IAS 2013 – old new basic science

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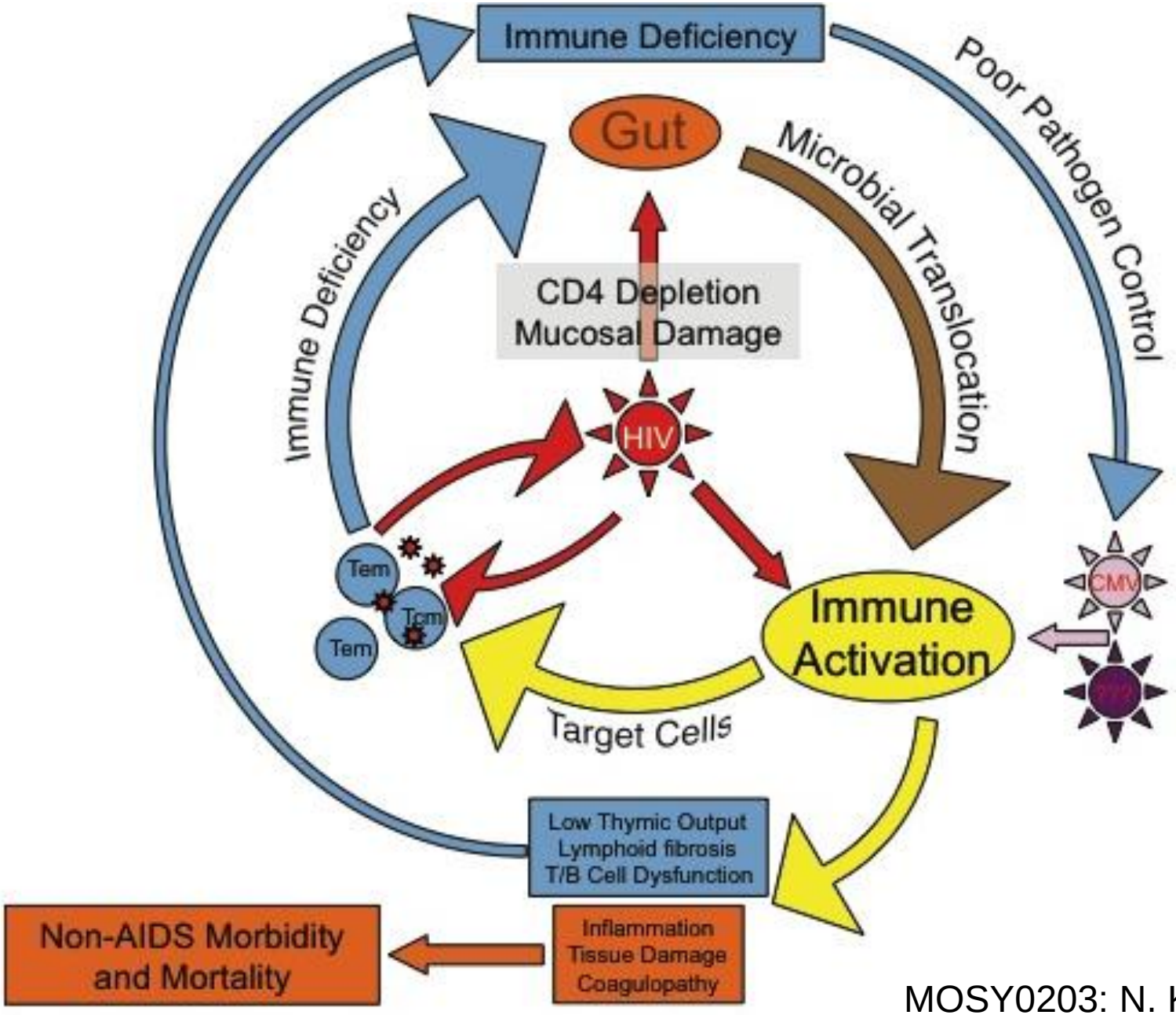
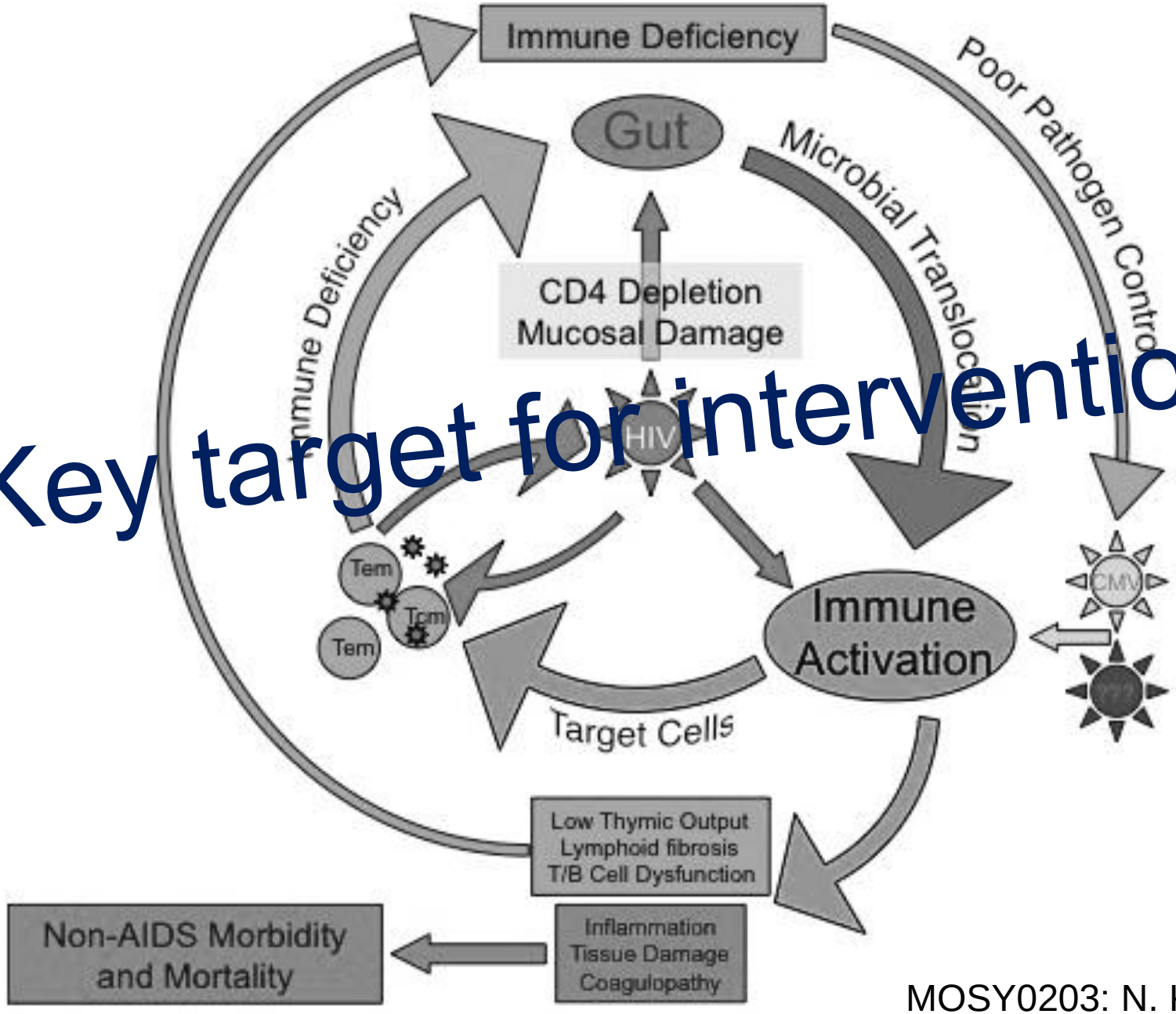
IAS 2013 – old new basic science

- Immune Pathogenesis
  - More on immune activation and inflammation
  - Non-AIDS complications of HIV
  - Lymphoid tissue fibrosis and architectural change
  - Disruption of mucosal integrity
- Targets for interventions



MOSY0203: N. KLATT
Immonl. Rev. 2013



Key target for intervention?

MOSY0203: N. KLATT
Immonl. Rev. 2013

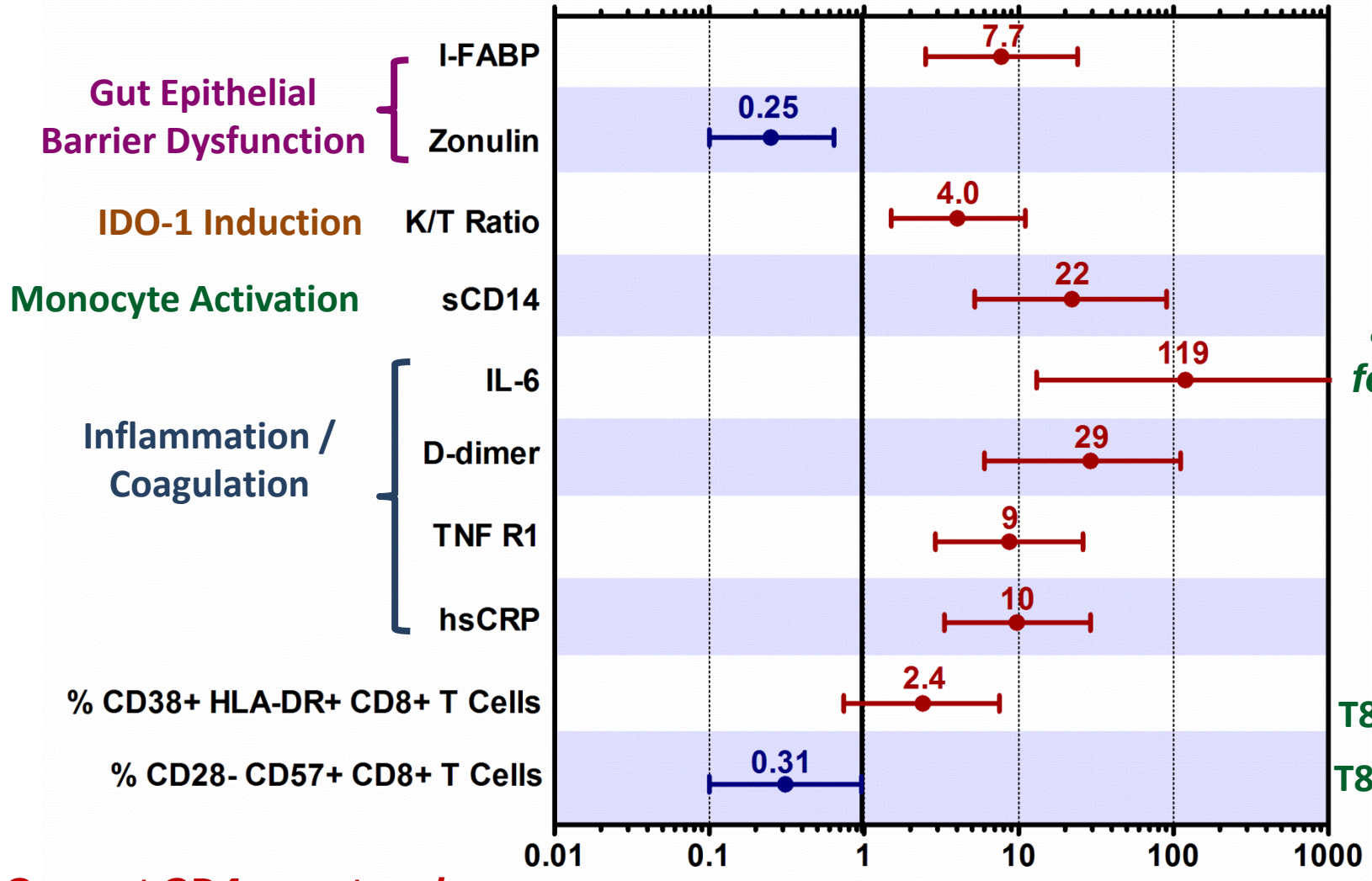
Innate Immnune Activation Markers Predict Mortality Independent of Nadir *AND* Current CD4 count

- Nested case-control study of immunologic predictors of mortality in HIV+ participants with HIV RNA levels <400 cp/ml on ART
- from two cohorts with routine blood archiving:
  - SOCA cohort of >2200 HIV+ participants (median CD4 nadir 30)
  - SCOPE: UCSF cohort of >1000 HIV+ (median CD4 nadir 88)
- Cases who died were sampled at a median of 5M before death
- Each case (SOCA 64/SCOPE 27) was matched to two living controls
  - Age, gender, pre-ART CD4 nadir
  - Duration of confirmed VL <400, history of CMV retinitis
- Soluble biomarkers measured on cryopreserved plasma
- Predictors of mortality assessed with conditional logistic regression

Hunt, CROI 2012, Abstr #278

Innate Immnune Activation Markers Predict Mortality Independent of Nadir *AND* Current CD4 count

MOBS0103: P. HUNT



Current CD4 count no longer predictive of mortality after adjusting for innate markers

Hunt, CROI 2012, Abstr #278 (see also : Tenorio, CROI 2013, Abstr# 790)

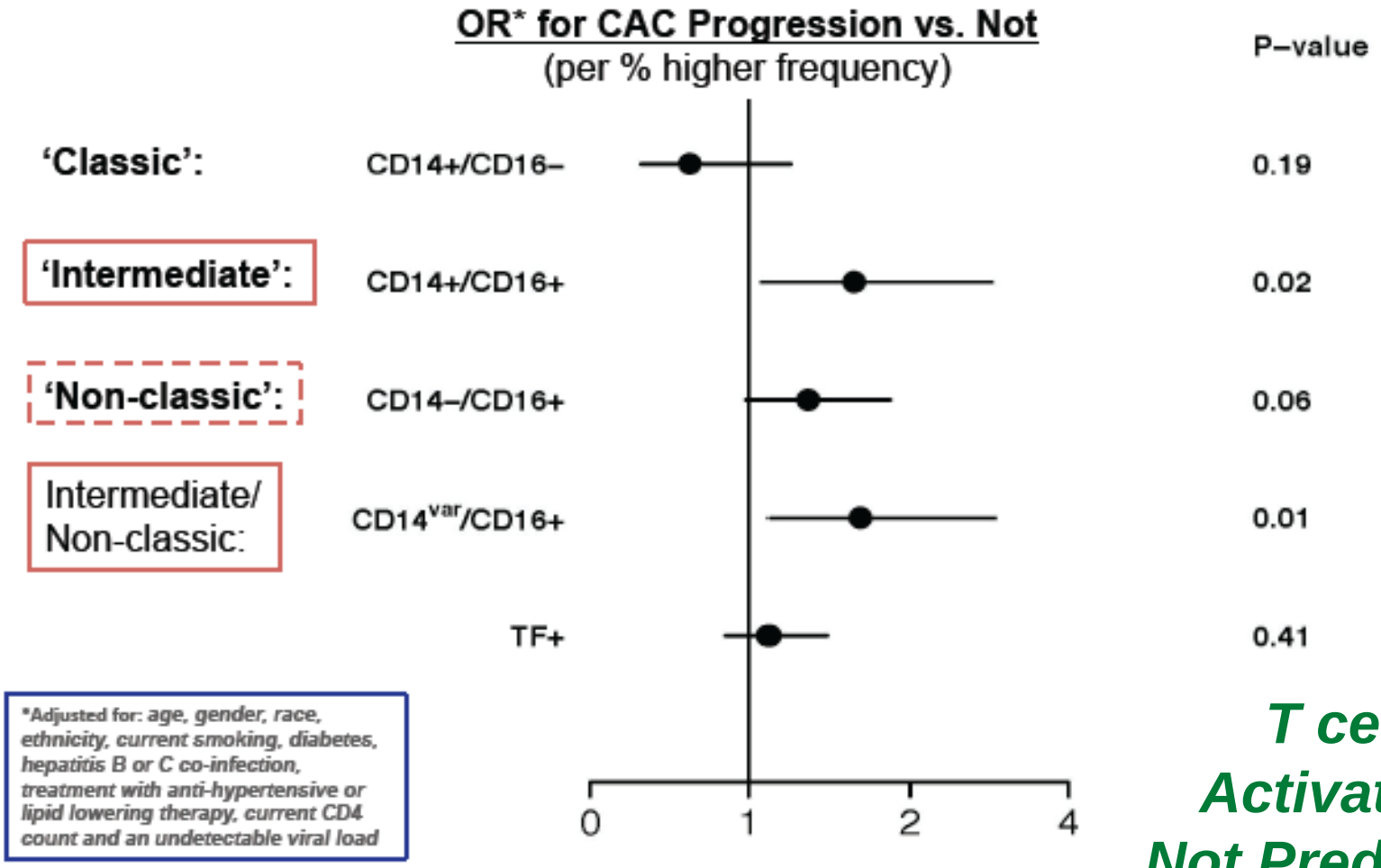
Monocyte Activation Predicts Coronary Artery Calcium Progression: SUN Study

- prospective HIV-natural history cohort composed largely of patients responding well to contemporary ART (n=436)
- coronary artery calcium (CAC) progression CT-scanning at baseline and two years later.
- Cellular markers of monocyte and T-cell activation also measured
- Incident CAC or significant worsening of baseline CAC occurred in 55 individuals
- multivariable analysis adjusting for multiple HIV-related characteristics and CVD risk factors,
- baseline monocyte expression of CD16, (with or without CD14, referred to as intermediate and non-classic monocyte phenotypes) mesured

- No correlation was seen with expression of the activation markers HLA-DR and CD38 or the senescence marker CD57 on either CD4 or CD8 T-cells

Baker, CROI 2013, Abstract #66LB

Monocyte Activation Predicts Coronary Artery Calcium Progression: SUN Study



T cell Activation Not Predictive

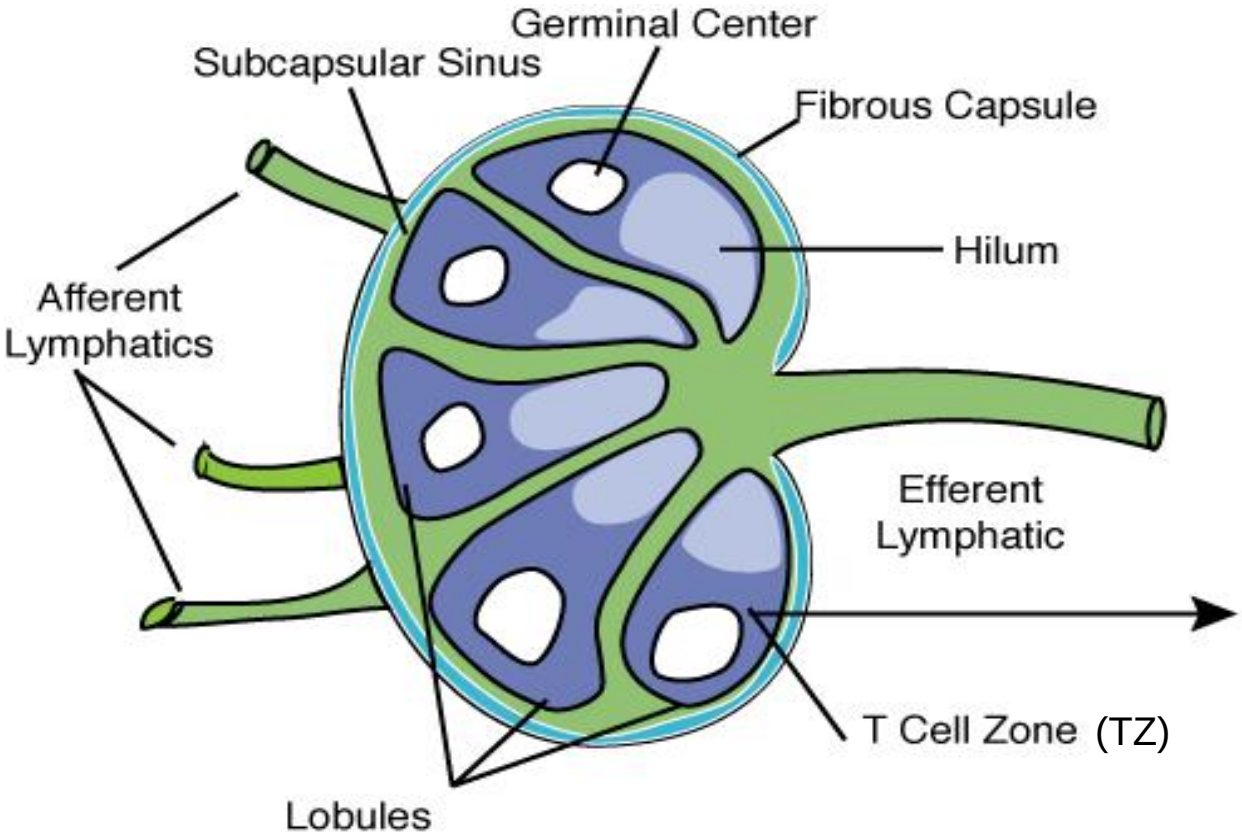
MOBS0103: P. HUNT

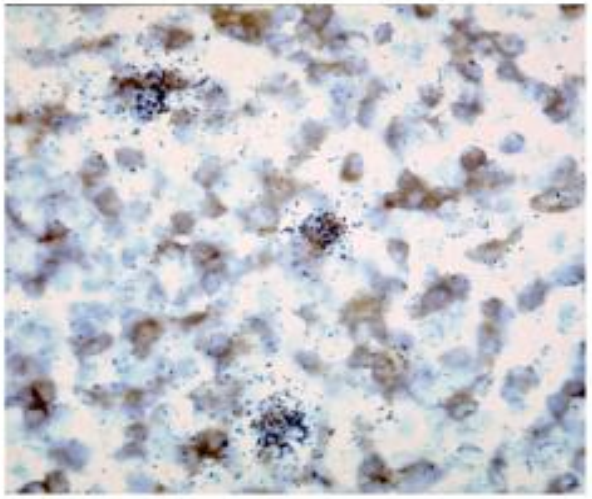
Baker, CROI 2013, Abstract #66LB

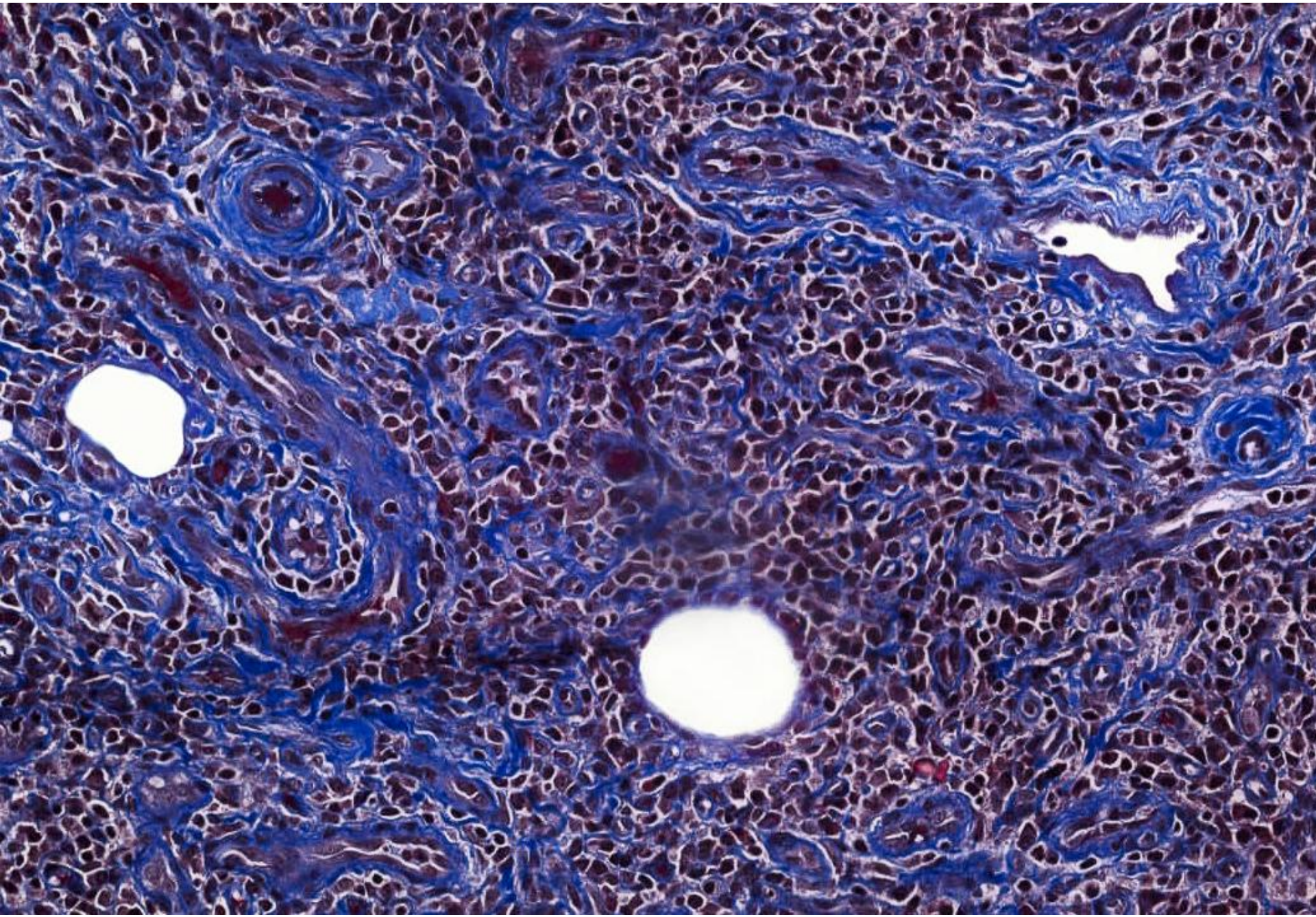
Immunologic pedictors of non-AIDS morbidity

- Several immunologic defects predict disease in treated HIV infection:
  - T cell / B bell activation and dysfunction (not shown here)
  - CD4 lymphopenia
  - **Innate immune activation and inflammation**
- Monocyte activation predicts coronary artery disease

The Lymph node : a major player

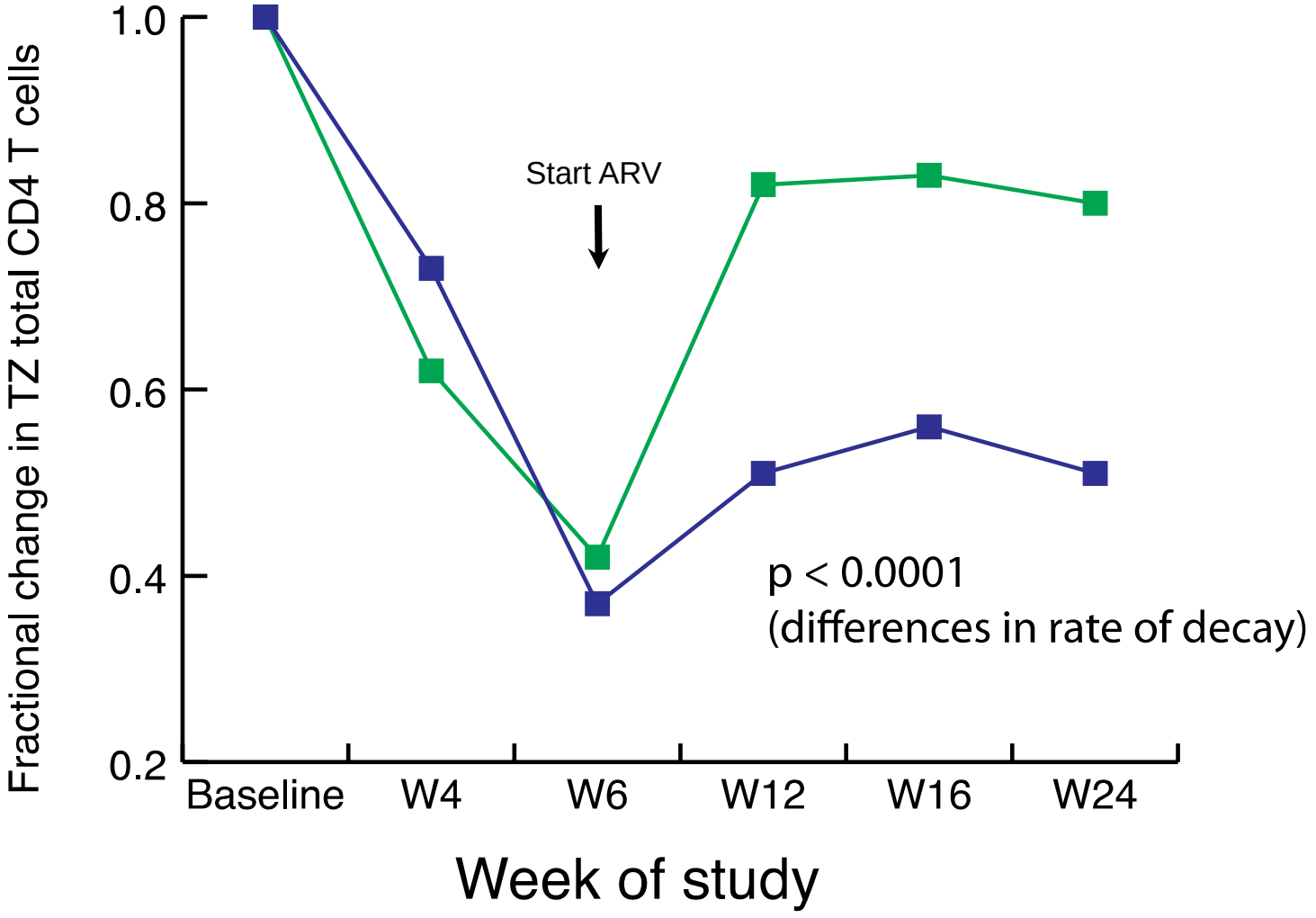






LYMPH NODE FIBROSIS in HIV infection TUSY0102: T. SCHACKER

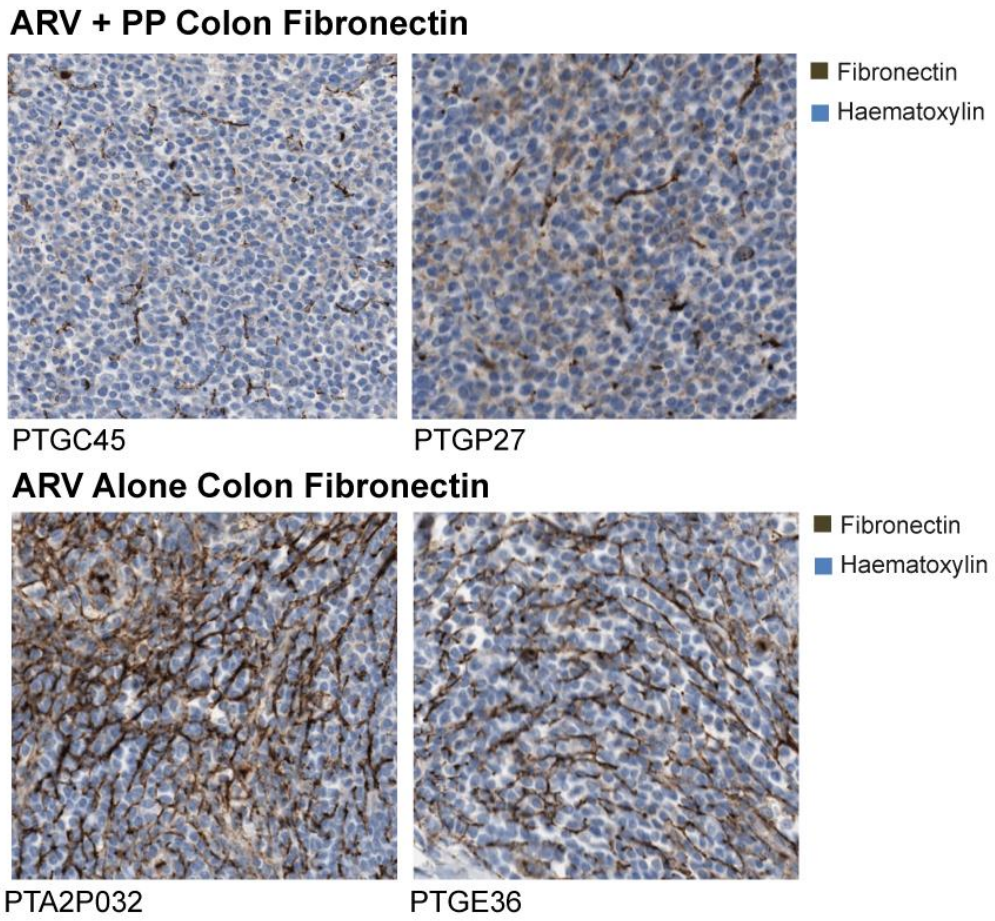
Pirfenidone (anti-fibrotic) therapy in macaque is associated with preservation of LN CD4 T cell population

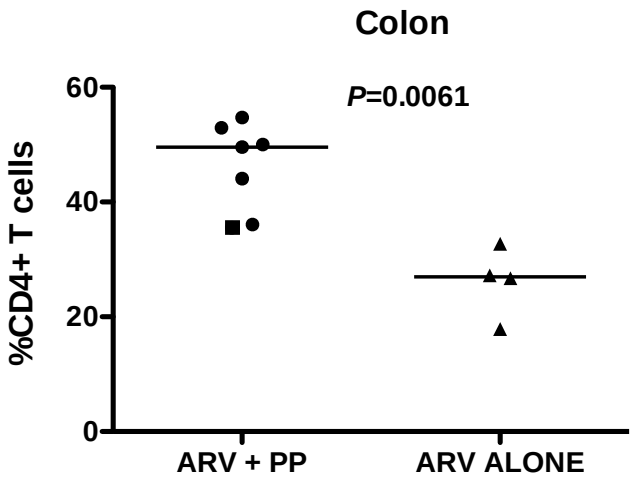


(Schacker)

TUSY0102: T. SCHACKER

In the gut : fibrosis and CD4 loss





Probiotics + ARV in SIV infected macaques decreased fibrosis and enhanced CD4 reconstitution

MOSY0203: N. KLATT

Therapeutic Options in Development

- **Chemokine receptor inhibitors:** maraviroc, TB-652
- **Anti-infective therapy:** CMV, EBV, HSV, HCV/HBV
- **Microbial translocation:** sevelamer, colostrum, rifaximin, pre-biotics, probiotics, isotrentinoin
- **Enhance T cell renewal:** growth hormone, IL-7
- **Anti-fibrotic drugs**: pirfenidone, ACE inhibitors, ARBs
- **Anti-aging:** caloric restriction, sirtuin activators, vitamin D, omega-3 fatty acids, sirolimus, diet, exercise

- **Anti-inflammatory drugs**
  - Chloroquine, hydroxychloroquine
  - Minocycline
  - NSAIDs (COX-2 inhibitors), aspirin
  - Statins
  - Methotrexate (low-dose; CIRT)
  - Talidomide, lenalidomide, pentoxyfylin
  - Biologics (e.g., TNF inibitors, IL-6 inhibitors, anti-INF-alpha)
- **Anti-coagulants:** low dose warfarin, dabigatran, aspirin, clopidogrel

S. DEEKS & P. HUNT

Links to original presentations

- http://pag.ias2013.org/

Complexity of the memory CD4+ T cell pool

TUAA0103: G. SILVESTRI

Proliferation and clonal expansion in response to antigenic stimulation

Naïve Cell → **Effector** **(short-lived, activated)**

Contraction phase

Memory cell pool

Memory stem cell →

Central Memory:
Resident in LNs, spleen.
Able to self-renew and differentiate into Tem.
CD62L+ CCR7+

→ **Effector Memory**:
Resident in periphery.
Able to respond quickly to re-exposure.
CD62L- CCR7-

T memory stem cell (Tscm) - the cell we need to clean?

- 1-3% of circulating and LN-based CD4+ and CD8+ T cells.
- Express more LFA-1 and CXCR3 than naïve cells, but less than T_{CM}
- Least differentiated memory subset, with high proliferative potential
- capable of self-renewal and differentiation into various memory cells
- spared in non-pathogenic SIV model (sooty mangabey)
- Infected in sick rhesus macaque and in HIV-1 infected humans

TUAA0103: G. SILVESTRI

T memory stem cell (Tscm) - the cell we need to clean?

- Large proportion of Tscm contain HIV-DNA and serve as a long-lasting reservoir for HIV-1
- Sequencing revealed close phylogenetic associations between
  - circulating plasma HIV-1 strains during early disease stages
  - and HIV-1 DNA isolated from CD4 Tscm after 6-12 years of therapy

- the wnt/beta-catenin pathway maintains Tscm in dormancy
- In vitro culture assays demonstrated that pharmaceutical beta-catenin inhibitors can promote differentiation of CD4 Tscm into more short-lived effector CD4 T cells.
- Evidence for synergistic activity of HDACi and beta-catenin inhibitors for increasing chromatin acetylation and HIV-1 reactivation.
- Activation of Tscm could facilitate eradication of HIV-infected cells

TUAA0102: M. Lichterfeld

Conclusion for IAS basic science

- no immediate consequence

- Possible nearer future strategies for reducing non-AIDS comorbidities and improving immune reconstitution via adjunctive treatments that
  - reduce mucosal barrier loss
  - lymphatic tissue architecture disruption
  - Inflammation and metabolic and ageing consequences
- More refined predictors for disease progression
  - More individualized indication for ART initiation?

- Further future strategies towards HIV cure and vaccine