CFAR CENTER FOR AIDS RESEARCH
Case Western Reserve University
University Hospitals of Cleveland

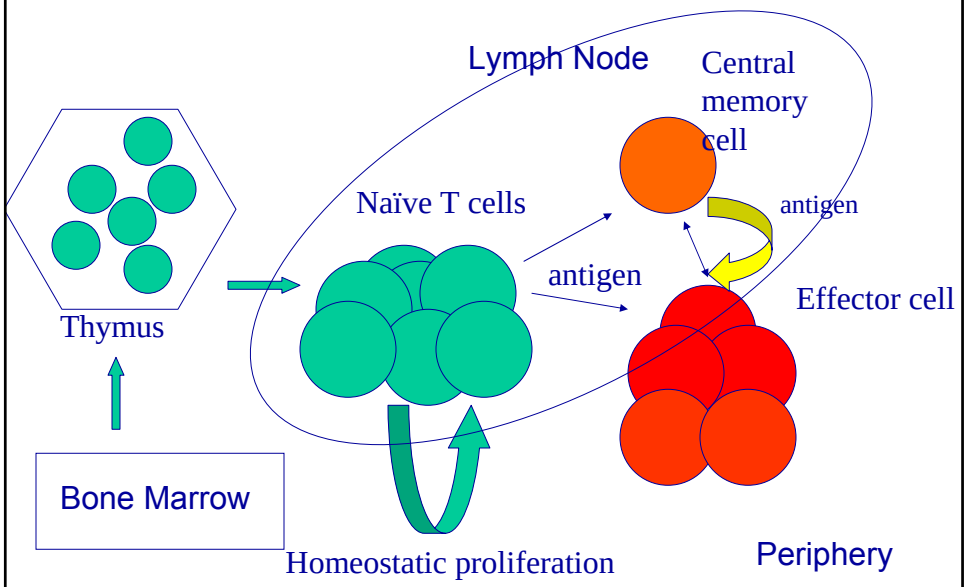
Immune responses to HAART in older patients

or

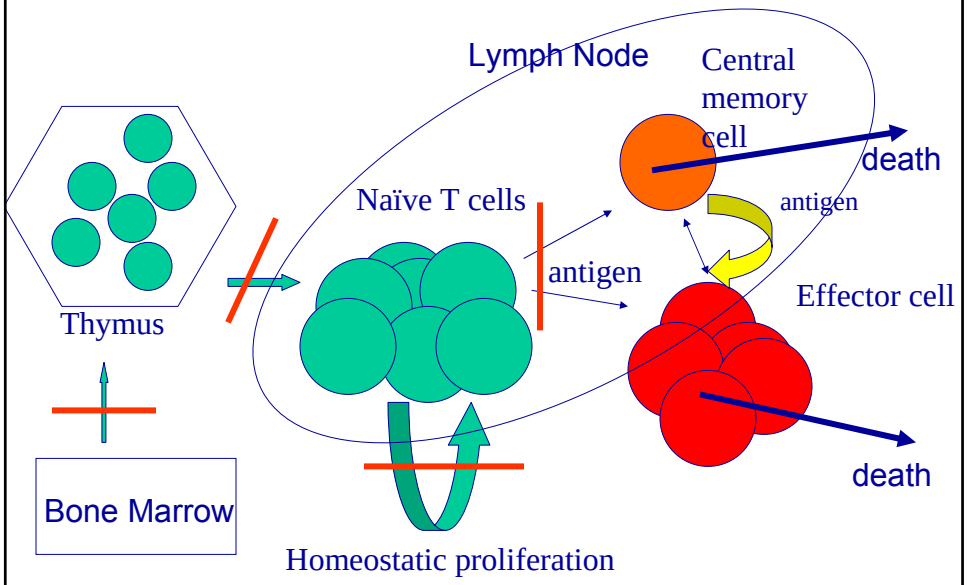
"Post molestam senectutem nos habebit humus"

ASP – IDSA Workshop on HIV and Aging
October 29-30, 2007

A rough guide to T cell homeostasis



CD4 T cell homeostasis in HIV infection



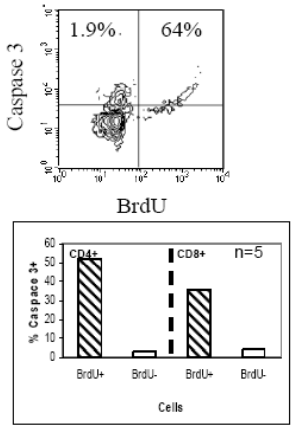
HIV infection is characterized by turnover (death) of circulating central memory (CM) T cells and expansion failure of naïve T cells

- Though correlated with viremia, CM T cells that are activated to enter cell cycle are not HIV reactive and look to be activated by **"bystander"** mechanisms (ie – not through the T cell receptor) Sieg et al, *J Inf Dis '05*
- After engagement of the T cell receptor, naïve CD4+ T cells fail to enter cell cycle and complete division

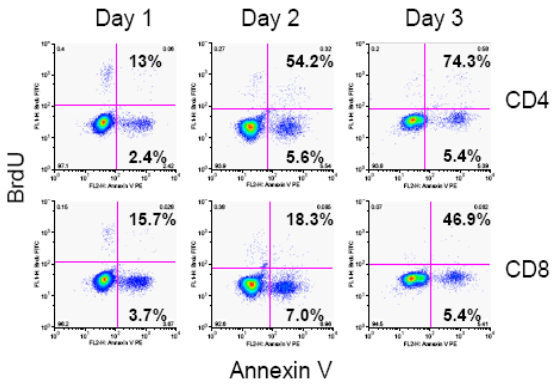
Sieg et al *J Immunol* '03
Luciano et al *J Immunol* '07

Circulating S phase CM T cells tend to die in HIV infection?

Circulating S phase cells express caspase 3

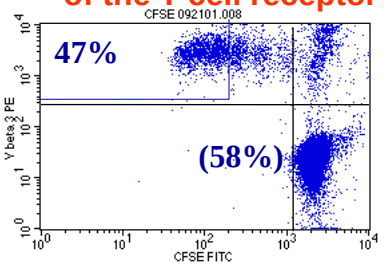


Circulating S phase cells die ex vivo

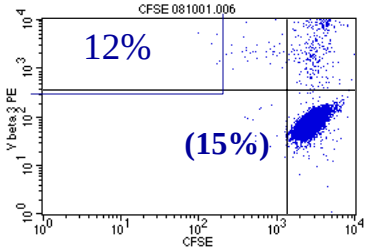


In HIV infection, naïve cells fail to expand after engagement of the T cell receptor

Healthy donor



HIV patient



Vβ3

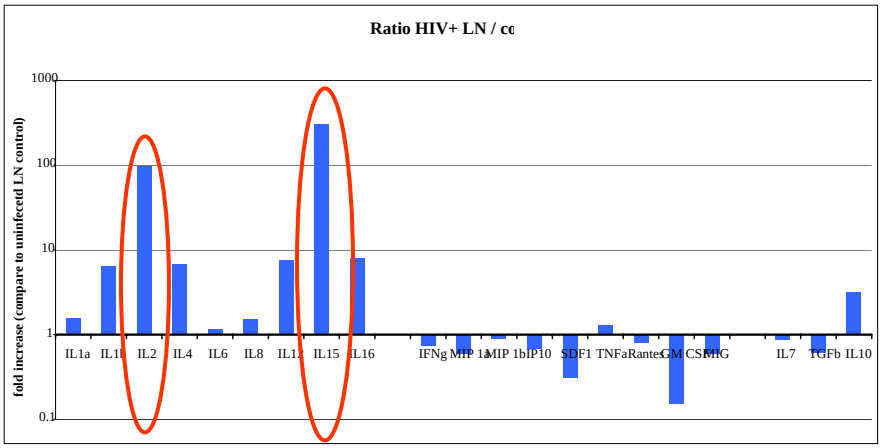
Proliferation

Sieg et al *J Immunol* 03

Cytokine expression is perturbed in the HIV infected lymph node

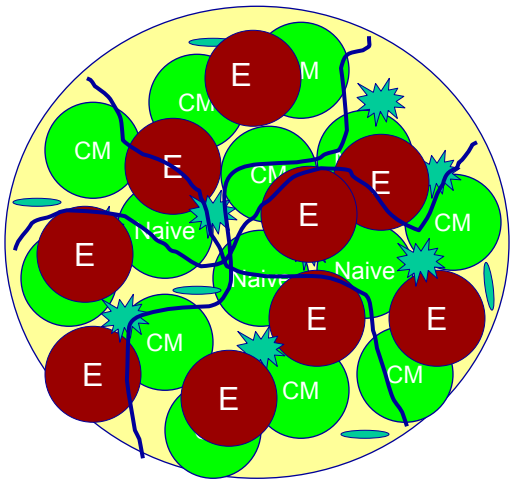
LN control n = 10
HIV+ LN n = 12

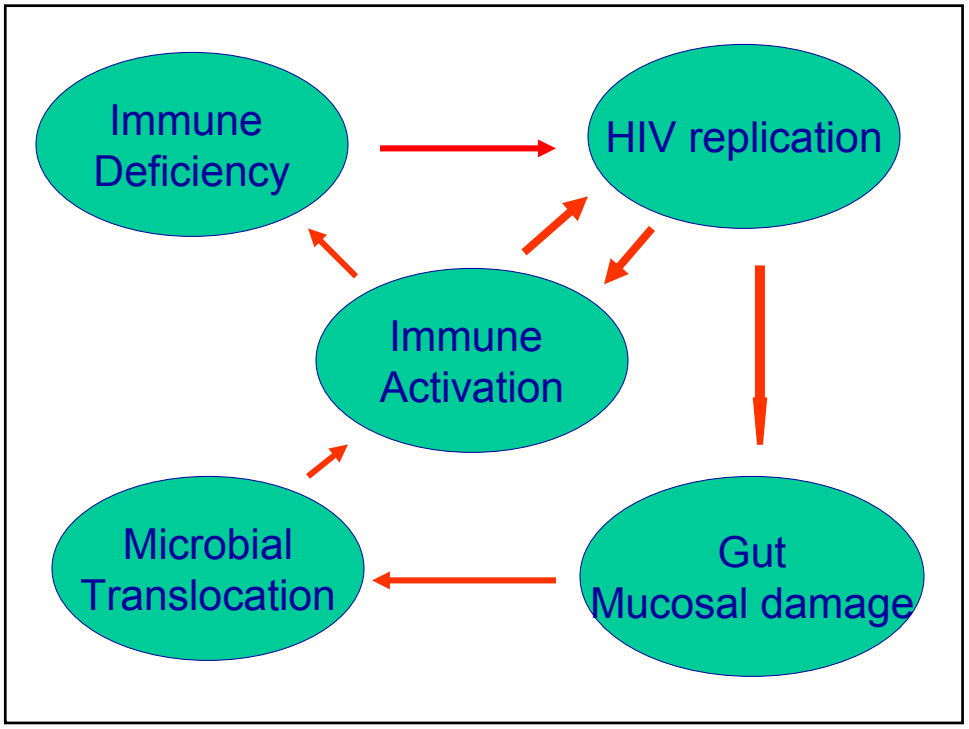
Are these cytokines driving bystander activation and turnover of central memory T cells?



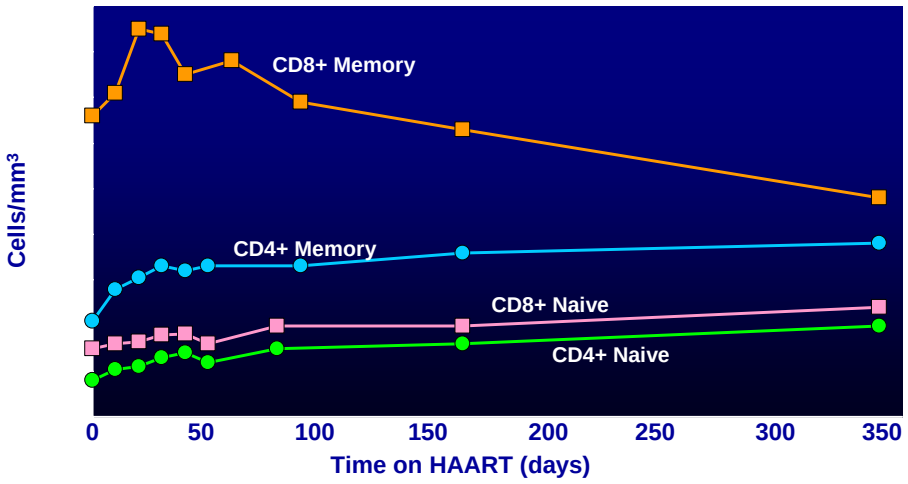
Biancotto et al, *Blood* '07

Activation of adapative and innate immune systems drives HIV pathogenesis in the lymph node





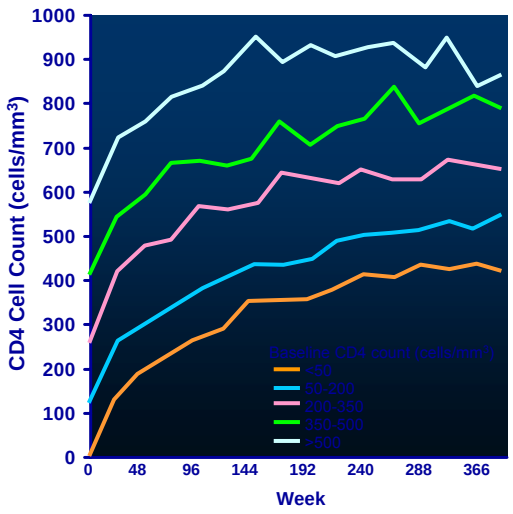
Lymphocyte Subset Changes Following HAART



Wu H, et al. *AIDS Res Hum Retroviruses.* 2001;17:1231-1240.

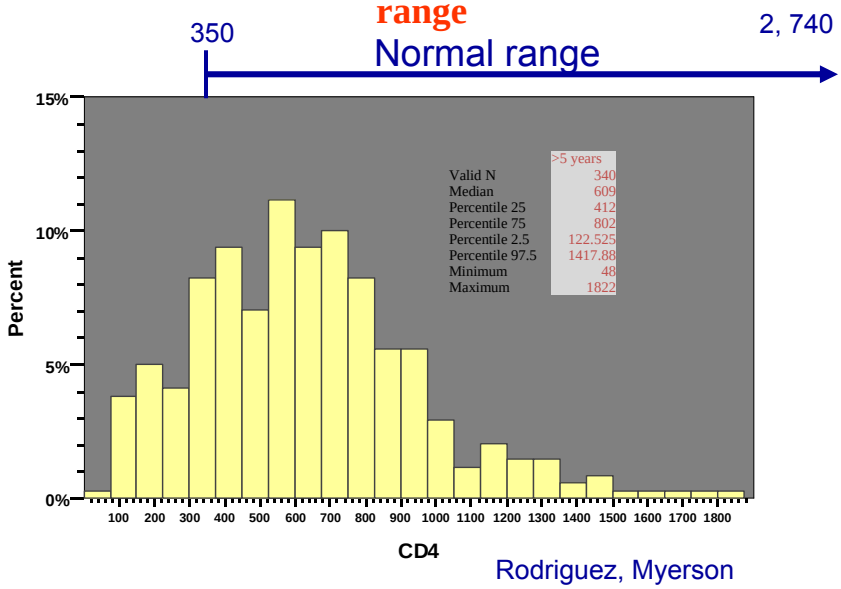
ATHENA Cohort: Increase in Mean CD4 Cell Counts at Year 7 With HAART

- **Treatment-naïve patients starting HAART (n=5299)**
  - **Baseline HIV RNA:**
    - **5 $\log_{10}$ copies/mL**
- **Results at 7 years (n=544 on uninterrupted HAART)**
  - **CD4 count ≥800 cells/mm^3**
    - **73% and 87% of patients with baseline CD4 of 350-500 and >500 cells/mm^3, respectively**
- **Conclusion**
  - **Restoration of CD4 cell counts ≥800 cells/mm^3 with HAART is feasible after 7 years for most patients with pretreatment CD4 cell counts >350 cells/mm^3**



Gras L, et al. *JAIDS.* 2007;45:183-192.

Even after > 5 yrs of HAART and current VL < 400, many pts have CD4 T cell counts below the normal range



Rodriguez, Myerson

After application of HAART, older patients:

- Tend to have less robust CD4 T cell increases (Hunt AIDS '03, Ghandi JAIDS '06)
- Tend to have less naïve CD4 T cell restoration (Lederman AIDS '00, Cohen AIDS '02)
- Are over represented among patients with poorer CD4 T cell restoration (Teixeira AIDS '01 , Kaufmann CID '05)
- Overall, poor immunologic responses are associated with poor clinical outcomes (Grabar AIM '00, Piketty JID '01, Moore JAIDS '05)

Kalayjian et al ACTG 5015 (JID '05)

- Compared immune restoration in response to HAART in 48 older (>45 yo) and 48 younger (18-35 yo) pts.
- Toxicities, virologic suppression comparable but 7 younger and 0 older had virologic relapse ($p < 0.01$)
- Older patients had less robust naïve T cell increases at 48 wks but comparable CD4 T cell increases.
- B cell, NK cell, monocyte changes comparable; activation indices (DR, 38, Fas) CD28 changes comparable.
- Thymic scores (by CT) fell in both groups but TREC content increased more in older pts.
- Baseline sTNFrII levels higher in older subjects but decreases with HAART were comparable. IL-7, sIL-2R levels were comparable.
- In subjects with larger thymuses, decreases in immune activation were correlated with T cell restoration while in those with smaller thymuses, baseline IL-7 levels predicted CD4 T cell restoration.

Key questions

- What are the characteristics of immune restoration in the HIV infected elderly
  - Phenotype, function of both innate and adaptive systems
- What are the key determinants and limitations of immune restoration in HIV infection?
  - Role of thymic output, extrathymic expansion, homeostatic cytokines?
  - Relationship to immune activation?
- What is the relationship between incomplete immune restoration and other complications of HIV infection in the elderly:
  - Malignancies (but only certain malignancies)
  - Cardiovascular Disease
  - Frailty?