HIV “Elite” Controllers

Why do some patients control their virus and what are the long-term clinical implications?

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Elite Controllers
- HIV seropositive
- Antiretroviral untreated
- No detectable HIV RNA (< 50 copies/mL)
- Any CD4

Far less prevalent than traditional LTNP (< 1% in most clinic-based cohorts but as high as 2-3% in undiagnosed persons presenting ERs or blood banks)

(Busch, CROI 09; Laeyendecker, JAIDS 08)
HIV Controllers

• How much virus is there?
• What are the mechanisms of control?
  – Host vs. virus?
  – T cell control vs. non-T cell control?
• What are the clinical consequences of long-term elite control?
  – Controllers as a mechanism to explore the virus and treatment independent effects of a chronic persistent infection on health

Most “elite” controllers have detectable viremia, and many have evidence of an apparent “set-point”

Hatano JV 09
When present, the ability of the virus to replicate is typically normal, arguing against acquisition of replication incompetent virus.

Replication competent HIV cultured from 6/10 controllers (Hopkins) and 8/9 (ANRS)

Virus exhibited normal replication kinetics

In other large surveys (MGH, n=78), genetic deletions were rare

Host mechanisms of control

*Immune system in controllers is always better than immune system in non-controllers*
UCSF SCOPE cohort: The level of “polyfunctional” IL2+INFγ+ gag-specific CD4+ T cells is most consistent correlate

Emu JV 2008

Similar trends are observed in gut mucosa

Ferre/Shacklett Blood 2009

% of rectal mucosal CD8+ T cells producing at least one cytokine in response to gag (IFNγ, TNFo, IL2, CD107 and MIPβ).
"Elite" control is consistently associated with at least three broadly defined T cell characteristics, including preserved proliferation and/or regenerative potential

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<tr>
<th>Correlate</th>
<th>Author</th>
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<tbody>
<tr>
<td>↑ CD8+ T cell proliferation</td>
<td>Migueles, Nat Imm 02</td>
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<td>Horton, JI 2006</td>
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<tr>
<td>↑ CD4+ T cell proliferation and CD4 “help” for CD8s</td>
<td>Rosenberg, Science 97</td>
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<td>Lighterfeld, JEM 04</td>
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<tr>
<td>↑ CD8 TCR diversity and clonal turnover</td>
<td>Almeidia, JEM 07</td>
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<tr>
<td>↑ IL2 production (HIV-specific CD4 and CD8)</td>
<td>Zimerali PNAS 05</td>
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<td>Emu JV 05, 07</td>
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<td>↓ Fox3a activity &amp; preserved CM CD4 cells</td>
<td>van Grevenynghe, NM 08</td>
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<tr>
<td>↑ telomerase activity (HIV-specific CD8 cells)</td>
<td>Lighterfeld, Blood 08</td>
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Decreased expression of markers associated with T cell dysfunction/terminal differentiation

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<tr>
<td>↓ CD38 (HIV-specific CD8)</td>
<td>Saez-Cirion, PNAS 07</td>
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<tr>
<td>↓ CTLA-4 (HIV-specific CD4 cells)</td>
<td>Kaufmann, Nat Imm 07</td>
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<tr>
<td>↓ PD-1 (HIV-specific cells)</td>
<td>Zhang, Blood 07</td>
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<td>Peretz, Abstract 356</td>
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Enhanced T cell mediated target-cell killing

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<tr>
<td>↓ HIV replication in autologous CD4 cells (mediated by CD8 cells)</td>
<td>Saez-Cirion, PNAS 07</td>
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<tr>
<td>↑ granzyme B killing of autologous CD4 cells</td>
<td>Migueles, Immunity 08</td>
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<tr>
<td>↑ gag-specific degranulation, cytokines</td>
<td>Betts, Blood 06</td>
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<td>Zimmerli, PNAS 05</td>
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<td>Almeida, JEM 07</td>
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<td>↑ perforin expression</td>
<td>Migueles, Immunity 08</td>
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<td>Hersperger, Abstract 357</td>
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<td>↑ interaction between T cells and NK cells</td>
<td>Martin, Nat Genetics 07</td>
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<td>Alter, JEM 07</td>
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However, many controllers have no detectable CD4 or CD8 responses and those who lack responses often lack protective HLAs

See also Pereyra et al, JID 2008
Interim Summary

- Elite control is clearly due in part to strong HIV specific T cells, but these are neither sufficient nor required

- CTL selected mutations and reductions in “fitness” may be important mechanism, but there are many exceptions and limited proof
  - Dramatic reductions in fitness as a consequence of antiretroviral drugs does not prevent virus rebound

- Many controllers lack any evidence of T cell control
  - NK cells, other?

But controllers have higher levels of CD8 “activation” than other aviremic groups, including those on HAART and HIV negatives

Activation higher in elites that other “aviremic” groups even after adjustment of CD4, age and other factors

Hunt JID 2008
(see also Lopez Abstract 366)
C-reactive protein levels are twice as high in controllers than HIV negatives, and comparable to that in other HIV infected groups.

Elite controllers also have consistently high levels of CMV-specific CD4+ T cell response (IFNγ).
LPS levels—a measure of microbial translocation—is persistently elevated in elite controllers, suggesting mucosal damage.

What are the consequences of chronic low level inflammation?
Some “elite” controllers gradually lose CD4+ T cells despite undetectable viral loads

4/58 Elites (7%) had AIDS

Guidelines recommend HAART

Higher CD8 T cell activation is associated with lower CD4 Counts in elite controllers

Hunt JID, 2008; see also Andrade CID 2008 and Learmont NEJM 99

Hunt JID 2008
Elite controllers also have higher levels of atherosclerosis than HIV negatives, after controlling for all known risk factors

![Graph showing mean intima-medial thickening (cm) for HIV negative, Elite controllers, Non-controllers, and HAART VL < 50](image)

**Clinical implications**

- Elite control is clearly preferred to no control, but is not a completely benign condition
  - Which is worse: inflammation (driven by the virus) or antiretroviral drugs?

- Therapeutic efforts aimed at achieving a T cell mediated “cure” may not fully restore health

- Vaccine efforts aimed at achieving control post-transmission may not be completely protective
  - Possible role in STEP trial failures?

- Chronic inflammation may be lower in the “non-T-cell controllers”, supporting more focused efforts aimed at defining these mechanisms
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