Fingolimod treatment at ART initiation delays SIV rebound following ART interruption

Maria Pino
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Targeting lymphoid sites of HIV persistence by blocking T cell egress via fingolimod (FTY720)

Promotes retention of multiple lymphocyte populations in lymphoid tissues.

Chiba et al. Pharmaceuticals 2012
FTY720 increases T cell numbers in LN

FTY720 administration in ART-treated, SIV-infected RMs:

• is well-tolerated, and induces peripheral T cell lymphopenia.
• Increases numbers of T cells in LN, including those with cytolytic potential.
• Reduces SIV-DNA content in circulation (due to very low number of CD4+ T cells).

Pino, Paganini et al. Submitted
Hypothesis

We hypothesize that retention of T cells in lymphoid tissues at ART initiation with FTY720 will:

(i) **Reduce** the peripheral blood reservoir by limiting CD4+ T cell recirculation.

(ii) **Sequester cytolytic T cells** with still preserved number in the lymph node.

(iii) **Increase the interaction of cytolytic T cells with SIV-infected T cells** and promote their elimination.

(iv) Help to **understand the main contributor** of plasma viremia (lymphoid tissues or peripheral lymphocytes/ cell-free virus or cell-associated virus).
Study design

RM characteristics:
- 22 RMs
- all Mamu*B08- &B17-

Gr1. Controls. (n=14 at ART initiation and 6 at ART interruption).

Gr2. ART + early FTY720 treatment (500 μg/Kg orally daily; 58-59 days). (n=8)

High barrier for cure (to mimic issues pertaining to treatment in PLWH): ART initiation at 42 days p.i., with complete seeding of the viral reservoir.
FTY720 induces peripheral lymphopenia

"*: Statistical differences performed longitudinally within the same treatment group; comparisons with baseline (pre vs post FTY720 time point).

"P" values: Statistical differences performed cross-sectionally at the same time point (treated vs non-treated group).
FTY720 does not accelerate plasma viral load decay despite extremely low levels of circulating CD4⁺ T cells

“*”: Statistical differences performed longitudinally within the same treatment group; comparisons with baseline (pre vs post FTY720 time point).
“P” values: Statistical differences performed cross-sectionally at the same time point (treated vs non-treated group).
FTY720 at ART initiation enhances retention of cytolytic cells in lymph nodes

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<table>
<thead>
<tr>
<th>Days Post FTY720 treatment</th>
<th>ratio CD8/CD4</th>
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<tr>
<td>-5</td>
<td>0.5</td>
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**p** = 0.03

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<thead>
<tr>
<th>Days post FTY720:</th>
<th>% CD8+ Perforin cells</th>
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<td>Only ART</td>
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<td>-5</td>
<td>14.7</td>
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<td>FTY720 treated</td>
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**p** = 0.013

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<th>Days post FTY720:</th>
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<td>58</td>
<td></td>
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<tr>
<td>FTY720 treated</td>
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"*": Statistical differences performed **longitudinally** within the same treatment group; comparisons with baseline (pre vs post FTY720 time point).

"P": Statistical differences performed **cross-sectionally** at the same time point (treated vs non-treated group).
**Early Impact of FTY720 on SIV-DNA and RNA content in LN**

"*": Statistical differences performed *longitudinally* within the same treatment group; comparisons with baseline (pre vs post FTY720 time point).

Claire Deleage
A subset of FTY720 treated animals delays SIV rebound and limits SIV replication after ART interruption.

Setpoint (d42 pi) vs d14 post ATI

- Controls
- FTY720 treated

ART off-ART

6/6 4/8 6/6 8/8

p=0.048

Days Post ATI

SIV/mac239 RNA copies/ml

Setpoint off-ART

SIV/mac239 RNA copies/ml

Setpoint off-ART

FTY720 treated

- Only ART
- FTY720 treated
A subset of FTY720 treated animals delays viral rebound and limits viral replication after ART interruption.

- Only ART
- FTY720 treated

![Graph showing viral rebound and replication](image-url)
A subset of FTY720 treated animals maintains lower frequency of infected LN Tfh cells
Preliminary conclusions and next steps

Administration of **FTY720**, a drug in clinical use for treatment of multiple sclerosis, at ART initiation in SIV-infected RMs:

i) **Does not increase pVL decay** despite extremely low levels of circulating CD4⁺ T cells:
   - pVL is independent of CD4⁺ T cell recirculation (inhibited by FTY720).
   - cell free virus (unaffected by FTY720) released from tissues is likely the main contributor to pVL.

ii) **Reduces T cells in blood**, and **increases their frequency in LN** (including those with cytolytic potential).

iii) **Results in delayed viral rebound, lower plasma viremia, and reduced frequency of SIV-infected LN Tfh cells in a subset of animals.**

iv) **Multiple virologic** (replication competent or intact SIV DNA) and **immunologic analyses** (SIV specific and non-specific responses) **are ongoing to determine** potential **mechanisms** and correlates of **viral rebound delay** and reduced infection of Tfh cells.
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