Two case reports on safety and impact of α4β7 integrin monoclonal antibody in treated primary HIV infection on HIV reservoirs

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Introduction

Gut-associated lymphoid tissue (GALT) is preferentially infected during primary HIV infection (PHI) & is a key site of HIV persistence[1]. α4β7 integrin, a gut-homing receptor expressed on CD4 T-cells, facilitates CD4 T-cell trafficking to GALT. A monoclonal antibody against α4β7 integrin (Vedolizumab, VDZ) is used to treat inflammatory bowel disease (IBD). Data from ART-treated SIV-infected primates showed HIV viral control following VDZ administration[2]. We present 2 cases of HIV+ individuals treated with ART in PHI, who received VDZ for IBD.

Methods

VDZ was administered as licensed for IBD - at 0, 2, 6 then every 8 weeks. Informed consent for blood sampling & gut biopsy was obtained. Routine clinical monitoring data was captured (CD4,CD8 & HIV viral load). Paired blood and gut biopsy samples from the terminal ileum (TI) & rectum were collected at a single time-point from participant A. Comparisons with blood & GALT samples from the HEATHER cohort (15 ART-treated PHI individuals) were made for β7 expression & total HIV DNA measured by flow cytometry and qPCR respectively. PBMCs from participant A, taken at the 3rd and 4th study visit, were used in a murine viral outgrowth experiment using a NRG humanised mouse model.

Table 1: Clinical Characteristics

	Participant A	Participant B
Age, years (sex)	31 (M)	53 (F)
IIBD Diagnosis	Crohn's Disease	Ulcerative Colitis
Year of HIV diagnosis	2016	2000
Days from PHI to ART	28	10
Months from PHI to Vedolizumab	3.5	202
Months on ART at time of gut biopsy	8	NA
Current CD4 count (cells/mm^3)	419	1054
Current VL (CPM)	<20	<20

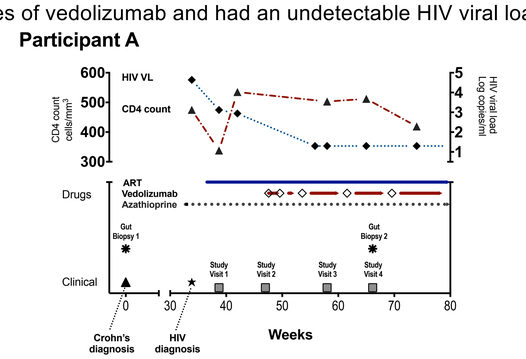
Abbreviations; M, male; F, female; PHI, primary HIV infection; CPM, copies per million; NA, not applicable

Results

The clinical characteristics are shown in Table 1. No adverse events were reported, and both patients had IBD responses clinically and endoscopically. The clinical course for Participant A & B is summarised in figure 2.

Figure 2: Participant A & B - clinical course

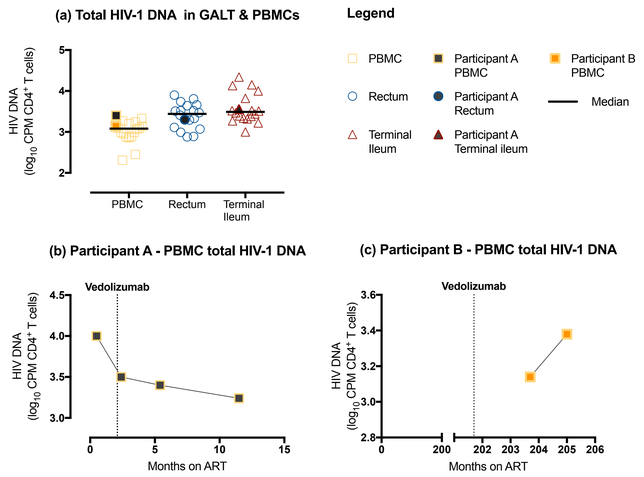
The clinical course for participant A & B is shown below. Of note at the time of the second gut biopsy participant A had received 4 doses of vedolizumab and had an undetectable HIV viral load.



HIV DNA in PBMCs for participant A (3.4 $Log_{10}/10^6$ CD4 at biopsy) and participant B (3.1 $Log_{10}/10^6$ CD4) was comparable to the median HEATHER HIV DNA (3.0 $Log_{10}/10^6$ CD4), see figure 3a. Despite only 8 months of ART since PHI, HIV DNA in GALT for participant A (TI 3.56, rectum 3.30 $Log_{10}/10^6$ CD4 was below the mean of HEATHER participants (TI 3.58, rectum 3.4 $log_{10}/10^6$ CD4) whose median (range) time on ART was longer at 34 (15-96) months. Only PBMC HIV DNA data post Vedolizumab treatment was available for participant B.

Figure 3: Total HIV DNA in PBMC & GALT

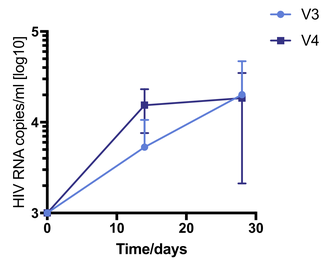
The jitter plot in (a) shows HIV DNA levels in a cohort of individuals treated in PHI (HEATHER) compared with HIV DNA measured from participant A & B. (b) shows the PBMC HIV DNA for participant A from ART initiation to 12 months (c) show the HIV DNA levels for participant B post VDZ treatment..



For participant A: β7 expression on blood CD4+ cells increased over the 3 study visits (12.7%, 13.7% & 22.1%, respectively); β7 expression on GALT CD4+ cells was lower for participant A compared to HEATHER participants & healthy controls. HIV RNA was detected from both time points (visit 3 & visit 4) from participant A in the murine outgrowth model despite Vedolizumab treatment, see figure 4

Figure 4: Murine VOA

This graph shows HIV RNA measured from the humanised murine VOA at day 14 and 28 post intraperitoneal injection of PBMCs, for participant A, at study visit 3 (V3) and study visit 4 (V4). n=3 mice per condition.



Conclusion

We report the first 2 cases of HIV+ individuals receiving Vedolizumab for IBD. It was shown to be safe, well-tolerated & associated with good IBD response. In addition, there was no negative impact on CD4 T cell count or HIV viral load. These preliminary data support further exploration of α4β7 integrin antibodies as a strategy to limit GALT HIV reservoir.

REFERENCES

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