

Reservoir and Immune Markers in Tissue Compartments in Early Treated People from the RV254/SEARCH010 Study

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HIV Persistence in Tissue Sanctuaries



Central Nervous System

Infection and immune activation
Neurocognitive impairment



Gut

Preferential infection of gut CD4 cells and irreversible immune damage



Lymph nodes

Persistent infection of Tfh and CD4 cells in B cell follicles inaccessible to CTL

Lessons learned from RV254

during acute HIV and after early ART

Viral burden
Inflammation
Immunity

*Colby, Nat Med 2018; Ananworanich, JIAS 2017, Ebiomedicine 2016; Peluso, AIDS 2017; Takata, Sci Transl Med 2017
Muir, Plos Pathog 2016; Deleage, JCI Insight 2016; Valcour, Plos One 2015; Schuetz, Plos Pathogens 2014*



SEARCH clinic, Bangkok

RV254/SEARCH010

Acute infection cohort with early ART

Real-time screening of
299,004 samples in Thailand



Acute HIV infection
**(n=564 enrolled/
703 identified)**



Immediate ART

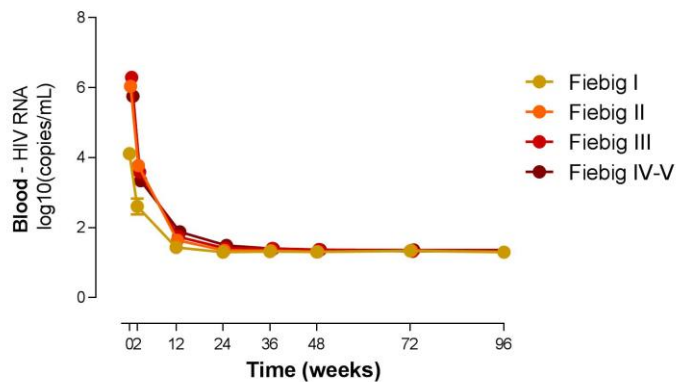
Data as of 17 August 2018

95% male, 91% MSM
26 years old, 81% CRF01_AE
19 days of infection
80 Fiebig I
130 Fiebig II
252 Fiebig III
70 Fiebig IV
32 Fiebig V

N of optional procedures
203 Sigmoid biopsy
336 Leukapheresis
353 Lumbar puncture
170 Inguinal LN biopsy
720 Brain MRI /MRS
1050 Genital Secretion

MHRP

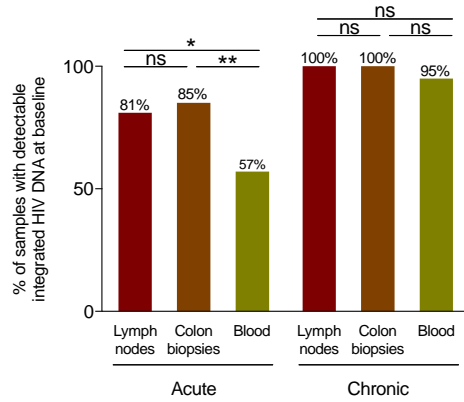
HIV RNA in Blood after Early ART



- Lower initial viral load in Fiebig I
- Rapid viral load decline and high viral suppression rates following ART in acute HIV



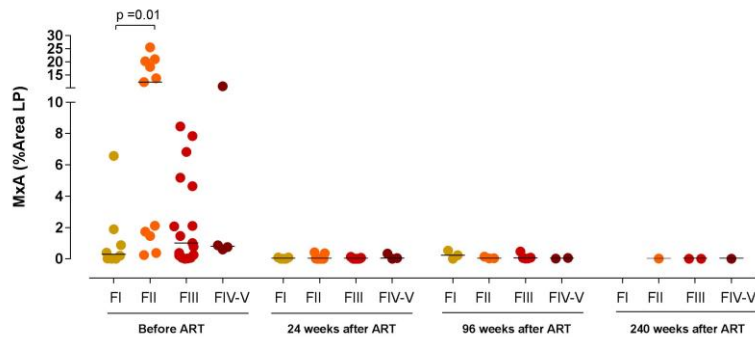
Detectable HIV DNA is More Common in Tissues vs. Blood During Acute HIV Infection



- Higher percentage of lymph node and sigmoid colon biopsies than blood have detectable levels of integrated HIV DNA during acute HIV

Louise Leyre, Nicolas Chomont (U Montreal)

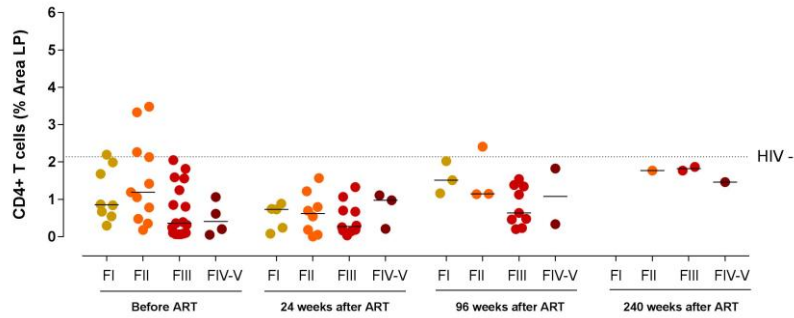
Resolution of Gut Inflammation



- Inflammation in gut occurs early in acute HIV and resolves following ART

Claire Deleage (Leidos NCI Frederick)

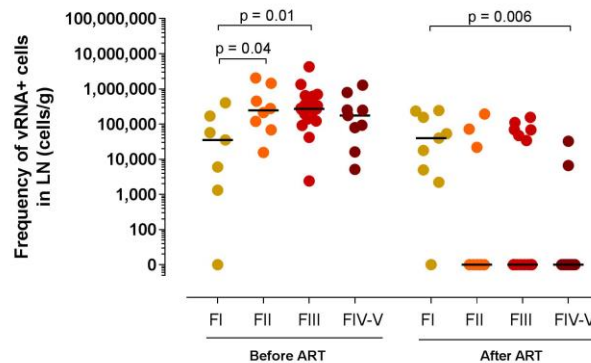
CD4 Recovery in Gut Lamina Propria



- CD4 depletion occurs early in infection and recovers with longer term ART

Claire Deleage (FNL- NCI Frederick)

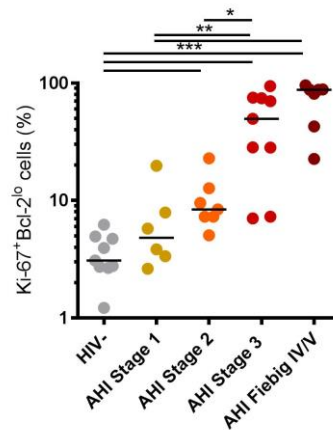
Persistence of RNA+ Cells in Lymph Nodes



- vRNA+ cells are detected as early as Fiebig I and persists in lymph nodes after 6-24 months of viral suppression

Timothy Schacker (U Minnesota)

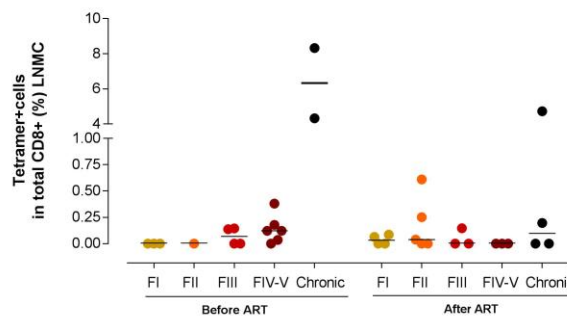
Effector CD8+ T Cells in Lymph Nodes during Acute HIV Infection



- Low frequencies of effector CD8 T cells in early acute HIV infection
- Increased frequency of effector CD8+ T seen at stage III (peak viremia) but memory potential begins to decline after stage III

Takata et al, *Sci Transl Med* 2017; Buranapraditkun (Chulalongkorn U) and Trautmann (MHRP)

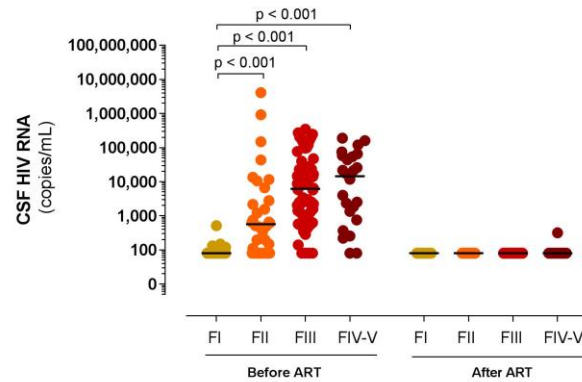
HIV-specific CD8+ T Cells in Lymph Nodes



- HIV-specific CD8+ T cells are at very low frequencies or undetectable during Fiebig I/II acute HIV infection
- Frequencies of HIV-specific CD8+ T cells are low under ART

Supanee Buranapraditkun (Chulalongkorn U), and Hiroshi Takata and Lydie Trautmann (MHRP)

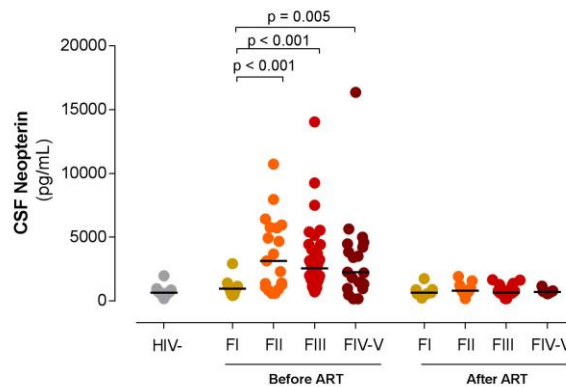
CSF HIV RNA during Acute HIV and after ART



- CSF viremia is lower in Fiebig I/II vs. Fiebig III/IV acute HIV
 - Viremia detected as early as 8 days post infection
- Post-ART CSF viral load is undetectable in almost everyone

Valcour, JID 2012; Linda Jagodzinski (MHRP), Serena Spudich (Yale)

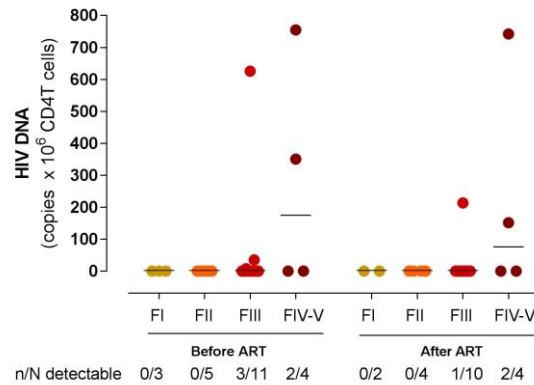
CSF Inflammatory Marker During Acute HIV and After ART



- CSF neopterin level in Fiebig I is similar to healthy controls and rises thereafter
 - Levels normalized after ART for all Fiebig stages

Bonnie Slike and Shelly Krebs (MHRP), Serena Spudich (Yale)

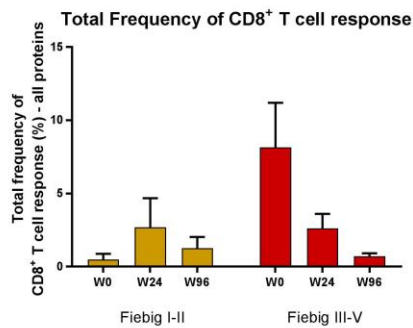
HIV DNA content measurement in CD₄T cells in CSF



- CSF CD₄T cells harboring HIV DNA are detected in some individuals before and after 2 years of ART

Caroline Subra and Lydie Trautmann (MHRP)

HIV-specific CD₈⁺ T cell Response in the CSF



- HIV-specific CD₈ T cells can be detected in CSF as early as Fiebig I/II acute infection and are found at higher frequency at Fiebig III-V
- HIV-specific T cell responses can be detected in the CSF after ART in all Fiebig stages

Caroline Subra and Lydie Trautmann (MHRP)

Conclusion: Tissue Compartments

- HIV infects cells in the tissues and blood early in acute HIV infection and the extent increases with time
 - Proviral and viral burden
 - Inflammation
- HIV-specific immune responses are infrequent in Fiebig I acute HIV and increases in Fiebig II onwards
 - Rationale for immune interventions to boost HIV-specific responses
- Early ART partially reverses HIV-related insults
 - Reduces the HIV viral burden significantly except for the lymph nodes
 - Mitigates inflammation, CD4 depletion and immune dysfunction

Thai Red Cross

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Donn Colby
Carlo Sacdalan
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Pomporn Tantivitayakul
Phillip Chan
Jintana Intasan
Many more

Chulalongkorn

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Buranapraditkun
Suneer Sirivichayakul
Rungsun Rerknimitr
Sukalya Lerdlum
Phandee
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MAKING AIDS HISTORY

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ViiV Healthcare
Merck
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