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Fingolimod for Multiple Sclerosis Boosts HIV Cellular Resistance and Limits Viral Reservoir Size

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Fingolimod therapy in a patient with Multiple Sclerosis is associated with low plasma viremia at HIV diagnosis, absence of intact proviruses after 3 years on ART and strong restriction of viral replication, transcription, and reservoir establishment.

Plain Language Summary

We report a patient with multiple sclerosis who acquired HIV while receiving fingolimod, a drug used to treat this neurodegenerative disease. Viral levels at diagnosis were lower than expected, and after three years of antiretroviral treatment, no replication-competent viruses were detected. Fingolimod was associated with enhanced antiviral activity, reduced expression of HIV receptors, and decreased cellular susceptibility to infection. Our results suggest that drugs of the fingolimod family may limit HIV infection and reservoir formation.

Background

- Fingolimod, a treatment for multiple sclerosis (MS), decreases autoreactive lymphocytes by node sequestration.
- *In vitro*, fingolimod decreases HIV-1 infection and viral reservoir (VR) by:
  - SAMHD1 phosphorylation inhibition.
  - Reducing lymphocyte activation and CD4 expression.

We identified an exceptional MS patient infected with HIV-1 while on fingolimod therapy.

Objective:

Analyze fingolimod impact on HIV-1 infection *in vivo* and *ex vivo*

Methods

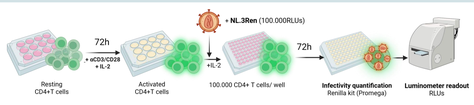
Participants and samples:



Intact Proviral DNA Assay (IPDA):



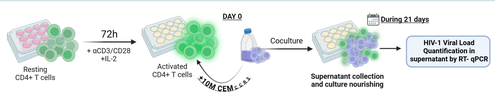
HIV in vitro infection :



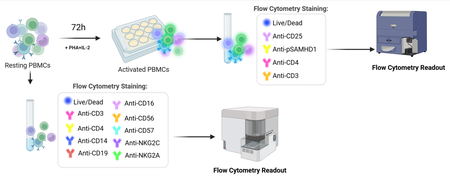
HIV icRNA quantification:



Viral outgrowth assay:



Flow cytometry:



Results

1

- At diagnosis, HIV+MS+ viral load was nine-fold lower than HIV+MS- treated at similar Fiebig (V-VI) (4.6 vs 5.5 Log10 copies/mL)(*Fig 1A*).
- One year after ART, HIV+MS+ showed lower intact (28-fold) and defective (six-fold) VR than the HIV+MS- treated at similar Fiebig (V-VI) (*Fig 1B*).
- After three years on ART, no intact proviruses were detected in the fingolimod-treated patient (HIV+MS+).

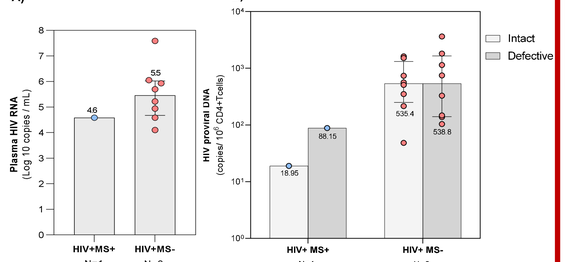


Fig 1. Plasma viral load and HIV-1 reservoir in fingolimod-treated HIV-1 patient and PWH controls.

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HIV-1 *in vitro* CD4+ T-cells infection was decreased in participants under fingolimod treatment (HIV+MS+ and HIV-MS+) vs HIV+MS- and HIV-MS- (*Fig 2*).

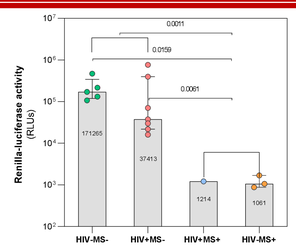


Fig 2. *In vitro* HIV-1 infectivity assays.

3

- Different HIV-1 transcripts (LongLTR, Pol, PolyA and TatRev) significantly increased after CD4+ T-cells activation in PWH (HIV+MS-) treated and virally suppressed (7.5, 38.7, 74.8 and 1151.7-folds respectively), while they were barely detected before and after activation in the HIV+MS+ (1.3, 1, 0.2 and 3.8-folds respectively)(*Fig 3*).

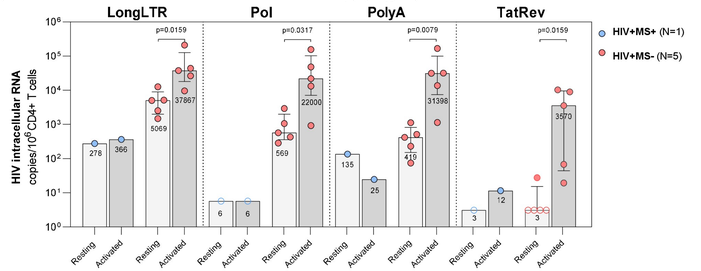


Fig 3. Transcriptionally active reservoir on resting and activated CD4+T-cells.

4

After 21 days of viral outgrowth assay, no virions were isolated from the HIV+MS+ participant.

5

- CD4+T-cells from HIV+MS+ and HIV-MS+ showed decreased CD4+ T-cell activation after PHA+IL2 stimulation (14.4% and 29.9%) vs HIV-MS- (73.2%) (*Fig6A*).
- SAMHD1 phosphorylation was reduced in CD4+ T-cells from HIV+MS+ and HIV-MS+ (21.3% and 13.7%) vs HIV-MS- (63.65%)(*Fig6B*).

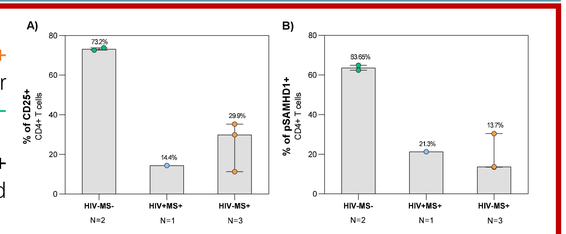


Fig 6. Expression of CD25 and pSAMHD1 in activated PBMCs.

6

- Fingolimod-treated participants showed reduced numbers of total T-cells (45.1% in HIV+MS+; 25.1% in HIV−MS+) vs 58.3% HIV−MS− and 60.7% HIV+MS−(*Fig 4A*).
  - CD8+ T-cell frequencies were similar across groups, with higher levels in HIV+MS+ (42.7%) (*Fig4B*).
  - CD4+ T cells were markedly decreased (2.4% HIV+MS+; 3.5% HIV−MS+) vs 41.2% HIV−MS− and 33.6% HIV+MS- (*Fig4C*).
  - CD4+ T-cells from fingolimod-treated participants showed decreased CD4 expression compared with fingolimod non-treated participants (*Fig4D).*

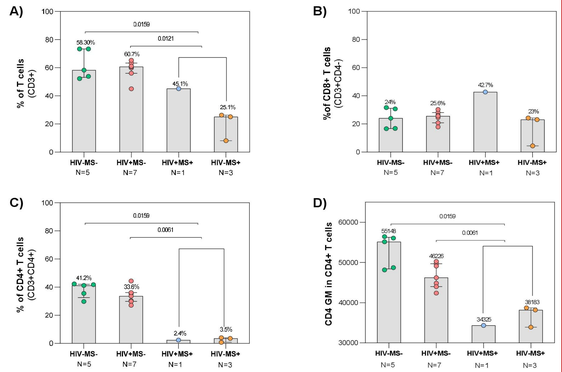


Fig 4. Phenotypic characterization of T cell subsets.

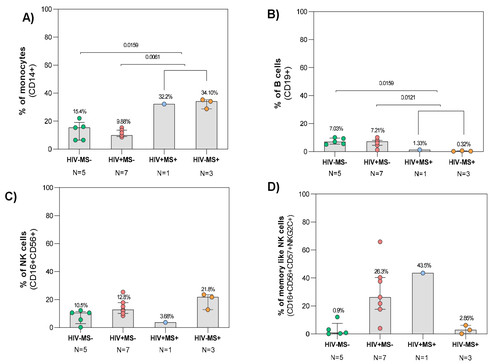


Fig 5. Phenotypic characterization of PBMC subpopulations.

- Fingolimod-treated participants showed increased monocyte frequencies (32.2% HIV+MS+; 34.1% HIV−MS+) vs 15.4% HIV−MS− and 9.88% HIV+MS− (*Fig5A*).
- B cells were markedly reduced in fingolimod-treated participants (1.33% HIV+MS+; 0.32% HIV−MS+) vs 7.03% HIV−MS− and 7.21% HIV+MS- (*Fig5B*).
- NK cell percentages were largely comparable, although reduced in HIV+MS+ (3.68%) (*Fig5C*).
  - NK memory-like cells (*CD57+NKG2C+)* were higher in HIV+MS+ (43.5%) and HIV+MS− (26.3%) vs HIV−MS+ (2.85%) and HIV−MS− (0.9%), without reaching statistical significance (*Fig5D*).

Conclusions

- We report **the first case of MS patient who acquired HIV during fingolimod treatment.**
- **Fingolimod restricts HIV infection and replication *in vivo* and *ex vivo* leading to indetectable intact VR.**
- Potential mechanisms of fingolimod induced restriction are **downregulation of CD4, block of CD4+ T-cell activation and increased SAMHD1 activity**.

ACKNOWLEDGMENTS: ...and study participants!