

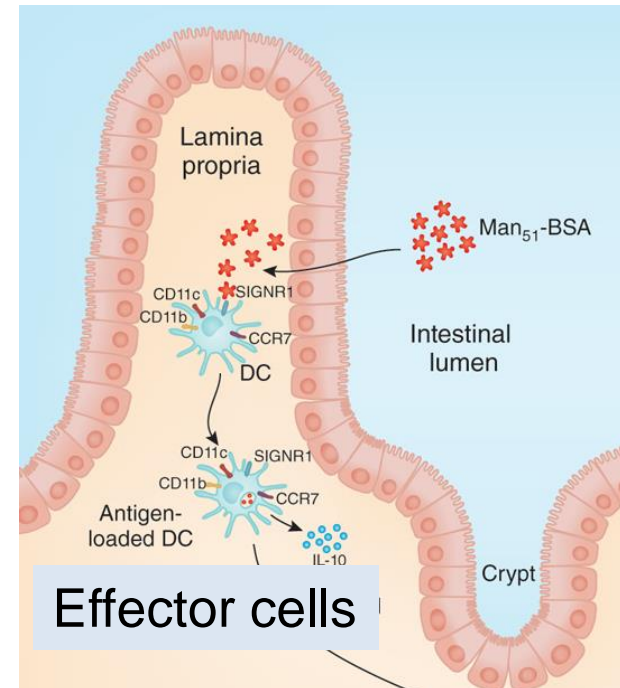


Sigmoid Lamina Propria CD4 T cell Depletion during Acute HIV Infection is Associated with Activated CD4/CD8 T cells, Inflammatory Biomarkers and Viral Burden in the Gut and Blood

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on behalf of the **RV254/SEARCH 010 Study Group**

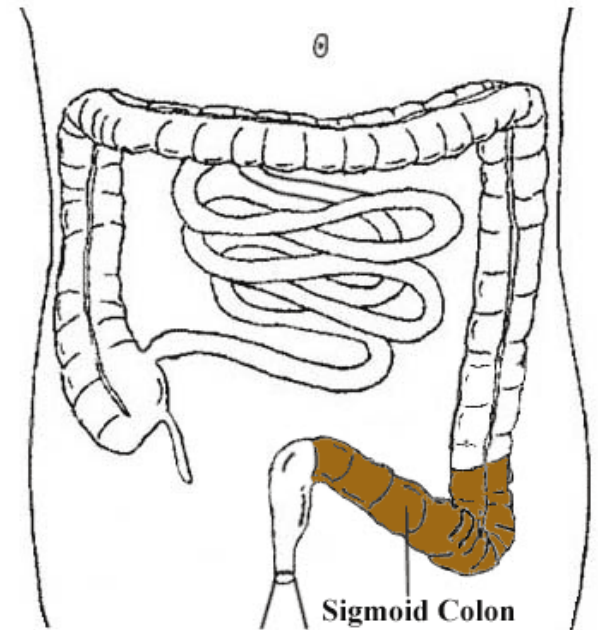
Background

- Lamina propria (LP) CD4 T cells are **depleted early** in HIV infection
 - setting the stage for ongoing immune activation and CD4 depletion in chronic infection
- **Timing of LP CD4 depletion** and factors contributing to this depletion in early acute HIV is not well understood
- **Objective**
 - Investigate LP CD4 depletion during acute HIV infection

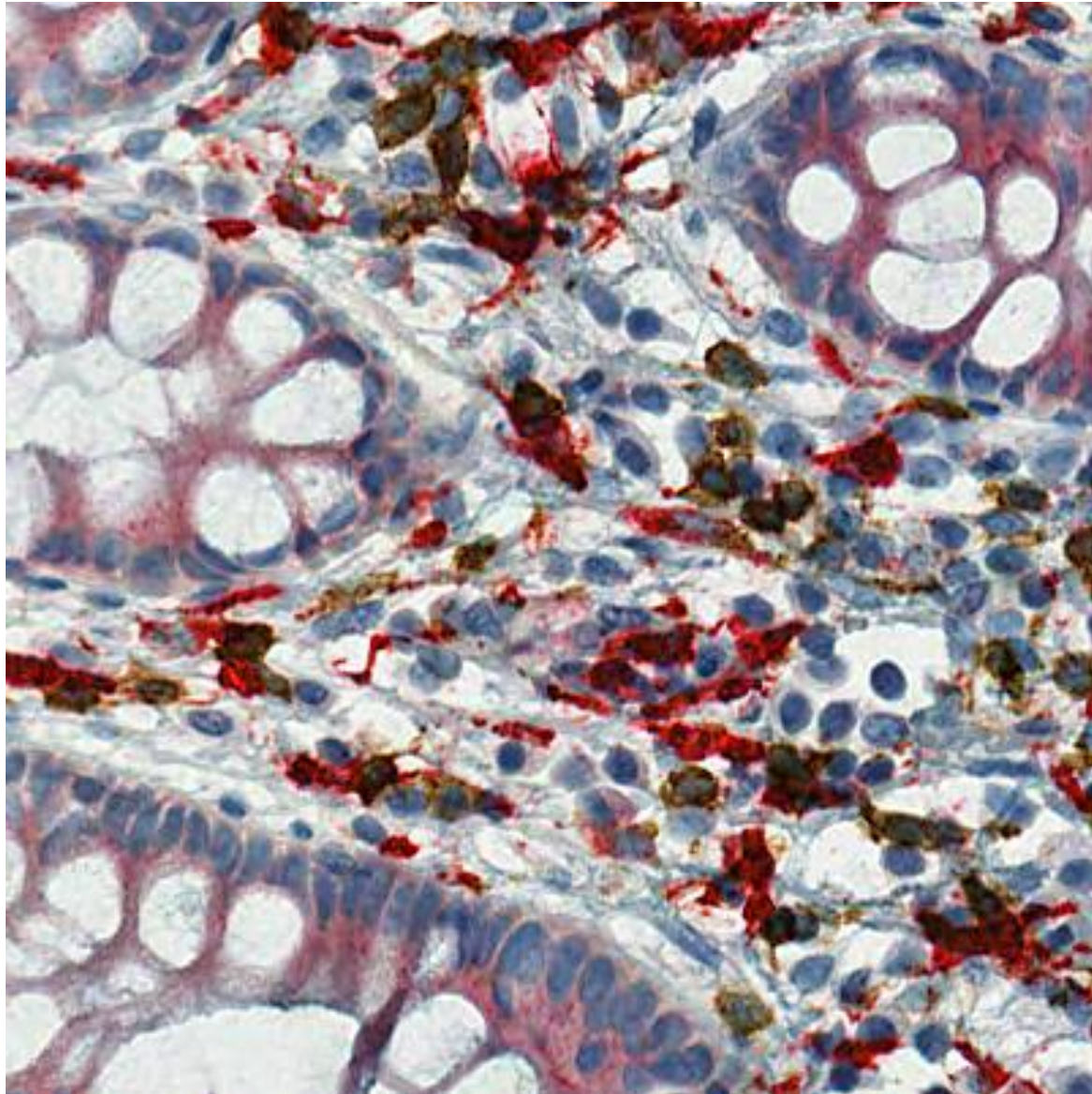


Methods

- Prospective screening and enrollment of acutely HIV-infected subjects in Bangkok, Thailand
 - Enrollment of HIV-uninfected and untreated chronically infected Thais as controls
- Peripheral blood (PB): CD4, HIV RNA, inflammatory biomarkers
 - sCD14, LPS, IFABP, D-dimer, HA, CRP, IL6
TNFa, TNF-RII, MCP, IP10, neopterin
- Sigmoid colon biopsy
 - Flow cytometry for total gut %CD4 and %activated CD4 and CD8+ T cells (MMC)
 - Gut HIV RNA



Immunohistochemistry (IHC) and Image Analysis for LP CD4%



Baseline Characteristics

Values (median)	Acute HIV	Chronic HIV	HIV uninfected
N	38	5	10
Age, years	28	24	31
%male	92%	100%	80%
HIV-related characteristics			
PB CD4, cells/mm ³	437	515	Not applicable
PB HIV RNA, log ₁₀ copies/ml	5.5	4.9	
Gut HIV RNA, log ₁₀ copies/mg tissue	2.8	Not done	
CRF01_AE	83%	Not done	

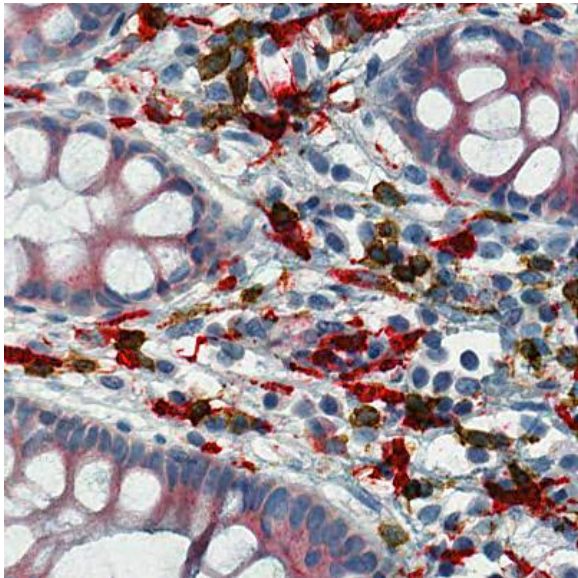
Baseline Characteristics: Acute HIV Infection

AHI staging	Fiebig I	Fiebig II	Fiebig III	Fiebig IV/V
Laboratory testing	RNA+ , p24-, IgM-	RNA+, p24+ , IgM-	IgM+ , IgG-, WB-	IgG -/+ WB IND/ + without p31
N	12	4	18	4
PB CD4, cells/mm ³	560	348	388*	362
PB HIVRNA, log ₁₀ copies/ml	4.3	6.0*	5.6*	5.9*
Gut HIVRNA, log ₁₀ copies/mg tissue	1.7	2.88	3.1*	2.9*

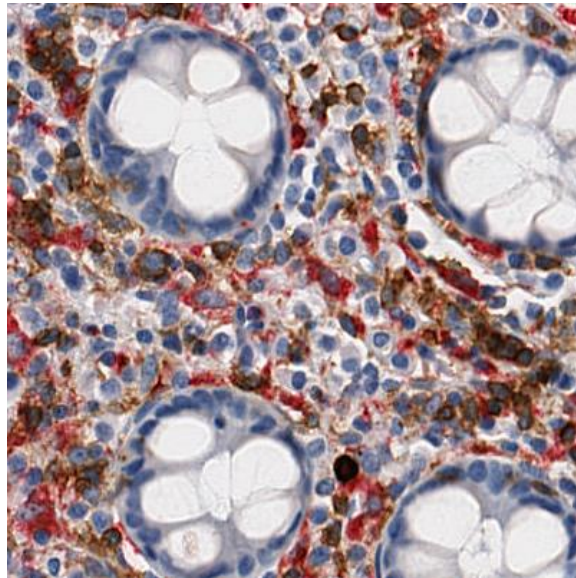
*p < 0.05

Decreases in LP CD4 in Fiebig 3 compared to Fiebig 1 and HIV- control

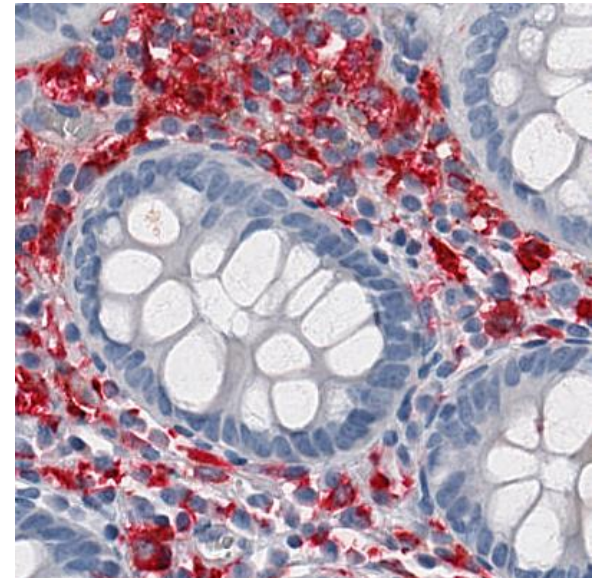
CD4+T cells/Myeloid cells



HIV- Control

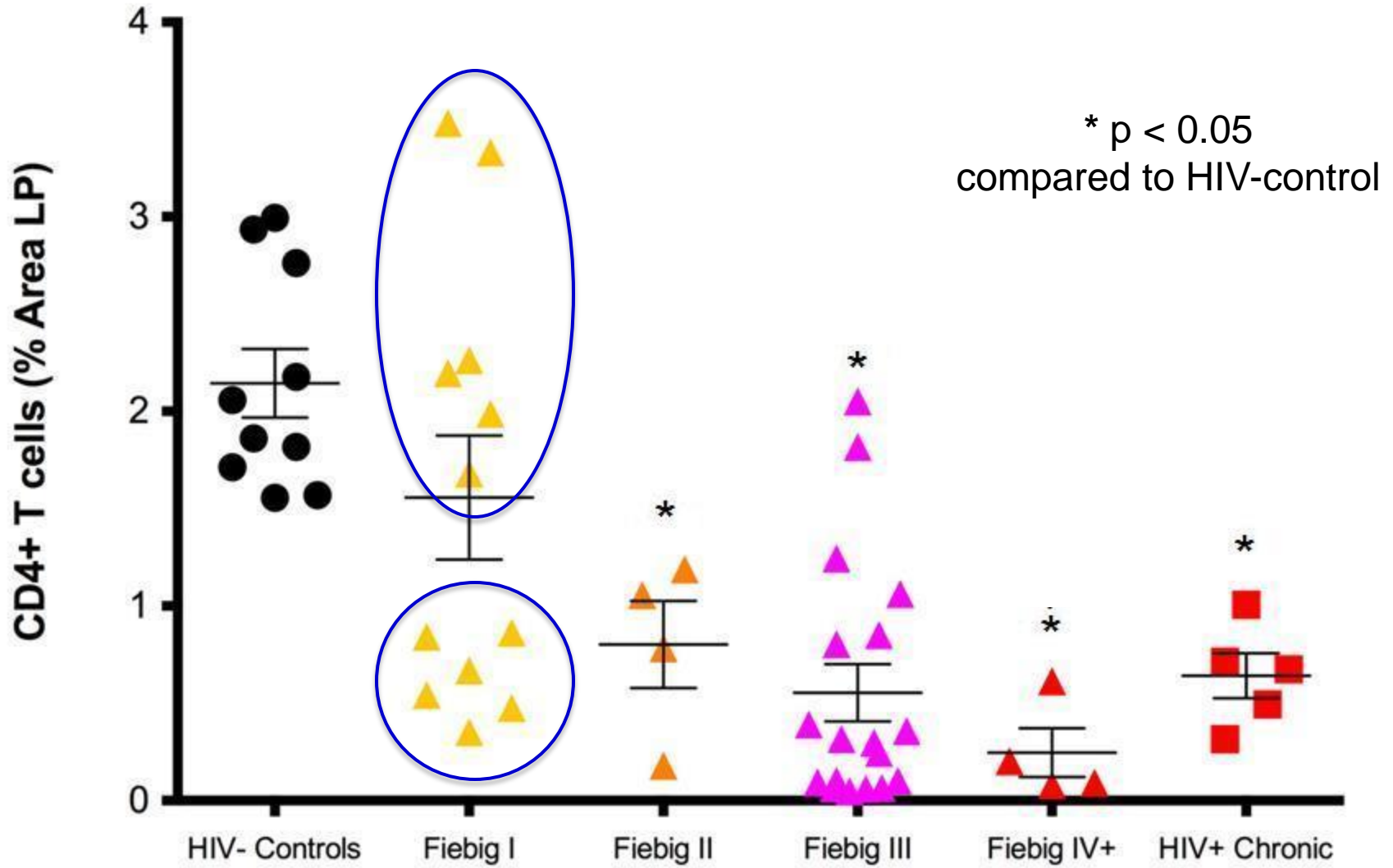


Fiebig 1



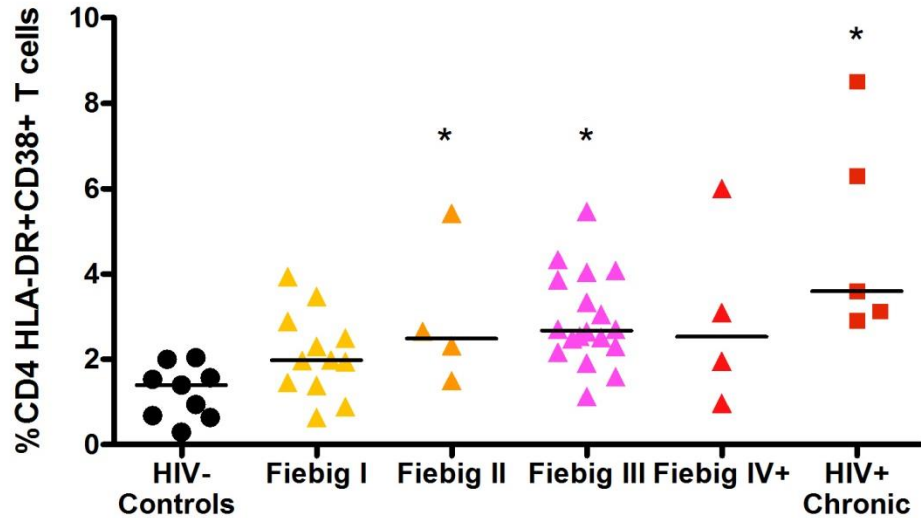
Fiebig 3

Lamina Propria CD4 by IHC

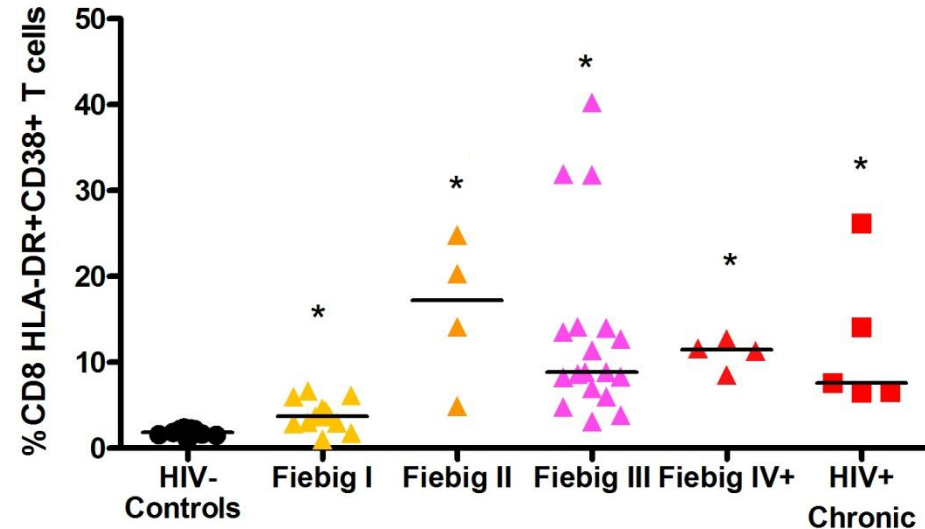


Flow cytometry (MMC)

Gut T cell activation during acute HIV infection



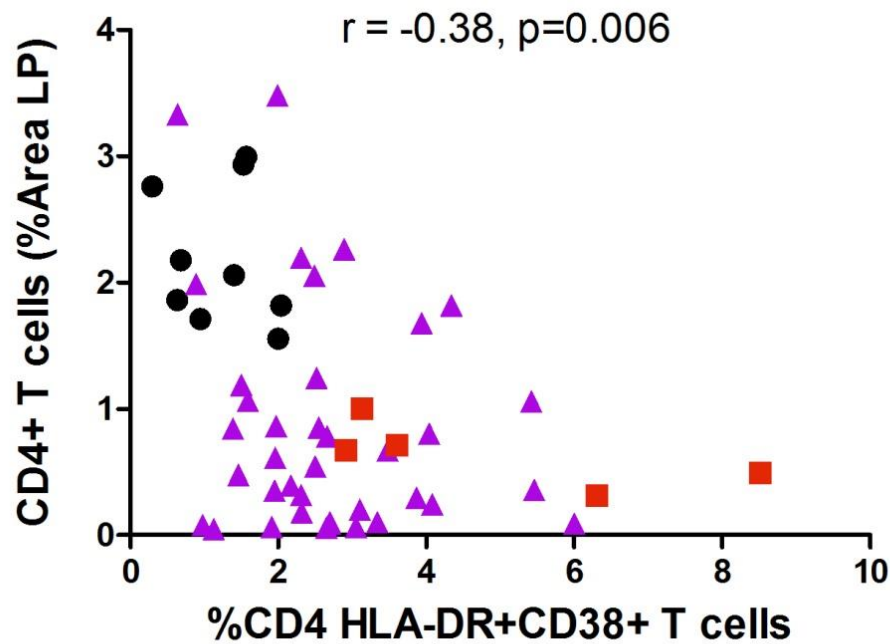
CD4+HLADR+38+



CD8+HLADR+38+

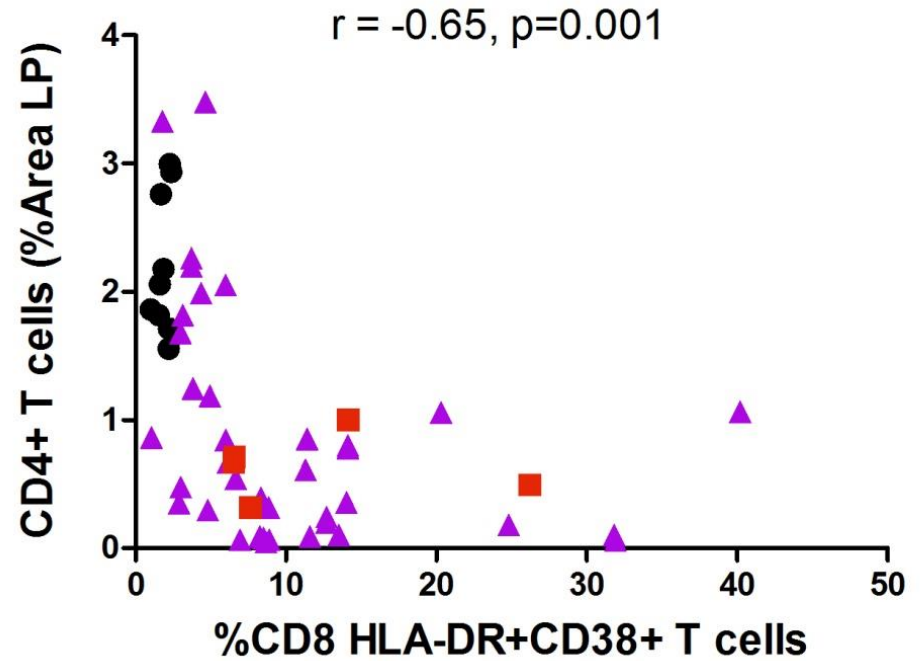
* p < 0.05 compared to HIV-control

Decreases of LP CD4 T cells correlated with colonic mucosal T cell activation



● HIV-Controls ■ HIV+Chronic ▲ Acute

CD4+HLADR+38+

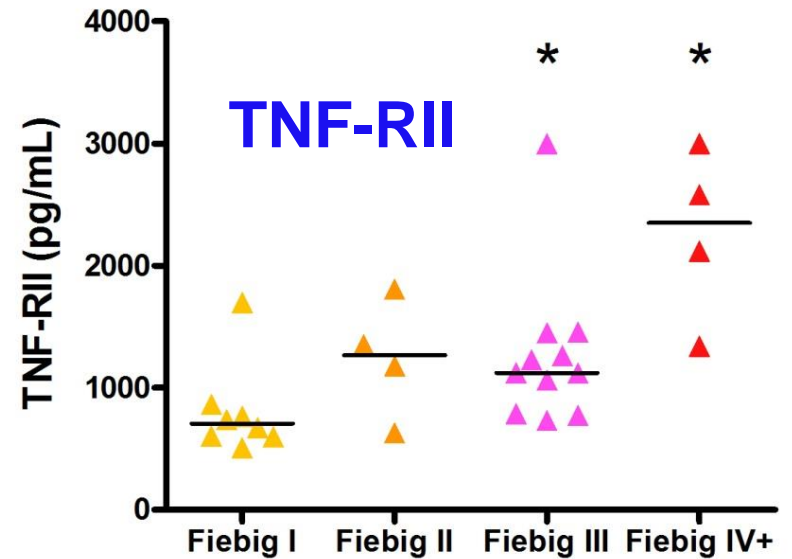
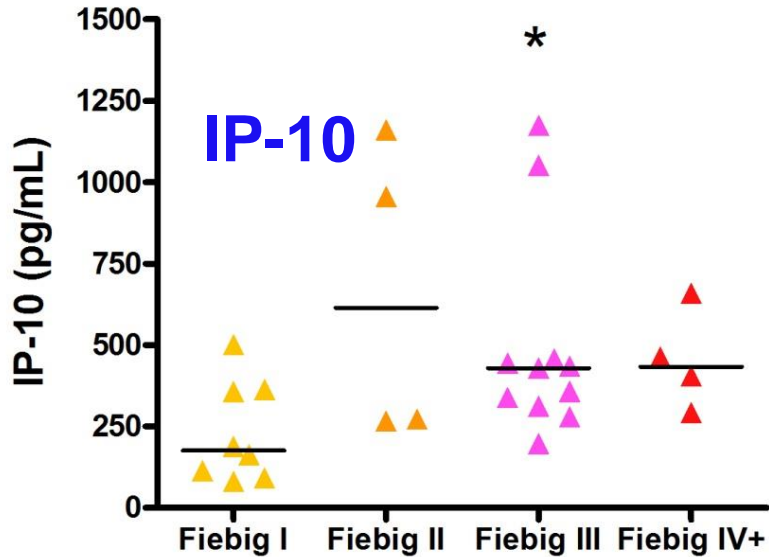
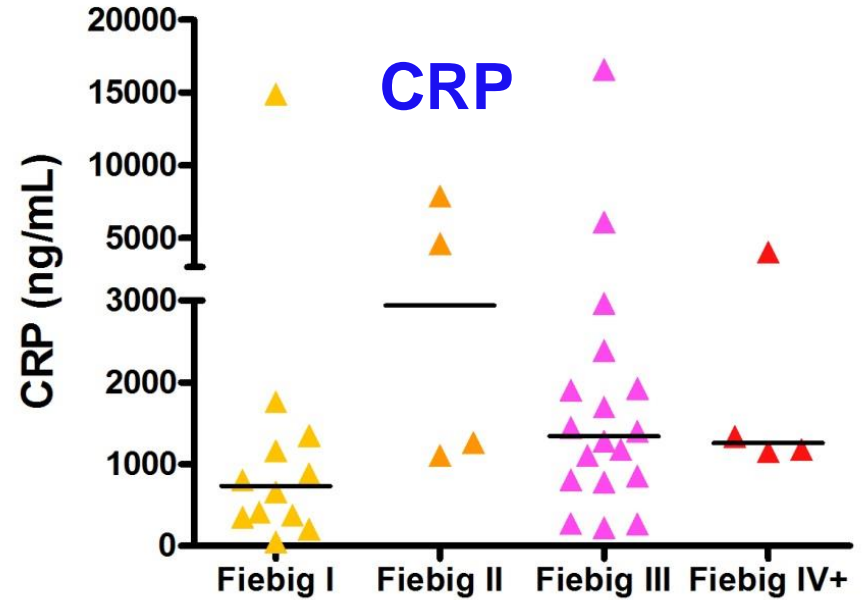
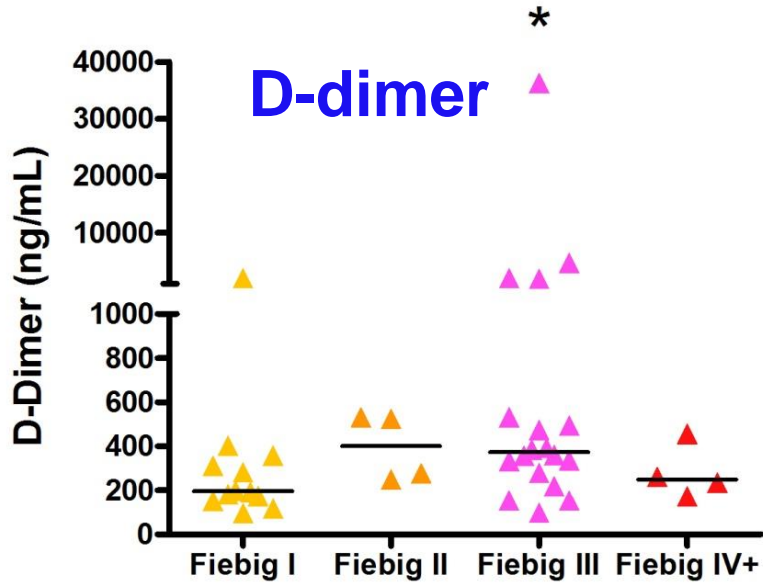


● HIV-Controls ■ HIV+Chronic ▲ Acute

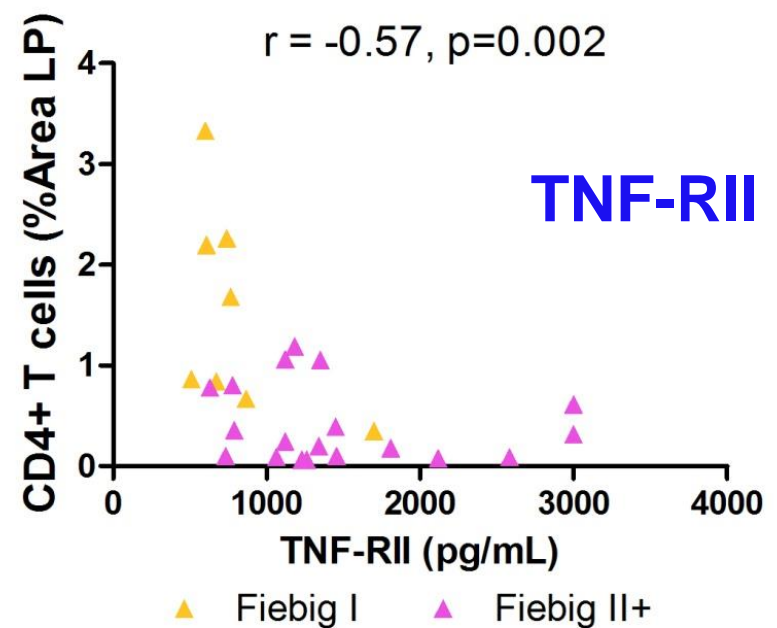
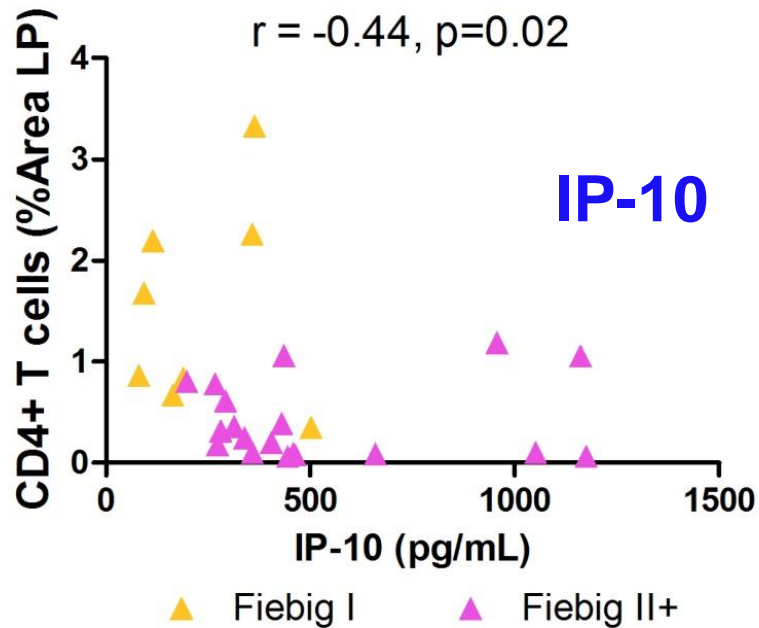
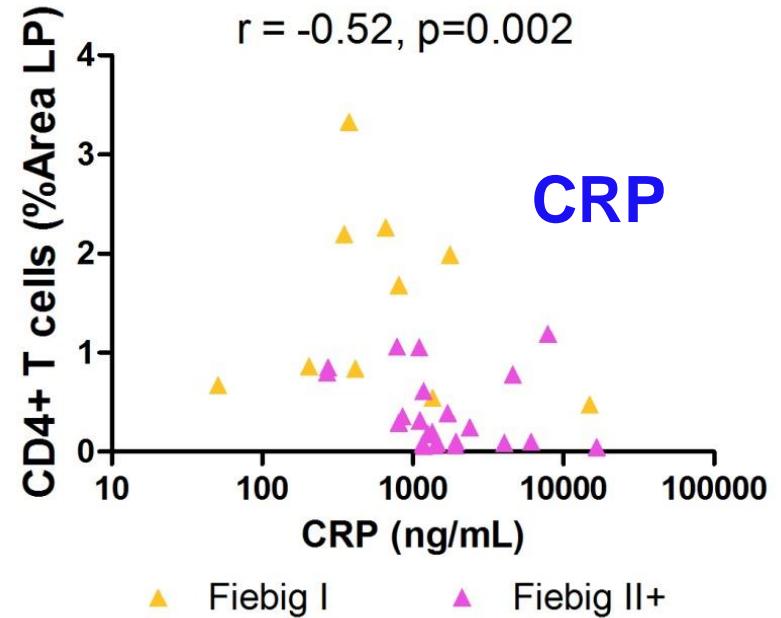
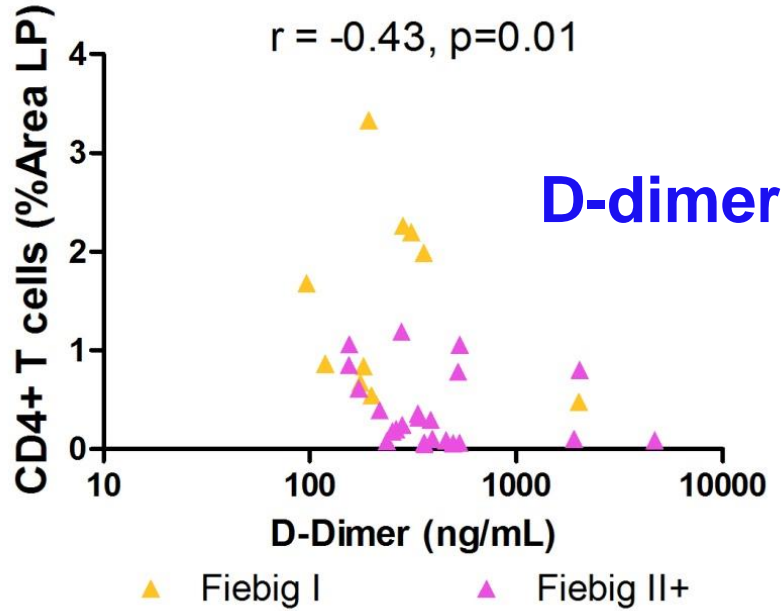
CD8+HLADR+38+

Similar inverse correlations are observed with activated T cells in peripheral blood

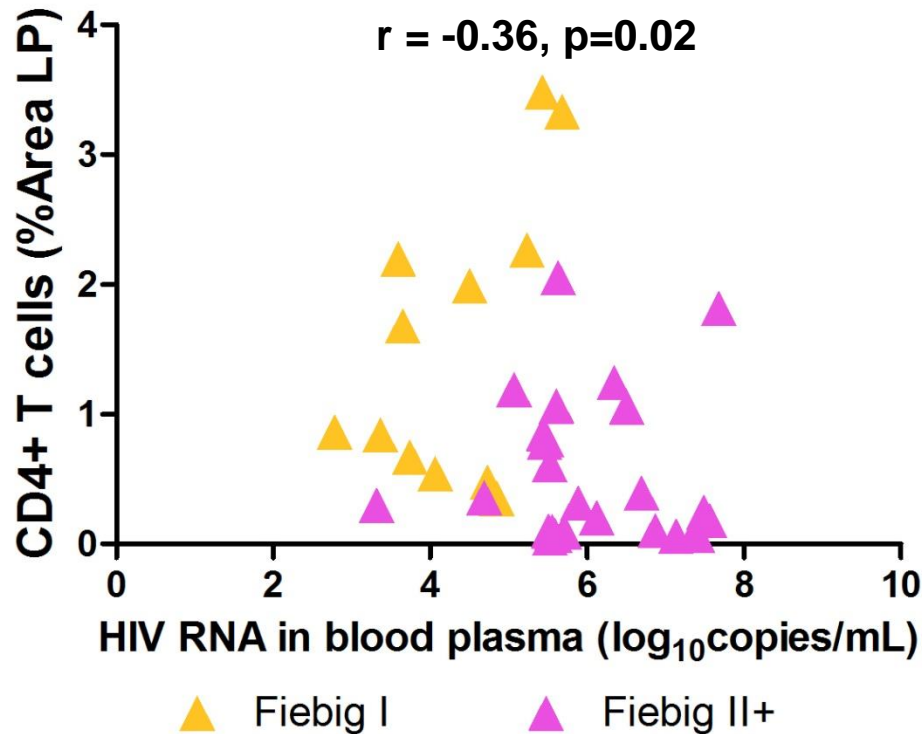
Levels of Plasma Biomarkers by Fiebig stage



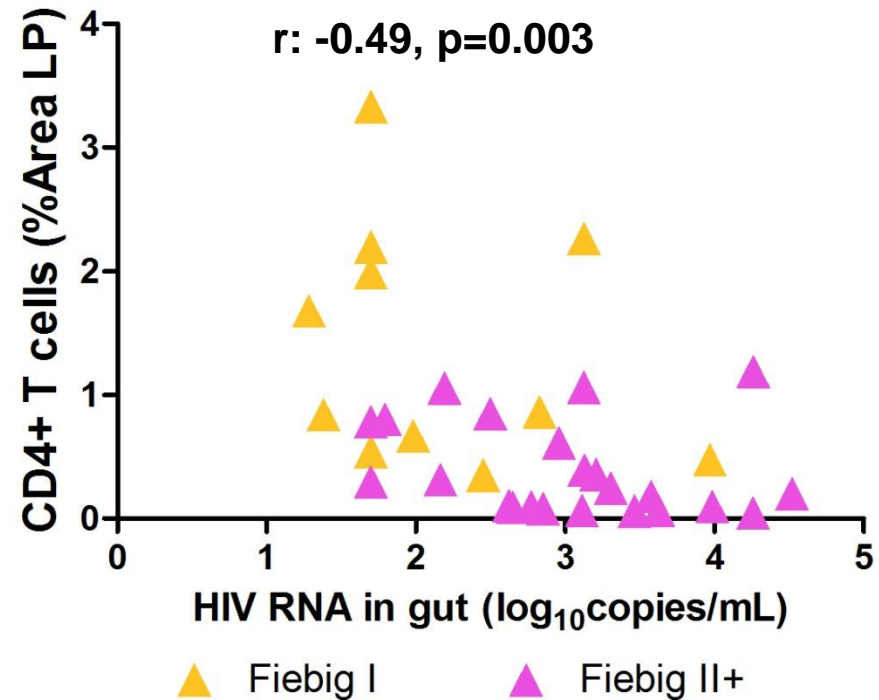
Decreases of LP CD4 T cells correlated with higher plasma biomarkers levels



Decreases of LP CD4 T cells correlated with high HIV RNA in blood and sigmoid colon



Blood



Sigmoid colon

What happens to lamina propria CD4 after ART?

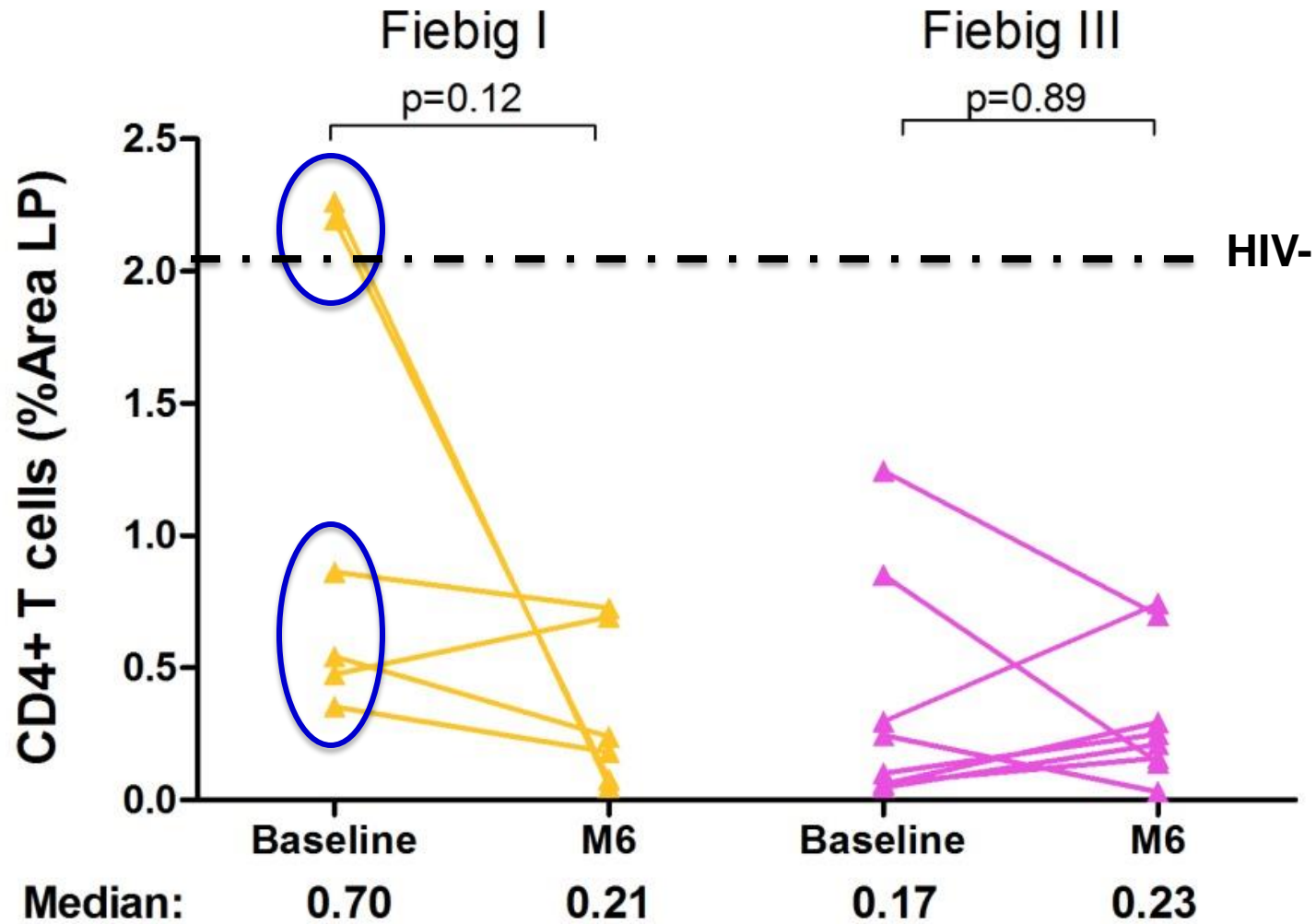
At month 6

All patients had

HIV RNA < 50 copies/ml in blood

HIV RNA < 50 copies/mg tissue of sigmoid colon

No reconstitution of lamina propria CD4+ T cells after 6 months of ART



Summary

- Significant depletion of sigmoid LP CD4 T cells occurs after Fiebig I and is associated with
 - Plasma inflammatory biomarkers
 - T cell activation and HIV viremia in blood and gut
- No short-term reconstitution of LP CD4 T cells after ART

Discussion

- Timing of LP CD4 depletion and its association with immune activation is consistent with the SIV literature^{1,2,3}
- In humans, significant gut CD4 depletion and immune activation occur in chronic HIV and persist after ART^{4,5}
- Available data from later acutely infected subjects (Fiebig IV+)
 - LP CD4 is depleted with partial reconstitution after ART^{6,7}
 - Gut Th17 depletion⁸ and altered homing receptors⁹ are associated with CD4 depletion and immune activation. Numbers but not function of Th17 is rapidly restored after ART.¹⁰
- Strength and weaknesses of our study
 - Population of early acutely infected subjects particularly Fiebig I
 - Small sample size and small pieces of gut tissue from sigmoid colon only. Analysis has not yet included other important parameters

¹Estes DJ, Plos Pathogens 2010; ²Tabb B, JID 2013; ³Ortiz AM, JCI 2011;

⁴Cicccone EJ, Mucosal Immunol 2010; ⁵Gordon SN, JI 2010;

⁶Mehandru S, Plos Med 2006; ⁷Guadalupe M, JV 2003; ⁸Kim CJ, JI 2013 ; ⁹Mavigner M, JCI 2012

Clinical Implications and future studies

- Fiebig I acute HIV infection may be a window of opportunity to intervene before significant gut CD4 depletion and immune activation occurs
- However short-term LP CD4 reconstitution after ART is not seen
 - Persistent LP CD4 depletion is seen in long-term treated acutely infected patients¹
 - Clinical consequence is not well understood
- Future studies
 - Longer term follow up after ART of LP CD4, Th17 and other relevant cell types, gut epithelial disruption and immune activation

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Volunteers

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