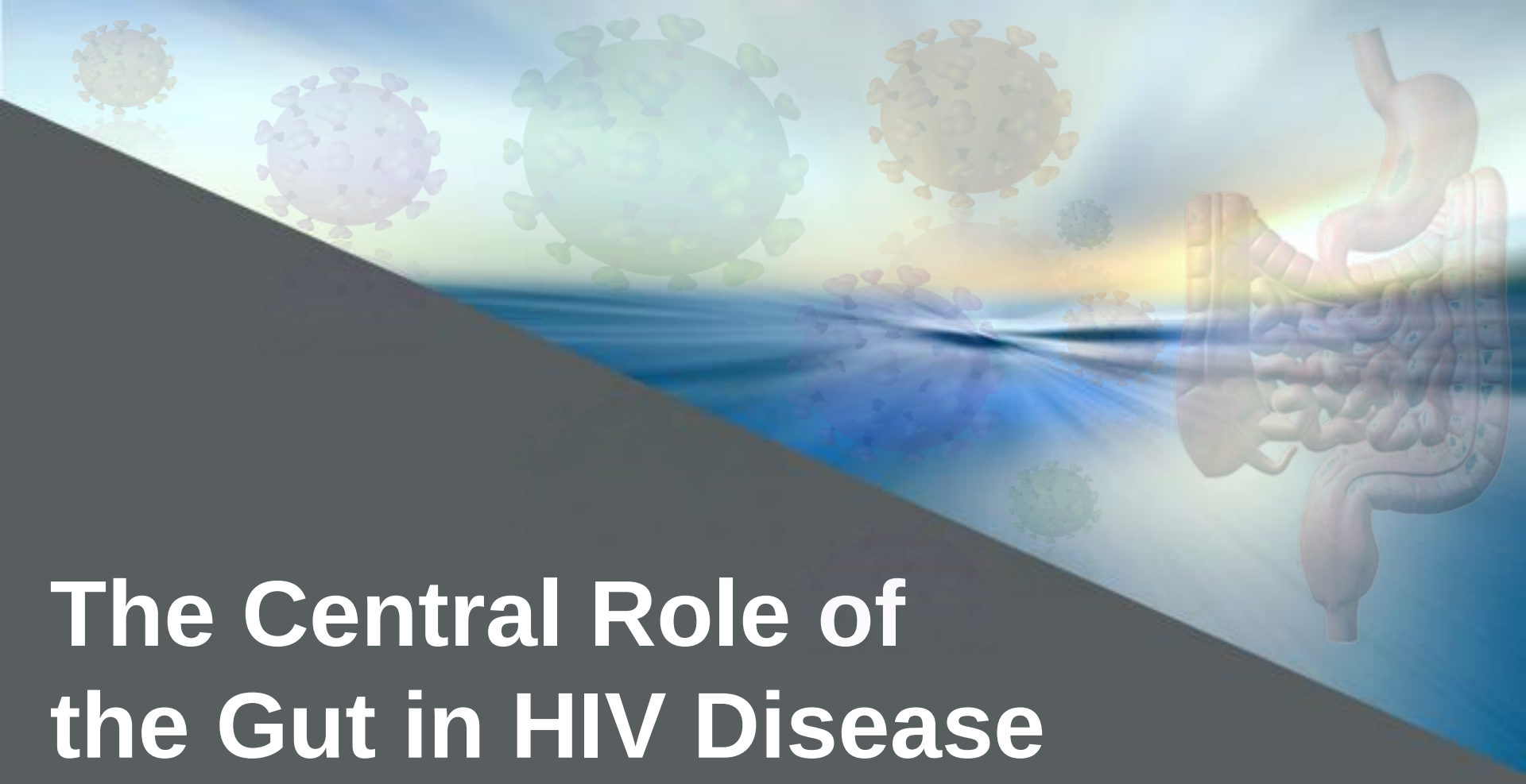


The Central Role of the Gut in HIV Disease

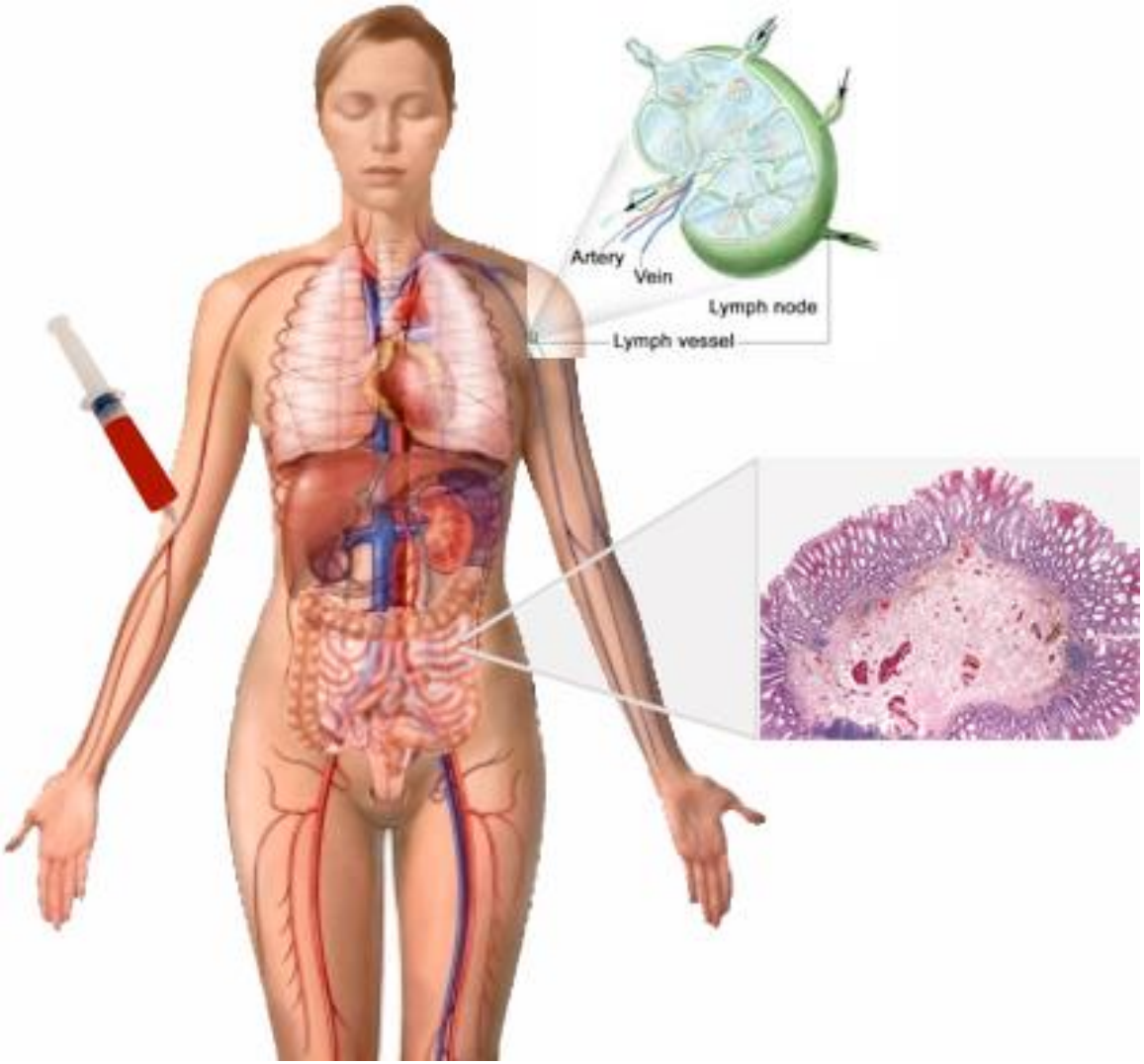
Jake Estes, PhD
Professor and Chief
VGTI and ONPRC, OHSU
September 18, 2019

OHSU

Background

- HIV rapidly establishes a disseminated productive infection **within** every LT within the body
  - Manifestations of HIV infection are classically seen in lymphatic organs (i.e. lymph nodes, spleen, gut, MALT, etc.)
- Infection triggers potent host inflammatory and adaptive immune responses, establishing and sustaining a state of chronic persistent immune activation / inflammation
- Chronic immune activation / inflammation are **hallmarks** of HIV-1 disease that continues throughout the course of infection in the absence of antiretroviral therapy (ART) and persists at elevated levels during ART
- **Understanding the mechanism(s) driving persistent chronic immune activation and inflammation (before and during ART) is critically important, as chronic IA / inflammation strongly correlates with increased morbidities and reduced mortality in ART suppressed individuals infected with HIV**

Limitations of Human Studies



- Enrollment challenges
- Access to clinical care
- Cost
- Ethical considerations and challenges
- Health risks
- Disease timing limitations
- Limited history / records
- Limited Tissue sampling

NHP Models of HIV Disease

Nonhuman primate (NHP) research has provided many critical insights into HIV disease that are simply NOT feasible in a clinical setting

- **Immune systems, anatomy, and physiology are highly similar**
- **Transmission and longitudinal studies are possible**
- **Environmental factors can be controlled (i.e. virus, route, etc.)**
- **Any anatomic site can be sampled**
- **Effects of additional infections can be studied**
- **Preventative efficacy can be studied**
- **Ability to deplete lymphocyte populations in vivo**

SIV+ macaques

HIV+ humans

Evidence for Microbial Translocation

nature medicine

Article | Published: 19 November 2006

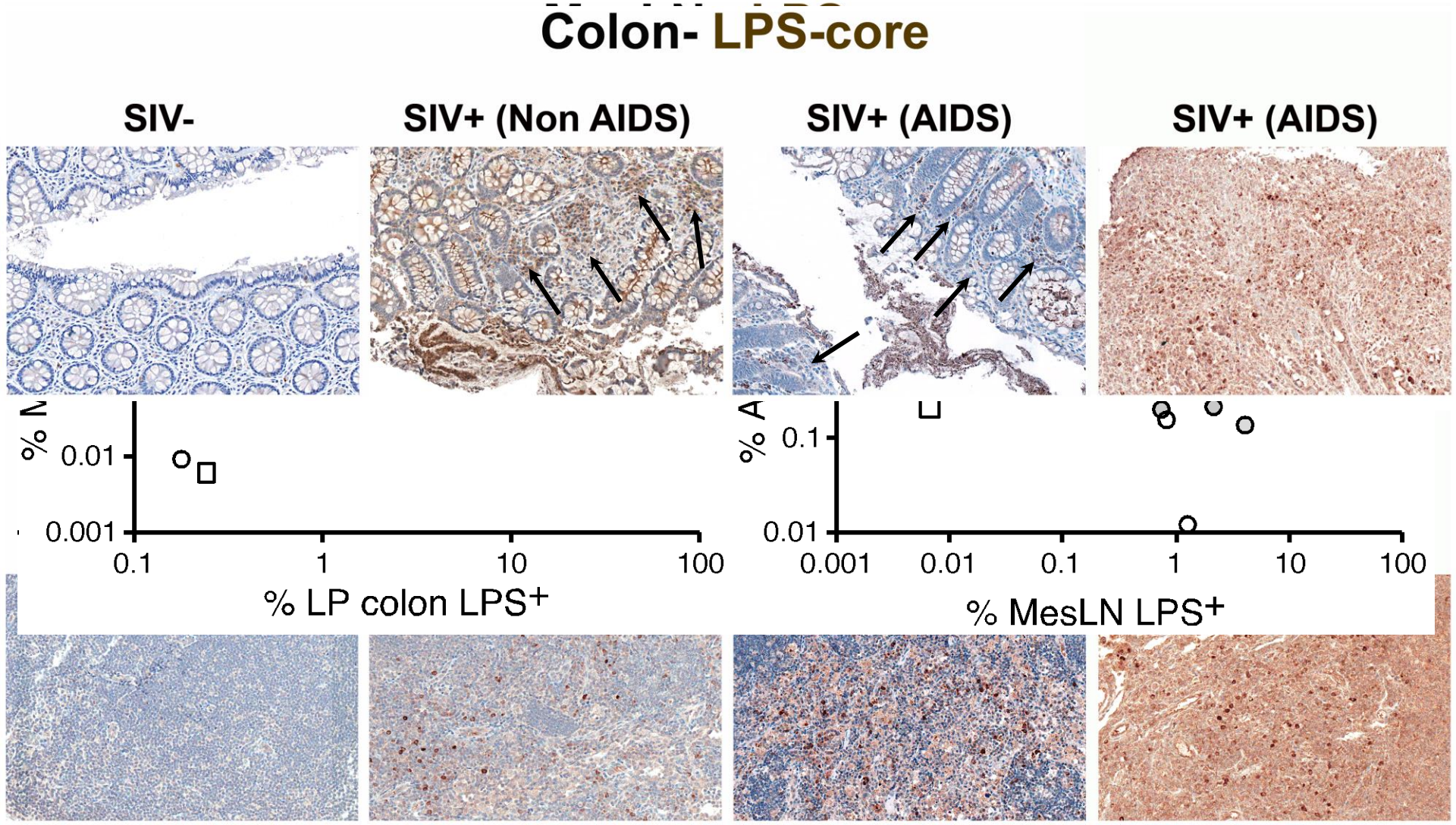
Plasma LPS, pg/ml

Microbial translocation is a cause of systemic immune activation in chronic HIV infection

Jason M Brenchley, David A Price, Timothy W Schacker, Tedi E Asher, Guido Silvestri, Srinivas Rao, Zachary Kazzaz, Ethan Bornstein, Olivier Lambotte, Daniel Altmann, Bruce R Blazar, Benigno Rodriguez, Leia Teixeira-Johnson, Alan Landay, Jeffrey N Martin, Frederick M Hecht, Louis J Picker, Michael M Lederman, Steven G Deeks & Daniel C Douek

Brenchley, et al. ***Nature Med***. 2006

Direct Evidence for GI Tract Damage leading to MT in SIV Infection

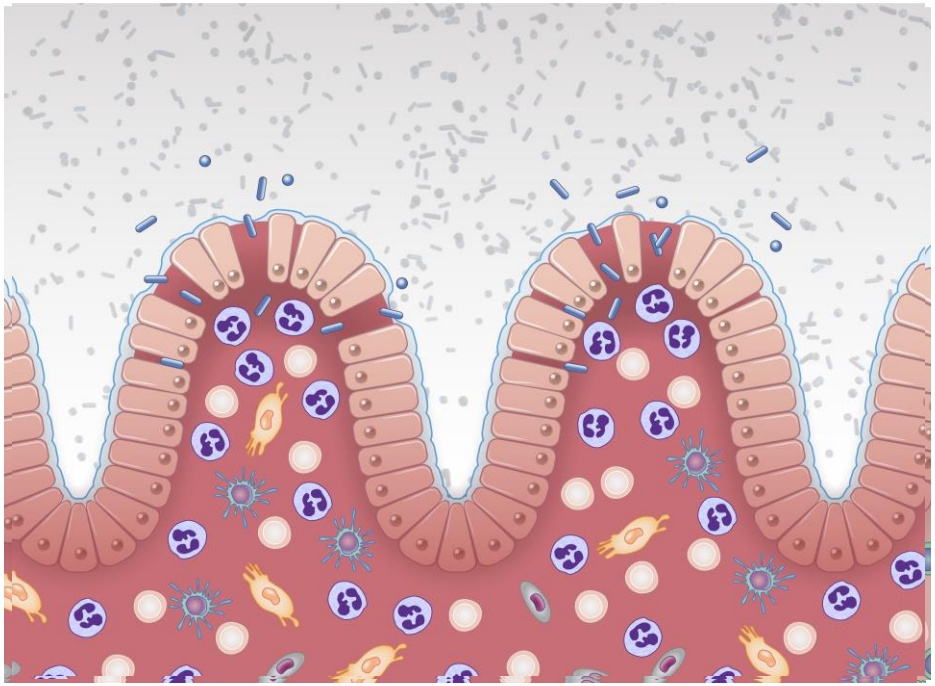


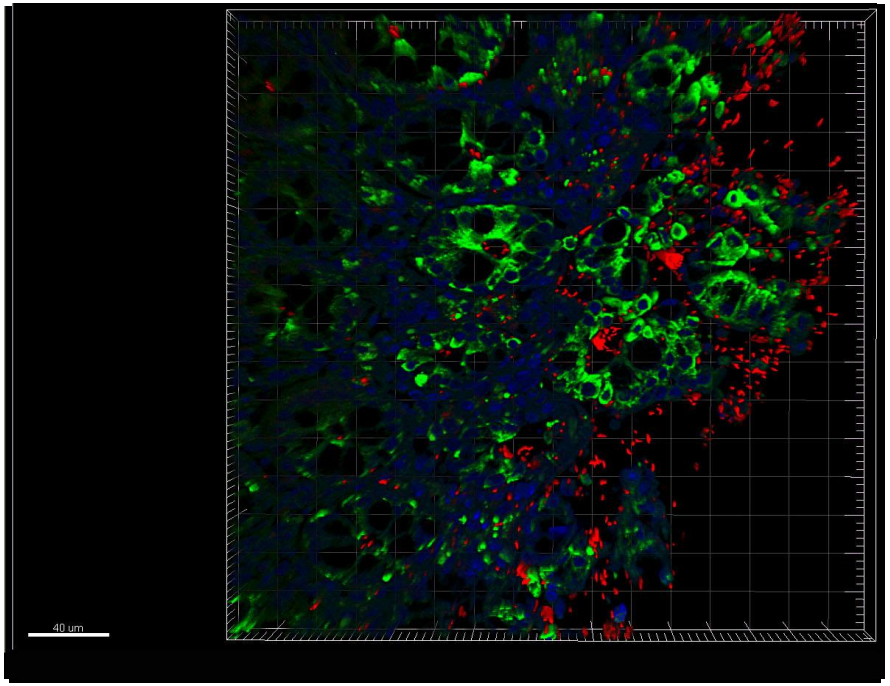
Estes, et al. ***PLoS Pathog***. 2010

Timing of GI Tract Damage leading to Microbial Translocation in SIV Infection

SIV NHP models to understand the timing and mechanisms leading to chronic inflammation and disease pathogenesis and progression

SIV



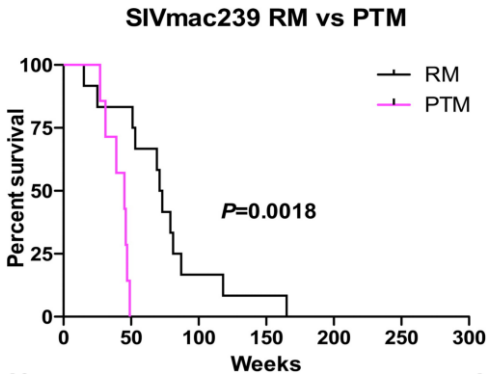


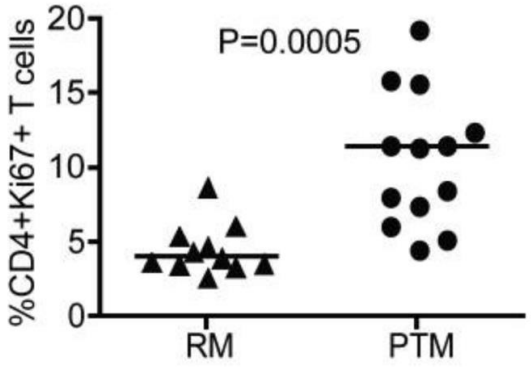
Epithelial Cytokeratin / E. coli / DAPI

Estes, et al. ***PLoS Pathog***. 2010

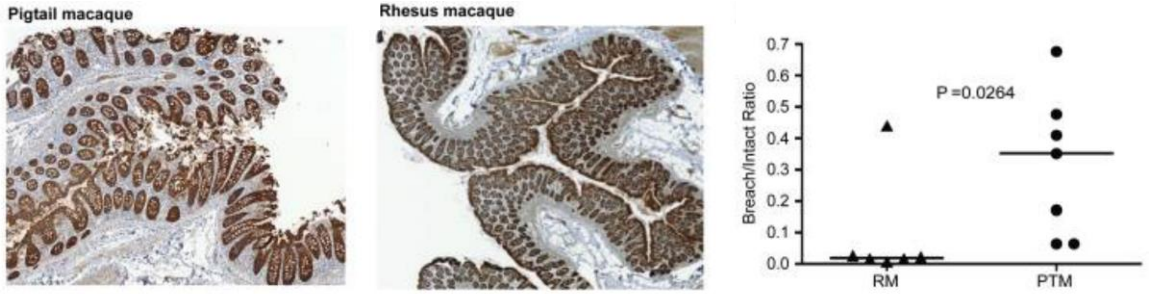
GI Tract Damage & Rapid Disease Progression

Does the extent of pre-existing GI tract damage and MT impact the time to disease progression following SIV infection?

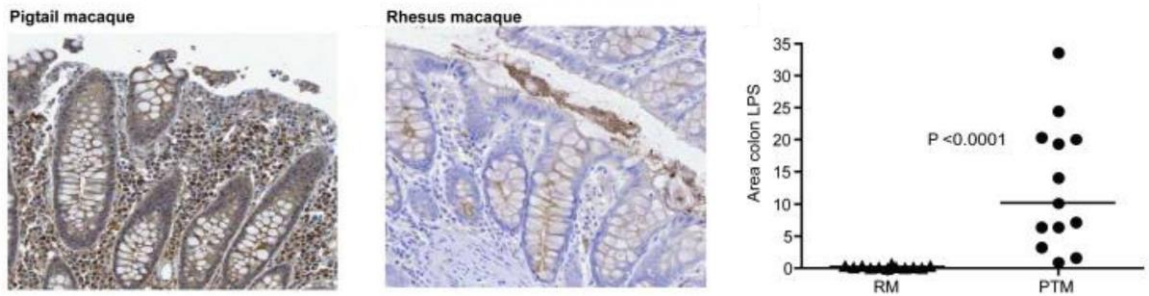


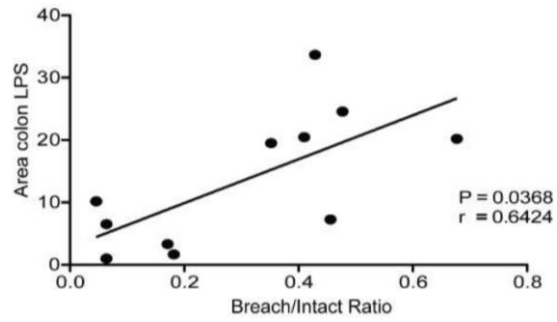


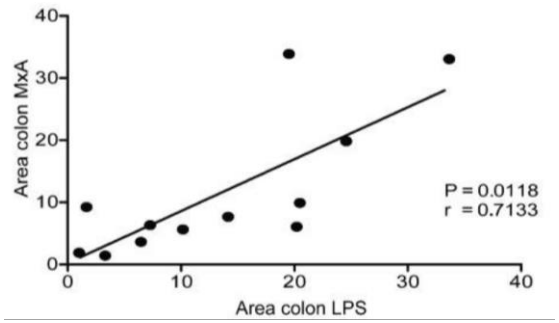
Claudin 3



LPS





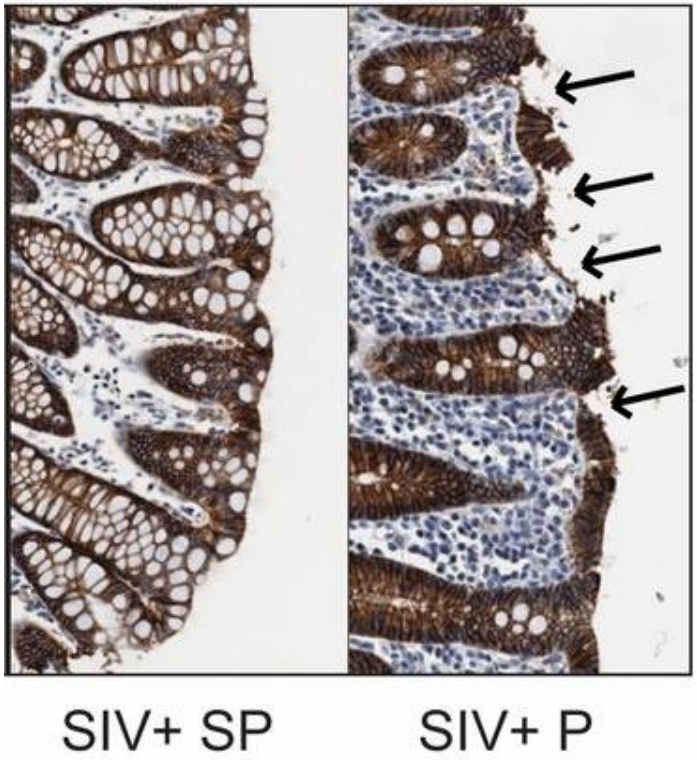


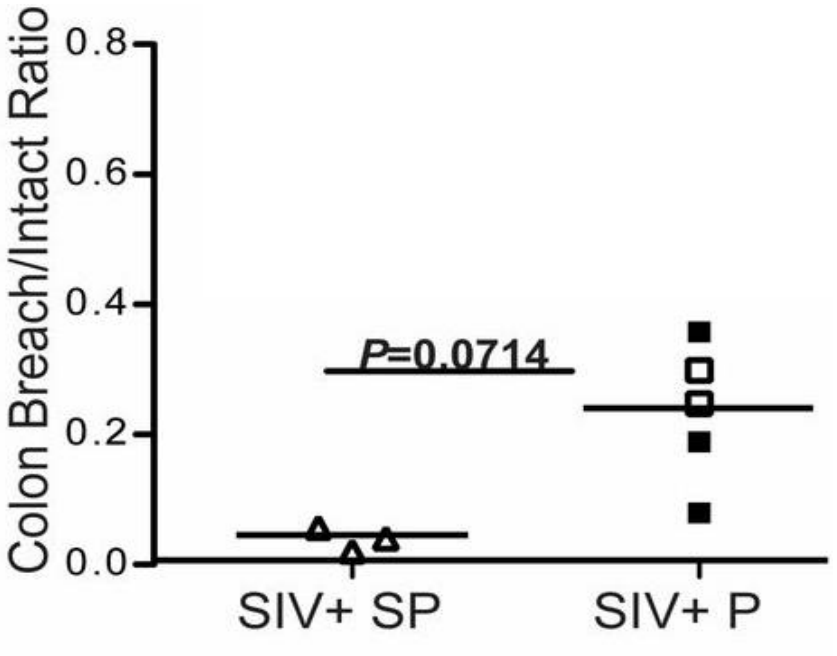
Klatt N et al. ***J Virol.*** 2012

Klatt N et al. ***Mucosal Immunol.*** 2010

GI Tract Damage & Rapid vs Slow Disease Progression

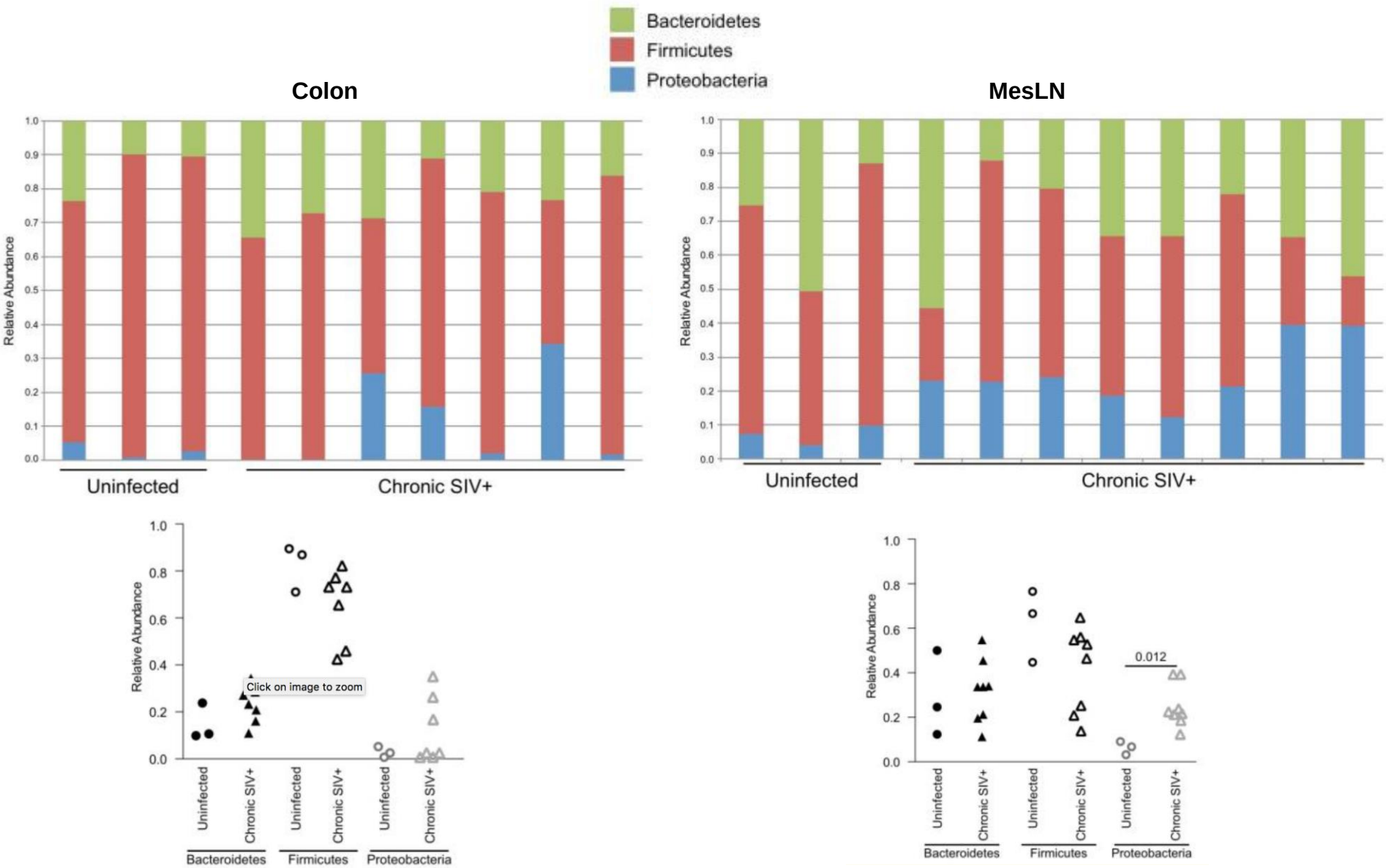
Does the extent of pre-existing GI tract damage and MT impact the time to disease progression following SIV infection?





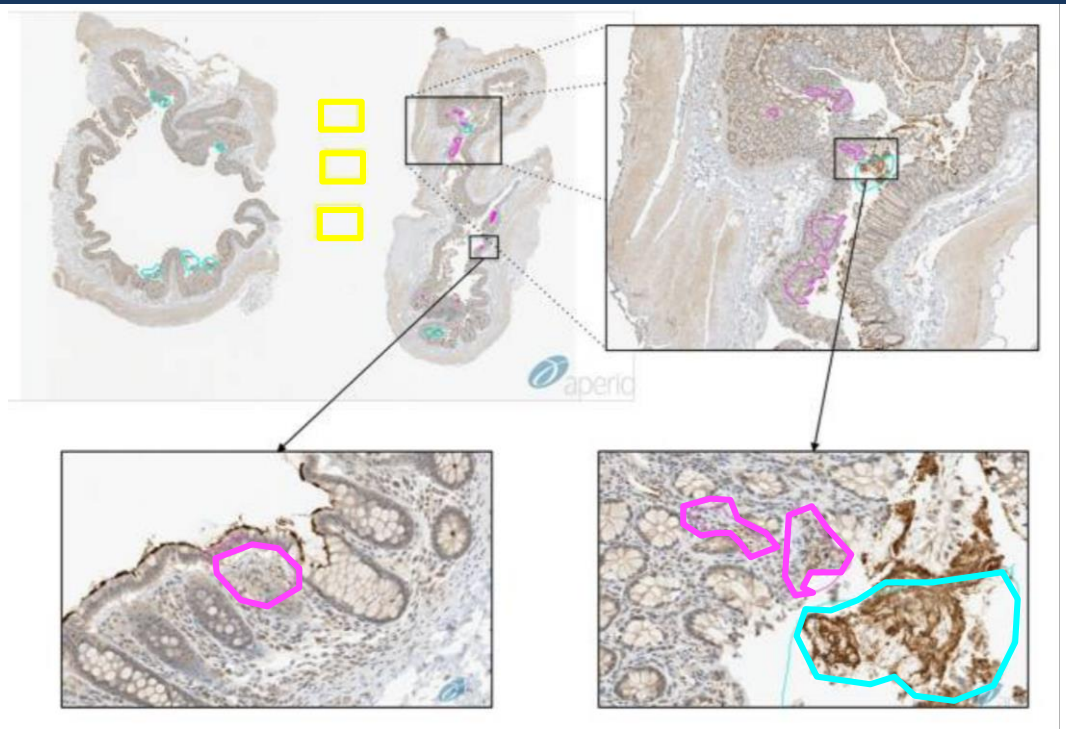
Canary LA et al. ***J Immunol.*** 2013

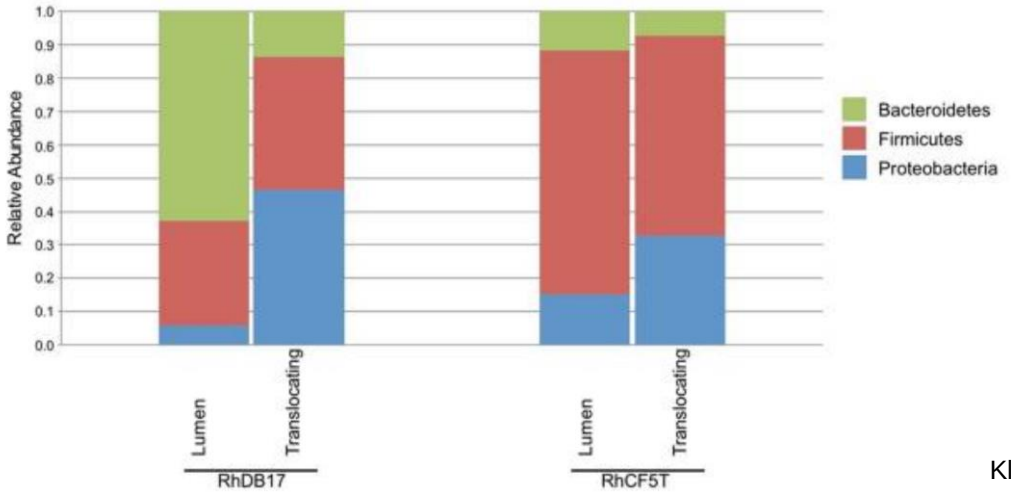
Preferential Microbial Translocation



Klase J, et al, ***Mucosal Immunol.*** 2015

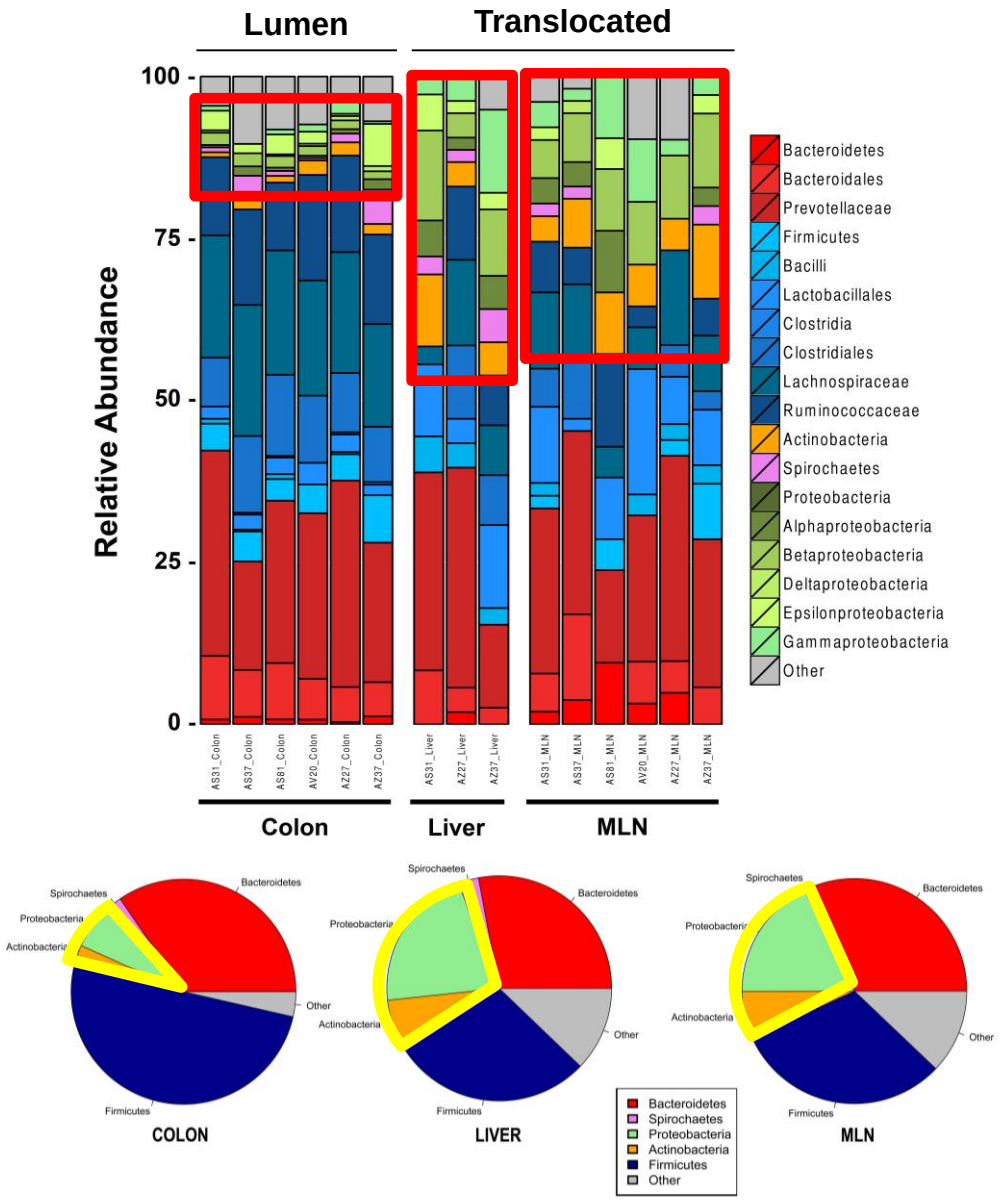
Preferential Microbial Translocation





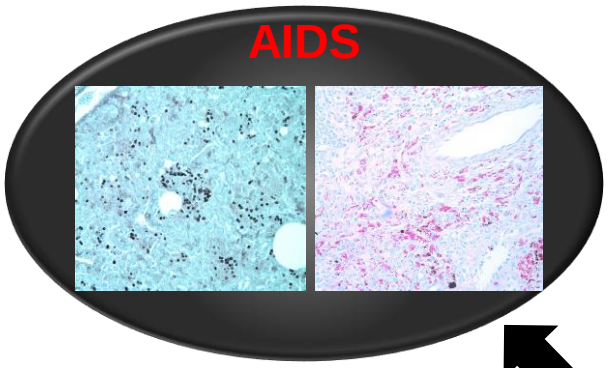
Klase J, et al, ***Mucosal Immunol.*** 2015

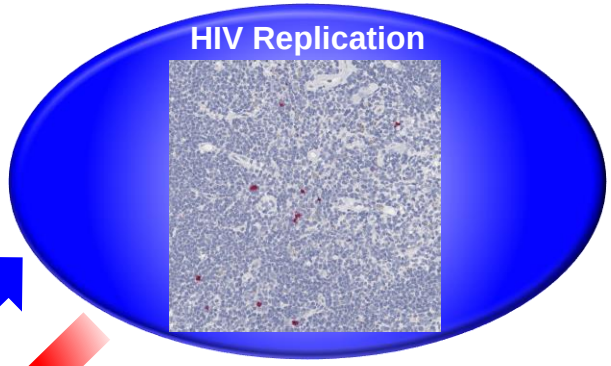
Experimental Colitis & Microbial Translocation

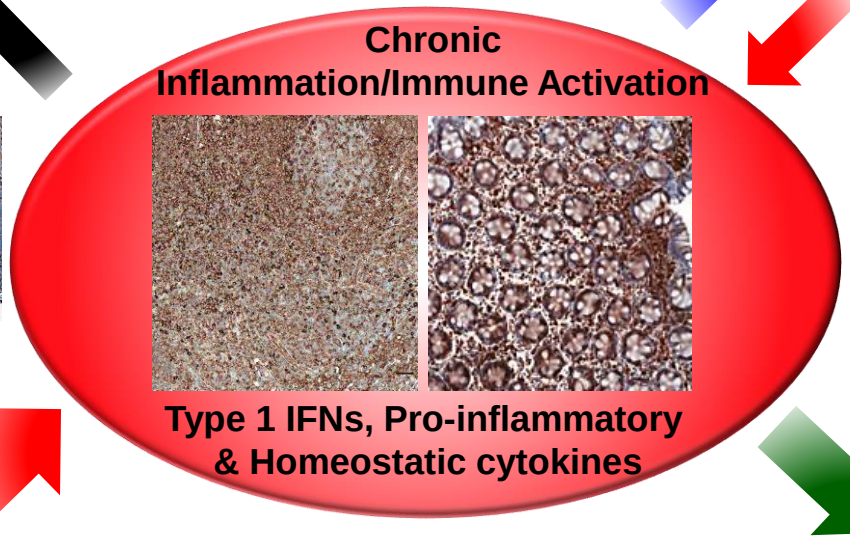


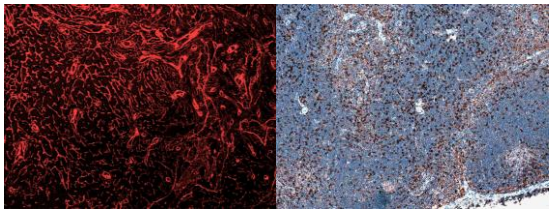
Hao et al. ***Nature Commun***. 2015

Central Role of Chronic IA / Inflam Driven by GI Damage in HIV Disease Progression

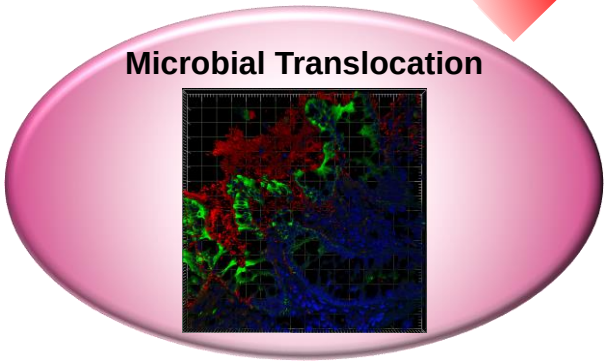


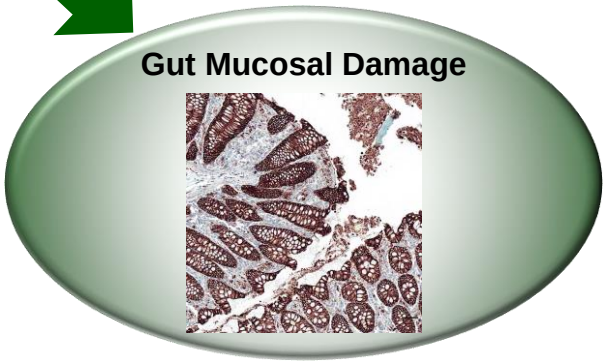






LT Fibrosis / FRC loss /
CD4+ T cell loss

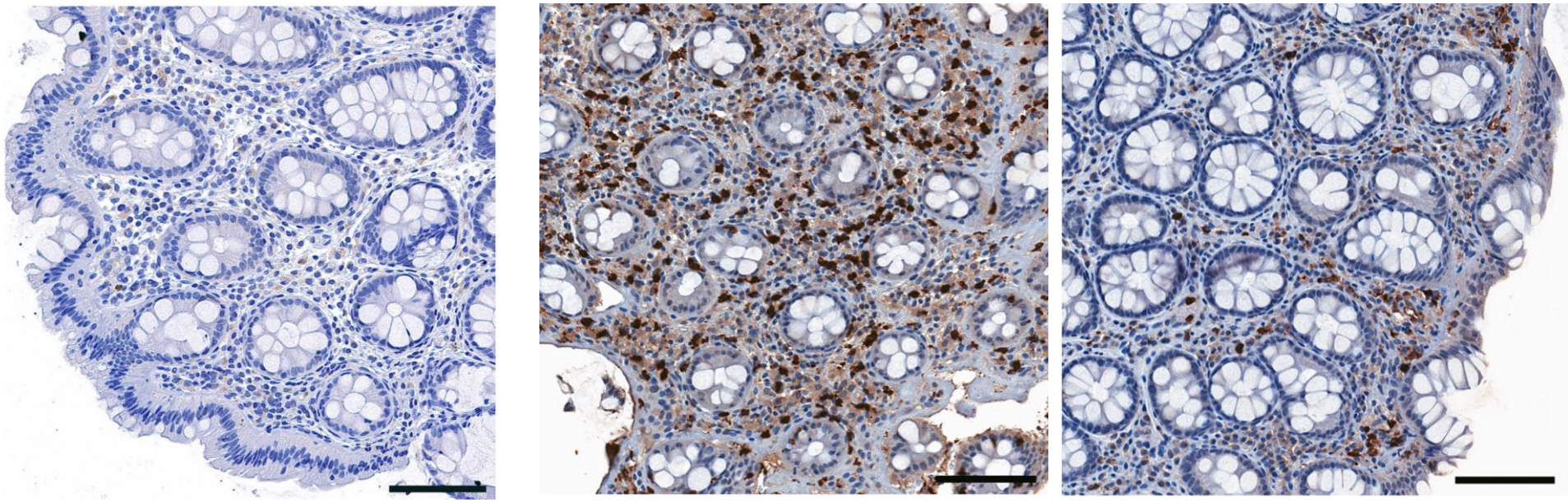




Persistent GI Tract Damage in HIV+ Individuals after long-term ART

Neutrophils (MPO)

HIV- | **HIV+ ART**



Neutrophil infiltration (GI tract damage) and mucosal apoptosis remain abnormally high despite ART for median of 10 years (4-12 years)

Somsouk et al. ***AIDS.*** 2015

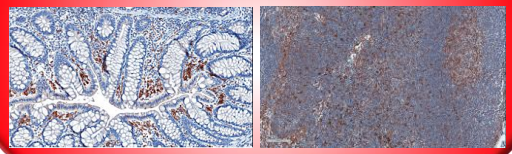
Persistent GI Damage Driving Sustained IA / Inflam in HIV+ Individuals during long-term ART

No AIDS

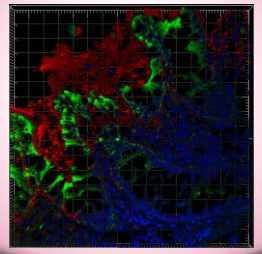
Comorbidities & Reduced Life Expectancy

ART

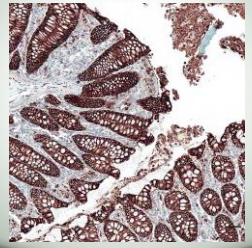
Systemic Inflammation/Immune Activation



Microbial Translocation



Gut Mucosal Damage



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Tim Schacker

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AIDS and Cancer Virus Program

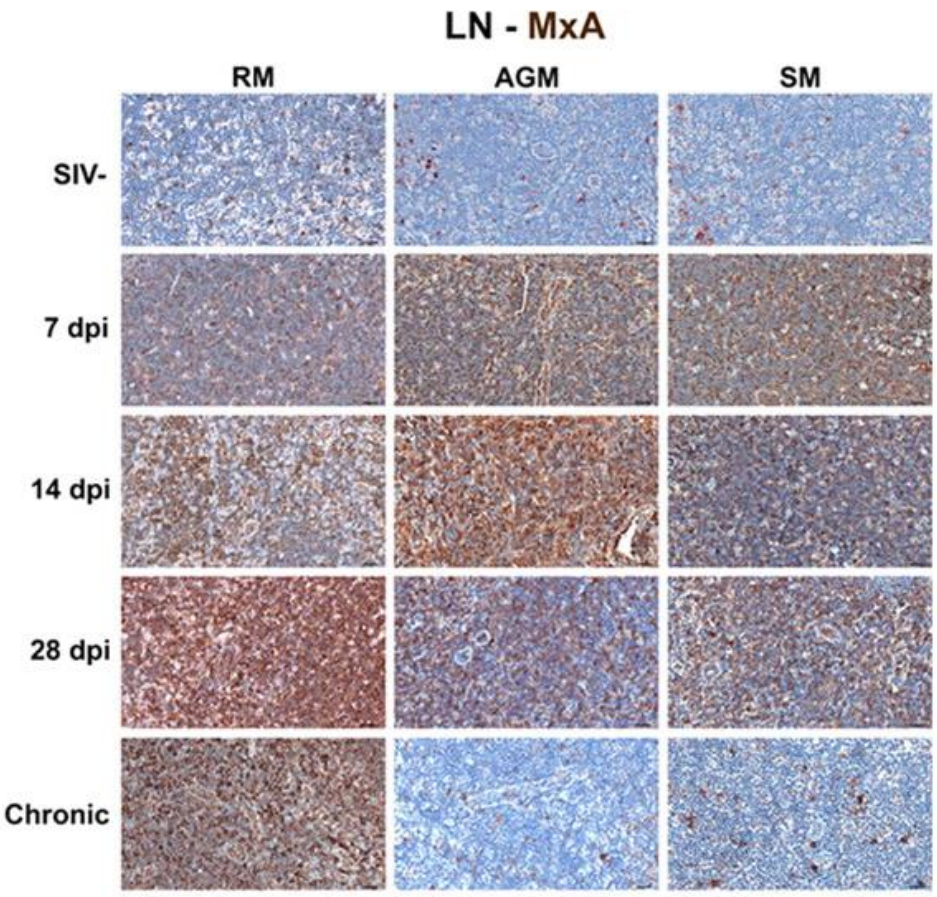
Delaney AIDS Research Enterprise DARE to find a cure

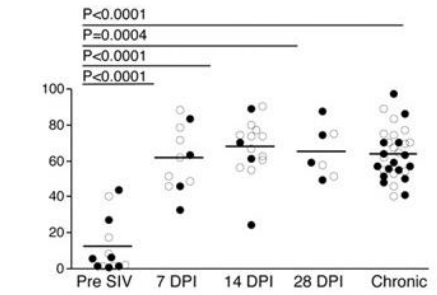
National Cancer Institute

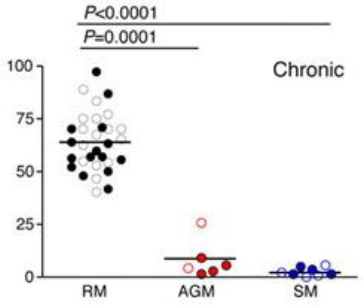
National Institutes of Health

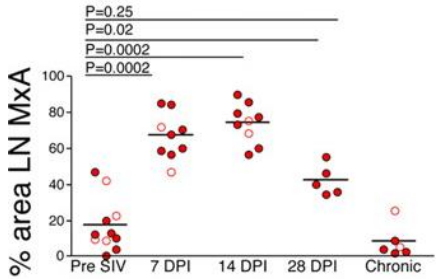
Department of Health & Human Services USA

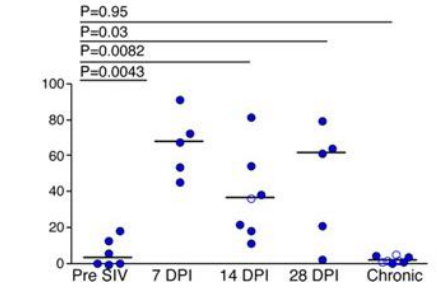
SIV Natural Host Resolution of Inflammation











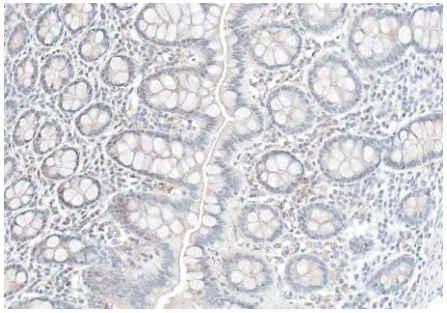
Harris LD, et al. ***J. Virol***. 2010

SIV and GI Tract Inflammation

Type 1 IFN inducible Myxovirus Resistance Protein 1

(Mx1)

Pre-Infection



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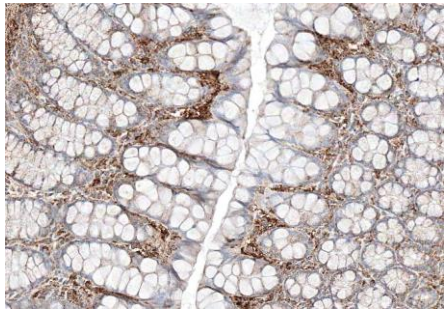

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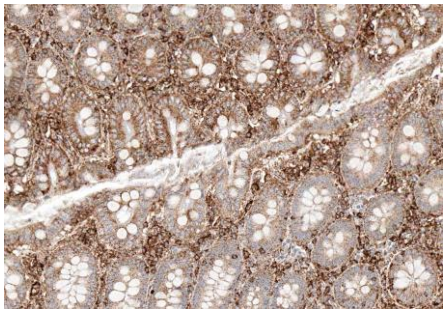
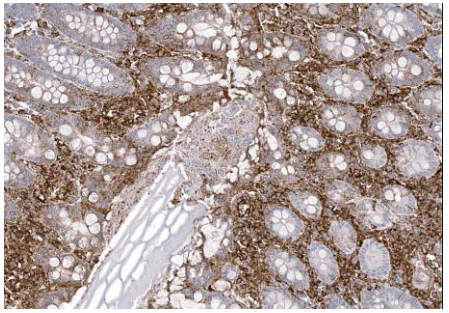


Chronic



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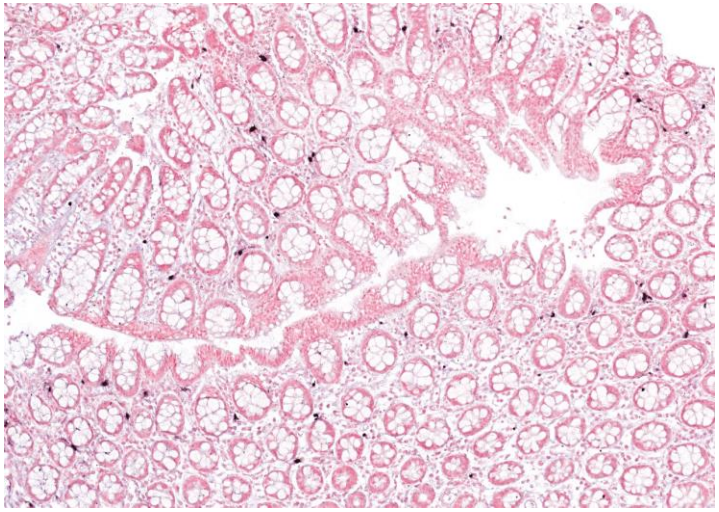

Chronic