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
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

Healthy donor

HIV patient

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

Sieg et al. J Immunol 03

Proliferation
Cytokine expression is perturbed in the HIV infected lymph node

Biancotto et al, *Blood* '07

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

Immune Deficiency

Immune Activation

Microbial Translocation

Gut Mucosal damage

Lymphocyte Subset Changes Following HAART

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/mm³
    - 73% and 87% of patients with baseline CD4 of 350-500 and >500 cells/mm³, respectively
- Conclusion
  - Restoration of CD4 cell counts ≥800 cells/mm³ with HAART is feasible after 7 years for most patients with pretreatment CD4 cell counts >350 cells/mm³


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?