

HIV Controllers and LTNP

Savita Pahwa, MD
Professor
Microbiology & Immunology
Pediatrics & Medicine

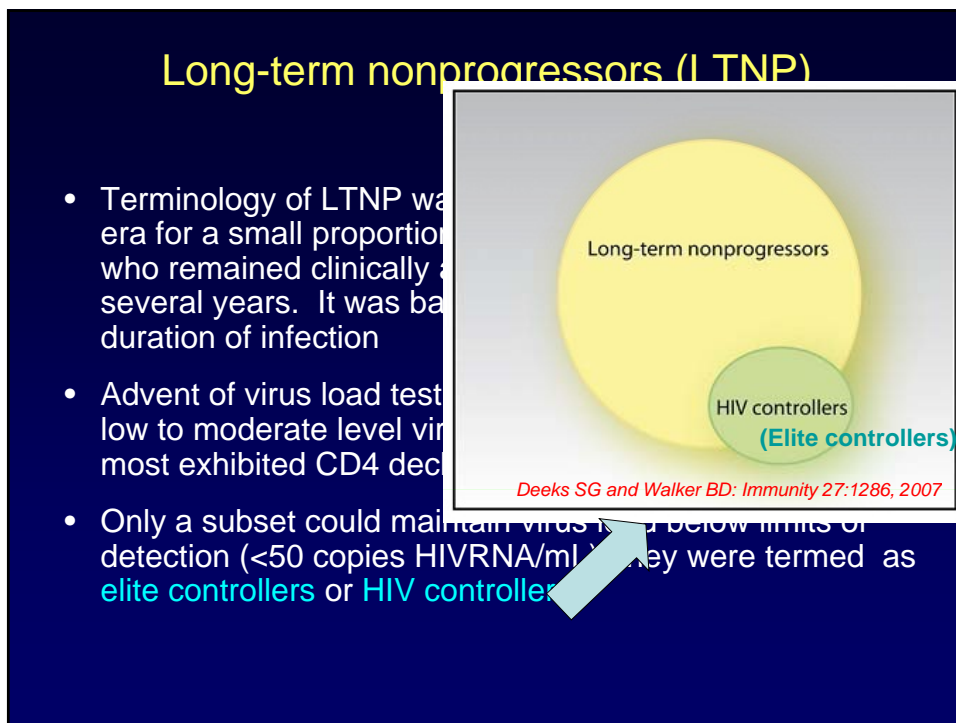
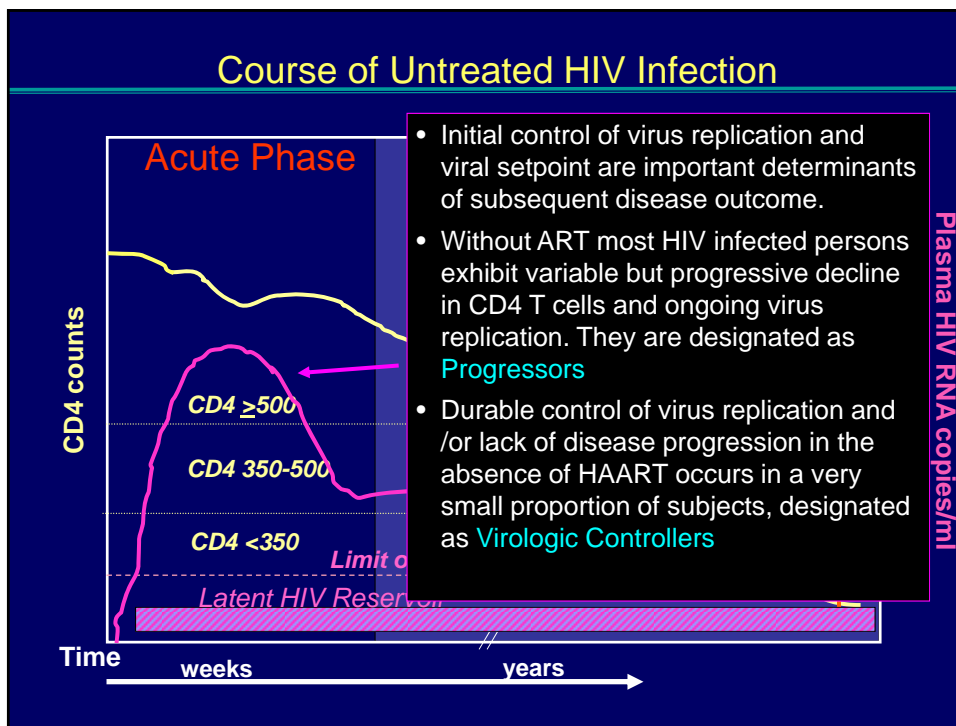
Director,
Developmental Center for AIDS Research

University of Miami Miller School of Medicine
AETC, Orlando May 14, 2010

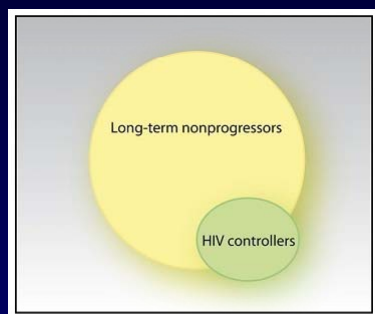
Disclosure of Financial Relationships

This speaker has no significant financial relationships with commercial entities to disclose.

This slide set has been peer-reviewed to ensure that there are no conflicts of interest represented in the presentation.



Elite Controllers (EC)



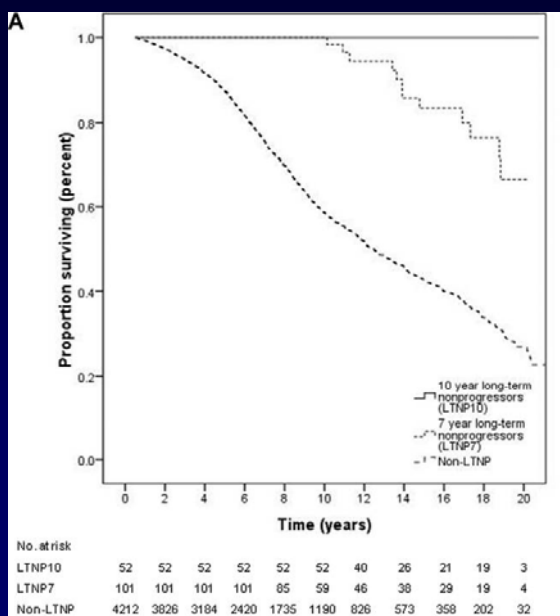
- EC: $\leq 1\%$ of HIV+
- Maintain durable HIV control to <50 copies/mL without HAART
- Rarely progress
- Also known as HIV controllers

Deeks SG and Walker BD: Immunity 27:1286, 2007

Definitions: LTNP

- Definition is based on immunologic control (i.e. stability of CD4 counts) and duration of follow-up
 - Clinically and immunologically stable for duration of 7-10* years without HAART
- Plasma virus load is usually $<2,000$ HIV RNA copies/ml
- Symptom-free
- Incidence among HIV+ persons: approx. 5%
- Most ultimately manifest deterioration in CD4 counts*
- * Stringent classification of LTNP (Okulicz, JF et al, JID 200:1714–23, 2009) reveals differences in outcomes based on duration (7 yrs vs 10 yrs) of LTNP status

Survival Analysis, LTNP



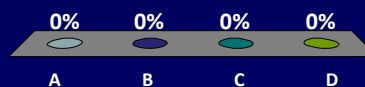
Kaplan-Meier analysis of time to death for 7- and 10-year long-term nonprogressors (LTNP7s and LTNP10s, respectively) and non-LTNPs

(Okulicz, JF et al, *JID* 200:1714–23, 2009)

Characteristics of Long Term Nonprogressors (LTNP)

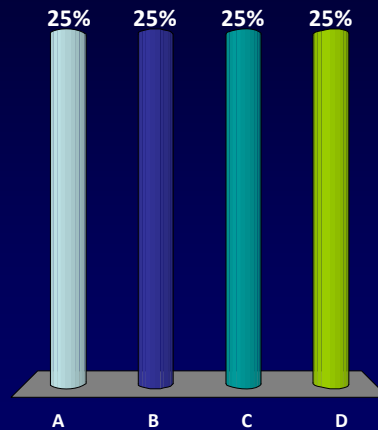
LTNP are HIV+ patients who

- Remain stable for a long time with HAART
- Remain stable for a long time without HAART
- Their plasma virus load is always undetectable
- They are also known as Elite Controllers



Approximate percentage of HIV infected persons that are classified as LTNP is:

- A. 25%
- B. 5%
- C. 50%
- D. <1%



Distinctions between Elite Controllers and LTNP

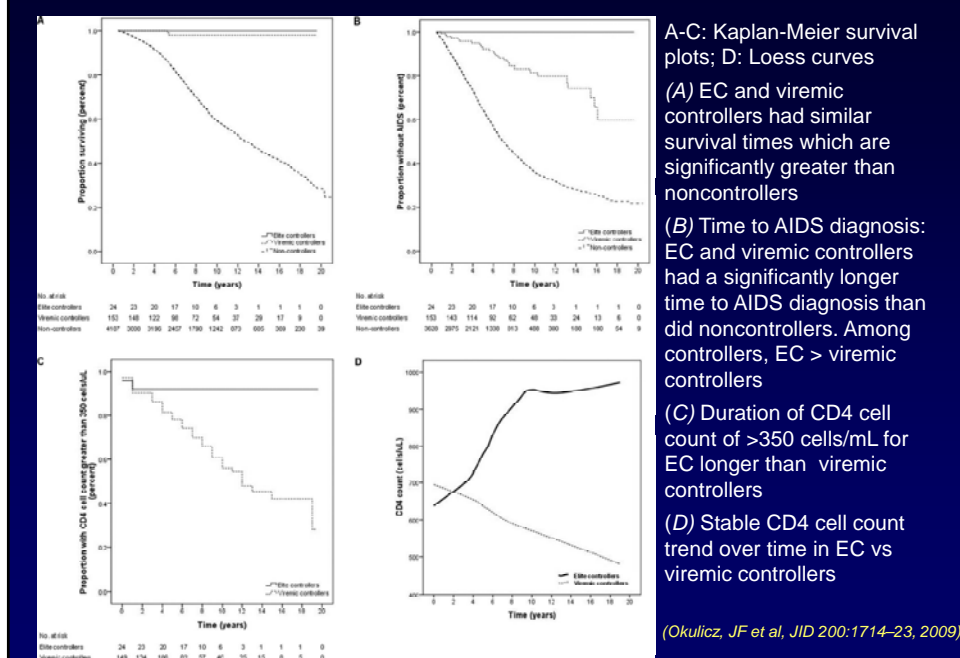


- EC are defined as having undetectable viremia by standard assays (<50 copies RNA/mL)
- LTNP are defined by ability to maintain normal CD4+ T cell counts for prolonged periods (≥ 10 years)
- Most LTNP have viral loads that are low but detectable; In EC, virus is undetectable
- Most EC exhibit minimal rates of CD4+ T cell decline over time; LTNP usually show CD4+ T cell decline over time.

More recent terminology is based on ability to control virus

1. **Virologic controllers:** spontaneous ability to control viremia without HAART (based upon at least one year follow-up)
 - a) **Elite controllers** with VL <50 copies HIV RNA/mL. This is the most unique group and disease progression is infrequent
 - b) **Viremic controllers** with VL >50-2000 HIV RNA copies/mL. Stability over 7-10 years earns the LTNP label. Most will progress (CD4, VL, symptoms) upon subsequent follow-up
2. **Non-controllers or Chronic progressors:** inability to control virus; VL >10,000 copies/mL without HAART

Survival plots: elite controllers, viremic controllers, & noncontrollers



Why are we so interested in Elite controllers?

- Developing a protective HIV vaccine is the over-arching goal of AIDS research
- Elite controllers potentially serve as models for effective HIV-1 vaccination
- Thus the understanding of virologic, genetic, and immunologic factors that contribute to elite suppression of viral replication is of key importance

Factors associated with virologic control

Complete or near complete HIV control: Epidemiologic factors are not revealing

- **Route of HIV acquisition** is not a strong predictor of immunologic non progression
- **Gender** is also not a limiting factor, with both male and female HIV controllers
- **Ethnicity:** Identified in multiple ethnicities
- **Race, geographic location, and/or viral subtype** -potential impact on immunologic and virologic outcomes remains unknown

Possible virologic and host factors involved in HIV control

- **Virus**
 - Mutations/defective virus
 - Viral Fitness
- **Host**
 - Genetics (polymorphisms influencing virus entry or HLA)
 - Anti-viral host restriction factors
 - Immune response
 - Innate Immunity
 - Cytotoxic CD8 T cells
 - CD4 T cells
 - Neutralizing antibody

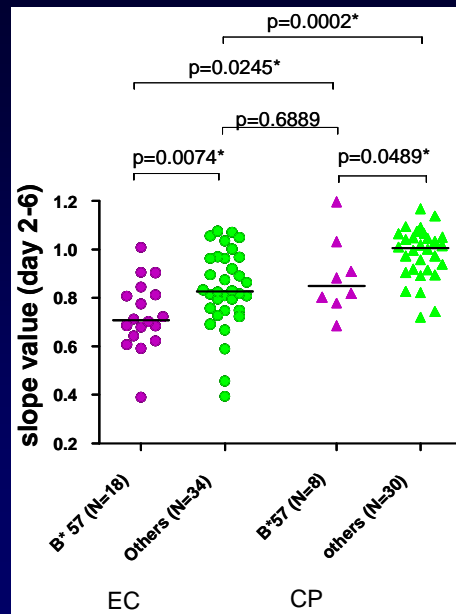
Intrinsic virologic factors are rarely implicated in Virologic Controllers

- **Attenuated virus:** Incidence of infection with defective virus is very rare; famous Australian cohort infected with Nef deletion mutant-many have since progressed
- **Replication defective virus:** Most EC are infected with pathogenic virus
- Defects in viral fitness are attributed to escape mutations in fitness-critical viral epitopes that cannot be compensated

Host factors in HIV Control

- **Known Factors**
 - CCR5 polymorphisms: delta 32 allele homozygosity prevents acquisition of HIV, and heterozygosity assoc with delayed progression to AIDS
 - HLA-B5701, and to a lesser extent HLA-B27 are associated with protection from progressive HIV disease (*Kiepiela et al., Nature 432: 769-775, 2004*)
- **Not yet established**
 - Host restriction factors: Apobec3G, Trim5a, tetherin, others-role in LTNP/EC not yet defined

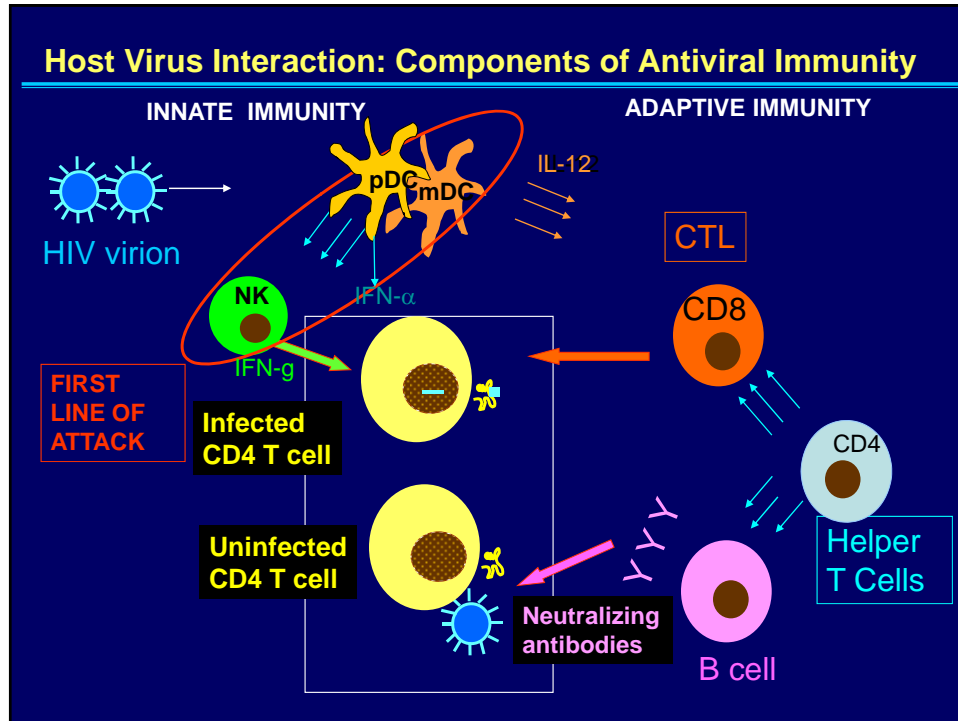
HLA influences viral replication capacity



Miura, Brockman et al, JVI 2009

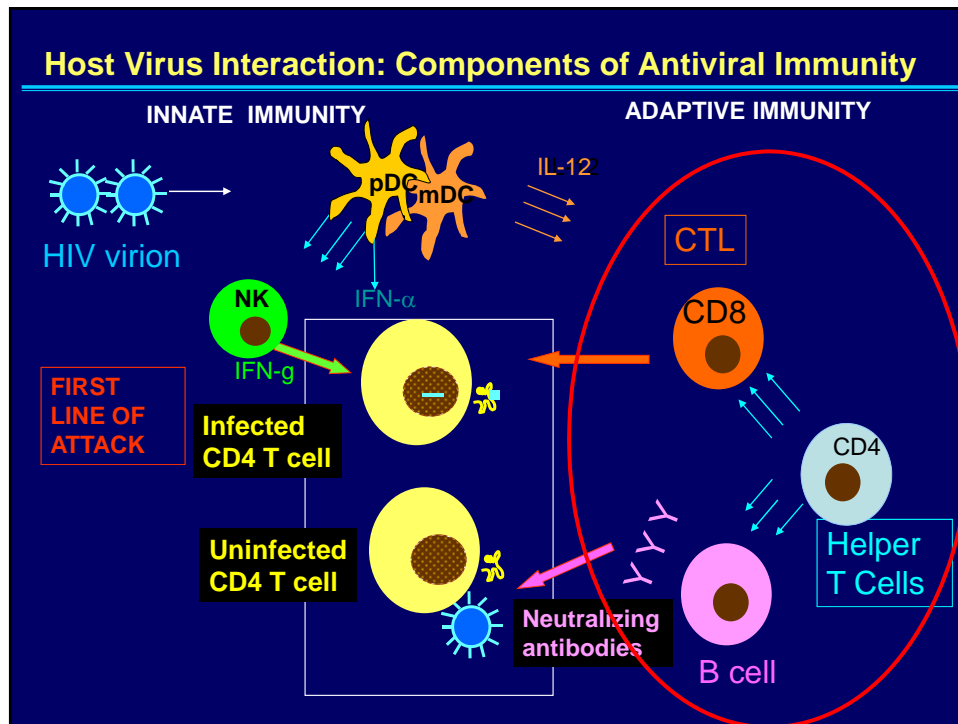
Possible virologic and host factors involved in HIV control

- Virus
 - Mutations/defective virus
 - Viral Fitness
- Host
 - Genetics (polymorphisms influencing virus entry or HLA)
 - Anti-viral host restriction factors
 - Immune response
 - Innate Immunity
 - Cytotoxic CD8 T cells
 - CD4 T cells
 - Neutralizing antibody



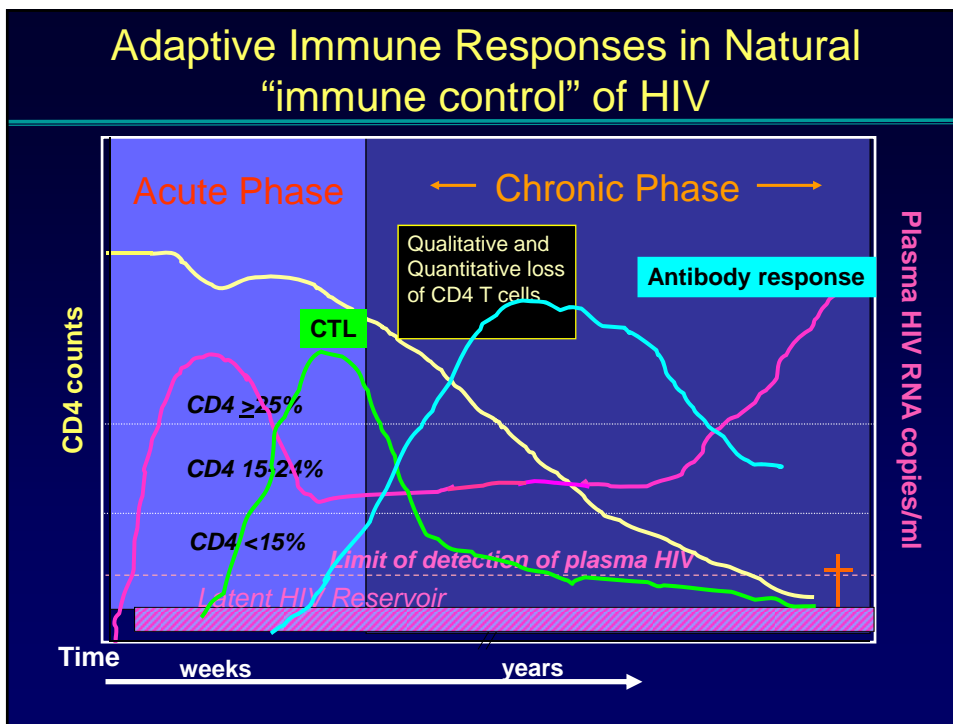
Host Factors: Innate Immunity

- Natural Killer cells: KIR3DS1 an activating NK cell receptor, and KIR3DL1 an inhibitory receptor confer added protection to HLA B57 (*Martin et al., Nat. Genet. 39: 733-740, 2007*)
- pDC are higher in LTNP (*Soumelis et al., Blood: 98: 906-912, 2001*)
- No definitive correlation has been made between innate immunity by standard immunologic measures with viral control



Host factors: adaptive Immunity

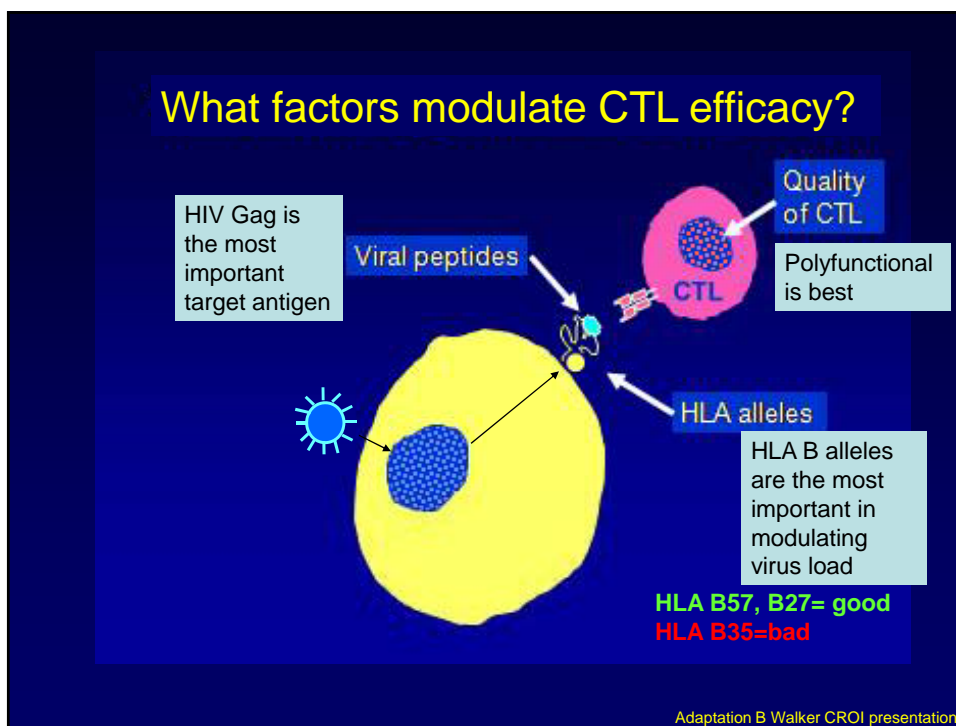
- Strong associations have been seen with
 - Adaptive CD8 T cell immune responses. This is the most consistent antiviral mechanism linked to virologic control
 - Adaptive CD4 T cell immune responses (50%)
- Antibody responses have not been strongly associated with virologic control



Identify the most well established factors for determining virus control in Elite Controllers

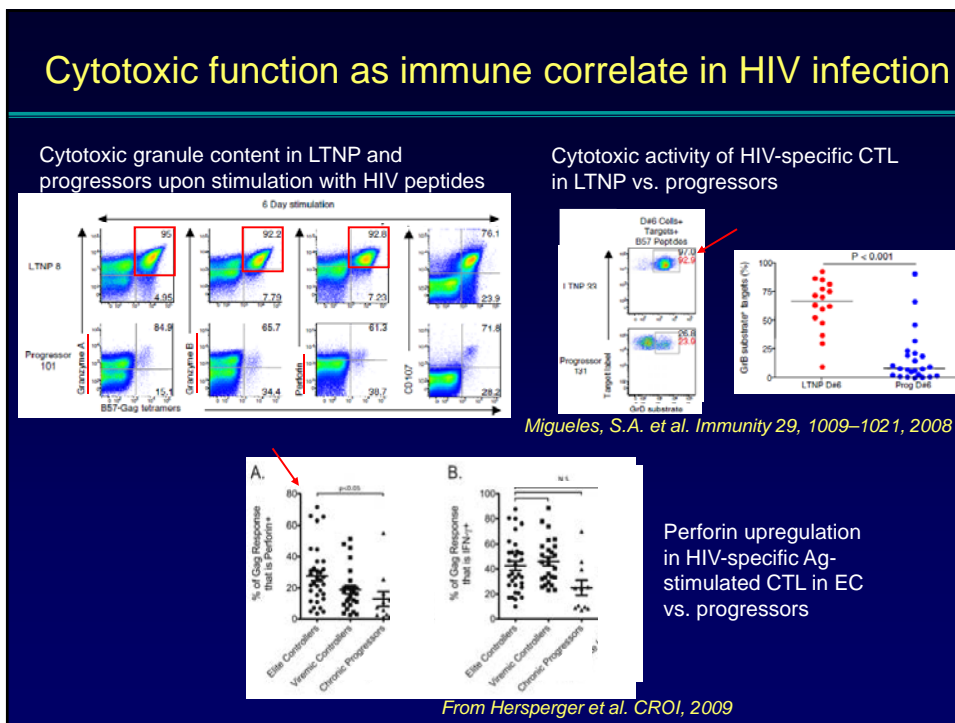
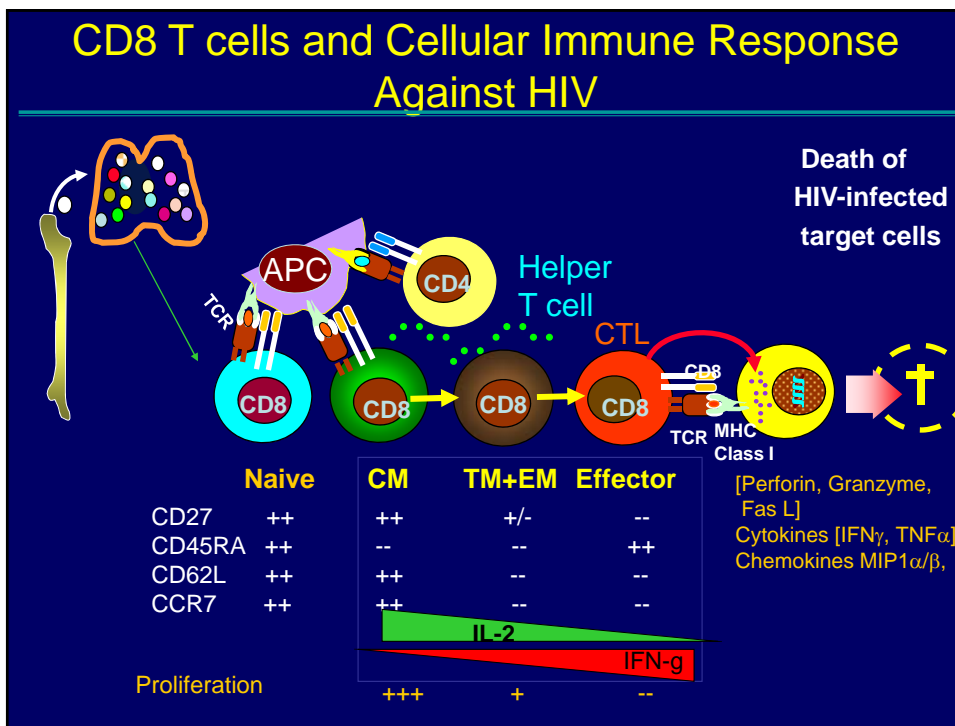
- A. Viral Factors
- B. Host genetic polymorphisms influencing virus entry or HLA
- C. Anti-viral host restriction factors
- D. Innate Immunity
- E. Cytotoxic CD8 T cells
- F. CD4 T cells
- G. Neutralizing antibody

A bar chart showing the percentage of elite controllers for each factor A through G. All factors (A, B, C, D, E, F, G) are represented by bars of equal height, each labeled with 14%.

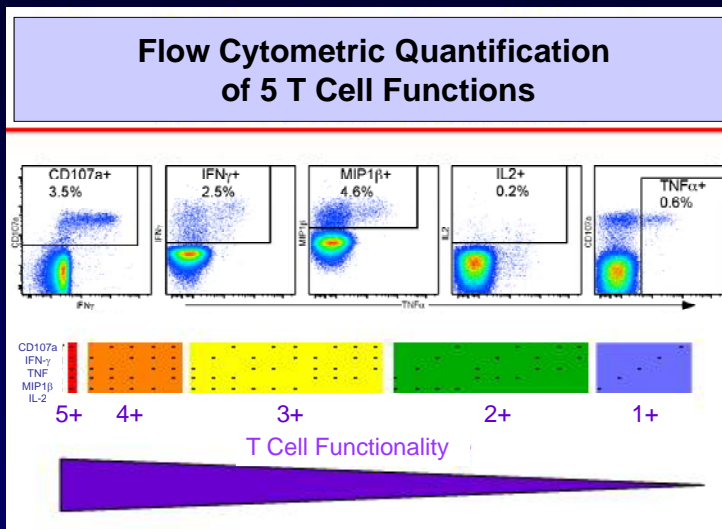


Antiviral Functions of CD8 T cells are better in virus controllers

- **Proliferation** upon encounter with HIV antigens and the ability to produce the cytolytic protein perforin (*Migueles et al., 2002*). HIV specific CD8 T cell proliferation seen only in EC and not in aviremic patients on suppressive HAART regimens
- **Polyfunctional cytokine response:** interferon-g, MIP-1b, TNF-a, interleukin-2, and/or CD107a (*Betts et al., 2006; Zimmerli et al., 2005*). Polyfunctional T cells are seen in blood and mucosal tissues (*Ferre, 2009*)
- **HIV inhibition:** freshly isolated CD8+ T cells of HIV controllers have higher capacities to inhibit HIV replication in infected autologous CD4+ T cells (*Saez-Cirion et al, 2007*)

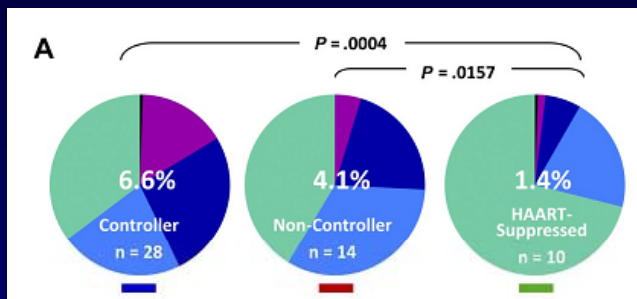


T cell Intracellular Cytokines

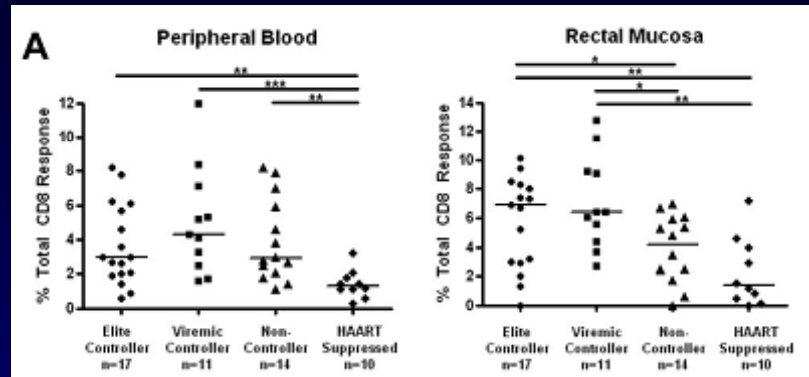


Signature of a “protective immune response”:
Polyfunctional T cells
Loss of polyfunctionality = poor immune response

HIV Gag-specific Polyfunctional Mucosal CD8 T cells



Ferre, A.L. et al. *Blood*
113: 3978– 3989, 2009



Total percentage of CD8 T cells from peripheral blood (left panels) or rectal mucosa (right panels) able to respond in any way (CD107a, IFN- γ , IL-2, MIP-1b, or TNF- α) to Gag stimulation

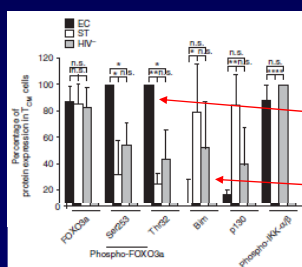
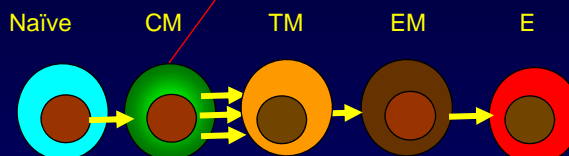
Ferre, A.L. et al. Blood
113: 3978–3989, 2009

CD4 T cells in HIV

CD4 T cells in HIV Infection: loss of CM cells

Loss of Central Memory CD4 T cells

↓↓↓ in progressors and treated aviremic but preserved in EC



TCM cells of EC are resistant to Fas-mediated apoptosis because

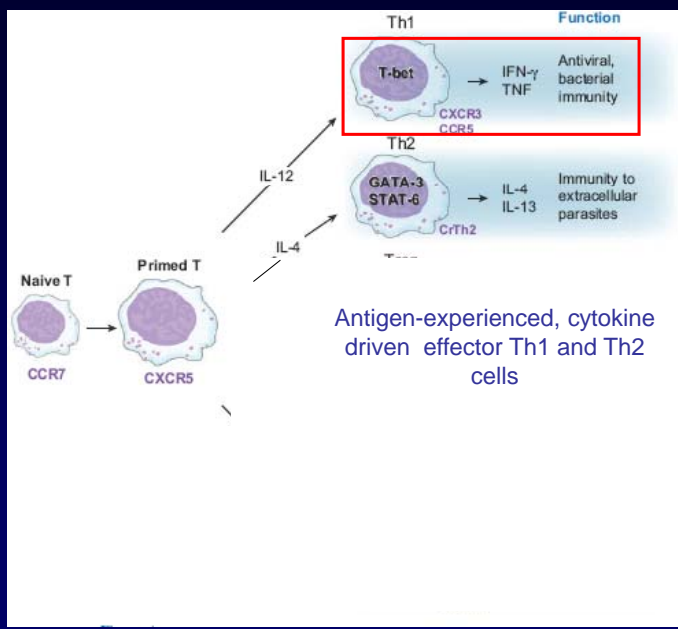
- higher levels of FOXO3a phosphorylation reduces FOXO3a transcriptional activity
- target molecules for apoptosis (Bim and P130 proteins) are reduced

van Grevenynghe et al, *Nature Med.* 14:266-274, 2008

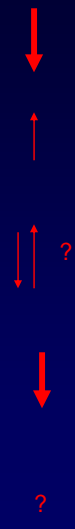
CD4 T cells: role in adaptive immunity against HIV

- CD4 T cells provide important helper function to T cells and B cells
- EC patients show antigen-specific CD4 T cell proliferation and polyfunctional responses
- EC CD4 T cells do not show immune exhaustion (CTLA4 and PD-1); virus replication upregulates these markers
- EC CD4 cells do not show reduced susceptibility to infection
- Several subsets of CD4 T cells exist and can be infected by HIV

CD4 T cell subsets: knowledge is evolving



King C, et al. Annu. Rev. Immunol. 2008



Summary of CD4 and CD8 T cells: Potential Mechanism for Virus Control in HIV “Controllers”

Mechanism	Evidence
Adaptive Immune Response	
HIV-specific CD8 ⁺ T cells	Controllers are enriched certain class I HLA alleles and often have CD8 ⁺ T cells that produce multiple cytokines and/or proliferate in response to HIV peptides
HIV-specific CD4 ⁺ T cells	Controllers often have CD4 ⁺ T cells that express high amounts of HIV-specific IL-2 and interferon- γ in response to HIV peptides

Saez-Cirion, A. et al., Trends Immun 2007

What is the Role of Immune Activation in HIV Disease Progression

Audience Response-3 Immune Activation in HIV

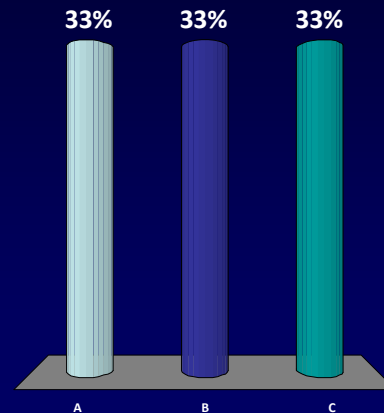
Indicate correct answers

- HIV Infection is associated with generalized persistent immune activation
- This type of immune activation is bad because it leads to destruction of immune cells by apoptosis
- Persistence of this type of immune activation is good because it makes killer CD8 T cells do their job

Immune Activation in HIV

Indicate correct answers

- A. HIV Infection is associated with generalized persistent immune activation
- B. This type of immune activation is bad because it leads to destruction of immune cells by apoptosis
- C. Persistence of this type of immune activation is good because it makes killer CD8 T cells do their job

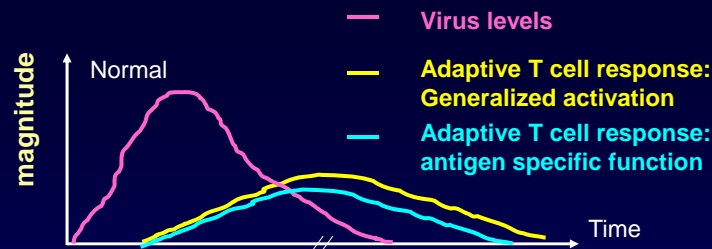


Generalized Immune Activation is.... not good

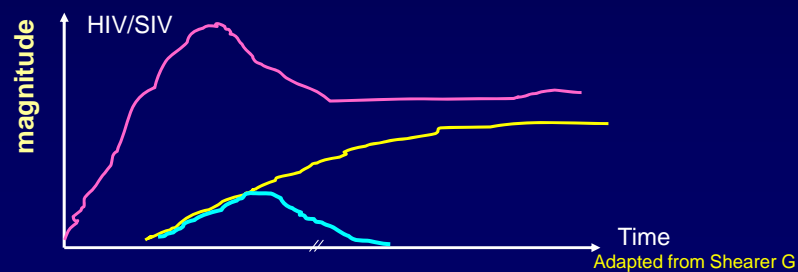
- Immune activation is marked by excessive frequency of HLADR+ CD38+ CD8 T cells
- Frequency of activated CD8 T cells are a better predictor of disease progression than loss of CD4 T cells or increase in virus load or virus tropism

(Giorgi,J, 1993)

Normal response to viral infections



Aberrant immune activation- immune activation persists even though HIV specific immune response wanes



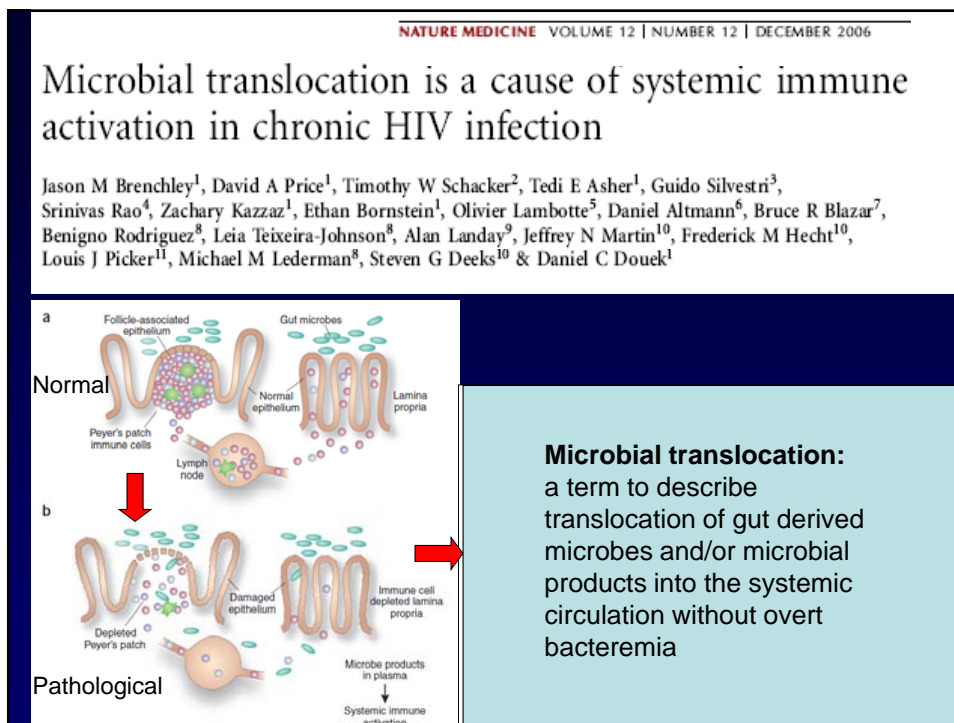
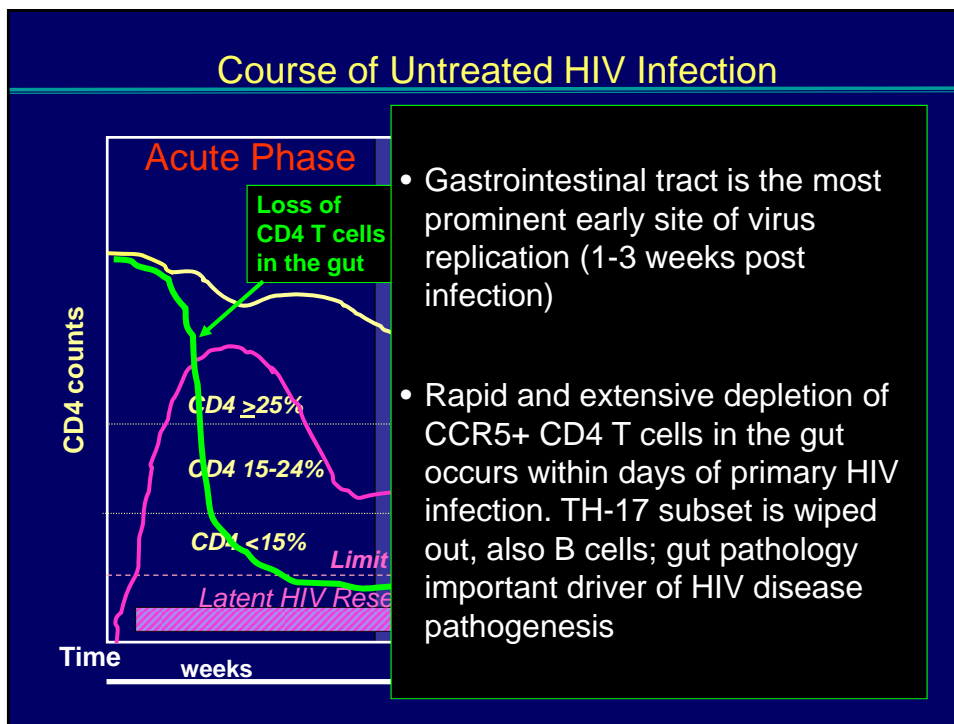
Generalized immune activation: What causes it and why is it so bad?

Exact cause not confirmed; most likely causes:

- HIV and its proteins drive aberrant immune activation
 - Stimulation of innate immune system
 - Direct and Indirect stimulation of T and B cells
 - Failure of immunoregulation (ie, loss of T-regulatory cells)
- HIV induced gut damage leads to microbial translocation
 - bacterial products drive immune activation of innate and adaptive immune system

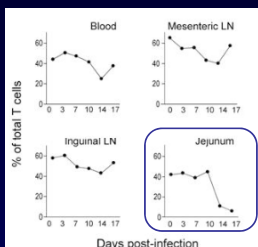
It is detrimental to host-

- Results in quantitative and qualitative loss of immunity by exacerbating HIV replication, causing immune exhaustion and apoptotic cell death

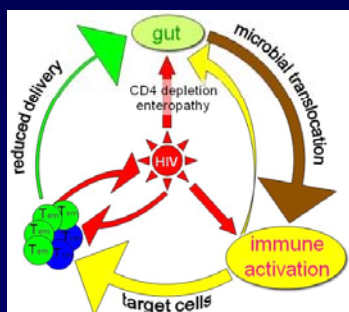


PATHOGENESIS OF HIV-MEDIATED IMMUNODEFICIENCY

Daniel Douek, Vaccine Res Ctr, NIAID, NIH, Bethesda, MD, US



massive depletion of CD4 T cells (CD4+ CCR5+) in the GI during acute SIV infection

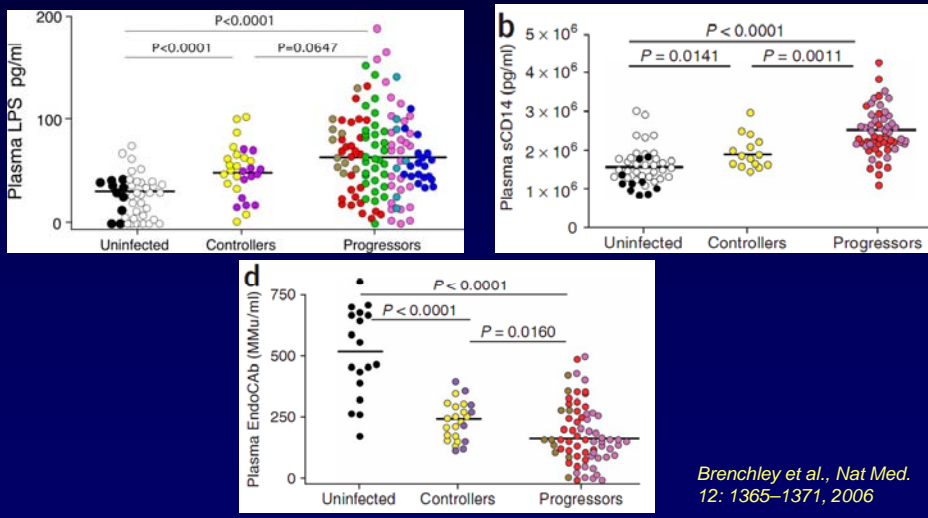


enteropathy & gut permeability

chronic systemic immune activation that drives infection of CD4 and maintains HIV replication

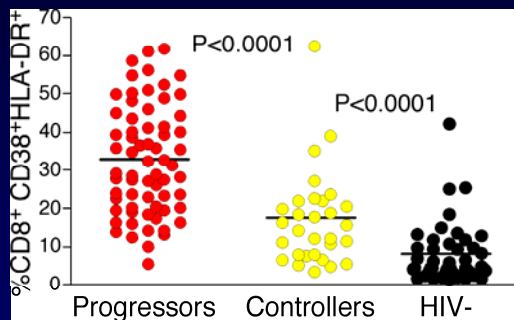
Microbial translocation is lower in Elite Controllers than in progressors

but elite controllers manifest higher levels of microbial translocation than uninfected persons



Brenchley et al., Nat Med. 12: 1365-1371, 2006

Do elite controllers have evidence of immune activation?

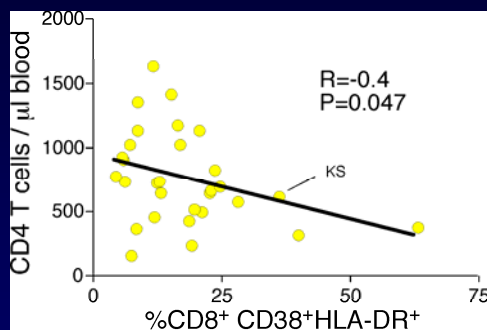


Elite controllers have lower frequencies of activated T cells compared to Progressors (but higher than uninfected individuals)

Brenchley et al., Nat Med. 12: 1365–1371, 2006

Immune Activation in Elite Controllers

Is immune activation detrimental in Elite Controllers?



Slow CD4 T cell depletion can occur in association with T cell activation

Hunt, P.W. et al. J. Infect. Dis. 197:126–133, 2008

Elite Controllers: Summary -1

- EC are natural viremic controllers and generally do not experience the depletion of CD4+ T cells seen in progressive HIV-1 infection except in association with immune activation
- EC also have a lower degree of mucosal CD4+ T cell depletion and lower levels of microbial translocation than patients with progressive disease

Elite Controllers Summary-2: Immune Mechanisms

- Polyfunctional CD8+T cell responses to HIV-1 stimulation are seen in primary HIV-1 infection. These responses are lost in patients who become progressors, but are maintained in EC
- Primary CD8+ T cells from EC (but not progressors) are capable of suppressing HIV-1 replication in autologous CD4+ T cells
- Patients on HAART have comparable viral loads to EC, but do not have the effective granzyme B-mediated killing of HIV-1-infected CD4+ T cells that is seen in EC
- A definable immunologic marker for durable control or a protective host genotype has still not been defined

Where do we go from here?

- Extensive viral and host genetic analyses, are currently underway through the HIV Controller Consortium; whole-genome association will be determined in 1000 elite controllers and 1000 viremic controllers (enrollment ongoing)
- Studies in NHP will provide additional insight of immune preservation despite ongoing viremia
- Systems biology approaches will dissect out unique intracellular pathways in immune regulation in distinct patient groups

Different course of SIV in two primate models

SIVsmm → SIVmac



Natural Host:
African Sooty mangabey

Slow or non-progression

Virus replication +

Absence of immune activation



Non-natural Host:
Asian Rhesus macaque

Rapid Progression

Virus replication ++

Immune activation +++

Thank you

Disclosure of Financial Relationships

This speaker has no significant financial relationships with commercial entities to disclose.

This slide set has been peer-reviewed to ensure that there are no conflicts of interest represented in the presentation.

We are studying EC, VC and LTNP

Please tell your patients about our interest

Eligibility:

- EC: VL < 50 copies for ≥ 1 year without HAART
- VC: VL bet 50-2000 copies for ≥ 1 year without HAART
- LTNP: CD4 > 350 for 7-10 yrs without HAART

Contact: Savita Pahwa, MD: 305-243-7732;

spahwa@med.miami.edu

Jeanne Tamargo: 305-243-8125