Interleukin-2 administration is a potent latency reversal agent in people with treated HIV infection

Michael L. Freeman, Ph.D.

Assistant Professor, Division of Infectious Diseases and HIV Medicine
Case Western Reserve University
Cleveland, Ohio USA

December 16, 2022

CONFLICTS OF INTEREST

- This work was supported by a competitive award from Gilead to Dr. Michael Lederman.

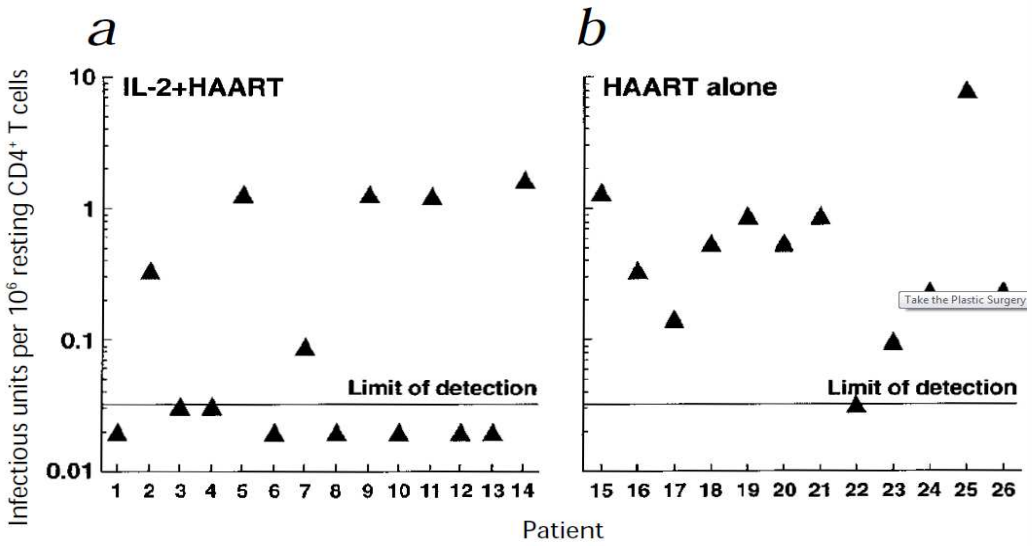
- Dr. Gregory Laird is an employee of Accelevir Diagnostics.
- *No other authors have any financial conflicts of interest to disclose.*

Does IL-2 administration decrease HIV reservoir size?

- IL-2 activates and expands CD4 and CD8 T cells, and activates NK cells
- IL-2 activates HIV expression from primary T cells *in vitro* more reliably than IL-15 does
- IL-2 activates HIV expression *in vivo*
- IL-2 is used clinically for treatment of malignancy

- IL-2 administration was explored for CD4 T cell restoration in SILCAAT and ESPRIT clinical trials
  - *Despite CD4 T cell expansion, no clinical benefits were observed*

IL-2 administration and frequency of replication competent HIV in peripheral blood



Median 39 months receiving IL-2 iv or sq in doses 3-18 million units per day, in 5-day cycles every 8 weeks

Kovacs, NEJM 1995; Patki, JCI 1996; Davey, JID 1997; Chun, JEM 1998; Chun, Nat Med 1999; Dybul, JID 2002; INSIGHT-ESPRIT, NEJM 2009; Raeber, Sci Transl Med 2022 (e.g.)

Our IL-2 treatment trial (AIDS 400)

Participant Characteristics:

- Nine men (7 White, 2 African-American)
- Median Age – 47 yrs (35-64)
- Median CD4 – 675/uL (478-1230)
- Median CD8 – 647/uL (284-1120)
- Plasma HIV – 2 participants had measurable levels at screen (21, 34 copies/mL)

Original Design:

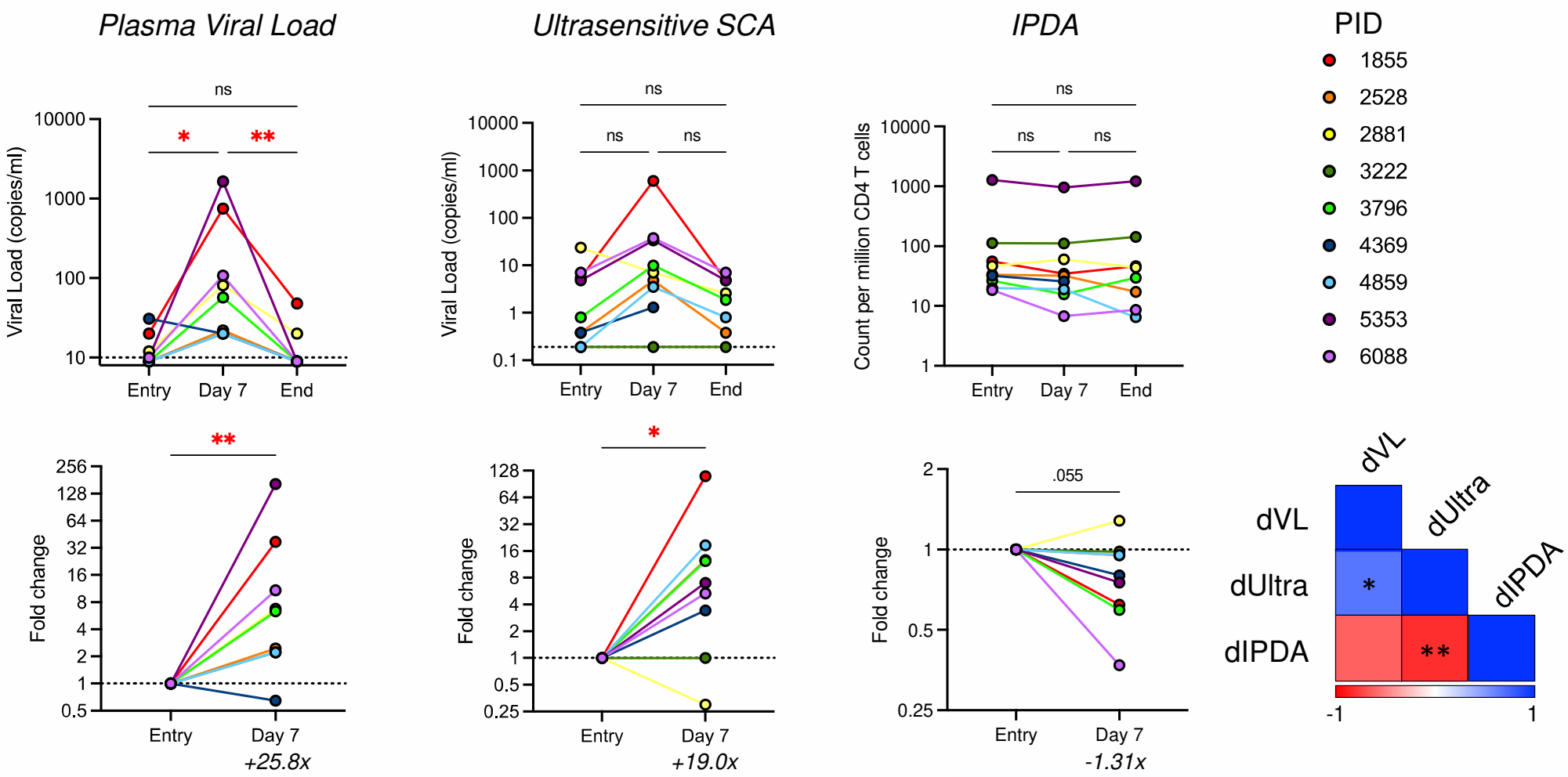
- Eight 4-day cycles of 5 million units twice-daily subcutaneous rIL-2 administration, eight weeks apart

What happened:

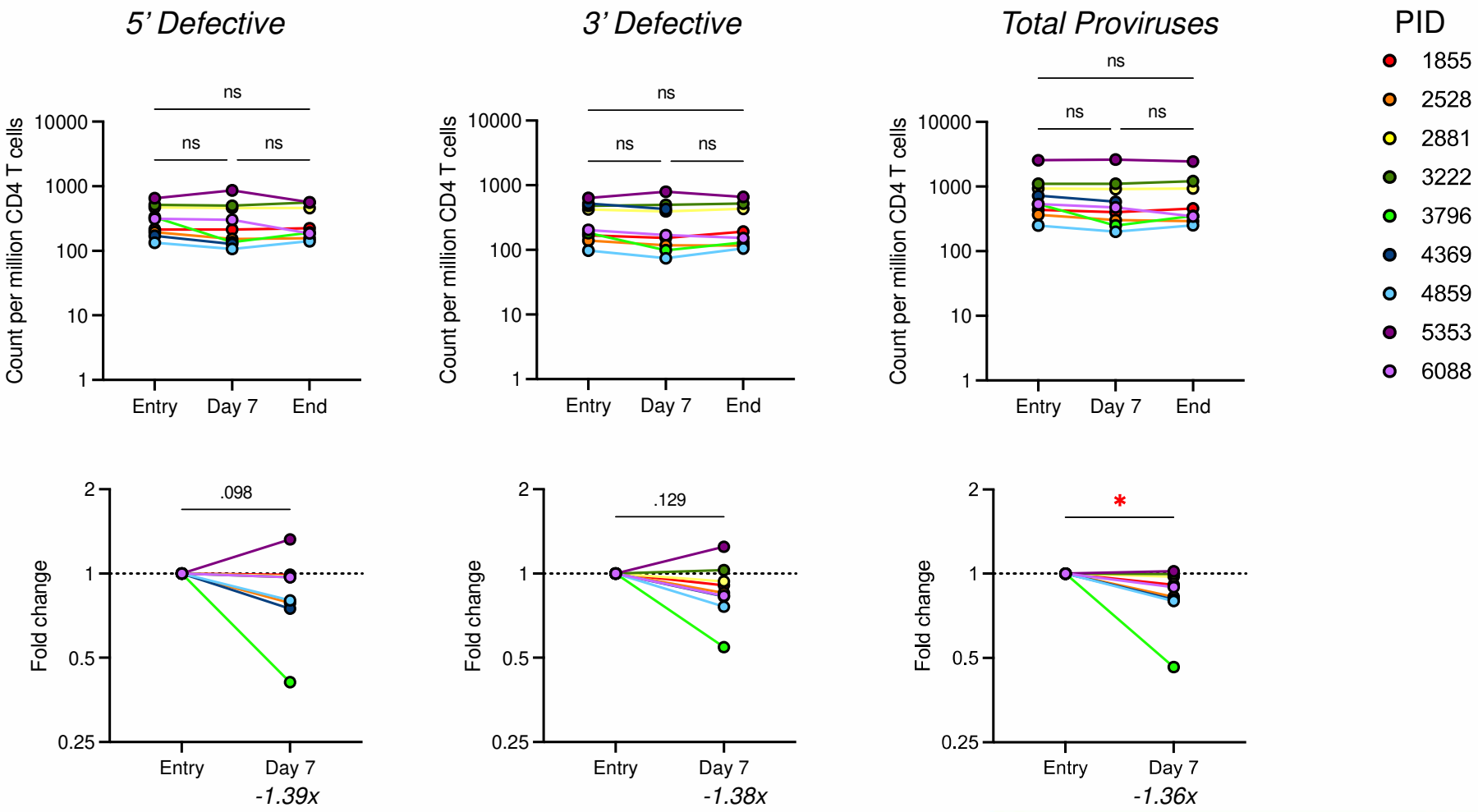
- All 9 participants completed the first 4-day cycle, and some received further cycles of rIL-2
- Study was terminated in consultation with the External Safety Monitoring Committee because of toxicities in 3 participants:
  - Systemic inflammation with capillary leak syndrome req. hospitalization (1)
  - Biochemical hypothyroidism (2)

This presentation focuses only on virologic and immunologic findings at three timepoints: (1) Entry, (2) Day 7 of first rIL-2 cycle, and (3) end-of-study off treatment

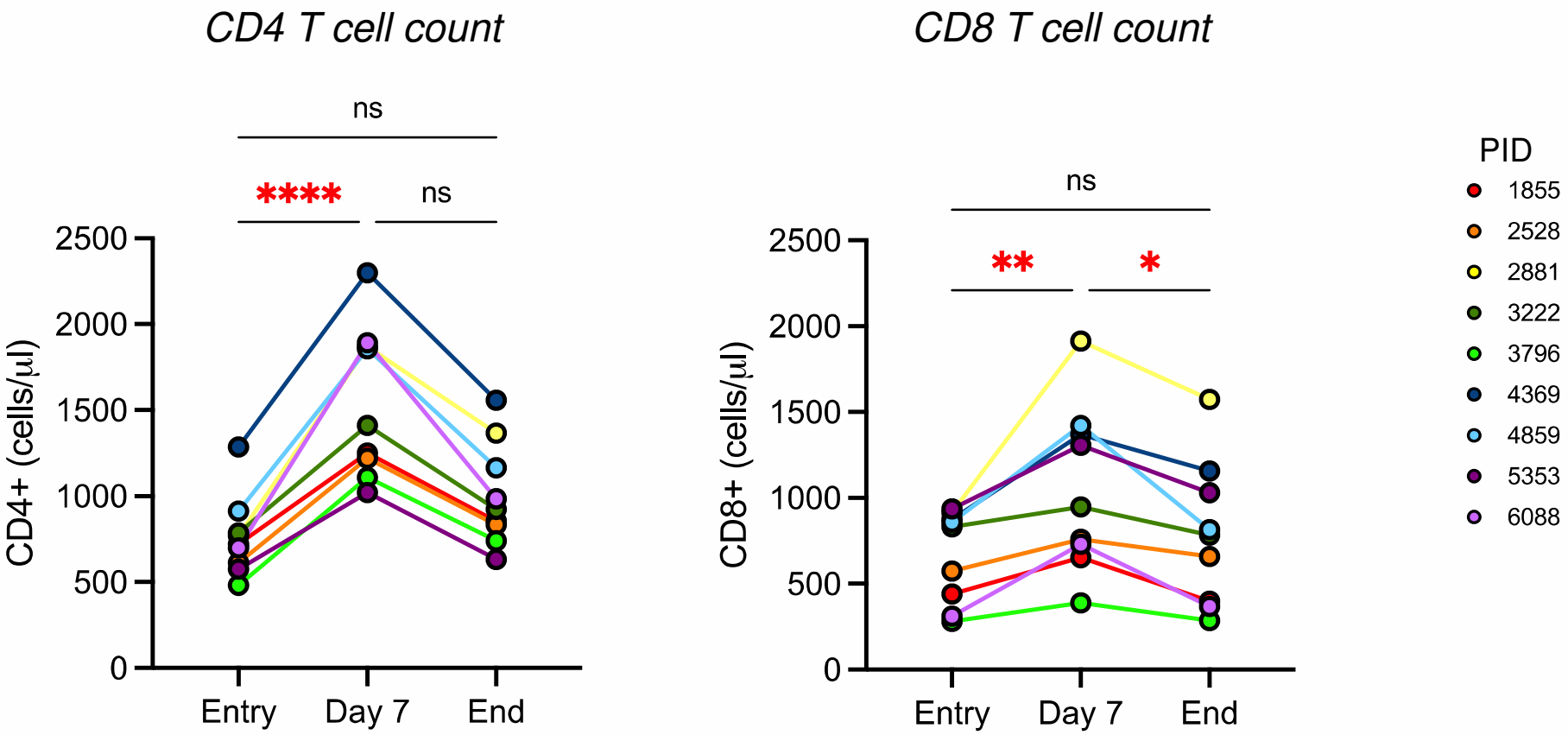
IL-2 potently induces HIV reactivation in vivo



Possible reduction of HIV reservoir by IL-2



IL-2 increases CD4 and CD8 T cell numbers

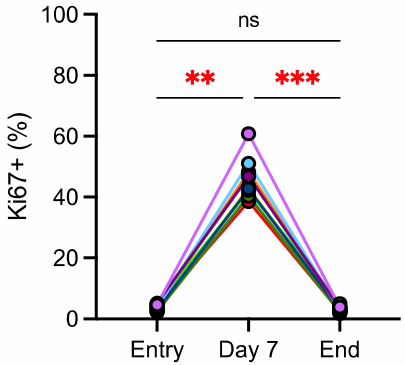


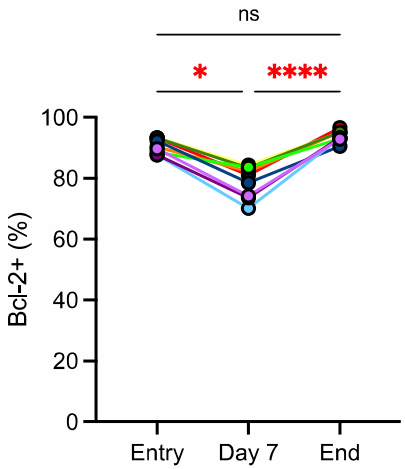
IL-2 promotes cell cycle entry and loss of Bcl-2 in T cells

Ki67+ (cell cycle entry)

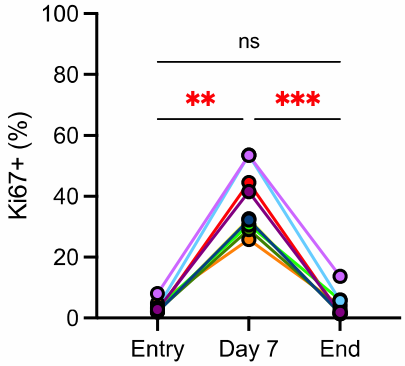
Bcl-2+ (pro-survival)

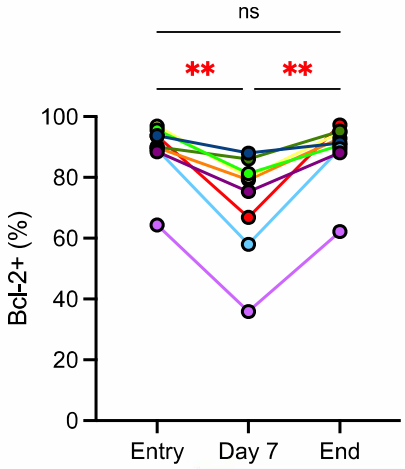
CD4





CD8

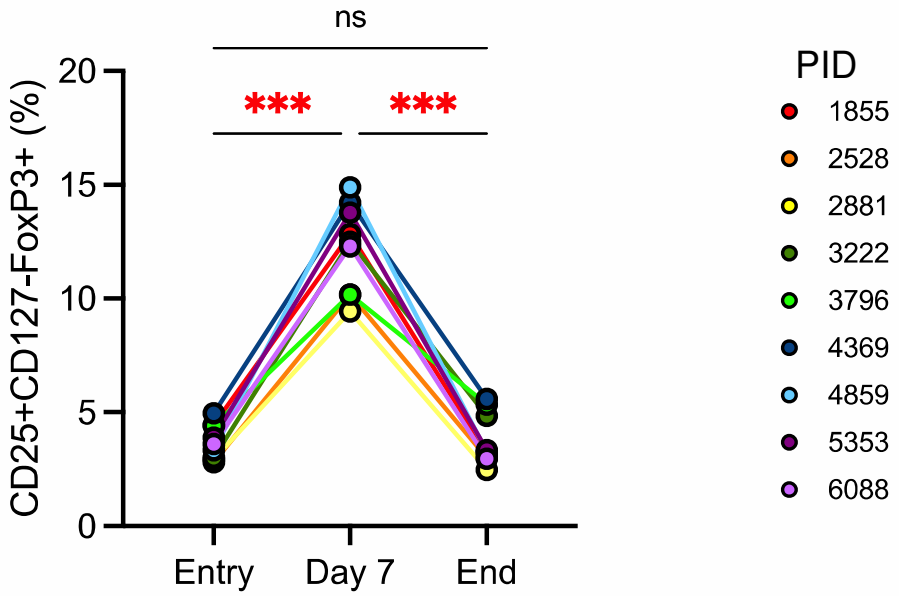




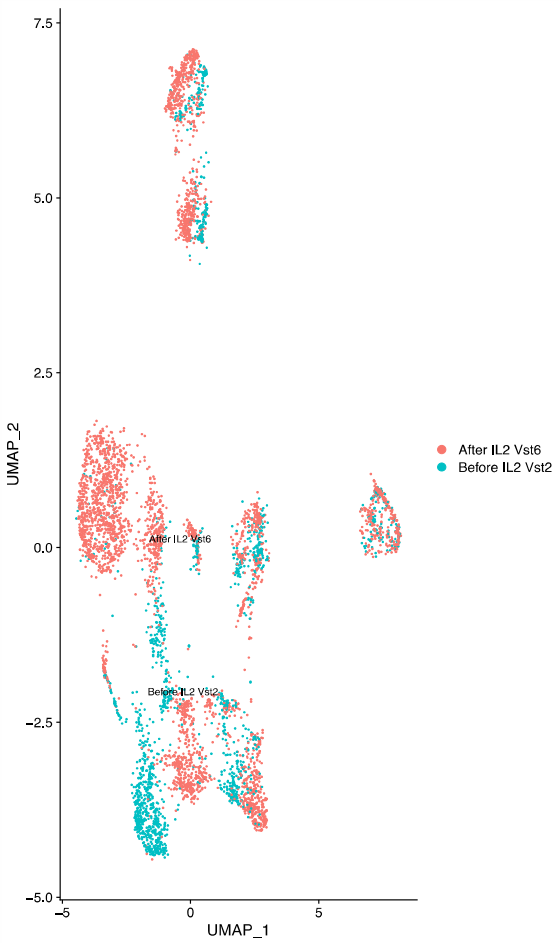
PID
- 1855
- 2528
- 2881
- 3222
- 3796
- 4369
- 4859
- 5353
- 6088

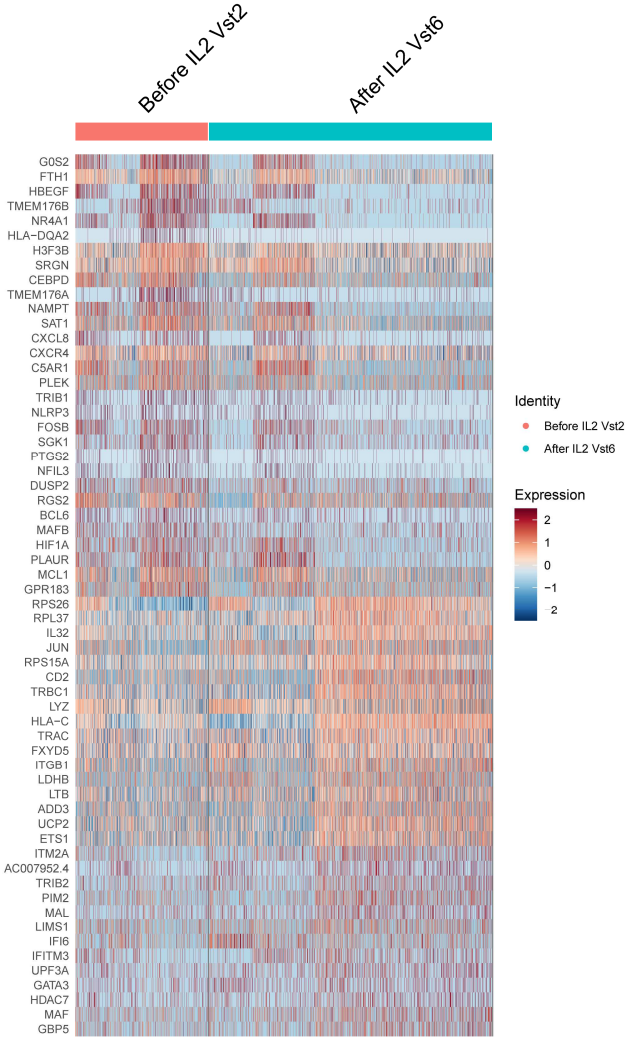
IL-2 promotes Treg-like CD4 T cell phenotype

CD4
CD25+CD127-FoxP3+
(Treg phenotype)



scRNA-seq identifies IL-2 response signature among CD4 T cells

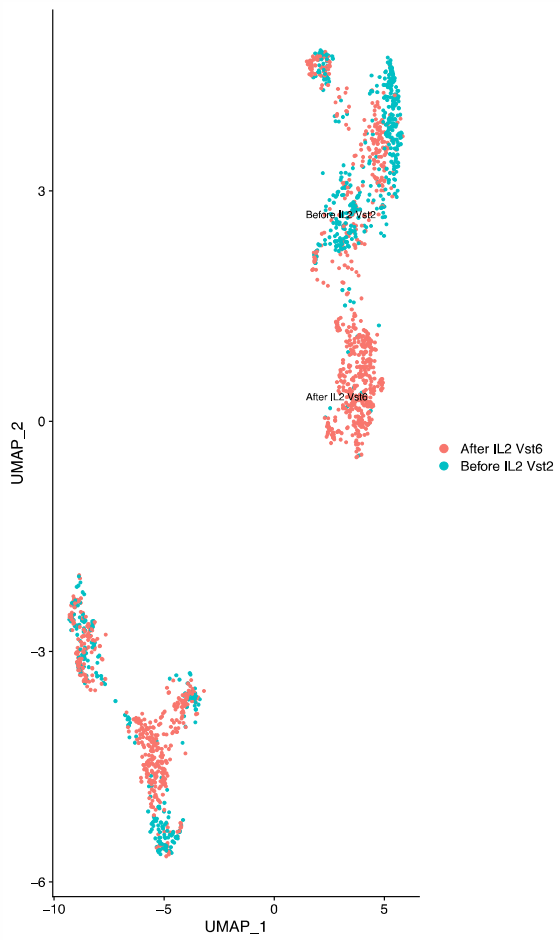


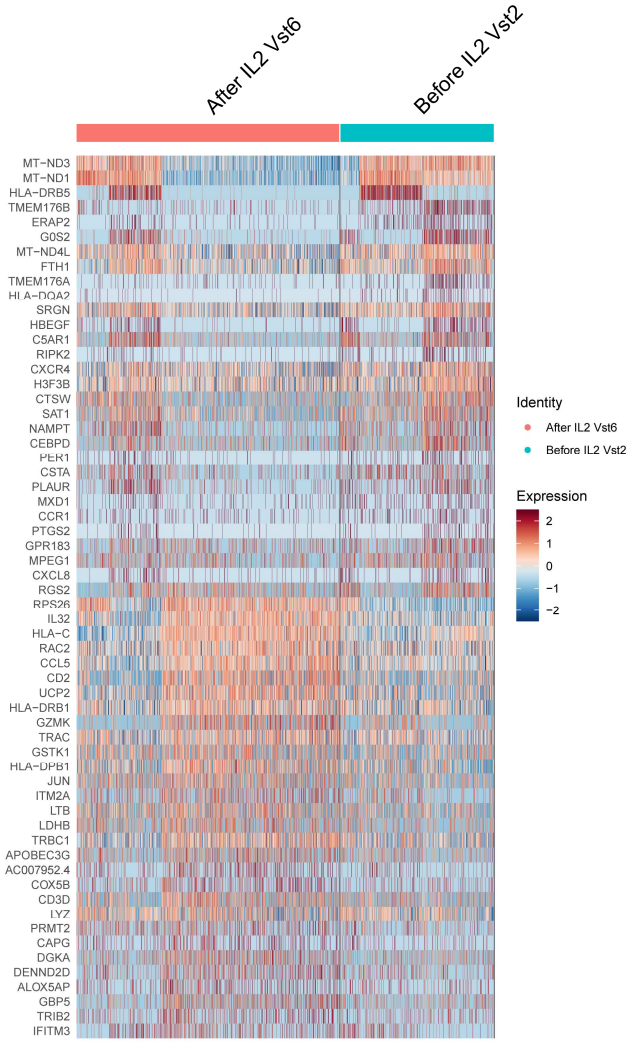


Some notable genes upregulated with IL-2:

- IL32
- LTB
- LYZ
- CD2
- TCF7

scRNA-seq identifies IL-2 response signature among CD8 T cells

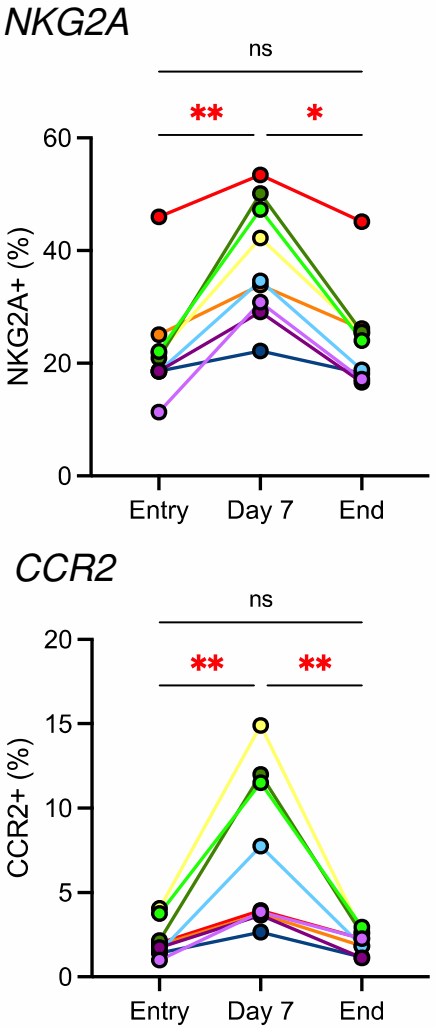


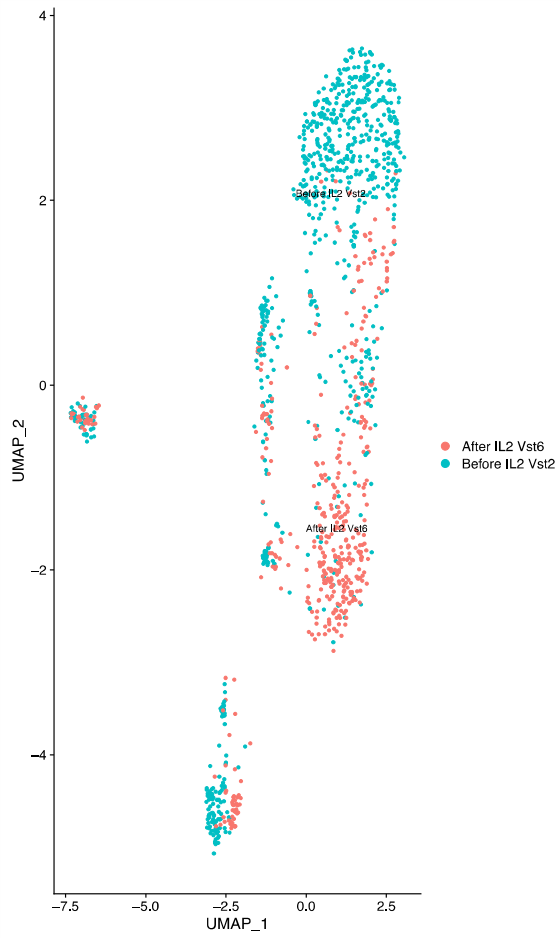


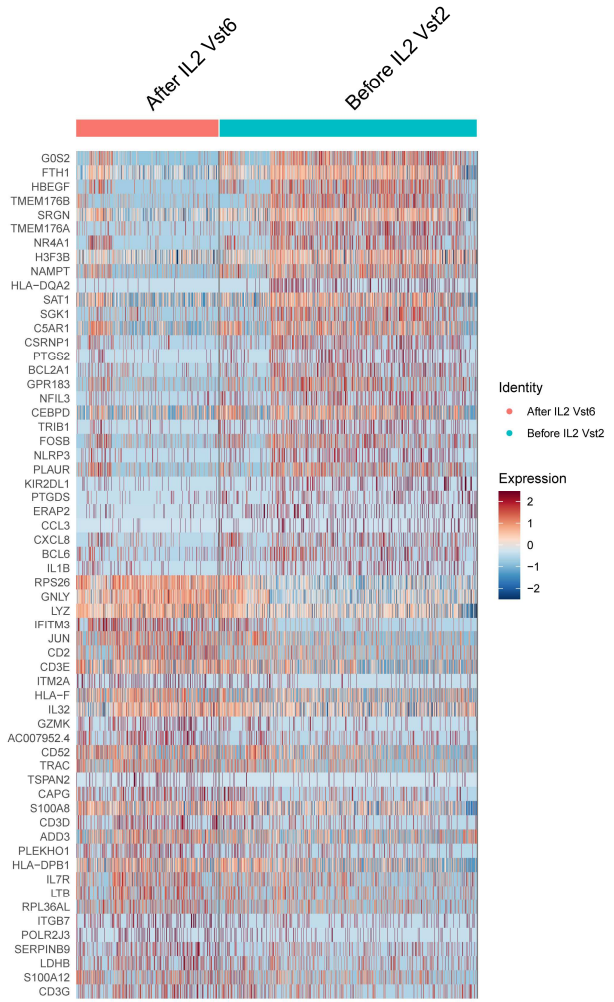
Some notable genes upregulated with IL-2:

- IL32
- LTB
- LYZ
- CD2
- GZMK

Phenotypic and transcriptional changes among NK cells



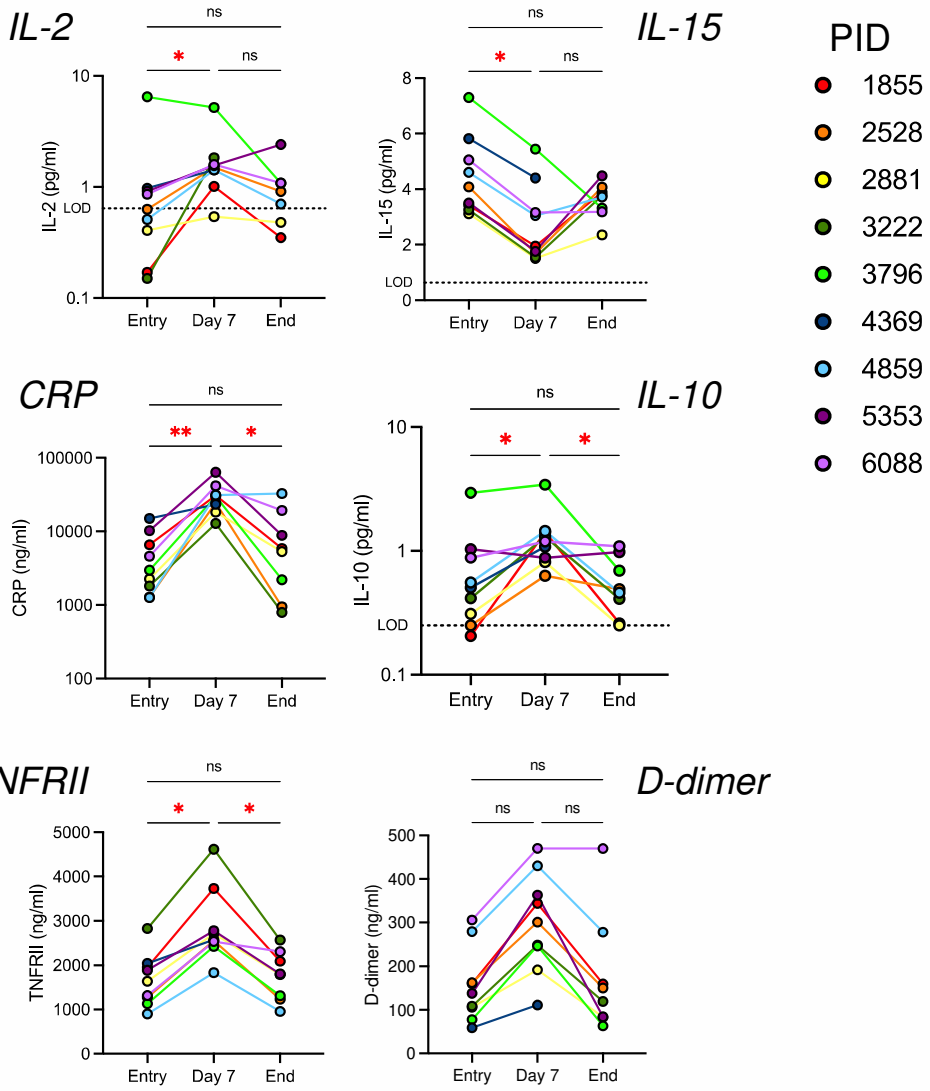


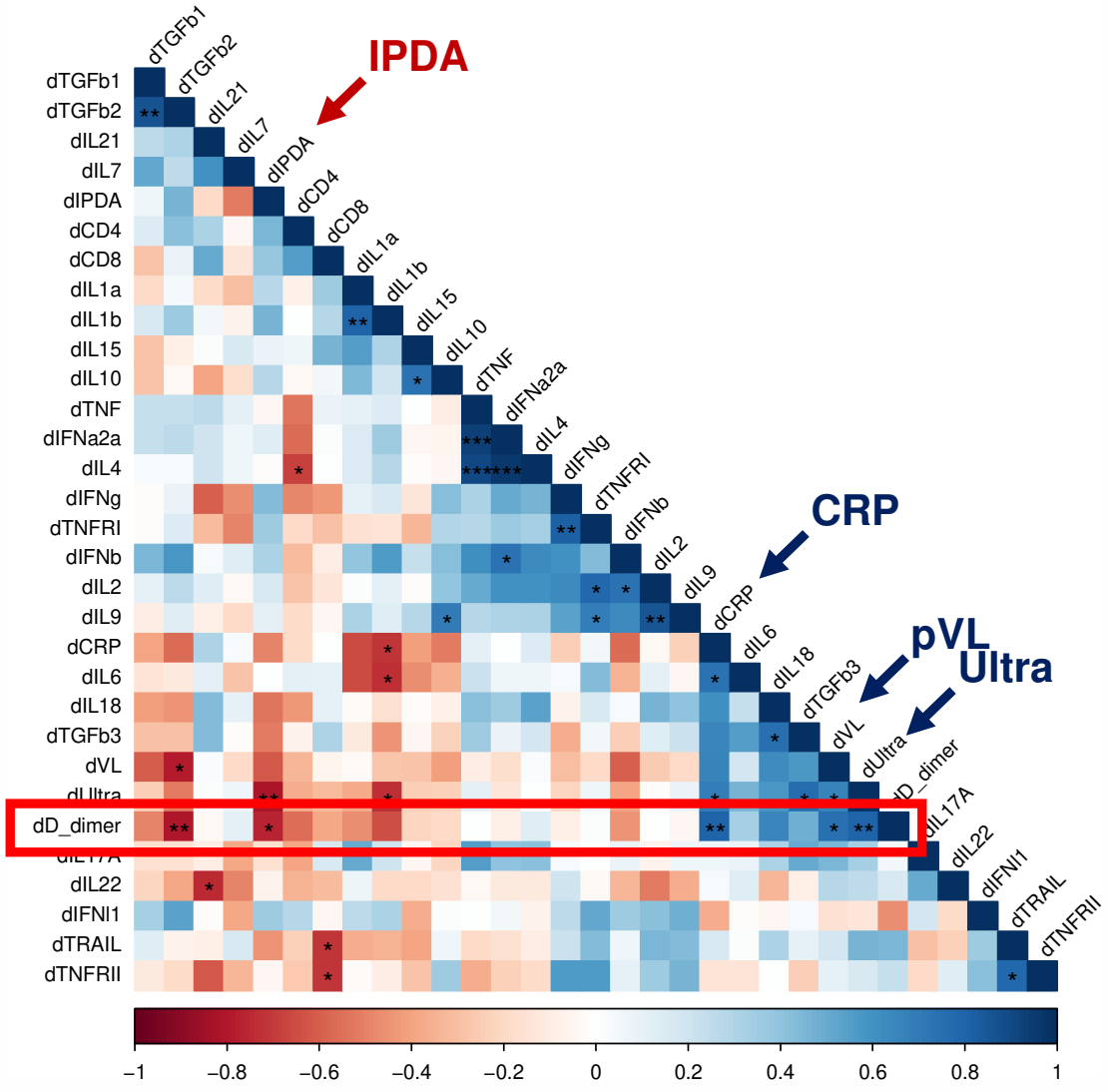


Some notable genes upregulated with IL-2:

- IL32
- LTB
- LYZ
- CD2
- GZMK
- GNLY

IL-2 triggers a systemic inflammatory response





Summary

- IL-2 administration was not well-tolerated in this small study among people with well-controlled HIV
- During the first cycle of IL-2 administration:
  - CD4 and CD8 T cell counts rose
  - “Treg-like” CD4 T cell proportions increased
  - Cycling of CD4 and CD8 T cells increased
  - Overall reduction in expression of the pro-survival element Bcl-2
  - Proportions of NK cells expressing NKG2A and CCR2 increased
  - Some inflammatory mediators, acute phase proteins and coagulation markers increased
  - Plasma levels of HIV significantly increased
  - Intact proviral DNA in circulating CD4 T cells tended to decrease (in 8 of 9 participants)

- **Key question(s)** being asked:
  - *Does IL-2 administration decrease HIV reservoir size?*
- **Key finding(s)** and take-home message:
  - *IL-2 potently induced plasma HIV viral load in participants with well controlled viremia on ART (trend toward decreased viral reservoir)*
  - *IL-2 activated and expanded T cells and activated NK cells*
  - *IL-2 administration was not well-tolerated*
- What are the **next steps**?
  - *Further study of IL-2 strategies in HIV cure research is warranted, such as using a lower dose of IL-2 or use in combination with other strategies*

Acknowledgments

CWRU:
Michael Lederman
Benigno Rodriguez∞
Jeffrey Jacobson
Scott Sieg
Jonathan Karn

Daniela Moisi
Brian Clagett
Konstantin Leskov

Jane Baum

Doctors, Nurses, and Participants!

Accelevir:
Gregory Laird

Funding:
Gilead *(to MML)*

Timothy Ray Brown and Benigno Rodriguez

∞*Deceased*