HIV and the Immune System: Complexities and Consequences

Brinda Emu, MD
28 February 2013
HIV from 1981

- 1981: First cases of PCP, Lymph Nodes, Kaposi Sarcoma
- 1982: "AIDS"
- 1983: HIV identified as cause of AIDS
- 1986: AZT is first licensed antiviral to target HIV
- 1991: HIV is leading cause of death in men aged 18-24
- 1996: "HAART": a cocktail of HIV medications
History of HIV from 1981:

- 1981: First cases of PCP, Kaposi Sarcoma
- 1982: "AIDS"
- 1986: HIV identified as cause of AIDS
- 1991: AZT is first licensed antiviral to target HIV
- 1996: HIV is leading cause of death in men aged 18-24
- 1996: "HAART", a cocktail of HIV medications
- 2006: Large Merck vaccine trial fails
- 2008: 1.1 million infected in US; 33 million worldwide
- 2008: 2.7 million new infections
- 2008: 2 million deaths
Priorities for HIV Care and Research

• Access to Care/HIV Medications
• Prevention of New Infections
• Treatment of Co-morbidities

• Vaccine Development
• HIV Cure
• Non-AIDS related mortality

Immunologic Complexities

Immunologic Consequences
Complexities of the Immune Response
Natural History of HIV Infection

- **Acute HIV infection**
  - Wide distribution of virus
  - Seeding of lymphoid organs

- **Clinical latency**

- **Opportunistic infections**

- **Onset of symptoms**

- **Death**

**CD4+ T cells (cells/μl)**

**HIV RNA (copies/ml plasma)**

**Time after infection**
Natural History of Untreated HIV Disease

Non-controllers: 90-95%
Natural History of Untreated HIV Disease

Long-term Non-progressors (LTNP): 5-10%
Natural History of Untreated HIV Disease

- Elite Controllers (EC): <1%
- Long-Term Non-Progressors (LTNP): 5-10%
Viral control is a predictor of progression to AIDS

Ho, D. D.  Science 1996

Majority of Elite Controllers do not progress to AIDS.

Are they a model for functional HIV cure?
How do Elite Controllers maintain control?

<table>
<thead>
<tr>
<th>Virus</th>
<th>Host</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Are they really infected?</td>
<td>• Adaptive immune response</td>
</tr>
<tr>
<td>– All seropositive (ELISA/ Western)</td>
<td>• Innate immune response</td>
</tr>
<tr>
<td>– Proviral DNA and plasma viral RNA present</td>
<td>• Levels of T cell activation</td>
</tr>
<tr>
<td>• Is the virus defective?</td>
<td></td>
</tr>
<tr>
<td>– Large deletions reported</td>
<td></td>
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<tr>
<td>– Replication competent virus also reported</td>
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<tr>
<td>– Blips of replication</td>
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<tr>
<td>– Transmission pairs identified</td>
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</table>
Study Design

Flow Cytometry:

“SCOPE” Cohort Study: San Francisco General Hospital
7000 patient cohort with specimens stored every 4 months
Stimulation of PBMCs with HIV Gag peptide pools
Staining for extracellular markers and intracellular cytokines

Comparator Groups

Elite controllers: Documented VL<75 copies/mL off therapy
Viremic Controllers: Documented VL<2000 copies/mL off therapy
Non-controllers: Viral load >10000 copies/mL
HAART Suppressed: Documented VL<75 copies/mL on therapy
# Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Elite N=30</th>
<th>Controller N=34</th>
<th>Non-Controller N=68</th>
<th>Suppressed (HAART) N=131</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>48</td>
<td>43</td>
<td>44</td>
<td>47</td>
</tr>
<tr>
<td>Years infected</td>
<td>16 (15-18)</td>
<td>14 (8-16)</td>
<td>13 (9-16)</td>
<td>13 (9-17)</td>
</tr>
<tr>
<td>CD4</td>
<td>711 (460-990)</td>
<td>471 (347-702)</td>
<td>238 (158-398)</td>
<td>447 (306-653)</td>
</tr>
<tr>
<td>CD8</td>
<td>822 (541-1116)</td>
<td>1115 (753-1454)</td>
<td>1554 (915-2414)</td>
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</tr>
<tr>
<td>HIV RNA (log)</td>
<td>1.88</td>
<td>2.82 (2.27-3.18)</td>
<td>4.46 (4.15-4.87)</td>
<td>1.88</td>
</tr>
</tbody>
</table>
T cell activation in HIV

- T cell activation result in “bystander” effects on the immune system
- CD8 T cell activation is independent predictor of survival
  - Measured by expression of CD38 and HLA-DR
- High levels of T cell activation predict CD4+ T cell decline
- Persistent T cell activation despite HAART predicts poor CD4+ T cell gains

ECs have lower levels of CD8+ T cell activation compared with controllers. 

\[ p = 0.003 \]
ECs have lower levels of CD8+ T cell activation compared with non-controllers.
ECs have higher levels of CD8+ T cell activation compared with Suppressed

%CD8 T cells CD38+HLADR+

- ELITE
- CONTROLLER
- NON-CONTROLLER
- SUPPRESSED

p=0.04
ECs have higher levels of CD8+ T cell activation compared with HIV seronegatives.
Control of Viral Replication associated with T cells

- LNTP have higher CD8 and CD4 responses
- Rise in CD8 correlates with fall in viral load
- Depletion of CD8 T cells in macaques results in higher SIV replication
- Dual functional T cells (secreting Interferon-γ and IL-2) associated with better viral control

Do Elite Controllers control virus in the same way as LTNP?

ECs Have Comparable Levels of CD4+ Dual-functional T Cells Compared to Viremic Controllers

\[ \text{Gag-specific CD4}^{+}\text{IFN}\gamma^{+}\text{IL2}^{+} \]

Elite Controller (VL<50) N=31  Viremic Controller (VL 50-2000) N=30

\[ P=0.22 \]
ECs Have Higher Levels of CD4+ Dual-functional T Cells Compared to Non-Controllers

P=0.0002
ECs Have Higher Levels of CD4+ Dual-functional T Cells Compared to HAART Suppressed

P<0.0001
Elite and Viremic Controllers Have High Levels of Dual-functional CD8 T Cells

- Elite Controller (VL<50) N=31
- Viremic Controller (VL 50-2000) N=30
- Non Controller (VL>10,000) N=29
- HAART Suppressed (VL<50) N=55
- HIV Negative N=37

P=0.0009
P<0.0001
Marked Heterogeneity of HIV-specific CD8+ Responses Among ECs

Gag-specific CD8+IFNγ+ IL2+

"Elite"  Controller  Non-controller  HAART Suppressed  HIV Negative
VL < 50  50-2000 > 10,000 < 75  n=56  n=77  n=37  n=40  n=38
n=56  n=77  n=37  n=40  n=38

< 0.0001
< 0.0001
< 0.0001
0.23

< 0.0001
Human Leukocyte Antigen (HLA)

- HLA molecules on the surface of cells bind peptides (bacteria, viruses, self) and present these to T cells.
Human Leukocyte Antigen (HLA)

- HLA molecules on the surface of cells bind peptides (bacteria, viruses, self) and present these to T cells
- T cells recognize HLA-peptide complex and become activated
Human Leukocyte Antigen (HLA)

- HLA molecules on the surface of cells bind peptides (bacteria, viruses, self) and present these to T cells
- T cells recognize HLA-peptide complex and become activated
- HLA type is determined genetically with hundreds of variants
Protective HLA types are enriched among Controllers

**Elite Controller** (N=22) 60%

**Viremic Controller** (N=21) 52%

**Non Controller** (N=73) 16%

***HLA types B57, B27, B13, B58, B81 are considered protective***

P = 0.001

P = 0.01
Controllers With Protective HLA Alleles Have Higher CD8 Gag-specific Responses

P = 0.01

[Bar graph showing comparison between non-protective and protective controllers for CD8 dual functional responses]
Controllers With Protective HLA Alleles Have Higher CD8 Gag-specific Responses

![Graph showing CD8 Dual Functional responses for Controllers and Non-Controllers with and without Protective HLA alleles.]

- **Controllers**
  - Non-Protective: 0.05 (NS)
  - Protective: 0.20 (P=0.01)

- **Non-Controllers**
  - Non-Protective: 0.10 (NS)
  - Protective: 0.12 (NS)
Summary of Elite Controllers

• Maintain tight viral control despite HIV infection

• High levels of dual-functional T cells
  – Marked heterogeneity!!!!

• Heterogeneity suggests different mechanisms of control
  – Protective HLA alleles enriched
  – Protective HLA alleles associated with CD8 T cell responses
  – Protective HLA alleles are not necessary for viral control
  – Protective HLA alleles are not sufficient for viral control
HIV Pathogenesis in HIV Elite Controllers

Seropositive, but no latent infection and no ongoing viral replication

Replication incompetent virus
HIV Pathogenesis in HIV Elite Controllers

- Replication-competent virus
  - Strong T cell response (previous exposure and/or protective HLA)
  - Kills virus prior to CD4 infection, no infection
  - Low level infection because of strong T cell response

Seropositive, but no latent Infection and no ongoing viral Replication

Replication Incompetent Virus
HIV Pathogenesis in HIV Elite Controllers

- Replication-competent virus
  - Other arms of host immune response (innate immunity, coreceptors, etc)
  - T cell response (previous exposure and/or protective HLA)
  - Low level infection because of strong T cell response
  - Seropositive, but no latent infection and no ongoing viral replication
  - Defective virus particle incapable of replication
- Kills virus prior to CD4 infection, no infection
- Lowers peak viral load, allowing cells to control viremia early
- Kills virus prior to CD4 infection, no infection
- Low level infection because of strong T cell response
Elite Controllers as a Model for HIV Cure?

• Elite controllers are a small, unique group of individuals who spontaneously suppress HIV replication

• They represent the “ideal” response to HIV infection

• Goal is to understand and “mimic” the host response in EC to develop effective vaccine strategies

• Important to remember that not all ECs control in the same way and careful attention is needed to determine what can be replicated
HIV and the Immune System: the Consequences
Adults and Adolescents Living with an AIDS Diagnosis, by Sex, 1993–2009—United States and 6 U.S. Dependent Areas

Note. All displayed data have been statistically adjusted to account for reporting delays, but not for incomplete reporting.
Dramatic Decrease in Mortality with HAART

Krentz, 2005, n=560
Increased Rates of Morbidity/Mortality

- Cardiovascular, Liver, Kidney Disease
- Metabolic Disorders
- Osteoporosis
- Malignancies

Many of these conditions are associated with aberrations of Immune Response
Overview of Talk

- CD4/CD8 T cell ratio
- Loss of Naïve T cell numbers
- CD28 T cell expansion
- CMV infection
- Similarity of HIV disease and aging
Groups Studied

- **HAART-suppressed**: On successful antiretroviral therapy with plasma viral load <75 copies/mL
- **Non-controllers**: Plasma viral load >10,000 copies/mL
- **HIV negative**: High-risk individuals presenting for post-exposure prophylaxis
### Patient characteristics

**N=50**

<table>
<thead>
<tr>
<th></th>
<th>Non-controller N=29</th>
<th>HAART Suppressed N=21</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>44 (33-66)</td>
<td>47 (32-61)</td>
</tr>
<tr>
<td><strong>Years infected</strong></td>
<td>15 (3-25)</td>
<td>10 (5-20)</td>
</tr>
<tr>
<td><strong>CD4</strong></td>
<td>274 (10-687)</td>
<td>497 (300-1079)</td>
</tr>
<tr>
<td><strong>CD8</strong></td>
<td>911 (230-2644)</td>
<td>1037 (484-1693)</td>
</tr>
<tr>
<td><strong>HIV RNA (log)</strong></td>
<td>4.46 (4.15-4.87)</td>
<td>1.88</td>
</tr>
</tbody>
</table>
HIV and CD4/CD8 ratio

- Decreased CD4/CD8 ratio reported as hallmark of infection
- CD4/CD8 ratio associated with increased T cell activation
- Inverted CD4/CD8 ratio predictor of mortality in general population

Decreased CD4/CD8 Ratio Persists Despite HIV therapy

<table>
<thead>
<tr>
<th>Group</th>
<th>CD4:CD8 Ratio</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>HIV Negative</td>
<td>2.00</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non Controller</td>
<td>0.90</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HAART Suppressed</td>
<td>0.50</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Legend**
- HIV Negative (N=44)
- Non Controller (N=38)
- HAART Suppressed (N=62)
Decreased CD4 and Increased CD8 contribute to Inverted Ratio

### CD4

- HIV Negative N=44
- Non Controller N=38
- HAART Suppressed N=62

### CD8

- HIV Negative N=44
- Non Controller N=38
- HAART Suppressed N=62

**0.005**

NS
Generation of CD8+ T cell memory

NAIVE ➔ EFFECTOR ➔ EFFECTOR MEMORY

NAIVE ➔ NON-EFFECTOR ➔ CENTRAL MEMORY
Function of T cell Subsets

Naïve
- IL-2
- Proliferation

Memory
- IL-2
- IL-4
- IFNg
- TNFa
- B cell diff

Memory
- IFNγ
- TNFα
- Perforin
- Granzyme
- Cytotoxic

Effector
Seronegative Subjects Maintain Naïve CD8+ T cells

CD45RA
CCR7
CD28
CD27

% of CD3+CD8+ Population

0 5 10 15 20 25 30 35 40 45 50

CD45RA
CCR7
CD28
CD27

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Progressive HIV Disease Causes Loss of Naïve T cells

Progressor
Seronegative

% of CD3+CD8+ Population

CD45RA
CCR7
CD28
CD27

SERONEGATIVE
PROGRESSOR
HAART Treatment Does Not Restore Naïve CD8+ T Cells

% of CD3+CD8+ Population

CD45RA
CCR7
CD28
CD27

HAART SUPPRESSED
PROGRESSOR
SERONEGATIVE
T cells can respond to cancer cells

T cells can respond to invading pathogens
Uncontrolled HIV Increases Frequency of CD8+CD28- Population

Graph showing the percentage of total CD8 T cells with different CD28 and CD27 statuses for SERONEGATIVE and PROGRESSOR groups.
Antiretroviral Therapy Does Not Restore CD28+:CD28- Balance
HIV and Expansion of CD28

• Expansion of CD28- T cells have been reported in HIV disease
• Telomere length of CD28- cells equal to those of HIV-uninfected centenarians

Effros, RB AIDS 1996
Consequences of HIV on the Immune System (Despite Effective Therapy)

- Continued decrease of CD4/CD8
- Continued decrease of Naïve CD8+ T Cells
- Persistent CD28- Expansion
- Increased secretion of IFN-γ
- Heightened CMV-specific responses
Changes in Immune System Seen During Human Aging

- Inverted CD4:CD8 ratio **
- Decline in CD4+ T cells
- Lower Naïve/Memory T cell ratio
- Accumulation of CD28- T cells **
- Increased production of IFNγ among CD8+ T cells
- Decreased ability to proliferate or produce IL-2
- Increased CMV seropositivity and CMV-specific T cell response **
- Increased levels of proinflammatory cytokines
Potential Implications for ARV-Treated Individuals

• Does HIV cause premature aging of the immune system?

• Do these abnormal phenotypes relate to clinical outcomes?

• Do these aberrancies improve with time on therapy?

• Does earlier treatment prevent some of these abnormal immunologic phenotypes?

• What is contribution of antiretroviral therapy itself to immunologic changes?
Ongoing studies

• Does HIV cause premature aging of the immune system?
  – Carefully controlled studies of HIV-infected and uninfected individual

• Do these abnormal phenotypes relate to clinical outcomes?
  – Association of phenotypes and clinical outcomes

• Do these aberrancies improve with time on therapy?
  – Longitudinal evaluation of patients on HAART

• Does earlier treatment prevent some of these abnormal immunologic phenotypes?

• What is contribution of antiretroviral therapy itself to immunologic changes?
Acknowledgements

Mike McCune
Steve Deeks
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Rebecca Hoh
Priscilla Hsue
Hiroyu Hatano

All participants in SCOPE cohort
There Is Marked Heterogeneity of HIV-specific CD4+ Responses Among Elite Controllers

Gag-specific CD4+IFNγ+ IL2+

Elite Controller (VL<50) N=31
Viremic Controller (VL 50-2000) N=30
Non Controller (VL>10,000) N=26
HAART Suppressed (VL<50) N=55
HIV Negative N=36
Elite Controllers Have Higher Levels CD8+IFN-γ+ Cells Compared With Suppressed

P<0.0001

Gag-specific CD8 IFN "bright"

Elite Controller (VL<50) N=31

Viremic Controller (VL 50-2000) N=30

Non Controller (VL>10,000) N=34

HAART Suppressed (VL<50) N=55
Cytokines being used: IL-2, IFN-γ, MIP1β, TNFα

- CD4: 6.86
- IL-2: 2.81
- IFNγ: 0.11
- TNFα: 13.6
- MIP1β: 0.11
Elite and Viremic Controllers Have High Gag Specific CD4 Responses
Controllers and Non-controllers Have High Levels of Gag-specific CD8 T Cells
Among All Groups, the Majority of CD8 Cells Produce 1 Cytokine Only
Controllers Have High Levels of T Cells That Secrete Four Cytokines

Graphs showing the levels of CD4 and CD8 cells in different groups:

- Elite
- Controller
- Non-controller
- Suppressed
HLA type and Gag-specific T-cell responses.

Gating strategy

Side Scatter

Number of cells

EMA-PE-Cy5.5

CD3 ECD
Gating strategy

CD3 ECD

CD8 Cascade Blue

CD8 Cascade Blue

IFN-GAMMA FITC

CD28 APC

CD28 APC

CCR7 PE-CY7

CCR7 PE-CY7

CD45RA PE

CD45RA PE

CD8 Cascade Blue

CD8 Cascade Blue

CD27 APC-CY7

CD27 APC-CY7

Gating strategy

- CD3 ECD
- CD8 Cascade Blue
- IFN-GAMMA FITC
- CD28 APC
- CCR7 PE-CY7
- CD45RA PE
- CD8 Cascade Blue
- CD27 APC-CY7
Increased IFN-γ but not IL-2 Production in Response to SEB

![Graph showing IFN-γ and IL-2 production levels](image)

- IL-2:
  - SERONEGATIVE: Low levels
  - PROGRESSOR: Moderate levels
  - HAART SUPPRESSED: Higher levels

- IFN-γ:
  - SERONEGATIVE: Low levels
  - PROGRESSOR: High levels
  - HAART SUPPRESSED: Very high levels

NS: Not significant
P<0.005: Statistically significant at p<0.005
Across Subsets, Maintained or Increased IFNγ Production with HIV
Decreased IL-2 Production in CD28-Subsets in Treated Individuals
CD38 Expression Better Predictor of Survival than Viral Load

Giorgi, J, JID, 1998
Increased Production of CMV-specific IFN-γ Responses in T cells of Elderly

Vescovini, J. Imm 2007
CMV-specific T cells in elderly are more differentiated
CD3 Counts remain stable even with Viral Replication

CD3

Cells/mL

HIV Negative N=22
Non Controller N=42
HAART Suppressed N=53
CMV-Specific IFNγ Response is Associated with Increased Frequency of Differentiated T cells

**CD4 CMV IFNγ Response**

- **P<0.0001**

**CD8 CMV IFNγ Response**

- **P=0.06**
During HAART, CD4 CMV-specific Response Associated with Decreased Frequency of Naïve CD4

![Graph 1: CD4 Naive vs. CD4 CMV IFNγ Response (P=0.01)]

![Graph 2: CD4 Highly Differentiated vs. CD4 CMV IFNγ Response (P=0.06)]
CMV-Specific IFN\(\gamma\) Response is Associated with Decreased Frequency of Naïve T cells

- CD4 Naive
- CD4 CMV IFN\(\gamma\) Response
  - \(P=0.002\)

- CD8 Naive
- CD8 CMV IFN\(\gamma\) Response
  - \(P=0.0003\)
Cell Receptors for HIV Entry

Chemokine Receptor 5 (CCR5)

CD4

Target cell

CCR5-Δ32: Mutant Protein

2006

Diagnosed with acute leukemia (AML).
Received standard chemotherapy* (10⁶ copies of HIV-1 RNA)

Relapsed 7 months later

Allogenic stem cell transplant from a CCR5Δ32 homozygous donor in Feb. 2007

AML Relapsed 1 year after transplantation

Re-induction chemotherapy

Day 391: received a second transplant from same donor

2013: Antiviral therapy has never been re-started because patient has remained HIV undetectable

Cured?

Virus not found
Antibody response negative
Fraction of Naïve CD4 or CD8 T cells do not increase with time.
Absolute number of Naïve T cells also did not increase.
Increased Differentiation of CD4 T Cells With HIV Infection

<table>
<thead>
<tr>
<th>CD45RA</th>
<th>CCR7</th>
<th>CD28</th>
<th>CD27</th>
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<tbody>
<tr>
<td>+</td>
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PROGRESSOR SERONEGATIVE
HAART Treatment Does Fully Decrease Frequency of Mature CD4
Naïve CD8 T cell percentage is not associated with Total CD4 count or Nadir

Naïve CD8 T cell percentage Not Associated With Length of Infection or Length of Viral Suppression

Naïve CD8 T cell percentage not associated with Age
Total T cell Proliferation Decreased with HAART

Expression of Ki67

CD8

P=0.05

P=0.13

CD4

P=0.12

P=0.81

HIV Negative

Non-Controller

HAART Suppressed
Ki67 Decreased in HAART Suppressed Individuals

Ki67 Expression Among CD8+ T cells

<table>
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<tr>
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</table>

- SERONEGATIVE
- PROGRESSOR
- HAART SUPPRESSED
Decrease in Naïve T cells with Aging

Gupta, S, Imm Rev 2005
Expansion of CD28- Cells with Age

Fagnoni, FF, Immunology 1996
CMV Seropositive individuals have Expansion of CD28- cells

Pawelec G, 2007
Naïve T cell populations Lost During Untreated HIV infection

Roederer M, JCI, 1995
CMV-specific Responses Persist with Viral Suppression

- >90% HIV+ individuals are also CMV seropositive
- Most HIV-infected individuals have robust CMV-specific T cell response, even in absence of HIV-specific T cell response
- CMV responses are associated with atherosclerosis among HIV-infected individuals
Decreased CD4/CD8 Ratio in Elderly Predicts 4-year Mortality

<table>
<thead>
<tr>
<th>CD4/CD8</th>
<th>Survivors</th>
<th>Non-survivors</th>
<th>% dead</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.0</td>
<td>5</td>
<td>17</td>
<td>77%</td>
<td>.005</td>
</tr>
<tr>
<td>&gt;1.0</td>
<td>65</td>
<td>50</td>
<td>43%</td>
<td></td>
</tr>
</tbody>
</table>

Wikby A, 2005
Elderly have increased CMV-specific CD8 T cells

- CMV Seropositivity associated with increased mortality
- Elderly have increased T cells specific for CMV-derived epitopes
- CMV-specific cells have restricted clonality, terminally differentiated, with some dysfunctional aspects