HIV-associated alterations of gut Th17 cell function correlate with microbial translocation and immune activation

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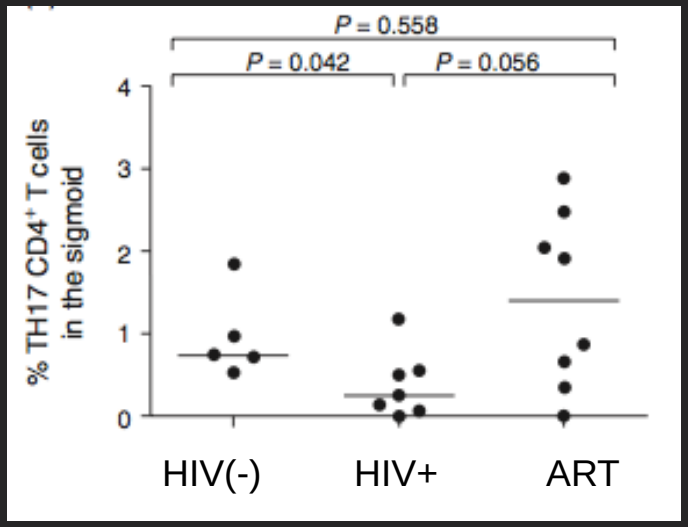
Th17 cells

- CD4 T cells that produce IL-17a.
- Provide immune defense against extracellular bacteria/fungi and maintain the gut epithelial barrier.
- Produces a combination of cytokines, both pro-inflammatory and regulatory.
  - TNF-α, IFN-γ, IL-22, and IL-10.
- Not all Th17 cells are the same.
  - *S. aureus* infection IL-17a and IL-10; *C. albicans* = IL-17a and IFN-γ (Zielinski. Nature, 2012).
  - Varies depending on microbial environment and cytokine milieu.

HIV and Th17 cells



- Gut Th17 cells are depleted in HIV (express high level of CCR5 and $\alpha_4\beta_{7)}$.
- Th17 depletion associated with microbial translocation and immune activation.
- Antiretroviral therapy (ART) can restore gut Th17 numbers, but what about their function?

Chege. AIDS, 2011

Hypothesis

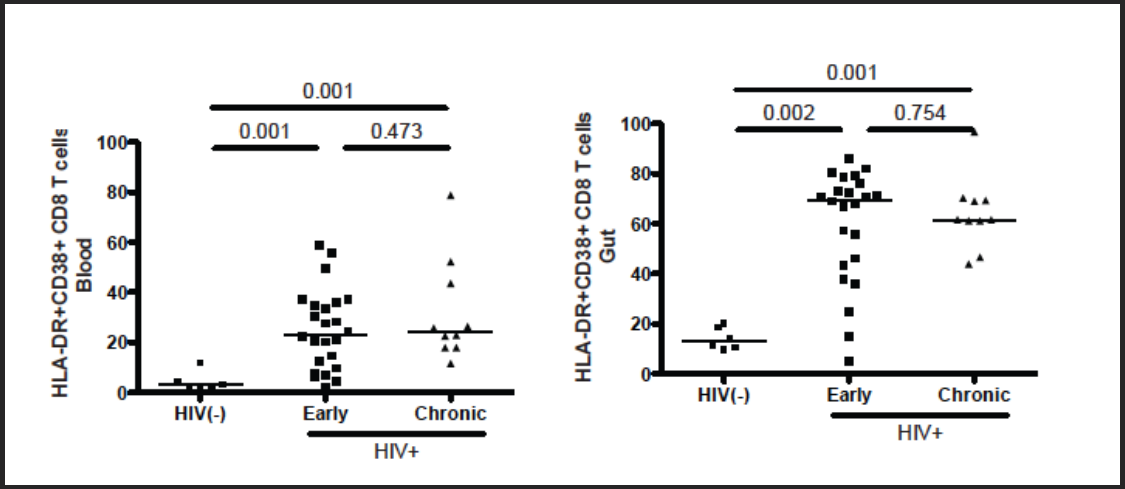
1. Functional alteration of gut Th17 cells during HIV infection contributes to microbial translocation and HIV disease progression.

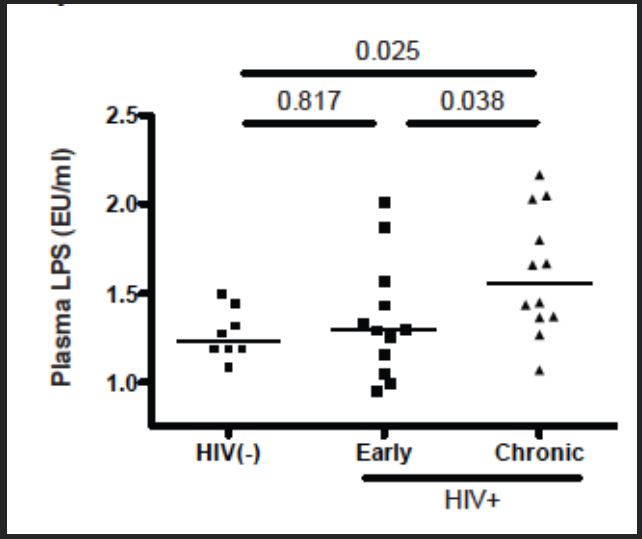
2. Functional restoration of gut Th17 cells will be slow and incomplete upon ART initiation, contributing ongoing microbial translocation and immune activation.

Method

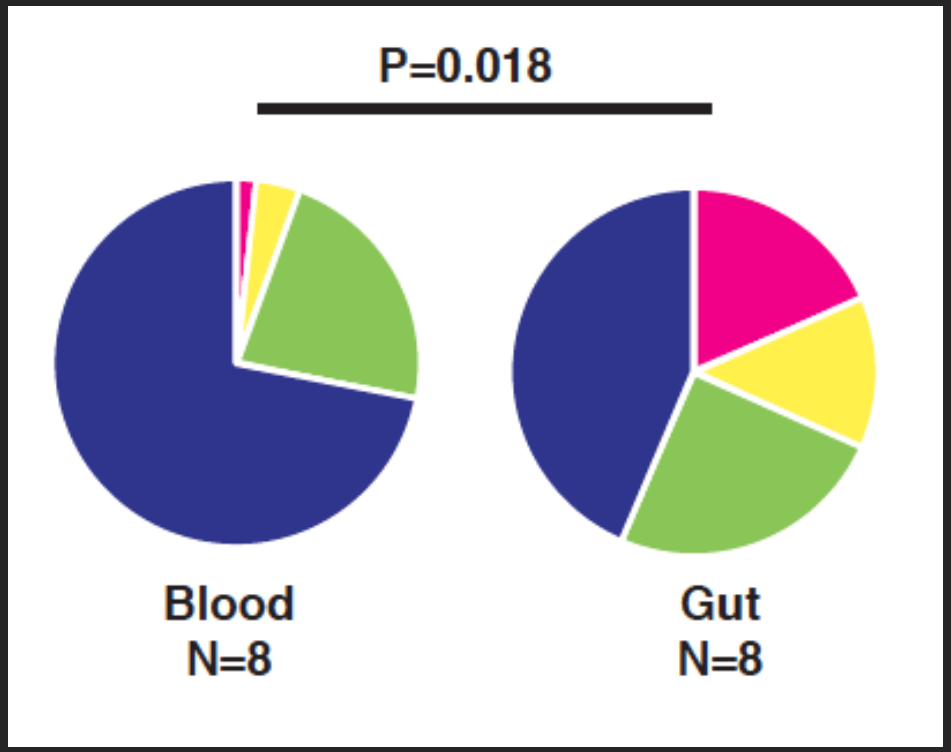
- Recruited 60 men from Toronto, Ontario
  - HIV (-), N=9
  - Early HIV+, N=24
  - Chronic HIV+, N=12
    - Short-term ART, N=5 (median, 13 months)
  - Long-term ART, N=15 (median, 13 years)
- Paired blood and sigmoid biopsies collected
- Analysis by flow cytometry

Early and Chronic HIV+



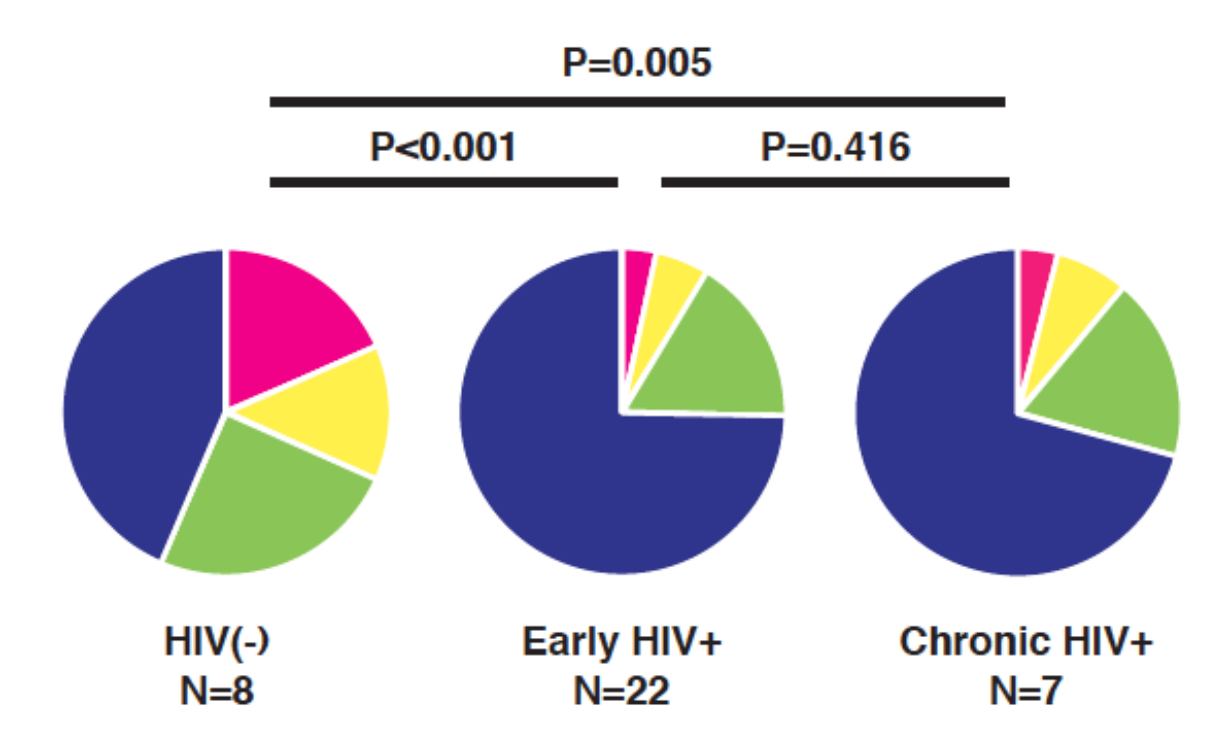


Gut Th17 cells more functional in HIV(-)



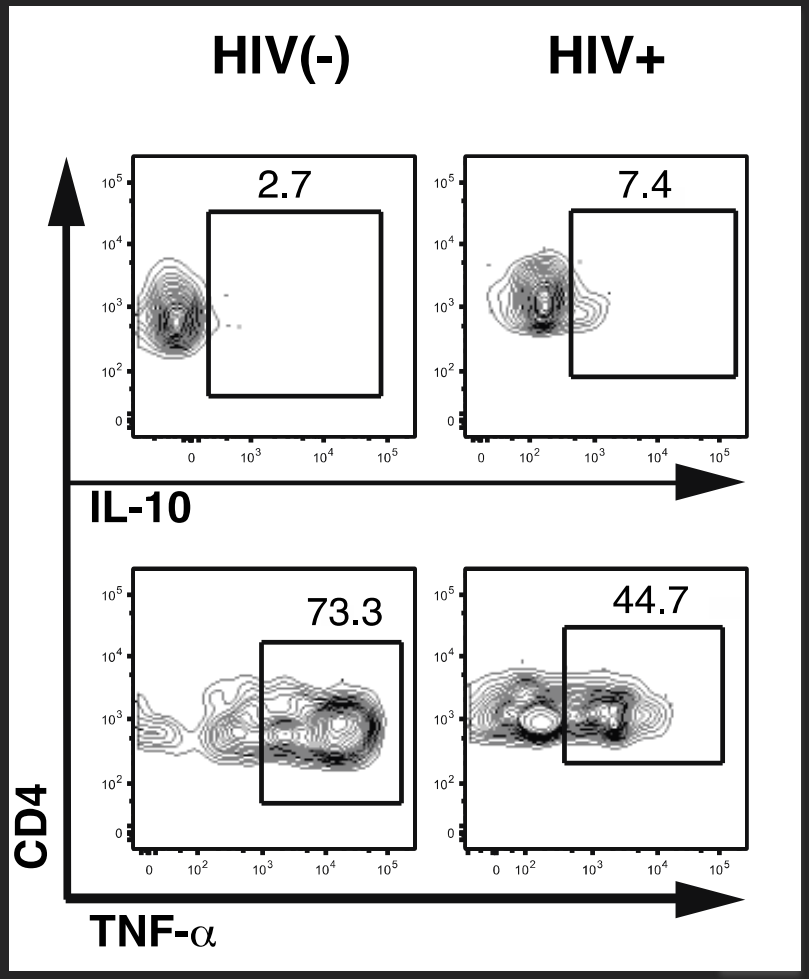
TNF-α, IFN-γ, and IL-22

HIV and gut Th17 polyfunction



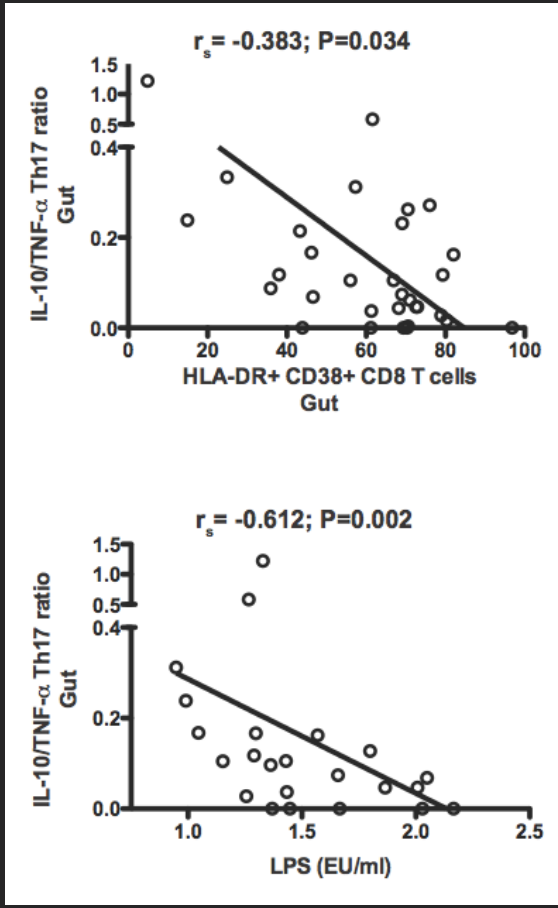
- No changes in blood Th17 polyfunction

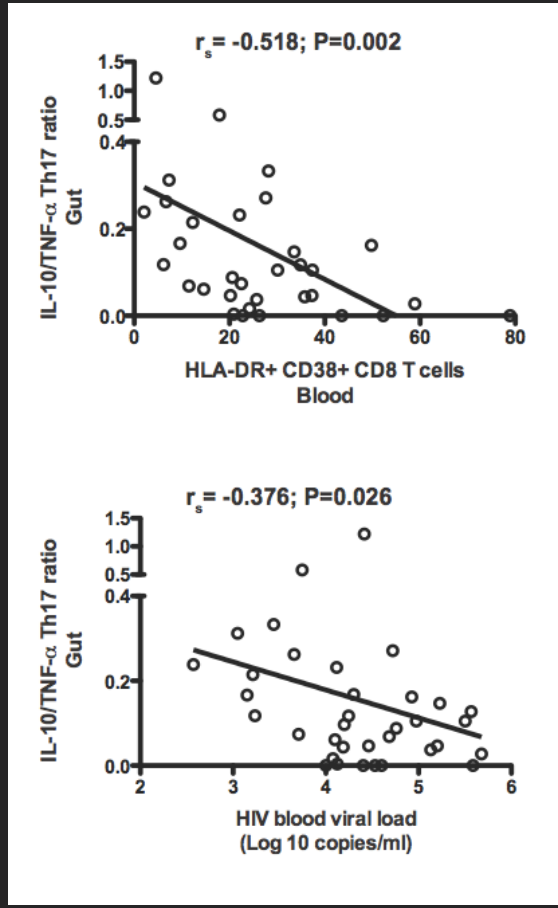
“Immunoregulatory” gut Th17 cells



- Ratio of IL-10/TNF-α producing Th17 cells
- Immunoregulatory gut Th17 cells were increased in HIV+

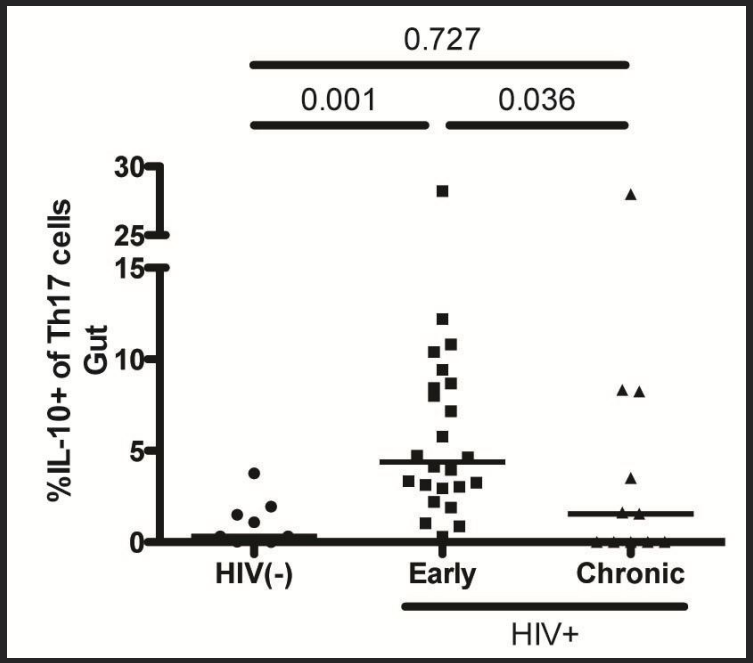
Immunoregulatory gut Th17 skewing

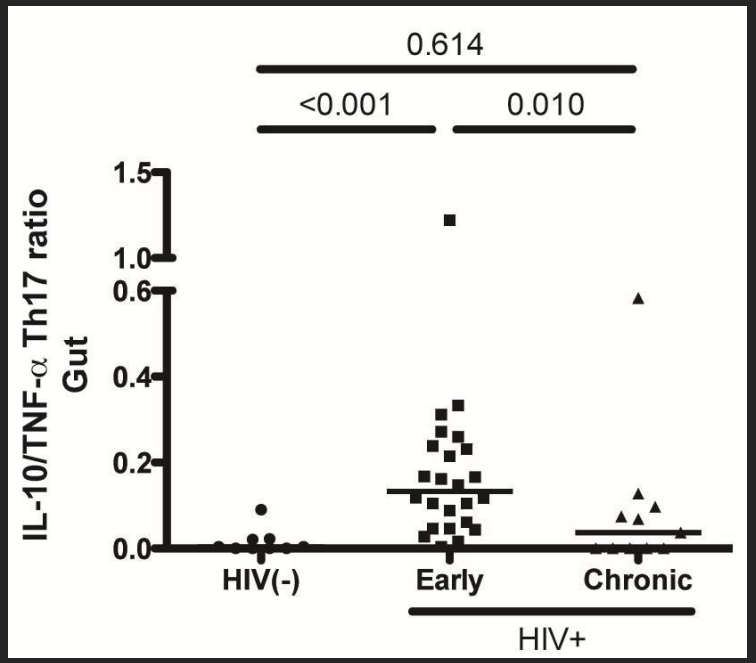




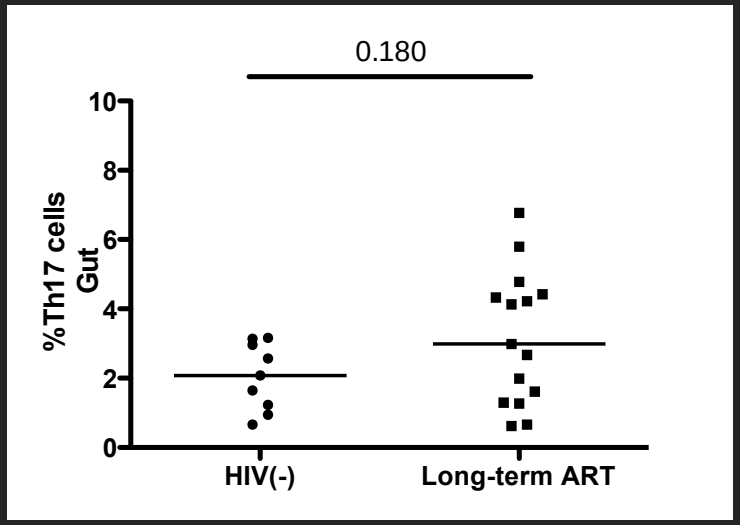
- Correlated inversely with:
  - Gut immune activation
  - Blood immune activation
  - Plasma LPS
  - Blood viral load

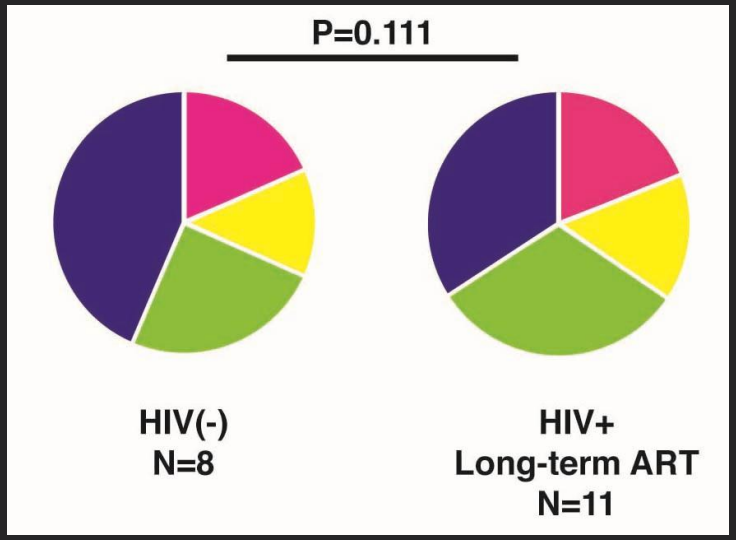
Immunoregulatory gut Th17 cells





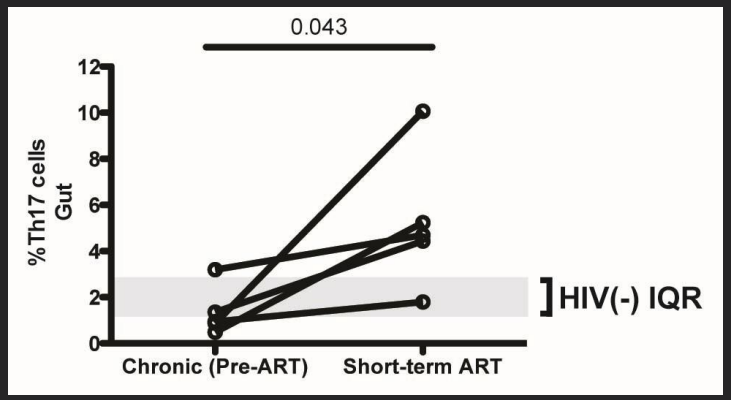
Impact of long-term ART

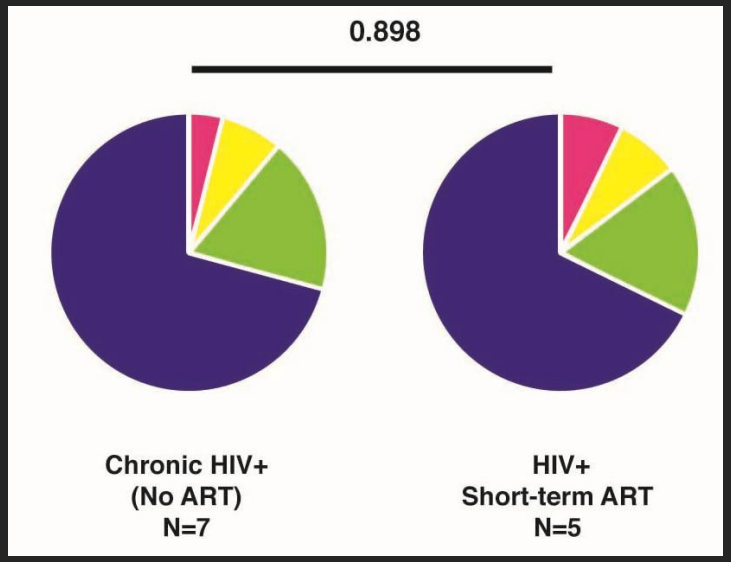




- Gut Th17 cells numbers and function reconstituted.
- Normal plasma LPS and immune activation.

Impact of short-term ART





- Gut Th17 cells numbers (% and absolute number) all restored.
- Th17 function not restored, LPS levels unchanged.
- Partial resolution of immune activation.

Summary

- Gut Th17 polyfunction is lost shortly after HIV infection, even before Th17 cell loss.
- Immunoregulatory skewing of Th17 cells soon after HIV infection may be protective, lost during chronic HIV.
  - Regulate gut inflammation, prevent structural damage, and/or control bacterial infection in the gut mucosa.
- Gut Th17 cell numbers are reconstituted soon after ART, but functional restoration takes much longer.
  - May contribute to ongoing microbial translocation and immune activation.
- Need other means of therapeutics to hasten recovery of gut Th17 function.

Acknowledgments

Kaul lab

Rupert Kaul, Duncan Chege, Prameet Sheth, Sanja Huibner, Kamnoosh Shahabi

University of Toronto

Mario Ostrowski, Gabor Kandel

Maple Leaf Medical Clinic

Colin Kovacs, Erika Benko, Mona Loutfy

Study volunteers

OHTN funding this study

CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

OHTN

Canadian Digestive Health Foundation