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Immunometabolism of innate lymphocytes in people living with HIV-1 versus HIV-2

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BACKGROUND

- **HIV-2** is characterised by **less T-cell activation and immune exhaustion** than HIV-1 and presents a unique model to study mechanisms of immune protection.
- Innate lymphocytes including **iNKT, MAIT and Vδ2+ T-cells** maintain gut barrier defence and mucosal inflammation which impacts chronic immune activation observed in HIV.
- We investigated **frequency, mitochondrial function and exhaustion profiles** of MAIT, iNKT and Vδ2+ T-cells in HIV-1, HIV-2, and healthy controls (HC) to **identify novel mechanisms of immune protection in HIV-2.**

METHODS

- PBMCs from people with HIV-1 (n=6) people with HIV-2 (n=6) and HC (n=6) were analysed by 26 colour flow cytometry.
- Conventional T-cell lineage markers, **iNKT, MAIT, and Vδ2+** subsets were assessed for frequency and expression of exhaustion markers (**PD1, TIGIT**) and mitochondrial function (**MTG, TMRM).**

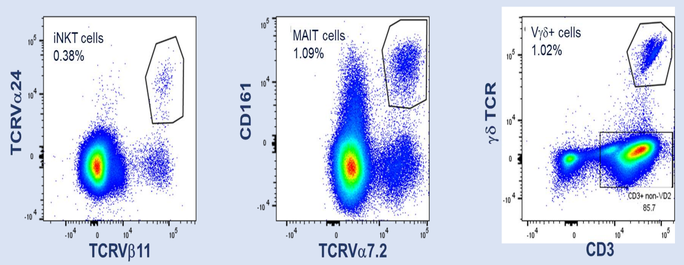


Figure 1. Gating strategies for (i) iNKT (ii) MAIT and (iii) Vδ2+ cells; all are gated on CD45+CD3+ PBMCs.

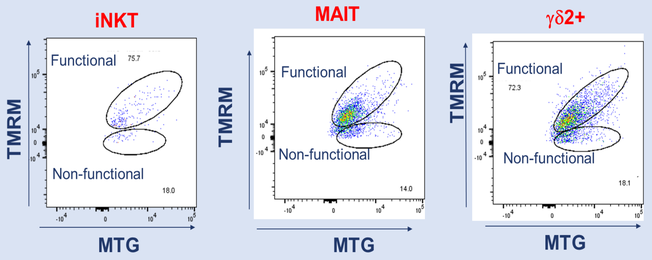


Figure 2. Gating strategies for mitochondrial markers (TMRM and MTG) in (i) iNKT (ii) MAIT and (iii) Vδ2+ cells. MTG+ TMRM+ are considered functional mitochondria.

Circulating MAIT and Vδ2+ frequencies are higher in HIV-1 than in HIV-2.

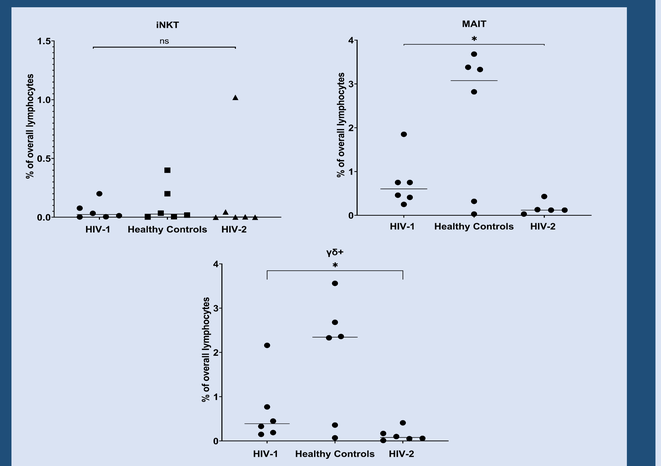


Figure 3. Median iNKT frequency was comparable between HIV-1, HIV-2 and HC. However, median **MAIT, and Vδ2+** frequencies were significantly higher in HIV-1 compared to HIV-2.

Vδ2+ cells have higher mitochondrial function and less exhaustion in HIV-2 compared to HIV-1.

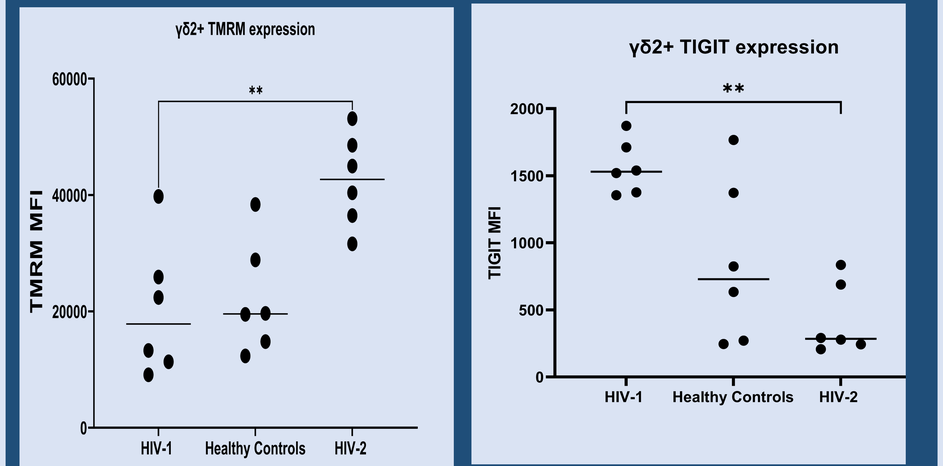


Figure 4. Median MFI for TMRM expression in **Vδ2+** cells was higher in HIV-2 compared to HIV-1. However, Median MFI for TIGIT in **Vδ2+** cells was higher in HIV-1 compared to HIV-2.

RESULTS

- Both HIV-1 and HIV-2 cohorts were virally suppressed, ART adherent and immunocompetent (CD4 and CD8 counts in range).
- **HIV-1 was associated with increased MAIT cell frequency** (p=0.03) (figure 3) and expression of TIGIT (p=<0.02) relative to HIV-2, although mitochondrial profile of MAIT was comparable in both HIV cohorts (p=0.4) .
- **Circulating Vδ2+ frequency was also higher (0.03) in HIV-1** than in HIV-2 (figure 3), but **mitochondrial activity (0.03) and expression of TIGIT (0.03) was markedly higher in HIV-2**, relative to HIV-1 and HC (figure 4)
- iNKT frequency, mitochondrial function and exhaustion profiles did not differ between cohorts.

CONCLUSIONS

- Preliminary analysis suggests that MAIT and Vδ2+ T-cell frequencies are higher in HIV-1 than in HIV-2.
- However, there is a higher proportion of functional mitochondria in Vδ2 cells in HIV-2 and both MAIT and Vδ2 appear more exhaustion in HIV-1 and HIV-2.
- **These data suggest that the innate lymphocyte pool is differentially impacted HIV types, which may influence gut reservoir size and clinical course of infection.**