THE IMPACT OF VORINOSTAT & THERAPEUTIC VACCINE ON GUT HIV DNA – THE RIVER GUT STUDY

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Introduction

The RIVER randomized trial examined the impact of a T-cell prime-boost vaccination with vorinostat plus ART (ART+V+V) compared with ART alone in treated primary HIV infection (PHI) on blood total HIV DNA. Tissue reservoirs such as the gut-associated lymphoid tissue (GALT) are important sites of HIV persistence and may be differentially affected by the intervention. This RIVER gut sub study compares HIV DNA, markers of immune activation & exhaustion in GALT, and microbial translocation by study arm.

Methods

Immediate ART was commenced within 4 weeks of confirmed PHI diagnosis at study enrolment. At week 24, when plasma HIV RNA was suppressed, participants were randomized (1:1) to receive either ART or ART plus a prime-boost T-cell vaccination (ChAdV63.HIVconsv and MVA.HIVconsv) followed by 10 doses of 400mg of vorinostat (ART+V+V). The RIVER study schema is show in figure 1. Following completion of the main RIVER study protocol individuals (from each arm) consented to the gut sub study; individuals underwent colonoscopy, with terminal ileum and rectal biopsies taken for total HIV DNA quantification (by qPCR) and assessment of immune activation and exhaustion (PD-1 and HLA-DR/CD38 expression on CD4+ cells) by flow cytometry. Plasma microbial translocation markers (sCD163 & sCD14) were measured in plasma using Luminex. P24 antigen was measured in stimulated tissue explant supernatants by ELISA.

Results

Eleven men were enrolled in the RIVER gut study, five in the ART-only arm and six in the ART+V+V arm, all were male. Participant characteristics are shown in table 1. The median time from completion of the main RIVER study protocol to gut biopsy was 6 months (range 3-15). The median total HIV DNA measured in the terminal ileum was 2.8 (ART+V+V) and 3.1 (ART) log_{10} copies per 10^6 gut cells (P=0.25), and in the rectum 2.8 (ART+V+V) and 3.0 (ART) log_{10} per 10^6 gut cells (P=0.14), figure 2a & 2b. The median p24 levels measured from explant supernatants (n=7) were similar in each arm at day 7, figure 2c No significant differences in expression of PD-1 and HLA-DR/CD38 co-expression on CD4+ T-cells from GALT were observed between study arm, figure 2.. Significantly higher sCD163 (P=0.03) but not sCD14 (P=0.55) levels were observed in plasma from participants in the ART+V+V arm compared with ART only, figure 4.

Figure 1. RIVER study schema

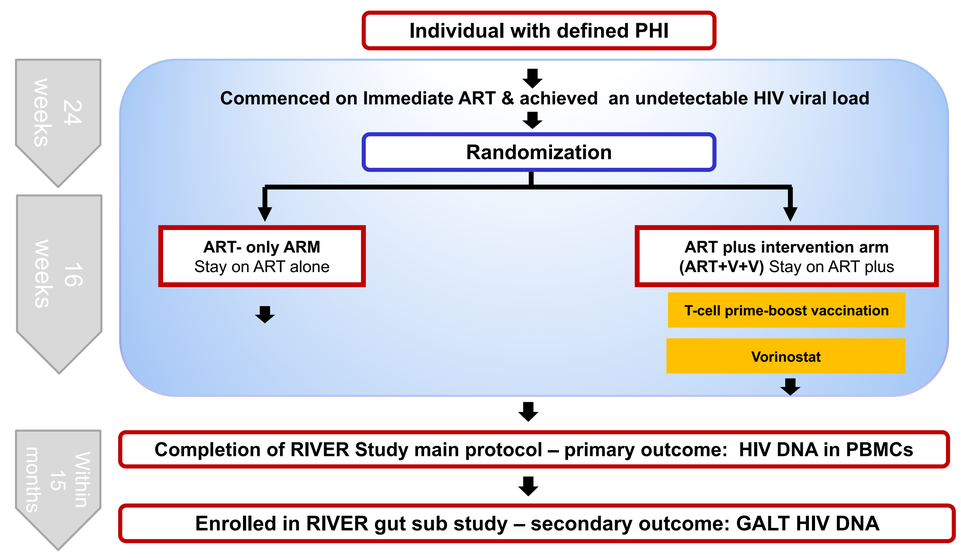


Table 1. RIVER gut study participants characteristics

	ART-plus-intervention Arm (n=6)	ART-only Arm (n=5)
Age	39 (30-45)	35 (31-35)
Results at Enrolment*:		
HIV viral load, Log_{10} CPM	4.1 (3.9-5.3)	4.9 (4.6-5.6)
CD4 count cells/mm^3	492 (435-561)	543 (449-548)
CD8 count cells/mm^3	966 (810-1203)	879 (860-905)
CD4/CD8 ratio	0.55 (0.35-0.90)	0.54 (0.49-0.58)
Median (IQR) time from:		
EDI to ART start, days	75 (35-79)	65 (33-82)
Positive HIV test to ART, days	23 (15-28)	13 (7-18)
Completed RIVER protocol to biopsy, months	9 (6-13)	6 (6-14)
ART start to biopsy	22 (21-24)	17 (16-22)
Results at time of Biopsy:		
CD4 count cells/mm^3	669 (626-904)	1058 (908-1167)
CD8 count cells/mm^3	539 (480-571)	623 (572-668)
CD4/CD8	1.40 (1.18-1.5)	1.60 (1.28-2.13)
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

FIGURE 2. Total HIV DNA measured from (a) terminal ileum and (b) rectum GALT from the RIVER study arms is show. The levels of p24 expression in tissue explant supernatants after seven days of activation with PHA & IL-2 is show in (c); ART plus intervention arm (blue) and ART-only arm (green)

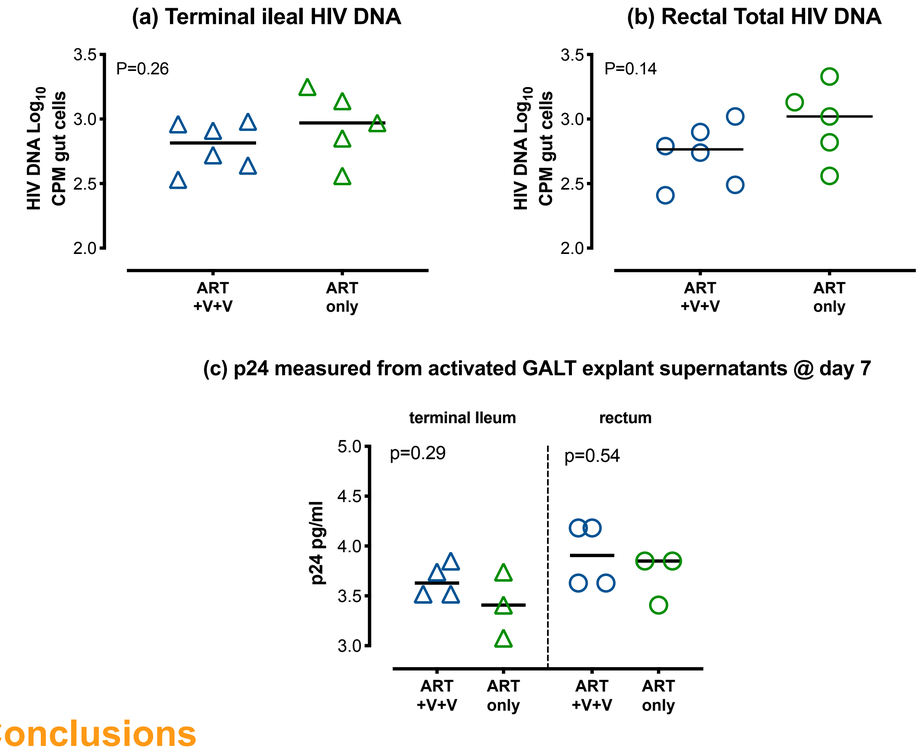
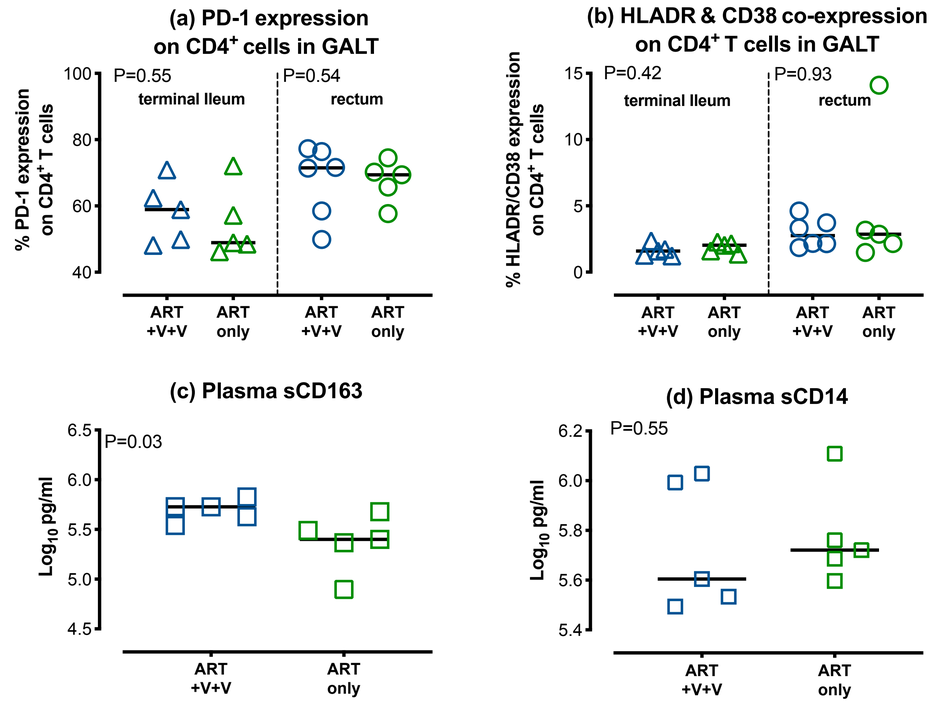


FIGURE 3. The (a) PD-1 expression and (b) HLA-DR/CD38 co-expression on $CD4^+$ T cells from GALT terminal ileum (triangles) and rectum (circles) is shown; Symbol colour indicates ART plus intervention arm (ART+V+V) in blue and ART-only arm (ART-only) in green. Plasma measured (c) sCD163 levels and (d) sCD14 levels in each study arm are shown.



Conclusions

These data suggest that vorinostat in combination with a T-cell prime-boost-vaccine did not impact the GALT HIV reservoir, nor measures of immune exhaustion & activation on GALT CD4 T-cells in ART+V+V treated individuals compared with ART alone during PHI. Measures of bacterial translocation appear to be increased in ART+V+V over ART-only warranting further investigation.

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