HIV Infection and Reactivation Heterogeneity in Tonsillar and Intestinal Models of HIV Persistence

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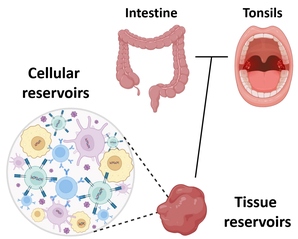
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BACKGROUND

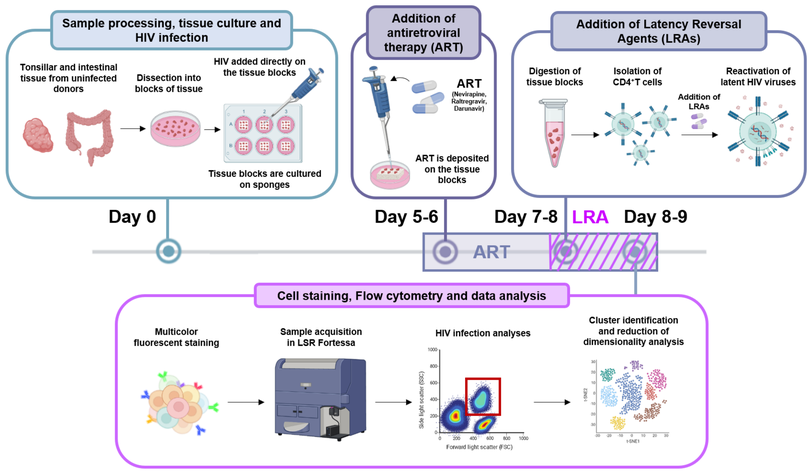
Tissue reservoirs constitute a significant source of latent and persistent HIV infection in people living with HIV (PLWH) on antiretroviral treatment (ART). However, the intrinsic characteristics of viral reservoirs within these tissue compartments remain largely unknown.

Using **intestinal (GUT)** and **tonsillar (TO) explants models** of HIV persistence, we have:

- Characterized the cellular composition of these anatomical reservoirs.
- Evaluated the effectiveness of various latency reversal agents (LRAs) in inducing viral reactivation after ART in different CD4⁺ T reservoirs.



EXPERIMENTAL DESIGN



KEY FINDINGS & CONCLUSIONS

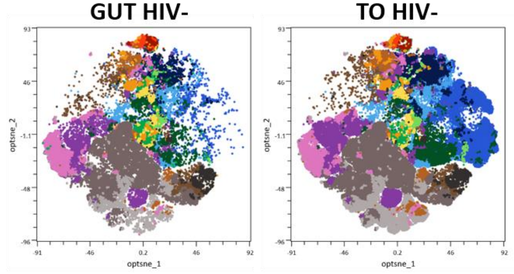
1. Intestinal and tonsillar tissues exhibit differences in the composition of the CD4⁺ T cell compartment despite the presence of all clusters in both tissues.
2. HIV infection primarily localizes within the T_{EM} clusters in both tissues, with varying degrees of contribution to the overall infection levels.
3. The responses to current LRAs vary between intestinal and tonsillar HIV reservoirs.
4. While some CD4⁺ T subsets constitute HIV reservoirs in both tissues, there are also unique cell reservoirs in the intestine and tonsils.
5. Distinct reactivation patterns are observed within the same CD4⁺ T cell subpopulations across the two tissues.

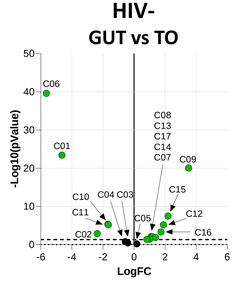
Our findings reveal that CD4⁺ T cell populations in the intestine and tonsils exhibited varying susceptibility to viral infection and reactivation. Further research is required to identify LRAs capable of targeting the distinct cellular reservoirs within these tissues.

RESULTS

Identification of CD4⁺ T populations in the explant models

- Identification of 17 subpopulations of CD4⁺ T cells based on the expression of the markers: CD45RO, CCR7, CD69, CD103, CD49a, PD1, CXCR5, CD127 and KLRG1.





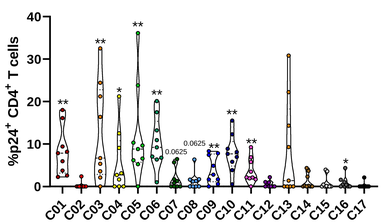
C01: $T_{EM\text{-}CD69^+\text{-}CD103^+\text{-}CD127^{mid}\text{-}CD49a^+}$
C02: $T_{CD69^+\text{-}CD103^+\text{-}CD49a^+}$
C03: T_{CD69^+}
C04: $T_{CM\text{-}CD69^+\text{-}PD1^+}$
C05: $T_{EM\text{-}CD69^+\text{-}PD1^+}$
C06: $T_{EM\text{-}CD69^+\text{-}CD127^+\text{-}CD49a^+}$
C07: $T_{CM\text{-}FH\text{-}CD69^+}$
C08: $T_{CM\text{-}CD69^+\text{-}CXCR5^+}$
C09: $T_{EM\text{-}FH\text{-}CD69^+}$
C10: $T_{EM\text{-}CD69^+}$
C11: T_{CM}
C12: $T_{CM\text{-}FH}$
C13: $T_{CD69^{mid}}$
C14: $T_{NA\text{-}CD69^+\text{-}CXCR5^+}$
C15: $T_{NA\text{-}CCR7^{mid}}$
C16: T_{NA}
C17: $T_{NA\text{-}CD69^+}$

Significant variation in the proportions of **14 out of 17** CD4⁺ T clusters between intestinal and tonsillar tissues.

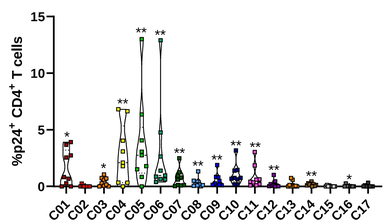
T_{EM} were predominant in the intestine whereas T_{CM}, T_{NA} and T_{FH} in the tonsil.

HIV infection predominantly occurred in CD4⁺ T_{EM} cells

- Infection levels were higher in the intestinal clusters compared to the tonsillar subsets.

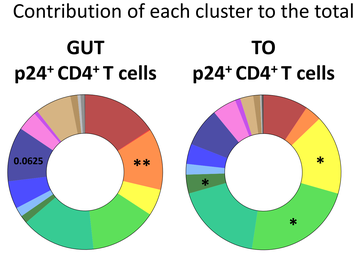


In the intestine, infection predominantly occurred within the T_{EM} clusters (**C01**, **C05**, **C06**, **C09** and **C10**).



In the tonsils, the majority of clusters were significantly infected but infection levels were higher in **C01**, **C04**, **C05** and **C06.**

- Contribution of each cluster to the total population of infected CD4⁺ T cells:

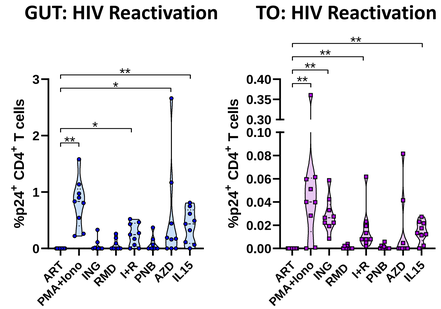


In both tissues, the T_{EM} clusters **C01**, **C05**, **C06** and **C10** contributed more to the total infection levels. **C03** also made a substantial contribution in the intestine; and **C04**, in the tonsils.

Significant inter-tissue differences were observed in the contribution of **C03**, **C04**, **C05** and **C07** to the total pool of infected cells.

Intestinal and tonsillar HIV reservoirs respond differently to current LRAs

- The effect of different LRAs was evaluated in the pool of total CD4⁺ T cells. LRAs studied include: Ingenol (ING), Romidepsin (RMD), ING + RMD, Panobinostat (PNB), AZD5582 (AZD) and IL-15.

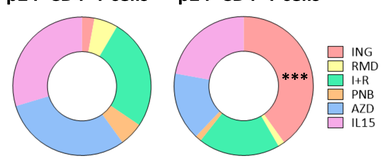


Contribution of the different LRAs to HIV reactivation in the total pool of virally reactivated CD4⁺ T cells.

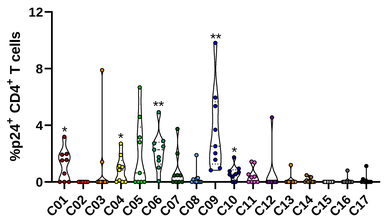
We observed a remarkable difference in the efficacy of **ING** in inducing viral reactivation in the intestinal and tonsillar reservoirs.

Both **I+R** and **IL-15** induced a potent and significant reactivation of intestinal and tonsillar HIV reservoirs.

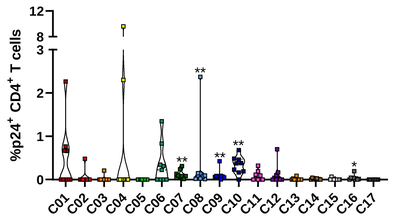
AZD showed effectiveness exclusively in reactivating the intestinal reservoirs, while **ING** only significantly reactivated tonsillar latently infected CD4⁺ T cells.



- Intestinal and tonsillar HIV reservoirs are constituted of distinct subpopulations of CD4⁺ T cells.

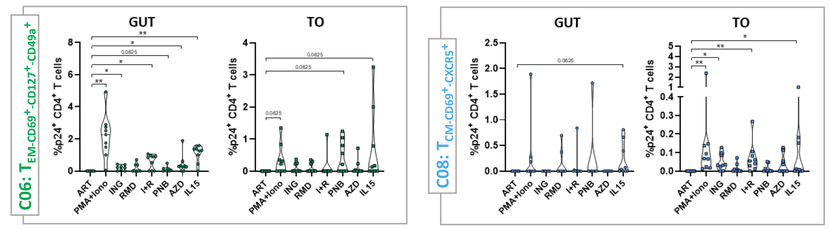


C01, **C04**, **C06**, **C09** and **C10** constitute HIV reservoirs in the intestinal tissue.



C07, **C08**, **C09**, **C10** and **C16** constitute HIV reservoirs in the tonsillar tissue.

- Heterogeneous responses of intestinal and tonsillar CD4⁺ T cell subpopulations to LRAs.



Same clusters showed distinct reactivation patterns to current LRAs across the two tissues.

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