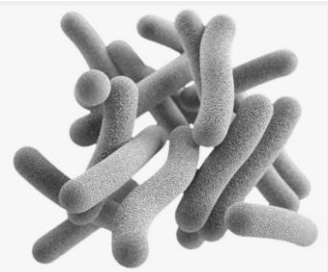
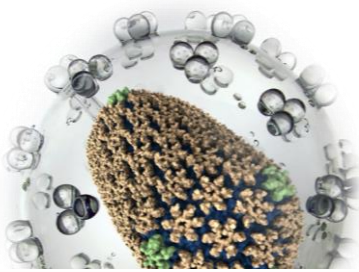


Tuberculosis promotes the persistence of genetically intact HIV

- Samantha Cronin
- Luciana Balboa
- Sarah Palmer
- Gabriel Duette

The Westmead Institute FOR MEDICAL RESEARCH | Centre for Virus Research

THE UNIVERSITY OF SYDNEY

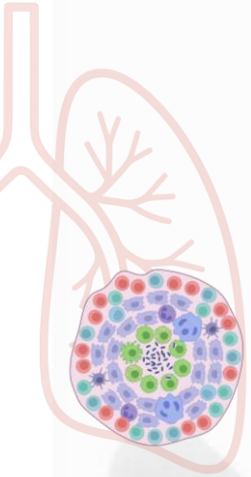


Conflicts of interest

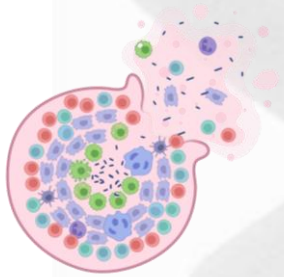
- No conflicts of interest to declare

HIV/TB co-infection

Mycobacterium tuberculosis (Mtb) is a bacterial pathogen that predominantly infects the lungs.



In approximately 90% of cases, *Mtb* establishes a latent, non-infectious state, with bacilli contained within granulomas (Gideon & Flynn, 2013).

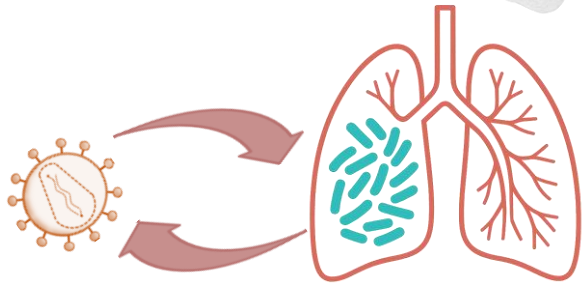


10% of latent *Mtb* infections reactivate, driven by immune failure and subsequent granuloma breakdown (WHO, 2024).

14 million people living with HIV are co-infected with *Mtb*

33% of HIV related deaths are attributed to tuberculosis disease

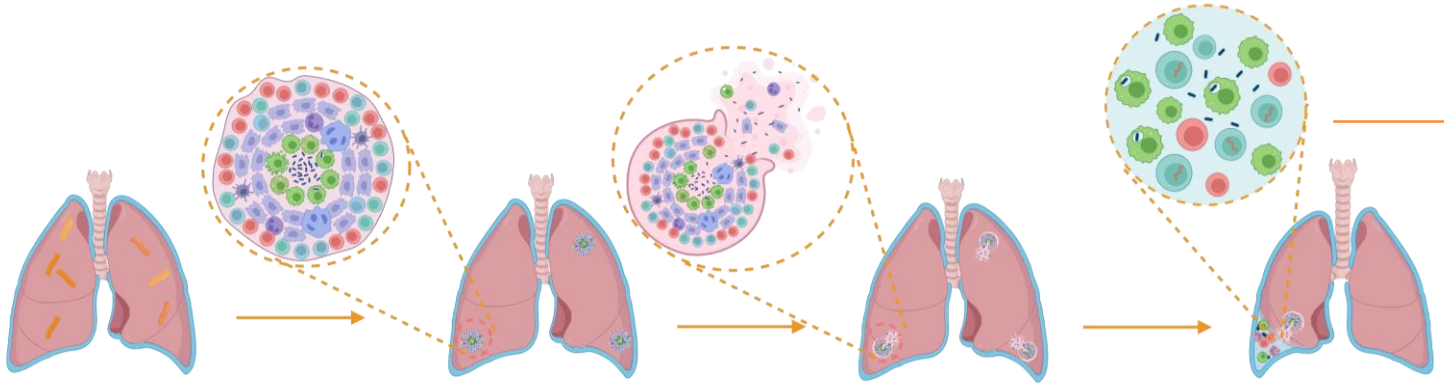
PLWH are 18 times more likely to develop active TB



Little is known about the effect of TB disease on the HIV reservoir

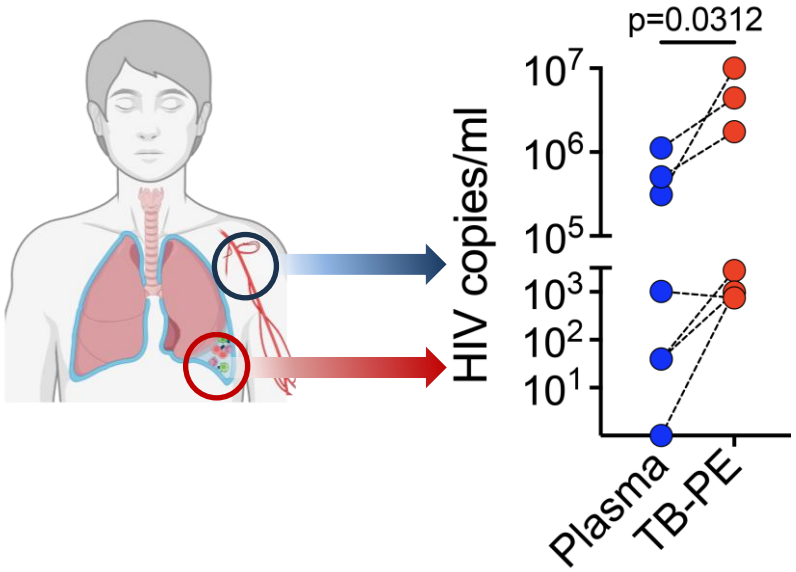
Esmail, H *et al*. Annual Review of Immunology (2018)
Pawlowski, A. *et al*. Plos Pathogens (2012)
Mancino, G. *et al*. The Journal of infectious diseases (1997)
Toossi, Z. *et al*. Journal of AIDS and human retrovirology (1997)

TB pleural effusion



TB-PE as a physiologically relevant fluid

- It is more frequent in individuals living with HIV/TB
- It contains high HIV titers



Toossi et al., 2001
Collins et al., 2002
Toossi et al., 2003

Article

Cell Reports

Tuberculosis Exacerbates HIV-1 Infection through IL-10/STAT3-Dependent Tunneling Nanotube Formation in Macrophages

Souriant et al. 2019

eLife

Tuberculosis-associated IFN-I induces Siglec-1 on tunneling nanotubes and favors HIV-1 spread in macrophages

Dupont et al. 2020

PLOS PATHOGENS

Fatty acid oxidation of alternatively activated macrophages prevents foam cell formation, but *Mycobacterium tuberculosis* counteracts this process *via* HIF-1α activation

Melanie Genoula, José Luis Marín Franco, Mariano Maio, Belén Dolotowicz, Malena Ferreyra, M. Ayelén Milillo, Rémi Mascarau,

Cell Reports

Host-derived lipids from tuberculous pleurisy impair macrophage microbicidal-associated metabolic activity

José Luis Marín Franco…Luciana Balboa

eLife

Elevated glycolytic metabolism of monocytes limits the generation of HIF-1α-driven migratory dendritic cells in tuberculosis

Mariano Maio, Joaquina Barros, Marine Joly, Zoi Vahlas, José Luis Marín Franco, Melanie Genoula, Sarah Monard,

TB-PE as a model for the TB-associated immune microenvironment

Article

Cell Reports

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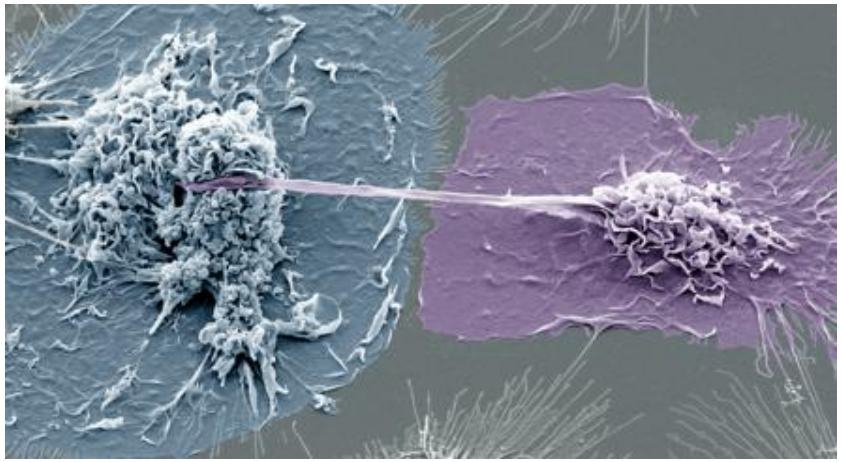


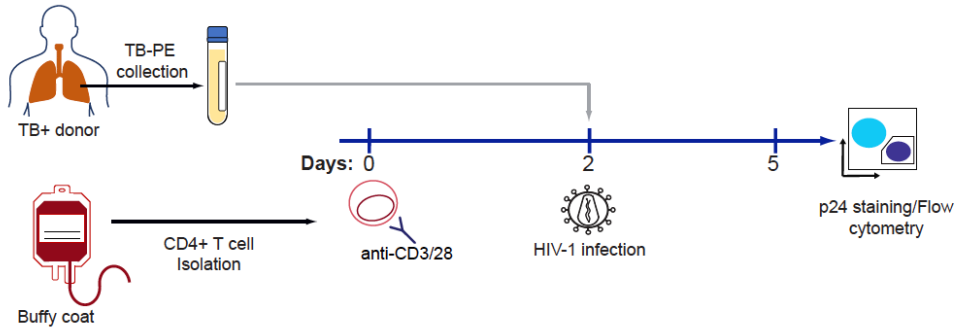
iScience

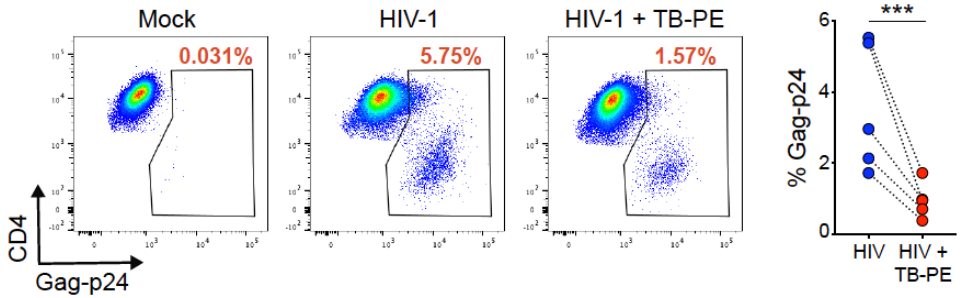
CellPress OPEN ACCESS

Article

The immunosuppressive tuberculosis-associated microenvironment inhibits viral replication and promotes HIV-1 latency in CD4$^+$ T cells

Samantha Cronin,[1,2,8] Anneke de Vries-Egan,[1,8] Zoï Vahlas,[3,4] Alejandro Czernikier,[5] Claudia Melucci,[5] Pehuén Pereyra Gerber,[6] Thomas O'Neil,[1,2] Brian Gloss,[1] Mayssa Sharabas,[1] Gabriela Turk,[5] Christel Verollet,[3,4] Luciana Balboa,[4,5,7,9] Sarah Palmer,[1,2,9] and Gabriel Duette[1,2,9,10,*]





HIV genetic landscape in PLWH/TB

PBMCs from 5 PLWH

PBMCs from 5 PLWH/TB

Full-length Individual Provirus Sequencing assay

PCR

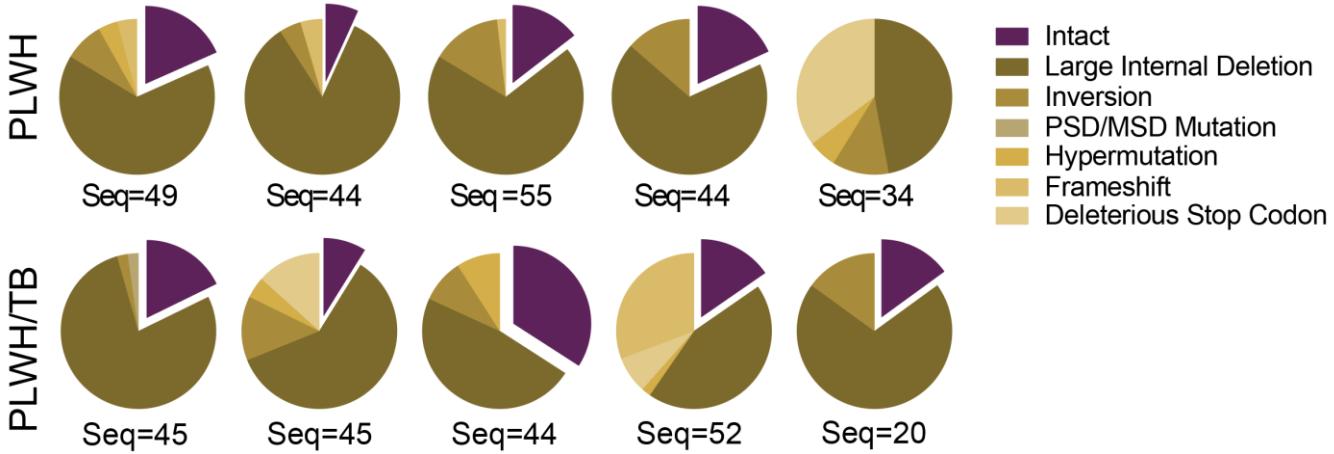
NGS

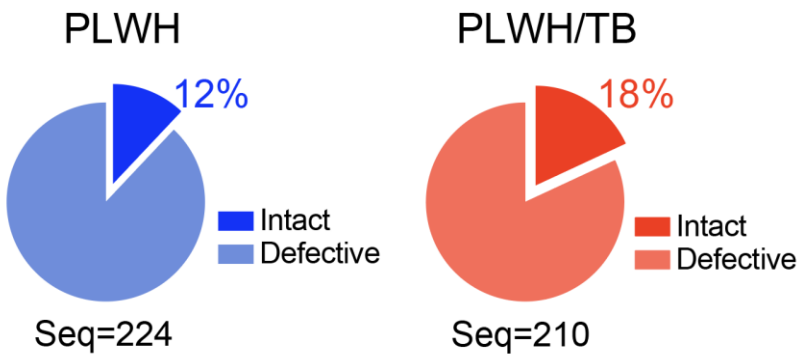
Seq. analysis

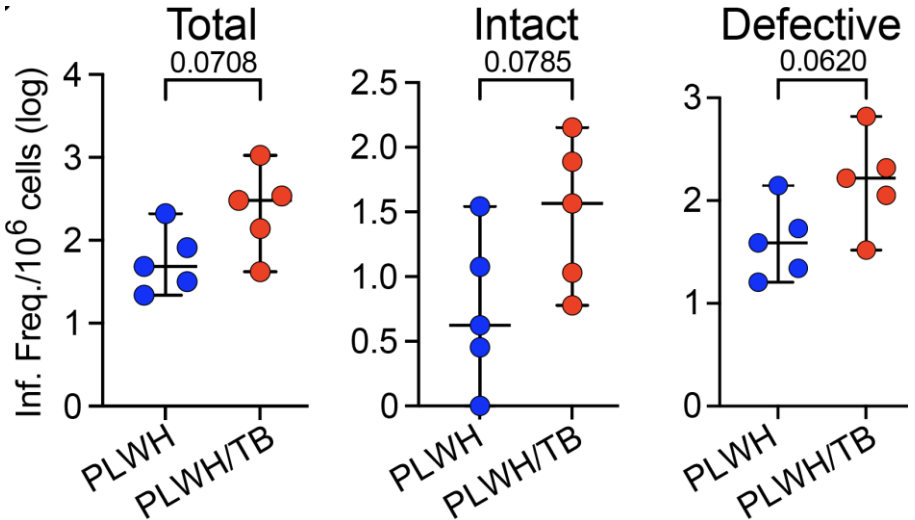
LTR primer

HIV DNA

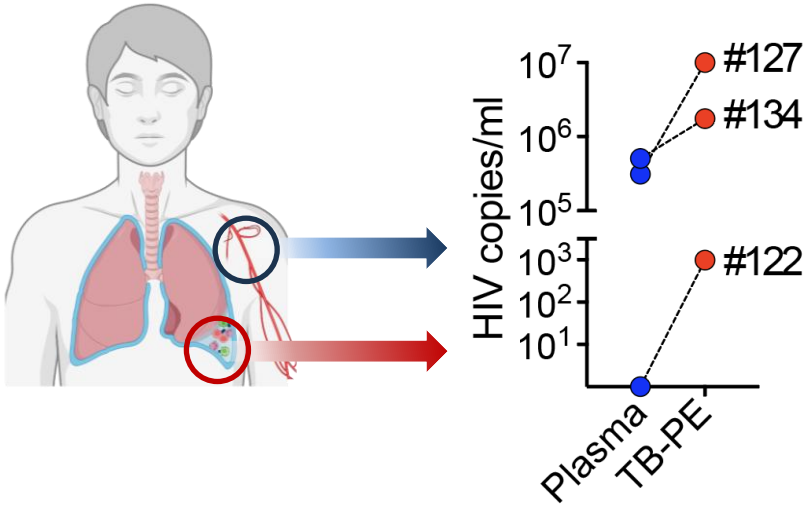
- Genetically intact
- Internal deletion
- Hypermutation
- Inversion
- Premature stop codon



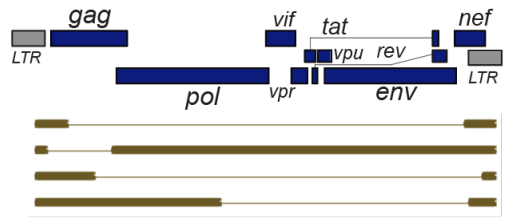


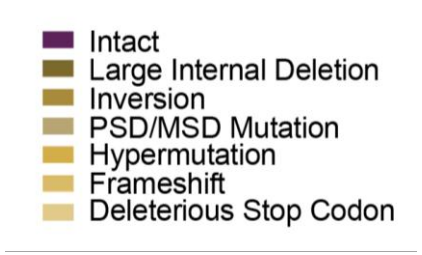


HIV genetic landscape in PLWH/TB

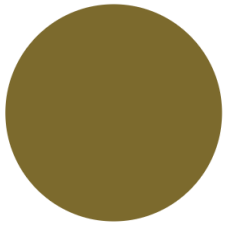


HIV proviral DNA





PBMC #122



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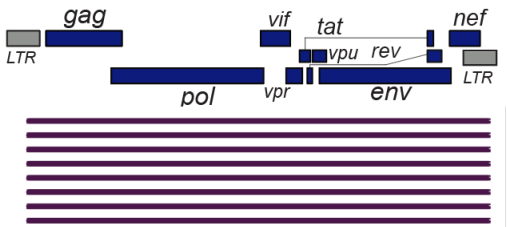
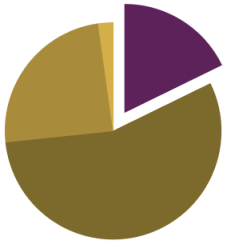


PEMC #122



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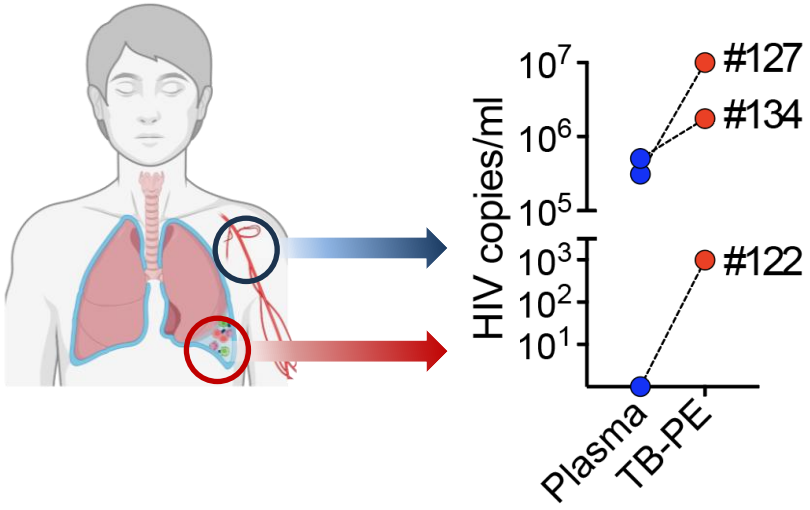
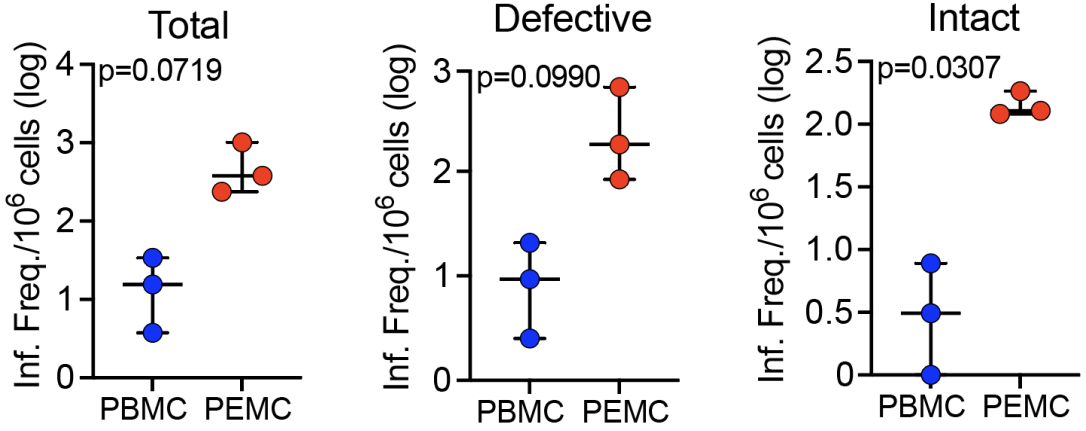
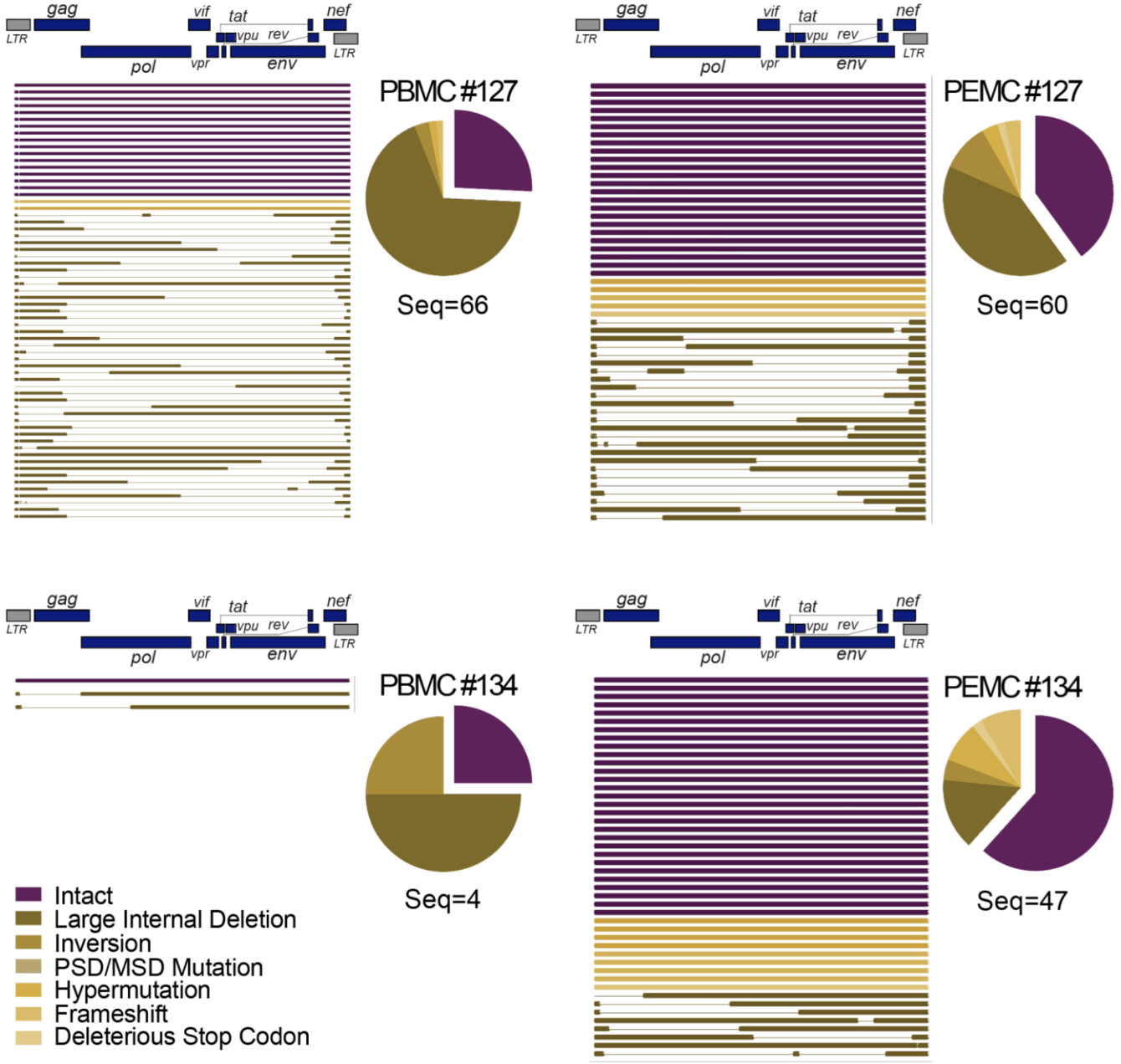
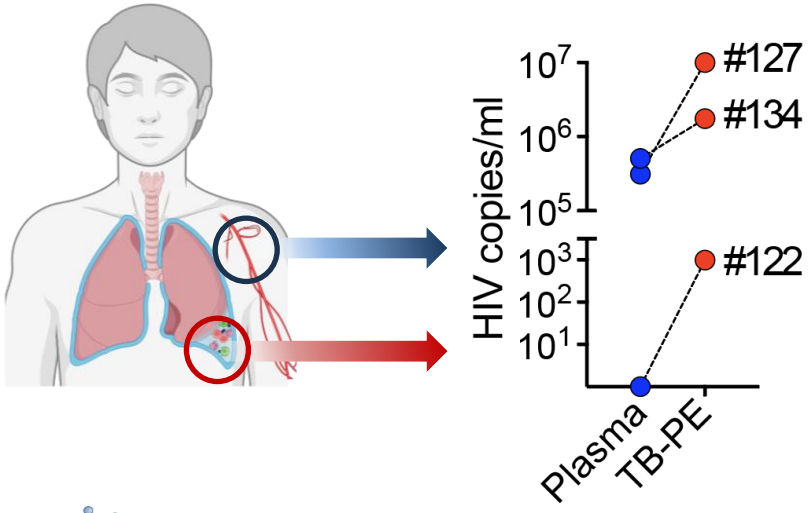
HIV genetic landscape in PLWH/TB

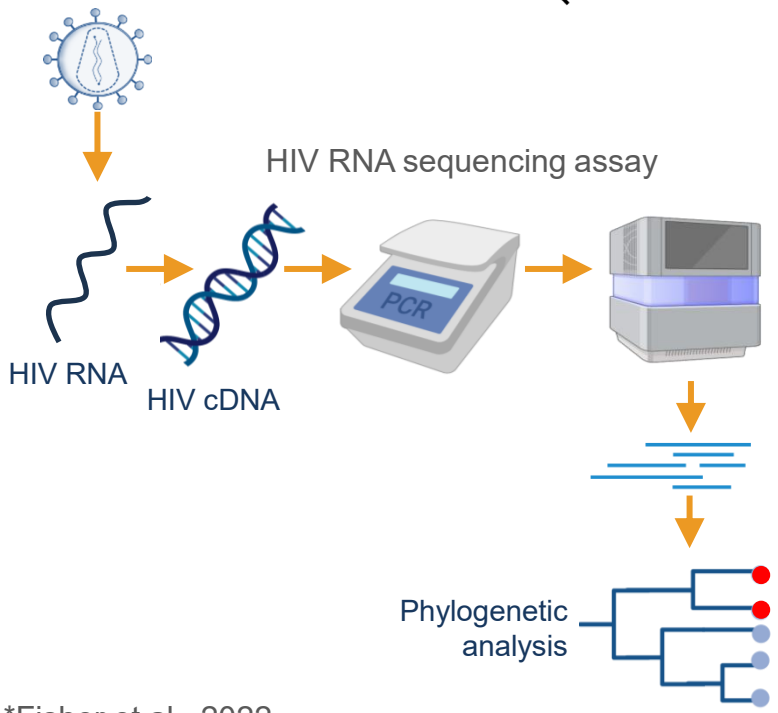






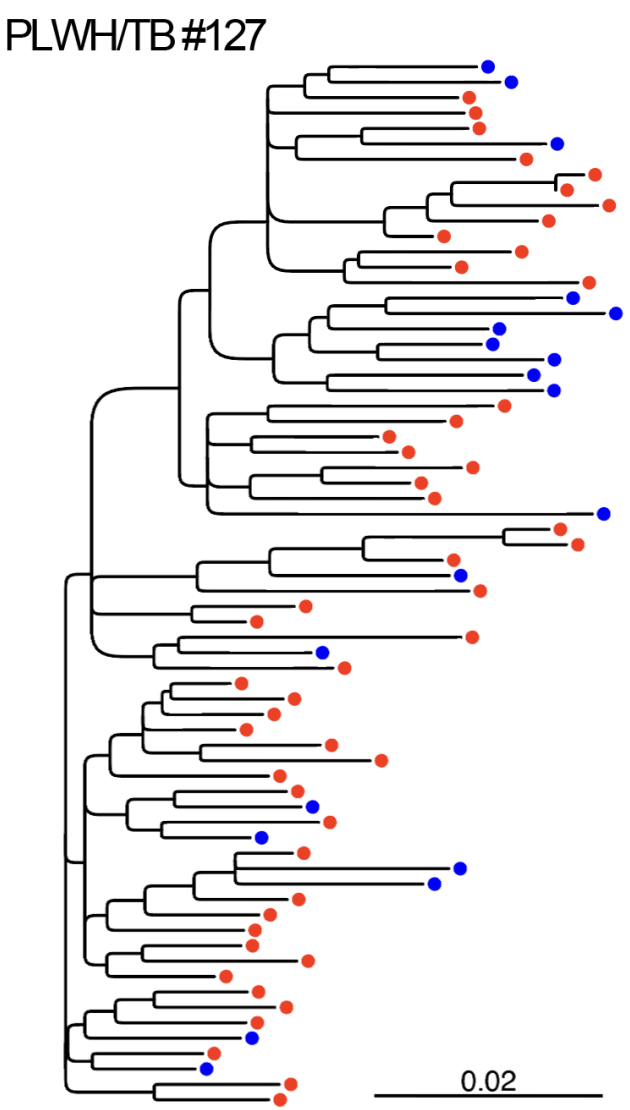
HIV genetic landscape in PLWH/TB

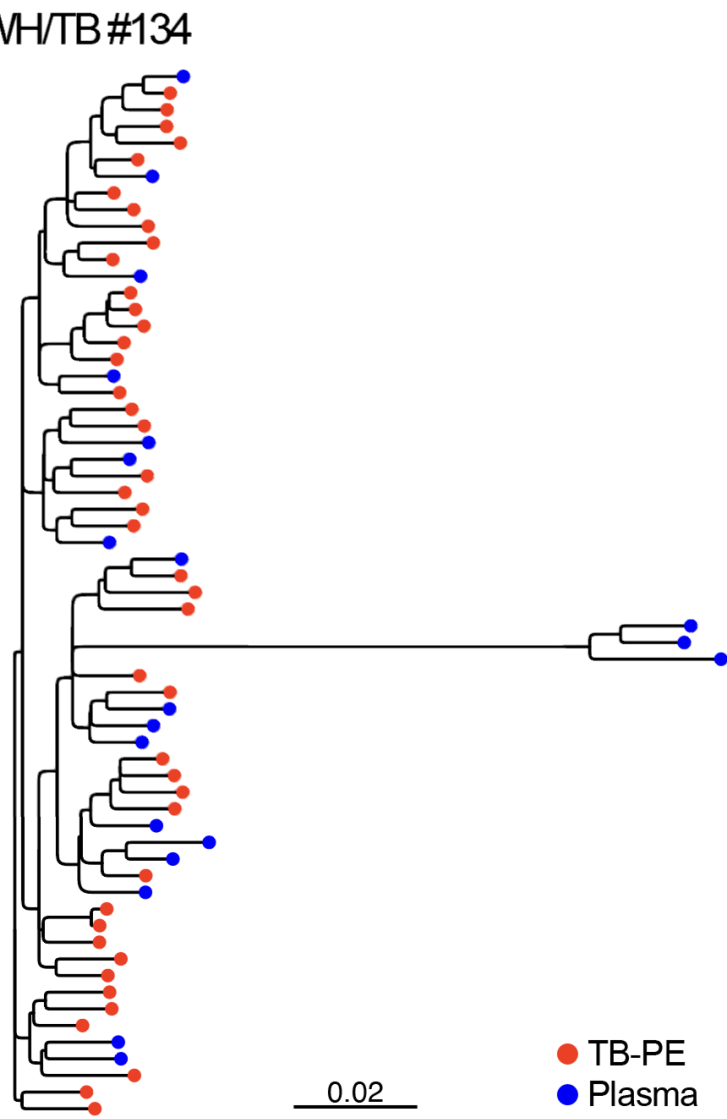




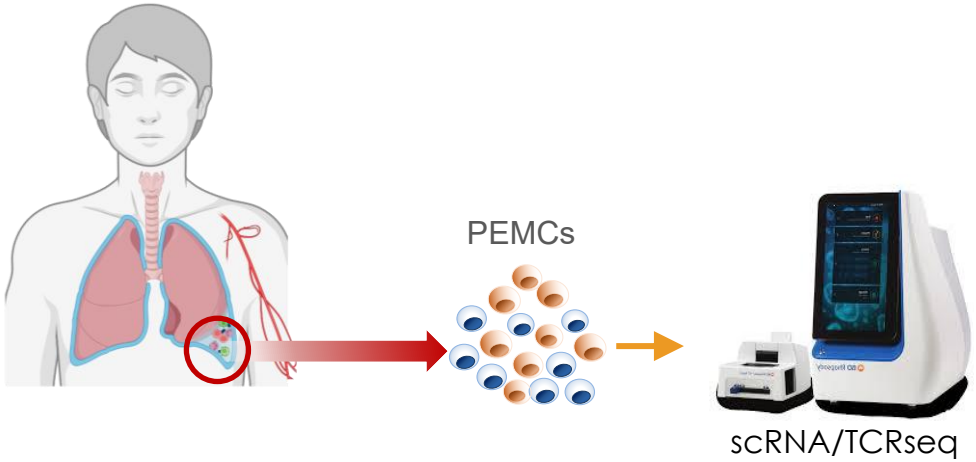
*Fisher et al., 2022

HIV genomic RNA

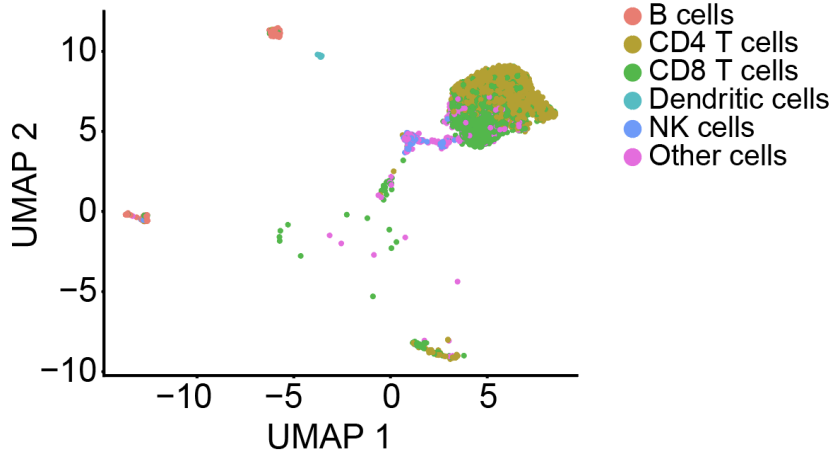




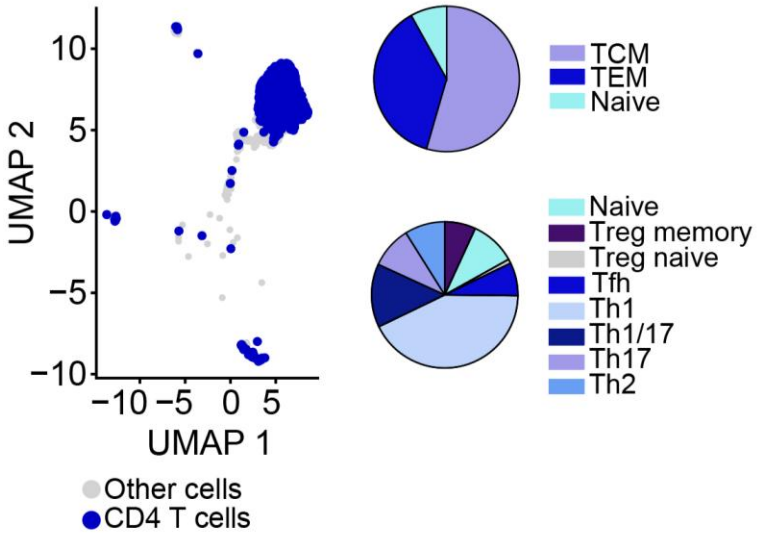
HIV cell targets at the site of the coinfection



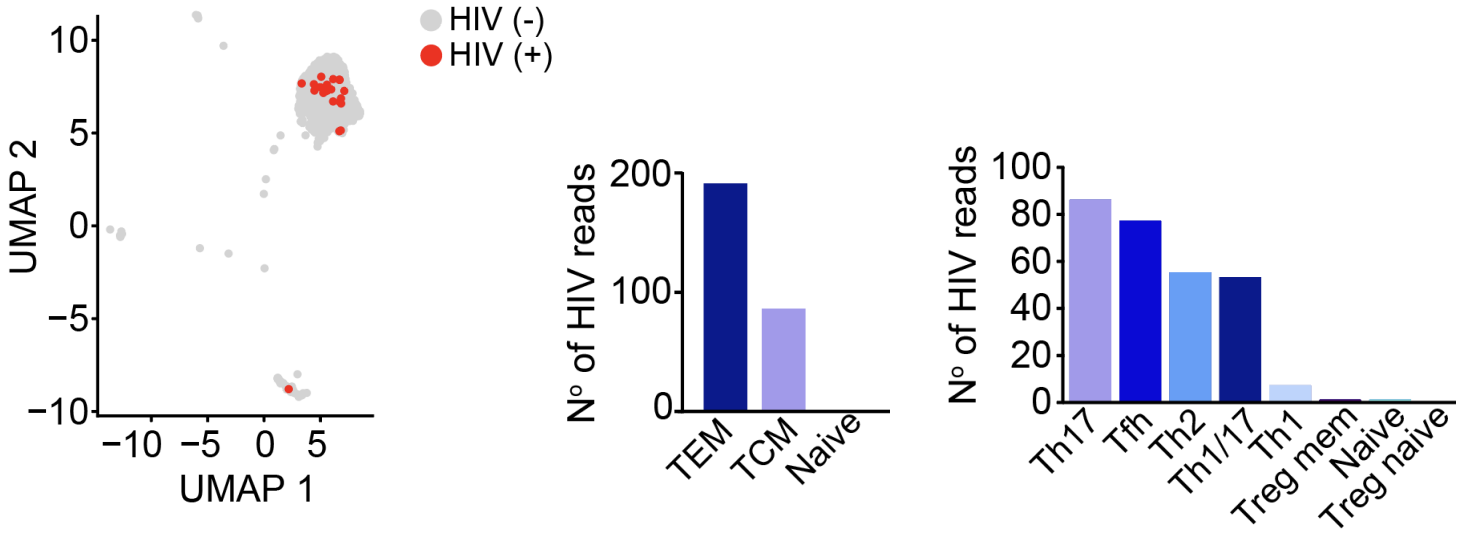
Mononuclear cells from TB-PE



CD4 T cells from TB-PE



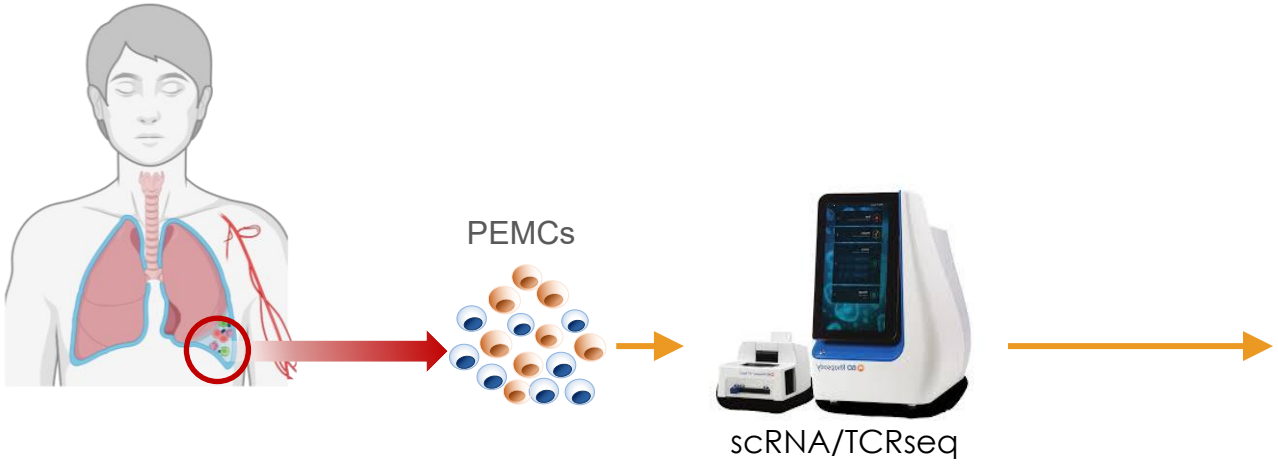
HIV-infected CD4 T cells



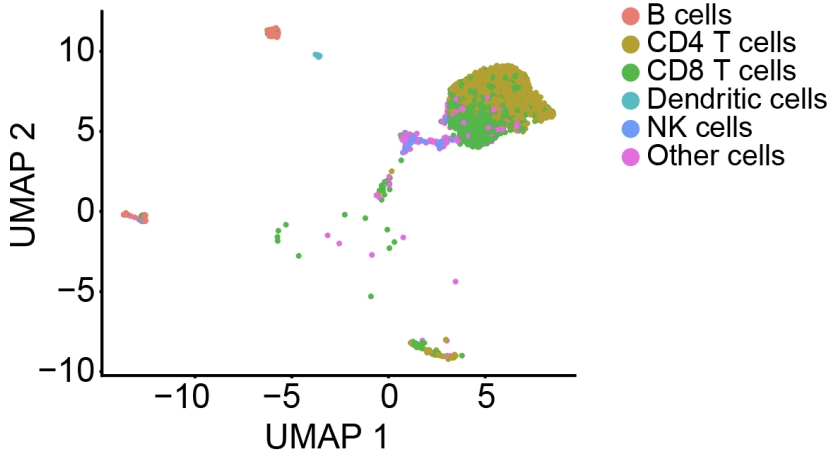
Why is the proportion of genetically intact HIV higher in TB-PE?

Is the CD8+T cell-mediated antiviral activity impaired at the site of the co-infection?

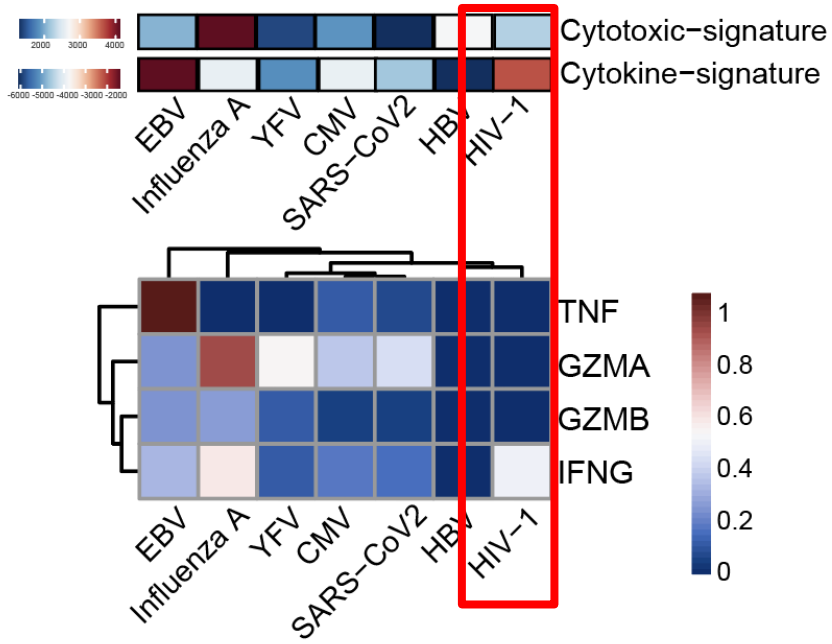
HIV-specific CD8 T cells at the site of the coinfection

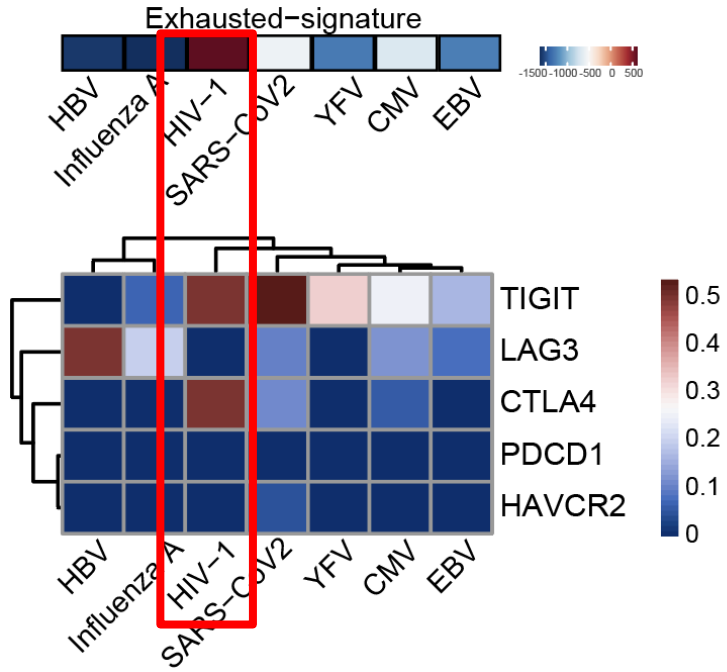


Mononuclear cells from TB-PE

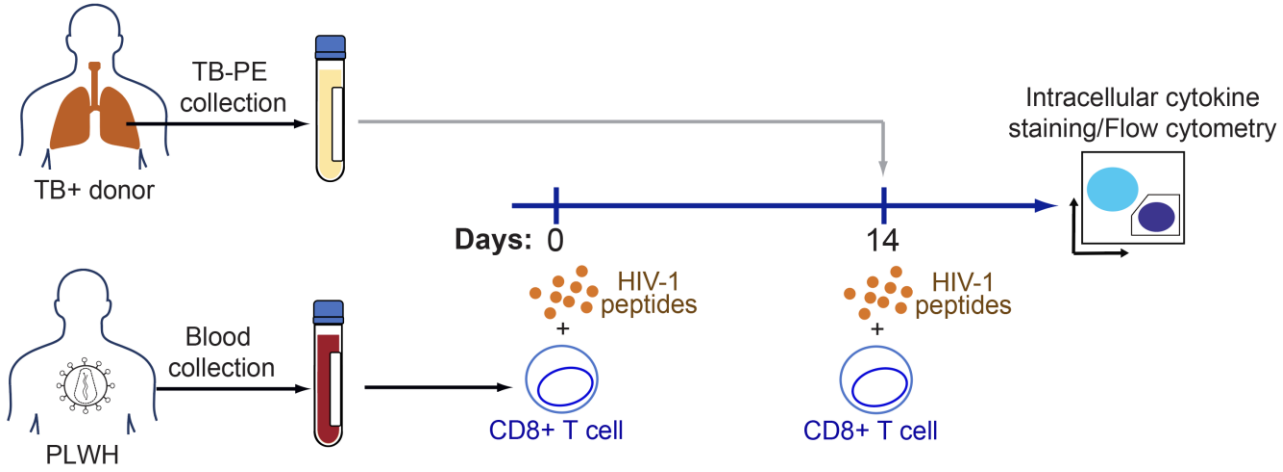


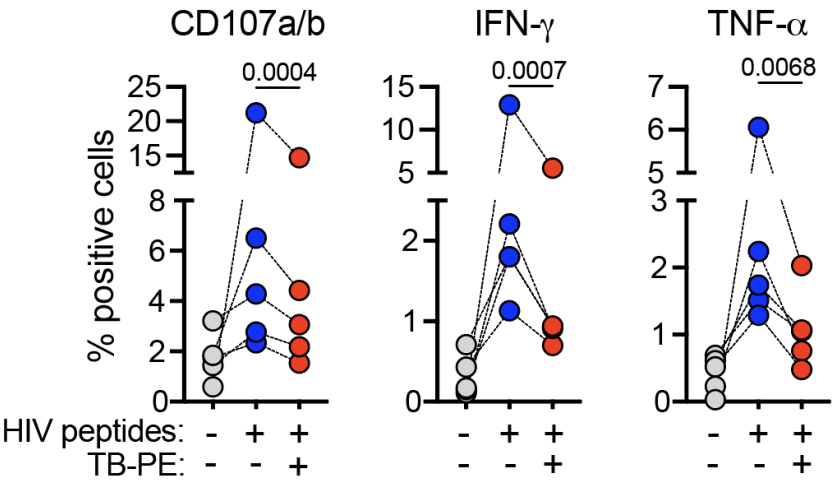
CD8 T cells from TB-PE

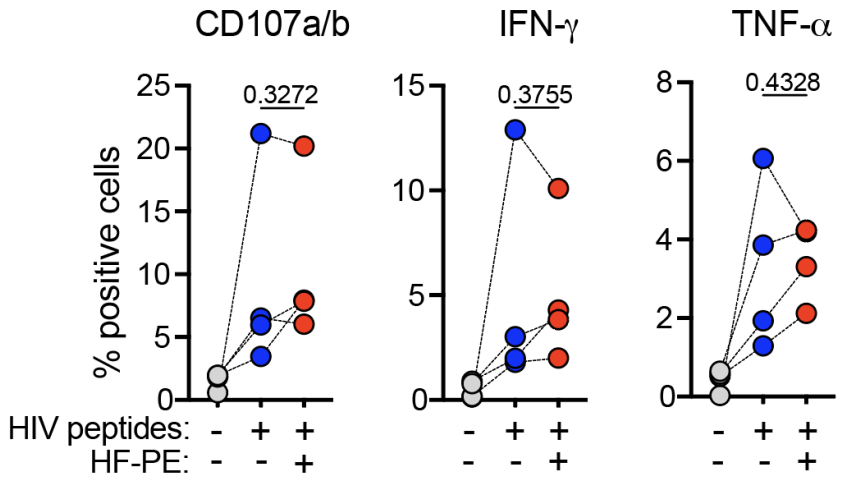


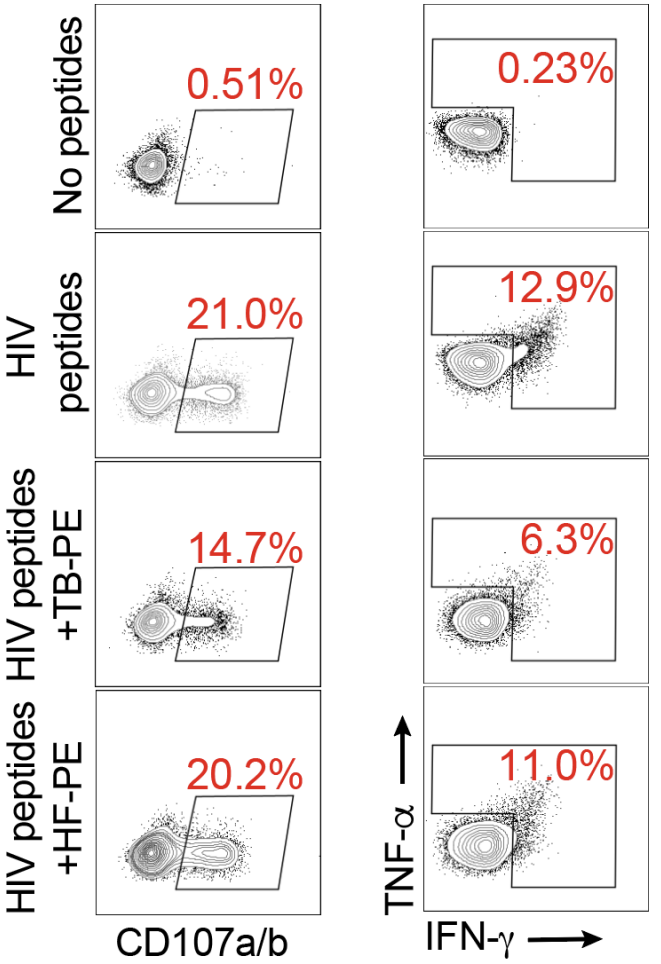


CD8 T cell effector functionality impacted by a TB-associated microenvironment

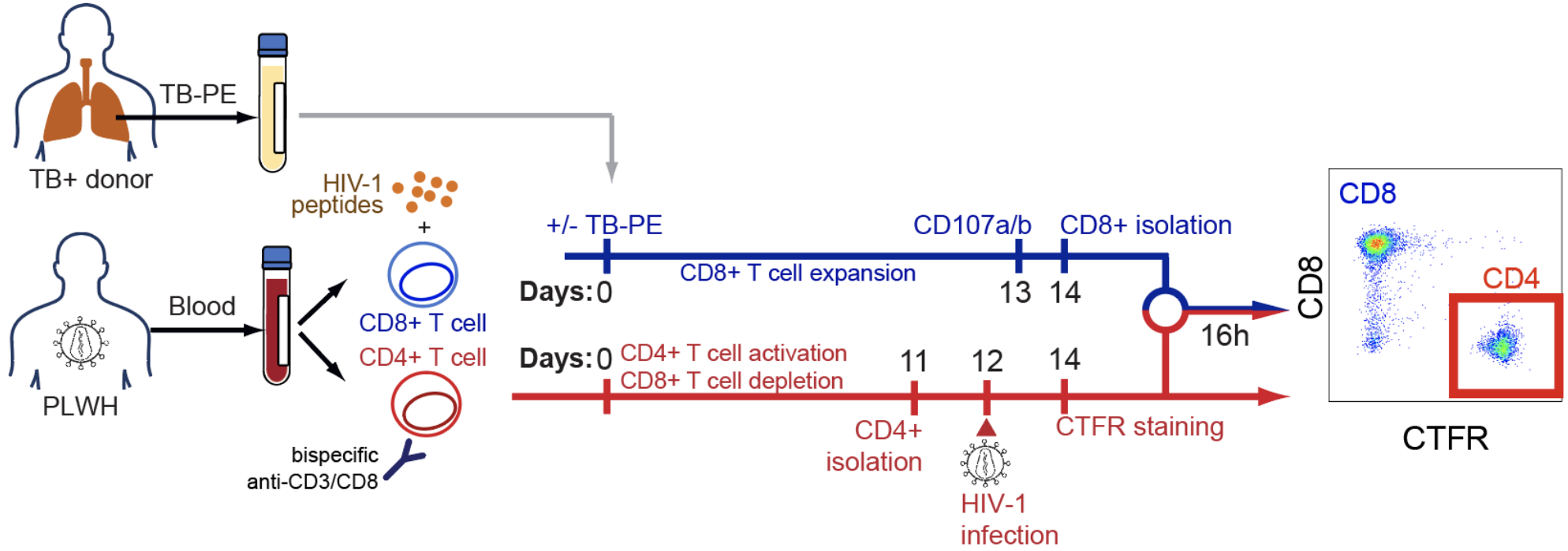


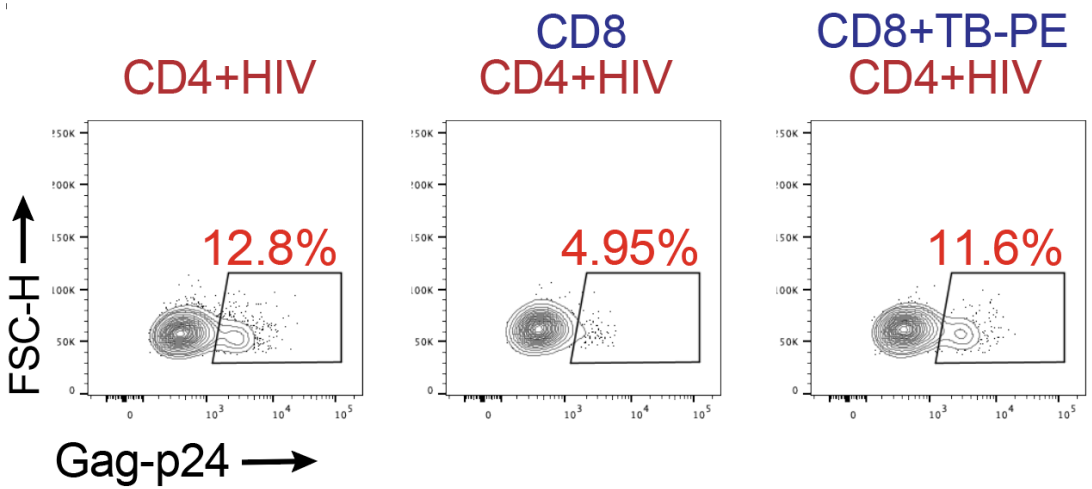


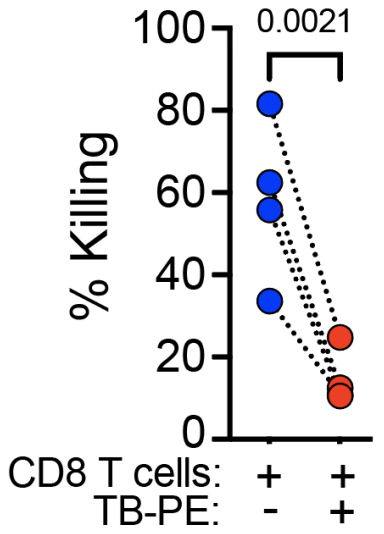




CD8 T cell effector functionality impacted by a TB-associated microenvironment







Conclusions

1. HIV infection frequency is increased in PBMCs from people with HIV/TB coinfection.

2. The proportion of genetically intact proviruses is higher at the site of coinfection.

3. TB-PE impairs the effector functionality of HIV-specific $CD8^+$ T cells.

The tuberculosis-associated microenvironment impacts CD8+ T cell functionality, leading to reduced viral control at the site of the coinfection.

Thanks!!!

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