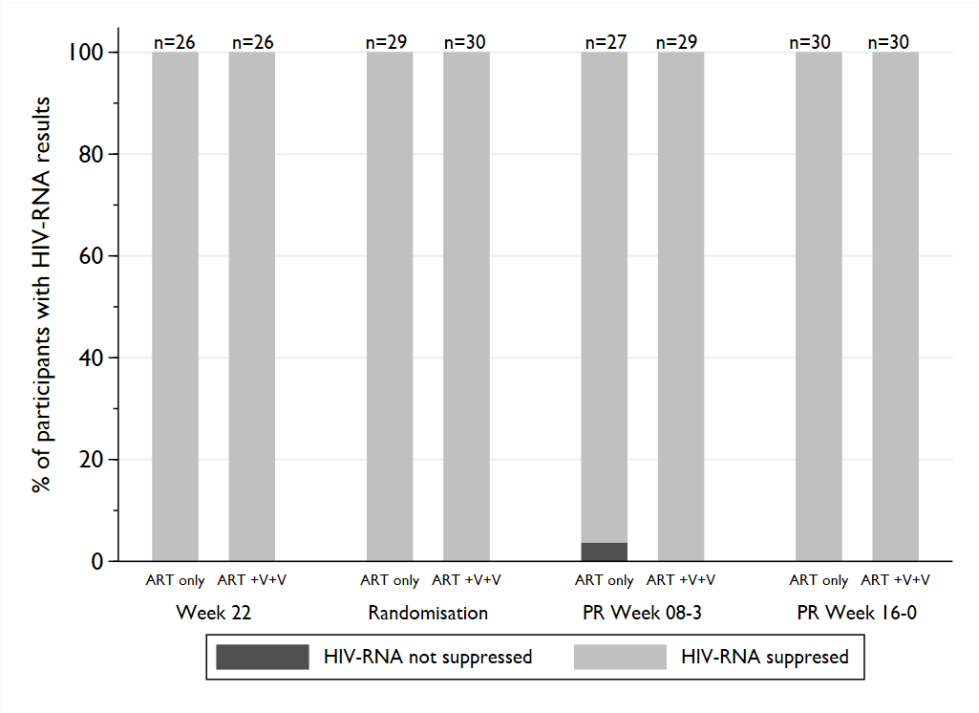
11.2.1 HIV-RNA UNTIL RANDOMISATION (STRATUM 1 ONLY)

Time-point	Number (%) undetectable	Median (IQR) [min-max]
Screening	3/52 (6%)	46152 (15649 – 955451) [<20 – 14000000]
Week 04	35/52 (67%)	58 (38 - 273) [<20 - 2067]
Week 12	49/52 (94%)	
Week 22	52/52 (100%	
Randomisation	51/51 (100%)	

Note: Only participants later randomised are included. One missing value for the randomisation visit.



11.2.2 HIV-RNA FROM RANDOMISATION



Detectable HIV-RNA post randomisation was reported for only one patient (R05517B; ART only arm), which was one single result (304 cop/mL), followed by <20 copies/mL one week later:

Visit	Sample date	HIV-RNA (copies/mL)
Week 22	06/07/2017	<20
Randomisation	11/07/2017	<20
PR Week 08	06/09/2017	=304
PR Week 09	12/09/2017	<20
PR Week 16	24/10/2017	<20

No non-adherence was reported at any of the study visits, and ART regimen was TRU/DRVc/RAL throughout the study without evidence of treatment interruption.

One further participant (R03811B, ART only) had slightly raised HIV-RNA discovered during monitoring however this was using the Taqman assay and <200 copies/mL throughout:

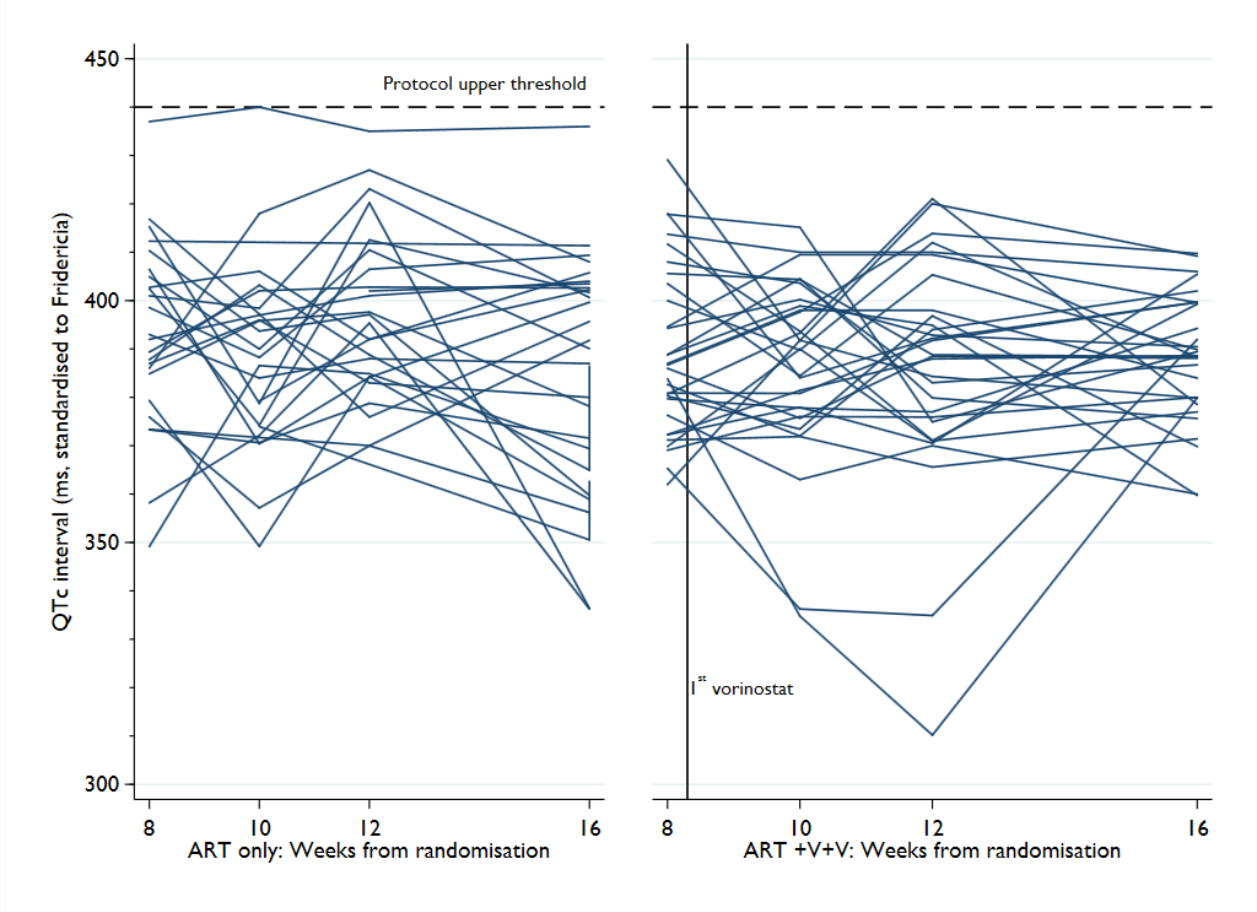
Visit	Sample date	HIV-RNA (copies/mL)
Week 22	27/03/2017	=70
Randomisation	05/04/2017	=63
PR Week 08	19/04/2017	=85
PR Week 09	15/06/2017	=37
PR Week 16	09/08/2017	=60

11.3 QTC INTERVAL

Toxicity criteria as shown in the DAIDS table (Dec, 2004):

GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Asymptomatic, QTc interval 0.45 – 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 – 0.49 sec OR Increase in interval 0.03 – 0.05 sec above baseline	Asymptomatic, QTc interval = 0.50 sec OR Increase in interval = 0.06 sec above baseline	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia

11.3.1 QTC INTERVAL FROM PR WEEK 8



11.3.2 QTC INTERVAL POST PR WEEK 8

	ART only N=30	ART +V+V N=30	Total N=60
Ever QTc grade 2 or higher			
no	27 (90%)	28 (93%)	55 (92%)
yes	3 (10%)	2 (7%)	5 (8%)

Note: QTc interval standardised to Fredericia. Difference between the arms: p=0.64

No participant had an absolute QTc interval longer than 450msec post-randomisation. No participant had a grade 3 or higher increase.